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Masson P, Henderson L, Chapman JR, Craig JC, Webster AC

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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 3
BACKGROUND 5
OBJECTIVES 5
METHODS 5
RESULTS 7
Figure 1. 8
Figure 2. 10
DISCUSSION 12
Figure 3. 13
AUTHORS' CONCLUSIONS 14
ACKNOWLEDGEMENTS 14
REFERENCES 15
CHARACTERISTICS OF STUDIES 28
DATA AND ANALYSES 37
Analysis 1.1. Comparison 1 Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 1 Recipient and kidney survival. 39
Analysis 1.2. Comparison 1 Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 2 Surviving with a functioning transplant. 40
Analysis 1.3. Comparison 1 Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 3 Acute rejection and chronic kidney scarring. 40
Analysis 1.4. Comparison 1 Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 4 Kidney function, blood pressure and lipids. 41
Analysis 1.5. Comparison 1 Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 5 Malignancy. 42
Analysis 1.6. Comparison 1 Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 6 Infections. 42
Analysis 1.7. Comparison 1 Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 7 Diabetes and use of blood pressure medicines. 43
Analysis 2.1. Comparison 2 High versus low dosage belatacept, Outcome 1 Recipient and kidney survival. 46
Analysis 2.2. Comparison 2 High versus low dosage belatacept, Outcome 2 Surviving with a functioning transplant. 46
Analysis 2.3. Comparison 2 High versus low dosage belatacept, Outcome 3 Acute rejection and chronic kidney scarring. 46
Analysis 2.4. Comparison 2 High versus low dosage belatacept, Outcome 4 Kidney function, blood pressure and lipids. 47
Analysis 2.5. Comparison 2 High versus low dosage belatacept, Outcome 5 Malignancy. 48
Analysis 2.6. Comparison 2 High versus low dosage belatacept, Outcome 6 Infections. 49
Analysis 2.7. Comparison 2 High versus low dosage belatacept, Outcome 7 Diabetes and use of blood pressure medicines. 50
APPENDICES 50
CONTRIBUTIONS OF AUTHORS 53
DECLARATIONS OF INTEREST 53
INDEX TERMS 53

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[Intervention Review]

Belatacept for kidney transplant recipients

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ABSTRACT

Background

Most people who receive a kidney transplant die from either cardiovascular disease or cancer before their transplant fails. The most common reason for someone with a kidney transplant to lose the function of their transplanted kidney necessitating return to dialysis is chronic kidney transplant scarring. Immunosuppressant drugs have side effects that increase risks of cardiovascular disease, cancer and chronic kidney transplant scarring. Belatacept may provide sufficient immunosuppression while avoiding unwanted side effects of other immunosuppressant drugs. However, high rates of post-transplant lymphoproliferative disease (PTLD) have been reported when belatacept is used in particular kidney transplant recipients at high dosage.

Objectives

1) Compare the relative efficacy of belatacept versus any other primary immunosuppression regimen for preventing acute rejection, maintaining kidney transplant function, and preventing death. 2) Compare the incidence of several adverse events: PTLD; other malignancies; chronic transplant kidney scarring (IF/TA); infections; change in blood pressure, lipid and blood sugar control. 3) Assess any variation in effects by study, intervention and recipient characteristics, including: differences in pre-transplant Epstein Barr virus serostatus; belatacept dosage; and donor-category (living, standard criteria deceased, or extended criteria deceased).

Search methods

We searched the Cochrane Renal Group's Specialised Register to 1 September 2014 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

Randomised controlled trials (RCT) that compared belatacept versus any other immunosuppression regimen in kidney transplant recipients were eligible for inclusion.

Data collection and analysis

Two authors independently extracted data for study quality and transplant outcomes and synthesized results using random effects meta-analysis, expressed as risk ratios (RR) and mean differences (MD), both with 95% confidence intervals (CI). Subgroup analyses and univariate meta-regression were used to investigate potential heterogeneity.

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Main results

We included five studies that compared belatacept and calcineurin inhibitors (CNI) that reported data from a total of 1535 kidney transplant recipients. Of the five studies, three (478 participants) compared belatacept and cyclosporin and two (43 recipients) compared belatacept and tacrolimus. Co-interventions included basiliximab (4 studies, 1434 recipients); anti-thymocyte globulin (1 study, 89 recipients); alemtuzumab (1 study, 12 recipients); mycophenolate mofetil (MMF, 5 studies, 1509 recipients); sirolimus (1 study, 26 recipients) and prednisone (5 studies, 1535 recipients).

Up to three years following transplant, belatacept and CNI-treated recipients were at similar risk of dying (4 studies, 1516 recipients: RR 0.75, 95% CI 0.39 to 1.44), losing their kidney transplant and returning to dialysis (4 studies, 1516 recipients: RR 0.91, 95% CI 0.61 to 1.38), and having an episode of acute rejection (4 studies, 1516 recipients: RR 1.56, 95% CI 0.85 to 2.86). Belatacept-treated kidney transplant recipients were 28% less likely to have chronic kidney scarring (3 studies, 1360 recipients: RR 0.72, 95% CI 0.55 to 0.94) and also had better graft function (measured glomerular filtration rate (GFR) (3 studies 1083 recipients): 10.89 mL/min/1.73 m^2, 95% CI 4.01 to 17.77; estimated GFR (4 studies, 1083 recipients): MD 9.96 mL/min/1.73 m^2, 95% CI 3.28 to 16.64) than CNI-treated recipients. Blood pressure was lower (systolic (2 studies, 658 recipients): MD -7.51 mm Hg, 95% CI -10.57 to -4.46; diastolic (2 studies, 658 recipients): MD -3.07 mm Hg, 95% CI -4.83 to -1.31, lipid profile was better (non-HDL (3 studies 1101 recipients): MD -12.25 mg/dL, 95% CI -17.93 to -6.57; triglycerides (3 studies 1101 recipients): MD -24.09 mg/dL, 95% CI -44.55 to -3.64), and incidence of new-onset diabetes after transplant was reduced by 39% (4 studies (1049 recipients): RR 0.61, 95% CI 0.40 to 0.93) among belatacept-treated versus CNI-treated recipients.

Risk of PTLD was similar in belatacept and CNI-treated recipients (4 studies, 1516 recipients: RR 2.79, 95% CI 0.61 to 12.66) and was no different among recipients who received different belatacept dosages (high versus low dosage: ratio of risk ratios (RRR) 1.06, 95% CI 0.11 to 9.80, test of difference = 0.96) or among those who were Epstein Barr virus seronegative compared with those who were seropositive before their kidney transplant (seronegative versus seropositive; RRR 1.49, 95% CI 0.15 to 14.76, test for difference = 0.73).

The belatacept dose used (high versus low), type of donor kidney the recipient received (extended versus standard criteria) and whether the kidney transplant recipient received tacrolimus or cyclosporin made no difference to kidney transplant survival, incidence of acute rejection or estimated GFR. Selective outcome reporting meant that data for some key subgroup comparisons were sparse and that estimates of the effect of treatment in these groups of recipients remain imprecise.

Authors' conclusions

There is no evidence of any difference in the effectiveness of belatacept and CNI in preventing acute rejection, graft loss and death, but treatment with belatacept is associated with less chronic kidney scarring and better kidney transplant function. Treatment with belatacept is also associated with better blood pressure and lipid profile and a lower incidence of diabetes versus treatment with a CNI. Important side effects (particularly PTLD) remain poorly reported and so the relative benefits and harms of using belatacept remain unclear. Whether short-term advantages of treatment with belatacept are maintained over the medium- to long-term or translate into better cardiovascular outcomes or longer kidney transplant survival with function remains unclear. Longer-term, fully reported and published studies comparing belatacept versus tacrolimus are needed to help clinicians decide which patients might benefit most from using belatacept.

PLAIN LANGUAGE SUMMARY

Belatacept for kidney transplant recipients

Kidney transplants can improve the quality and length of life for patients with end-stage kidney disease (ESKD) compared with chronic dialysis. To prevent a kidney transplant from being rejected by the body, immune-system suppressing drugs (most commonly a calcineurin inhibitors (CNI)) are used. CNI are associated with high blood pressure, high lipid levels, an increased risk of developing diabetes, and chronic scarring of the kidney transplant. Chronic kidney scarring is the main reason that kidney transplants lose function in people who do not die before their kidney transplant fails. Belatacept might be an alternative immune-system suppressing drug which prevents rejection but which also causes fewer side-effects than CNI.

We included five studies that compared belatacept and calcineurin inhibitors (CNI) and enrolled 1535 kidney transplant recipients. We found that belatacept was no different to a CNI at being able to prevent acute rejection and at keeping a transplanted kidney working. Recipients who received belatacept had lower blood pressure, less diabetes and better kidney transplant function than recipients who received a CNI. The chance of dying after a kidney transplant was similar in recipients treated with belatacept and CNI.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Belatacept versus calcineurin inhibitors (CNI) for kidney transplant recipients

Patient or population: Kidney transplant recipients

Settings: multinational

Intervention: Belatacept (any dosage)

Comparison: CNI

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	CNI	Belatacept				
Death	57.5 per 1000	43.0 per 1000 (22.4 to 82.8)	0.75 (0.39 to 1.44)	1516 (4)	High quality	
Loss of kidney transplant	59.5 per 1000	54.1 per 1000 (36.3 to 82.1)	0.91 (0.61 to 1.38)	1516 (4)	High quality	
Acute rejection	164.7 per 1000	257.0 per 1000 (140.0 to 471.0)	1.56 (0.85 to 2.86)	1516 (4)	High quality	
Chronic kidney scarring	413.3 per 1000	297.4 per 1000 (227.2 to 388.2)	0.72 (0.55 to 0.94)	1350 (3)	High quality	
Malignancy	37.7 per 1000	37.7 per 1000 (21.9 to 64.8)	1.00 (0.58 to 1.72)	1516 (4)	Moderate quality	
PTLD	10.9 per 1000	30.4 per 1000 (6.6 to 138.0)	2.79 (0.61 to 12.66)	1516 (4)	Moderate quality	Very low quality for Epstein Barr virus and belatacept dosage subgroups
New onset diabetes	67.2 per 1000	50.0 per 1000 (26.9 to 62.5)	0.61 (0.40 to 0.93)	1049 (4)	Moderate quality	
Delayed graft function	321.0 per 1000	298.5 per 1000 (253.6 to 349.9)	0.93 (0.79 to 1.09)	1209 (2)	High quality	

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Presence of donor specific antibodies	18.5 per 1000	2.6 per 1000 (0.2 to 24.2)	0.14 (0.01 to 1.31)	1209 (2)	Moderate quality

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

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

PTLD - post-transplant lymphoproliferative disorder

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BACKGROUND

Description of the condition

Kidney transplantation can offer most people with end-stage kidney disease (ESKD) improved quality and length of life compared with remaining on chronic dialysis (Wong 2012). Short-term survival of a kidney transplant has improved significantly over the last 20 years since the introduction of cyclosporin, but medium- to long-term kidney and recipient outcomes have not. One-year kidney transplant survival in the United States is 95% for recipients of living and 89% for recipients of deceased donor kidneys whereas five-year kidney transplant survival falls to 80% for recipients of living and 67% for recipients of deceased donor kidneys (SRTR 2010). This trend is also evident in Australia and New Zealand where one-year first kidney transplant survival for living and deceased donor kidneys is 97% and 92%, falling to 90% and 82% by five years (ANZDATA 2012).

Most people who receive a kidney transplant die with a transplant that is still working. Cardiovascular disease and cancer are the biggest causes of death among people with a kidney transplant. Calcineurin inhibitors (CNI) cause high blood pressure, diabetes and high blood lipid levels, as well as impaired immune system detection of cancer cells and antiviral immune activity (Buell 2005; Meier-Kriesche 2004; Nankivell 2003; Vanrenterghem 2008; Vincenti 2007). Of those kidney transplant recipients who do not die with their transplant still working, chronic kidney transplant scarring is the biggest cause of losing kidney function (requiring recommencement of dialysis). Chronic kidney transplant scarring (also known as interstitial fibrosis/tubular atrophy or IF/TA) can be caused by toxicity from CNI, but also by ischaemia-reperfusion injury at around the time of the transplant and immune injury from acute or chronic rejection after the transplant (Nankivell 2003). Avoiding cardiovascular disease, cancer and chronic transplant kidney scarring may improve medium- and long-term recipient and kidney transplant outcomes.

Description of the intervention

Belatacept – a biologic immunosuppressive agent – is an inhibitor of T-cell co-stimulation, was approved by the United States Food and Drug Administration (FDA) in June 2011 for use in adult recipients of kidney transplants. It was approved on the basis of results from three randomised controlled trials (RCTs) which enrolled 1425 recipients comparing belatacept to cyclosporin in a regimen with concomitant use of MMF and steroids. In all three studies, belatacept was demonstrated to be non-inferior to cyclosporin in preventing acute rejection in kidney transplants (BENEFIT Study 2008; BENEFIT-EXT 2009; Vincenti 2007).

How the intervention might work

A direct antagonist of the ligands CD80 and CD86 present on antigen-presenting cells, belatacept prevents activation of the T-cell CD28 receptor. This specificity is designed to eliminate the non-immunological activity associated with conventional immunosuppressive agents while providing potent inhibition of T-cell activation and proliferation required for preventing acute rejection (Sayegh 1998).

Why it is important to do this review

CNI avoidance, minimisation and substitution strategies have all been tried in clinical studies in the past (Ekberg 2009; Flechner 2011; Watson 2005). None of these regimens found the optimal balance between sufficient immunosuppression to avoid kidney transplant rejection and the avoidance of unwanted side effects. FDA approval for belatacept use is limited to a low dose regimen in Epstein Barr seropositive adult kidney transplant recipients because early clinical studies reported an increased incidence of PTLD when belatacept was used in Epstein Barr seronegative recipients or in a high dosage regimen (Vincenti 2005). Before belatacept can be used widely, clinicians require a more comprehensive understanding of its benefits and harms to ensure that it is used appropriately and safely for specific kidney transplant recipients (Webster 2009).

This review aimed to synthesise data from RCTs that compared belatacept with other primary maintenance immunosuppression regimens.

OBJECTIVES

1. Compare the relative efficacy of belatacept versus any other primary immunosuppression regimen for preventing acute rejection, maintaining kidney transplant function, and preventing death.
2. Compare the incidence of several adverse events: PTLD; other malignancies; chronic transplant kidney scarring; infections; change in blood pressure, lipid and blood sugar control.
3. Assess any variation in effects by study, intervention and recipient characteristics, including: differences in pre-transplant Epstein Barr virus serostatus; belatacept dosage; and donor-category (living, standard criteria deceased, or extended criteria deceased).

METHODS

Criteria for considering studies for this review

Types of studies

We included all RCT and quasi-RCT, whether published or available only in abstract form.

Types of participants

We included all adults and children receiving a kidney transplant from a living or deceased donor (standard or extended criteria), in whom belatacept was tested versus any other immunosuppressive agent in a primary induction and maintenance regimen. Kidney transplant recipients in whom belatacept was tested against any other immunosuppressive agent in a secondary immunosuppression regimen were excluded, i.e. when treatment was changed due to acute rejection or chronic kidney scarring or calcineurin-inhibitor (CNI) toxicity. We also excluded recipients who received another solid organ in addition to a kidney transplant (e.g. kidney and pancreas).

Types of interventions

1. Belatacept given in combination with any other immunosuppressive co-intervention in which control recipients received no belatacept, placebo, or another agent that the belatacept arm did not receive

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2. Belatacept given in combination with any other immunosuppressive co-intervention in which control recipients received a dosage comparison (e.g. high versus low dosage belatacept).

Types of outcome measures

The following binary outcome measures were considered.

1. Recipient and kidney survival
   a. Death (any cause)
   b. Loss of kidney transplant (loss of a kidney transplant requiring return to dialysis)
   c. Surviving with a working transplant
2. Incidence and grade of acute rejection
3. Incidence and grade of chronic kidney transplant scarring
4. Incidence of delayed kidney transplant (graft) function (DGF)
5. Incidence of malignancies: all-cause, skin cancers (basal cell carcinoma (BCC), squamous cell carcinoma (SCC)), PTLD
6. Incidence of infections: cytomegalovirus (CMV viraemia and CMV disease), polyoma virus (BK viraemia and BK virus-associated nephropathy), pneumonia, tuberculosis (TB), urinary tract infection (UTI)
7. Incidence of diabetes
8. Use of antihypertensive agents.

The following continuous outcomes were analysed.

1. Kidney transplant function: measured glomerular filtration rate (GFR), estimated GFR (eGFR)
2. Cardiovascular and biochemical measures: mean systolic and diastolic blood pressure (SBP, DBP), total cholesterol, high density lipoprotein (HDL), non-HDL, low density lipoprotein (LDL), triglycerides (TGs), serum blood glucose

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's Specialised Register to 1 September 2014 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

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

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

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

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

Data collection and analysis

Selection of studies

The search strategies described identified eligible studies. Titles and abstracts resulting from the searches were then screened by two authors who independently assessed retrieved abstracts and if necessary the full text of these studies to determine which studies satisfied the inclusion criteria. Disagreement about inclusion was resolved by discussion with a third author. Where more than one report of a study existed, we grouped reports together and used the first complete (index) study publication as the primary data source. We examined any prior or subsequent report for supplementary outcomes or data to ensure the inclusion of all relevant information.

Data extraction and management

Data extraction was carried out independently by two authors using standardised data extraction forms. All data were entered into RevMan 5.2 and additional statistical analyses were done using STATA 11.2 software (Statacorp, TX, USA).

Assessment of risk of bias in included studies

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

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

Measures of treatment effect

For binary outcomes, results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment we calculated the mean difference (MD) with 95% CI.

Dealing with missing data

We first tried to clarify unclear or missing data by directly contacting the author of the study report. For the three largest studies (BENEFIT Study 2008; BENEFIT-EXT 2009; Vincenti 2005) we held a teleconference with representatives from Bristol Myers Squibb (the manufacturers of belatacept) in an attempt to access unpublished data for particular outcomes in certain patient subgroups. Specifically, we requested data on PTLD stratified by recipient pre-transplant Epstein Barr virus serostatus and whether recipients were randomised to the high or low dosage belatacept treatment arm.

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Assessment of heterogeneity

Heterogeneity amongst studies was analysed using a Cochran Q test (n-1 degrees of freedom), with an alpha of 0.05 used for statistical significance and with the I^2 test calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

We planned to use funnel plots to assess the potential existence of publication and small study biases but this was not informative due to the small number of included studies (Higgins 2011).

Data synthesis

We pooled data from individual studies using a random-effects model, because the random effects model provides a more conservative estimate of effect in the presence of known or unknown potential heterogeneity (Higgins 2003).

Subgroup analysis and investigation of heterogeneity

Subgroups analyses were pre-specified and included belatacept dosage (high or low), kidney donor source (living, standard- or extended-criteria deceased), calcineurin inhibitor (tacrolimus or cyclosporine) and pre-transplant Epstein Barr serostatus (negative or positive). For binary outcomes, we presented results as the ratio of risk ratios (RRR and 95%CI), showing the proportional change in risk for the study or participant character listed versus the reference range comparison. For continuous outcomes, results were presented as the difference in mean differences (DMD and 95%CI). Tests of heterogeneity among pooled subgroup estimates were calculated using univariate random-effects meta-regression.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

After searching the Cochrane Renal Group's Specialised Register (to 1 September 2014) we identified 642 reports. After duplicate removal and screening of titles and abstracts 250 full-text reports were assessed. A further 56 reports were excluded (duplicates (43), study protocols (6), not primary immunosuppression (7)). After we grouped the remaining reports, 13 potential studies (194 reports) were identified. We identified five included studies (174 reports), three excluded studies (15 reports), and five ongoing studied (5 reports) (Figure 1).

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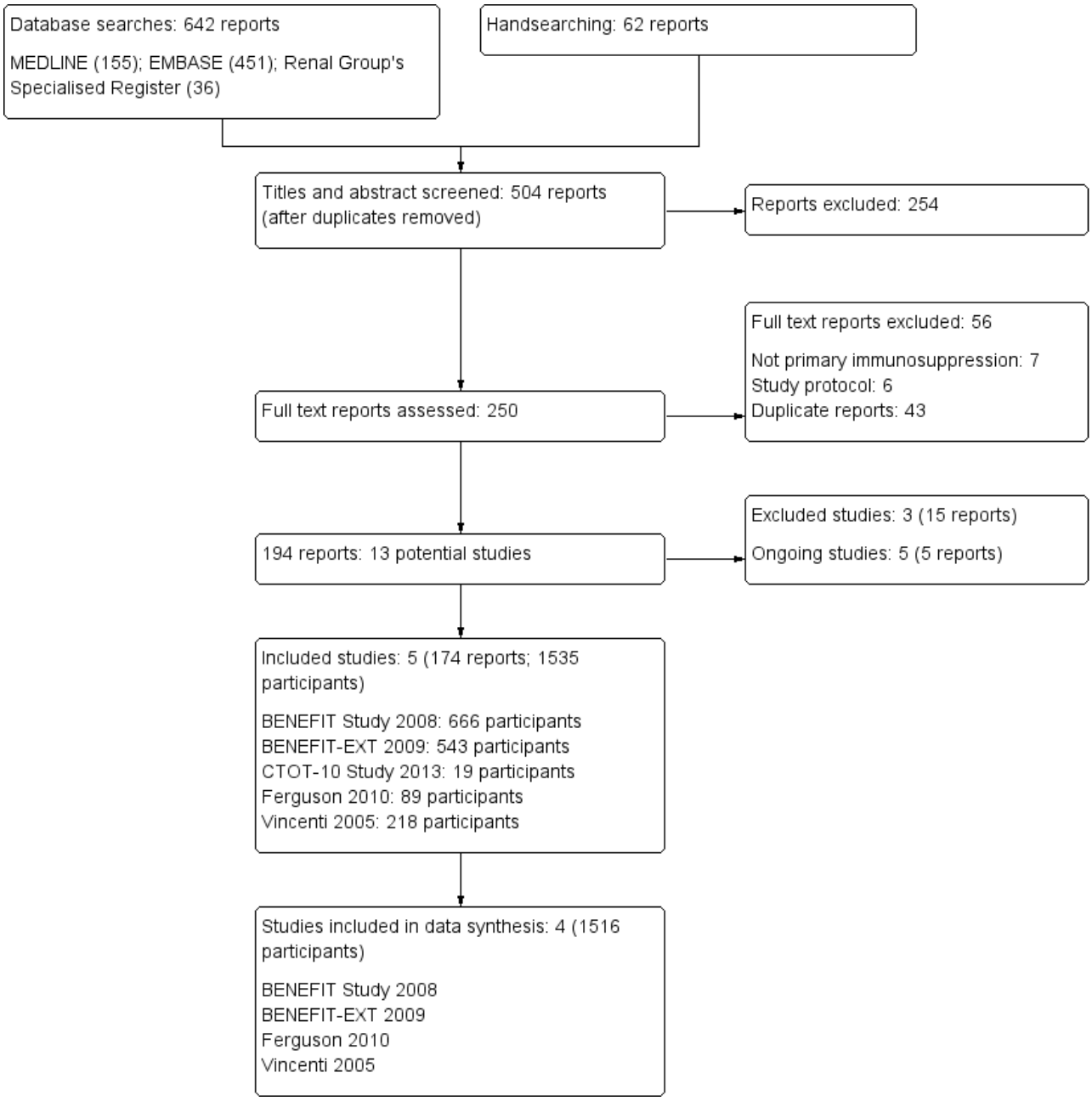
Figure 1. Flow chart showing study selection procedure



Included studies

We included five studies (174 reports published in 10 journals) that involved 1535 randomised kidney transplant recipients. One study (CTOT-10 Study 2013) met our inclusion criteria but did not contribute data to the meta-analysis because data for key clinical outcomes were only in abstract form and we were unable to calculate reliable risk ratios at common time-points. This three arm phase II study compared belatacept maintenance therapy (used at an unknown dosage) with either tacrolimus or no CNI in 19 participants induced with either alemtuzumab or basiliximab. This study was stopped prematurely before one year of follow-up because of an excess incidence of kidney transplant thrombosis.

Study characteristics

Of the studies included in our meta-analysis, study participants varied from 89 (Ferguson 2010) to 666 (BENEFIT Study 2008). Four studies (BENEFIT Study 2008; BENEFIT-EXT 2009; Ferguson 2010; Vincenti 2005) were multinational, multicentre, parallel design RCTs with three treatment arms, conducted in Europe and North America from 2001. Two studies were phase II (Ferguson 2010; Vincenti 2005) and two were phase III (BENEFIT Study 2008; BENEFIT-EXT 2009) studies. Duration of completed follow-up varied from one (Ferguson 2010) to five years. Studies that reported five-year results (BENEFIT Study 2008; BENEFIT-EXT 2009; Vincenti 2005) were long-term extensions which only included participants who were still alive with a functioning kidney at three years, and so we only present analyses based on outcomes at three years to

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avoid the selection bias of these longer-term analyses. Studies were powered to variably detect non-inferiority or superiority of belatacept versus CNI for a variety of primary outcomes. Ferguson 2010 and Vincenti 2005 were non-inferiority studies with primary outcomes of acute rejection at six months. BENEFIT Study 2008 had three co-primary outcomes, powered to detect superiority in kidney function and non-inferiority in composite patient and graft survival and incidence of acute rejection. BENEFIT-EXT 2009 was powered to detect non-inferiority in composite patient and graft survival, and superiority in kidney function.

Main intervention

Four studies (536 participants; BENEFIT Study 2008; BENEFIT-EXT 2009; Vincenti 2005; Ferguson 2010) used high dose belatacept regimens and three studies (472 participants; BENEFIT Study 2008; BENEFIT-EXT 2009; Vincenti 2005) used low dose belatacept. High dose belatacept recipients received 10 mg/kg on days 1 and 5, then every two weeks until week 12, then every four weeks until week 24; and then 5 mg/kg every four weeks thereafter. Low dose belatacept participants received 10 mg/kg on days 1 and 5, then every two weeks until week 4, then every four weeks until week 12 and then 5 mg/kg every four weeks thereafter.

Belatacept was compared with cyclosporin in three studies (478 participants; BENEFIT Study 2008; BENEFIT-EXT 2009; Vincenti 2005) and tacrolimus in one study (30 participants; Ferguson 2010). CNI formulation was not clearly stated in any study. Cyclosporin target levels varied among studies: 100 to 250 ng/mL for years 1 to 3 (BENEFIT Study 2008); 150 to 300 ng/mL in months 0 to 1, 100 to 250 ng/mL in months 2 to 12 (BENEFIT-EXT 2009); 150 to 400 ng/mL in months 0 to 1, 150 to 300 ng/mL in months 2 to 12 (Vincenti 2005), and for tacrolimus; 8 to 12 ng/mL until day 30, 5 to 10 ng/mL thereafter (Ferguson 2010).

Co-interventions

Co-interventions also varied. Three studies (1415 participants; BENEFIT Study 2008; BENEFIT-EXT 2009; Vincenti 2005) used basiliximab for induction, and one study (89 participants; Ferguson 2010) used antithymocyte globulin. All participants received perioperative intravenous (IV) methylprednisolone, although durations varied: days 0 and 1 (BENEFIT Study 2008; BENEFIT-EXT 2009; Vincenti 2005); and days 0, 1 and 2 (Ferguson 2010). All but one study (Ferguson 2010) prescribed maintenance prednisone, tapered variably to no less than 2.5 mg/d by day 15 (BENEFIT Study 2008), 5 mg to 7 mg/d by months 9 to 12 (BENEFIT-EXT 2009) or no less than 5 mg/d by 6 months (Vincenti 2005). All studies used mycophenolate mofetil (MMF) (1490 participants) at a dose of 2 g/d with reductions allowed for symptomatic or haematological side effects, with the exception of a subgroup of 26 recipients in the Ferguson 2010 study who instead received sirolimus. Studies treated episodes of acute rejection similarly. Acute rejection less severe than Banff 2A criteria received pulsed intravenous methylprednisolone. Banff 2B or worse acute rejection was treated with either corticosteroids or T-cell depleting therapy at the investigator's discretion in three studies (BENEFIT Study 2008; BENEFIT-EXT 2009; Ferguson 2010) whereas one study routinely used T-cell depleting therapy (Vincenti 2005). Three studies universally prescribed anti-viral prophylaxis for at least 3 months post transplant or upon initiating T-cell depleting agents and used Pneumocystis jejuni prophylaxis for 6 months (BENEFIT Study 2008; BENEFIT-EXT 2009; Ferguson 2010). One study did not provide details of their bacterial and viral prophylaxis protocols (Vincenti 2005).

Baseline donor and recipient characteristics

One study (543 participants, BENEFIT-EXT 2009) exclusively recruited extended criteria deceased donor kidney transplant recipients. The other three studies recruited a total of 973 living donor or standard-criteria deceased donor kidney recipients (of which at least 488 were living donor and 485 standard-criteria deceased donor kidney transplant recipients). Recipients of extended criteria donor kidneys were older (mean age 56.2 years) than recipients of standard criteria or living donor kidney transplants (mean age 44.6 years). No study included recipients younger than 18 years. One study (Ferguson 2010) excluded recipients who were seronegative for Epstein Barr virus at baseline, and of the other four studies, one (Vincenti 2005) did not provide details of participants' serostatus. Three studies (BENEFIT Study 2008; BENEFIT-EXT 2009; Ferguson 2010) included a total of 1176 pre-transplant Epstein Barr virus seropositive and 136 pre-transplant seronegative participants. Sensitization (determined by panel reactive antibody titre) did not vary between studies, with most participants being non-sensitized. Eighteen percent (BENEFIT Study 2008), 20% (BENEFIT-EXT 2009) and 34% (Ferguson 2010) of participants had diabetes before receiving a kidney transplant. It was unclear how many participants had pre-existing diabetes in Vincenti 2005. The most common cause of ESKD was glomerulonephritis; 22% (BENEFIT Study 2008), 26% (BENEFIT-EXT 2009) and 35% (Vincenti 2005) of kidney transplant recipients. Similar proportions of recipients had ESKD caused by diabetes, hypertension, and polycystic kidney disease amongst studies.

Outcome ascertainment and definitions

Data for acute rejection and chronic kidney scarring were obtained from kidney transplant biopsies, scored according to the Banff '97 diagnostic categories for kidney allograft biopsies. Four studies (BENEFIT-EXT 2009; BENEFIT Study 2008; Ferguson 2010; Vincenti 2005) performed indication biopsies based on protocol-defined reasons for clinical suspicion of acute rejection. Three studies performed pre-specified protocol transplant biopsies at 12 months (BENEFIT-EXT 2009; BENEFIT Study 2008; Vincenti 2005). Severe acute rejection included kidney biopsies scored as Banff IIA or worse. Chronic kidney scarring included mild (affecting < 25% of the kidney cortex), moderate (25 to 50% of the cortex), and severe changes (affecting > 50% of the cortex).

Excluded studies

We excluded three studies (Kamar 2013; Kirk 2012; Rostaing 2011) in which belatacept was not used in a primary immunosuppression regimen, but rather as a switch from conventional immunosuppression at some time distant from kidney transplantation.

Ongoing studies

Five ongoing studies were identified that met inclusion criteria but have not yet published any results (EudraCT2006-00311417; EudraCT2011-00616240; EudraCT2013-00117820; NCT01729494; NTR4242).

Risk of bias in included studies

Study methodology reporting is summarised in Figure 2.

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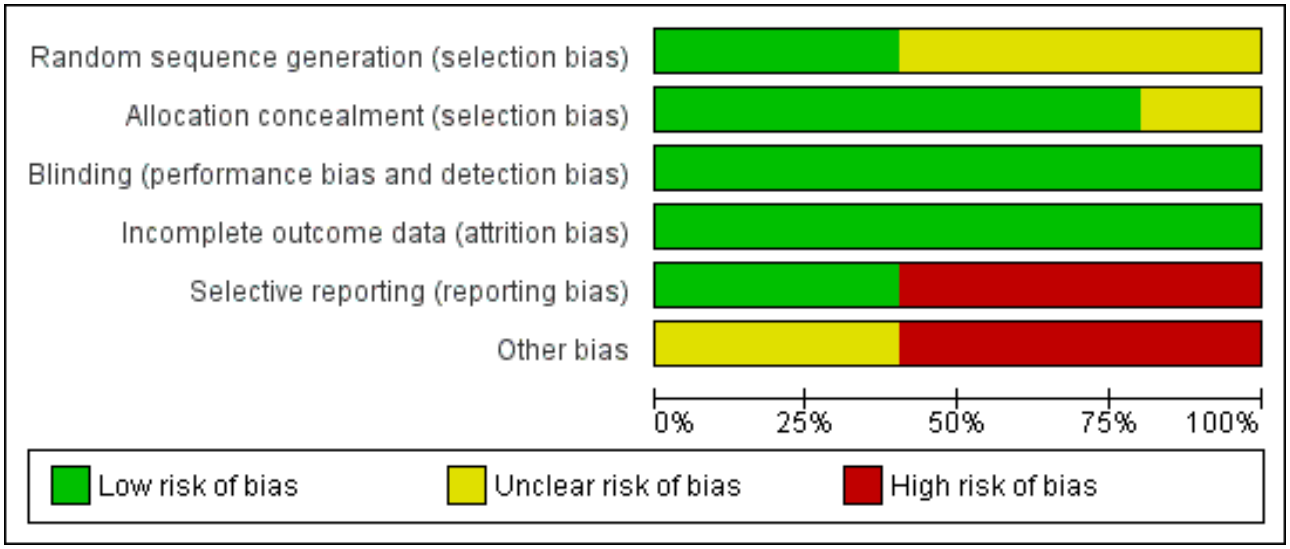
Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Of the studies included in meta-analysis, two reported adequate sequence generation (BENEFIT Study 2008; BENEFIT-EXT 2009) and two described the process in insufficient detail to allow a confident judgement of the risk of bias (Ferguson 2010; Vincenti 2005). Four studies reported adequate allocation concealment (BENEFIT Study 2008; BENEFIT-EXT 2009; Ferguson 2010; Vincenti 2005). We deemed no study to be at high risk of selection bias.

Blinding

We judged that all four studies (BENEFIT Study 2008; BENEFIT-EXT 2009; Ferguson 2010; Vincenti 2005) were at low risk of performance and detection bias despite the blinding of neither participants nor outcome assessors. Belatacept was administered intravenously, and CNI orally with no placebo infusion described in the study protocols. However, the outcomes assessed were objective measures recorded by standardized and validated methods which we thought were unlikely to be influenced by a lack of blinding (e.g. estimated GFR).

Incomplete outcome data

All studies (BENEFIT Study 2008; BENEFIT-EXT 2009; Ferguson 2010; Vincenti 2005) adequately addressed incomplete outcome data for up to three years post kidney transplant. Long-term extension data was presented between three and five years following kidney transplant in three studies (BENEFIT-EXT 2009; BENEFIT Study 2008; Vincenti 2005). We considered that this data was biased by survival of the kidney transplant recipients themselves (and their kidney transplants) to at least three years following transplant and so presented our analyses based on three year outcome data available for the full intention-to-treat populations.

Selective reporting

Two studies were at high risk of selective reporting (BENEFIT Study 2008; BENEFIT-EXT 2009). This arose because key outcomes were not uniformly reported at standardized time-points amongst studies including for key outcomes such as graft loss, PTLD and diabetes. In addition, for clinical outcomes where we expected that the risk of particular adverse events might vary by specific subgroups of patients (for example the risk of PTLD by a recipient's pre-transplant Epstein Barr virus status), data was often not published at all or not published in enough detail to contribute to data synthesis. Finally, even after directly requesting missing data from data custodians (BENEFIT-EXT 2009; BENEFIT Study 2008), we received no data that was not already available in the public domain. The other two studies (Ferguson 2010; Vincenti 2005) provided insufficient information to permit judgement and so remain unclear in their potential for reporting bias.

Other potential sources of bias

Bristol Myers Squibb - the manufacturer of belatacept - funded three of the studies (BENEFIT Study 2008; BENEFIT-EXT 2009; Vincenti 2005).

Effects of interventions

See: **Summary of findings for the main comparison**

Belatacept versus calcineurin inhibitors

Up to three years after a kidney transplant, belatacept and CNI-treated kidney recipients were at similar risk of dying (Analysis 1.1.1 (4 studies, 1516 recipients): RR 0.75, 95% CI 0.39 to 1.44; I^2 = 38%), losing their kidney transplant (Analysis 1.1.2 (4 studies, 1516 recipients): RR 0.91, 95% CI 0.61 to 1.38; I^2 = 0%) and surviving with a functioning kidney transplant (Analysis 1.2 (4 studies 1516 recipients): RR 1.01, 95% CI 0.96 to 1.06; I^2 = 42%).

Acute rejection occurred with similar incidence in recipients who received belatacept and CNI (Analysis 1.3.1 (4 studies, 1516 participants): RR 1.56, 95% CI 0.85 to 2.86; I^2 = 63%) with no difference in the chances of the rejection being severe (Analysis 1.3.2 (2 studies, 194 recipients): RR 1.02, 95% CI 0.76 to 1.37; I^2 = 34%). Overall, chronic kidney scarring was significantly reduced by 28% (Analysis 1.3.3 (3 studies, 1360 recipients): RR 0.72, 95% CI 0.55

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to 0.94; I^2 = 63%) in belatacept-treated recipients but not severe chronic rejection (Analysis 1.3.4 (3 studies, 1360 recipients): RR 0.75, 95% CI 0.42 to 1.32; I^2 = 0%).

Belatacept-treated kidney transplant recipients had better kidney function (Analysis 1.4.1 (measured GFR (3 studies 1083 recipients): MD 10.89 mL/min/1.73 m^2, 95% CI 4.01 to 17.77; I^2 = 79%) (Analysis 1.4.2 (eGFR (4 studies, 1143 recipients): MD 9.96 mL/min/1.73 m^2, 95% CI 3.28 to 16.64; I^2 = 79%), lower blood pressure (Analysis 1.4.3 (systolic (2 studies, 658 participants): MD -7.51 mm Hg, 95% CI -10.77 to -4.46; I^2 = 0%) (Analysis 1.4.4 (diastolic (2 studies, 658 recipients): MD -3.07 mm Hg, 95% CI -4.83 to -1.31; I^2 = 0%) and had a smaller rise in non-HDL cholesterol (Analysis 1.4.5 (3 studies, 1101 participants): MD -12.25 mg/dL, 95% CI -17.93 to -6.57; I^2 = 11%) and triglycerides during the study (Analysis 1.4.6 (3 studies, 1101 recipients): MD -24.09 mg/dL, 95% CI -44.55 to -3.64; I^2 = 69%) than recipients who received a CNI.

The risk of any malignancy (Analysis 1.5.1 (4 studies, 1516 recipients): RR 1.00, 95% CI 0.58 to 1.72; I^2 = 0%) and PTLD (Analysis 1.5.2 (4 studies, 1516 recipients): RR 2.79, 95% CI 0.61 to 12.66; I^2 = 0%) and was similar in both treatment arms.

Any infection (Analysis 1.6.1 (4 studies, 1516 recipients): RR 0.98, 95% CI 0.87 to 1.09; I^2 = 49%) and serious infections (Analysis 1.6.2 (2 studies, 1209 recipients): RR 0.96, 95% CI 0.83 to 1.12; I^2 = 0%) occurred with similar incidence. Specifically, tuberculosis (Analysis 1.6.3 (2 studies, 1209 recipients): RR 3.96, 95% CI 0.72 to 21.67; I^2 = 0%), CMV disease (Analysis 1.6.4 (2 studies, 1209 recipients): RR 1.51, 95% CI 0.91 to 2.50; I^2 = 0%), and polyoma-virus related (BK) nephropathy (Analysis 1.6.5 (1 study, 666 recipients): RR 0.25, 95% CI 0.05 to 1.35) were equally likely in recipients receiving belatacept as those receiving a CNI.

We observed a 39% reduction in the risk of developing new-onset diabetes (Analysis 1.7.1 (4 studies, 1049 participants): RR 0.61, 95% CI 0.40 to 0.93; I^2 = 0%) and a 17% reduction in the number of kidney transplant recipients who needed to take one or two blood pressure medicines following their transplant (Analysis 1.7.2 (2 studies, 755 recipients): RR 0.79, 95% CI 0.67 to 0.92; I^2 = 0%) amongst those who received belatacept versus those who received a CNI. There was no difference between the groups for those patients requiring three or blood pressure medicines (Analysis 1.7.3 (3 studies, 1298 recipients): RR 0.83, 95% CI 0.65 to 1.07; I^2 = 51%).

Presence of new donor-specific antibodies was no different between recipients of belatacept or a CNI (Summary of findings for the main comparison (2 studies, 1209 recipients): RR 0.41, 95% CI 0.01 to 1.31). Delayed graft function occurred at a similar rate in kidney transplant recipients who received belatacept to recipients who received a CNI (Summary of findings for the main comparison (2 studies, 1209 recipients): RR 0.93, 95% CI0.79 to 1.09).

High versus low dosage belatacept

Three studies (949 recipients) compared high versus low dosage belatacept (BENEFIT Study 2008; BENEFIT-EXT 2009; Vincenti 2005).

High and low dosage treated kidney transplant recipients had similar risks of dying (Analysis 2.1.1 (3 studies, 949 recipients): RR 1.24, 95% CI 0.75 to 2.06; I^2 = 0%), losing their kidney transplant (Analysis 2.1.2 (3 studies, 949 recipients): RR 0.96, 95% CI 0.59 to 1.56; I^2 = 0%), and surviving with a functioning kidney at up to three years (Analysis 2.2 (3 studies, 949 recipients): RR 0.98, 95% CI 0.95 to 1.02; I^2 = 0%).

Acute rejection (Analysis 2.3.1 (3 studies, 949 recipients): RR 1.17, 95% CI 0.88 to 1.55; I^2 = 0%), severe acute rejection (Analysis 2.3.2 (2 studies, 152 recipients): RR 1.28, 95% CI 0.67 to 2.43; I^2 = 88%), chronic kidney scarring (Analysis 2.3.3 (3 studies, 910 recipients): RR 0.94, 95% CI 0.74 to 1.20; I^2 = 27%), and severe chronic kidney scarring (Analysis 2.3.4 (3 studies, 910 recipients): RR 0.77, 95% CI 0.34 to 1.75; I^2 = 10%) occurred with similar incidence in with either dosage.

There was no difference in kidney transplant function (Analysis 2.4.1 (measured GFR (3 studies, 735 recipients): RR 0.37 mL/min/1.73m^2, 95% CI -3.49 to 4.23; I^2 = 12%) (Analysis 2.4.2, eGFR (3 studies, 747 recipients): MD 0.13 mL/min/1.73m^2, 95% CI -2.94 to + 3.20; I^2 = 0%), blood pressure (Analysis 2.4.3 (systolic (2 studies 659 recipients): MD +1.16 mm Hg, CI -1.33 to + 3.66; I^2 = 0%) (Analysis 2.4.4 (diastolic (2 studies 659 recipients): MD 0.00 mm Hg, 95% CI -1.52 to +1.52; I^2 = 0%), change in non-HDL cholesterol (Analysis 2.4.5 (2 studies, 671 recipients), MD 0.59 mg/dL, 95% CI -5.54 to +6.72; I^2 = 0%), or change in triglycerides during the study (Analysis 2.4.6 (2 studies, 671 recipients): MD 8.82 mg/dL, 95% CI -6.63 to 24.28; I^2 = 0%) in recipients who received high dosage belatacept compared with those who received low dosage belatacept.

Any malignancy (Analysis 2.5.1 (3 studies, 949 participants): RR 1.27, 95% CI 0.52 to 3.13; I^2 = 0%) and PTLD (Analysis 2.5.2 (2 studies, 949 recipients): RR 1.25, 95% CI 0.39 to 3.99; I^2 = 0%) were equally likely in recipients treated with high dosage belatacept as in recipients treated with low dosage belatacept.

Any infection (Analysis 2.6.1 (3 studies, 949 recipients): RR 0.98, 95% CI 0.92 to 1.04; I^2 = 0%) and serious infections (Analysis 2.6.2 (2 studies, 804 recipients): RR 0.89, 95% CI 0.73 to 1.09; I^2 = 17%) occurred with similar incidence. Tuberculosis (Analysis 2.6.3 (2 studies, 804 recipients): RR 0.99, 95% CI 0.23 to 4.17; I^2 = 31%), CMV disease (Analysis 2.6.4 (3 studies, 949 recipients): RR 1.02, 95% CI 0.74 to 1.40; I^2 = 0%), and BK nephropathy (Analysis 1.6.5 (1 study, 445 recipients): RR 1.03, 95% CI 0.06 to 16.40) were equally likely in recipients receiving high or low dosage belatacept.

We observed no difference in the effect of dosage on the incidence of new-onset diabetes (Analysis 2.7.1 (3 studies, 739 recipients): RR 0.91, 95% CI 0.33 to 2.51; I^2 = 48%). Use of one or two (Analysis 2.7.2 (1 study, 445 recipients): RR 1.15, 95% CI 0.91 to 1.45) or three or more blood pressure medicines (Analysis 2.7.3 (2 studies, 804 recipients): RR 1.10, 95% CI 0.91 to 1.32; I^2 = 0%) were similar in the different belatacept dosage groups.

Variation in treatment effect by key study intervention and participant characteristics

Subgroup analyses were performed for main clinical outcomes to examine whether key study and participant characteristics modified overall results. Stratified into high and low belatacept dosage groups, there was no difference in treatment effects between groups for comparisons of belatacept versus CNI for recipient and graft survival (RRR 0.99, 95% CI 0.92 to 1.07, test for difference = 0.88), acute rejection (RRR 1.18, 95% 95% CI 0.49 to 2.81, test for difference = 0.71), PTLD (RRR 1.06, 95% CI 0.11 to 9.80, test for difference = 0.96 or eGFR (DMD -0.25 mL/min/1.73 m^2, 95% CI -9.18 to +8.69, test for difference = 0.96). The relative

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effects of belatacept versus CNI did not vary between extended-criteria versus living or standard-criteria donor kidney recipients for recipient and graft survival (RRR 1.03, 95% CI 0.88 to 1.21, test for difference = 0.69) or eGFR (DMD -1.21 mL/min/1.73 m^2, 95% CI -20.1 to +17.7, test for difference = 0.90). Comparing the relative effects of tacrolimus and cyclosporin against belatacept, there was no difference in recipient and graft survival (RRR 0.89, 95% CI 0.74 to 1.06, test for difference = 0.11), eGFR (DMD -0.95, 95% CI -19.4 to +17.5, test for difference = 0.92) or acute rejection (RRR 1.71 95% CI 0.01 to 393.06, test for difference = 0.71), though estimates were imprecise for rare events such as acute rejection. Epstein Barr virus serostatus did not appear to affect the relative risk of PTLD (RRR 1.49, 95% CI 0.15 to 14.76, test for difference = 0.73), though again the imprecision of this estimate or effect made meaningful interpretation difficult.

Sensitivity analyses

The small number of included studies precluded meaningful sensitivity analyses.

Reporting bias

We intended to examine funnel plots for asymmetry to detect publication bias, small-study effects and differences in estimates of effect arising from study methodological quality. However, this was not informative due to the small number of included studies.

DISCUSSION

The availability of new biologic agents like belatacept (which may avoid the unwanted side-effects of currently used immunosuppression regimens) means that established treatment strategies require re-evaluation. Transplant clinicians need reliable estimates of the relative benefits and harms of treatment with belatacept, particularly because high rates of PTLD have been reported when belatacept is used at high dosage or in recipients who are Epstein Barr virus seronegative before their kidney transplant.

Summary of main results

Treatment with belatacept was associated with similar rates of death, kidney transplant survival and acute rejection to treatment with a CNI in the first three years following a kidney transplant. Belatacept-treated kidney transplant recipients had less new-onset diabetes after transplant, lower blood pressure, better kidney transplant function and less chronic kidney scarring seen on kidney biopsies than CNI-treated kidney transplant recipients. PTLD occurred at similar rates in recipients treated with high and low dosage belatacept and did not appear to significantly differ in incidence between Epstein Barr virus seropositive and seronegative kidney transplant recipients. Estimates of relative effects in subgroups of patients receiving high versus low dosage belatacept and in subgroups who were Epstein Barr virus seropositive versus seronegative were imprecise because of selective outcome reporting of PTLD. All other malignancies and infections reported occurred at similar rates. The main deficiency in the published data was that outcomes were reported selectively and inconsistently which limited between-study comparisons and the opportunities for data synthesis.

Overall completeness and applicability of evidence

This is the first synthesis of data from all studies evaluating the benefits and harms of primary immunosuppression with belatacept. We undertook an extensive literature search and sought data from every report of each study, identifying 12% of included reports from hand-searching of conference abstracts, and contacting triallists and study data custodians directly where data was missing or unclear. We also explicitly examined important subgroup effects to explore potential differences that might arise from immunosuppressive co-interventions, donor and recipient characteristics. There were data gaps, particularly relating to PTLD, belatacept dosage and Epstein Barr virus serostatus. Despite direct communication with Bristol-Myers-Squibb over a number of months and requests for unpublished data (specifically for particular patient subgroups where data was sparse) we did not obtain any new informative data which was not already in the public domain and so the data we present is subject to outcome reporting bias. Further data is being collected in three post-marketing clinical studies required by the FDA as a condition of belatacept licence approval which may help address some current data deficiencies. The first study is the creation of a belatacept registry which will collect data on the incidence of PTLD. The second study will analyse the pattern of use of belatacept in routine clinical practice using the United Network for Organ Sharing database, whilst the third will use these data to compare rates of PTLD between belatacept and CNI-based immunosuppression regimens.

Although kidney transplant recipients included in studies were generally representative of the ESKD who receive kidney transplants, there were important exceptions. Recipients aged less than 18 years old were excluded from all studies, immediately limiting the generalisability of our findings to the adult transplant population. Approximately 40% of patients on the United States' active kidney transplant waiting list are sensitised with a PRA of > 20% (OPTN 2013). In our review, recipients were generally non-sensitized. Sensitized patients spend more time on the kidney transplant waiting list, have an increased risk of acute rejection and are at higher risk of producing donor-specific antibodies following a kidney transplant. These all increase the risk of death and kidney transplant loss and so the effectiveness of belatacept in recipients with levels of PRA > 20% may not be represented by our data (Gloor 2009; Hidalgo 2009). Thirty percent of standard criteria kidney transplants performed in Australia in 2010 were from living donors (ANZDATA 2012). In our study, 50% of recipients received a standard criteria kidney, but we could not analyse outcomes separately for living and deceased donor kidney recipients by drug treatment allocation groups as only the overall number receiving a living donor or a deceased donor was provided in reports. Donor factors which significantly affect deceased donor transplant outcomes have lesser effects on living donor transplant outcomes (Rao 2009).

The main limitation in applying our findings to contemporary clinical practice is that belatacept still remains relatively untested against tacrolimus. Eighty six percent of new kidney transplant recipients now receive tacrolimus for primary immunosuppression (ANZDATA 2012). Only two percent (30 participants) of kidney transplant recipients included in our meta-analysis received tacrolimus (Ferguson 2010). Tacrolimus and cyclosporine vary in their effects on blood pressure, lipids, blood sugar regulation and risk of infection with polyoma virus, and so the relative effects

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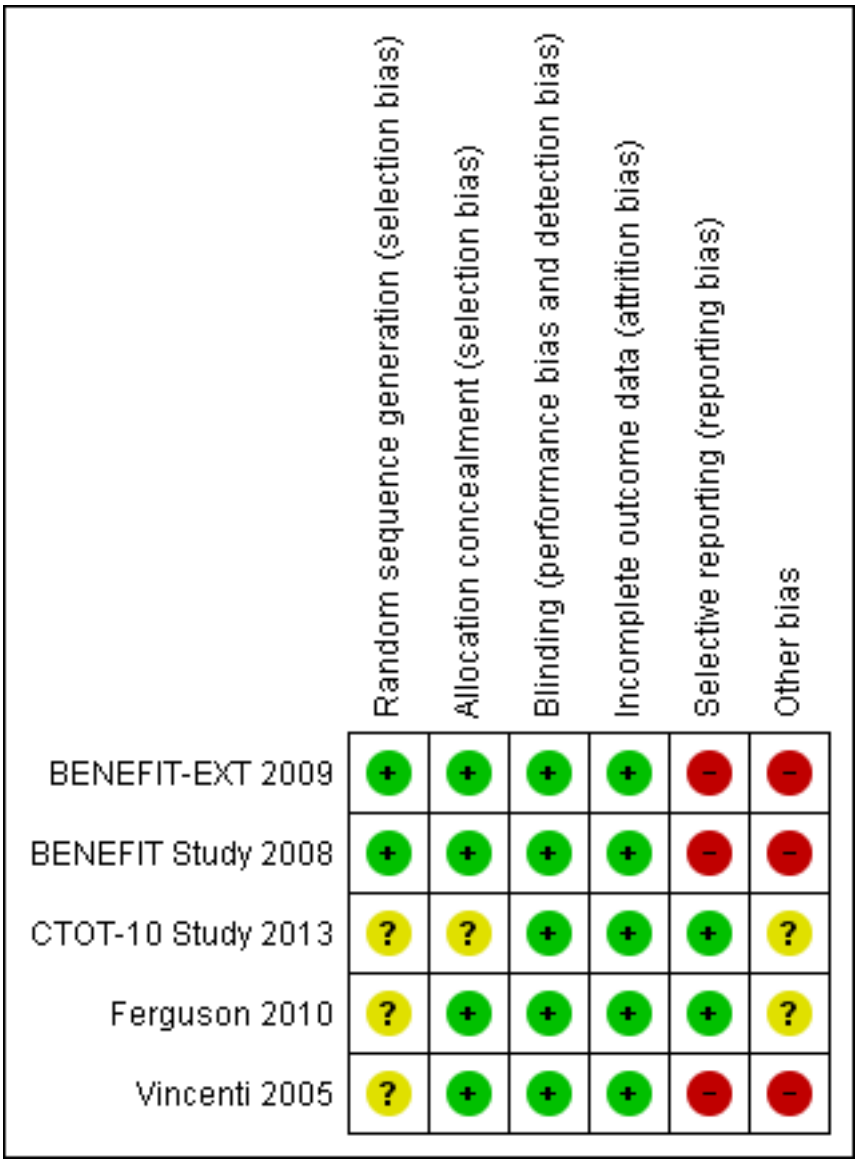
of belatacept and CNI we observed may not be replicated when belatacept is used in mainstream clinical practice (Webster 2005).

Quality of the evidence

Overall study quality was good (Figure 2), though selective outcome reporting was suspected in two of the included studies with data for the main safety concern surrounding belatacept – PTLD in different belatacept dosage and Epstein Barr virus serostatus groups – mainly derived from FDA licensing documentation and not the original study reports (Figure 3). Even after directly requesting data for these subgroups from Bristol Myers Squibb, data were not provided. The potential for selective outcome reporting bias remains, and estimates of effect for key clinical outcomes (including PTLD in different patient and dosage groups) remain imprecise. Opportunities for synthesizing data were also limited by incomplete reporting of statistical data for key recipient and patient-centred outcomes. These included data for blood pressure, physical and mental well-being scores, symptom distress scores, and health-related quality of life (Dobbels 2014). The design, conduct and analysis of included studies were frequently difficult to assess because of omission of important methodological detail in the study reports. No single study adequately addressed all domains of the risk of bias assessment (Figure 2) despite using multiple sources of data. It is therefore impossible to exclude the possibility that some internal biases may be present in the results of the meta-analysis (Begg 1996; Moher 2009).

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



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AUTHORS' CONCLUSIONS

Implications for practice

Belatacept is a valid alternative to CNI for the maintenance immunosuppression of kidney transplant recipients, though some uncertainty remains about its effects in specific subgroups of patients. Pragmatically, the balance between benefits and harms of treatment with belatacept might favour treatment of transplant candidates in whom there is concern about the side-effects of CNI, for example in recipients with pre-transplant impaired glucose tolerance or poorly controlled hypertension. Until further data becomes available for core outcomes at standardized time-points, the precision of estimates of effects for some outcomes will remain poor, and so belatacept must be used carefully, and adverse events reported routinely. The medium to long-term effect of belatacept on the incidence of cancers remains largely unknown and ongoing surveillance using linked kidney and cancer registry data and data from post-marketing cohort studies must be integrated into our current understanding of benefits and harms when informing clinical decision making.

Implications for research

There are three main implications for future research. Firstly, triallists should comprehensively report their results according to existing international guidelines, and publishing journals and editors should rigorously enforce these standards (Begg 1996; Masson 2013). The FDA's limited approval to use belatacept only at low dosage in Epstein Barr seropositive kidney transplant recipients means that future studies are unlikely to help clarify the uncertain effects of high dosage belatacept, or the use of belatacept at any dosage in Epstein Barr seronegative recipients. Unpublished study data should be made available for sharing in a data repository, so as to maximise the usefulness and usage of data and promote transparency (Godlee 2012). These initiatives would allow more informative synthesis and between-study comparisons, and would help address some of the current deficiencies in the literature regarding the effectiveness of belatacept in specific recipient subgroups. Secondly, contemporary studies should reflect contemporary clinical practice, and new studies must test belatacept against tacrolimus. Finally, surrogate markers of definitive endpoints in studies of kidney transplantation remain unvalidated and researchers should conduct longer term studies with sufficient power to demonstrate significant differences in effect for core clinical and patient-centred outcomes (White 2010).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

BENEFIT Study 2008

Methods	• Study design: parallel RCT • Study duration: January 2006 to June 2008 • Duration of follow-up: 12 months post-transplant
Participants	• Country: International (Europe, North America, Australasia) • Setting: 100 centres • Patients > 18 y; living/standard-criteria donor; cold ischaemic time < 24 h • PRA > 20% in 10% participants • Epstein Barr virus: positive (577); negative (89) • Pre-existing diabetes: 18% • Donors: living (386); deceased (280) • Number: high dose group (219); low dose group (226); CSA group (221) • Mean age (years): high dose group (43.6); low dose group (42.6); CSA group (43.5) • Sex (M/F): high dose group (115/104); low dose group (147/79); CSA group (166/55) • Exclusion criteria: recipients of extended criteria kidneys; prior or concurrent nonrenal solid organ transplants; first-time patients with a PRA ≥ 50% or retransplants with a panel reactive antibody ≥ 30%
Interventions	High dose belatacept group • 10 mg/kg on days 1, 5, and weeks 2, 4, 6, 8, 10, 12, 16, 20, 24 • 5 mg/kg every 4 weeks for months 7 to 12

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BENEFIT Study 2008 *(Continued)*

	Low dose belatacept group • 10 mg/kg on days 1, 5, and weeks 2, 4, 8, 12 • 5 mg/kg every 4 weeks for months 3 to 12 CSA group • Initial dose: 4 to 10 mg/kg adjusted to 150 to 300 ng/mL (0 to 1 months) • 100 to 250 ng/mL (2 to 12 months) Co-interventions (all groups) • Basiliximab: 20 mg on days 0 and 4 • Methylprednisolone: 500 mg on day 0; 250 mg on day 1 • MMF: 2 g/d • Prednisone: tapering regimen from day 2
Outcomes	• Mortality • Graft loss • Patient and graft survival • Measured and eGFR • Incidence and grade of acute rejection • Incidence and grade of chronic allograft nephropathy • Incidence of malignancy • Change in lipids (non-HDL cholesterol, triglycerides) from baseline • BP and use of antihypertensive medications (≥ 1, ≥ 3) • Incidence of diabetes • Infections: UTI, pneumonia, CMV, TB, BK virus
Notes	• Phase III clinical study • CMV and pneumocystis prophylaxis given • Acute rejection treatment: ≤ Banff 2A, methylprednisolone; ≥ Banff 2B, methylprednisolone or T-cell depletion

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation by computer-generated sequence
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinded to belatacept dosage allocation but not to whether recipients received belatacept or CNI. No dummy IV infusion for recipients allocated CNI
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT to 3 years following kidney transplant
Selective reporting (reporting bias)	High risk	Reports of PTLD by dosage and Epstein Barr virus status from FDA approval reports, not original manuscripts and data not provided despite directly requesting from Bristol Myers Squibb
Other bias	High risk	Funded by Bristol Myers Squibb

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BENEFIT-EXT 2009

Methods	• Study design: parallel RCT • Duration of study: March 2005 and is still ongoing • Duration of follow-up: 3 years
Participants	• Country: International (Europe, North America, Australasia) • Setting: 79 centres • Patients > 18 y who received an extended-criteria deceased donor kidney • PRA: > 20% in 1.5% recipients • Epstein Barr virus: positive (510); negative (47) • Pre-existing diabetes: 20% • Number: high dose group (184); low dose group (175); CSA group (184) • Mean age ± SD (years): high dose group (56.7 ± 13); low dose group (53.1 ± 12); CSA group (55.7 ± 12) • Sex (M/F): high does group (120/64); low dose group (130/45); CSA group (116/68) • Exclusion criteria: NS
Interventions	High dose belatacept group • 10 mg/kg on days 1, 5, and weeks 2, 4, 6, 8, 10, 12, 16, 20, 24 • 5 mg/kg every 4 weeks for months 7 to 12 Low dose belatacept group • 10 mg/kg on days 1, 5, and weeks 2, 4, 8, 12 • 5 mg/kg every 4 weeks for months 3 to 12 CSA group • Initial dose: 4 to 10 mg/kg adjusted to 150 to 300 ng/mL (0 to 1 months) • 100 to 250 ng/mL (2 to 12 months) Co-interventions (all groups) • Basiliximab: 20 mg on days 0 and 4 • Methylprednisolone: 500 mg on day 0; 250 mg on day 1 • MMF: 2 g/d • Prednisone: tapering regimen from day 2
Outcomes	• Mortality • Graft loss • Patient and graft survival • Measured and eGFR • Incidence and grade of acute rejection • Incidence and grade of chronic allograft nephropathy • Incidence of malignancy • Change in lipids (non-HDL cholesterol, triglycerides) from baseline • BP and use of antihypertensive medications (≥ 1, ≥ 3) • Incidence of NODAT • Infections: UTI, pneumonia, CMV, TB
Notes	• Definition of extended criteria donor: donors ≥ 60 y; or donors ≥ 50 y and had at least two other risk factors (cerebrovascular accident, hypertension or SCr > 1.5 mg/dL); or an anticipated cold ischaemia • Phase III clinical study • CMV and pneumocystis prophylaxis given

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BENEFIT-EXT 2009 *(Continued)*

- Acute rejection treatment: ≤ Banff 2A, methylprednisolone; ≥ Banff 2B, methylprednisolone or T-cell depletion

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation by computer-generated sequence
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinded to belatacept dosage allocation but not to whether recipients received belatacept or CNI. No dummy IV infusion for recipients allocated CNI
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT to 3 years following kidney transplant
Selective reporting (reporting bias)	High risk	Standard deviations missing for continuous outcomes (eGFR). Reports of PTLD by dosage and Epstein Barr virus status from FDA approval reports, not original manuscripts and data not provided despite directly requesting from Bristol Myers Squibb
Other bias	High risk	Funded by Bristol Myers Squibb

CTOT-10 Study 2013

Methods	• Study design: parallel RCT • Study duration: NS • Mean duration of follow-up: 40 weeks
Participants	• Country: USA • Setting: phase II, multi-centre study • First living or standard-donor criteria kidney recipients; aged 18 to 65 y • PRA: < 30% • Epstein Barr virus seronegative: none • Number: group 1 (6); group 2 (6); group 3 (7) • Age: NS • Sex (M/F): NS • Exclusion criteria: extended-criteria donor kidneys
Interventions	Group 1 (control) • Alemtuzumab induction, tacrolimus maintenance Group 2 • Alemtuzumab induction, belatacept maintenance Group 3 • Basiliximab induction, 3 months taper of tacrolimus, belatacept maintenance

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CTOT-10 Study 2013 *(Continued)*

	Co-interventions (all groups) • Short-term prednisone and maintenance mycophenolate mofetil 1g twice daily
Outcomes	• Primary outcome: incidence of adverse events and serious adverse events
Notes	• Sponsored by National Institute of Allergy and Infectious Diseases • Halted prematurely (mean 40 weeks follow-up) because four recipients had vascular thrombosis, three lost their grafts and there was a high incidence of acute rejection

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in abstracts
Allocation concealment (selection bias)	Unclear risk	Not described in abstracts
Blinding (performance bias and detection bias) All outcomes	Low risk	Open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes for all enrolled patients described in detail at time of study termination
Selective reporting (reporting bias)	Low risk	Adverse events reported fully in keeping with primary outcomes stated in protocol, though only in abstract form
Other bias	Unclear risk	Insufficient data published for reliable judgment

Ferguson 2010

Methods	• Study design: parallel RCT • Study duration: July 2007 to May 2009 • Duration of follow-up: 12 months
Participants	• Country: international (USA, Spain, Italy) • Setting: 25 centres • Patients > 18 y; standard-criteria deceased or living donor; recipients all Epstein Barr virus positive • Number: belatacept-MM group (33); belatacept-SRL group (26); CNI group (30) • Mean age ± SD (years): belatacept-MMF group (49.2 ± 11.1); belatacept-SRL group (52.7 ± 10.8); CNI group (53.6 ± 13.2) • Sex (M/F): belatacept-MM group (25/8); belatacept-SRL group (20/6); CNI group (22/8) • Exclusion criteria: recipients of extended criteria donor kidneys according to an expanded UNOS definition; any prior or concurrent nonrenal solid organ transplant; high immunological risk features including current (pretransplant) panel-reactive antibodies (PRA) ≥ 50% (> 30% if retransplant) or with any prior graft loss due to acute rejection; underlying kidney disease that could recur in the allograft; infection; HIV, hepatitis B or hepatitis C virus, or latent tuberculosis; history of malignancy in the previous 5 y (other than non-melanoma skin cancer cured by resection); seronegative for Epstein Barr virus (EBV) or with a body mass index > 35 kg/m^2; Female patients of childbearing potential not using an adequate method of contraception during the study

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Ferguson 2010 *(Continued)*

Interventions	Belatacept-MMF group
	• Belatacept
	  ○ 10 mg/kg on days 1, 5 and weeks 2, 4, 6, 8, 10, 12, 16, 20, 24
	  ○ 5 mg/kg every 4 weeks for months 7 to 12
	• MMF: 2 g/d
	Belatacept-SRL group
	• Belatacept
	  ○ 10 mg/kg on days 1, 5 and weeks 2, 4, 6, 8, 10, 12, 16, 20, 24
	  ○ 5 mg/kg every 4 weeks for months 7 to 12
	• SRL: 5 mg/d, levels 7 to 12 ng/mL to month 6, 5 to 10 ng/mL thereafter
	CNI group
	• Tacrolimus: 0.1 mg/kg/d adjusted to keep trough levels 8 to 12 ng/mL to day 30, 5 to 10 ng/mL thereafter
	• MMF: 2 g/d
	Co-interventions (both groups)
	• Thymoglobulin: 1.5 mg/kg on days 0 to 3
	• Methylprednisolone IV: 500 mg, 250 mg, 125 mg and 60 mg on days 0 to 3 respectively

Outcomes	• Patient and graft survival • eGFR • Incidence and grade of acute rejection • Incidence and grade of chronic allograft nephropathy • Incidence of malignancy • Change in lipids (HDL, LDL, non-HDL and total cholesterol, triglycerides) from baseline • Use of antihypertensive medications (≥ 3) • Incidence of NODAT • Infections: any; serious
Notes	• Belatacept groups combined for meta-analyses • Phase II clinical study. CMV and pneumocystis prophylaxis given • Acute rejection treatment: ≤ Banff 2A, methylprednisolone; ≥ Banff 2B, methylprednisolone or T-cell depletion

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Central, interactive voice response system
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinded to belatacept dosage allocation but not to whether recipients received belatacept or CNI. No dummy IV infusion for recipients allocated CNI
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT to 3 years

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Ferguson 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	Outcomes reported match protocol
Other bias	Unclear risk	Not described

Vincenti 2005

Methods	• Study design: parallel RCT • Study duration: March 2001 to December 2003 • Duration of follow-up: 12 months
Participants	• Country: international (Europe, North America) • Setting: 22 centres • Patients > 18 y; standard criteria donor • Number: high dose group (74); low dose group (71); CSA group (73) • Mean age (years): high dose group (46.5); low dose group (42.1); CSA group (46.1) • Sex (M/F): high dose group (54/20); low dose group (48/23); CSA group (49/24) • Exclusion criteria: underlying kidney disease in the recipient that could recur in the allograft, including focal and segmental glomerulosclerosis, type I or II membranoproliferative glomerulonephritis, the haemolytic–uraemic syndrome, and thrombotic thrombocytopenic purpura; active hepatitis B or C or any other infection that would normally preclude transplantation; human immunodeficiency virus infection; a history of or evidence of cancer; a positive T-cell lymphocytotoxic crossmatch with the use of donor lymphocytes and recipient serum; a history of drug or alcohol abuse or psychotic disorders; previous treatment with basiliximab; use of any investigational drug within 30 days before the visit on day 1; a donor age of more than 60 y or < 6 y; a donor whose heart was not beating at the time of organ harvest; and a cold-ischaemia time of more than 36 hours
Interventions	High dose belatacept group • 10 mg/kg for days 1, 5, and weeks 2, 4, 6, 8, 10, 12, 16, 20, 24 • 5 mg/kg every 4 or 8 weeks for months 7 to 12 Low dose belatacept group • 10 mg/kg days for 1, 5, and weeks 2, 4, 8, 12 • 5 mg/kg every 4 or 8 weeks for months 3 to 12 Cyclosporin group • Initial dose: 4 to 10 mg/kg adjusted to 150 to 400 ng/mL (0 to 1 months); 150-300 ng/mL (2 to 12 months) Co-interventions (all groups) • Basiliximab: 20 mg days 0 and 4 • Methylprednisolone: 500 mg on day 0, 250 mg on day 1 • MMF: 2 g/d • Prednisolone: tapering regimen from day 2
Outcomes	• Mortality • Graft loss • Measured and eGFR • Incidence and grade of acute rejection • Incidence and grade of chronic allograft nephropathy • Incidence of malignancy

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Vincenti 2005 *(Continued)*

- Change in lipids (non-HDL cholesterol, triglycerides) from baseline
- Incidence of NODAT
- Infections: Any, UTI, CMV

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Randomisation performed centrally
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinded to dose of belatacept. Unblinded to cyclosporin administration
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT to 3 years. Loss to follow-up small
Selective reporting (reporting bias)	High risk	Epstein Barr virus serostatus not reported (except in FDA report of belatacept approval)
Other bias	High risk	Supported by Bristol-Myers Squibb

BP - blood pressure; CMV - cytomegalovirus; CNI - calcineurin inhibitor; eGFR - estimated GFR; GFR - glomerular filtration rate; HDL - high-density lipoprotein; ITT - intention-to-treat; LDL - low-density lipoprotein; MMF - Mycophenolate mofetil; NODAT - new onset diabetes after transplantation; NS - not stated; PRA - panel reactive antibodies; PTLD - post-transplant lymphoproliferative disorder; RCT - randomised controlled trial; SCr - serum creatinine; SRL - sirolimus; TB - tuberculosis; UTI - urinary tract infection

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

Study	Reason for exclusion
Kamar 2013	Not primary immunosuppressive regimen; switch from CNI-based regimen to belatacept
Kirk 2012	Not primary immunosuppressive regimen
Rostaing 2011	Not primary immunosuppressive regimen; switch from CNI-based regimen to belatacept versus continued CNI at 12 months

CNI - calcineurin inhibitor

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

EudraCT2006-00311417

Trial name or title	A randomized, open-label, multi-center, parallel-group study of belatacept-based corticosteroid-free regimens in renal transplant
Methods	Open label RCT

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EudraCT2006-00311417 *(Continued)*

Participants	Adult recipients of a living or deceased-donor kidney transplant
Interventions	Belatacept versus tacrolimus, both with thymoglobulin and MMF
Outcomes	Primary: incidence acute rejection at 6 months Secondary: severity of rejection, death, metabolic/cardiovascular comorbidities
Starting date	September 2007
Contact information	Bristol Myers Squibb
Notes	

EudraCT2011-00616240

Trial name or title	New-onset diabetes mellitus after renal transplantation. A multicentre, prospective randomized, open study to evaluate belatacept-based versus tacrolimus-based immunosuppression
Methods	Open label RCT
Participants	Patients aged either > 60, or > 45 at high risk of glucose metabolism disorder after kidney transplant
Interventions	Belatacept versus tacrolimus
Outcomes	Primary: incidence of glucose metabolism disorder at 6 months. Secondary: acute rejection, graft survival and function
Starting date	May 2013
Contact information	Frances Mateos. Hospital Vall d'Hebron. Department of Nephrology
Notes	

EudraCT2013-00117820

Trial name or title	Cardiovascular risk prediction and biomarkers in renal transplant recipients treated with belatacept compared to calcineurin inhibitors
Methods	Open label RCT
Participants	Adult recipients of living or deceased-donor kidney transplants
Interventions	Belatacept versus CNI
Outcomes	Primary: cardiovascular risk calculated by risk calculator in transplant recipients Secondary: blood pressure, lipids, glucose, graft function
Starting date	October 2013
Contact information	Elin Karlberg, Uppsala University Hospital, Sweden

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EudraCT2013-00117820 *(Continued)*

Notes	

NCT01729494

Trial name or title	Belatacept early steroid withdrawal trial
Methods	Open label RCT
Participants	315, > 18 y, recipient of living or deceased-donor kidney transplant
Interventions	Belatacept versus tacrolimus, both with early steroid withdrawal and either alemtuzumab or ATG induction
Outcomes	Primary: composite patient death or graft loss of eGFR < 45
Starting date	September 2012
Contact information	E. Steve Woddle, University of Cincinnati, USA
Notes	

NTR4242

Trial name or title	Belatacept study (BMS no. 55230)
Methods	Open label, unblinded RCT
Participants	40
Interventions	Belatacept versus tacrolimus
Outcomes	Primary: CD4+ and CD8+ cell counts Secondary: incidence acute rejection, eGFR (MDRD), infections, malignancy, PTLD
Starting date	October 2013
Contact information	DA Hesselink, Erasmus Medical Centre, Rotterdam, The Netherlands
Notes	

ATG - antithymocyte globulin; CNI - calcineurin inhibitor; eGFR - estimated glomerular filtration rate; MDRD - Modification of Diet in Renal Disease; MMF - mycophenolate mofetil; PTLD - post-transplant lymphoproliferative disorder; RCT - randomised controlled trial

DATA AND ANALYSES

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Comparison 1. Any dosage belatacept versus calcineurin inhibitor (CNI)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recipient and kidney survival	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Death (any cause)	4	1516	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.39, 1.44]
1.2 Loss of kidney transplant	4	1516	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.61, 1.38]
2 Surviving with a functioning transplant	4	1516	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.06]
3 Acute rejection and chronic kidney scarring	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Acute rejection	4	1516	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.85, 2.86]
3.2 Severe acute rejection (≥ Banff 2A)	3	200	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.76, 1.37]
3.3 Chronic kidney scarring	3	1360	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.55, 0.94]
3.4 Severe chronic kidney scarring	3	1360	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.42, 1.32]
4 Kidney function, blood pressure and lipids	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Measured GFR	3	1083	Mean Difference (IV, Random, 95% CI)	10.89 [4.01, 17.77]
4.2 eGFR	4	1133	Mean Difference (IV, Random, 95% CI)	9.96 [3.28, 16.64]
4.3 Systolic BP	2	658	Mean Difference (IV, Random, 95% CI)	-7.51 [-10.57, -4.46]
4.4 Diastolic BP	2	658	Mean Difference (IV, Random, 95% CI)	-3.07 [-4.83, -1.31]
4.5 non-HDL (change from baseline)	3	1101	Mean Difference (IV, Random, 95% CI)	-12.25 [-17.93, -6.57]
4.6 Triglycerides (change from baseline)	3	1101	Mean Difference (IV, Random, 95% CI)	-24.09 [-44.55, -3.64]
5 Malignancy	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Any malignancy	4	1516	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.58, 1.72]
5.2 PTLD	4	1516	Risk Ratio (M-H, Random, 95% CI)	2.79 [0.61, 12.66]
6 Infections	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

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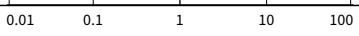
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Any infection	4	1516	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.87, 1.09]
6.2 Serious infection	2	1209	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.83, 1.12]
6.3 Tuberculosis	2	1209	Risk Ratio (M-H, Random, 95% CI)	3.96 [0.72, 21.67]
6.4 CMV disease	2	1209	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.91, 2.50]
6.5 BK nephropathy	1	666	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.05, 1.35]
7 Diabetes and use of blood pressure medicines	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 New-onset diabetes	4	1049	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.40, 0.93]
7.2 1 or 2 blood pressure medicines	2	755	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.67, 0.92]
7.3 3 or more blood pressure medicines	3	1298	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.65, 1.07]

Analysis 1.1. Comparison 1 Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 1 Recipient and kidney survival.

Study or subgroup	Belatacept n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Death (any cause)					
Ferguson 2010	1/59	0/30		3.92%	1.55[0.07,36.94]
Vincenti 2005	1/145	4/73		7.85%	0.13[0.01,1.11]
BENEFIT Study 2008	19/445	15/221		41%	0.63[0.33,1.21]
BENEFIT-EXT 2009	37/359	17/184		47.23%	1.12[0.65,1.93]
Subtotal (95% CI)	**1008**	**508**		**100%**	**0.75[0.39,1.44]**
Total events: 58 (Belatacept), 36 (CNI)					
Heterogeneity: Tau^2=0.15; Chi^2=4.87, df=3(P=0.18); I^2=38.34%					
Test for overall effect: Z=0.86(P=0.39)					
1.1.2 Loss of kidney transplant					
Ferguson 2010	4/59	0/30		2.04%	4.65[0.26,83.62]
Vincenti 2005	4/145	2/73		6.08%	1.01[0.19,5.37]
BENEFIT Study 2008	19/445	10/221		30.39%	0.94[0.45,1.99]
BENEFIT-EXT 2009	33/359	20/184		61.49%	0.85[0.5,1.43]
Subtotal (95% CI)	**1008**	**508**		**100%**	**0.91[0.61,1.38]**
Total events: 60 (Belatacept), 32 (CNI)					
Heterogeneity: Tau^2=0; Chi^2=1.34, df=3(P=0.72); I^2=0%					
Test for overall effect: Z=0.42(P=0.67)					
Test for subgroup differences: Chi^2=0.25, df=1 (P=0.62), I^2=0%					



More common: CNI — More common: belatacept

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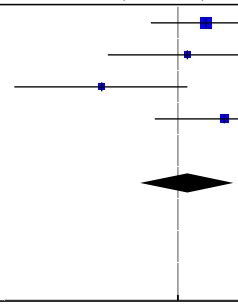
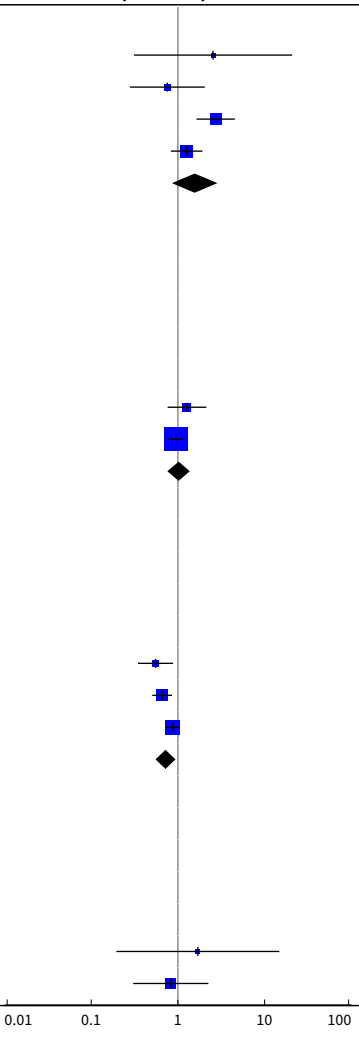
Analysis 1.2. Comparison 1 Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 2 Surviving with a functioning transplant.

Study or subgroup	Belatacept n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
BENEFIT Study 2008	407/445	197/221		34.87%	1.03[0.97,1.08]
BENEFIT-EXT 2009	291/359	147/184		20.63%	1.01[0.93,1.11]
Ferguson 2010	54/59	30/30		19.42%	0.92[0.84,1.01]
Vincenti 2005	140/145	67/73		25.08%	1.05[0.98,1.13]
Total (95% CI)	**1008**	**508**		**100%**	**1.01[0.96,1.06]**
Total events: 892 (Belatacept), 441 (CNI)					
Heterogeneity: Tau^2=0; Chi^2=5.17, df=3(P=0.16); I^2=41.99%					
Test for overall effect: Z=0.36(P=0.72)					



Analysis 1.3. Comparison 1 Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 3 Acute rejection and chronic kidney scarring.

Study or subgroup	Belatacept n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Acute rejection					
Ferguson 2010	5/59	1/30		7.02%	2.54[0.31,20.79]
Vincenti 2005	9/145	6/73		20.52%	0.76[0.28,2.04]
BENEFIT Study 2008	88/445	16/221		34.77%	2.73[1.64,4.54]
BENEFIT-EXT 2009	64/359	26/184		37.69%	1.26[0.83,1.92]
Subtotal (95% CI)	**1008**	**508**		**100%**	**1.56[0.85,2.86]**
Total events: 166 (Belatacept), 49 (CNI)					
Heterogeneity: Tau^2=0.21; Chi^2=8.02, df=3(P=0.05); I^2=62.57%					
Test for overall effect: Z=1.44(P=0.15)					
1.3.2 Severe acute rejection (≥ Banff 2A)					
Ferguson 2010	0/5	0/1			Not estimable
BENEFIT Study 2008	56/88	8/16		25.95%	1.27[0.76,2.13]
BENEFIT-EXT 2009	51/64	22/26		74.05%	0.94[0.77,1.16]
Subtotal (95% CI)	**157**	**43**		**100%**	**1.02[0.76,1.37]**
Total events: 107 (Belatacept), 30 (CNI)					
Heterogeneity: Tau^2=0.02; Chi^2=1.51, df=1(P=0.22); I^2=33.71%					
Test for overall effect: Z=0.12(P=0.91)					
1.3.3 Chronic kidney scarring					
Vincenti 2005	26/106	20/45		20.29%	0.55[0.35,0.88]
BENEFIT Study 2008	94/445	71/221		35.77%	0.66[0.51,0.85]
BENEFIT-EXT 2009	162/359	95/184		43.94%	0.87[0.73,1.05]
Subtotal (95% CI)	**910**	**450**		**100%**	**0.72[0.55,0.94]**
Total events: 282 (Belatacept), 186 (CNI)					
Heterogeneity: Tau^2=0.03; Chi^2=5.32, df=2(P=0.07); I^2=62.41%					
Test for overall effect: Z=2.44(P=0.01)					
1.3.4 Severe chronic kidney scarring					
Vincenti 2005	4/106	1/45		7%	1.7[0.2,14.77]
BENEFIT Study 2008	10/445	6/221		32.83%	0.83[0.3,2.25]



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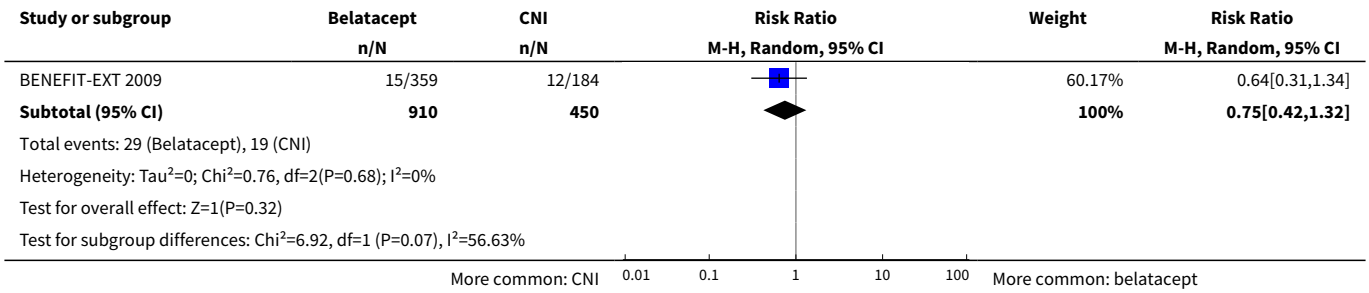
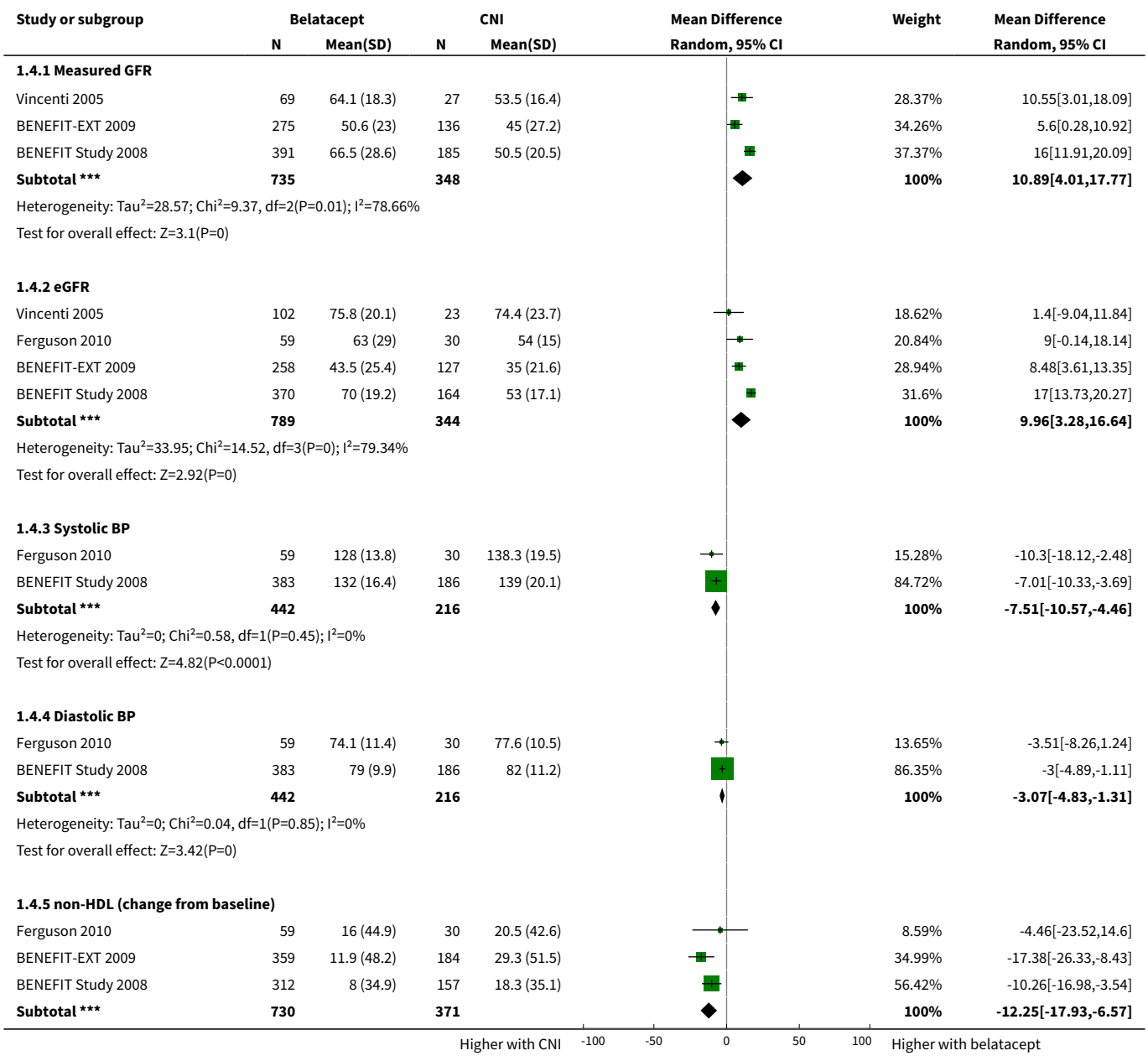


Analysis 1.4. Comparison 1 Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 4 Kidney function, blood pressure and lipids.



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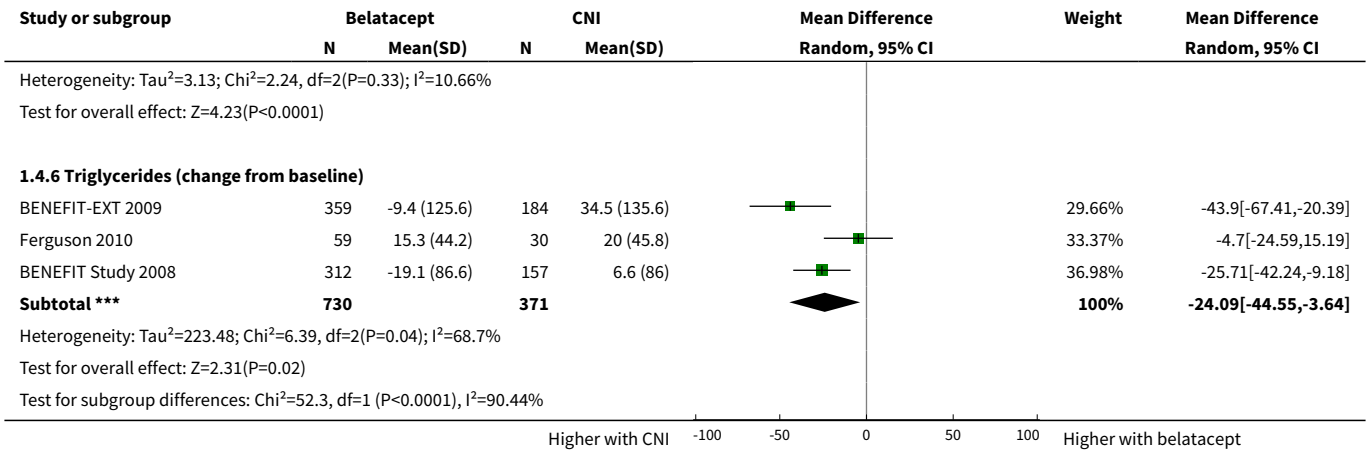
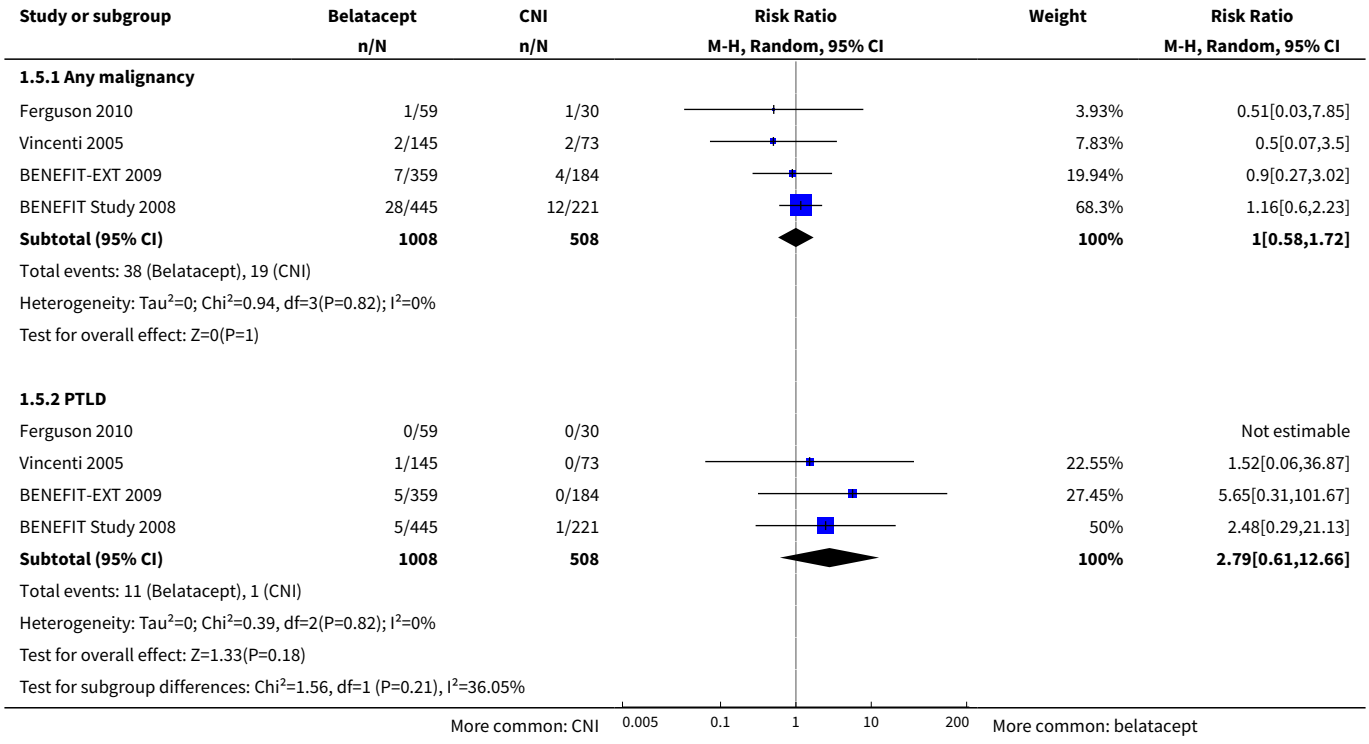
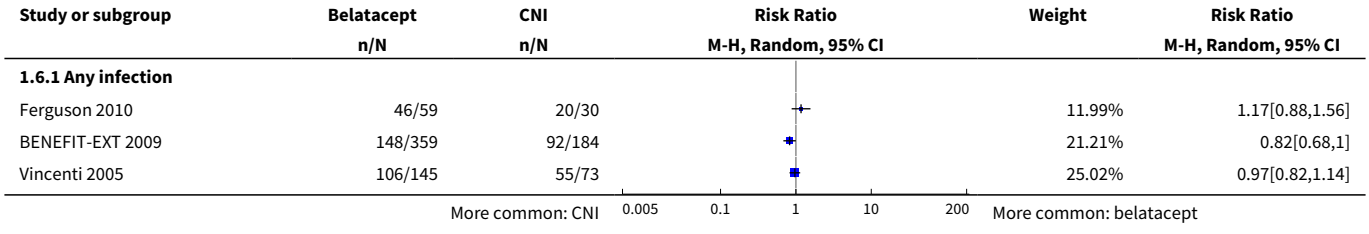


Analysis 1.5. Comparison 1 Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 5 Malignancy.



Analysis 1.6. Comparison 1 Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 6 Infections.



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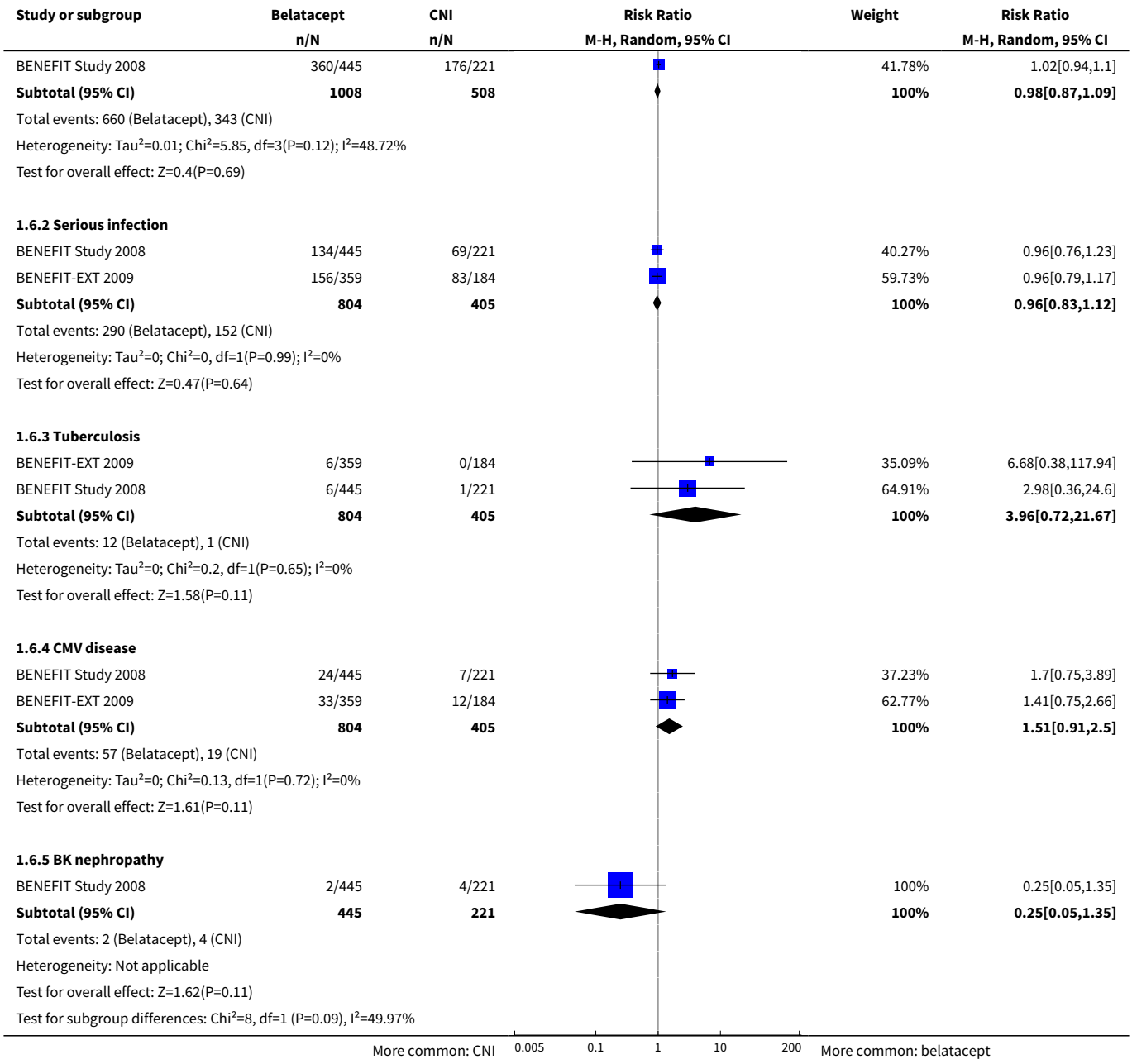
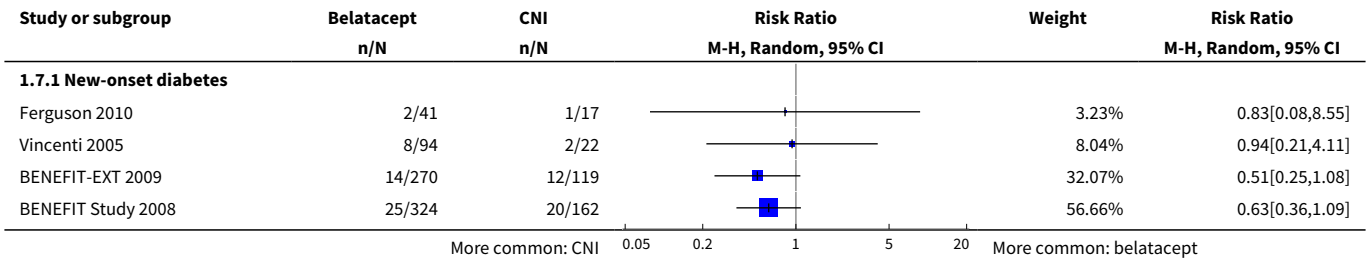


Analysis 1.7. Comparison 1 Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 7 Diabetes and use of blood pressure medicines.



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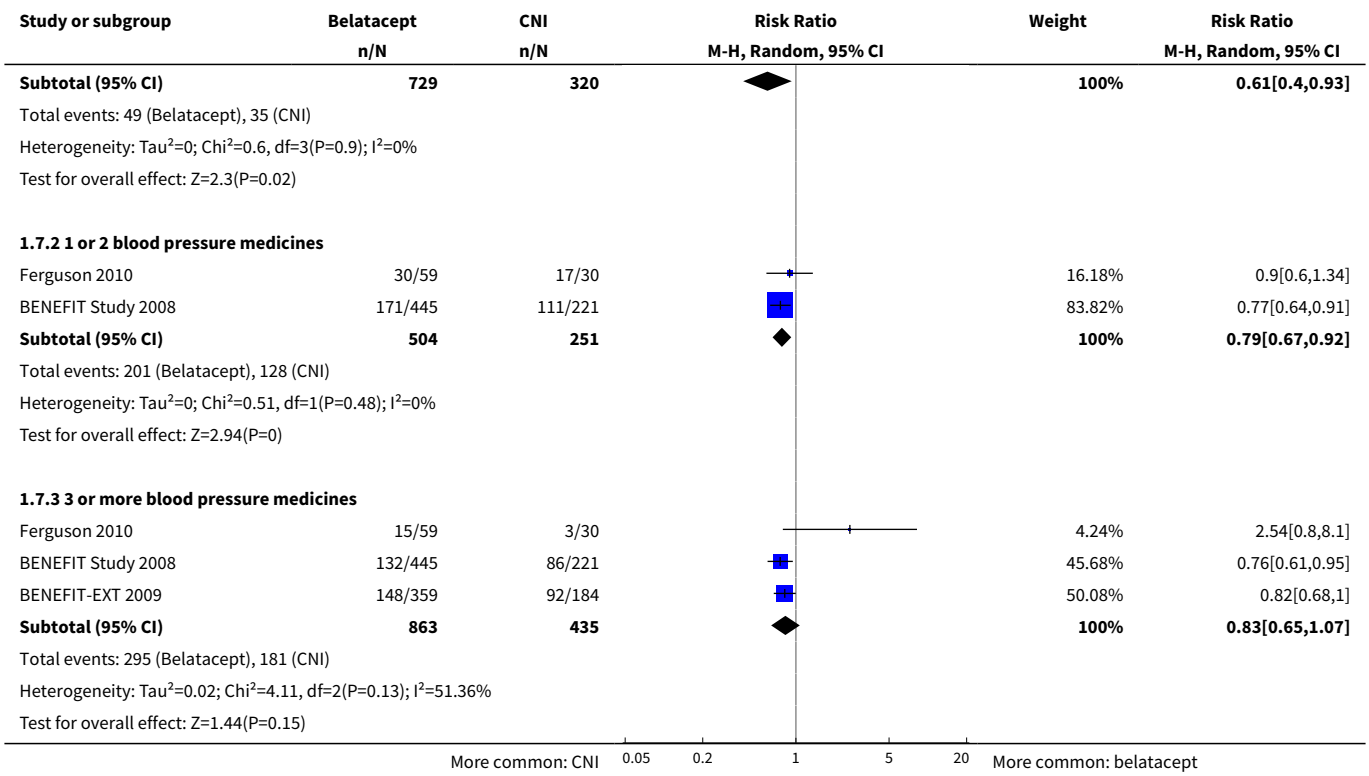

Comparison 2. High versus low dosage belatacept

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recipient and kidney survival	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Death (any cause)	3	949	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.75, 2.06]
1.2 Loss of kidney transplant	3	949	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.59, 1.56]
2 Surviving with a functioning transplant	3	949	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.94, 1.02]
3 Acute rejection and chronic kidney scarring	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Acute rejection	3	949	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.88, 1.55]
3.2 Severe acute rejection (≥ Banff 2A)	2	152	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.67, 2.43]
3.3 Chronic kidney scarring	3	910	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.74, 1.20]
3.4 Severe chronic kidney scarring	3	910	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.34, 1.75]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Kidney function, blood pressure and lipids	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Measured GFR	3	735	Mean Difference (IV, Random, 95% CI)	0.37 [-3.49, 4.23]
4.2 eGFR	3	747	Mean Difference (IV, Random, 95% CI)	0.13 [-2.94, 3.20]
4.3 Systolic BP	2	659	Mean Difference (IV, Random, 95% CI)	1.16 [-1.33, 3.66]
4.4 Diastolic BP	2	659	Mean Difference (IV, Random, 95% CI)	0.0 [-1.52, 1.52]
4.5 non-HDL (change from baseline)	2	671	Mean Difference (IV, Random, 95% CI)	0.59 [-5.54, 6.72]
4.6 Triglycerides (change from baseline)	2	671	Mean Difference (IV, Random, 95% CI)	8.82 [-6.63, 24.28]
5 Malignancy	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Any malignancy	3	949	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.52, 3.13]
5.2 PTLD	3	949	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.39, 3.99]
6 Infections	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Any infection	3	949	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.04]
6.2 Serious infection	2	804	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.09]
6.3 Tuberculosis	2	804	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.23, 4.17]
6.4 CMV disease	3	949	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.74, 1.40]
6.5 BK nephropathy	1	445	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.06, 16.40]
7 Diabetes and use of blood pressure medicines	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 New-onset diabetes	3	739	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.33, 2.51]
7.2 1 or 2 blood pressure medicines	1	445	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.91, 1.45]
7.3 3 or more blood pressure medicines	2	804	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.91, 1.32]

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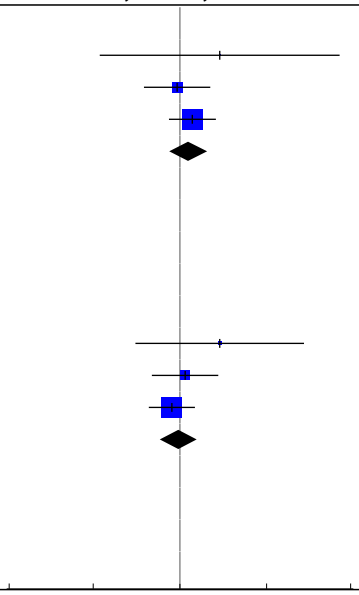
Analysis 2.1. Comparison 2 High versus low dosage belatacept, Outcome 1 Recipient and kidney survival.

Study or subgroup	High dosage belatacept n/N	Low dosage belatacept n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Death (any cause)					
Vincenti 2005	1/74	0/71		2.49%	2.88[0.12,69.55]
BENEFIT Study 2008	9/219	10/226		32.49%	0.93[0.38,2.24]
BENEFIT-EXT 2009	22/184	15/175		65.03%	1.39[0.75,2.6]
Subtotal (95% CI)	**477**	**472**		**100%**	**1.24[0.75,2.06]**
Total events: 32 (High dosage belatacept), 25 (Low dosage belatacept)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.82$, df=2(P=0.66); $I^2=0\%$					
Test for overall effect: Z=0.85(P=0.39)					
2.1.2 Loss of kidney transplant					
Vincenti 2005	3/74	1/71		4.8%	2.88[0.31,27.03]
BENEFIT Study 2008	10/219	9/226		31.02%	1.15[0.48,2.77]
BENEFIT-EXT 2009	17/184	20/175		64.18%	0.81[0.44,1.49]
Subtotal (95% CI)	**477**	**472**		**100%**	**0.96[0.59,1.56]**
Total events: 30 (High dosage belatacept), 30 (Low dosage belatacept)					
Heterogeneity: $Tau^2=0$; $Chi^2=1.39$, df=2(P=0.5); $I^2=0\%$					
Test for overall effect: Z=0.17(P=0.86)					
Test for subgroup differences: $Chi^2=0.54$, df=1 (P=0.46), $I^2=0\%$					



More common: high dosage — More common: low dosage

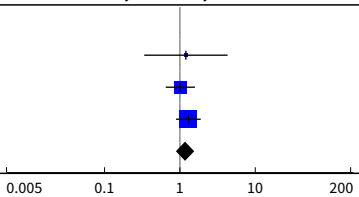
Analysis 2.2. Comparison 2 High versus low dosage belatacept, Outcome 2 Surviving with a functioning transplant.

Study or subgroup	Belatacept n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
BENEFIT Study 2008	202/219	208/226		48.12%	1[0.95,1.06]
BENEFIT-EXT 2009	145/184	145/175		13.96%	0.95[0.86,1.05]
Vincenti 2005	70/74	70/71		37.92%	0.96[0.9,1.02]
Total (95% CI)	**477**	**472**		**100%**	**0.98[0.94,1.02]**
Total events: 417 (Belatacept), 423 (CNI)					
Heterogeneity: $Tau^2=0$; $Chi^2=1.45$, df=2(P=0.48); $I^2=0\%$					
Test for overall effect: Z=1.13(P=0.26)					

More common: CNI — More common: belatacept

Analysis 2.3. Comparison 2 High versus low dosage belatacept, Outcome 3 Acute rejection and chronic kidney scarring.

Study or subgroup	High dosage belatacept n/N	Low dosage belatacept n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Acute rejection					
Vincenti 2005	5/74	4/71		4.85%	1.2[0.34,4.29]
BENEFIT-EXT 2009	33/184	31/175		39.86%	1.01[0.65,1.58]
BENEFIT Study 2008	49/219	39/226		55.29%	1.3[0.89,1.89]
Subtotal (95% CI)	**477**	**472**		**100%**	**1.17[0.88,1.55]**



More common: high dosage — More common: low dosage

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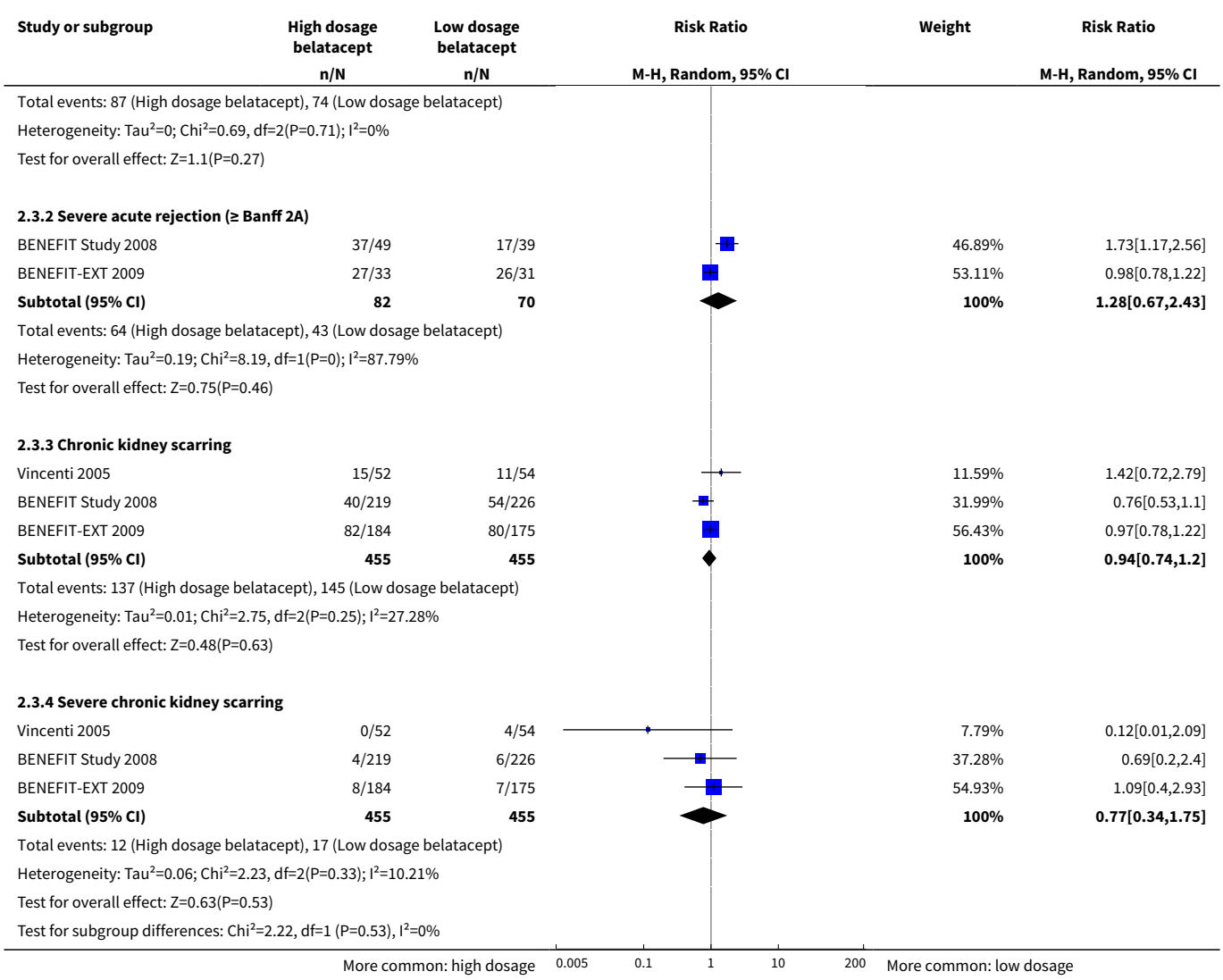
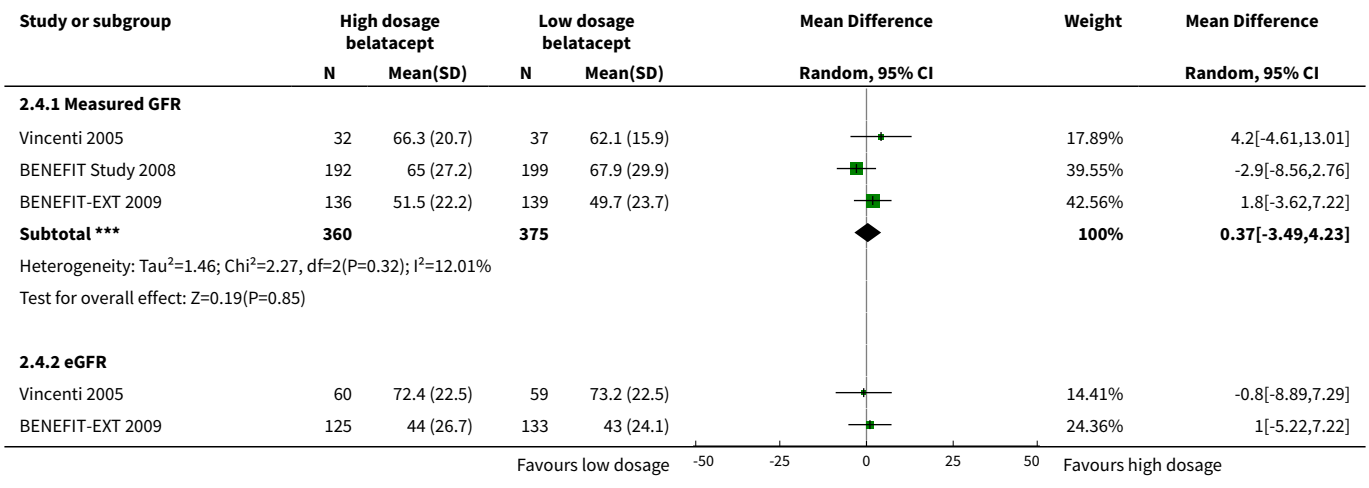


Analysis 2.4. Comparison 2 High versus low dosage belatacept, Outcome 4 Kidney function, blood pressure and lipids.



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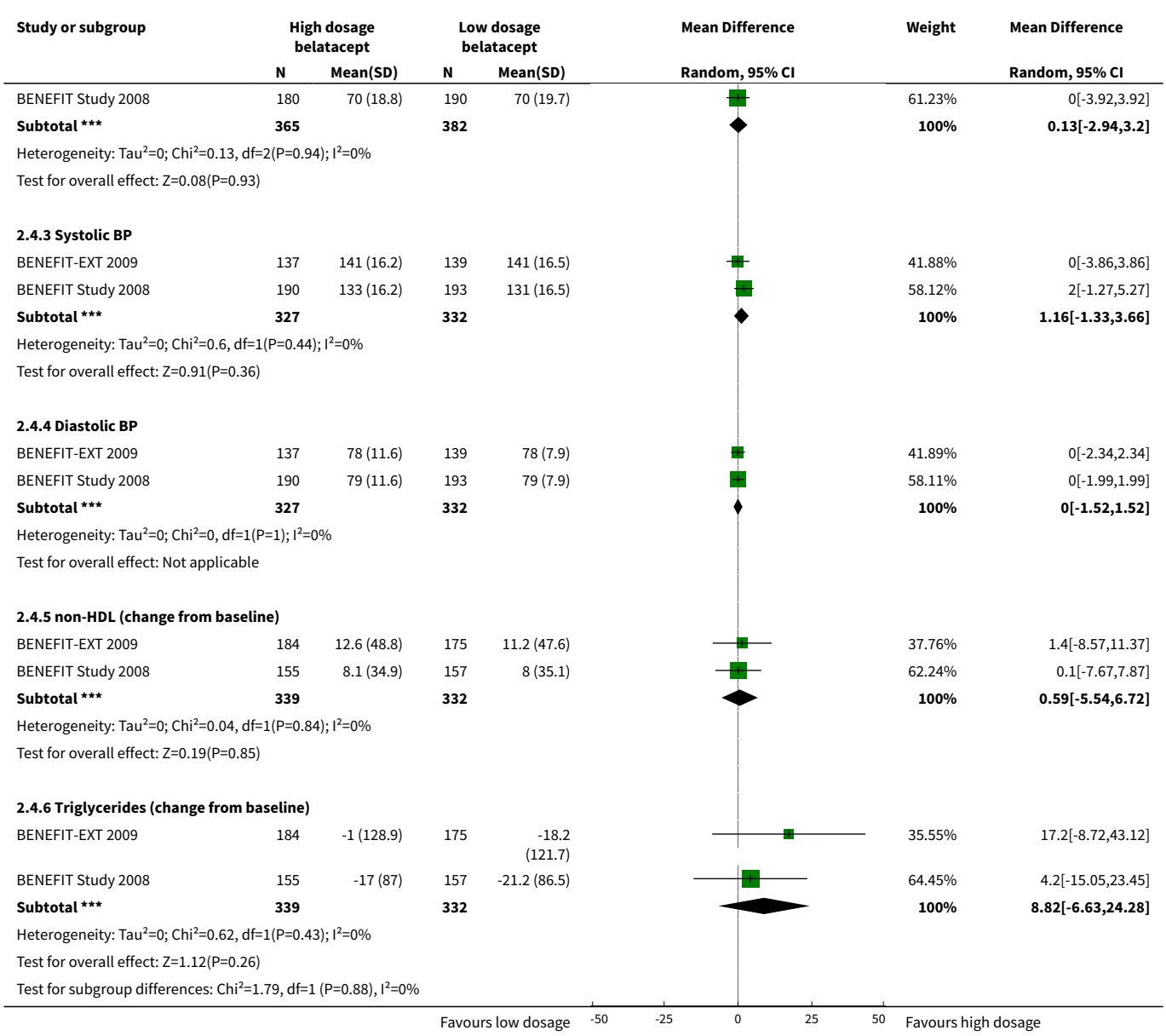
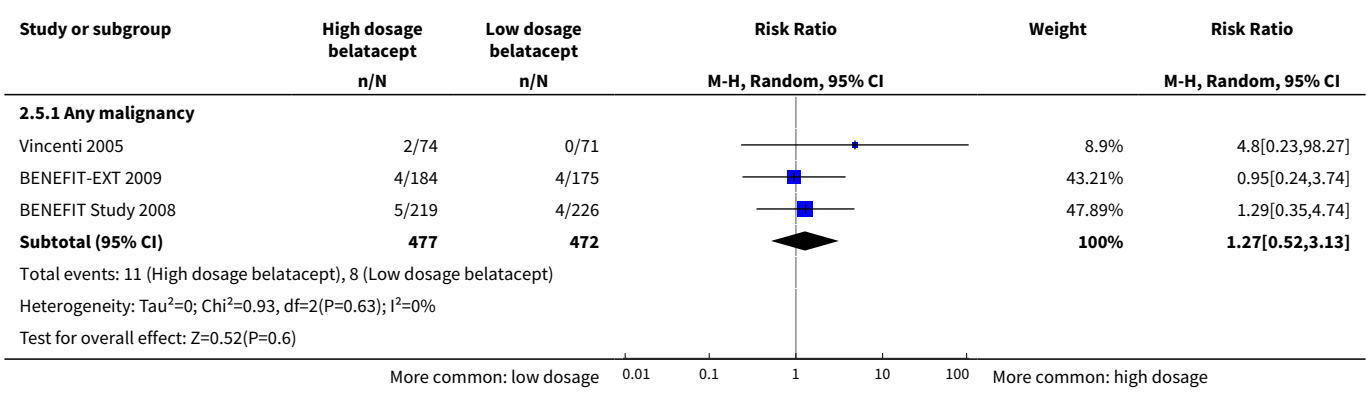


Analysis 2.5. Comparison 2 High versus low dosage belatacept, Outcome 5 Malignancy.



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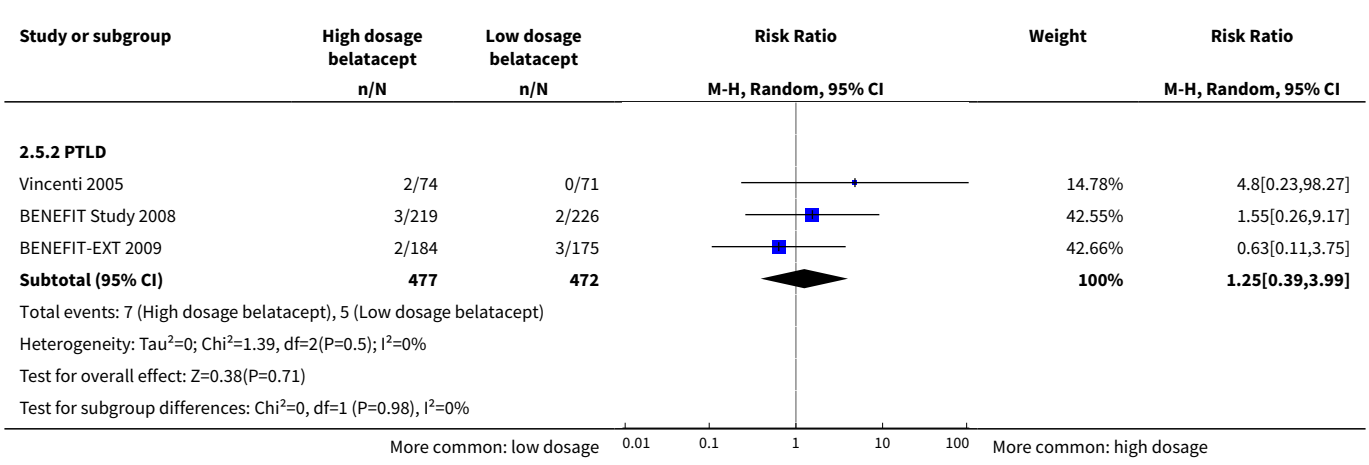
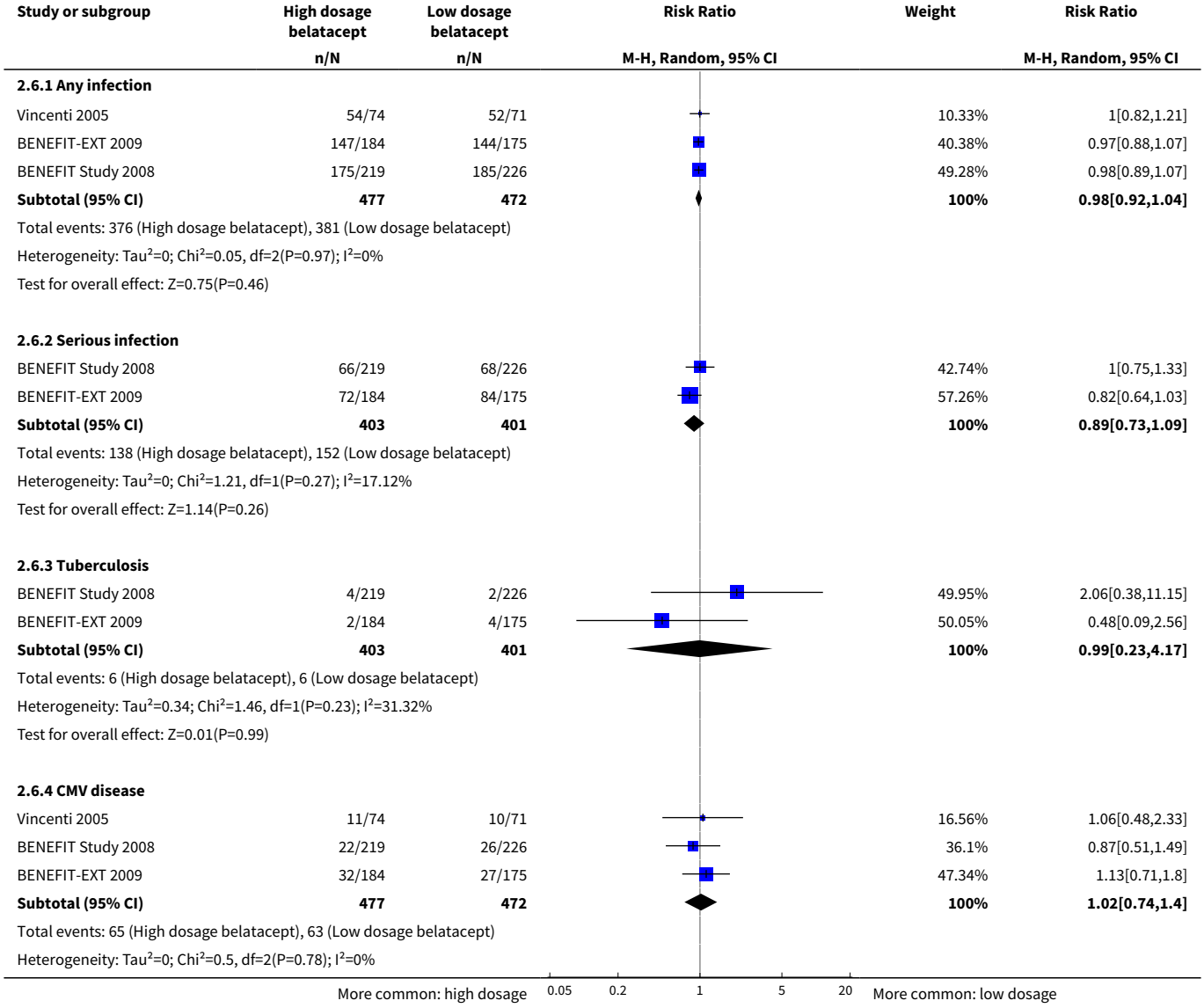


Analysis 2.6. Comparison 2 High versus low dosage belatacept, Outcome 6 Infections.



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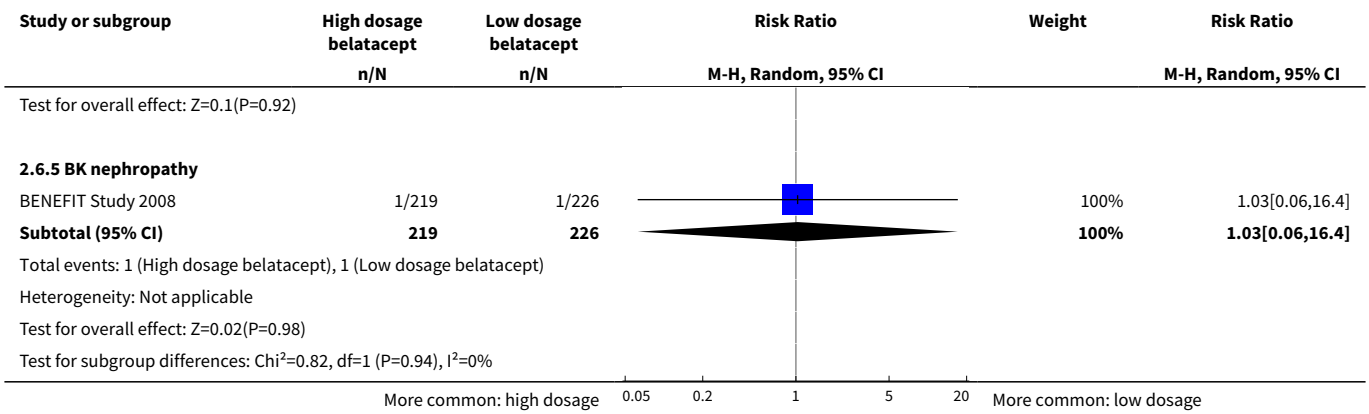
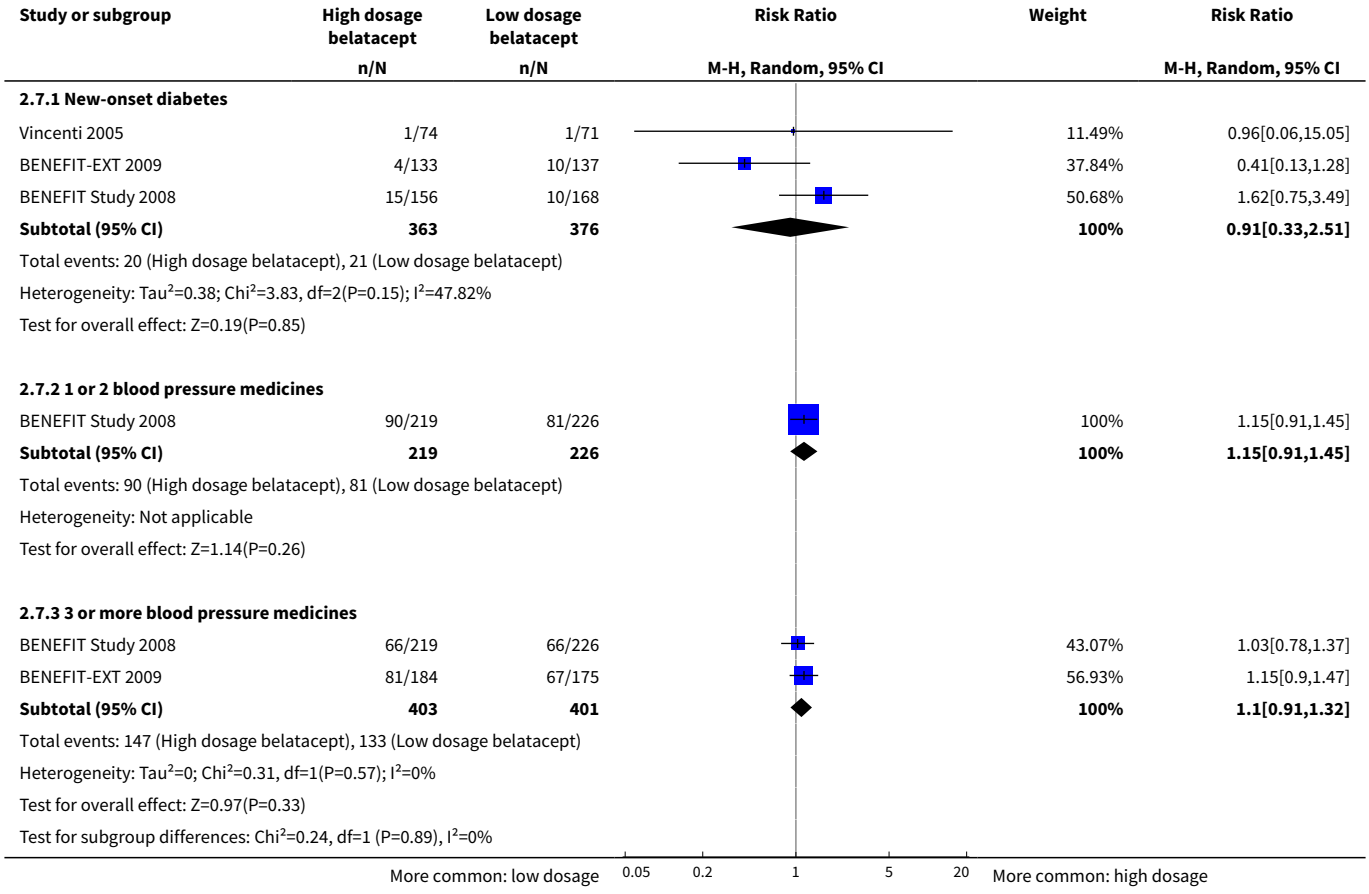


Analysis 2.7. Comparison 2 High versus low dosage belatacept, Outcome 7 Diabetes and use of blood pressure medicines.



APPENDICES

Appendix 1. Electronic search strategies

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Database	Search terms
CENTRAL	1. MeSH descriptor Kidney Transplantation, this term only 2. (kidney transplant*):ti,ab,kw in Clinical Trials 3. (#1 OR #2) 4. (Belatacept):ti,ab,kw in Clinical Trials 5. (lea29y):ti,ab,kw in Clinical Trials 6. (bms 224818):ti,ab,kw in Clinical Trials 7. (costimulation blocker*):ti,ab,kw or (co-stimulation blocker*):ti,ab,kw in Clinical Trials 8. (#4 OR #5 OR #6 OR #7) 9. (#3 AND #8)
MEDLINE (OVID SP)	1. Kidney Transplantation/ 2. Belatacept.tw. 3. lea29y.tw. 4. "bms 224818".tw. 5. (costimulation blocker$ or co-stimulation blocker$).tw. 6. or/2-5 7. and/1,6
EMBASE (OVID SP)	1. exp kidney transplantation/ 2. belatacept/ 3. Belatacept.tw. 4. lea 29y.tw. 5. lea29y.tw. 6. bms 224818.tw. 7. (costimulation blocker$ or co-stimulation blocker$).tw. 8. or/2-7 9. and/1,8

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).

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(Continued)

	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they can-

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(Continued)

	not be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: PM
2. Study selection: PM, LH
3. Extract data from studies: PM, LH
4. Enter data into RevMan: PM, LH
5. Carry out the analysis: PM, AW
6. Interpret the analysis: PM, AW, JCC,
7. Draft the final review: PM, LH, ACW, JRC, JCC
8. Disagreement resolution: AW, JCC
9. Update the review: PM, LH, AW, JCC

DECLARATIONS OF INTEREST

- Philip Masson: none known
- Lorna Henderson: none known
- Jeremy R Chapman: none known
- Jonathan C Craig: none known
- Angela C Webster: none known

INDEX TERMS

Medical Subject Headings (MeSH)

*Kidney Transplantation [mortality]; Abatacept; Alemtuzumab; Antibodies, Monoclonal [therapeutic use]; Antibodies, Monoclonal, Humanized [therapeutic use]; Antilymphocyte Serum [therapeutic use]; Basiliximab; Calcineurin Inhibitors [*therapeutic use]; Cyclosporine [therapeutic use]; Graft Rejection [mortality] [*prevention & control]; Graft Survival; Immunoconjugates [adverse effects] [*therapeutic use]; Immunosuppressive Agents [adverse effects] [*therapeutic use]; Lymphoproliferative Disorders [etiology]; Mycophenolic Acid [analogs & derivatives] [therapeutic use]; Prednisone [therapeutic use]; Randomized Controlled Trials as Topic; Recombinant Fusion Proteins [therapeutic use]; Sirolimus [therapeutic use]; Tacrolimus [therapeutic use]

MeSH check words

Humans

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