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Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients (Review)

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[Intervention Review]

Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients

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ABSTRACT

Background

The risk of cytomegalovirus (CMV) infection in solid organ transplant recipients has resulted in the frequent use of prophylaxis with the aim of preventing the clinical syndrome associated with CMV infection.

Objectives

To determine the benefits and harms of antiviral medications to prevent CMV disease and all-cause mortality in solid organ transplant recipients.

Search methods

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, reference lists and abstracts from conference proceedings without language restriction.

Selection criteria

Randomised and quasi-randomised controlled trials comparing antiviral medications with placebo or no treatment, trials comparing different antiviral medications and trials comparing different regimens of the same antiviral medications in recipients of any solid organ transplant.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted data from each trial. Statistical analyses were performed using the random effects model and results expressed as relative risk (RR) for dichotomous outcomes with 95% confidence intervals (CI). Subgroup analysis and univariate meta-regression were performed using restricted maximum-likelihood to estimate the between study variance. Multivariate meta-regression was performed to investigate whether the results were altered after allowing for differences in drugs used, organ transplanted and recipient CMV serostatus at the time of transplantation.

Main results

Thirty two trials (3737 participants) were identified. Prophylaxis with aciclovir, ganciclovir or valaciclovir compared with placebo or no treatment significantly reduced the risk for CMV disease (19 trials; RR 0.42, 95% CI 0.34 to 0.52), CMV infection (17 trials; RR 0.61, 95% CI 0.48 to 0.77), and all-cause mortality (17 trials; RR 0.63, 95% CI 0.43 to 0.92) primarily due to reduced mortality from CMV disease (seven trials; RR 0.26, 95% CI 0.08 to 0.78). Prophylaxis reduced the risk of herpes simplex and herpes zoster disease, bacterial and protozoal infections but not fungal infection, acute rejection or graft loss. Meta-regression showed no significant difference in the risk of CMV disease or all-cause mortality by organ transplanted or CMV serostatus; no conclusions were possible for CMV negative recipients of negative organs. In direct comparison trials, ganciclovir was more effective than aciclovir in preventing CMV disease (seven trials; RR 0.37, 95% Cl 0.23 to 0.60). Valganciclovir and intravenous ganciclovir were as effective as oral ganciclovir.

Authors' conclusions

Prophylaxis with antiviral medications reduces CMV disease and CMV-associated mortality in solid organ transplant recipients. They should be used routinely in CMV positive recipients and in CMV negative recipients of CMV positive organ transplants.

PLAIN LANGUAGE SUMMARY

Prophylaxis with antiviral medications reduces CMV disease and CMV-associated mortality in solid organ transplant recipients

Cytomegalovirus (CMV) is the most common virus pathogen in solid organ transplant recipients (kidney, heart, liver, lung and pancreas) being a major cause of morbidity and mortality during the first six months after transplantation. Two main strategies to prevent CMV disease have been adopted: prophylaxis of organ recipients with antiviral agents, or 'pre-emptive therapy' of organ recipients, who develop evidence of CMV infection during routine screening. This review looked at the benefits and harms of antiviral medication to prevent CMV disease in solid organ transplant recipients. Thirty two trials (3737 participants) were identified. This review shows that the antiviral medications, ganciclovir, valaciclovir and aciclovir reduced the risk of CMV disease, all-cause mortality due to reduced mortality from CMV disease, clinical disease caused by herpes simplex and herpes zoster, bacterial infections and protozoal infections. For CMV disease and mortality, the relative benefits of aciclovir, ganciclovir and valaciclovir appear consistent across recipients of heart, kidney and liver transplants. These benefits occur in both CMV positive recipients and CMV negative recipients of CMV positive organs, are irrespective of whether immunosuppression includes antilymphocyte antibody therapy and are not dependent on the time of outcome assessment. In comparison trials, ganciclovir is more effective than aciclovir and as effective as valganciclovir, which is currently the most commonly used antiviral medication to prevent CMV disease in transplant recipients. More studies are needed in lung and heart transplant recipients and to determine the optimum duration and dosage of medications for all solid organ transplant recipients.

BACKGROUND

Cytomegalovirus (CMV) is the most common virus pathogen in solid organ transplant recipients being a major cause of morbidity and mortality during the first six months post-transplant (Fishman 1998; Rubin 2000). The overall incidence of symptomatic CMV disease in the transplant population ranges from 30% to 50% with the incidence and severity being highest among lung recipients (Linden 2000). Approximately 50% of deaths following lung transplantation are attributed to infection (Michaels 2000). Like all herpes viruses, CMV has the propensity to establish lifelong 'latency' infection in the host after the initial infection has resolved. Therefore, a solid organ recipient may be infected either by exogenous virus or by reactivation of latent virus if they were CMV positive pre-transplant. Those at highest risk of symptomatic CMV disease are CMV seronegative patients who receive organs from CMV seropositive donors, and CMV seropositive patients on heavily immunosuppressive regimens (Fishman 1998; Rubin 2000).

CMV may manifest as a non-specific illness characterised by fever, mononucleosis, leucopenia and thrombocytopenia, or as a variety of clinical syndromes including pneumonitis, hepatitis, encephalitis and focal gastrointestinal disease. In addition, CMV infection causes morbidity in organ recipients through indirect effects on their immune response (Rubin 1989), and is associated with increased risk of allograft injury and rejection (Grattan 1989; Keenan 1991), opportunistic infections (Fishman 1995; Hadley 1995; Van den Berg 1996) and late onset malignancies such as EBV-lymphoproliferative disease (Basgoz 1995). For these reasons, many strategies have been proposed to prevent CMV infection, and /or prevent systematic disease. Two main strategies to prevent CMV disease have been adopted: prophylaxis of organ recipients with antiviral agents and/or immunoglobulins, or 'pre-emptive therapy' of organ recipients, who develop evidence of CMV infection during screening (Rubin 1989). Prophylaxis among kidney transplant recipients has commonly been limited to CMV negative recipients of CMV positive kidneys and to recipients receiving antibodies to lymphocyte antigens. Pre-emptive therapy relies upon monitoring for CMV infection by newly available sensitive techniques such as antigenemia or polymerase chain reaction (PCR) that allow the diagnosis to be made much earlier than traditional culture methods (Emery 2000).

There remains a lack of consensus on the merits of the various CMV prophylaxis protocols available (Fishman 1998). A meta-analysis of prophylactic treatment versus placebo/no treatment is currently published in *The Cochrane Library* (Couchoud 1998a). As this is now due for an update, more recent articles comparing prophylaxis with antiviral medications (including aciclovir, ganciclovir, valaciclovir, valganciclovir) have been included. In addition this review has been modified to include studies comparing one prophylactic antiviral medication with another. In this review we have examined the effect of prophylaxis with antiviral agents in recipients of solid organ transplant recipients on CMV disease, all CMV infection, the incidence of acute rejection, graft loss, opportunistic infections and death. We have compared the treatment effect of each regimen between different solid organs and between different risk groups. Finally, the study has evaluated potential harms caused by antiviral medications, namely nephrotoxicity, bone marrow suppression, and emergence of resistant CMV strains. Subsequent reviews will evaluate pre-emptive therapy on detection of CMV viraemia and the use of other agents (immunoglobulins, vaccines, interferon) alone or in combination with antiviral medications.

OBJECTIVES

The aim of this review was to assess the benefits and harms of antiviral medications for preventing symptomatic CMV disease in solid organ transplant recipients of all ages, irrespective of CMV serostatus prior to transplantation. The secondary aims were to evaluate the efficacy of antiviral medications in preventing all CMV infection (symptomatic and asymptomatic where CMV is detected only by laboratory investigation) and in decreasing the incidence of acute rejection, graft loss, death (all-cause mortality and mortality due to CMV disease), opportunistic infections and to evaluate the harms of each antiviral medication.

Firstly, the review compared studies of antiviral medications with placebo/no treatment. Secondly, it has explored comparisons between two or more antiviral agents and/or two different doses of the same antiviral agent. Thirdly, it has compared the treatment effect of each regimen between different solid organs and finally, between the different risk groups (i.e. pre-existent CMV serostatus and/or level of immunosuppression).

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials and quasi-randomised controlled trials have been included.

Types of participants

Participants of all ages, irrespective of CMV serostatus prior to transplantation, who have undergone at least one solid organ transplant (kidney, liver, lung, heart, pancreas). Bone marrow and other cellular transplants were excluded.

Types of interventions

Interventions included antiviral medications (aciclovir, ganciclovir, valaciclovir, valganciclovir). Comparisons were made between antiviral medications and placebo/no treatment, two different antiviral medications, or two varying doses of an antiviral medication.

Trials of pre-emptive treatment (i.e. treatment on detection of CMV viraemia), immunoglobulin alone or with antiviral medications, vaccines or interferon were excluded. Treatment regimens for symptomatic CMV disease were excluded.

Types of outcome measures

The primary outcome measures were the incidence of CMV disease (documented CMV infection with clinical symptoms) and all-cause mortality. Secondary outcomes included the incidence all CMV infection (symptomatic and asymptomatic), acute rejection, graft loss, death due to CMV disease, opportunistic infections, time to CMV disease, harms (including nephrotoxicity, bone marrow suppression, and emergence of resistant CMV strains). All outcomes were recorded as present/absent except time to the development of CMV disease.

The definition of CMV infection used was that defined by the trial investigators. This was usually the isolation of CMV from a cultured specimen from any site, or positive histopathology or CMV antigen detection in a tissue specimen, or the presence of CMV p65 antigenemia, or an elevation in CMV viral load as detected by qualitative or quantitative PCR (as defined by the investigator). The definition of symptomatic CMV disease used was that defined by the trial investigators. This was usually the diagnosis of CMV infection in association with one or more of the following: CMV syndrome (temperature of 38ºC or more with no other documented source in association with one or more of atypical lymphocytosis, leukopenia or thrombocytopenia), pneumonitis, focal gastrointestinal disease, liver function abnormality, or encephalitis. Graft loss was defined as the need for dialysis for kidney transplantation or re-transplantation for other organs during the follow-up period of the study. Acute rejection was defined as used by the individual authors. This was either biopsy proven or clinical, defined by rise in creatinine levels with respect to kidney transplants or response to rejection treatment.

Search methods for identification of studies

A systematic and comprehensive literature search was carried out to identify eligible RCTs (Table 1 - *Electronic search strategies)*. There was no language restriction. We searched;
1. The Cochrane Renal Group's Specialised Register (February 2004).
2. The Cochrane Central Register of Controlled Trials (CENTRAL in *The Cochrane Library* Issue 1, 2004).
3. MEDLINE (1966 to February 2004) using the optimally sensitive search strategy developed for identification of RCTs (Dickersin 1994).
4. EMBASE (1980 to February 2004)using the optimally sensitive search strategy developed for identification of RCTs (Lefebvre 1996).

The Trials Search Coordinator (Ruth Mitchell) ensured that all relevant trials had been identified. Additional studies were located through article reference lists and from abstracts from international meetings.

Data collection and analysis

Included and excluded studies

Two reviewers (EH, CAJ) independently screened titles and abstracts retrieved from the searches and identified those trials that met the inclusion criteria. This process favoured over-selection in order to include all relevant trials. The full article was retrieved if uncertainty existed or when the abstract was not available. Any disagreement with article selection was resolved through discussion and consultation with a third reviewer (JC).

Four reviewers (EH, CAJ, PGB, KK) independently extracted data from eligible studies. Participant characteristics (number, age, sex, comorbidities), intervention (type of treatment, dose, duration, co-interventions) and primary and secondary outcome measures were recorded. Authors were contacted to obtain missing information on allocation concealment. Any discrepancies in data extraction were resolved in discussion. In the instance where results of a study are published more than once, the most complete data were extracted from all sources and used in the analysis only once.

Study quality

The quality of studies to be included was assessed independently by two of four reviewers (EH, CAJ, PGB, KK) without blinding to authorship or journal of publication using the checklist developed for the Cochrane Renal Group. Discrepancies were resolved by consensus and when necessary by discussion with JC. The quality items assessed were allocation concealment, intention-to-treat analysis, completeness of follow-up and blinding of investigators, participants and outcome assessors (Hollis 1999; Moher 1998; Schultz 1995).

Quality checklist

1. Allocation concealment

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

2. Blinding

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

The above are considered not blinded if the treatment group could be identified in >20% of participants due to side effects of treatment or the treatment groups could be identified through different routes or frequency of administration of trial medications.

3. Intention-to-treat analysis

A. Yes: specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment
B. No: not reported and lack of intention-to-treat analysis confirmed on study assessment. (Patients who were randomised but were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation).
C. Not stated: not reported and could be determined (Studies with 100% follow up of patients included so that patient exclusion after randomisation cannot be excluded)

4. Completeness of follow-up

Percentage of participants lost to follow up or with no data for the primary outcome of effectiveness

Statistical assessment

Dichotomous outcomes were expressed as relative risks with 95% confidence intervals while continuous outcomes was stated as weighted mean differences. Data was pooled using a random effects model to calculate a summary estimate of effect. Heterogeneity was formally tested using Cochran's Q statistic and the I^2 statistic (Higgins 2003), which is derived from Q and describes the percentage of total variation that is due to heterogeneity beyond chance. In order to explore clinical differences between trials that might be expected to influence the magnitude of the treatment effect for the primary outcomes of CMV disease and all-cause mortality, subgroup analysis and univariate meta-regression was performed using STATA software (StataCorp LP, Texas, USA)

using restricted maximum-likelihood to estimate the between study variance. The potential sources of variability were defined a priori and were organ transplanted, antiviral medication used, use of immunosuppressive regimen including antibody therapy, treatment duration, donor/recipient CMV status at transplant, the time from transplant that the outcomes were measured and methodological quality. Multivariate meta-regression was performed to investigate whether the results were altered after allowing for the differences in drug used, organ transplanted and recipient CMV serostatus at the time of transplantation.

RESULTS

Description of studies

From the retrieved reports, 1120 articles were initially identified. The titles were screened and 927 articles were excluded. The remaining 193 abstracts were screened, 81 full text reports were reviewed and 32 trials (3737 participants) were included (Figure 1 - *Flow chart of trial selection*). Nineteen trials compared aciclovir (Balfour 89 - Kidney; Barkholt 99 - Liver; Gavalda 97-Liver; Kletzmayr 96-Kidney; Rostaing 94 - Kidney; Saliba 93-Liver), ganciclovir (Ahsan 97-Kidney; Brennan 97-Kidney; Cohen 93-Liver; Conti 95-Kidney; Gane 97-Liver; Hibberd 95-Kidney; Leray 95-Kidney; Macdonald 95-Heart; Merigan 92-Heart; Pouteil-Noble 96 - K; Rondeau 93-Kidney) or valaciclovir (Egan 02-Heart; Lowance 99-Kidney) with placebo or no treatment. Fifteen trials excluded CMV negative recipients of CMV negative donors. Eleven trials compared different antiviral medications (Badley 97-Liver, Duncan 93-Lung, Flechner 98-Kidney, Green 97-Liver, Martin 94-Liver; Nakazato 93-Liver; Paya 04-All; Reischig 04 - Kidney; Rubin 02-all; Winston 03-Liver; Winston 95-Liver) and two trials (Hertz 98-heart/lung; Winston 04-Liver) compared different regimens of ganciclovir administration. Recipients of transplants other than heart, kidney and liver were not included in trials comparing treatment with placebo or no treatment and in only three comparison trials. All identified trials were in the English language. Among trials comparing antiviral medications with placebo/no treatment, no significant publication bias could be demonstrated on funnel plot (Figure 2 - *Funnel plot of 19 trials comparing antiviral medications with placebo or no treatment*). There were too few trials comparing ganciclovir and aciclovir to subject the data to a funnel plot.

Figure 1. Flow-chart indicating the process of identification of randomized controlled trials (RCTs) included in this systematic review.

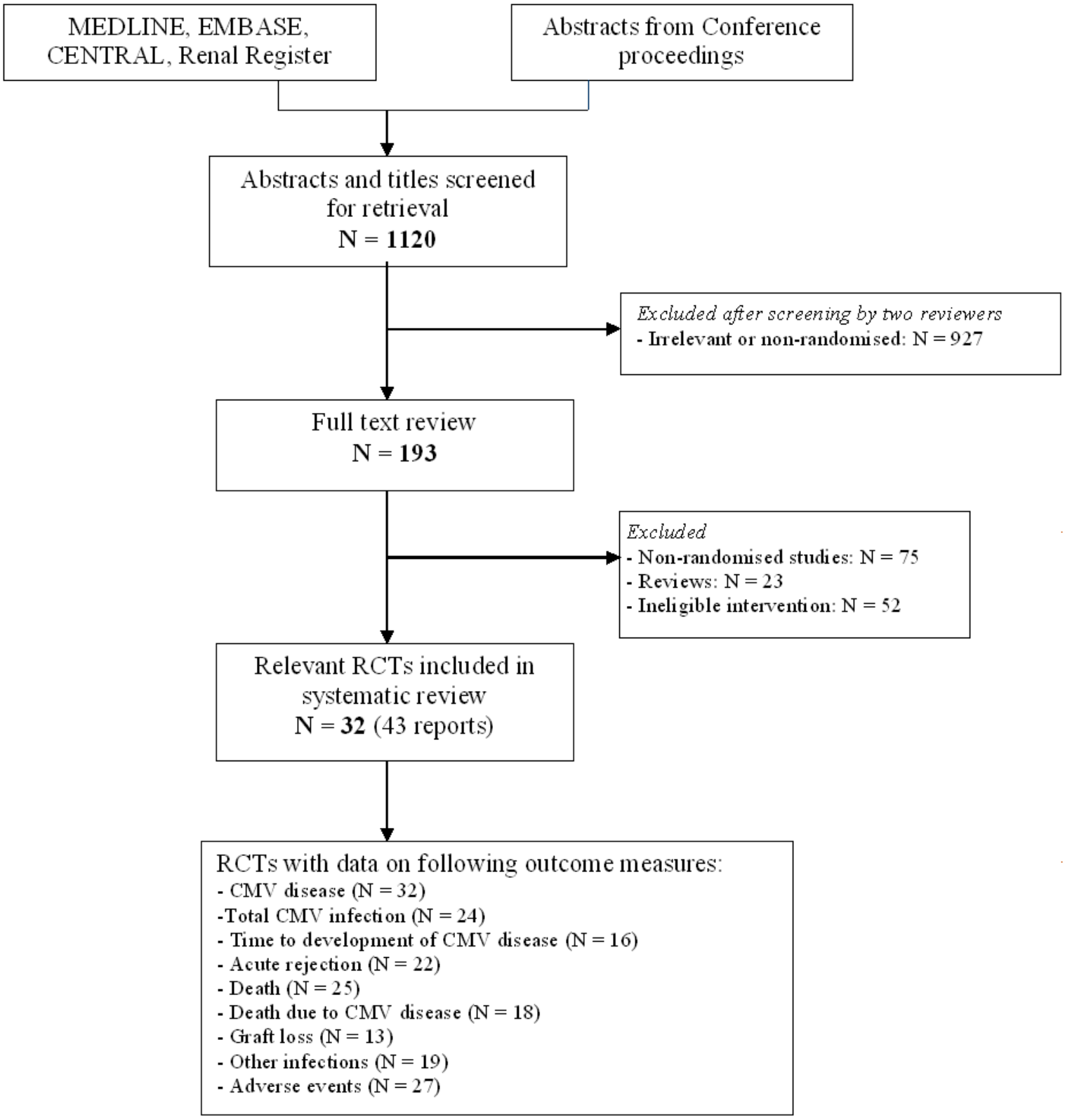
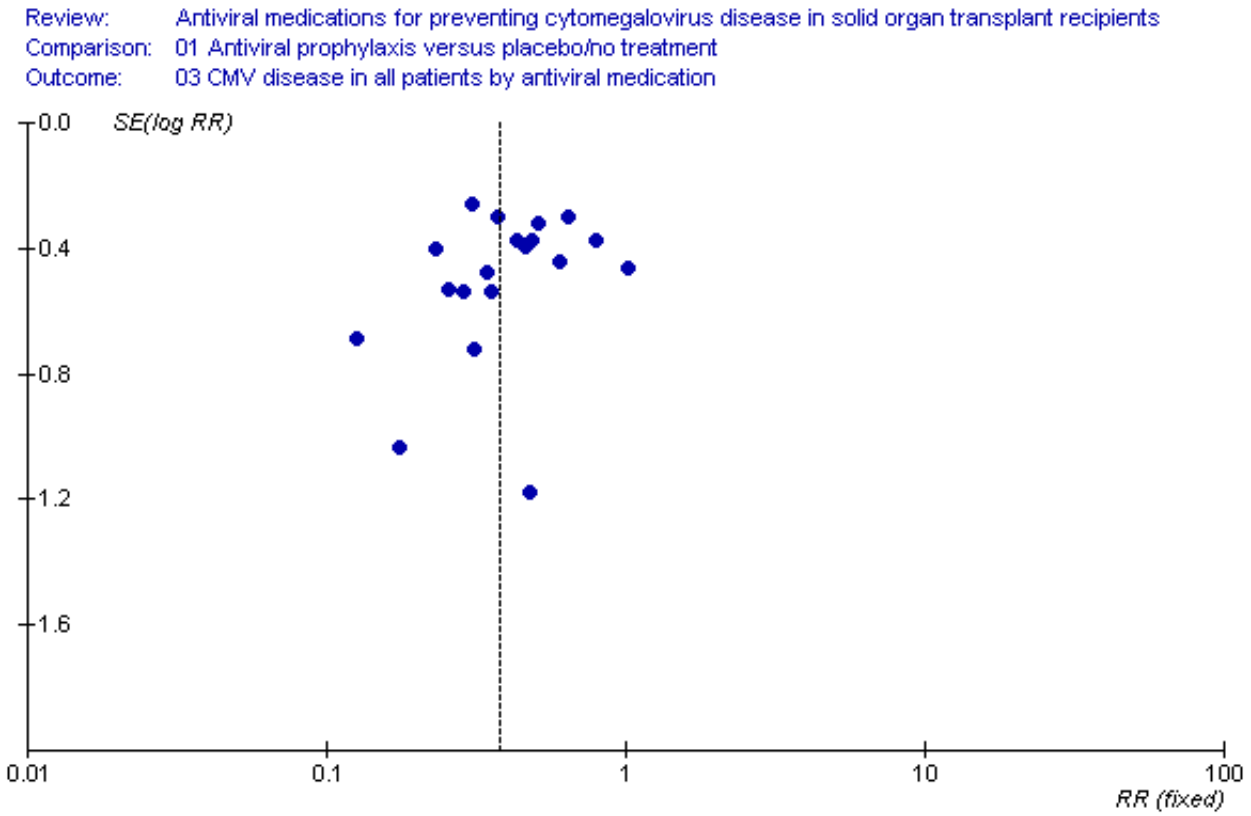


Figure 2. Funnel plot of 19 trials comparing antiviral medications with placebo or no treatment



Risk of bias in included studies

Allocation concealment

Of 19 trials comparing prophylaxis with placebo or no treatment, four (21%) trials reported adequate allocation concealment (Cohen 93-Liver; Egan 02-Heart; Pouteil-Noble 96 - K; Saliba 93-Liver), one trial had inadequate allocation concealment (Brennan 97-Kidney) and the information was not available in 14 trials. Of 11 trials comparing different medications, six (55%) trials reported adequate allocation concealment (Badley 97-Liver; Flechner 98-Kidney; Green 97-Liver; Paya 04-All; Reischig 04 - Kidney; Rubin 02-all) and the information was not available for five trials. Information on allocation concealment was not available for the last two trials (Hertz 98-heart/lung; Winston 04-Liver).

Blinding

Six trials (19%) reported blinding of investigators and participants including five trials comparing prophylaxis with placebo (Balfour 89 - Kidney; Barkholt 99 - Liver; Gane 97-Liver; Lowance 99-Kidney; Macdonald 95-Heart) and one trial comparing valganciclovir with ganciclovir (Paya 04-All). Three trials (9%) reported blinding of outcome assessors (Barkholt 99 - Liver; Lowance 99-Kidney; Macdonald 95-Heart); all were trials comparing prophylaxis with placebo.

Intention-to-treat analysis

Nineteen trials (63%) carried out an intention-to-treat analysis. Of these 13 trials compared prophylaxis with placebo/no treatment (Brennan 97-Kidney; Cohen 93-Liver; Egan 02-Heart; Gane 97-Liver; Gavalda 97-Liver; Hibberd 95-Kidney; Lowance 99-Kidney; Macdonald 95-Heart; Merigan 92-Heart; Pouteil-Noble 96 - K; Rostaing 94 - Kidney; Saliba 93-Liver; Winston 95-Liver), four compared different antiviral medications (Duncan 93-Lung; Flechner 98-Kidney; Green 97-Liver; Nakazato 93-Liver) and two compared different regimens of ganciclovir (Hertz 98-heart/lung; Winston 04-Liver).

Completeness of follow-up

More than 95% of participants completed the trial in 31 trials (97%).

Effects of interventions

1). Antiviral medication versus placebo/no treatment (comparison 01)

Nineteen trials (1981 patients) compared antiviral medications with placebo or no treatment. Six trials administered aciclovir (Balfour 89 - Kidney; Barkholt 99 - Liver; Gavalda 97-Liver; Kletzmayr 96-Kidney; Rostaing 94 - Kidney; Saliba 93-Liver), 11 trials administered ganciclovir (Ahsan 97-Kidney; Brennan 97-Kidney; Cohen 93-Liver; Conti 95-Kidney; Gane 97-Liver; Hibberd 95-Kidney; Leray 95-Kidney; Macdonald 95-Heart; Merigan 92-Heart; Pouteil-Noble 96 - K; Rondeau 93-Kidney) and two trials administered valaciclovir (Egan 02-Heart; Lowance 99-Kidney).

CMV disease and CMV infection

The average risk of CMV disease was 30% (range 11% to 72%). Prophylaxis with all agents significantly reduced the risk for CMV disease overall (outcome 01.01, 19 trials, 1981 patients: RR 0.42,

95% CI 0.34 to 0.52), CMV syndrome (outcome 01.02, 11 trials, 1570 patients: RR 0.41, 95% CI 0.29 to 0.57) and CMV invasive organ disease (outcome 01.03, 12 trials, 1628 patients: RR 0.34, 95% CI 0.21 to 0.55) compared with placebo or no treatment. No significant heterogeneity between studies was detected in the effect of prophylaxis on CMV disease, syndrome and invasive organ disease.

Time to onset of CMV disease was reported in 11 trials. In nine trials, prophylaxis significantly increased the time from transplant to the onset of CMV disease. Different methods of reporting prevented these data being combined in a meta-analysis.

The average risk of CMV infection in the placebo/no treatment arms of all trials was 49% (range 36% to 100%). Prophylaxis significantly reduced CMV infection (outcome 01.04, 17 trials, 1786 patients: RR 0.61, 95% CI 0.48 to 0.77). Considerable heterogeneity existed between studies for CMV infection (I^2 = 76.2%) with no explanation apparent, but the summary estimates for individual trials favoured prophylaxis in 15/17 trials.

Subgroup analyses for CMV disease (Table 2- *Potential sources of variability - CMV disease and all-cause mortality)*
Subgroup analyses according to antibody status, antiviral medications, organ transplanted, treatment duration, use of antilymphocyte therapy, time to outcome assessment, trial quality and other aspects of trial design did not demonstrate any differences in treatment effects. Multivariate meta-regression showed no significant difference in CMV disease after allowing for potential confounding or effect-modification by prophylactic drug used, organ transplanted or recipient serostatus in CMV positive recipients and CMV negative recipients of CMV positive donors.

CMV disease in patients stratified by antibody status
Subgroup analysis revealed that treatment efficacy in CMV disease did not vary significantly according to recipient serostatus. Medications significantly reduced the risk of CMV disease (outcome 02.01: RR 0.34, 95% CI 0.24 to 0.50) in CMV positive recipients (donor positive or negative). Medication significantly reduced the risk of CMV disease (outcome 02.02: RR 0.52, 95% CI 0.36 to 0.74) in CMV negative recipients of CMV positive organs.

Subgroup analysis showed that treatment efficacy did not vary in CMV positive recipients if they received a CMV positive organ (outcome 02.04: RR 0.18, 95% CI 0.09 to 0.36) or CMV negative organ (outcome 02.05: RR 0.32, 95% CI 0.11 to 0.95).

Insufficient data (outcome 02.04, four trials, 38 patients, 2 events) were available to determine the efficacy of prophylaxis on CMV disease in CMV negative recipients of CMV negative donors.

CMV disease in all patients stratified by antiviral medication
The treatment efficacy did not vary according to antiviral medication used on sub group analysis. When analysed separately aciclovir (outcome 03.01: RR 0.45, 95% CI 0.29 to 0.69), ganciclovir (outcome 03.02: RR 0.44, 95% CI 0.34 to 0.58) and valaciclovir (outcome 03.03: RR 0.30, 95% CI 0.19 to 0.49) significantly reduced the risk for CMV disease compared with placebo or no treatment.

CMV disease in all patients stratified by transplanted organ
The treatment efficacy on CMV disease did not vary according to organ transplanted. Prophylaxis was effective in reducing the risk of CMV disease in kidney (outcome 04.01: RR 0.42, 95% CI 0.31 to 0.57), liver (outcome 04.02: RR 0.49, 95% CI 0.29 to 0.84) and heart transplant recipients (outcome 04.03: RR 0.39, 95% CI 0.25 to 0.63).

CMV disease in ganciclovir treated patients stratified by treatment duration
In ganciclovir trials, duration of treatment was arbitrarily divided into less than six weeks and six weeks or more. There was no difference in treatment efficacy (outcome 05). Effect of duration could not be assessed for other medications, which were generally administered for three months.

CMV disease in patients stratified for the use of antilymphocyte antibody
Subgroup analysis showed no difference in treatment efficacy against CMV disease if the immunosuppressive regimen did (outcome 11.01: RR 0.43, 95% CI 0.33 to 0.55) or did not (outcome 12.01: RR 0.47, 95% CI 0.29 to 0.76) include an anti-lymphocyte antibody given during prophylaxis for induction or rejection.

All-cause mortality
The average all-cause mortality rate reported at one year or less post-transplant in the placebo/no treatment arms of all trials was 7.1% (Range 0% to 37%). Prophylaxis significantly reduced all-cause mortality (outcome 07, 17 trials, 1838 patients: RR 0.63, 95% CI 0.43 to 0.92).

CMV-related death and other causes
In seven trials which reported the number of deaths due to CMV disease, the average mortality rates in the placebo/no treatment arms due to CMV disease and to non-CMV causes were 2.3% (range 0.3% to 7.4%) and 5.7% (0% to 15.6%) respectively. Prophylaxis significantly reduced the risk of death due to CMV disease (outcome 06.01: RR 0.26, 95% CI 0.08 to 0.78) but not the risk from non-CMV causes (outcome 06.02: RR 0.77, 95% CI 0.44 to 1.17).

Subgroup analyses for all-cause mortality (Table 2- *Potential sources of variability - CMV disease and all-cause mortality)*
Subgroup analyses according to antibody status, antiviral medications, organ transplanted, treatment duration, use of antilymphocyte therapy, time to outcome assessment, trial quality and other aspects of trial design did not demonstrate any differences in all-cause mortality. Multivariate meta-regression showed no significant difference in all cause mortality after allowing for potential confounding or effect-modification by prophylactic drug used, organ transplanted or recipient serostatus in CMV positive recipients and CMV negative recipients of CMV positive donors.

All-cause mortality stratified by antibody status
No differences in all-cause mortality were seen with CMV positive recipients (outcome 08.01: RR 0.59, 95% CI 0.30 to 1.18) or CMV negative recipients of CMV positive organs (outcome 08.02: RR 1.42 95% CI 0.44 to 4.66) on subgroup analysis . Data were not available to determine the effect of antiviral medications on all-cause mortality in CMV positive recipients of CMV negative organs.

All-cause mortality stratified by transplanted organ
All-cause mortality was reduced (outcome 09: RR 0.63, 95% CI 0.43 to 0.92). However the reduction could not be demonstrated for individual organs because of the small number of events and patients for individual organs.

All-cause mortality in ganciclovir treated patients stratified by treatment duration
There was no difference in all-cause mortality (outcome 10).

All cause mortality in trials stratified according to use of antilymphocyte therapy
There was no difference in all-cause mortality whether or not antibody therapy was administered (outcome 11.02, outcome 12.02).

Additional outcomes *(Table 3- Summary of outcomes for antiviral medication versus placebo/no treatment)*
For graft loss, acute rejection, invasive fungal infection and PTLD there was no significant difference between antiviral prophylaxis and placebo or no treatment (outcome 13.01, 13.02, 13.04, 13.06). The risk of acute rejection did not differ on subgroup analysis between trials using biopsy diagnosis (outcome 14.01, five trials: RR 0.97, 95% CI 0.71 to 1.31 and those using clinical criteria (outcome 14.02, eight trials: RR 0.91, 95% CI 0.76 to 1.08). In one trial (Lowance 99-Kidney) using valaciclovir with subgroups pre-specified according to CMV serostatus, prophylaxis significantly reduced the risk of acute rejection in CMV negative recipients of CMV positive kidneys (outcome 15.02: RR 0.51, 95% CI 0.35 to 0.74) compared with CMV positive recipients (outcome 15.03: RR 0.84, 95% CI 0.63 to 1.10) (test of interaction $\chi^2 = 4.33$; P = 0.04). This difference is responsible for the heterogeneity demonstrated between valacyclovir trials for acute rejection (outcome 15.01).

Prophylaxis with aciclovir, ganciclovir or valaciclovir reduced the risk for clinical disease caused by herpes simplex and herpes zoster (outcome 13.03: RR 0.27, 95% CI 0.19 to 0.40). Combining the trials of different medications showed that bacterial (outcome 13.05: RR 0.65, 95% CI 0.44 to 0.96) and protozoal infections (outcome 13.07: RR 0.31, 95% CI 0.01 to 0.99) were significantly reduced by prophylaxis.

Sixteen trials reported data on adverse effects of medications. Except for six placebo-controlled trials, we could not determine baseline adjusted effects of medications on leucopenia, kidney function and neurological dysfunction as the numbers of patients with these abnormalities were not reported for the no treatment groups. In placebo-controlled trials, valaciclovir significantly increased the risk for hallucinations (8.5% compared with 0.97%) (outcome 16.09: RR 8.78, 95% CI 2.69 to 28.71). There was a trend towards an increase in neurological dysfunction with aciclovir but the difference was not significant (outcome 16.03). No significant differences were identified for leucopenia or reduced kidney function with any medication (outcome 16).

Sub group analyses by methodological quality for CMV disease (comparison 02) and all-cause mortality (comparison 03)
Subgroup analysis, stratifying trials by methodological quality and aspects of trial design, specified*a priori,* showed that treatment efficacy to reduce CMV disease and all-cause mortality did not vary significantly among trials.

Time of outcome assessment: There was no difference in treatment efficacy for CMV disease and all-cause mortality if outcome was assessed at 3-6 months or 9-12 months.

Trial publication date: Trials were arbitrarily divided into those published before 1997 and those published in or after 1997. There was no difference in treatment efficacy.

Trial quality: Trials were divided according to quality assessment (adequate allocation concealment or other, blinding or no blinding, intention to treat analysis carried out or not). On subgroup analysis, no differences in treatment efficacy for CMV disease or all cause mortality were detected for allocation concealment, blinding or intention-to-treat analysis.

2). Ganciclovir versus aciclovir (comparison 04)
Eight trials compared ganciclovir with aciclovir (Badley 97-Liver; Duncan 93-Lung; Flechner 98-Kidney; Martin 94-Liver; Nakazato 93-Liver; Rubin 02-all; Winston 03-Liver; Winston 95-Liver).

CMV disease and CMV infection
In head-to-head trials, ganciclovir was more effective than aciclovir in preventing CMV disease in all recipients (outcome 01.01, 7 trials; 1113 patients: RR 0.37, 95% CI 0.23 to 0.60), in CMV positive recipients (outcome 02.01: RR 0.27, 95% CI 0.13 to 0.55) and in CMV negative recipients of CMV positive organs (outcome 03.01: RR 0.64, 95% CI 0.41 to 0.99). There were insufficient data in CMV negative recipients of CMV negative donors to determine if a difference in efficacy exists (outcome 04).

On subgroup analysis, no differences in efficacy could be demonstrated between studies in which the experimental group received ganciclovir for three months (outcome 01.05, four trials: RR 0.28, 95% CI 0.09 to 0.82) and those in which the experimental group received ganciclovir followed by aciclovir (outcome 01.06, three trials: RR 0.38, 95% CI 0.22 to 0.64). On subgroup analysis no differences in efficacy could be demonstrated between different organ transplants for CMV disease (outcome 05.01, 03, 05) or for CMV infection (outcome 05.02, 04, 06).

Ganciclovir was also more effective than aciclovir in reducing CMV infection (outcome 01.04: RR 0.44; 95% CI 0.28 to 0.67) in all recipients and in CMV positive recipients (outcome 02.02: RR 0.30, 95% CI 0.16 to 0.58) but not in CMV negative recipients of CMV positive organs (outcome 03.04: RR 0.63, 95% CI 0.36 to 1.09) but there was significant heterogeneity among studies.

Death
There were no significant differences in the risk of death due to CMV disease (outcome 06-04: RR 0.33, 95% CI 0.07 to 1.58) or all cause mortality (outcome 06.02: RR 1.13, 95% CI 0.82 to 1.58).

Additional outcomes
No significant differences were reported for acute rejection (outcome 07.01), graft loss (outcome 07.02), other viral infections (outcome 07.03), fungal infections (outcome 07.04), bacterial infections (outcome 07.05), protozoal infections (outcome 07.06) or obliterative bronchiolitis in lung transplant recipients (outcome 07.07). Three trials or fewer provided outcomes for graft loss, obliterative bronchiolitis and for opportunistic infections other than other viral infections.

Leucopenia was significantly more common with ganciclovir compared with aciclovir (outcome 07.08: RR 3.28, 95% CI 1.48 to 7.25) but no significant differences were demonstrated for renal (outcome 07.09) or neurological dysfunction (outcomes 07.10).

3). Ganciclovir/aciclovir versus ganciclovir (Comparison 05)

One study (Green 97-Liver) compared ganciclovir given for 14 days followed by aciclovir to one year with ganciclovir for 14 days in 48 children, who had received liver transplants. No significant differences in efficacy were demonstrated for CMV disease (outcome 01.01), CMV infection (outcome 01.02), all-cause mortality (outcome 02) or EBV infections (outcome 03) though confidence intervals were wide so that differences could not be excluded.

4). Valganciclovir versus ganciclovir (Comparison 06)
One trial (Paya 04-All) compared valganciclovir with ganciclovir in CMV negative recipients of CMV positive organs and included patients receiving kidney, liver, heart and combined kidney-pancreas transplants.

CMV disease and CMV infection
Valganciclovir and ganciclovir were not significantly different in the prevention of CMV disease at six months (outcome 01.01) or one year post-transplant (outcome 01.02). Similarly there were no significant differences at six months and one year in the prevention of CMV syndrome (outcomes 01.03, 01.04) and CMV invasive organ disease (outcomes 01.05, 01.06). Subgroup analysis showed that, at six months, valganciclovir was significantly more effective than ganciclovir in kidney transplant recipients (outcome 01.08: RR 0.27, 95% CI 0.01 to 0.75) compared with liver, heart or kidney-pancreas transplant recipients (outcome 01.07, 01.09, 01.10) (test of interaction $\chi^2 = 6.34$; P = 0.01).

There were no significant differences at six months (outcome 01.11) and one year (outcome 01.12) in the prevention of CMV infection.

Death
No significant differences were detected between medications in death due to CMV disease (outcome 02.01) or all-cause mortality (outcome 02.02)

Additional outcomes
No significant differences were detected in acute rejection, graft loss and opportunistic infections (outcomes 03.01, 03.02, 03.03). Neutrophil counts below 1000/mm^3 occurred in 13% of patients treated with valganciclovir compared with 8% treated with ganciclovir but the difference was not significant (outcome 03.07). No differences were detected in cessation of medications due to neutropenia, anaemia, thrombocytopenia or tremor (outcomes 03.04, 03.5, 03.06, 03.07, 03.08).

5). Valaciclovir versus ganciclovir (comparison 07)
One trial (Reischig 04 - Kidney) compared valaciclovir with ganciclovir in kidney transplant recipients.

CMV disease and CMV infection
The risk of CMV disease (outcome 01.01) and CMV infection (outcome 01,02) did not differ significantly with valaciclovir compared with ganciclovir prophylaxis.

All-cause mortality
No significant differences were detected in all-cause mortality (outcome 02).

Additional outcomes
Acute rejection occurred significantly less often with valaciclovir compared with ganciclovir (outcome 03.01: RR 0.34, 95% CI 0.12 to 0.96). No difference in the risk of graft loss was detected (outcome 03.03).

No differences were detected in the risk of leucopenia, thrombocytopenia, anaemia or neurological dysfunction (outcomes 03.03, 03.04, 03.05, 03.06).

6). Prophylaxis with different regimens of ganciclovir (Comparison 08)
One trial (Hertz 98-heart/lung) compared daily with thrice weekly intravenous ganciclovir in heart-lung transplant recipients. One trial (Winston 04-Liver) compared oral with intravenous ganciclovir in CMV negative recipients of CMV positive liver transplants.

Daily versus thrice weekly ganciclovir
No significant differences were detected in CMV disease, CMV syndrome, CMV invasive tissue disease or CMV infection (outcomes 01.01, 01.02, 01.03, 01.04). In addition no differences in all-cause mortality and death due to CMV disease (outcomes 01.05, 01.06) or in bacteraemia, bronchiolitis obliterans or leucopenia (outcomes 01.07, 01.08, 01.09) were detected.

Oral versus intravenous ganciclovir
No significant differences were detected in CMV disease, CMV syndrome or CMV invasive tissue disease (outcomes 02.01, 02.02, 02.03). In addition no differences in all-cause mortality (outcome 02.04) or in leucopenia and the need to cease medications due to leucopenia (outcomes 02.05, 02.06) were detected.

DISCUSSION

This study shows that the antiviral medications, ganciclovir, valaciclovir and aciclovir, improve outcomes for solid organ transplant recipients far beyond the primary indication for use. In addition to reducing the risk of CMV disease by 60%, these medications reduce all-cause mortality by 40% predominantly due to reduced mortality from CMV disease, clinical disease caused by *H. simplex* and *H. zoster* (70%), bacterial infections (35%), and protozoal infections (70%). For CMV disease and mortality, the relative benefits of aciclovir, ganciclovir and valaciclovir appear consistent across recipients of heart, kidney and liver transplants. These benefits occur in both CMV positive recipients and CMV negative recipients of CMV positive organs, are irrespective of whether immunosuppression includes antilymphocyte antibody therapy and are not dependent on the time of outcome assessment.

It can be questioned whether these results are relevant to current clinical practice in which valganciclovir is the most commonly prescribed antiviral medication for CMV prophylaxis (Baliga 2004). This systematic review of 19 trials (1981 patients) published between 1989 and 2002 has demonstrated a consistent reduction in CMV disease and all-cause mortality with aciclovir, ganciclovir or valaciclovir compared with placebo or no treatment. Therefore it can no longer be considered ethical to examine the efficacy of valganciclovir or future antiviral medications in placebo-controlled trials. In the only published trial (Paya 04-All) comparing valganciclovir (the prodrug of ganciclovir) and ganciclovir, no significant differences in the risk for CMV disease, all-cause mortality and other outcomes have been demonstrated indicating that outcomes demonstrated in this systematic review in placebo/no treatment trials can be extrapolated to valganciclovir.

There was no clear reduction in graft loss or acute rejection, although a small but clinically important benefit has not been excluded. The summary RR for both outcomes favour antiviral medication but the 95% CIs are relatively wide and are consistent with there being no effect. The exception was in a predefined sub-group in a single trial (Lowance 99-Kidney) in which CMV prophylaxis reduced the risk for biopsy-proven acute rejection in CMV negative recipients of CMV positive kidney transplants by 50%.

Valacyclovir significantly increased the risk for hallucinations, based upon data from a single large trial (Lowance 99-Kidney). There was no significant increase in adverse effects with aciclovir or ganciclovir though confidence intervals were wide. Very few trials adequately reported harms so that significant differences in adverse effects between medication and placebo cannot be excluded. Other differences in side-effect profiles between medications are possible but have not been demonstrated.

Our major findings, that CMV antiviral prophylaxis prevents CMV disease and all-cause mortality, irrespective of organ transplanted and CMV serostatus, are strengthened by two features of the data; the consistency of these findings across all studies and the finding that almost all eligible studies reported both major outcomes of interest (lack of outcome reporting bias). Nineteen eligible studies were identified and the summary estimate favours antiviral medication for the outcome 'prevention of CMV disease' in 18 trials. Similarly, 17 trials contributed data to the all-cause mortality outcome. With fewer events, the play of chance would be expected to be greater, but only two trials (Macdonald 95-Heart; Merigan 92-Heart) had point estimates suggesting increased mortality from CMV prophylaxis. Unlike the outcome of CMV disease, no individual trial demonstrated a significant reduction in all-cause mortality with antiviral medication. This was evident only from the meta-analytic estimate. The overall I^2 was 12.6% for CMV disease and 0% for all-cause mortality demonstrating very low heterogeneity beyond chance, despite the clear differences in patient groups (*Table of included studies*). Supporting this contention, as shown in Table 2 (*Potential sources of variability - CMV and all-cause mortality)*, no pre-defined potential source of variability for the effects of antiviral medication was significant, including standard quality items for trial conduct and reporting such as allocation concealment, blinding and intention-to-treat. We cannot exclude a difference in the magnitude of the effect of antiviral medication in solid organ transplant recipients. However any difference is likely to be clinically unimportant since data from 19 trials and about 2000 patients was insufficient to demonstrate any difference. In addition the remarkable consistency in results across all trials suggests any undetected difference would be in magnitude and not direction of effect.

The data is relatively sparse in three areas, and further research is still needed. For the outcome of all-cause mortality in heart transplant recipients, there are few relevant trials (2), patients (205) and events (4) making the effects of antiviral medications on heart transplant recipients very uncertain. Both trials had higher death rates in the active arms but confidence intervals were very wide, results are consistent with other patient groups (liver and kidney), and the likely pathway for benefit - reduction in CMV disease - is evident in this patient group.

Second, there are very scant data in seronegative donor to seronegative recipient group, even though this group is frequently given antiviral agents to prevent CMV disease (Baliga 2004). These patients are almost exclusively not enrolled in trials, because of low event rates, and because of the absence of biological mechanism by which CMV disease could be prevented in patients not exposed to CMV disease.

Third, our conclusions on the other benefits of antiviral medications and the adverse effects of these drugs (Table 3 - *Summary of outcomes for antiviral medication versus placebo/no treatment*) must be considered more cautiously because of the imprecision of summary estimates and because many eligible trials did not report these outcomes, and so these results may be biased. The direction of the bias cannot be determined without obtaining additional data from the authors regarding these outcomes.

Having demonstrated that antiviral medications as a drug class reduce all-cause mortality and CMV disease, we then sought to determine which antiviral regimen was the most beneficial. Indirect comparisons demonstrated no difference between antiviral medications administered. In head-to-head trials ganciclovir was significantly more effective than aciclovir in preventing CMV disease, demonstrating the importance of assessing the comparative effects of medications in direct comparison trials. This difference may be explainable by differences in duration of therapy in the indirect trials. Aciclovir was administered for 84 days or more while ganciclovir was given for a shorter duration (9 to 42 days) in 7/11 ganciclovir trials, and so agent and duration was evaluated rather than agent alone, as in direct comparison trials.

One large trial (Paya 04-All) demonstrated no significant difference in efficacy between ganciclovir and its prodrug, valganciclovir. Although one small trial demonstrated no difference in efficacy to prevent CMV disease between ganciclovir and valaciclovir (Reischig 04 - Kidney), the wide confidence intervals of the summary estimate (RR 0.51, 95% CI 0.05 to 5.42) indicate that a significant difference in efficacy cannot be excluded. Based upon existing trial data, aciclovir is inferior to ganciclovir, and no clear superiority has been demonstrated between ganciclovir and valganciclovir.

The results of this review confirm and expand the findings of three previous systematic reviews (Couchoud 1998b; Fiddian 2002; Gourishankar 2001), which included 12, 10 and 9 trials respectively comparing antiviral medications with placebo or no treatment for prevention of CMV disease. All found that prophylaxis reduced the risk for CMV disease in solid organ transplant recipients. One review (Couchoud 1998b) found no effect on mortality (10 trials: RR 0.69, 95% CI 0.41 to 1.18) and a second (Fiddian 2002), which included two studies using immunoglobulin and antiviral agents, found that prophylaxis with aciclovir or valacyclovir significantly reduced all-cause mortality (1321 patients: OR 0.60, 95% CI 0.40 to 0.90). Our systematic review differs from previous studies because of the larger number of trials, focussing on antiviral medications only and including comparisons of different antiviral medications so that conclusions on the comparative effects of agents can be made. In addition our study included a detailed exploration of potential heterogeneity. The finding of a reduction in all-cause mortality is largely explainable by a reduced mortality due to CMV disease though a reduction in mortality due to other causes cannot be totally excluded. The latter is biologically plausible since CMV disease leads to an increase in other opportunistic infections in heart and liver transplant recipients (George 1997; Valentine 1999) suggesting a mechanism whereby the prevention of CMV disease

may prevent other infective complications which contribute to overall mortality.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review has shown that prophylaxis of CMV positive recipients and CMV negative recipients of CMV positive organs with antiviral medications given for three months post solid organ transplantation reduces the risk of CMV disease and all-cause mortality and may well reduce the risk of other opportunistic infections. What are the implications of this study to clinical practice? Current treatment guidelines (Jassal 1998; Van der Bij 2001) recommend CMV prophylaxis for all recipients of solid organ transplants, who receive immunosuppression with antilymphocyte antibody products and for CMV negative recipients of CMV positive organs. In liver and heart transplant recipients, prophylaxis is also recommended for all CMV positive recipients of solid organ transplants because of the higher risk for CMV disease. Prophylaxis is not generally recommended for CMV positive kidney transplant recipients or for donor negative/recipient negative recipients (Jassal 1998) based on the low incidence of CMV disease in these groups. Our data would suggest that the recommendations for use are too narrow because the benefits for patient survival and the constant relative benefits for CMV disease, irrespective of CMV serostatus, have not been recognised previously.

The absolute effects of antiviral medications on the prevention of CMV disease and all-cause mortality are shown quantitatively in groups of patients at different baseline risk for these outcomes (Table 4 - *Effects of antiviral medication on CMV disease and all-cause mortality*). The primary determinants for CMV disease are organ transplanted and serostatus whereas organ transplanted is the most important determinant for all-cause mortality. This table shows that benefit exceeds harm for all but the lowest risk groups assuming equal importance of the outcomes. However, given that the clinical importance of all-cause mortality and CMV disease are significantly greater than the adverse effects of medications, most patients and clinicians, when provided with this information, are likely to use CMV prophylaxis with antiviral medications across all risk categories, except in the seronegative donor and recipient group for which there are few data.

Implications for research

There are no data from randomised controlled trials on the efficacy of prophylaxis compared with placebo in lung transplants and few data in heart transplants. However such trials are no longer ethical based on the demonstration of efficacy in other organ transplants. Future trials may be required in the seronegative donor-recipient group depending on the prevalence of CMV disease in this group with newer and more potent immunosuppressive regimens. Further trials are required to determine optimum duration and dosage of medications. Currently valganciclovir is most commonly used for prophylaxis. It remains possible that smaller doses than currently recommended may be effective for prophylaxis as demonstrated for intravenous ganciclovir (Hertz 98-heart/lung). In addition trials are required to evaluate the comparative effects, including harms, of antiviral medications in clinical use at present or in the future. More information is required on the efficacy of prophylaxis with different regimens of immunosuppressive regimens used for prevention and treatment of rejection. Overall prophylaxis did not reduce the risk for acute rejection or graft loss. Further information is required to determine whether prophylaxis can reduce the risk for rejection in particular groups of patients, whether it affects the number or severity of rejection episodes and whether it reduces graft loss at time periods beyond one year.

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REFERENCES

References to studies included in this review

Ahsan 97-Kidney *{published data only}*

Ahsan N, Holman MJ, Yang HC. Efficacy of oral ganciclovir in prevention of cytomegalovirus infection in post-kidney transplant patients. *Clinical Transplantation* 1997;**11**(6):633-9. [MEDLINE: 9408699]

Badley 97-Liver *{published data only}*

Badley AD, Seaberg EC, Porayko MK, Wiesner RH, Keating MR, Wilhelm MP, et al. Prophylaxis of cytomegalovirus infection in liver transplantation: A randomized trial comparing a combination of ganciclovir and acyclovir to acyclovir. *Transplantation* 1997;**64**(1):66-73. [MEDLINE: 9233703]

Balfour 89 - Kidney *{published data only}*

Balfour HH, Jr, Chace BA, Stapleton JT, Simmons RL, Fryd DS. A randomized, placebo-controlled trial of oral acyclovir for the prevention of cytomegalovirus disease in recipients of renal allografts. *New England Journal of Medicine* 1989;**320**(21):1381-7. [MEDLINE: 2541335]

Barkholt 99 - Liver *{published data only}*

Barkholt L, Lewensohn-Fuchs I, Ericzon BG, Tyden G, Andersson J. High-dose acyclovir prophylaxis reduces cytomegalovirus disease in liver transplant patients. *Transplant Infectious Disease* 1999;**1**(2):89-97. [MEDLINE: 11428976]

Brennan 97-Kidney *{published data only}*

Brennan DC, Garlock KA, Singer GG, Schnitzler MA, Lippmann BJ, Buller RS, et al. Prophylactic oral ganciclovir compared with deferred therapy for control of cytomegalovirus in renal transplant recipients. *Transplantation* 1997;**64**(12):1843-6. [MEDLINE: 9422429]

Cohen 93-Liver *{published data only}*

Cohen AT, O'Grady JG, Sutherland S, Sallie R, Tan K-C, Williams R. Controlled trial of prophylactic versus therapeutic use of ganciclovir after liver transplantation in adults. *Journal of Medical Virology* 1993;**40**(1):5-9. [MEDLINE: 8390559]

Conti 95-Kidney *{published data only}*

Conti DJ, Freed BM, Singh TP, Gallichio M, Gruber SA, Lempert N, et al. Preemptive ganciclovir therapy in cytomegalovirus-seropositive renal transplants recipients. *Archives of Surgery* 1995;**130**(11):1217-22. [MEDLINE: 7487465]

Duncan 93-Lung *{published data only}*

Duncan SR, Grgurich WF, Iacono AT, Burckart GJ, Yousem SA, Paradis IL, et al. A comparison of ganciclovir and acyclovir to prevent cytomegalovirus after lung transplantation. *American Journal of Respiratory & Critical Care Medicine* 1994;**150**(1):146-52. [MEDLINE: 8025741]

Egan 02-Heart *{published data only}*

Egan JJ, Carroll KB, Yonan N, Woodcock A, Crisp A. Valacyclovir prevention of cytomegalovirus reactivation after heart transplantation: a randomized trial. *Journal of Heart & Lung Transplantation* 2002;**21**(4):460-6. [MEDLINE: 11927223]

Flechner 98-Kidney *{published data only}*

Flechner SM, Avery RK, Fisher R, Mastroianni BA, Papajcik DA, O'Malley KJ, et al. A randomized prospective controlled trial of oral acyclovir versus oral, ganciclovir for cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Transplantation* 1998;**66**(12):1682-8. [MEDLINE: 9884259]

Gane 97-Liver *{published data only}*

Gane E, Saliba F, Valdecasas GJ, O'Grady J, Pescovitz MD, Lyman S, et al. Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. The Oral Ganciclovir International Transplantation Study Group. *Lancet* 1997;**350**(9093):1729-33. [MEDLINE: 9413463]

Saliba F, Bismuth H, Gane E, Valdecasas G, O'grady J, Behrend M, Pescovitz M, Pruett T, Hockerstedt K, Broelsch C, Mino-Fugarolas G, Houssin D, Davis C, Henry M, Erhard J, Kam I, King P, Lyman S, Robinson CA, Le Ganciclovir Internationale Transplantation Study Group. [A randomized double blind versus placebo multicenter study of efficacy and tolerance of oral ganciclovir in the prevention of cytomegalovirus disease in hepatic transplanted patients]. *Gastroenterologie Clinique et Biologique* 1997;**21**(2 bis):A157. [CN-00339304]

Gavalda 97-Liver *{published data only}*

Gavalda J, De Otero J, Murio E, Vargas V, Rossello J, Calico I, et al. Two grams daily of oral acyclovir reduces the incidence of cytomegalovirus disease in CMV-seropositive liver transplant recipients. *Transplant International* 1997;**10**(6):462-5. [MEDLINE: 9428121]

Green 97-Liver *{published data only}*

Green M, Kaufmann M, Wilson J, Reyes J. Comparison of intravenous ganciclovir followed by oral acyclovir with intravenous ganciclovir alone for prevention of cytomegalovirus and Epstein- Barr virus disease after liver transplantation in children. *Clinical Infectious Diseases* 1997;**25**(6):1344-9. [MEDLINE: 9431375]

Hertz 98-heart/lung *{published data only}*

Hertz MI, Jordan C, Savik SK, Fox JMK, Park S, Bolman II RM, et al. Randomized trial of daily versus three-times-weekly prophylactic ganciclovir after lung and heart-lung transplantation. *Journal of Heart & Lung Transplantation* 1998;**17**(9):913-20. [MEDLINE: 9773865]

Hibberd 95-Kidney *{published data only}*

Hibberd PL, Tolkoff-Rubin NE, Conti D, Stuart F, Thistlethwaite JR, Neylan JF, et al. Preemptive ganciclovir therapy to prevent cytomegalovirus disease, in cytomegalovirus antibody-positive renal transplant recipients. A randomized controlled trial. *Annals of Internal Medicine* 1995;**123**(1):18-26. [MEDLINE: 7762909]

Kletzmayr 96-Kidney *{published data only}*

Kletzmayr J, Kotzmann H, Popow-Kraupp T, Kovarik J, Klauser R. Impact of high-dose oral acyclovir prophylaxis on cytomegalovirus (CMV) disease in CMV high-risk renal transplant

recipients. *Journal of the American Society of Nephrology* 1996;**7**(2):325-30. [MEDLINE: 8785404]

Leray 95-Kidney *{published data only}*

Leray H, Mourad G, Chong G, Segondy M, Mion C. Prophylactic treatment of cytomegalovirus primary infection with ganciclovir in renal transplant recipients. *Transplantation Proceedings* 1995;**27**(4):2448. [MEDLINE: 7652875]

Lowance 99-Kidney *{published data only}*

Lowance D, Neumayer HH, Legendre CM, Squifflet JP, Kovarik J, Brennan PJ, et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group. *New England Journal of Medicine* 1998;**340**(19):1462-70. [MEDLINE: 10320384]

Macdonald 95-Heart *{published data only}*

Macdonald PS, Keogh AM, Marshman D, Richens D, Harvison A, Kaan AM, et al. A double-blind placebo-controlled trial of low-dose ganciclovir to prevent cytomegalovirus disease after heart transplantation. *Journal of Heart & Lung Transplantation* 1995;**14**(1):32-8. [MEDLINE: 7727473]

Martin 94-Liver *{published data only}*

Martin M, Manez R, Linden P, Estores D, Torre-Cisneros J, Kusne S, et al. A prospective randomized trial comparing sequential ganciclovir-high dose acyclovir to high dose acyclovir for prevention of cytomegalovirus disease in adult liver transplant recipients. *Transplantation* 1994;**58**(7):779-85. [MEDLINE: 7940710]

Merigan 92-Heart *{published data only}*

Merigan TC, Renlund DG, Keay S, Bristow MR, Starnes V, O'Connell JB, et al. A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. *New England Journal of Medicine* 1992;**326**(18):1182-6. [MEDLINE: 1313549]

Nakazato 93-Liver *{published data only}*

Nakazato PZ, Burns W, Moore P, Garcia-Kennedy R, Cox K, Esquivel C. Viral prophylaxis in hepatic transplantation: Preliminary report of a randomized trial of acyclovir and gancyclovir. *Transplantation Proceedings* 1993;**25**(2):1935-7. [MEDLINE: 7682357]

Paya 04-All *{published data only}*

Paya C, Humar A, Dominguez E, Washburn K, Blumberg E, Alexander B, et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *American Journal of Transplantation* 2004;**4**(4):611-20. [MEDLINE: 15023154]

Pouteil-Noble 96 - K *{published data only}*

Pouteil-Noble C, Megas F, Chapuis F, Bosshard S, Colin C, Hadj-Aissa A, et al. Cytomegalovirus prophylaxis by ganciclovir followed by high-dose acyclovir in renal transplantation: A randomized, controlled trial. *Transplantation Proceedings* 1996;**28**(5):2811. [MEDLINE: 8908072]

Reischig 04 - Kidney *{published and unpublished data}*

Reischig T, Jindra P, Mares J, Opatrny K, Jr, Treska V, Cechura M, et al. Valacyclovir for cytomegalovirus prophylaxis reduces the risk of acute renal allograft rejection: a randomized comparison of oral ganciclovir and valacyclovir [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):493.

* Reischig T, Opatrny K, Jr, Bouda M, Treska V, Jindra P, Svecova MT, et al. A randomized prospective controlled trial of oral ganciclovir versus oral valacyclovir for prophylaxis of cytomegalovirus disease after renal transplantation. *Transplant International* 2992;**15**(12):615-22. [MEDLINE: 12478408]

Rondeau 93-Kidney *{published data only}*

Rondeau E, Bourgeon B, Peraldi MN, Lang P, Buisson C, Schulte KM, et al. Effect of prophylactic ganciclovir on cytomegalovirus infection in renal transplant recipients. *Nephrology Dialysis Transplantation* 1993;**8**(9):858-62. [MEDLINE: 8255520]

Rostaing 94 - Kidney *{published data only}*

Rostaing L, Crespin A, Icart J, Lloveras JJ, Durand D, Martinet O, et al. Cytomegalovirus (CMV) prophylaxis by acyclovir in pre-transplant CMV-positive renal transplant recipients. *Transplant International* 1994;**7 Suppl 1**:331-5. [MEDLINE: 11271244]

Rubin 02-all *{published data only}*

Rubin RH, Kemmerly SA, Conti D, Doran M, Murray BM, Neylan JF, et al. Prevention of primary cytomegalovirus disease in organ transplant recipients with oral ganciclovir or oral acyclovir prophylaxis. *Transplant Infectious Disease* 2000;**2**(3):112-7. [MEDLINE: 11429021]

Saliba 93-Liver *{published data only}*

Saliba F, Eyraud D, Samuel D, David MF, Arulnaden JL, Dussaix E, et al. Randomized controlled trial of acyclovir for the prevention of cytomegalovirus infection and disease in liver transplant recipients. *Transplantation Proceedings* 1993;**25**(1 Pt 2):1444-5. [MEDLINE: 8382876]

Winston 03-Liver *{published data only}*

Winston DJ, Busuttil RW. Randomized controlled trial of oral ganciclovir versus oral acyclovir after induction with intravenous ganciclovir for long-term prophylaxis of cytomegalovirus disease in cytomegalovirus-seropositive liver transplant recipients. *Transplantation* 2003;**75**(2):229-33. [MEDLINE: 12548129]

Winston 04-Liver *{published data only}*

Winston DJ, Busuttil RW. Randomized controlled trial of sequential intravenous and oral ganciclovir versus prolonged intravenous ganciclovir for long-term prophylaxis of cytomegalovirus disease in high-risk cytomegalovirus-seronegative liver transplant recipients with cytomegalovirus-seropositive donors. *Transplantation* 2004;**77**(2):305-8. [MEDLINE: 14742998]

Winston 95-Liver *{published data only}*

Winston DJ, Wirin D, Shaked A, Busuttil RW. Randomised comparison of ganciclovir and high-dose acyclovir for long-

term cytomegalovirus prophylaxis in liver-transplant recipients. *Lancet* 1995;**346**(8967):69-74. [MEDLINE: 7603215]

References to studies excluded from this review

Ahsan 1998 *{published data only}*

Ahsan N, Holman MJ, Sonderbye L, Langhoff E, Yang HC. Oral ganciclovir in the prevention of cytomegalovirus infection in postkidney transplant 'CMV at risk' recipients: A controlled, comparative study of two regimens (750 mg Bid and 500 mg Bid). *Transplantation Proceedings* 1998;**30**(4):1383-5. [MEDLINE: 9636560]

Arbo 2000 *{published data only}*

Arbo MD, Snydman DR, Wong JB, Goldberg HS, Schmid CH, Pauker SG. Cytomegalovirus immune globulin after liver transplantation: a cost-effectiveness analysis. *Clinical Transplantation* 2000;**14**(1):19-27. [MEDLINE: 10693631]

Brennan 1997 *{published data only}*

Brennan DC, Garlock KA, Lippmann BA, Buller RS, Gaudreault-Keener M, Lowell JA, et al. Control of cytomegalovirus-associated morbidity in renal transplant patients using intensive monitoring and either preemptive or deferred therapy. *Journal of the American Society of Nephrology* 1997;**8**(1):118-25. [MEDLINE: 9013456]

Brennan 2001 *{published data only}*

Brennan DC. Cytomegalovirus in renal transplantation. *Journal of the American Society of Nephrology* 2001;**12**(4):848-55. [MEDLINE: 11274248]

Couchoud 1998a *{published data only}*

Couchoud C, Cucherat M, Haugh M, Pouteil-Noble C. Cytomegalovirus prophylaxis with antiviral agents in solid organ transplantation: a meta-analysis. *Transplantation* 1998;**65**(5):641-647. [MEDLINE: 696]

Dickinson 1996 *{published data only}*

Dickinson BI, Gora-Harper ML, McCraney SA, Gosland M. Studies evaluating high-dose acyclovir, intravenous immune globulin, and cytomegalovirus hyperimmunoglobulin for prophylaxis against cytomegalovirus in kidney transplant recipients. *Annals of Pharmacotherapy* 1996;**30**(12):1452-64. [MEDLINE: 8968459]

Falagas 1997 *{published data only}*

Falagas ME, Snydman DR, Ruthazer R, Griffith J, Werner BG, Freeman R, et al. Cytomegalovirus immune globulin (CMVIG) prophylaxis is associated with increased survival after orthotopic liver transplantation. The Boston Center for Liver Transplantation CMVIG Study Group. *Clinical Transplantation* 1997;**11**(5 Pt 1):432-7. [MEDLINE: 9361936]

Fehir 1989 *{published data only}*

Fehir KM, Decker WA, Samo T, Young JB, Lederer E, Lawrence EC. Immune globulin (GAMMAGARD) prophylaxis of CMV infections in patients undergoing organ transplantation and allogeneic bone marrow transplantation. *Transplantation Proceedings* 1989;**21**(1 Pt 3):3107-9. [MEDLINE: 2539691]

Fishman 2000 *{published data only}*

Fishman JA, Doran MT, Volpicelli SA, Cosimi AB, Flood JG, Rubin RH. Dosing of intravenous ganciclovir for the prophylaxis and treatment of cytomegalovirus infection in solid organ transplant recipients. *Transplantation* 2000;**69**(3):389-94. [MEDLINE: 10706048]

Gerna 2003 *{published data only}*

Gerna G, Baldanti F, Lilleri D, Parea M, Torsellini M, Castiglioni B, et al. Human cytomegalovirus pp67 mRNAemia versus pp65 antigenemia for guiding preemptive therapy in heart and lung transplant recipients: a prospective, randomized, controlled, open-label trial. *Transplantation* 2003;**75**(7):1012-9. [MEDLINE: 12698090]

Glowacki 1994 *{published data only}*

Glowacki LS, Smaill FM. Use of immune globulin to prevent symptomatic cytomegalovirus disease in transplant recipients--a meta-analysis. [see comment]. *Clinical Transplantation* 1994;**8**(1):10-8. [MEDLINE: 8136560]

Griffiths 1997 *{published data only}*

Griffiths PD. Prophylaxis against CMV infection in transplant patients. *Journal of Antimicrobial Chemotherapy* 1997;**39**(3):299-301. [MEDLINE: 9096177]

Jung 2001 *{published data only}*

Jung C, Engelmann E, Borner K, Offermann G. Preemptive oral ganciclovir therapy versus prophylaxis to prevent symptomatic cytomegalovirus infection after kidney transplantation. *Transplantation Proceedings* 2001;**33**(8):3621-3. [MEDLINE: 11750538]

Jurim 1996 *{published data only}*

Jurim O, Martin P, Winston DJ, Shackleton C, Holt C, Feller J, et al. Failure of ganciclovir prophylaxis to prevent allograft reinfection following orthotopic liver transplantation for chronic hepatitis B infection. *Liver Transplantation & Surgery* 1996;**2**(5):370-4. [MEDLINE: 9346678]

Kim 2000 *{published data only}*

Kim WR, Badley AD, Wiesner RH, Porayko MK, Seaberg EC, Keating MR, et al. The economic impact of cytomegalovirus infection after liver transplantation. *Transplantation* 2000;**69**(3):357-61. [MEDLINE: 10706042]

King 1999 *{published data only}*

King SM. Immune globulin versus antivirals versus combination for prevention of cytomegalovirus disease in transplant recipients. *Antiviral Research* 1999;**40**(3):115-37. [MEDLINE: 10027647]

Kletzmayr 2000 *{published data only}*

Kletzmayr J, Kreuzwieser E, Watkins-Riedel T, Berlakovich G, Kovarik J, Klauser R. Long-term oral ganciclovir prophylaxis for prevention of cytomegalovirus infection and disease in cytomegalovirus high-risk renal transplant recipients. *Transplantation* 2000;**70**(8):1174-80. [MEDLINE: 11063336]

Koetz 2001 *{published data only}*

Koetz AC, Delbruch R, Furtwangler A, Hufert FT, Neumann-Haefelin D, Kirste G, et al. Cytomegalovirus pp65 antigen-guided preemptive therapy with ganciclovir in solid organ transplant recipients: a prospective double-blind, placebo-controlled study. *Transplantation* 2001;**72**(7):1325-7. [MEDLINE: 11602864]

Kuypers 1999 *{published data only}*

Kuypers DR, Vanrenterghem YF. Prophylaxis of cytomegalovirus infection in renal transplantation: new data for an old problem. *Nephrology Dialysis Transplantation* 1999;**14**(10):2304-8. [MEDLINE: 10528649]

Laske 1991 *{published data only}*

Laske A, Gallino A, Mohacsi P, Bauer EP, Carrel T, Von Segesser LK, et al. Prophylactic treatment with ganciclovir for cytomegalovirus infection in heart transplantation. *Transplantation Proceedings* 1991;**23**(1 Pt 2):1170-3. [MEDLINE: 1846456]

Laske 1992 *{published data only}*

Laske A, Carrel T, Niederhauser U, Bauer E, Pasic M, Von Segesser LK, et al. The prevention of cytomegalus infection after heart transplantation. *Helvetica Chirurgica Acta* 1992;**58**(4):527-32. [EMBASE: 1992114614]

Lumbreras 1993 *{published data only}*

Lumbreras C, Otero JR, Herrero JA, Gomez R, Lizasoain M, Aguado JM, et al. Ganciclovir prophylaxis decreases frequency and severity of cytomegalovirus disease in seropositive liver transplant recipients treated with OKT3 monoclonal antibodies. *Antimicrobial Agents & Chemotherapy* 1993;**37**(11):2490-2. [MEDLINE: 8285641]

Martin 1993 *{published data only}*

Martin M. Antiviral prophylaxis for CMV infection in liver transplantation. *Transplantation Proceedings* 1993;**25**(5 Suppl 4):10-4. [MEDLINE: 8212301]

Martin 1994 *{published data only}*

Martin M. Combination antiviral strategies in managing cytomegalovirus infection. *Transplantation Proceedings* 1994;**26**(5 Suppl 1):28-30. [MEDLINE: 7940973]

Martin 1995 *{published data only}*

Martin M. Prophylactic cytomegalovirus management strategies. *Transplantation Proceedings* 1995;**27**(5 Suppl 1):23-7. [MEDLINE: 7482812]

McGavin 2001 *{published data only}*

McGavin JK, Goa KL. Ganciclovir: an update of its use in the prevention of cytomegalovirus infection and disease in transplant recipients. *Drugs* 2001;**61**(8):1153-83. [MEDLINE: 11465876]

Moreno 1999 *{published data only}*

Moreno J, Montero JL, Gavilan F, Costan G, Herrero C, Cardenas M, et al. Open clinical trial with oral acyclovir for the prophylaxis of disease by Cytomegalovirus in low risk liver transplant recipients. *Enfermedades Infecciosas y Microbiologia Clinica* 1999;**17**(8):382-5. [MEDLINE: 10563084]

Mullen 1998 *{published data only}*

Mullen GM, Silver MA, Malinowska K, Lawless CE, Lichtenberg RC, Barath PC, et al. Effective oral ganciclovir prophylaxis against cytomegalovirus disease in heart transplant recipients. *Transplantation Proceedings* 1998;**30**(8):4110-2. [MEDLINE: 9865316]

Paya 2002 *{published data only}*

Paya CV, Wilson JA, Espy MJ, Sia IG, DeBernardi MJ, Smith TF, et al. Preemptive use of oral ganciclovir to prevent cytomegalovirus infection in liver transplant patients: a randomized, placebo-controlled trial. *Journal of Infectious Diseases* 2002;**185**(7):854-60. [MEDLINE: 11920308]

Queiroga 2003 *{published data only}*

Quieroga M, Castro MC, Araujo LM, Alves CF, Kakehashi E, Panutti C, et al. A prospective, randomized controlled trial comparing oral ganciclovir with weekly monitored CMV-antigenemia in renal transplant patients with a high-risk for CMV infection [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):511.

Rayes 2001 *{published data only}*

Rayes N, Seehofer D, Schmidt CA, Oettle H, Muller AR, Steinmuller T, et al. Prospective randomized trial to assess the value of preemptive oral therapy for CMV infection following liver transplantation. *Transplantation* 2001;**72**(5):881-5. [MEDLINE: 11571454]

Sagedal 2003 *{published data only}*

Sagedal S, Nordal KP, Hartmann A, Midvedt K, Foss A, Asberg A, et al. Pre-emptive therapy of CMVpp65 antigen positive renal transplant recipients with oral ganciclovir: a randomized, comparative study. *Nephrology Dialysis Transplantation* 2003;**18**(9):1899-908. [MEDLINE: 12937241]

Schafers 1988 *{published data only}*

Schafers H-J, Wahlers T, Jurmann M, Fieguth H-G, Milbradt H, Flik J, et al. Hyperimmuneglobulin for cytomegalovirus prophylaxis following heart transplantation. *Journal of Hospital Infection* 1988;**Vol 12**(Suppl D):61-5. [MEDLINE: 2902131]

Schnitzler 2000 *{published data only}*

Schnitzler MA, Metheney TG, Rueda JF, Woodward RS, Lowell JA, Singer GG, et al. A 3-year follow-up of pre-emptive vs deferred treatment of cytomegalovirus disease in renal transplantation. *Clinical Drug Investigation* 2000;**19**(5):367-74. [MEDLINE: 127; EMBASE: 2000190076]

Singh 1994 *{published data only}*

Sing N, Yu VL, Mieles L, Wagener MM, Miner RC, Gayowsky T. High-dose acyclovir compared with short-course preemptive ganciclovir therapy to prevent cytomegalovirus disease in liver transplant recipients. *Annals of Internal Medicine* 1994;**120**(5):375-81. [MEDLINE: 8304654]

Singh 1995 *{published data only}*

Singh TP, Gruber SA, Lempert N, Freed B, Conti DJ. Efficacy of cytomegalovirus prophylaxis in renal retransplantation. *Transplantation Proceedings* 1995;**27**(1):964-5. [MEDLINE: 7879247]

Singh 2000 *{published data only}*

Sing N, Paterson DL, Gayowsky T, Wagener MM, Marino IR. Cytomegalovirus antigenemia directed pre-emptive prophylaxis with oral versus iv ganciclovir for the prevention of cytomegalovirus disease in liver transplant recipients. *Transplantation* 2000;**70**(5):717-22. [MEDLINE: 11003347]

Snydman 1991a *{published data only}*

Snydman DR. Cytomegalovirus infections in the immunocompromised transplant patient. Prevention of cytomegalovirus disease with intravenous immune globulin. *Transplantation Proceedings* 1991;**23**(2 Suppl 1):20-5. [MEDLINE: 1647560]

Snydman 1991b *{published data only}*

Snydman DR, Werner BG, Tilney NL, Kirkman RL, Milford EL, Cho SI, et al. Final analysis of primary cytomegalovirus disease prevention in renal transplant recipients with a cytomegalovirus-immune globulin: comparison of the randomized and open-label trials. *Transplantation Proceedings* 1991;**23**(1 Pt 2):1357-60. [MEDLINE: 1846464]

Snydman 1994 *{published data only}*

Snydman DR, Werner BG, Dougherty NN, Griffith J, Rohrer RH, Freeman R, et al. A further analysis of the use of cytomegalovirus immune globulin in orthotopic liver transplant patients at risk for primary infection. Boston Center for Liver Transplantation CMVIG-Study Group. *Transplantation Proceedings* 1994;**26**(5 Suppl 1):23-7. [MEDLINE: 7940972]

Snydman 2001a *{published data only}*

Snydman DR. Historical overview of the use of cytomegalovirus hyperimmune globulin in organ transplantation. *Transplant Infectious Disease* 2001;**3**(Suppl 2):6-13. [MEDLINE: 11926753]

Speich 1999 *{published data only}*

Speich R, Thurnheer R, Gaspert A, Weder W, Boehler A. Efficacy and cost effectiveness of oral ganciclovir in the prevention of cytomegalovirus disease after lung transplantation. *Transplantation* 1999;**67**(2):315-20. [MEDLINE: 10075601]

Stratta 1992 *{published data only}*

Stratta RJ, Shaefer MS, Cushing KA, Markin RS, Reed EC, Langnas AN, et al. A randomized prospective trial of acyclovir and immune globulin prophylaxis in liver transplant recipients receiving OKT3 therapy. *Archives of Surgery* 1992;**127**(1):55-64. [MEDLINE: 1310385]

Turgeon 1998 *{published data only}*

Turgeon N, Fishman JA, Basgoz N, Tolkoff-Rubin NE, Doran M, Cosimi AB, et al. Effect of oral acyclovir or ganciclovir therapy after preemptive intravenous ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus seropositive renal and liver transplant recipients receiving antilymphocyte antibody therapy. *Transplantation* 1998;**66**(12):1780-6. [MEDLINE: 9884276]

Valantine 1995 *{published data only}*

Valantine HA. Prevention and treatment of cytomegalovirus disease in thoracic organ transplant patients: Evidence for a beneficial effect of hyperimmune globulin. *Transplantation Proceedings* 1995;**27**(5 Suppl 1):49-57. [MEDLINE: 7482821]

Valantine 1999 *{published data only}*

Valantine HA, Gao S-Z, Menon SG, Renlund DG, Hunt SA, Oyer P, et al. Impact of prophylactic immediate posttransplant ganciclovir on development of transplant atherosclerosis: A post hoc analysis of a randomized, placebo-controlled study. *Circulation* 1999;**100**(1):61-6. [MEDLINE: 10393682]

Wittes 1996 *{published data only}*

Wittes JT, Kelly A, Plante KM. Meta-analysis of CMVIG studies for the prevention and treatment of CMV infection in transplant patients. *Transplantation Proceedings* 1996;**28**(6 Suppl 2):17-24. [MEDLINE: 9037273]

Yang 1998 *{published data only}*

Yang CW, Kim YO, Kin YS, Kin SY, Moon IS, Ahn HJ, et al. Clinical course of cytomegalovirus (CMV) viremia with and without ganciclovir treatment in CMV-seropositive kidney transplant recipients. *American Journal of Nephrology* 1998;**18**(5):373-8. [MEDLINE: 9730559]

Yang 1999 *{published data only}*

Yang HC, Holman MJ, Langhoff E, Dellock CA, Gupta M, Ulsh PJ, et al. A comparative study of 500 mg BID and 250 mg BID of prophylactic oral ganciclovir in post-kidney transplant 'CMV at risk' recipients. *Transplantation Proceedings* 1999;**31**(1-2):1125-6. [MEDLINE: 10083502]

Additional references

Baliga 2004

Baliga RS, Kadambi PV, Javaid B, Harland R, Williams JW, Thistlethwaite JR, et al. A nationwide survey of cytomegalovirus prophylaxis and treatment in the transplant community [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):495.

Basgoz 1995

Basgoz N, Preiksaitis J. Post-transplant lymphoproliferative disorder. *Infectious Diseases Clinics of North America* 1995;**9**(4):901-23. [MEDLINE: 8747772]

Couchoud 1998b

Couchoud C. Cytomegalovirus prophylaxis with antiviral agents for solid organ transplantation. *Cochrane Database of Systematic Reviews* 1998, Issue 4. [CD001320]

Dickersin 1994

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**(6964):1286-91. [MEDLINE: 7718048]

Emery 2000

Emery VC, Sabin CA, Cope AV, Gor D, Hassan-Walker AF, Griffiths PD. Application of viral-load kinetics to identify patients who develop cytomegalovirus disease after transplantation. *Lancet* 2000;**355**(9220):2032-6. [MEDLINE: 10885354]

Fiddian 2002

Fiddian P, Sabin CA, Griffiths PD. Valacyclovir provides optimum acyclovir exposure for prevention of cytomegalovirus and related outcomes after organ transplantation. *Journal of Infectious Diseases* 2002;**186 Suppl 1**:110-5. [MEDLINE: 12353195]

Fishman 1995

Fishman JA. Pneumocystis carinii and parasitic infections in transplantation. *Infectious Disease Clinics of North America* 1995;**9**(4):1005-44. [MEDLINE: 8747777]

Fishman 1998

Fishman JA, Rubin RH. Infection in organ-transplant recipients. *New England Journal of Medicine* 1998;**338**(24):1741-51. [MEDLINE: 9624195]

George 1997

George MJ, Snydman DR, Werner BG, Griffith J, Falagas ME, Dougherty NN, et al. The independent role of cytomegalovirus as a risk factor for invasive fungal disease in orthotopic liver transplant recipients. Boston Center for Liver Transplantation CMVIG-Study Group. Cytogam, MedImmune, Inc. Gaithersburg, Maryland. *American Journal of Medicine* 1997;**103**(2):106-13. [MEDLINE: 9274893]

Gourishankar 2001

Gourishankar S, Wong W, Dorval M. Meta-analysis of prophylaxis of CMV disease in solid organ transplantation: is Ganciclovir a superior agent to Acyclovir?. Transplantation Proceedings. 2001; Vol. 33, issue 1-2:1870-2. [MEDLINE: 11267547]

Grattan 1989

Grattan MT, Moreno-Cabral CE, Starnes BA, Oyer PE, Stinson EB, Shumway NE. Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis. *JAMA* 1989;**261**(24):3561-6. [MEDLINE: 2542633]

Hadley 1995

Hadley S, Karchmer AW. Fungal infections in solid organ transplant recipients. *Infectious Disease Clinics of North America* 1995;**9**(4):1045-74. [MEDLINE: 8747778]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Hollis 1999

Hollis S, Cambell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999;**319**(7211):670-4. [MEDLINE: 10480822]

Jassal 1998

Jassal SV, Roscoe JM, Zaltzman JS, Mazzulli T, Krajden M, Gadawski M, et al. Clinical practice guidelines: prevention of cytomegalovirus disease after renal transplantation. *Journal of the American Society of Nephrology* 1998;**9**(9):1697-708. [MEDLINE: 9727379]

Keenan 1991

Keenan RJ, Lega ME, Dummer JS, Paradis IL, Dauber JH, Rabinowich H, et al. Cytomegalovirus serologic status and postoperative infection correlated with risk of developing chronic rejection after pulmonary transplantation. *Transplantation* 1991;**51**(2):433-8. [MEDLINE: 1847251]

Lefebvre 1996

Lefebvre C, McDonald S. Development of a sensitive search strategy for reports of randomised controlled trials in Embase. Fourth International Cochrane Colloquium; 1996 Oct 20-24; Adelaide (Australia). 1996.

Linden 2000

Linden PK. Infections in liver transplant recipients. In: Glauser MP, Pizzo PA editor(s). Management of infections in immunocompromised patients. 1st Edition. United Kingdom: WB Saunders, 2000:295-322.

Michaels 2000

Michaels M, Green M. Infections in lung and heart-lung transplant recipients. In: Glauser MP, Pizzo PA editor(s). Management of infections in immunocompromised patients. 1st Edition. United Kingdom: WB Saunders, 2000:363-93.

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet* 1998;**352**(9128):609-13. [MEDLINE: 9746022]

Rubin 1989

Rubin RH. The indirect effects of cytomegalovirus infection on the outcome of organ transplantation. *JAMA* 1989;**261**(24):3607-9. [MEDLINE: 2542634]

Rubin 2000

Rubin RH, Rosenberg E. Infection in solid organ transplant: an introduction. In: Glauser MP, Pizzo PA editor(s). Management of infections in immunocompromised patients. 1st Edition. United Kingdom: WB Saunders, 2000:246-65.

Schultz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12. [MEDLINE: 7823387]

Valentine 1999

Valantine HA. Role of CMV in transplant coronary artery disease and survival after heart transplantation. *Transplant Infectious Disease* 1999;**1 Suppl 1**:25-30. [MEDLINE: 11565583]

Van den Berg 1996

Van den Berg AP, Klompmaker IJ, Haagsma EB, Peeters PM, Meerman L, Verwer R, et al. Evidence for increased rate of bacterial infections in liver transplant patients with cytomegalovirus infection. *Clinical Transplantation* 1996;**10**(2):224-31. [MEDLINE: 8664524]

Van der Bij 2001

Van der Bij W, Speich R. Management of cytomegalovirus infection and disease after solid-organ transplantation. *Clinical Infectious Diseases* 2001;**33 Suppl 1**:32-7. [MEDLINE: 11389520]

References to other published versions of this review

Hodson 2005

Hodson EM, Jones CA, Webster AC, Strippoli GFM, Barclay BG, Kable K, et al. Antiviral medications to prevent cytomegalovirus disease and early death in solid-organ transplant recipients: a systematic review of randomised controlled trials. *Lancet* 2005;**365**(9477):2105-15. [MEDLINE: 15964447]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ahsan 97-Kidney

Methods	Country: USA Setting/Design: Tertiary single centre/Parallel Time frame: 1/3/1995-31/12/1995 Randomisation method: Block randomisation Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No. 1/44 excluded after randomisation from GCV group Follow-up period: 9 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients, D/R+, D+/R-, D-/R- if diabetic or receiving OKT-3 TREATMENT GROUP Number: 22 Age: 50.4 ± 2.3 y (mean ± SEM) Sex (M/F): 10/11 CD/LD: 18/3 CONTROL GROUP Number: 22 Age: 47.6 ± 2.1 y Sex (M/F): 12/11 CD/LD: 7/15 EXCLUSIONS: NS
Interventions	TREATMENT GROUP GCV 750 mg po bd for 12 weeks starting day 1 CONTROL GROUP No treatment CO-INTERVENTIONS CSA, AZA, prednisone, OKT-3 (CD recipients)
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV infection: CMV culture, IgM 3. All-cause mortality 4. Death due to CMV disease 5. Acute rejection

Ahsan 97-Kidney *(Continued)*

	6. Graft loss 7. Opportunistic infections
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: none STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Badley 97-Liver

Methods	Country: USA Setting/Design: Tertiary multicentre/Parallel Time frame: 1/1/1991-30/6/1994 Randomisation method: Central randomisation Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No; 3 excluded after randomisation & before treatment Follow-up period: 1 year Loss to follow-up: 0%
Participants	INCLUSION CRITERIA First liver transplant TREATMENT GROUP Number: 83 Age: 16-68 y (range) Sex (M/F): 50/33 CONTROL GROUP Number: 84 Age: 16-68 y Sex (M/F): 46/38 EXCLUSIONS: Allergy to GCV/ACV, Creatinine > 3 mg/dL or GFR < 10, Stage 3/4 coma post transplant, existing CMV infection
Interventions	TREATMENT GROUP GCV 5 mg/kg bd IV for 14 days starting first day post-transplant, ACV 800 mg po qds to 120 days CONTROL GROUP ACV 800 mg po qds to 120 days CO-INTERVENTIONS CSA, AZA (one centre), prednisone
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome

Badley 97-Liver *(Continued)*

	3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Acute rejection 7. Opportunistic infections 8. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 3 excluded STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Balfour 89 - Kidney

Methods	Country: USA Setting/Design: Tertiary single centre/Parallel Time frame: 13/8/1985 - 20/5/1988 Randomisation method: Computer generated Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No; 14/118 excluded after randomisation Follow-up period: 1 year Loss to follow-up: 6% at 1 year, 0% at 6 months
Participants	INCLUSION CRITERIA Cadaveric renal transplant recipients aged > 10 y TREATMENT GROUP Number: 53 Age: 43 y (15-67) (median/range) Sex (M/F): 36/17 CONTROL GROUP Number: 51 Age: 42 y (17-68) Sex (M/F): 34/17 EXCLUSIONS: Intolerance of ACV
Interventions	TREATMENT GROUP ACV 800 mg po qds for 12 weeks starting day of transplant CONTROL GROUP Placebo 1 tablet qds for 12 weeks starting day of transplant CO-INTERVENTIONS: CSA, AZA, prednisone
Outcomes	STUDY OUTCOMES

Balfour 89 - Kidney *(Continued)*

	1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture, Rising CMV antibody 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Graft loss 9. Opportunistic infections 10. Adverse events
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: none reported STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Barkholt 99 - Liver

Methods	Country: Sweden Setting/Design: Tertiary single centre/parallel Time frame: 5/1993-12/1994 Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: Yes - Data analysis: NS Intention-to-treat: No. 5 excluded Follow-up period: 3 mths Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Liver transplant recipients, all CMV serostatus TREATMENT GROUP Number: 28 Age: 41 ± 17 y (mean ± SD) Sex (M/F): 16/12 CONTROL GROUP Number: 27 Age: 47 ± 15 y Sex (M/F): 12/15 EXCLUSIONS: Age < 6 y, HIV infection, CMV therapy in previous 4 wk
Interventions	TREATMENT GROUP ACV 800 mg (1 tablet) qds po for 12 weeks starting 6 hours pre-transplant CONTROL GROUP Placebo 1 tablet qds po for 12 weeks starting 6 hours pre-transplant

Barkholt 99 - Liver *(Continued)*

	CO-INTERVENTIONS: CSA, AZA, prednisone
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV infection: CMV culture, CMV DNA, IgM 3. All-cause mortality 4. Death due to CMV disease 5. Acute rejection 6. Graft loss 7. Opportunistic infections 8. Adverse reactions
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 5 excluded STOP OR END POINT/S:NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Brennan 97-Kidney

Methods	Country: USA Setting/Design: Tertiary single centre/parallel Time frame: NS Randomisation method: Odd and even numbers according to last digit of medical record number Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 6 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients, D/R+, D+/R- recipients TREATMENT GROUP Number: 19 Age: 50.6 ± 2.8 y (mean ± SEM) Sex (M/F): 13/6 CONTROL GROUP Number: 23 Age: 44.2 ± 3.0 y Sex (M/F): 5/18 EXCLUSIONS: D-/R- recipients
Interventions	TREATMENT GROUP GCV 1000 mg po tds for 12 weeks starting at transplant CONTROL GROUP

Brennan 97-Kidney *(Continued)*

	No treatment except ACV low dose to prevent Herpes simplex CO-INTERVENTIONS: CSA, AZA, prednisone, ATG
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV DNA 5. All-cause mortality 6. Acute rejection 7. Opportunistic infections 8. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S:NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Cohen 93-Liver

Methods	Country: UK Setting/Design: Tertiary single centre/Parallel Time frame: NS Randomisation method: Random numbers Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 18 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Liver transplant recipients, D/R+, D+/R- TREATMENT GROUP Number: 33 Age: 42.4 y (mean) Sex (M/F): 15/18 CONTROL GROUP Number: 32 Age: 46.3 y (mean) Sex (M/F): 16/16 EXCLUSIONS: Acute renal failure, multiple organ system failure, D-/R- recipients
Interventions	TREATMENT GROUP GCV 5 mg/kg IV bd for 14 days starting on Day 14

Cohen 93-Liver *(Continued)*

	CONTROL GROUP No treatment CO-INTERVENTIONS: CSA, AZA, prednisone
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture, IgM 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Graft loss 9. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Conti 95-Kidney

Methods	Country: USA Setting/Design: Tertiary single centre/Parallel Time frame: 1/1992-1/1994 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: NS Follow-up period: 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients, D/R+, receiving ALG for induction or rejection TREATMENT GROUP Number: 22 Age: 43 y (mean) Sex (M/F): 11/11 CONTROL GROUP Number: 18 Age: 45 y Sex (M/F): 12/6 EXCLUSIONS: NS

Conti 95-Kidney *(Continued)*

Interventions	TREATMENT GROUP GCV 5 mg/kg/d IV during ALG therapy (median 10 days) starting on first day of ALG CONTROL GROUP No treatment CO-INTERVENTIONS: CSA, AZA, prednisone, ALG
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. All-cause mortality 5. Acute rejection 6. Graft loss 7. Opportunistic infections 8. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S:NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Duncan 93-Lung

Methods	Country: USA Setting/Design: Tertiary single centre/Parallel Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 1 year Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Lung transplant recipients, D/R+, D+/R-, neutrophils > 1000/mm3, creatinine >2.5mg/dL TREATMENT GROUP Number: 13 Age: 41.8 ± 9.6 y (mean ± SD) Sex (M/F): 9/4 CONTROL GROUP Number: 12 Age: 45.6 ± 8.4 y Sex (M/F): 7/5

Duncan 93-Lung *(Continued)*

	EXCLUSIONS: D-/R-
Interventions	TREATMENT GROUP GCV 5 mg/kg qds IV x 14 days starting day 7; GCV 5 mg/kg/d IV for days 21-28 days; GCV 5 mg/kg IV 5 times/wk to day 90 CONTROL GROUP GCV 5mg/kg qds IV x 14 days starting day 7; GCV 5 mg/kg/d IV for days 21-28 days; ACV 800 mg po qds to day 90 CO-INTERVENTIONS: CSA, AZA
Outcomes	STUDY OUTCOMES 1. CMV tissue invasive disease 2. CMV infection: CMV culture of bronchial lavage 3. All-cause mortality 4. Death due to CMV disease 5. Obliterative bronchiolitis 6. Graft loss 7. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Egan 02-Heart

Methods	Country: UK Setting/Design: Tertiary single centre/Parallel Time frame: 9/1994-2/1998 Randomisation method: Computer generated randomisation schedule Blinding - Participants: Unclear - Investigators: Unclear - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 6 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Heart transplant recipients, D/R+ TREATMENT GROUP Number: 14 Age: 51.6 y (39-63) (mean, range) Sex (M/F): 11/1 CONTROL GROUP Number: 13

Egan 02-Heart *(Continued)*

	Age: 50.4 y (31-62) Sex (M/F): 10/3 EXCLUSIONS: Active herpes infection, Required other antiviral agents
Interventions	TREATMENT GROUP VACV 2000 mg po qds for 90 days starting within 72 hours of transplant CONTROL GROUP ACV 200 mg po qdsfor 90 days starting within 72 hours of transplant for herpes simplex CO-INTERVENTIONS: CSA, AZA, prednisone, ATG
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV antigenaemia, culture 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Graft loss 9. Opportunistic infections 10. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: none STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Flechner 98-Kidney

Methods	Country: USA Setting/Design: Tertiary single centre/Parallel Time frame: 4/1996-12/1997 Randomisation method: Central randomisation with computer generated list Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 6-27 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients > 18 yrs & < 101 kg, D/R+, D+/R- TREATMENT GROUP Number: 40 Age: 47.9 y (mean)

Flechner 98-Kidney *(Continued)*

	Sex (M/F): 30/10 CONTROL GROUP Number: 39 Age: 50.2 y Sex (M/F): 31/8 EXCLUSIONS: D-/R-, Allergy to GCV/ACV, AIDS, WBC < 3000, Plts < 100,000, previous viral hepatitis
Interventions	TREATMENT GROUP GCV 1000 mg po tds for 84 days starting on day 1 CONTROL GROUP ACV 800 mg po qds for 84 days starting on day 1 CO-INTERVENTIONS: CMV IgG given to D+/R- recipients in each group; CSA, AZA (1/3 rd), MMF (2/3 rd), OKT-3
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Opportunistic infections
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S:NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Gane 97-Liver

Methods	Country: USA, Europe Setting/Design: Tertiary multicentre/Parallel Time frame: 12/1993-4/1995 Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: Yes - Data analysis: NS Intention-to-treat: Yes Follow-up period: 1 year Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Primary liver transplant recipients, D/R+, D+/R-, age > 18 y

Gane 97-Liver *(Continued)*

	TREATMENT GROUP Number: 150 Age: 46.8 ± 11.6 y (mean ± SD) Sex (M/F): 92/58 CONTROL GROUP Number: 154 Age: 48.1 ± 10.9 y Sex (M/F): 82/72 EXCLUSIONS: Multiple organ transplant, D-/R- (2 patients inadvertently randomised and included in analysis), unable to take oral medications, neutrophils < 1000, platelets < 25,000, Creatinine > 300
Interventions	TREATMENT GROUP GCV 1000 mg (4 tablets) tds po till day 98 starting within 10 days of transplant CONTROL GROUP Matching placebo 4 tablets tds po till day 98 starting within 10 days of transplant CO-INTERVENTIONS: CSA, TAC (52 patients), ALG (61 patients)
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV antigenaemia, IgM, CMV culture 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Graft loss 9. Opportunistic infection 10. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gavalda 97-Liver

Methods	Country: Spain Setting/Design: Tertiary single centre/Parallel Time frame: 6/1991-11/1993 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 12 months

Gavalda 97-Liver *(Continued)*

	Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Primary liver transplant recipient, D/R+ TREATMENT GROUP Number: 37 Age: 57 y (34-66) (median/range) Sex (M/F): 25/12 CONTROL GROUP Number: 36 Age: 54 y (20-65) Sex (M/F): 23/13 EXCLUSIONS: Second transplant recipients
Interventions	TREATMENT GROUP ACV 400 mg po 5 times daily for 16 weeks starting 3-30 days (median 7 days) post-transplant CONTROL GROUP No treatment CO-INTERVENTIONS: CSA, prednisone
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Opportunistic infections 7. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S:NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Green 97-Liver

Methods	Country: USA Setting/Design: Tertiary single centre/Parallel Time frame: 7/1992-3/1994 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes

Green 97-Liver *(Continued)*

	Follow-up period: 1 year Loss to follow-up: 0%
Participants	INCLUSION CRITERIA First liver transplant recipients < 18 y TREATMENT GROUP Number: 24 Age: 4.9 y (mean) Sex (M/F): NS CONTROL GROUP Number: 24 Age: 4.3 y Sex (M/F): NS EXCLUSIONS: Multi-organ recipient
Interventions	TREATMENT GROUP GCV 5 mg/kg bd IV for 14 days starting Day 1; ACV 800 mg/m^2 qds po to 1 year CONTROL GROUP GCV 5 mg/kg bd IV for 14 days starting Day 1 CO-INTERVENTIONS: TAC, prednisone
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive tissue disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Opportunistic infections
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S:NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Hertz 98-heart/lung

Methods	Country: USA Setting/Design: Tertiary single centre/parallel Time frame: 31/1/1993-31/1/1996 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes

Hertz 98-heart/lung *(Continued)*

	Follow-up period: 1 year Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Lung or heart/lung transplant recipients; D/R+; D+/R- TREATMENT GROUP Number: 35 Age: 46.4 ± 11.4 y (mean ± SD) Sex (M/F): 15/20 CONTROL GROUP Number: 37 Age: 49.1 ± 8.7 y Sex (M/F): 14/23 EXCLUSIONS: D-/R-
Interventions	TREATMENT GROUP GCV 5mg/kg bd IV on days 8-21; 5mg/kg IV three times per week to 90 days CONTROL GROUP GCV 5mg/kg bd IV on days 8-21; 5mg/kg IV daily to 90 days CO-INTERVENTIONS: CSA, AZA, prednisone
Outcomes	STUDY OUTCOMES 1. CMV diseaese 2. CMV syndrome 3. CMV tissue invasive disease 4. CMV infection: CMV culture of bronchial lavage 5. All-cause mortality 6. Death due to CMV disease 7. Opportunistic infections 8. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Hibberd 95-Kidney

Methods	Country: USA Setting/Design: Tertiary multicentre/Parallel Time frame: 11/1990-9/1992 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS

Hibberd 95-Kidney *(Continued)*

	- Data analysis: NS Intention-to-treat: Yes Follow-up period: 6 months Loss to follow-up: 1.8% (2 lost to FU at 32 days & 78 days)
Participants	INCLUSION CRITERIA Kidney transplant recipients receiving antilympocyte preparations for induction or treatment of rejection. D/R+ TREATMENT GROUP Number: 64 Age: 44.2 ± 1.62 y (mean ± SEM) Sex (M/F): 36/28 CONTROL GROUP Number: 49 Age: 42.8 ± 1.99 y Sex (M/F): 33/16 EXCLUSIONS: Age < 20 y, pregnant, multiorgan recipient, treatment with other antiviral agent
Interventions	TREATMENT GROUP GCV 2.5 mg/kg/d IV during ALG therapy (median duration 9 days) starting within 24 hrs of first dose of ALG CONTROL GROUP No treatment CO-INTERVENTIONS: CSA,AZA, prednisone, ALG or OKT-3
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Death due to CMV disease 7. Graft loss 8. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kletzmayr 96-Kidney

Methods	Country: Austria Setting/Design: Tertiary single centre/Parallel Time frame: NS Randomisation method: NS. 2:1 ratio

Kletzmayr 96-Kidney *(Continued)*

	Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No. 2 excluded from analysis as discontinued treatment Follow-up period: 1 year Loss to follow-up: 5.6%
Participants	INCLUSION CRITERIA Kidney transplant recipients. D+/R- TREATMENT GROUP Number: 22 Age: 46 ± 14 y (mean ± SD) Sex (M/F): 17/5 CONTROL GROUP Number: 10 Age: 44 ± 13 y Sex (M/F): 7/3 EXCLUSIONS: NS
Interventions	TREATMENT GROUP ACV 800 mg tds po for 3 months starting first post-op day CONTROL GROUP No treatment CO-INTERVENTIONS: CSA, AZA, prednisone
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV infection: CMV antigenaemia, CMV culture, IgM 3. All-cause mortality 4. Acute rejection 5. Graft loss
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Leray 95-Kidney

Methods	Country: France Setting/Design: Tertiary single centre/Parallel Time frame: 1/1991-7/1994 Randomisation method: NS Blinding

Leray 95-Kidney *(Continued)*

	- Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: NS Follow-up period: Unclear Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients. D+/R- TREATMENT GROUP Number: 13 Age: NS Sex (M/F): NS CONTROL GROUP Number: 10 Age: NS Sex (M/F): NS EXCLUSIONS: NS
Interventions	TREATMENT GROUP GCV 5 mg/kg IV bd for 14 days starting 14 days post-transplant CONTROL GROUP No treatment CO-INTERVENTIONS: CSA, AZA, prednisone, ALG
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV infection: CMV antigenaemia, CMV culture, IgM 3. Acute rejection 4. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: none reported STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Lowance 99-Kidney

Methods	Country: USA/Europe Setting/Design: Tertiary multicentre/Parallel Time frame: 7/7/1992-11/12/1996 Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes

Lowance 99-Kidney *(Continued)*

	- Outcome assessors: Yes - Data analysis: NS Intention-to-treat: Yes Follow-up period: 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients, D/R+, D+/R- TREATMENT GROUP Number: 306; 204 D/R+; 102 D+/R- Age: D/R+ 43.6 ± 13.1 y (mean ± SD); D+/R- 40.3 ± 14.2 y Sex (M/F): D/R+ 153/51; D+/R- 60/42 CONTROL GROUP Number: 310; D/R+ 204; D+/R- 106 Age: D/R+ 45.1 ± 13 y; D+/R- 45.6 ± 13.5 y Sex (M/F): D/R+ 124/80; D+/R- 65/41 EXCLUSIONS: D-/R-, active herpes infection, antiviral therapy in previous 2 months
Interventions	TREATMENT GROUP VACV 2000 mg qds po for 90 days starting within 3 days of transplant CONTROL GROUP Placebo qds po for 90 days starting within 3 days of transplant CO-INTERVENTIONS: CSA, AZA, TAC (6), MMF (7), ATG or ALG (251), OKT-3 (102)
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Opportunistic infections 9. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION:None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Macdonald 95-Heart

Methods	Country: Australia Setting/Design: Tertiary single centre/Parallel Time frame: NS Randomisation method: Random numbers table

Macdonald 95-Heart *(Continued)*

	Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Heart transplant recipients, D/R+, D+/R- TREATMENT GROUP Number: 28 Age: 48 ± 15 y (mean ± SD) Sex (M/F): 24/4 CONTROL GROUP Number: 28 Age: 45 ± 15 y Sex (M/F): 25/3 EXCLUSIONS: D-/R-
Interventions	TREATMENT GROUP GCV 5mg/kg IV 3 times/wk for 6 weeks starting pre-transplant CONTROL GROUP Placebo IV 3 times/wk for 6 weeks starting pre-transplant CO-INTERVENTIONS: CSA, AZA, prednisone, ATG
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Opportunistic infections 7. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Martin 94-Liver

Methods	Country: USA Setting/Design: Tertiary single centre/Parallel Time frame: 1/2/1991-31/8/1991

Martin 94-Liver *(Continued)*

	Randomisation method: Fixed block randomisation Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analysis: No Intention-to-treat: No: 4 excluded after randomisation Follow-up period: 24 weeks Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Liver transplant recipients > 18 y TREATMENT GROUP Number: 68 Age: 48.1 ± 13.2 y (mean ± SD) Sex (M/F): 43/25 CONTROL GROUP Number: 71 Age: 47 ± 12.9 y Sex (M/F): 35/36 EXCLUSIONS: Fulminant hepatic failure, Stage 3/4 hepatic coma, hepatic malignancies with pre-operative chemotherapy
Interventions	TREATMENT GROUP GCV 5 mg/kg bd IV for 14 days starting 2 days post-transplant; ACV 800 mg po qds to 10 weeks CONTROL GROUP ACV 800 mg po qds for 10 weeks starting 2 days post-transplant CO-INTERVENTIONS: TAC
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive tissue disease 4. CMV infection: CMV culture, IgM 5. All-cause mortality 6. Acute rejection 7. Graft loss 8. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 1 excluded did not receive medication STOP OR END POINT/S:NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Merigan 92-Heart

Methods	Country: USA Setting/Design: Tertiary multicentre/Parallel Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 120 days Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Heart transplant recipients, D/R+, D+/R- TREATMENT GROUP Number: 76 Age: 47.1 ± 1.55 y (mean ± SEM) Sex (M/F): 68/8 CONTROL GROUP Number: 73 Age: 47.6 ± 1.4 y Sex (M/F): 63/10 EXCLUSIONS: D-/R-, Combined heart-lung transplant recipients, antiviral agents in previous 7 days, WBC < 1500, Platelets < 50,000, GFR < 10 or > 400
Interventions	TREATMENT GROUP GCV 5 mg/kg IV bd for 14 days starting on day 1 post-transplant but delay for 2-7 days in 21% CONTROL GROUP Placebo IV bd for 14 days starting on day 1 post-transplant but delay for 2-7 days in 23% CO-INTERVENTIONS: CSA, AZA, prednisone, OKT-3
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Opportunistic infections 7. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Nakazato 93-Liver

Methods	Country: USA Setting/Design: Tertiary single centre/Parallel Time frame: 27/8/1990-1/11/1991 Randomisation method: NS Blinding - Participants: NS - Investigators: NS - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 1 year Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Liver transplant recipients TREATMENT GROUP Number: 52 Age: 38.7 ± 21.5 y (mean ± SD) Sex (M/F): NS CONTROL GROUP Number: 52 Age: 34.9 ± 22.8 y Sex (M/F): NS EXCLUSIONS: NS
Interventions	TREATMENT GROUP GCV 5 mg/kg/d IV during inpatient periods in first 3 months post-transplant; ACV 5 mg/kg/d po to 3 months CONTROL GROUP ACV 5 mg/kg/d IV during inpatient periods in first 3 months post-transplant; ACV 5 mg/kg/d po to 3 months CO-INTERVENTIONS: IgG IV 200mg/kg/d during inpatient periods in first 3 months post-transplant; CSA (81), TAC (23), prednisone
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV culture/histopathology & symptoms 2. All-cause mortality 3. Acute rejection 4. Graft loss 5. Opportunistic infections 6. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S:NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Paya 04-All

Methods	Country: USA/Europe/Canada/Australia Setting/Design: Tertiary multicentre/parallel Time frame: 4/2000 - 8/2001 Randomisation method: Central; 2:1 randomisation Blinding - Participants: Yes (double dummy) - Investigators: Yes - Outcome assessors: Yes - Data analysis: NS Intention-to-treat: No Follow-up period: 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Solid organ transplant recipient >12 y (liver, kidney, heart, kidney-pancreas); D+/R-; first transplant; adequate liver and renal function. TREATMENT GROUP Number: 245 Age: 45.7 y (mean) Sex (M/F): 179/66 CONTROL GROUP Number: 127 Age: 45.3 y Sex (M/F): 95/32 EXCLUSIONS: Retransplant, history of CMV infection/disease, CMV therapy in previous 30 days, severe uncontrolled diarrhoea, malabsorption
Interventions	TREATMENT GROUP VGCV 900 mg daily po starting within 10 days of transplant for 100 days CONTROL GROUP GCV 1000 mg tds po starting within 10 days of transplant for 100 days CO-INTERVENTIONS: Immunosuppression according to protocol of centre
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV tissue invasive disease 4. CMV infection: CMV-DNA; infection confirmed in central lab 5. All-cause mortality 6. Death due to CMV disease 7. Acute rejection 8. Graft loss 9. Opportunistic infections 10. Adverse reactions
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: 2 excluded from safety analysis as did not receive medication. 8 excluded from primary outcome analysis as not D=/R- STOP OR END POINT/S ADDITIONAL DATA REQUESTED FROM AUTHORS
Risk of bias	

Paya 04-All *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Pouteil-Noble 96 - K

Methods	Country: France Setting/Design: Tertiary single centre/Parallel Time frame: NS Randomisation method: NS Blinding - Participants: Unclear - Investigators: Unclear - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 6 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients, all CMV serostatus TREATMENT GROUP Number: 24 Age: NS Sex (M/F): NS CONTROL GROUP Number: 26 Age: NS Sex (M/F): NS EXCLUSIONS: NS
Interventions	TREATMENT GROUP GCV 5 mg/kg/d IV for 14 days starting on day of transplant and then ACV 800 mg tds po to 3 months CONTROL GROUP Placebo given as above CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV infection: CMV culture, IgM 3. All-cause mortality
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement

Pouteil-Noble 96 - K *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate

Reischig 04 - Kidney

Methods	Country: Czech Republic Setting/Design: Tertiary single centre/parallel Time frame: 4/1999 - ? Randomisation method: Random number generation Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No (2 excluded for graft loss) Follow-up period: 6 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients; D/R+, D+/R- TREATMENT GROUP Number: 35 Age: 45 ± 12 y (mean ± SD) Sex (M/F): 26/9 CONTROL GROUP Number: 36 Age: 48 ± 11 y Sex (M/F): 25/11 EXCLUSIONS: D-/R-, unknown CMV status, active CMV infection, treatment with antiviral agents, WBC < 4000, Platelets < 150,000, allergy to study drugs
Interventions	TREATMENT GROUP VACV 2000 mg qds po starting within 3 days of transplant for 3 months CONTROL GROUP GCV 1000 mg tds po starting within 3 days of transplant for 3 months CO-INTERVENTIONS: ACV low dose to prevent herpes simplex; CSA, MMF, prednisone, ATG or OKT-3 (9)
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV infection: CMV-DNA, CMV antigenaemia, CMV culture 3. All-cause mortality 4. Acute rejection 5. Graft loss 6. Adverse reactions
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS
Risk of bias	

Reischig 04 - Kidney *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Rondeau 93-Kidney

Methods	Country: France Setting/Design: tertiary multicentre/Parallel Time frame: 1/1990-7/1992 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: NS Follow-up period: 3 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients, D+/R- TREATMENT GROUP Number: 17 Age: 43.8 ± 2.9 y (mean ± SEM) Sex (M/F): 13/4 CONTROL GROUP Number: 15 Age: 43.5 ± 3.3 y Sex (M/F): 6/9 EXCLUSIONS: Living related donor transplant recipients, WBC < 1500, platelets < 50,000, treatment with another antiviral agent
Interventions	TREATMENT GROUP GCV 5 mg/kg IV bd for 14 days starting day 14 post-transplant CONTROL GROUP No treatment CO-INTERVENTIONS
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture, IgM 5. All-cause mortality 6. Acute rejection 7. Graft loss
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S:NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Rondeau 93-Kidney *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rostaing 94 - Kidney

Methods	Country: France Setting/Design: Tertiary single centre/Parallel Time frame: 4/1992-2/1993 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: Mean 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients. D/R+ TREATMENT GROUP Number: 19 Age: 50.4 ± 11.3 y (mean ± SD) Sex (M/F): 13/6 CONTROL GROUP Number: 18 Age: 45.1 ± 11.1 y Sex (M/F): 14/4 EXCLUSIONS: D+/R-, D-/R- recipients
Interventions	TREATMENT GROUP ACV 6mg/kg/d IV x 3 days and then ACV 800 mg po qds for 3 months starting day 1 CONTROL GROUP No treatment CO-INTERVENTIONS: CSA, AZA, prednisone, ATG
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture 5. All-cause mortality 6. Acute rejection 7. Graft loss 8. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S:NS

Rostaing 94 - Kidney *(Continued)*

ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rubin 02-all

Methods	Country: USA Setting/Design: Tertiary multicentre/Parallel Time frame: 1/11/1996-21/1/1999 Randomisation method: Central but otherwise US Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No: 11 not included (7 did not meet inclusion criteria, 3 lost to FU, 1 died) Follow-up period: 12 months Loss to follow-up: 0% of evaluated patients
Participants	INCLUSION CRITERIA First kidney, liver or heart transplant recipients >12 yrs, D+/R- TREATMENT GROUP Number: 77 Age: 46 ± 13 y (mean ± SD) Sex (M/F): 60/17 CONTROL GROUP Number: 78 Age: 45 ± 12 y Sex (M/F): 61/17 EXCLUSIONS: D/R+, D-/R-
Interventions	TREATMENT GROUP GCV 5 mg/kg/d IV for 5-10 days starting within 72 hours of transplant; GCV 1000 mg tds po to 12 weeks CONTROL GROUP GCV 5 mg/kg/d IV for 5-10 days starting within 72 hours of transplant; ACV 400 mg tds po to 12 weeks CO-INTERVENTIONS: CSA (141), TAC (27), AZA (57), MMF (101), antibody therapy (56)
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV antigenaemia, CMV culture 5. All-cause mortality 6. Acute rejection 7. Opportunistic infections 8. Adverse effects 9. Time to CMV disease

Rubin 02-all *(Continued)*

Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Saliba 93-Liver

Methods	Country: France Setting/Design: Tertiary single centre/Parallel Time frame: 2/1990-2/1991 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis:NS Intention-to-treat: Yes Follow-up period: 3 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Liver transplant recipients, D/R+ TREATMENT GROUP Number: 60 Age: 45.3 ± 12 y (mean ± SD) Sex (M/F): 36/24 CONTROL GROUP Number: 60 Age: 44.5 ± 13 y Sex (M/F): 35/35 EXCLUSIONS: D+/R-, D-/R- recipients
Interventions	TREATMENT GROUP ACV 500mg/m^2/d IV x 10 days; 800mg qds po to 3 months CONTROL GROUP No treatment CO-INTERVENTIONS: CSA, AZA, prednisone
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV infection: CMV culture 3. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None

Saliba 93-Liver *(Continued)*

STOP OR END POINT/S:NS

ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Winston 03-Liver

Methods	Country: USA Setting/Design: Tertiary single centre/parallel Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Liver transplant recipients; D/R+ TREATMENT GROUP Number: 110 Age: 51 y (7-78) (mean/range) Sex (M/F): 58/52 CONTROL GROUP Number: 109 Age: 51 y (7-71) Sex (M/F): 58/51 EXCLUSIONS: D+/R-, D-/R- recipients
Interventions	TREATMENT GROUP GCV 6 mg/kg/d IV to day 14 starting day of transplant; GCV 1000 mg tds po to day 100 CONTROL GROUP GCV 6 mg/kg/d IV to day 14 starting day of transplant; ACV 800 mg qds po to day 100 CO-INTERVENTIONS: CSA (58), TAC (164), AZA (128), MMF (85), prednisone
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV DNA, CMV culture 2. CMV syndrome 3. CMV tissue invasive disease 4. All-cause mortality 5. Death due to CMV disease 6. Acute rejection 7. Opportunistuc infections 8. Adverse effects

Winston 03-Liver *(Continued)*

Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: Unclear STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Winston 04-Liver

Methods	Country: USA Setting/Design: Tertiary single centre/parallel Time frame: 6/1997-4/2000 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 1 yearr Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Liver transplant recipients; D+/R- TREATMENT GROUP Number: 32 Age: 49 y (13-67) (mean/range) Sex (M/F): 24/8 CONTROL GROUP Number: 32 Age: 46 y (6-73) Sex (M/F): 23/9 EXCLUSIONS: D/R+, D-/R-
Interventions	TREATMENT GROUP GCV 6 mg/kg IV daily days 1-14; GCV 1000 mg tds po on days 15-86 CONTROL GROUP GCV 6 mg/kg IV daily days 1-14; GCV 6mg/kg IV Mon-Fri from days 15-86 CO-INTERVENTIONS: CSA (10), TAC (54), MMF (29), AZA (3), prednisone
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV tissue invasive disease 4. All-cause mortality 5. Opportunistic infections 6. Adverse effects

Winston 04-Liver *(Continued)*

Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Winston 95-Liver

Methods	Country: USA Setting/Design: Tertiary single centre/parallel Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 4 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA First liver transplant recipients >12 yrs; all serologies TREATMENT GROUP Number: 124 Age: 52 y (20-72) (mean/range) Sex (M/F): 67/57 CONTROL GROUP Number: 126 Age: 47 y (20-74) Sex (M/F): 67/59 EXCLUSIONS: Second transplants
Interventions	TREATMENT GROUP GCV 6 mg/kg/d IV to day 30; GCV 6 mg/kg/d IV Mon-Fri to day 100 CONTROL GROUP ACV 10 mg/kg IV 8 hourly till discharge; ACV 800 mg po qds to day 100 CO-INTERVENTIONS: CSA, TAC (38), AZA, prednisone
Outcomes	STUDY OUTCOMES 1. CMV disease 2. CMV syndrome 3. CMV invasive organ disease 4. CMV infection: CMV culture, isolation from any site 5. All-cause mortality 6. Death due to CMV disease

Winston 95-Liver *(Continued)*

	7. Acute rejection 8. Opportunistic infections 9. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

CMV = Cytomegalovirus
NS = not stated
D/R+ = Donor CMV positive or negative, recipient CMV positive
D+/R- = Donor CMV positive, recipient CMV negative
D-/R- = Donor CMV negative, recipient CMV negative
OKT-3 = Monoclonal anti CD3 antibody
ATG = Antithymocyte globulin
ALG = Antilymphocyte globulin
GCV = Ganciclovir
ACV = Aciclovir
VACV = Valaciclovir
VGCV = Valganciclovir
CSA = Cyclosporin
AZA = Azathioprine
TAC = Tacrolimus
MMF = Mycophenolate
IgG = Immunoglobulin G

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

Study	Reason for exclusion
Ahsan 1998	Not RCT (sequential)
Arbo 2000	Economic evalution of previous trial
Brennan 1997	Pre-emptive study
Brennan 2001	Review article
Couchoud 1998a	Systematic review
Dickinson 1996	IgG to prevent CMV
Falagas 1997	Included both unrandomised patients and patients from a previous trial
Fehir 1989	Nonrandomised patients included
Fishman 2000	Retrospective study

Study	Reason for exclusion
Gerna 2003	Diagnostic test systematic review
Glowacki 1994	Systematic review
Griffiths 1997	Review article
Jung 2001	Pre-emptive study
Jurim 1996	Subgroup of previous trial - outcome Hepatitis B
Kim 2000	Economic evaluation of previous study
King 1999	IgG versus antiviral to prevent CMV
Kletzmayr 2000	Not RCT- historical controls
Koetz 2001	Pre-emptive study
Kuypers 1999	Review article
Laske 1991	Review article
Laske 1992	Review article
Lumbreras 1993	Not RCT - historical controls
Martin 1993	Review article
Martin 1994	Review article
Martin 1995	Review article
McGavin 2001	GCV review
Moreno 1999	Not RCT
Mullen 1998	Retrospective study
Paya 2002	Pre-emptive study
Queiroga 2003	Pre-emptive study
Rayes 2001	Pre-emptive study
Sagedal 2003	Pre-emptive study
Schafers 1988	Not RCT (sequential)
Schnitzler 2000	Reanalysis of previous study (1992)
Singh 1994	Pre-emptive study
Singh 1995	Not RCT
Singh 2000	Pre-emptive study

Study	Reason for exclusion
Snydman 1991a	Review article
Snydman 1991b	Compares results to previous study
Snydman 1994	Compares results to previous study
Snydman 2001a	Historical controls
Speich 1999	Not RCT (sequential)
Stratta 1992	Nonrandomised patients included
Turgeon 1998	Not RCT (sequential)
Valantine 1995	IgG trial
Valantine 1999	Post hoc analysis
Wittes 1996	Systematic review
Yang 1998	Pre-emptive study
Yang 1999	Unable to determine if patients randomised

DATA AND ANALYSES

Comparison 1. Antiviral prophylaxis versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease and CMV infection in all treated patients	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 All symptomatic CMV disease	19	1981	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.34, 0.52]
1.2 CMV syndrome	11	1570	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.29, 0.57]
1.3 CMV organ involvement	12	1628	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.21, 0.55]
1.4 Total CMV infection	17	1786	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.48, 0.77]
2 All symptomatic CMV disease stratified by antibody status	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 CMV antibody +ve recipients	13	1348	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.24, 0.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 CMV +ve donor / CMV -ve recipient	10	423	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.37, 0.73]
2.3 CMV -ve donor / CMV -ve recipient	4	38	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.09, 11.03]
2.4 CMV +ve donor / CMV +ve recipient	5	276	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.09, 0.37]
2.5 CMV -ve donor / CMV +ve recipient	5	160	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.11, 0.95]
3 CMV disease in all patients by antiviral medication	19	1981	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.34, 0.52]
3.1 Aciclovir	6	421	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.29, 0.69]
3.2 Ganciclovir	11	917	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.34, 0.58]
3.3 Valaciclovir	2	643	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.19, 0.49]
4 CMV disease for different organ transplants	19	1980	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.35, 0.55]
4.1 CMV disease in kidney transplant recipients	11	1132	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.31, 0.57]
4.2 CMV disease in liver transplant recipients	5	616	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.29, 0.84]
4.3 CMV disease in heart transplant recipients	3	232	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.25, 0.63]
5 CMV disease and ganciclovir duration	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Six weeks or less	7	478	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.36, 0.68]
5.2 More than 6 weeks	4	439	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.21, 0.53]
6 Death	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 CMV disease	7	1300	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.08, 0.78]
6.2 Other causes	7	1300	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.44, 1.17]
7 All-cause mortality according to antiviral medication	17	1838	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.43, 0.92]
7.1 Aciclovir	5	301	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.38, 1.20]
7.2 Ganciclovir	10	894	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.29, 1.65]
7.3 Valaciclovir	2	643	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.22, 1.15]

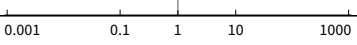
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 All-cause mortality according to CMV status	9	1026	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.41, 1.32]
8.1 All-cause mortality in CMV +ve recipients	7	738	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.30, 1.18]
8.2 All-cause mortality in CMV -ve recipients of CMV +ve organs	4	288	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.44, 4.66]
9 All-cause mortality for different organ transplants	17	1838	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.43, 0.92]
9.1 All-cause mortality in kidney transplant recipients	10	1109	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.24, 1.00]
9.2 All-cause mortality in liver transplant patients	4	497	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.39, 1.00]
9.3 All-cause mortality in heart transplant recipients	3	232	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.39, 8.51]
10 All-cause mortality and ganciclovir duration	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Six weeks or less	6	455	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.17, 4.92]
10.2 More than 6 weeks	4	439	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.30, 1.30]
11 ATG therapy and antiviral efficacy	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 CMV disease in all treated patients	11	666	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.33, 0.55]
11.2 All-cause mortality	10	643	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.33, 2.02]
12 Immunosuppression without ATG induction and antiviral efficacy	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 CMV disease in all treated patients	6	649	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.29, 0.76]
12.2 All-cause mortality	5	529	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.39, 1.00]
13 Additional outcomes - all medications	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Graft loss	10	825	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.47, 1.17]
13.2 Acute rejection	13	1420	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.78, 1.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.3 Herpes simplex and H. zoster infection	9	1483	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.19, 0.40]
13.4 Invasive fungal infection	3	189	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.19, 1.73]
13.5 Bacterial infection	3	174	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.44, 0.96]
13.6 EBV-associated PTLD	2	359	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.11, 9.51]
13.7 Protozoal infections	2	114	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.10, 0.99]
14 Acute rejection according to method of diagnosis	13	1420	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.78, 1.05]
14.1 Biopsy-proven acute rejection	5	821	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.71, 1.32]
14.2 Clinical diagnosis of acute rejection or method not stated	8	599	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.76, 1.08]
15 Valaciclovir - additional outcomes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 Total with acute rejection	2	643	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.55, 1.19]
15.2 Acute rejection in donor CMV +ve / recipient CMV -ve grafts	1	208	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.35, 0.74]
15.3 Acute rejection in CMV +ve recipients	1	408	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.63, 1.10]
16 Adverse effects	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 Leucopenia with aciclovir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.2 Renal dysfunction with aciclovir	2	159	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.27, 4.70]
16.3 Neurological dysfunction with aciclovir	1	55	Risk Ratio (M-H, Random, 95% CI)	10.62 [0.62, 183.26]
16.4 Leucopenia with ganciclovir	3	509	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.37, 2.65]
16.5 Renal dysfunction with ganciclovir	3	509	Risk Ratio (M-H, Random, 95% CI)	2.36 [0.91, 6.15]
16.6 Neurological dysfunction with ganciclovir	3	509	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.98, 2.58]
16.7 Leucopenia with valaciclovir	1	616	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.62, 1.78]

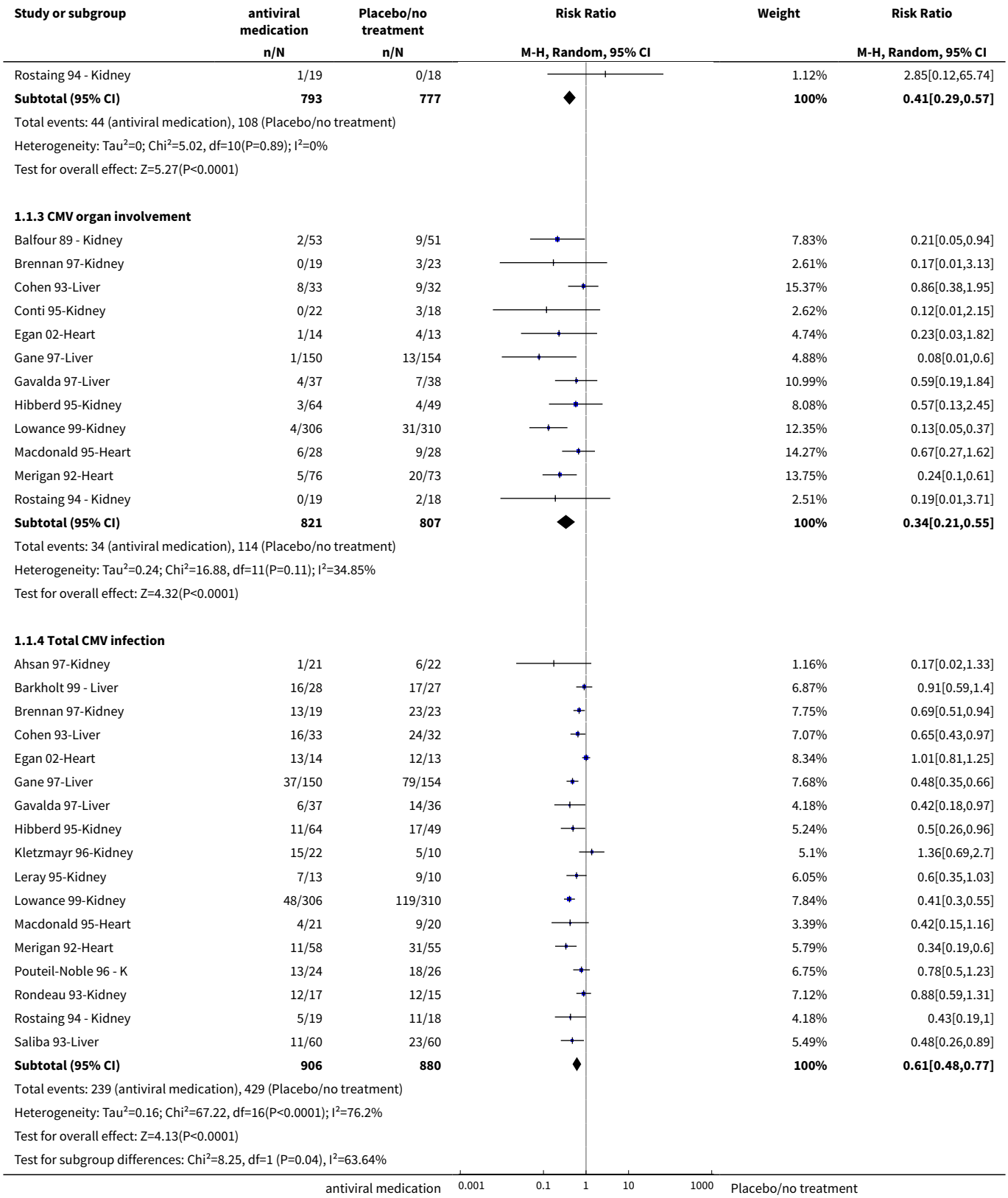
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
16.8 Renal dysfunction with valaciclovir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.9 Neurological dysfunction with valaciclovir	1	616	Risk Ratio (M-H, Random, 95% CI)	8.78 [2.69, 28.71]

Analysis 1.1. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 1 CMV disease and CMV infection in all treated patients.

Study or subgroup	antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 All symptomatic CMV disease					
Ahsan 97-Kidney	1/21	6/22		0.98%	0.17[0.02,1.33]
Balfour 89 - Kidney	4/53	15/51		3.54%	0.26[0.09,0.72]
Barkholt 99 - Liver	7/28	14/27		6.44%	0.48[0.23,1.01]
Brennan 97-Kidney	4/19	14/23		4.28%	0.35[0.14,0.88]
Cohen 93-Liver	9/33	11/32		6.48%	0.79[0.38,1.65]
Conti 95-Kidney	2/22	13/18		2.14%	0.13[0.03,0.49]
Egan 02-Heart	2/14	6/13		1.97%	0.31[0.08,1.27]
Gane 97-Liver	7/150	31/154		5.73%	0.23[0.11,0.51]
Gavalda 97-Liver	4/37	11/36		3.45%	0.35[0.12,1.01]
Hibberd 95-Kidney	9/64	16/49		6.59%	0.43[0.21,0.89]
Kletzmayr 96-Kidney	9/22	4/10		4.45%	1.02[0.41,2.54]
Leray 95-Kidney	6/13	9/10		8.52%	0.51[0.28,0.96]
Lowance 99-Kidney	18/306	60/310		11.81%	0.3[0.18,0.5]
Macdonald 95-Heart	6/28	10/28		4.87%	0.6[0.25,1.43]
Merigan 92-Heart	12/76	31/73		9.42%	0.37[0.21,0.67]
Pouteil-Noble 96 - K	6/24	14/26		5.86%	0.46[0.21,1.01]
Rondeau 93-Kidney	8/17	11/15		9.29%	0.64[0.36,1.16]
Rostaing 94 - Kidney	1/19	2/18		0.76%	0.47[0.05,4.78]
Saliba 93-Liver	4/60	14/60		3.42%	0.29[0.1,0.82]
Subtotal (95% CI)	**1006**	**975**		**100%**	**0.42[0.34,0.52]**
Total events: 119 (antiviral medication), 292 (Placebo/no treatment)					
Heterogeneity: Tau²=0.03; Chi²=20.59, df=18(P=0.3); I²=12.59%					
Test for overall effect: Z=8.35(P<0.0001)					
1.1.2 CMV syndrome					
Balfour 89 - Kidney	2/53	6/51		4.58%	0.32[0.07,1.52]
Brennan 97-Kidney	4/19	11/23		11.76%	0.44[0.17,1.16]
Cohen 93-Liver	1/33	2/32		2%	0.48[0.05,5.09]
Conti 95-Kidney	2/22	10/18		5.77%	0.16[0.04,0.65]
Egan 02-Heart	1/14	2/13		2.13%	0.46[0.05,4.53]
Gane 97-Liver	6/150	19/154		13.97%	0.32[0.13,0.79]
Gavalda 97-Liver	0/37	4/36		1.33%	0.11[0.01,1.94]
Hibberd 95-Kidney	6/64	12/49		13.46%	0.38[0.15,0.95]
Lowance 99-Kidney	14/306	29/310		28.96%	0.49[0.26,0.91]
Merigan 92-Heart	7/76	13/73		14.92%	0.52[0.22,1.22]

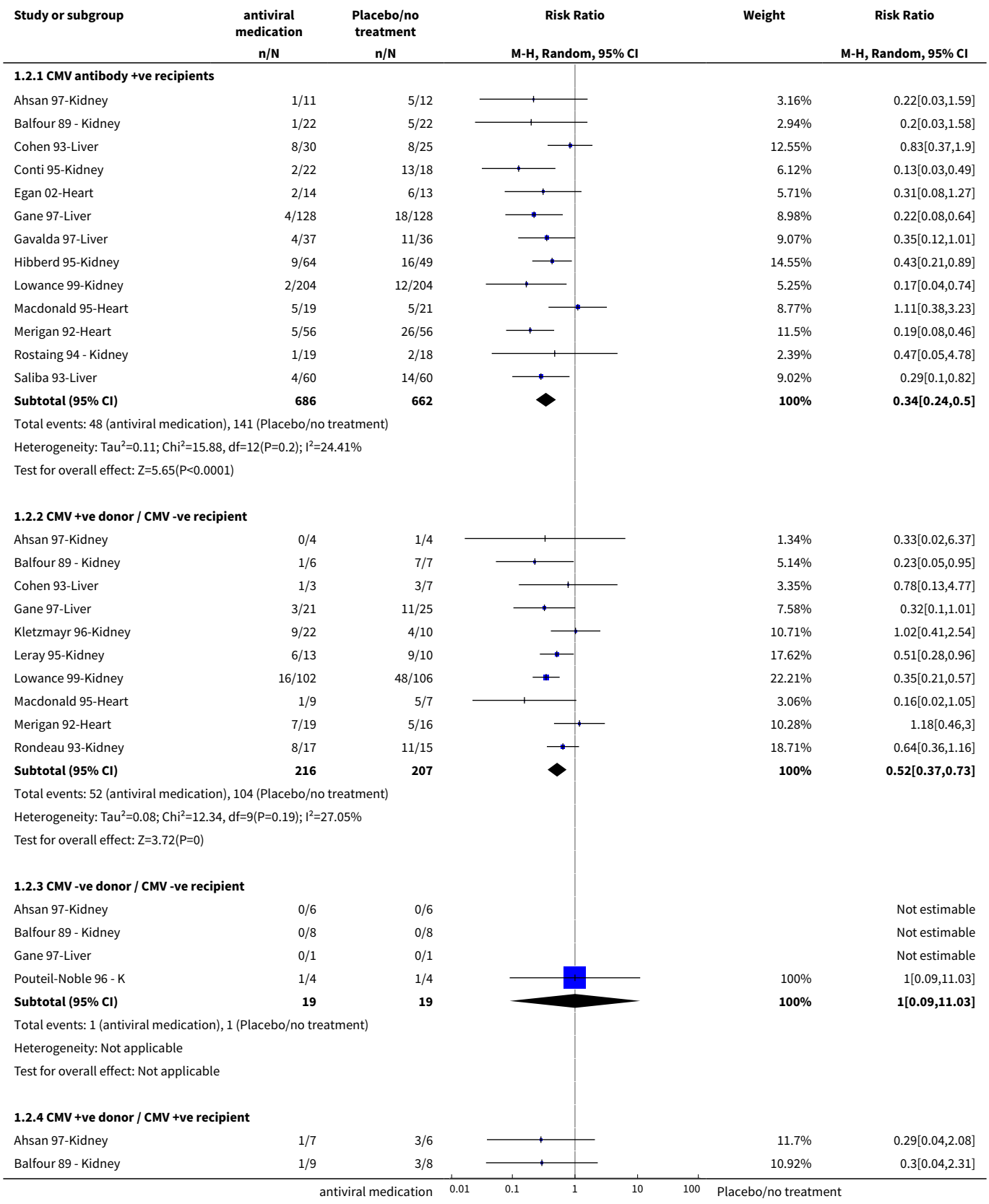


antiviral medication — Placebo/no treatment



Study or subgroup	antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Rostaing 94 - Kidney	1/19	0/18		1.12%	2.85[0.12,65.74]
Subtotal (95% CI)	**793**	**777**		**100%**	**0.41[0.29,0.57]**
Total events: 44 (antiviral medication), 108 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=5.02, df=10(P=0.89); I^2=0%					
Test for overall effect: Z=5.27(P<0.0001)					
1.1.3 CMV organ involvement					
Balfour 89 - Kidney	2/53	9/51		7.83%	0.21[0.05,0.94]
Brennan 97-Kidney	0/19	3/23		2.61%	0.17[0.01,3.13]
Cohen 93-Liver	8/33	9/32		15.37%	0.86[0.38,1.95]
Conti 95-Kidney	0/22	3/18		2.62%	0.12[0.01,2.15]
Egan 02-Heart	1/14	4/13		4.74%	0.23[0.03,1.82]
Gane 97-Liver	1/150	13/154		4.88%	0.08[0.01,0.6]
Gavalda 97-Liver	4/37	7/38		10.99%	0.59[0.19,1.84]
Hibberd 95-Kidney	3/64	4/49		8.08%	0.57[0.13,2.45]
Lowance 99-Kidney	4/306	31/310		12.35%	0.13[0.05,0.37]
Macdonald 95-Heart	6/28	9/28		14.27%	0.67[0.27,1.62]
Merigan 92-Heart	5/76	20/73		13.75%	0.24[0.1,0.61]
Rostaing 94 - Kidney	0/19	2/18		2.51%	0.19[0.01,3.71]
Subtotal (95% CI)	**821**	**807**		**100%**	**0.34[0.21,0.55]**
Total events: 34 (antiviral medication), 114 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.24; Chi^2=16.88, df=11(P=0.11); I^2=34.85%					
Test for overall effect: Z=4.32(P<0.0001)					
1.1.4 Total CMV infection					
Ahsan 97-Kidney	1/21	6/22		1.16%	0.17[0.02,1.33]
Barkholt 99 - Liver	16/28	17/27		6.87%	0.91[0.59,1.4]
Brennan 97-Kidney	13/19	23/23		7.75%	0.69[0.51,0.94]
Cohen 93-Liver	16/33	24/32		7.07%	0.65[0.43,0.97]
Egan 02-Heart	13/14	12/13		8.34%	1.01[0.81,1.25]
Gane 97-Liver	37/150	79/154		7.68%	0.48[0.35,0.66]
Gavalda 97-Liver	6/37	14/36		4.18%	0.42[0.18,0.97]
Hibberd 95-Kidney	11/64	17/49		5.24%	0.5[0.26,0.96]
Kletzmayr 96-Kidney	15/22	5/10		5.1%	1.36[0.69,2.7]
Leray 95-Kidney	7/13	9/10		6.05%	0.6[0.35,1.03]
Lowance 99-Kidney	48/306	119/310		7.84%	0.41[0.3,0.55]
Macdonald 95-Heart	4/21	9/20		3.39%	0.42[0.15,1.16]
Merigan 92-Heart	11/58	31/55		5.79%	0.34[0.19,0.6]
Pouteil-Noble 96 - K	13/24	18/26		6.75%	0.78[0.5,1.23]
Rondeau 93-Kidney	12/17	12/15		7.12%	0.88[0.59,1.31]
Rostaing 94 - Kidney	5/19	11/18		4.18%	0.43[0.19,1]
Saliba 93-Liver	11/60	23/60		5.49%	0.48[0.26,0.89]
Subtotal (95% CI)	**906**	**880**		**100%**	**0.61[0.48,0.77]**
Total events: 239 (antiviral medication), 429 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.16; Chi^2=67.22, df=16(P<0.0001); I^2=76.2%					
Test for overall effect: Z=4.13(P<0.0001)					
Test for subgroup differences: Chi^2=8.25, df=1 (P=0.04), I^2=63.64%					

Analysis 1.2. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 2 All symptomatic CMV disease stratified by antibody status.

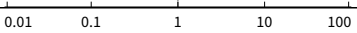


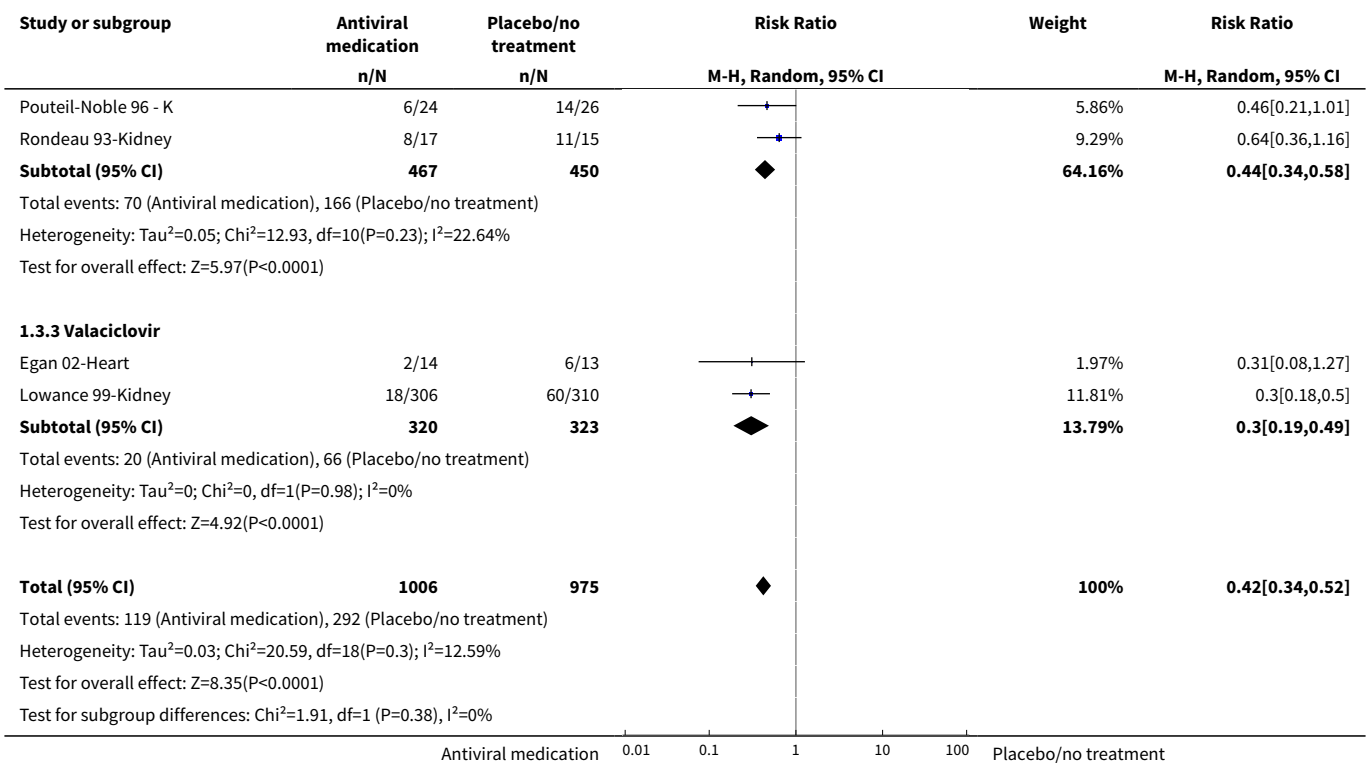
Study or subgroup	antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 CMV antibody +ve recipients					
Ahsan 97-Kidney	1/11	5/12		3.16%	0.22[0.03,1.59]
Balfour 89 - Kidney	1/22	5/22		2.94%	0.2[0.03,1.58]
Cohen 93-Liver	8/30	8/25		12.55%	0.83[0.37,1.9]
Conti 95-Kidney	2/22	13/18		6.12%	0.13[0.03,0.49]
Egan 02-Heart	2/14	6/13		5.71%	0.31[0.08,1.27]
Gane 97-Liver	4/128	18/128		8.98%	0.22[0.08,0.64]
Gavalda 97-Liver	4/37	11/36		9.07%	0.35[0.12,1.01]
Hibberd 95-Kidney	9/64	16/49		14.55%	0.43[0.21,0.89]
Lowance 99-Kidney	2/204	12/204		5.25%	0.17[0.04,0.74]
Macdonald 95-Heart	5/19	5/21		8.77%	1.11[0.38,3.23]
Merigan 92-Heart	5/56	26/56		11.5%	0.19[0.08,0.46]
Rostaing 94 - Kidney	1/19	2/18		2.39%	0.47[0.05,4.78]
Saliba 93-Liver	4/60	14/60		9.02%	0.29[0.1,0.82]
Subtotal (95% CI)	**686**	**662**		**100%**	**0.34[0.24,0.5]**
Total events: 48 (antiviral medication), 141 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.11; Chi^2=15.88, df=12(P=0.2); I^2=24.41%					
Test for overall effect: Z=5.65(P<0.0001)					
1.2.2 CMV +ve donor / CMV -ve recipient					
Ahsan 97-Kidney	0/4	1/4		1.34%	0.33[0.02,6.37]
Balfour 89 - Kidney	1/6	7/7		5.14%	0.23[0.05,0.95]
Cohen 93-Liver	1/3	3/7		3.35%	0.78[0.13,4.77]
Gane 97-Liver	3/21	11/25		7.58%	0.32[0.1,1.01]
Kletzmayr 96-Kidney	9/22	4/10		10.71%	1.02[0.41,2.54]
Leray 95-Kidney	6/13	9/10		17.62%	0.51[0.28,0.96]
Lowance 99-Kidney	16/102	48/106		22.21%	0.35[0.21,0.57]
Macdonald 95-Heart	1/9	5/7		3.06%	0.16[0.02,1.05]
Merigan 92-Heart	7/19	5/16		10.28%	1.18[0.46,3]
Rondeau 93-Kidney	8/17	11/15		18.71%	0.64[0.36,1.16]
Subtotal (95% CI)	**216**	**207**		**100%**	**0.52[0.37,0.73]**
Total events: 52 (antiviral medication), 104 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.08; Chi^2=12.34, df=9(P=0.19); I^2=27.05%					
Test for overall effect: Z=3.72(P=0)					
1.2.3 CMV -ve donor / CMV -ve recipient					
Ahsan 97-Kidney	0/6	0/6			Not estimable
Balfour 89 - Kidney	0/8	0/8			Not estimable
Gane 97-Liver	0/1	0/1			Not estimable
Pouteil-Noble 96 - K	1/4	1/4		100%	1[0.09,11.03]
Subtotal (95% CI)	**19**	**19**		**100%**	**1[0.09,11.03]**
Total events: 1 (antiviral medication), 1 (Placebo/no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.2.4 CMV +ve donor / CMV +ve recipient					
Ahsan 97-Kidney	1/7	3/6		11.7%	0.29[0.04,2.08]
Balfour 89 - Kidney	1/9	3/8		10.92%	0.3[0.04,2.31]

Study or subgroup	antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Conti 95-Kidney	2/18	11/11		34.13%	0.14[0.04,0.44]
Gane 97-Liver	2/76	14/77		21.97%	0.14[0.03,0.62]
Gavalda 97-Liver	2/32	8/32		21.29%	0.25[0.06,1.09]
Subtotal (95% CI)	**142**	**134**		**100%**	**0.19[0.09,0.37]**
Total events: 8 (antiviral medication), 39 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.91, df=4(P=0.92); I^2=0%					
Test for overall effect: Z=4.84(P<0.0001)					
1.2.5 CMV -ve donor / CMV +ve recipient					
Ahsan 97-Kidney	0/4	2/6		14.69%	0.28[0.02,4.66]
Balfour 89 - Kidney	0/13	2/14		13.36%	0.21[0.01,4.08]
Conti 95-Kidney	0/4	2/7		14.57%	0.32[0.02,5.39]
Gane 97-Liver	2/52	4/51		42.51%	0.49[0.09,2.56]
Gavalda 97-Liver	0/5	2/4		14.87%	0.17[0.01,2.73]
Subtotal (95% CI)	**78**	**82**		**100%**	**0.32[0.11,0.95]**
Total events: 2 (antiviral medication), 12 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.55, df=4(P=0.97); I^2=0%					
Test for overall effect: Z=2.05(P=0.04)					
Test for subgroup differences: Chi^2=8.24, df=1 (P=0.08), I^2=51.44%					

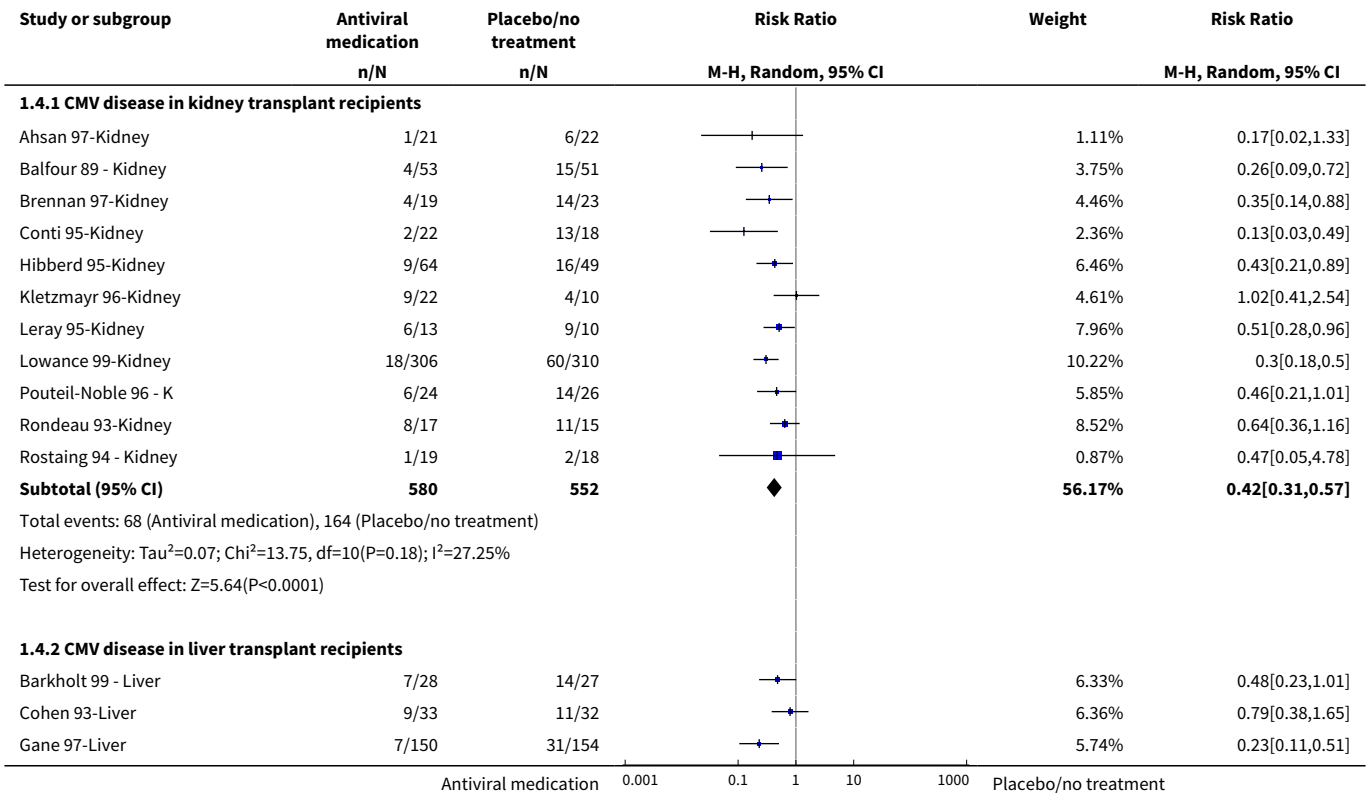
Analysis 1.3. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 3 CMV disease in all patients by antiviral medication.

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Aciclovir					
Balfour 89 - Kidney	4/53	15/51		3.54%	0.26[0.09,0.72]
Barkholt 99 - Liver	7/28	14/27		6.44%	0.48[0.23,1.01]
Gavalda 97-Liver	4/37	11/36		3.45%	0.35[0.12,1.01]
Kletzmayr 96-Kidney	9/22	4/10		4.45%	1.02[0.41,2.54]
Rostaing 94 - Kidney	1/19	2/18		0.76%	0.47[0.05,4.78]
Saliba 93-Liver	4/60	14/60		3.42%	0.29[0.1,0.82]
Subtotal (95% CI)	**219**	**202**		**22.05%**	**0.45[0.29,0.69]**
Total events: 29 (Antiviral medication), 60 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.02; Chi^2=5.42, df=5(P=0.37); I^2=7.81%					
Test for overall effect: Z=3.68(P=0)					
1.3.2 Ganciclovir					
Ahsan 97-Kidney	1/21	6/22		0.98%	0.17[0.02,1.33]
Brennan 97-Kidney	4/19	14/23		4.28%	0.35[0.14,0.88]
Cohen 93-Liver	9/33	11/32		6.48%	0.79[0.38,1.65]
Conti 95-Kidney	2/22	13/18		2.14%	0.13[0.03,0.49]
Gane 97-Liver	7/150	31/154		5.73%	0.23[0.11,0.51]
Hibberd 95-Kidney	9/64	16/49		6.59%	0.43[0.21,0.89]
Leray 95-Kidney	6/13	9/10		8.52%	0.51[0.28,0.96]
Macdonald 95-Heart	6/28	10/28		4.87%	0.6[0.25,1.43]
Merigan 92-Heart	12/76	31/73		9.42%	0.37[0.21,0.67]





Analysis 1.4. Comparison 1 Antiviral prophylaxis versus placebo/ no treatment, Outcome 4 CMV disease for different organ transplants.



Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gavalda 97-Liver	10/36	11/36		6.53%	0.91[0.44,1.87]
Saliba 93-Liver	4/60	14/60		3.65%	0.29[0.1,0.82]
Subtotal (95% CI)	**307**	**309**		**28.62%**	**0.49[0.29,0.84]**
Total events: 37 (Antiviral medication), 81 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.22; Chi^2=9.33, df=4(P=0.05); I^2=57.13%					
Test for overall effect: Z=2.57(P=0.01)					
1.4.3 CMV disease in heart transplant recipients					
Egan 02-Heart	2/14	6/13		2.19%	0.31[0.08,1.27]
Macdonald 95-Heart	5/28	10/28		4.41%	0.5[0.2,1.28]
Merigan 92-Heart	12/76	31/73		8.61%	0.37[0.21,0.67]
Subtotal (95% CI)	**118**	**114**		**15.21%**	**0.39[0.25,0.63]**
Total events: 19 (Antiviral medication), 47 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.4, df=2(P=0.82); I^2=0%					
Test for overall effect: Z=3.92(P<0.0001)					
Total (95% CI)	**1005**	**975**		**100%**	**0.44[0.35,0.55]**
Total events: 124 (Antiviral medication), 292 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.06; Chi^2=24.15, df=18(P=0.15); I^2=25.47%					
Test for overall effect: Z=7.32(P<0.0001)					
Test for subgroup differences: Chi^2=0.38, df=1 (P=0.83), I^2=0%					

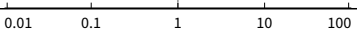
Antiviral medication — Placebo/no treatment

Analysis 1.5. Comparison 1 Antiviral prophylaxis versus placebo/ no treatment, Outcome 5 CMV disease and ganciclovir duration.

Study or subgroup	antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Six weeks or less					
Cohen 93-Liver	9/33	11/32		13.93%	0.79[0.38,1.65]
Conti 95-Kidney	2/22	13/18		4.93%	0.13[0.03,0.49]
Hibberd 95-Kidney	9/64	16/49		14.15%	0.43[0.21,0.89]
Leray 95-Kidney	6/13	9/10		17.75%	0.51[0.28,0.96]
Macdonald 95-Heart	6/28	10/28		10.73%	0.6[0.25,1.43]
Merigan 92-Heart	12/76	31/73		19.38%	0.37[0.21,0.67]
Rondeau 93-Kidney	8/17	11/15		19.13%	0.64[0.36,1.16]
Subtotal (95% CI)	**253**	**225**		**100%**	**0.49[0.36,0.68]**
Total events: 52 (antiviral medication), 101 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.04; Chi^2=7.95, df=6(P=0.24); I^2=24.52%					
Test for overall effect: Z=4.4(P<0.0001)					
1.5.2 More than 6 weeks					
Ahsan 97-Kidney	1/21	6/22		5.24%	0.17[0.02,1.33]
Brennan 97-Kidney	4/19	14/23		24.95%	0.35[0.14,0.88]
Gane 97-Liver	7/150	29/154		34.24%	0.25[0.11,0.55]
Pouteil-Noble 96 - K	6/24	14/26		35.58%	0.46[0.21,1.01]
Subtotal (95% CI)	**214**	**225**		**100%**	**0.33[0.21,0.53]**
Total events: 18 (antiviral medication), 63 (Placebo/no treatment)					

Antiviral medication — Placebo/no treatment

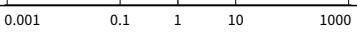
Study or subgroup	antiviral medication	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=1.7, df=3(P=0.64); I²=0%					
Test for overall effect: Z=4.67(P<0.0001)					
Test for subgroup differences: Chi²=1.99, df=1 (P=0.16), I²=49.69%					



Antiviral medication — Placebo/no treatment

Analysis 1.6. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 6 Death.

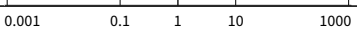
Study or subgroup	Antiviral medication	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.6.1 CMV disease					
Ahsan 97-Kidney	0/21	1/22		12.42%	0.35[0.01,8.11]
Balfour 89 - Kidney	0/53	2/51		13.55%	0.19[0.01,3.92]
Barkholt 99 - Liver	1/28	2/27		22.43%	0.48[0.05,5.01]
Cohen 93-Liver	0/33	1/32		12.28%	0.32[0.01,7.66]
Gane 97-Liver	0/150	7/154		15.1%	0.07[0,1.19]
Hibberd 95-Kidney	0/64	1/49		12.17%	0.26[0.01,6.16]
Lowance 99-Kidney	0/306	1/310		12.04%	0.34[0.01,8.26]
Subtotal (95% CI)	**655**	**645**		**100%**	**0.26[0.08,0.78]**
Total events: 1 (Antiviral medication), 15 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=1.32, df=6(P=0.97); I²=0%					
Test for overall effect: Z=2.4(P=0.02)					
1.6.2 Other causes					
Ahsan 97-Kidney	0/21	0/22			Not estimable
Balfour 89 - Kidney	2/53	1/51		4.34%	1.92[0.18,20.58]
Barkholt 99 - Liver	5/28	8/27		25.13%	0.6[0.23,1.61]
Cohen 93-Liver	1/33	5/32		5.57%	0.19[0.02,1.57]
Gane 97-Liver	10/150	9/154		32.02%	1.14[0.48,2.73]
Hibberd 95-Kidney	1/64	1/49		3.23%	0.77[0.05,11.94]
Lowance 99-Kidney	7/306	13/310		29.72%	0.55[0.22,1.35]
Subtotal (95% CI)	**655**	**645**		**100%**	**0.71[0.44,1.17]**
Total events: 26 (Antiviral medication), 37 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=3.74, df=5(P=0.59); I²=0%					
Test for overall effect: Z=1.34(P=0.18)					
Test for subgroup differences: Chi²=2.72, df=1 (P=0.1), I²=63.21%					



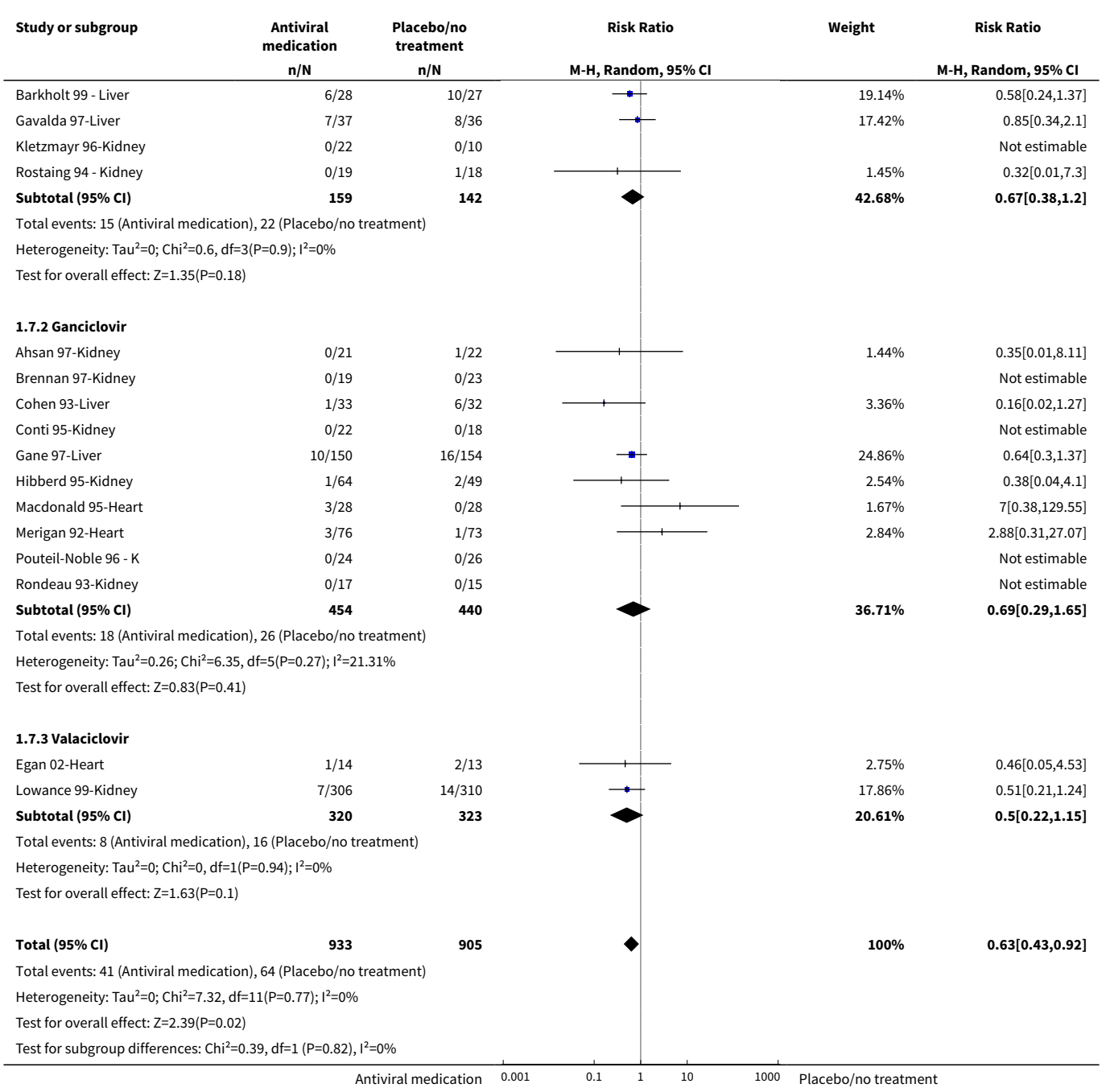
Antiviral medication — Placebo/no treatment

Analysis 1.7. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 7 All-cause mortality according to antiviral medication.

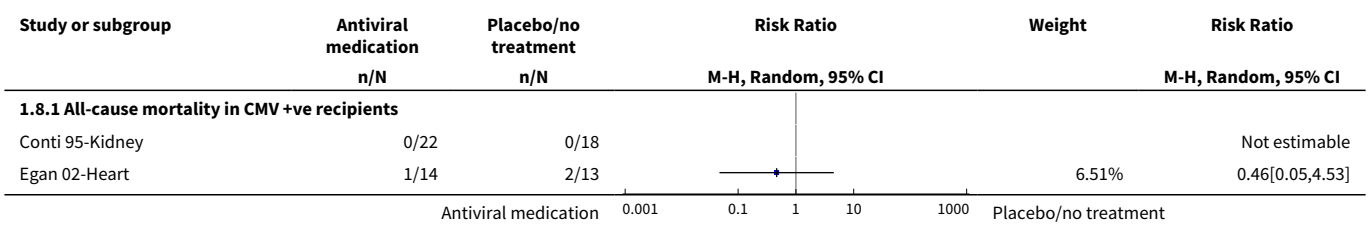
Study or subgroup	Antiviral medication	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.7.1 Aciclovir					
Balfour 89 - Kidney	2/53	3/51		4.67%	0.64[0.11,3.68]

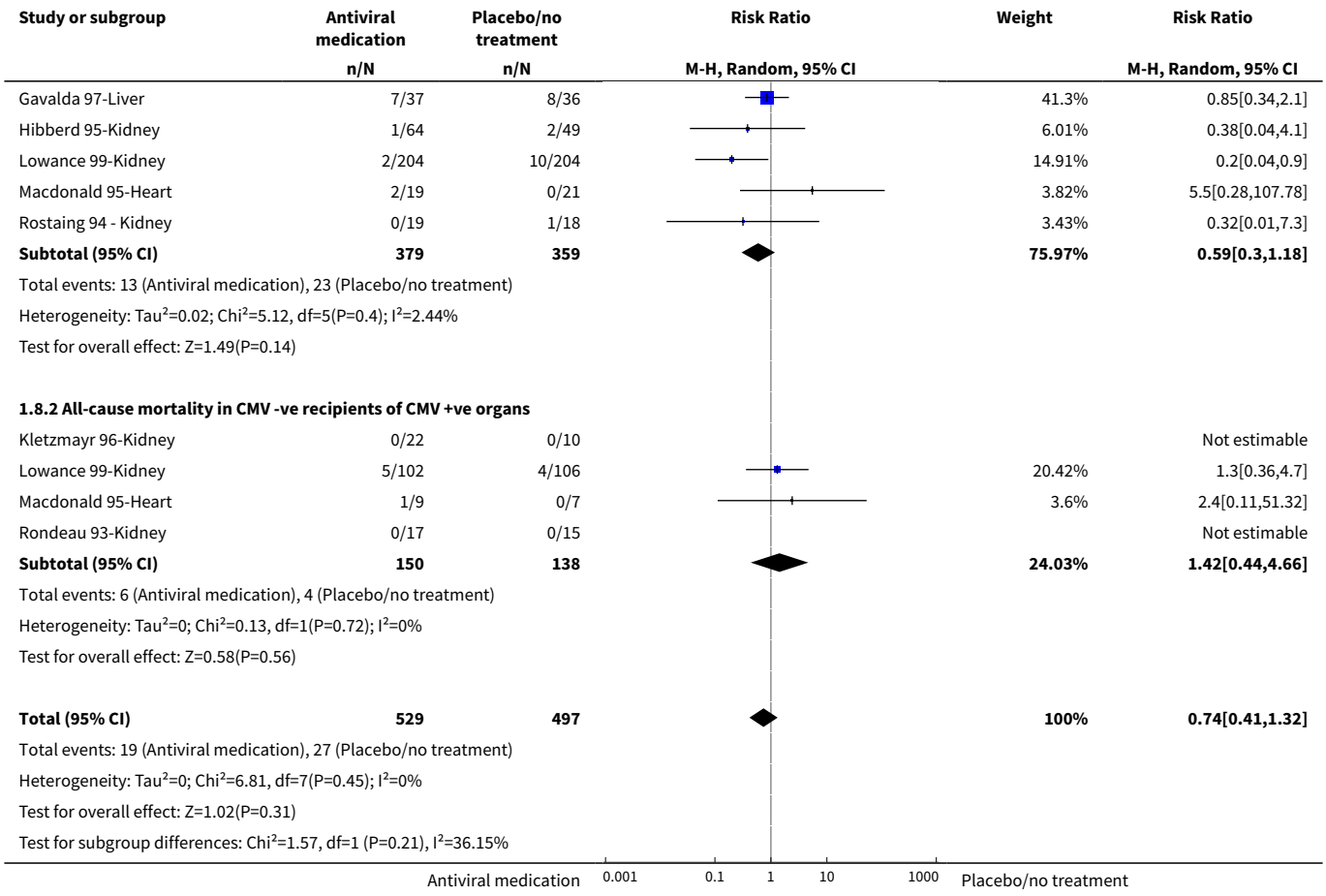


Antiviral medication — Placebo/no treatment



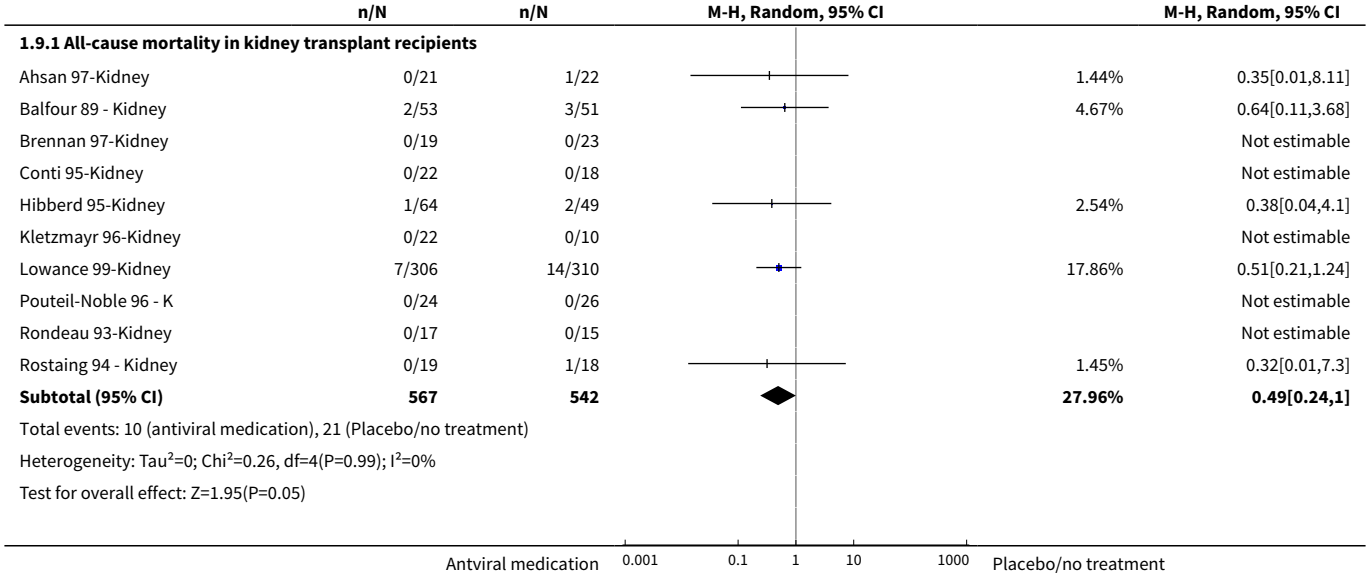
Analysis 1.8. Comparison 1 Antiviral prophylaxis versus placebo/ no treatment, Outcome 8 All-cause mortality according to CMV status.



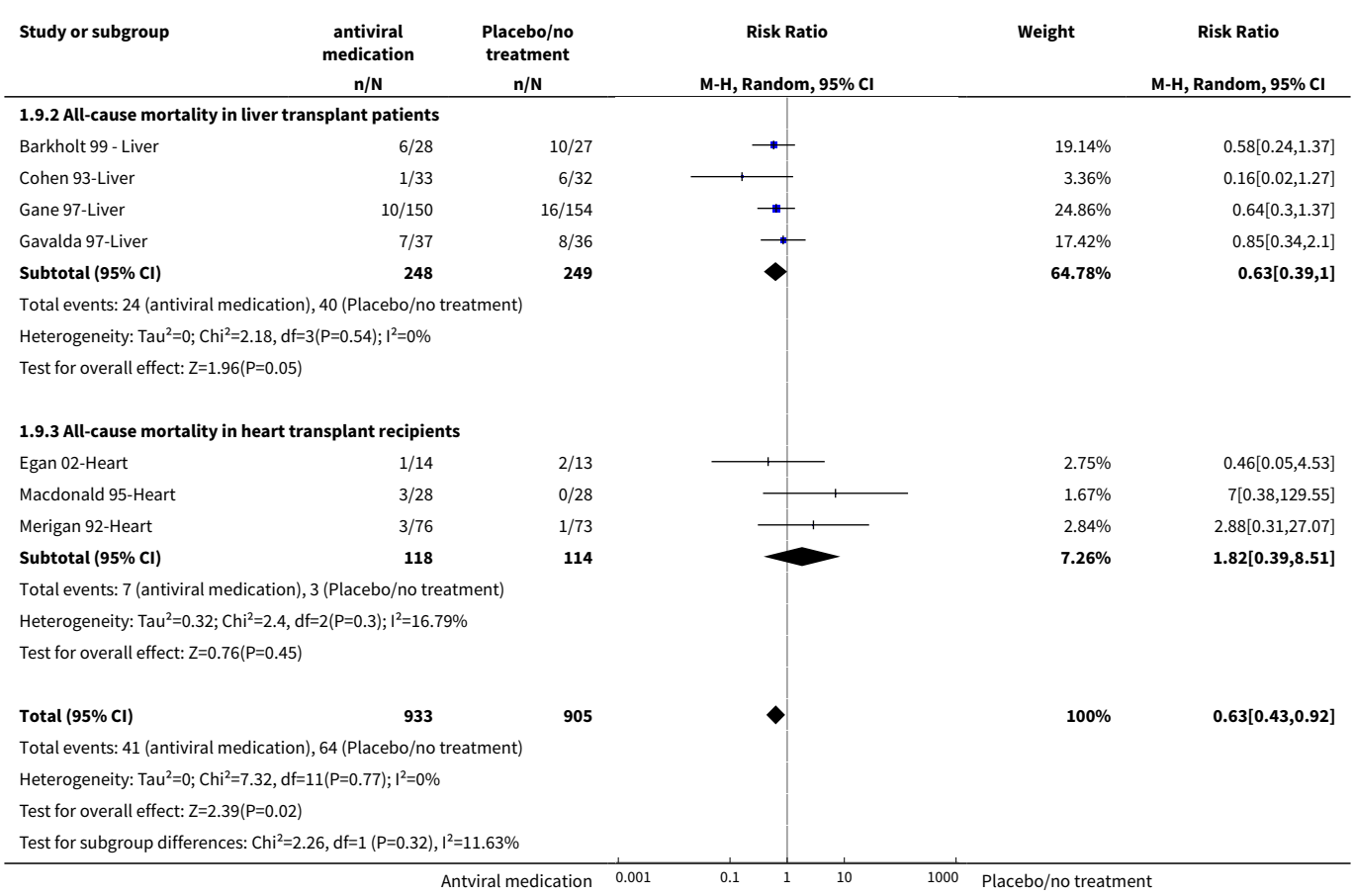


Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gavalda 97-Liver	7/37	8/36		41.3%	0.85[0.34,2.1]
Hibberd 95-Kidney	1/64	2/49		6.01%	0.38[0.04,4.1]
Lowance 99-Kidney	2/204	10/204		14.91%	0.2[0.04,0.9]
Macdonald 95-Heart	2/19	0/21		3.82%	5.5[0.28,107.78]
Rostaing 94 - Kidney	0/19	1/18		3.43%	0.32[0.01,7.3]
Subtotal (95% CI)	**379**	**359**		**75.97%**	**0.59[0.3,1.18]**
Total events: 13 (Antiviral medication), 23 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.02; Chi^2=5.12, df=5(P=0.4); I^2=2.44%					
Test for overall effect: Z=1.49(P=0.14)					
1.8.2 All-cause mortality in CMV -ve recipients of CMV +ve organs					
Kletzmayr 96-Kidney	0/22	0/10			Not estimable
Lowance 99-Kidney	5/102	4/106		20.42%	1.3[0.36,4.7]
Macdonald 95-Heart	1/9	0/7		3.6%	2.4[0.11,51.32]
Rondeau 93-Kidney	0/17	0/15			Not estimable
Subtotal (95% CI)	**150**	**138**		**24.03%**	**1.42[0.44,4.66]**
Total events: 6 (Antiviral medication), 4 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.13, df=1(P=0.72); I^2=0%					
Test for overall effect: Z=0.58(P=0.56)					
Total (95% CI)	**529**	**497**		**100%**	**0.74[0.41,1.32]**
Total events: 19 (Antiviral medication), 27 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=6.81, df=7(P=0.45); I^2=0%					
Test for overall effect: Z=1.02(P=0.31)					
Test for subgroup differences: Chi^2=1.57, df=1 (P=0.21), I^2=36.15%					

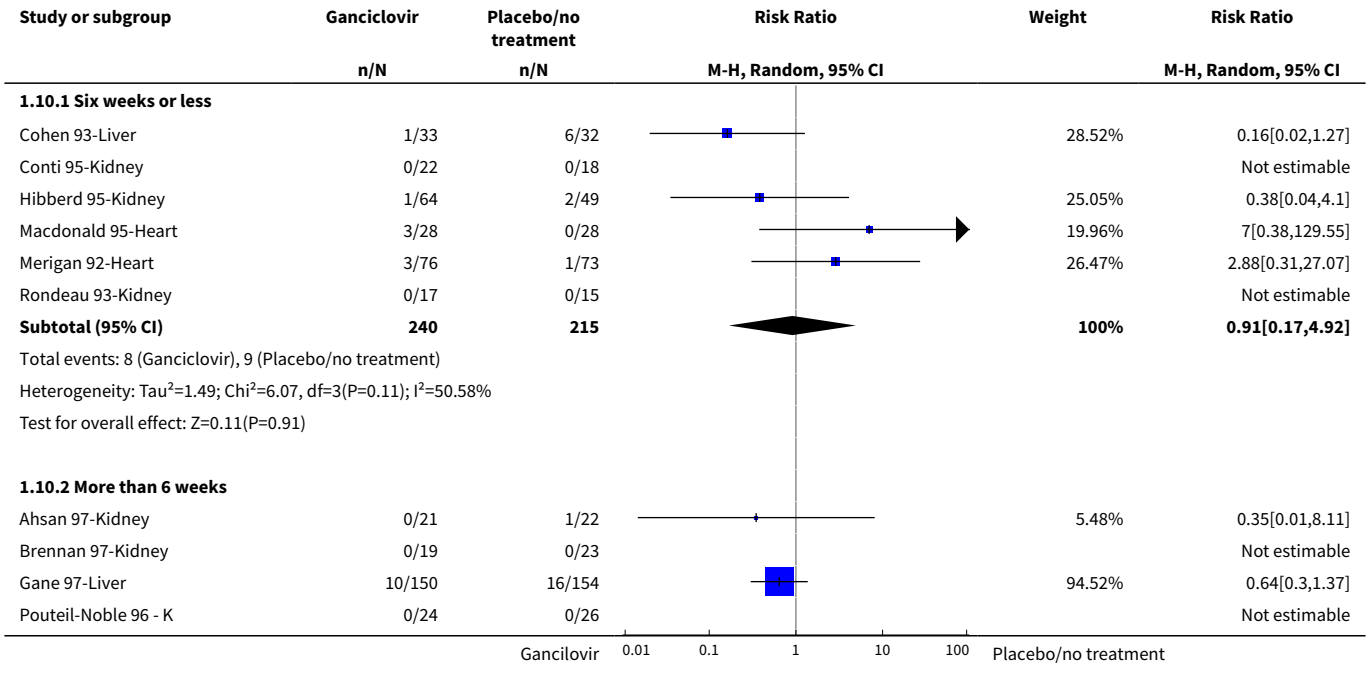
Analysis 1.9. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 9 All-cause mortality for different organ transplants.



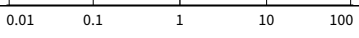
Study or subgroup	antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 All-cause mortality in kidney transplant recipients					
Ahsan 97-Kidney	0/21	1/22		1.44%	0.35[0.01,8.11]
Balfour 89 - Kidney	2/53	3/51		4.67%	0.64[0.11,3.68]
Brennan 97-Kidney	0/19	0/23			Not estimable
Conti 95-Kidney	0/22	0/18			Not estimable
Hibberd 95-Kidney	1/64	2/49		2.54%	0.38[0.04,4.1]
Kletzmayr 96-Kidney	0/22	0/10			Not estimable
Lowance 99-Kidney	7/306	14/310		17.86%	0.51[0.21,1.24]
Pouteil-Noble 96 - K	0/24	0/26			Not estimable
Rondeau 93-Kidney	0/17	0/15			Not estimable
Rostaing 94 - Kidney	0/19	1/18		1.45%	0.32[0.01,7.3]
Subtotal (95% CI)	**567**	**542**		**27.96%**	**0.49[0.24,1]**
Total events: 10 (antiviral medication), 21 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.26, df=4(P=0.99); I^2=0%					
Test for overall effect: Z=1.95(P=0.05)					



Analysis 1.10. Comparison 1 Antiviral prophylaxis versus placebo/ no treatment, Outcome 10 All-cause mortality and ganciclovir duration.



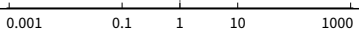
Study or subgroup	Ganciclovir	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Subtotal (95% CI)	**214**	**225**		**100%**	**0.62[0.3,1.3]**
Total events: 10 (Ganciclovir), 17 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=0.14, df=1(P=0.71); I²=0%					
Test for overall effect: Z=1.27(P=0.2)					
Test for subgroup differences: Chi²=0.17, df=1 (P=0.68), I²=0%					



Gancilovir Placebo/no treatment

Analysis 1.11. Comparison 1 Antiviral prophylaxis versus placebo/ no treatment, Outcome 11 ATG therapy and antiviral efficacy.

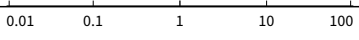
Study or subgroup	Antiviral medication	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.11.1 CMV disease in all treated patients					
Ahsan 97-Kidney	1/21	6/22		1.6%	0.17[0.02,1.33]
Balfour 89 - Kidney	4/53	15/51		6.16%	0.26[0.09,0.72]
Brennan 97-Kidney	4/19	14/23		7.61%	0.35[0.14,0.88]
Conti 95-Kidney	2/22	13/18		3.6%	0.13[0.03,0.49]
Egan 02-Heart	2/14	6/13		3.31%	0.31[0.08,1.27]
Hibberd 95-Kidney	9/64	16/49		12.46%	0.43[0.21,0.89]
Leray 95-Kidney	6/13	9/10		16.99%	0.51[0.28,0.96]
Macdonald 95-Heart	6/28	10/28		8.78%	0.6[0.25,1.43]
Merigan 92-Heart	12/76	31/73		19.31%	0.37[0.21,0.67]
Rondeau 93-Kidney	8/17	11/15		18.95%	0.64[0.36,1.16]
Rostaing 94 - Kidney	1/19	2/18		1.23%	0.47[0.05,4.78]
Subtotal (95% CI)	**346**	**320**		**100%**	**0.43[0.33,0.55]**
Total events: 55 (Antiviral medication), 133 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=8.99, df=10(P=0.53); I²=0%					
Test for overall effect: Z=6.52(P<0.0001)					
1.11.2 All-cause mortality					
Ahsan 97-Kidney	0/21	1/22		8.3%	0.35[0.01,8.11]
Balfour 89 - Kidney	2/53	3/51		26.91%	0.64[0.11,3.68]
Brennan 97-Kidney	0/19	0/23			Not estimable
Conti 95-Kidney	0/22	0/18			Not estimable
Egan 02-Heart	1/14	2/13		15.82%	0.46[0.05,4.53]
Hibberd 95-Kidney	1/64	2/49		14.61%	0.38[0.04,4.1]
Macdonald 95-Heart	3/28	0/28		9.65%	7[0.38,129.55]
Merigan 92-Heart	3/76	1/73		16.37%	2.88[0.31,27.07]
Rondeau 93-Kidney	0/17	0/15			Not estimable
Rostaing 94 - Kidney	0/19	1/18		8.34%	0.32[0.01,7.3]
Subtotal (95% CI)	**333**	**310**		**100%**	**0.82[0.33,2.02]**
Total events: 10 (Antiviral medication), 10 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=4.73, df=6(P=0.58); I²=0%					
Test for overall effect: Z=0.44(P=0.66)					
Test for subgroup differences: Chi²=1.83, df=1 (P=0.18), I²=45.31%					



Antiviral medication Placebo/no treatment

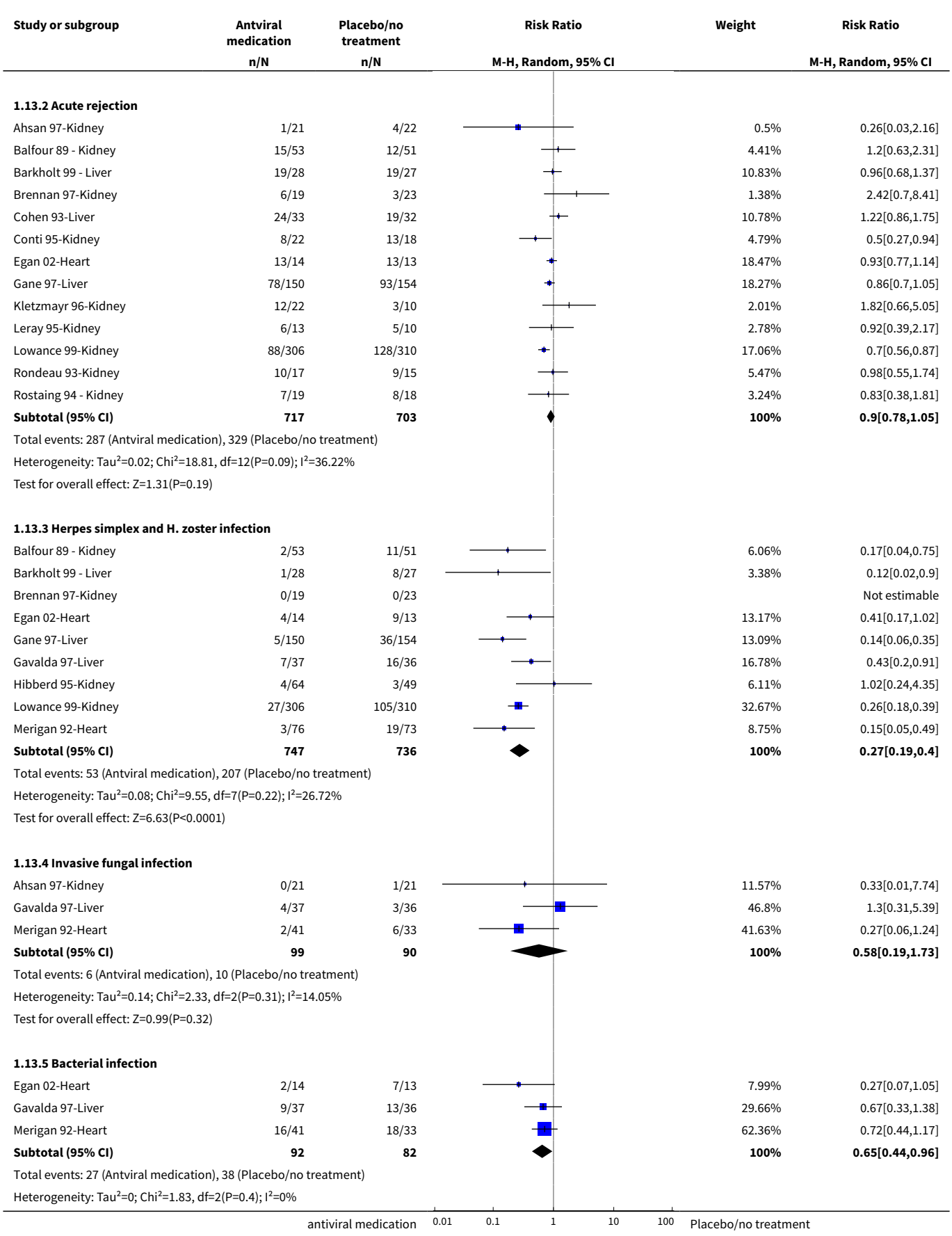
Analysis 1.12. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 12 Immunosuppression without ATG induction and antiviral efficacy.

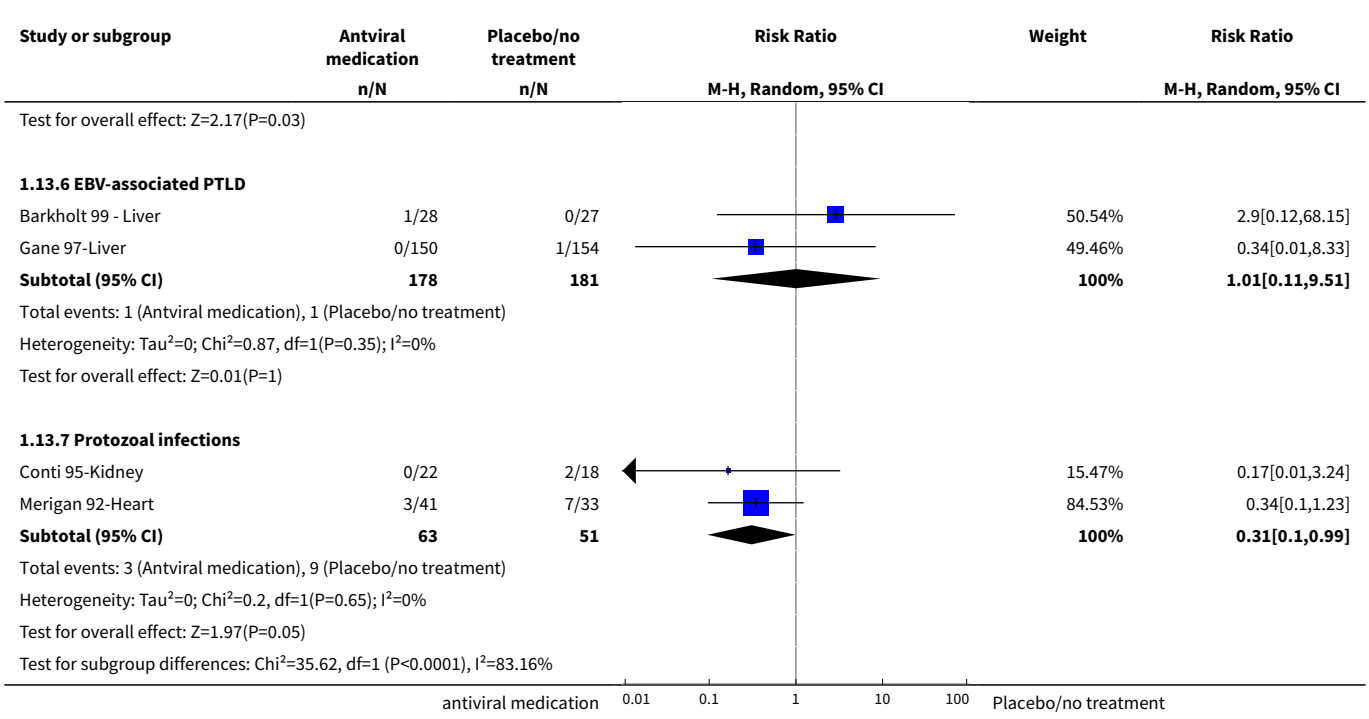
Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 CMV disease in all treated patients					
Barkholt 99 - Liver	7/28	14/27		19.55%	0.48[0.23,1.01]
Cohen 93-Liver	9/33	11/32		19.62%	0.79[0.38,1.65]
Gane 97-Liver	7/150	31/154		18.35%	0.23[0.11,0.51]
Gavalda 97-Liver	4/37	11/36		13.37%	0.35[0.12,1.01]
Kletzmayr 96-Kidney	9/22	4/10		15.8%	1.02[0.41,2.54]
Saliba 93-Liver	4/60	14/60		13.31%	0.29[0.1,0.82]
Subtotal (95% CI)	**330**	**319**		**100%**	**0.47[0.29,0.76]**
Total events: 40 (Antiviral medication), 85 (Placebo/no treatment)					
Heterogeneity: Tau²=0.17; Chi²=9.49, df=5(P=0.09); I²=47.29%					
Test for overall effect: Z=3.07(P=0)					
1.12.2 All-cause mortality					
Barkholt 99 - Liver	6/28	10/27		29.55%	0.58[0.24,1.37]
Cohen 93-Liver	1/33	6/32		5.19%	0.16[0.02,1.27]
Gane 97-Liver	10/150	16/154		38.37%	0.64[0.3,1.37]
Gavalda 97-Liver	7/37	8/36		26.9%	0.85[0.34,2.1]
Kletzmayr 96-Kidney	0/22	0/10			Not estimable
Subtotal (95% CI)	**270**	**259**		**100%**	**0.63[0.39,1]**
Total events: 24 (Antiviral medication), 40 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=2.18, df=3(P=0.54); I²=0%					
Test for overall effect: Z=1.96(P=0.05)					
Test for subgroup differences: Chi²=0.7, df=1 (P=0.4), I²=0%					



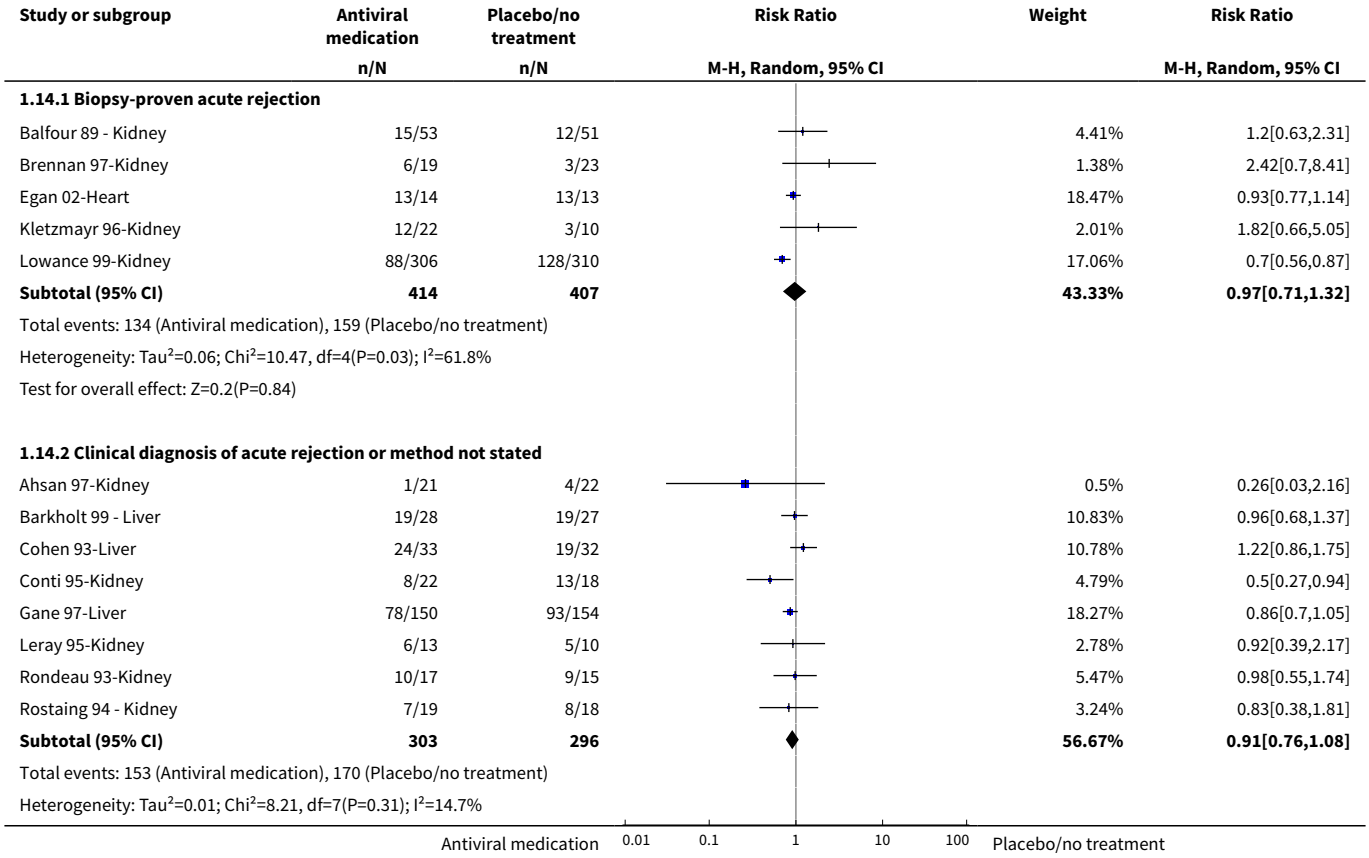
Analysis 1.13. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 13 Additional outcomes - all medications.

Study or subgroup	Antviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Graft loss					
Ahsan 97-Kidney	0/21	0/22			Not estimable
Balfour 89 - Kidney	3/53	5/51		11.05%	0.58[0.15,2.29]
Barkholt 99 - Liver	4/28	4/27		12.79%	0.96[0.27,3.47]
Cohen 93-Liver	3/33	5/32		11.59%	0.58[0.15,2.24]
Conti 95-Kidney	2/22	2/18		6.08%	0.82[0.13,5.25]
Gane 97-Liver	8/150	10/154		25.8%	0.82[0.33,2.02]
Hibberd 95-Kidney	6/64	6/49		18.39%	0.77[0.26,2.23]
Kletzmayr 96-Kidney	2/22	2/10		6.4%	0.45[0.07,2.78]
Rondeau 93-Kidney	1/17	2/15		3.98%	0.44[0.04,4.39]
Rostaing 94 - Kidney	2/19	1/18		3.93%	1.89[0.19,19.13]
Subtotal (95% CI)	**429**	**396**		**100%**	**0.74[0.47,1.17]**
Total events: 31 (Antviral medication), 37 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=1.59, df=8(P=0.99); I²=0%					
Test for overall effect: Z=1.27(P=0.2)					





Analysis 1.14. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 14 Acute rejection according to method of diagnosis.



Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.12(P=0.26)					
Total (95% CI)	**717**	**703**		**100%**	**0.9[0.78,1.05]**
Total events: 287 (Antiviral medication), 329 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.02; Chi^2=18.81, df=12(P=0.09); I^2=36.22%					
Test for overall effect: Z=1.31(P=0.19)					
Test for subgroup differences: Chi^2=0.13, df=1 (P=0.71), I^2=0%					

Antiviral medication 0.01 0.1 1 10 100 Placebo/no treatment

Analysis 1.15. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 15 Valaciclovir - additional outcomes.

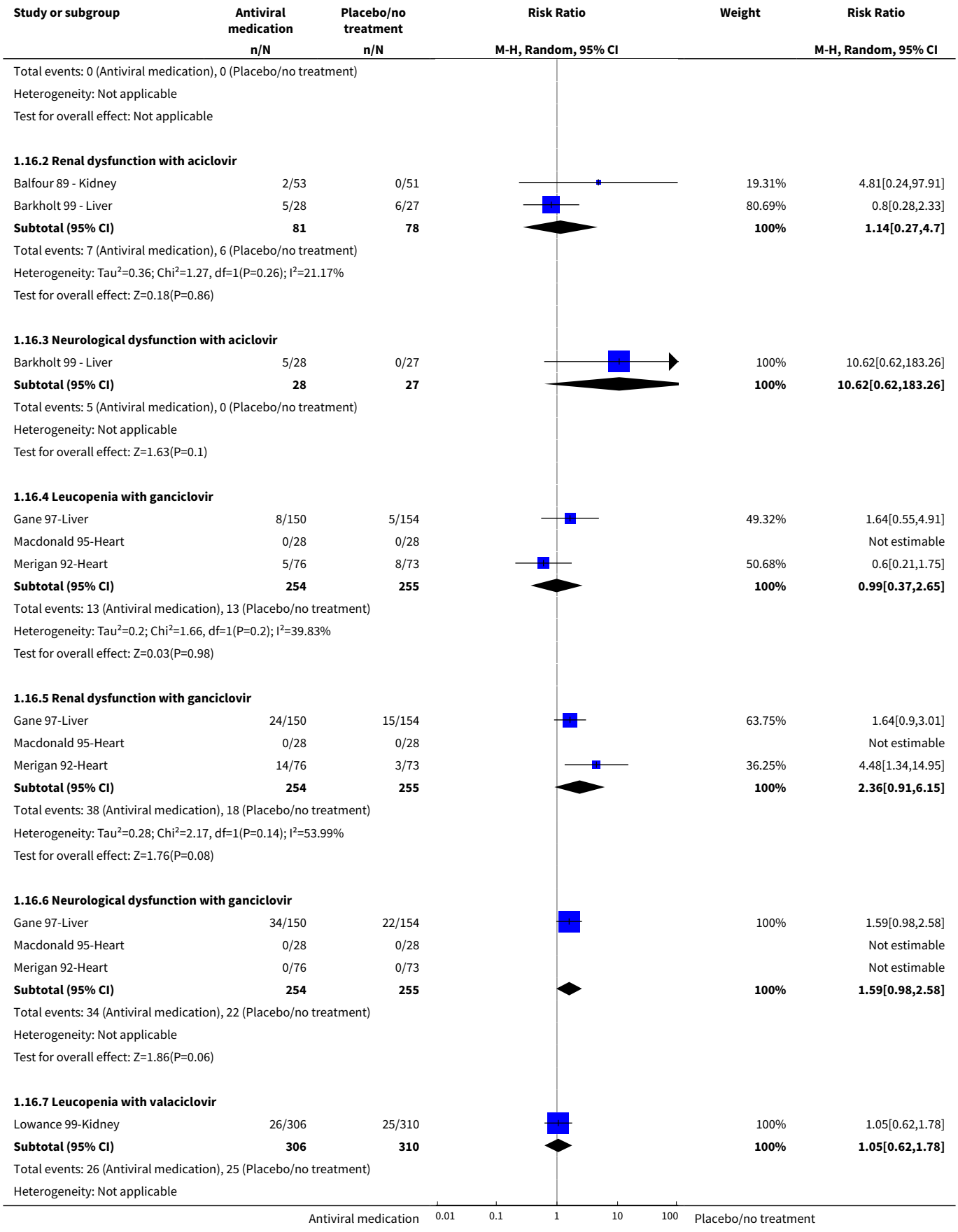
Study or subgroup	Valaciclovir n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 Total with acute rejection					
Egan 02-Heart	13/14	13/13		50.85%	0.93[0.77,1.14]
Lowance 99-Kidney	88/306	128/310		49.15%	0.7[0.56,0.87]
Subtotal (95% CI)	**320**	**323**		**100%**	**0.81[0.55,1.19]**
Total events: 101 (Valaciclovir), 141 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.07; Chi^2=6.79, df=1(P=0.01); I^2=85.27%					
Test for overall effect: Z=1.08(P=0.28)					
1.15.2 Acute rejection in donor CMV +ve / recipient CMV -ve grafts					
Lowance 99-Kidney	27/102	55/106		100%	0.51[0.35,0.74]
Subtotal (95% CI)	**102**	**106**		**100%**	**0.51[0.35,0.74]**
Total events: 27 (Valaciclovir), 55 (Placebo/no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.55(P=0)					
1.15.3 Acute rejection in CMV +ve recipients					
Lowance 99-Kidney	61/204	73/204		100%	0.84[0.63,1.1]
Subtotal (95% CI)	**204**	**204**		**100%**	**0.84[0.63,1.1]**
Total events: 61 (Valaciclovir), 73 (Placebo/no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.26(P=0.21)					
Test for subgroup differences: Chi^2=4.73, df=1 (P=0.09), I^2=57.74%					

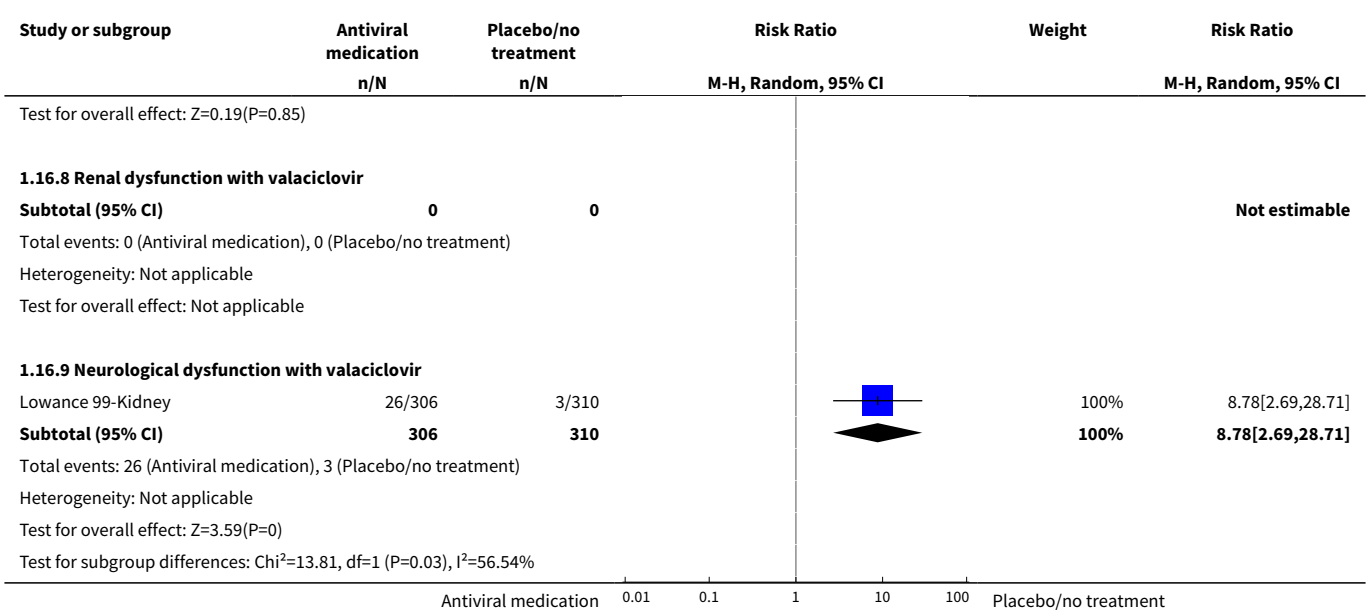
Valaciclovir 0.01 0.1 1 10 100 Placebo/no treatment

Analysis 1.16. Comparison 1 Antiviral prophylaxis versus placebo/no treatment, Outcome 16 Adverse effects.

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.16.1 Leucopenia with aciclovir					
Subtotal (95% CI)	**0**	**0**			**Not estimable**

Antiviral medication 0.01 0.1 1 10 100 Placebo/no treatment





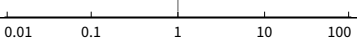
Comparison 2. Effect of methodological quality on CMV disease in trials of prophylaxis versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allocation concealment	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Adequate allocation concealment	4	262	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.31, 0.79]
1.2 Unclear or inadequate allocation concealment	15	1719	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.33, 0.51]
2 Blinding of participants/investigators	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Blinding	5	1135	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.25, 0.48]
2.2 No blinding	14	846	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.37, 0.59]
3 Intention-to-treat analysis (ITT)	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ITT undertaken	10	1569	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.30, 0.48]
3.2 ITT not undertaken	9	412	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.33, 0.68]
4 CMV disease by time of outcome assessment or trial publication date	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Outcome at 9-12 months	8	1277	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.22, 0.58]
4.2 Outcome at 3-6 months	11	704	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.36, 0.58]
4.3 Trials published before 1997	12	821	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.37, 0.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 Trials published in 1997 and later	7	1160	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.24, 0.44]

Analysis 2.1. Comparison 2 Effect of methodological quality on CMV disease in trials of prophylaxis versus placebo/no treatment, Outcome 1 Allocation concealment.

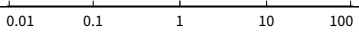
Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Adequate allocation concealment					
Cohen 93-Liver	9/33	11/32		37.16%	0.79[0.38,1.65]
Egan 02-Heart	2/14	6/13		10.67%	0.31[0.08,1.27]
Pouteil-Noble 96 - K	6/24	14/26		33.32%	0.46[0.21,1.01]
Saliba 93-Liver	4/60	14/60		18.86%	0.29[0.1,0.82]
Subtotal (95% CI)	**131**	**131**		**100%**	**0.5[0.31,0.79]**
Total events: 21 (Antiviral medication), 45 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.01; Chi^2=3.15, df=3(P=0.37); I^2=4.88%					
Test for overall effect: Z=2.96(P=0)					
2.1.2 Unclear or inadequate allocation concealment					
Ahsan 97-Kidney	1/21	6/22		1.21%	0.17[0.02,1.33]
Balfour 89 - Kidney	4/53	15/51		4.34%	0.26[0.09,0.72]
Barkholt 99 - Liver	7/28	14/27		7.85%	0.48[0.23,1.01]
Brennan 97-Kidney	4/19	14/23		5.25%	0.35[0.14,0.88]
Conti 95-Kidney	2/22	13/18		2.64%	0.13[0.03,0.49]
Gane 97-Liver	7/150	29/154		6.92%	0.25[0.11,0.55]
Gavalda 97-Liver	4/37	11/36		4.23%	0.35[0.12,1.01]
Hibberd 95-Kidney	9/64	16/49		8.03%	0.43[0.21,0.89]
Kletzmayr 96-Kidney	9/22	4/10		5.46%	1.02[0.41,2.54]
Leray 95-Kidney	6/13	9/10		10.33%	0.51[0.28,0.96]
Lowance 99-Kidney	18/306	60/310		14.22%	0.3[0.18,0.5]
Macdonald 95-Heart	6/28	10/28		5.96%	0.6[0.25,1.43]
Merigan 92-Heart	12/76	31/73		11.41%	0.37[0.21,0.67]
Rondeau 93-Kidney	8/17	11/15		11.24%	0.64[0.36,1.16]
Rostaing 94 - Kidney	1/19	2/18		0.94%	0.47[0.05,4.78]
Subtotal (95% CI)	**875**	**844**		**100%**	**0.41[0.33,0.51]**
Total events: 98 (Antiviral medication), 245 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.03; Chi^2=16.32, df=14(P=0.29); I^2=14.24%					
Test for overall effect: Z=7.75(P<0.0001)					
Test for subgroup differences: Chi^2=0.52, df=1 (P=0.47), I^2=0%					



Antiviral medication — Placebo/no treatment

Analysis 2.2. Comparison 2 Effect of methodological quality on CMV disease in trials of prophylaxis versus placebo/no treatment, Outcome 2 Blinding of participants/investigators.

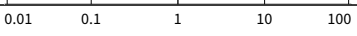
Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Blinding					
Balfour 89 - Kidney	4/53	15/51		9.69%	0.26[0.09,0.72]
Barkholt 99 - Liver	7/28	14/27		19.05%	0.48[0.23,1.01]
Gane 97-Liver	7/150	29/154		16.42%	0.25[0.11,0.55]
Lowance 99-Kidney	18/306	60/310		41.02%	0.3[0.18,0.5]
Macdonald 95-Heart	6/28	10/28		13.81%	0.6[0.25,1.43]
Subtotal (95% CI)	**565**	**570**		**100%**	**0.35[0.25,0.48]**
Total events: 42 (Antiviral medication), 128 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=3.69, df=4(P=0.45); I^2=0%					
Test for overall effect: Z=6.45(P<0.0001)					
2.2.2 No blinding					
Ahsan 97-Kidney	1/21	6/22		1.34%	0.17[0.02,1.33]
Brennan 97-Kidney	4/19	14/23		6.15%	0.35[0.14,0.88]
Cohen 93-Liver	9/33	11/32		9.57%	0.79[0.38,1.65]
Conti 95-Kidney	2/22	13/18		2.99%	0.13[0.03,0.49]
Egan 02-Heart	2/14	6/13		2.75%	0.31[0.08,1.27]
Gavalda 97-Liver	4/37	11/36		4.89%	0.35[0.12,1.01]
Hibberd 95-Kidney	9/64	16/49		9.75%	0.43[0.21,0.89]
Kletzmayr 96-Kidney	9/22	4/10		6.41%	1.02[0.41,2.54]
Leray 95-Kidney	6/13	9/10		12.93%	0.51[0.28,0.96]
Merigan 92-Heart	12/76	31/73		14.49%	0.37[0.21,0.67]
Pouteil-Noble 96 - K	6/24	14/26		8.58%	0.46[0.21,1.01]
Rondeau 93-Kidney	8/17	11/15		14.25%	0.64[0.36,1.16]
Rostaing 94 - Kidney	1/19	2/18		1.04%	0.47[0.05,4.78]
Saliba 93-Liver	4/60	14/60		4.86%	0.29[0.1,0.82]
Subtotal (95% CI)	**441**	**405**		**100%**	**0.47[0.37,0.59]**
Total events: 77 (Antiviral medication), 162 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.01; Chi^2=13.8, df=13(P=0.39); I^2=5.81%					
Test for overall effect: Z=6.33(P<0.0001)					
Test for subgroup differences: Chi^2=2.09, df=1 (P=0.15), I^2=52.27%					



Analysis 2.3. Comparison 2 Effect of methodological quality on CMV disease in trials of prophylaxis versus placebo/no treatment, Outcome 3 Intention-to-treat analysis (ITT).

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 ITT undertaken					
Brennan 97-Kidney	4/19	14/23		6.78%	0.35[0.14,0.88]
Cohen 93-Liver	9/33	11/32		10.88%	0.79[0.38,1.65]
Gane 97-Liver	7/150	29/154		9.31%	0.25[0.11,0.55]
Gavalda 97-Liver	4/37	11/36		5.34%	0.35[0.12,1.01]
Hibberd 95-Kidney	9/64	16/49		11.11%	0.43[0.21,0.89]
Lowance 99-Kidney	18/306	60/310		23.26%	0.3[0.18,0.5]

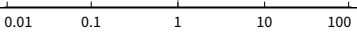
Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Merigan 92-Heart	12/76	31/73		17.23%	0.37[0.21,0.67]
Pouteil-Noble 96 - K	6/24	14/26		9.68%	0.46[0.21,1.01]
Rostaing 94 - Kidney	1/19	2/18		1.1%	0.47[0.05,4.78]
Saliba 93-Liver	4/60	14/60		5.31%	0.29[0.1,0.82]
Subtotal (95% CI)	**788**	**781**		**100%**	**0.38[0.3,0.48]**
Total events: 74 (Antiviral medication), 202 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=6.61, df=9(P=0.68); I^2=0%					
Test for overall effect: Z=7.87(P<0.0001)					
2.3.2 ITT not undertaken					
Ahsan 97-Kidney	1/21	6/22		2.95%	0.17[0.02,1.33]
Balfour 89 - Kidney	4/53	15/51		9.37%	0.26[0.09,0.72]
Barkholt 99 - Liver	7/28	14/27		14.98%	0.48[0.23,1.01]
Conti 95-Kidney	2/22	13/18		6.08%	0.13[0.03,0.49]
Egan 02-Heart	2/14	6/13		5.66%	0.31[0.08,1.27]
Kletzmayr 96-Kidney	9/22	4/10		11.31%	1.02[0.41,2.54]
Leray 95-Kidney	6/13	9/10		18.22%	0.51[0.28,0.96]
Macdonald 95-Heart	6/28	10/28		12.13%	0.6[0.25,1.43]
Rondeau 93-Kidney	8/17	11/15		19.29%	0.64[0.36,1.16]
Subtotal (95% CI)	**218**	**194**		**100%**	**0.47[0.33,0.68]**
Total events: 45 (Antiviral medication), 88 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.09; Chi^2=11.4, df=8(P=0.18); I^2=29.79%					
Test for overall effect: Z=4.04(P<0.0001)					
Test for subgroup differences: Chi^2=1.02, df=1 (P=0.31), I^2=2.39%					



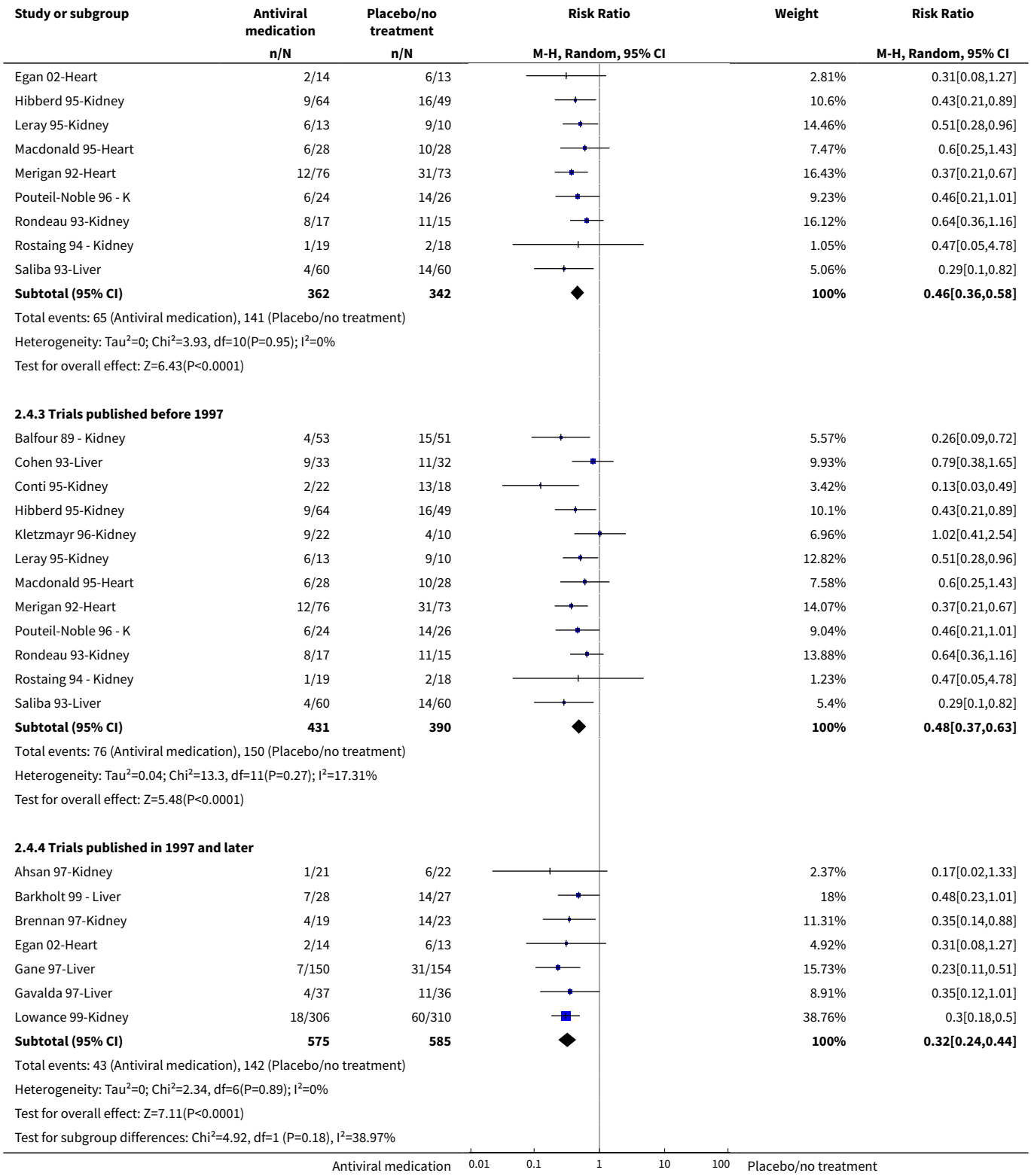
Antiviral medication — Placebo/no treatment

Analysis 2.4. Comparison 2 Effect of methodological quality on CMV disease in trials of prophylaxis versus placebo/no treatment, Outcome 4 CMV disease by time of outcome assessment or trial publication date.

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Outcome at 9-12 months					
Ahsan 97-Kidney	1/21	6/22		4.51%	0.17[0.02,1.33]
Balfour 89 - Kidney	4/53	15/51		11.59%	0.26[0.09,0.72]
Cohen 93-Liver	9/33	11/32		15.92%	0.79[0.38,1.65]
Conti 95-Kidney	2/22	13/18		8.33%	0.13[0.03,0.49]
Gane 97-Liver	7/150	31/154		15.04%	0.23[0.11,0.51]
Gavalda 97-Liver	4/37	11/36		11.41%	0.35[0.12,1.01]
Kletzmayr 96-Kidney	9/22	4/10		13.22%	1.02[0.41,2.54]
Lowance 99-Kidney	18/306	60/310		19.97%	0.3[0.18,0.5]
Subtotal (95% CI)	**644**	**633**		**100%**	**0.36[0.22,0.58]**
Total events: 54 (Antiviral medication), 151 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.23; Chi^2=14.91, df=7(P=0.04); I^2=53.05%					
Test for overall effect: Z=4.21(P<0.0001)					
2.4.2 Outcome at 3-6 months					
Barkholt 99 - Liver	7/28	14/27		10.3%	0.48[0.23,1.01]
Brennan 97-Kidney	4/19	14/23		6.47%	0.35[0.14,0.88]



Antiviral medication — Placebo/no treatment



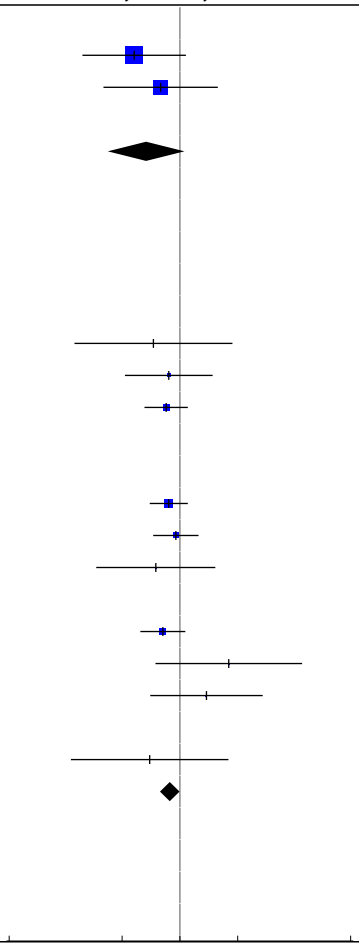
Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Egan 02-Heart	2/14	6/13		2.81%	0.31[0.08,1.27]
Hibberd 95-Kidney	9/64	16/49		10.6%	0.43[0.21,0.89]
Leray 95-Kidney	6/13	9/10		14.46%	0.51[0.28,0.96]
Macdonald 95-Heart	6/28	10/28		7.47%	0.6[0.25,1.43]
Merigan 92-Heart	12/76	31/73		16.43%	0.37[0.21,0.67]
Pouteil-Noble 96 - K	6/24	14/26		9.23%	0.46[0.21,1.01]
Rondeau 93-Kidney	8/17	11/15		16.12%	0.64[0.36,1.16]
Rostaing 94 - Kidney	1/19	2/18		1.05%	0.47[0.05,4.78]
Saliba 93-Liver	4/60	14/60		5.06%	0.29[0.1,0.82]
Subtotal (95% CI)	**362**	**342**		**100%**	**0.46[0.36,0.58]**
Total events: 65 (Antiviral medication), 141 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=3.93, df=10(P=0.95); I^2=0%					
Test for overall effect: Z=6.43(P<0.0001)					
2.4.3 Trials published before 1997					
Balfour 89 - Kidney	4/53	15/51		5.57%	0.26[0.09,0.72]
Cohen 93-Liver	9/33	11/32		9.93%	0.79[0.38,1.65]
Conti 95-Kidney	2/22	13/18		3.42%	0.13[0.03,0.49]
Hibberd 95-Kidney	9/64	16/49		10.1%	0.43[0.21,0.89]
Kletzmayr 96-Kidney	9/22	4/10		6.96%	1.02[0.41,2.54]
Leray 95-Kidney	6/13	9/10		12.82%	0.51[0.28,0.96]
Macdonald 95-Heart	6/28	10/28		7.58%	0.6[0.25,1.43]
Merigan 92-Heart	12/76	31/73		14.07%	0.37[0.21,0.67]
Pouteil-Noble 96 - K	6/24	14/26		9.04%	0.46[0.21,1.01]
Rondeau 93-Kidney	8/17	11/15		13.88%	0.64[0.36,1.16]
Rostaing 94 - Kidney	1/19	2/18		1.23%	0.47[0.05,4.78]
Saliba 93-Liver	4/60	14/60		5.4%	0.29[0.1,0.82]
Subtotal (95% CI)	**431**	**390**		**100%**	**0.48[0.37,0.63]**
Total events: 76 (Antiviral medication), 150 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.04; Chi^2=13.3, df=11(P=0.27); I^2=17.31%					
Test for overall effect: Z=5.48(P<0.0001)					
2.4.4 Trials published in 1997 and later					
Ahsan 97-Kidney	1/21	6/22		2.37%	0.17[0.02,1.33]
Barkholt 99 - Liver	7/28	14/27		18%	0.48[0.23,1.01]
Brennan 97-Kidney	4/19	14/23		11.31%	0.35[0.14,0.88]
Egan 02-Heart	2/14	6/13		4.92%	0.31[0.08,1.27]
Gane 97-Liver	7/150	31/154		15.73%	0.23[0.11,0.51]
Gavalda 97-Liver	4/37	11/36		8.91%	0.35[0.12,1.01]
Lowance 99-Kidney	18/306	60/310		38.76%	0.3[0.18,0.5]
Subtotal (95% CI)	**575**	**585**		**100%**	**0.32[0.24,0.44]**
Total events: 43 (Antiviral medication), 142 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=2.34, df=6(P=0.89); I^2=0%					
Test for overall effect: Z=7.11(P<0.0001)					
Test for subgroup differences: Chi^2=4.92, df=1 (P=0.18), I^2=38.97%					

Comparison 3. Effect of methodological quality on all cause mortality in trials of prophylaxis versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allocation concealment	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Adequate	3	142	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.06, 1.20]
1.2 Inadequate/unclear	14	1695	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.45, 0.99]
2 Blinding of participants and investigators	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Blinding	5	1135	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.39, 0.98]
2.2 No blinding	12	702	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.33, 1.27]
3 Intention-to-treat analysis (ITT)	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ITT undertaken	9	1448	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.40, 0.98]
3.2 ITT not undertaken	8	389	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.32, 1.29]
4 All-cause mortality and time of outcome assessment or trial publication date	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Outcome at 9-12 months	10	1370	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.40, 0.97]
4.2 Outcome at 4-6 months	7	468	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.31, 1.33]
4.3 Outcome in trials published before 1997	10	678	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.25, 2.08]
4.4 Outcome in trials published in 1997 or later	7	1160	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.41, 0.94]

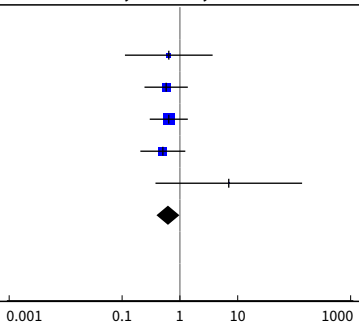
Analysis 3.1. Comparison 3 Effect of methodological quality on all cause mortality in trials of prophylaxis versus placebo/no treatment, Outcome 1 Allocation concealment.

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Adequate					
Cohen 93-Liver	1/33	6/32		55.02%	0.16[0.02,1.27]
Egan 02-Heart	1/14	2/13		44.98%	0.46[0.05,4.53]
Pouteil-Noble 96 - K	0/24	0/26			Not estimable
Subtotal (95% CI)	**71**	**71**		**100%**	**0.26[0.06,1.2]**
Total events: 2 (Antiviral medication), 8 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=1(P=0.5); I^2=0%					
Test for overall effect: Z=1.73(P=0.08)					
3.1.2 Inadequate/unclear					
Ahsan 97-Kidney	0/21	1/22		1.53%	0.35[0.01,8.11]
Balfour 89 - Kidney	2/53	3/51		4.97%	0.64[0.11,3.68]
Barkholt 99 - Liver	6/28	10/27		20.39%	0.58[0.24,1.37]
Brennan 97-Kidney	0/19	0/23			Not estimable
Conti 95-Kidney	0/22	0/18			Not estimable
Gane 97-Liver	10/150	16/154		26.47%	0.64[0.3,1.37]
Gavalda 97-Liver	7/37	8/36		18.56%	0.85[0.34,2.1]
Hibberd 95-Kidney	1/64	2/49		2.7%	0.38[0.04,4.1]
Kletzmayr 96-Kidney	0/22	0/10			Not estimable
Lowance 99-Kidney	7/306	14/310		19.03%	0.51[0.21,1.24]
Macdonald 95-Heart	3/28	0/28		1.78%	7[0.38,129.55]
Merigan 92-Heart	3/76	1/73		3.03%	2.88[0.31,27.07]
Rondeau 93-Kidney	0/17	0/15			Not estimable
Rostaing 94 - Kidney	0/19	1/17		1.54%	0.3[0.01,6.91]
Subtotal (95% CI)	**862**	**833**		**100%**	**0.67[0.45,0.99]**
Total events: 39 (Antiviral medication), 56 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=5.56, df=9(P=0.78); I^2=0%					
Test for overall effect: Z=2.03(P=0.04)					
Test for subgroup differences: Chi^2=1.37, df=1 (P=0.24), I^2=27.26%					



Analysis 3.2. Comparison 3 Effect of methodological quality on all cause mortality in trials of prophylaxis versus placebo/no treatment, Outcome 2 Blinding of participants and investigators.

Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Blinding					
Balfour 89 - Kidney	2/53	3/51		6.85%	0.64[0.11,3.68]
Barkholt 99 - Liver	6/28	10/27		28.07%	0.58[0.24,1.37]
Gane 97-Liver	10/150	16/154		36.44%	0.64[0.3,1.37]
Lowance 99-Kidney	7/306	14/310		26.19%	0.51[0.21,1.24]
Macdonald 95-Heart	3/28	0/28		2.46%	7[0.38,129.55]
Subtotal (95% CI)	**565**	**570**		**100%**	**0.62[0.39,0.98]**
Total events: 28 (Antiviral medication), 43 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=2.94, df=4(P=0.57); I^2=0%					

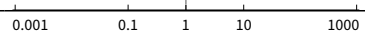


Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=2.04(P=0.04)					
3.2.2 No blinding					
Ahsan 97-Kidney	0/21	1/22		4.53%	0.35[0.01,8.11]
Brennan 97-Kidney	0/19	0/23			Not estimable
Cohen 93-Liver	1/33	6/32		10.56%	0.16[0.02,1.27]
Conti 95-Kidney	0/22	0/18			Not estimable
Egan 02-Heart	1/14	2/13		8.64%	0.46[0.05,4.53]
Gavalda 97-Liver	7/37	8/36		54.8%	0.85[0.34,2.1]
Hibberd 95-Kidney	1/64	2/49		7.97%	0.38[0.04,4.1]
Kletzmayr 96-Kidney	0/22	0/10			Not estimable
Merigan 92-Heart	3/76	1/73		8.94%	2.88[0.31,27.07]
Pouteil-Noble 96 - K	0/24	0/26			Not estimable
Rondeau 93-Kidney	0/17	0/15			Not estimable
Rostaing 94 - Kidney	0/19	1/17		4.56%	0.3[0.01,6.91]
Subtotal (95% CI)	**368**	**334**		**100%**	**0.65[0.33,1.27]**
Total events: 13 (Antiviral medication), 21 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=4.5, df=6(P=0.61); I^2=0%					
Test for overall effect: Z=1.26(P=0.21)					
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.91), I^2=0%					

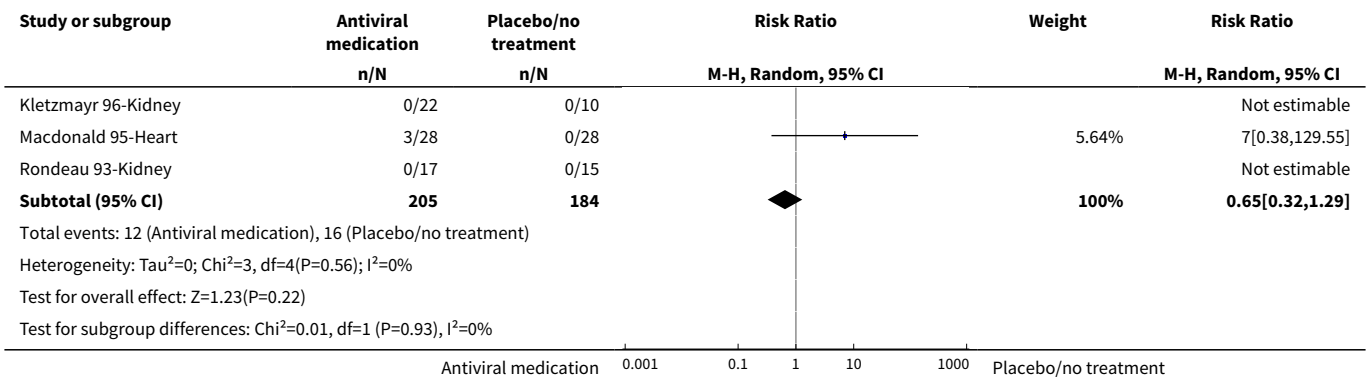
Antiviral medication — Placebo/no treatment

Analysis 3.3. Comparison 3 Effect of methodological quality on all cause mortality in trials of prophylaxis versus placebo/no treatment, Outcome 3 Intention-to-treat analysis (ITT).

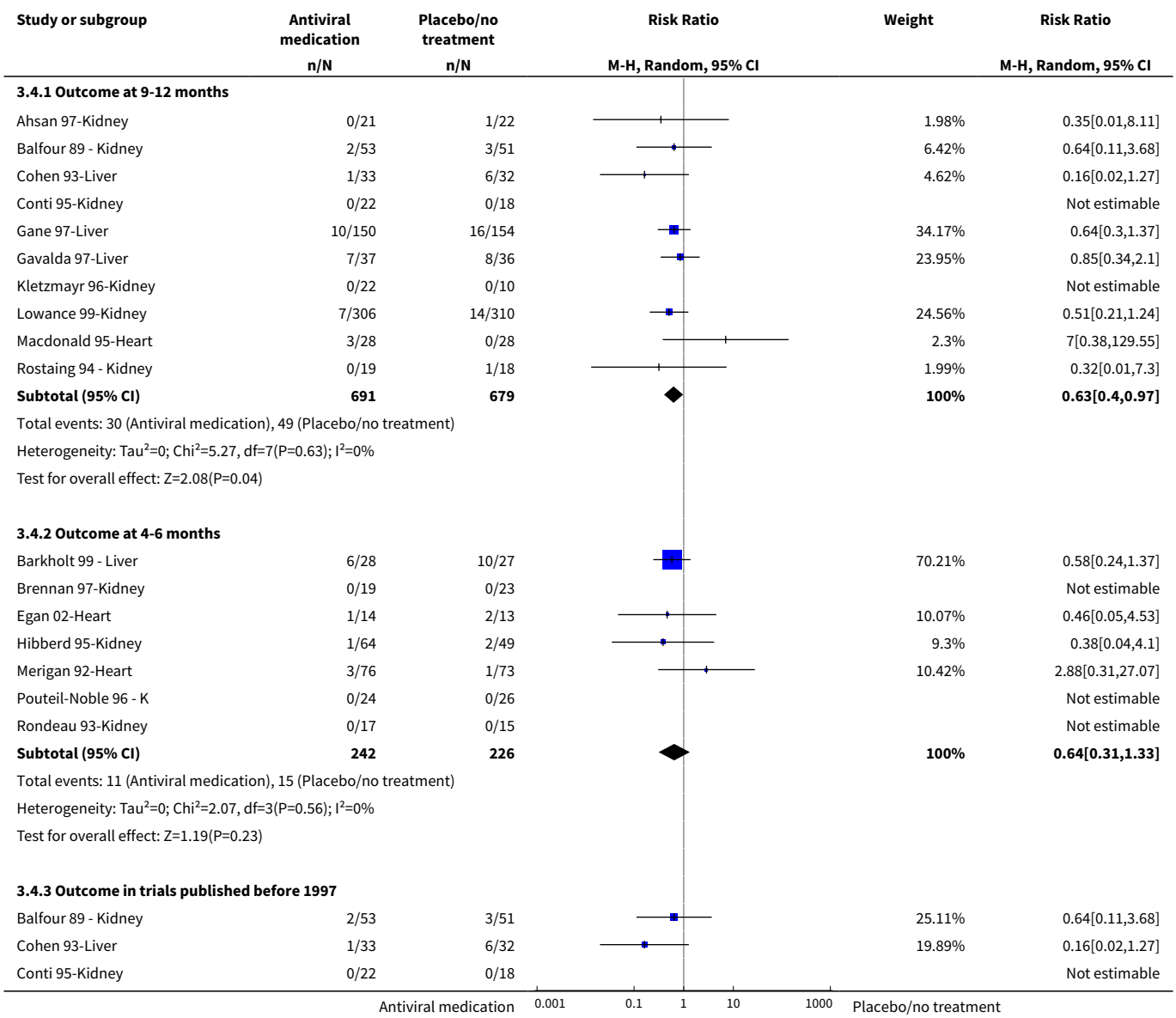
Study or subgroup	Antiviral medication n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 ITT undertaken					
Brennan 97-Kidney	0/19	0/23			Not estimable
Cohen 93-Liver	1/33	6/32		4.78%	0.16[0.02,1.27]
Gane 97-Liver	10/150	16/154		35.34%	0.64[0.3,1.37]
Gavalda 97-Liver	7/37	8/36		24.77%	0.85[0.34,2.1]
Hibberd 95-Kidney	1/64	2/49		3.61%	0.38[0.04,4.1]
Lowance 99-Kidney	7/306	14/310		25.4%	0.51[0.21,1.24]
Merigan 92-Heart	3/76	1/73		4.04%	2.88[0.31,27.07]
Pouteil-Noble 96 - K	0/24	0/26			Not estimable
Rostaing 94 - Kidney	0/19	1/17		2.06%	0.3[0.01,6.91]
Subtotal (95% CI)	**728**	**720**		**100%**	**0.62[0.4,0.98]**
Total events: 29 (Antiviral medication), 48 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=4.51, df=6(P=0.61); I^2=0%					
Test for overall effect: Z=2.06(P=0.04)					
3.3.2 ITT not undertaken					
Ahsan 97-Kidney	0/21	1/22		4.85%	0.35[0.01,8.11]
Balfour 89 - Kidney	2/53	3/51		15.74%	0.64[0.11,3.68]
Barkholt 99 - Liver	6/28	10/27		64.51%	0.58[0.24,1.37]
Conti 95-Kidney	0/22	0/18			Not estimable
Egan 02-Heart	1/14	2/13		9.26%	0.46[0.05,4.53]

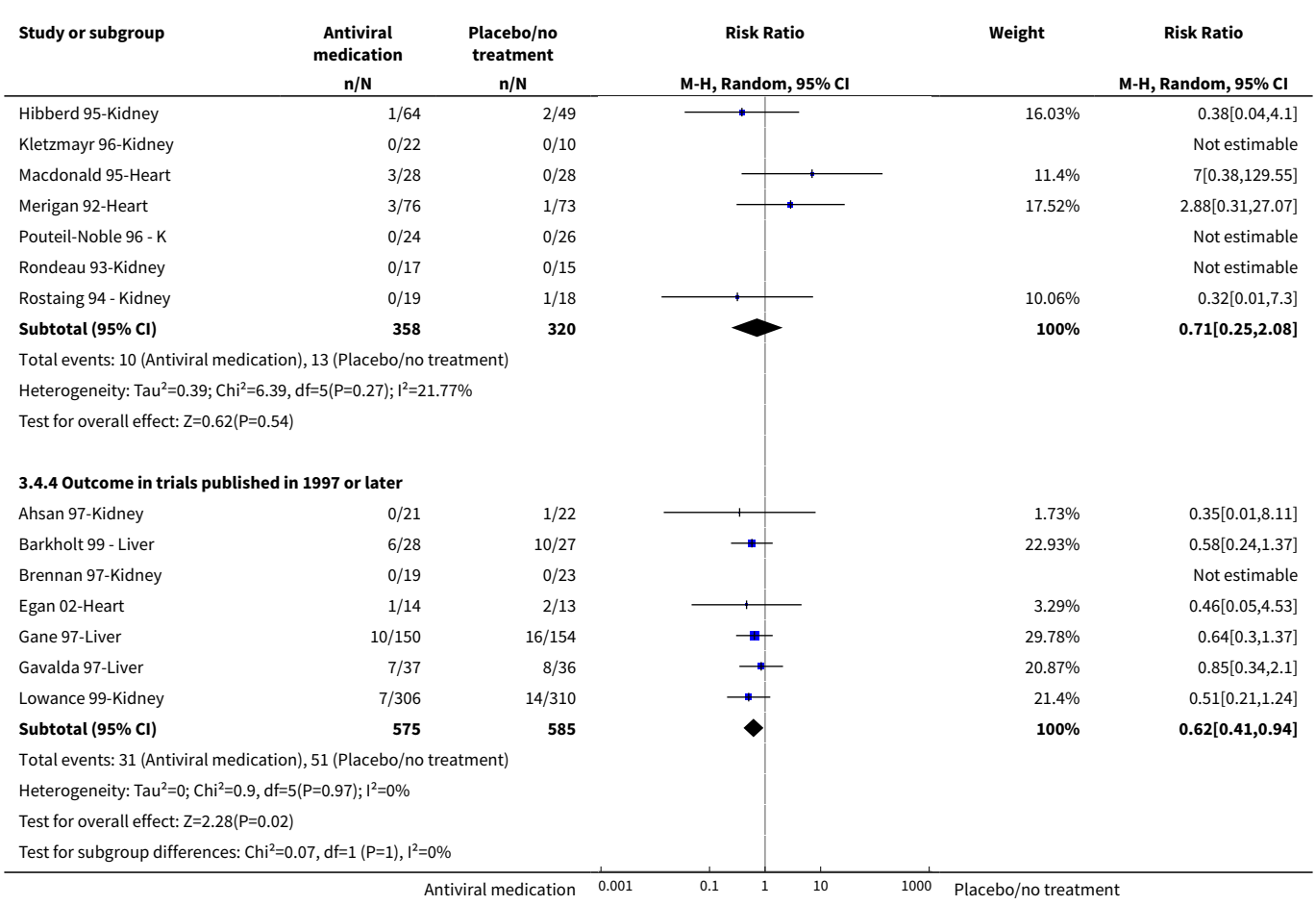


Antiviral medication — Placebo/no treatment



Analysis 3.4. Comparison 3 Effect of methodological quality on all cause mortality in trials of prophylaxis versus placebo/no treatment, Outcome 4 All-cause mortality and time of outcome assessment or trial publication date.





Comparison 4. Ganciclovir versus aciclovir

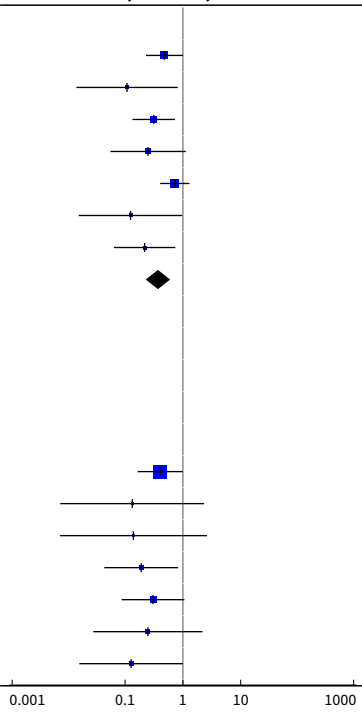
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease and CMV infection in all treated patients	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 CMV disease in all patients	7	1113	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.23, 0.60]
1.2 CMV organ involvement	7	1034	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.15, 0.49]
1.3 CMV syndrome	6	1009	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.16, 1.02]
1.4 CMV infection	6	815	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.28, 0.67]
1.5 CMV disease in patients treated with ganciclovir for 3 months	4	703	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.09, 0.82]

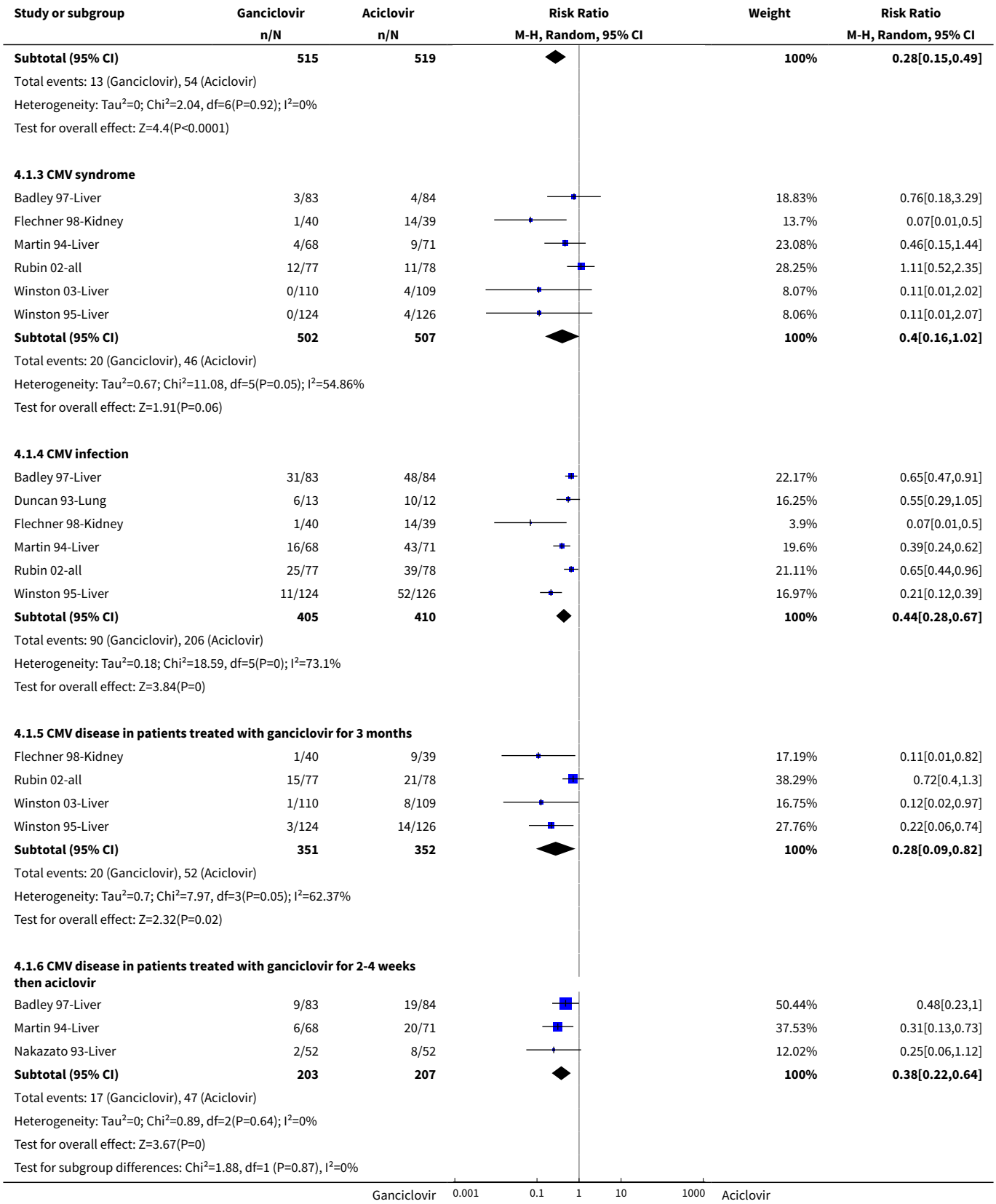
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 CMV disease in patients treated with ganciclovir for 2-4 weeks then aciclovir	3	410	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.22, 0.64]
2 CMV antibody +ve recipients	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 All symptomatic CMV disease	5	722	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.13, 0.55]
2.4 CMV infection	5	522	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.16, 0.58]
3 CMV +ve donors / CMV -ve recipients	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 All symptomatic CMV disease	5	246	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.41, 0.99]
3.4 CMV infection	4	228	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.36, 1.09]
4 CMV -ve donor / CMV -ve recipient	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 CMV disease	3	41	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.07, 3.07]
5 Effect of prophylaxis for different transplanted organs	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 CMV disease in kidney transplant patients	2	168	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.07, 1.35]
5.2 CMV disease in liver transplant patients	5	791	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.23, 0.59]
5.3 CMV disease in heart or lung transplant patients	2	75	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.10, 3.00]
5.4 CMV infection in kidney transplant patients	2	168	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.04, 0.95]
5.5 CMV infection in liver transplant patients	4	572	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.25, 0.73]
5.6 CMV infection in heart or lung transplant patients	2	75	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.50, 1.55]
6 Death	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Death associated with CMV disease	6	832	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.07, 1.58]
6.2 All-cause mortality	8	1138	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.82, 1.58]
7 Additional outcomes	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Acute rejection	6	1009	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.87, 1.10]
7.2 Graft loss	3	268	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.27, 1.13]
7.3 Other viral infections	4	740	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.32, 2.01]
7.4 Invasive fungal infections	3	401	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.40, 1.10]
7.5 Bacterial infections	1	167	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.78, 1.53]
7.6 Protozoal infections	1	167	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.16]
7.7 Obliterative bronchiolitis in lung transplant recipients	1	25	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.42, 1.54]
7.8 Leucopenia	6	955	Risk Ratio (M-H, Random, 95% CI)	3.28 [1.48, 7.25]
7.9 Renal dysfunction	4	661	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.83, 1.10]
7.10 Neurological dysfunction	2	306	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.24, 4.15]

Analysis 4.1. Comparison 4 Ganciclovir versus aciclovir, Outcome 1 CMV disease and CMV infection in all treated patients.

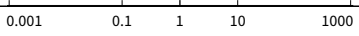
Study or subgroup	Ganciclovir n/N	Aciclovir n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 CMV disease in all patients					
Badley 97-Liver	9/83	19/84		22.56%	0.48[0.23,1]
Flechner 98-Kidney	1/40	9/39		5.16%	0.11[0.01,0.82]
Martin 94-Liver	6/68	20/71		19.18%	0.31[0.13,0.73]
Nakazato 93-Liver	2/52	8/52		8.55%	0.25[0.06,1.12]
Rubin 02-all	15/77	21/78		27.79%	0.72[0.4,1.3]
Winston 03-Liver	1/110	8/109		4.97%	0.12[0.02,0.97]
Winston 95-Liver	3/124	14/126		11.8%	0.22[0.06,0.74]
Subtotal (95% CI)	**554**	**559**		**100%**	**0.37[0.23,0.6]**
Total events: 37 (Ganciclovir), 99 (Aciclovir)					
Heterogeneity: Tau^2=0.13; Chi^2=9.01, df=6(P=0.17); I^2=33.38%					
Test for overall effect: Z=4.01(P<0.0001)					
4.1.2 CMV organ involvement					
Badley 97-Liver	6/83	15/84		41.04%	0.4[0.17,0.99]
Duncan 93-Lung	0/13	3/12		4.02%	0.13[0.01,2.33]
Flechner 98-Kidney	0/40	3/39		3.84%	0.14[0.01,2.61]
Martin 94-Liver	2/68	11/71		15.29%	0.19[0.04,0.83]
Rubin 02-all	3/77	10/78		21.09%	0.3[0.09,1.06]
Winston 03-Liver	1/110	4/109		6.98%	0.25[0.03,2.18]
Winston 95-Liver	1/124	8/126		7.75%	0.13[0.02,1]





Analysis 4.2. Comparison 4 Ganciclovir versus aciclovir, Outcome 2 CMV antibody +ve recipients.

Study or subgroup	Ganciclovir n/N	Aciclovir n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 All symptomatic CMV disease					
Badley 97-Liver	6/65	12/65		48.93%	0.5[0.2,1.25]
Flechner 98-Kidney	1/26	4/26		10.93%	0.25[0.03,2.09]
Martin 94-Liver	2/54	12/54		22.32%	0.17[0.04,0.71]
Winston 03-Liver	1/110	8/109		11.55%	0.12[0.02,0.97]
Winston 95-Liver	0/106	9/107		6.27%	0.05[0,0.9]
Subtotal (95% CI)	**361**	**361**		**100%**	**0.27[0.13,0.55]**
Total events: 10 (Ganciclovir), 45 (Aciclovir)					
Heterogeneity: Tau^2=0.06; Chi^2=4.31, df=4(P=0.37); I^2=7.19%					
Test for overall effect: Z=3.59(P=0)					
4.2.4 CMV infection					
Badley 97-Liver	20/65	38/65		28.22%	0.53[0.35,0.8]
Duncan 93-Lung	4/10	7/9		20.99%	0.51[0.22,1.19]
Flechner 98-Kidney	1/26	7/26		7.88%	0.14[0.02,1.08]
Martin 94-Liver	9/54	32/54		24.51%	0.28[0.15,0.53]
Winston 95-Liver	4/106	40/107		18.41%	0.1[0.04,0.27]
Subtotal (95% CI)	**261**	**261**		**100%**	**0.3[0.16,0.58]**
Total events: 38 (Ganciclovir), 124 (Aciclovir)					
Heterogeneity: Tau^2=0.35; Chi^2=13.44, df=4(P=0.01); I^2=70.25%					
Test for overall effect: Z=3.61(P=0)					
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.83), I^2=0%					



Analysis 4.3. Comparison 4 Ganciclovir versus aciclovir, Outcome 3 CMV +ve donors / CMV -ve recipients.

Study or subgroup	Gancyclovir n/N	Aciclovir n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 All symptomatic CMV disease					
Badley 97-Liver	3/12	7/13		16.12%	0.46[0.15,1.4]
Flechner 98-Kidney	0/14	5/13		2.49%	0.08[0.01,1.4]
Martin 94-Liver	3/7	7/11		21.01%	0.67[0.26,1.77]
Rubin 02-all	15/77	21/78		57.56%	0.72[0.4,1.3]
Winston 95-Liver	1/10	1/11		2.82%	1.1[0.08,15.36]
Subtotal (95% CI)	**120**	**126**		**100%**	**0.64[0.41,0.99]**
Total events: 22 (Gancyclovir), 41 (Aciclovir)					
Heterogeneity: Tau^2=0; Chi^2=2.78, df=4(P=0.6); I^2=0%					
Test for overall effect: Z=2(P=0.05)					
4.3.4 CMV infection					
Badley 97-Liver	9/12	11/13		41.62%	0.89[0.59,1.32]
Flechner 98-Kidney	0/14	7/13		3.68%	0.06[0,0.99]
Rubin 02-all	25/77	39/78		42.05%	0.65[0.44,0.96]
Winston 95-Liver	2/10	6/11		12.65%	0.37[0.09,1.42]
Subtotal (95% CI)	**113**	**115**		**100%**	**0.63[0.36,1.09]**
Total events: 36 (Gancyclovir), 63 (Aciclovir)					
Heterogeneity: Tau^2=0.15; Chi^2=7.18, df=3(P=0.07); I^2=58.2%					
Test for overall effect: Z=1.64(P=0.1)					

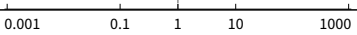
Study or subgroup	Gancyclovir n/N	Aciclovir n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=0, df=1 (P=0.98), I²=0%					

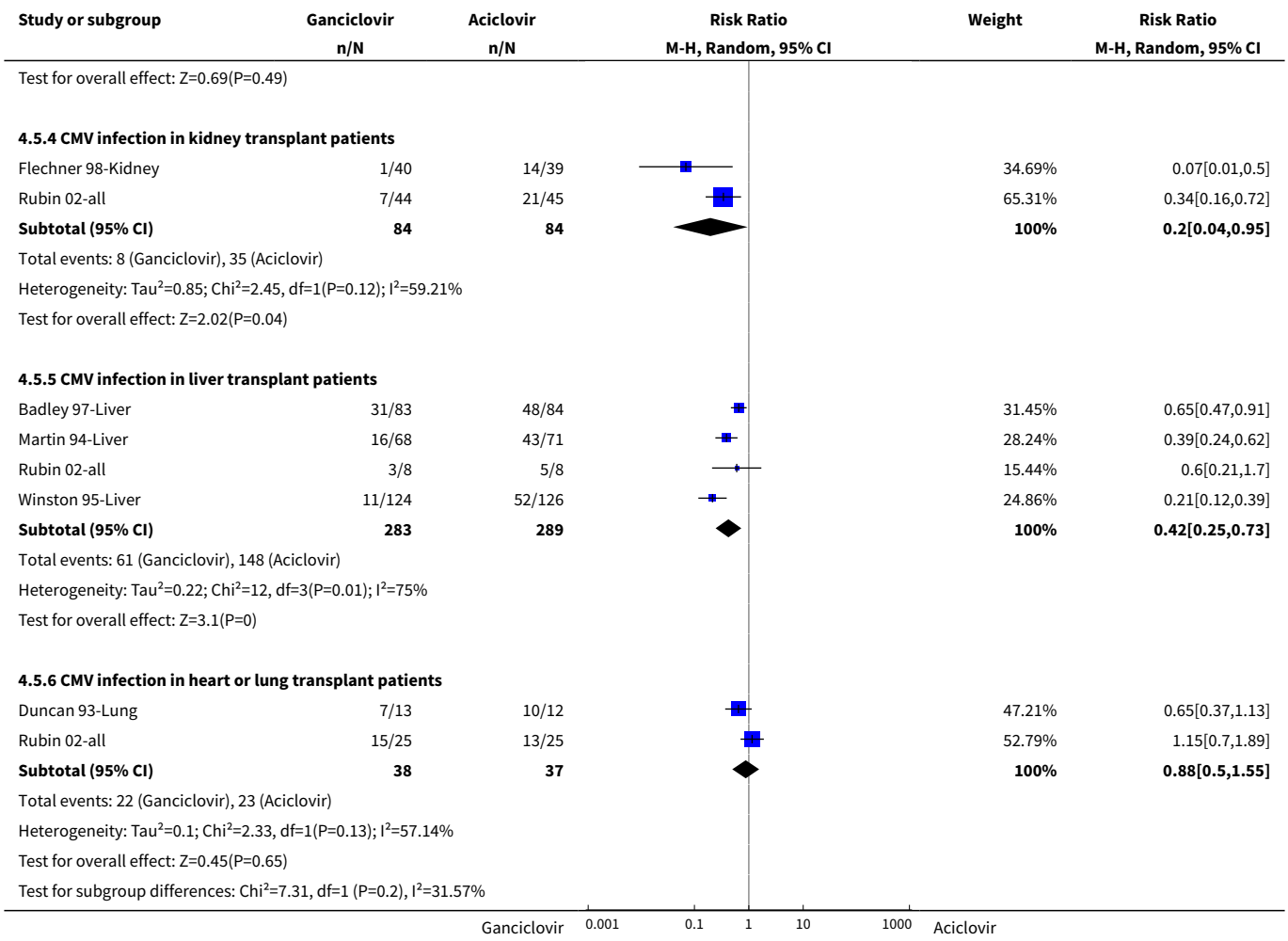
Analysis 4.4. Comparison 4 Ganciclovir versus aciclovir, Outcome 4 CMV -ve donor / CMV -ve recipient.

Study or subgroup	Ganciclovir n/N	Aciclovir n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.4.1 CMV disease					
Badley 97-Liver	0/6	0/6			Not estimable
Martin 94-Liver	1/7	1/6		56.3%	0.86[0.07,10.96]
Winston 95-Liver	0/8	2/8		43.7%	0.2[0.01,3.61]
Subtotal (95% CI)	**21**	**20**		**100%**	**0.45[0.07,3.07]**
Total events: 1 (Ganciclovir), 3 (Aciclovir)					
Heterogeneity: Tau²=0; Chi²=0.57, df=1(P=0.45); I²=0%					
Test for overall effect: Z=0.81(P=0.42)					

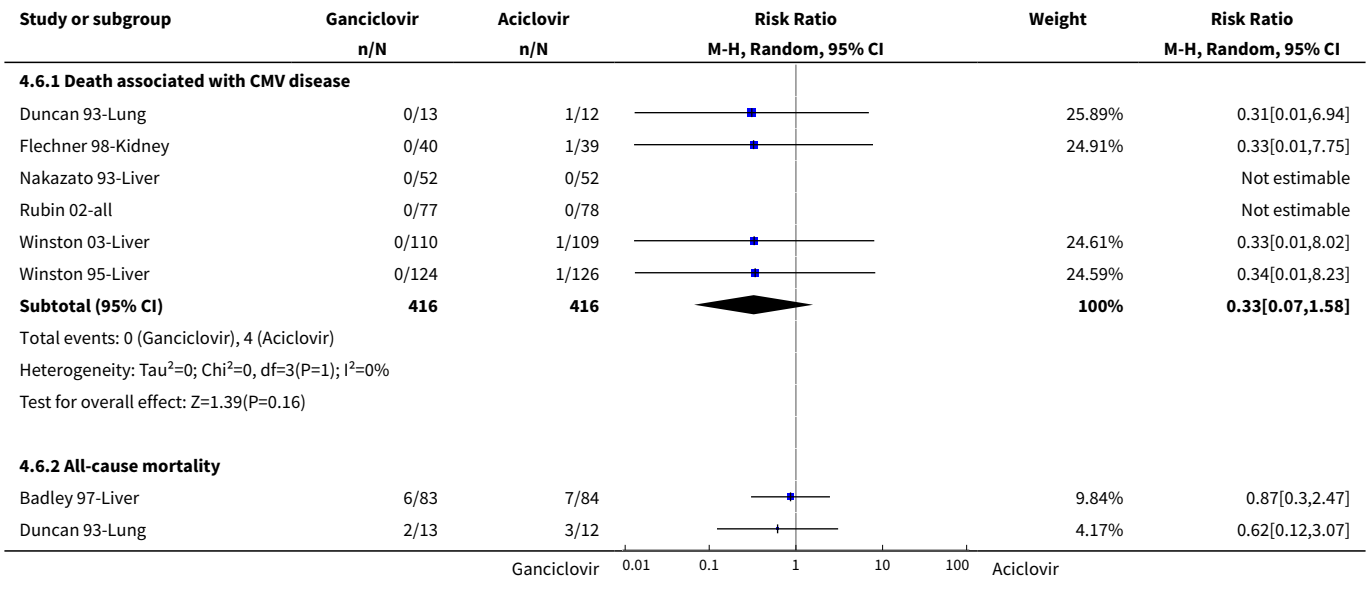
Analysis 4.5. Comparison 4 Ganciclovir versus aciclovir, Outcome 5 Effect of prophylaxis for different transplanted organs.

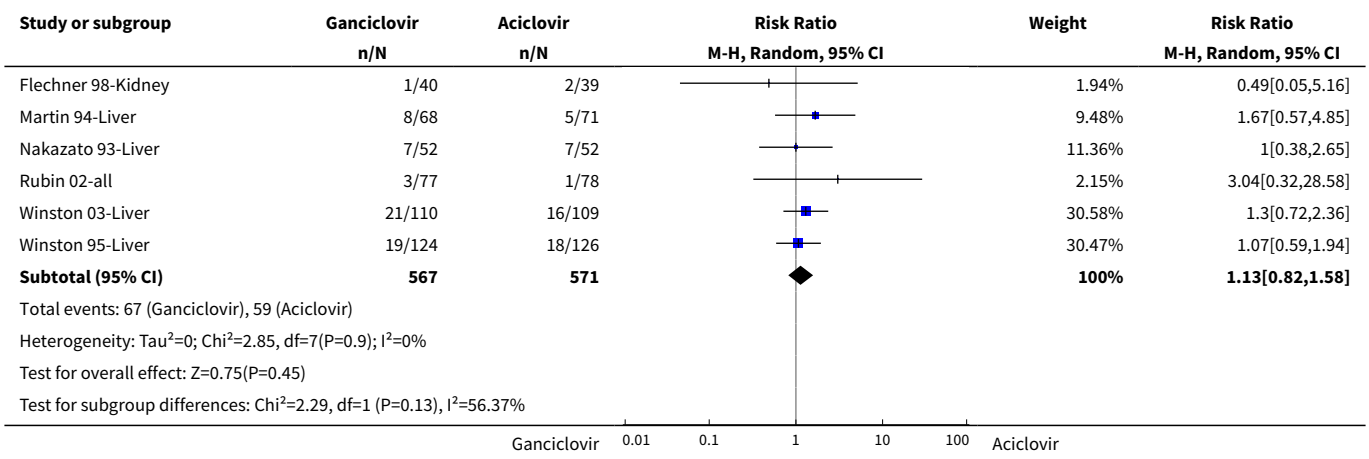
Study or subgroup	Ganciclovir n/N	Aciclovir n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.5.1 CMV disease in kidney transplant patients					
Flechner 98-Kidney	1/40	9/39		34.52%	0.11[0.01,0.82]
Rubin 02-all	5/44	10/45		65.48%	0.51[0.19,1.38]
Subtotal (95% CI)	**84**	**84**		**100%**	**0.3[0.07,1.35]**
Total events: 6 (Ganciclovir), 19 (Aciclovir)					
Heterogeneity: Tau²=0.64; Chi²=1.98, df=1(P=0.16); I²=49.44%					
Test for overall effect: Z=1.57(P=0.12)					
4.5.2 CMV disease in liver transplant patients					
Badley 97-Liver	9/83	19/84		41.39%	0.48[0.23,1]
Martin 94-Liver	6/68	20/71		30.79%	0.31[0.13,0.73]
Rubin 02-all	2/8	2/8		7.71%	1[0.18,5.46]
Winston 03-Liver	1/110	8/109		5.23%	0.12[0.02,0.97]
Winston 95-Liver	3/124	14/126		14.88%	0.22[0.06,0.74]
Subtotal (95% CI)	**393**	**398**		**100%**	**0.37[0.23,0.59]**
Total events: 21 (Ganciclovir), 63 (Aciclovir)					
Heterogeneity: Tau²=0; Chi²=3.86, df=4(P=0.42); I²=0%					
Test for overall effect: Z=4.15(P<0.0001)					
4.5.3 CMV disease in heart or lung transplant patients					
Duncan 93-Lung	0/13	3/12		25.09%	0.13[0.01,2.33]
Rubin 02-all	8/25	9/25		74.91%	0.89[0.41,1.93]
Subtotal (95% CI)	**38**	**37**		**100%**	**0.55[0.1,3]**
Total events: 8 (Ganciclovir), 12 (Aciclovir)					
Heterogeneity: Tau²=0.84; Chi²=1.73, df=1(P=0.19); I²=42.34%					



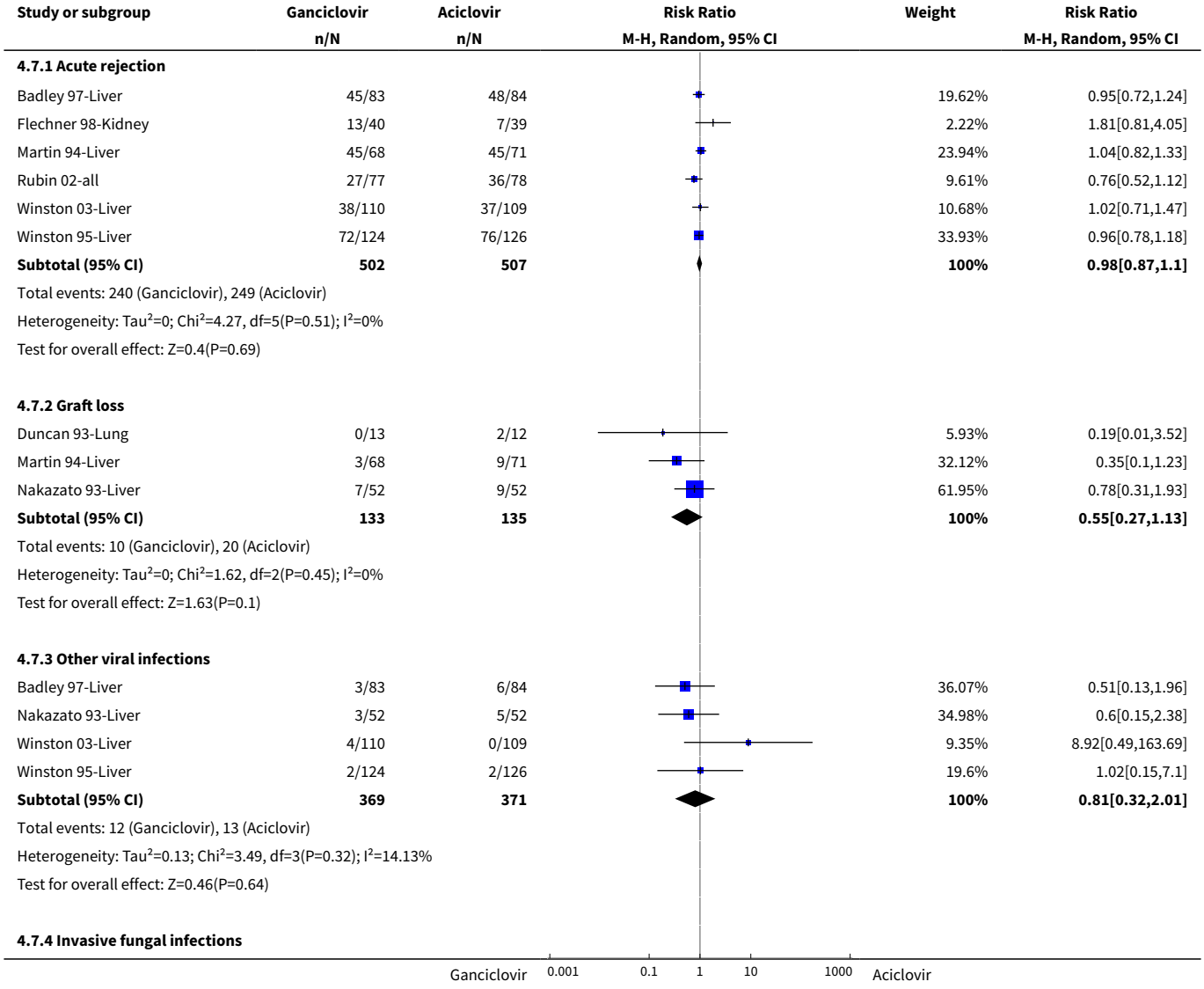


Analysis 4.6. Comparison 4 Ganciclovir versus aciclovir, Outcome 6 Death.

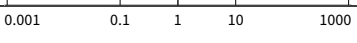


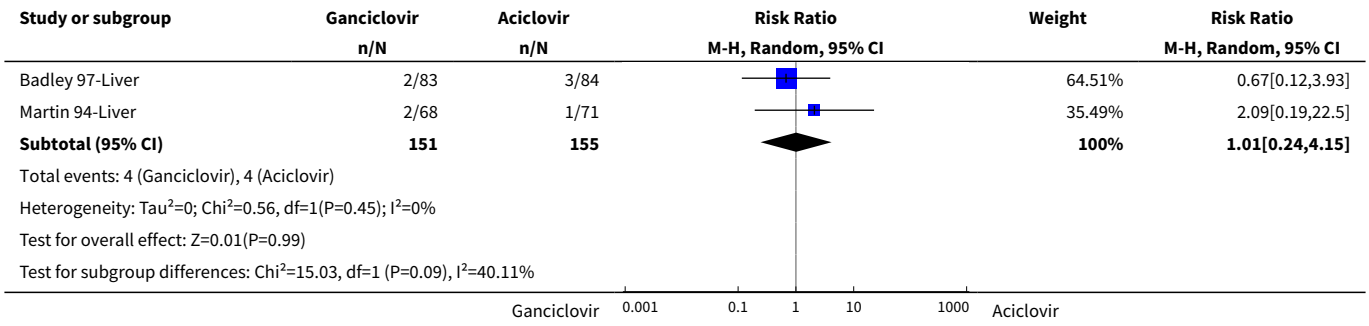


Analysis 4.7. Comparison 4 Ganciclovir versus aciclovir, Outcome 7 Additional outcomes.



Study or subgroup	Ganciclovir n/N	Aciclovir n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Badley 97-Liver	18/83	26/84		92.78%	0.7[0.42,1.18]
Flechner 98-Kidney	1/40	2/39		4.48%	0.49[0.05,5.16]
Rubin 02-all	0/77	2/78		2.74%	0.2[0.01,4.15]
Subtotal (95% CI)	**200**	**201**		**100%**	**0.67[0.4,1.1]**
Total events: 19 (Ganciclovir), 30 (Aciclovir)					
Heterogeneity: Tau^2=0; Chi^2=0.72, df=2(P=0.7); I^2=0%					
Test for overall effect: Z=1.59(P=0.11)					
4.7.5 Bacterial infections					
Badley 97-Liver	39/83	36/84		100%	1.1[0.78,1.53]
Subtotal (95% CI)	**83**	**84**		**100%**	**1.1[0.78,1.53]**
Total events: 39 (Ganciclovir), 36 (Aciclovir)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					
4.7.6 Protozoal infections					
Badley 97-Liver	0/83	1/84		100%	0.34[0.01,8.16]
Subtotal (95% CI)	**83**	**84**		**100%**	**0.34[0.01,8.16]**
Total events: 0 (Ganciclovir), 1 (Aciclovir)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					
4.7.7 Obliterative bronchiolitis in lung transplant recipients					
Duncan 93-Lung	7/13	8/12		100%	0.81[0.42,1.54]
Subtotal (95% CI)	**13**	**12**		**100%**	**0.81[0.42,1.54]**
Total events: 7 (Ganciclovir), 8 (Aciclovir)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.51)					
4.7.8 Leucopenia					
Badley 97-Liver	2/83	0/84		6.91%	5.06[0.25,103.82]
Duncan 93-Lung	0/13	0/12			Not estimable
Martin 94-Liver	1/68	0/71		6.22%	3.13[0.13,75.54]
Rubin 02-all	12/77	2/78		29.44%	6.08[1.41,26.26]
Winston 03-Liver	5/110	1/109		13.89%	4.95[0.59,41.72]
Winston 95-Liver	7/124	4/126		43.55%	1.78[0.53,5.92]
Subtotal (95% CI)	**475**	**480**		**100%**	**3.28[1.48,7.25]**
Total events: 27 (Ganciclovir), 7 (Aciclovir)					
Heterogeneity: Tau^2=0; Chi^2=1.94, df=4(P=0.75); I^2=0%					
Test for overall effect: Z=2.93(P=0)					
4.7.9 Renal dysfunction					
Badley 97-Liver	7/83	4/84		1.38%	1.77[0.54,5.82]
Duncan 93-Lung	4/13	2/12		0.86%	1.85[0.41,8.32]
Winston 03-Liver	35/110	41/109		14.65%	0.85[0.59,1.22]
Winston 95-Liver	88/124	93/126		83.11%	0.96[0.82,1.12]
Subtotal (95% CI)	**330**	**331**		**100%**	**0.96[0.83,1.1]**
Total events: 134 (Ganciclovir), 140 (Aciclovir)					
Heterogeneity: Tau^2=0; Chi^2=2.21, df=3(P=0.53); I^2=0%					
Test for overall effect: Z=0.62(P=0.54)					
4.7.10 Neurological dysfunction					

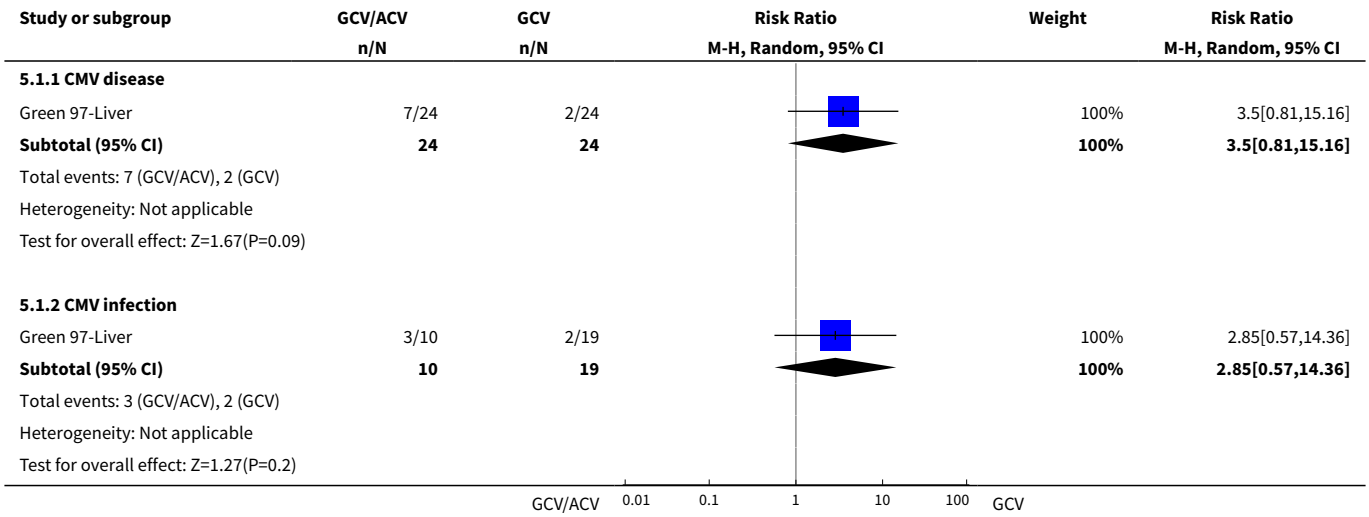


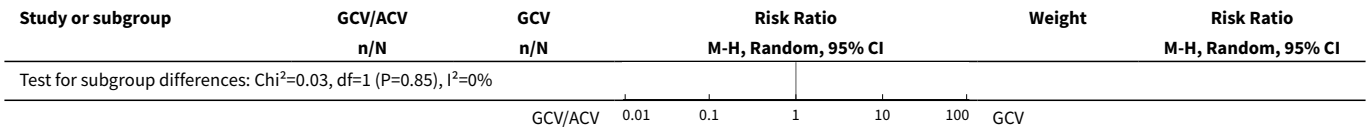


Comparison 5. Ganciclovir / aciclovir versus ganciclovir

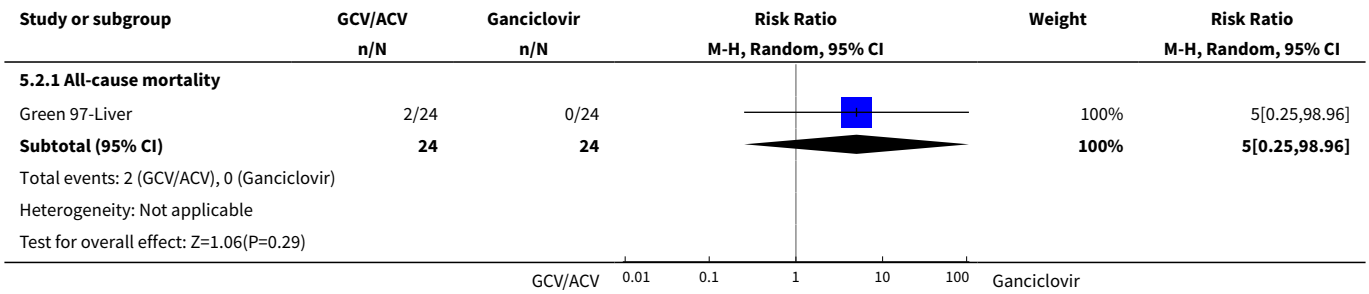
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 CMV disease and CMV infection in all treated patients	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 CMV disease	1	48	Risk Ratio (M-H, Random, 95% CI)	3.5 [0.81, 15.16]
1.2 CMV infection	1	29	Risk Ratio (M-H, Random, 95% CI)	2.85 [0.57, 14.36]
2 Death	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 All-cause mortality	1	48	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.25, 98.96]
3 Additional outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 EBV infection	1	48	Risk Ratio (M-H, Random, 95% CI)	1.6 [0.61, 4.19]

Analysis 5.1. Comparison 5 Ganciclovir / aciclovir versus ganciclovir, Outcome 1 CMV disease and CMV infection in all treated patients.

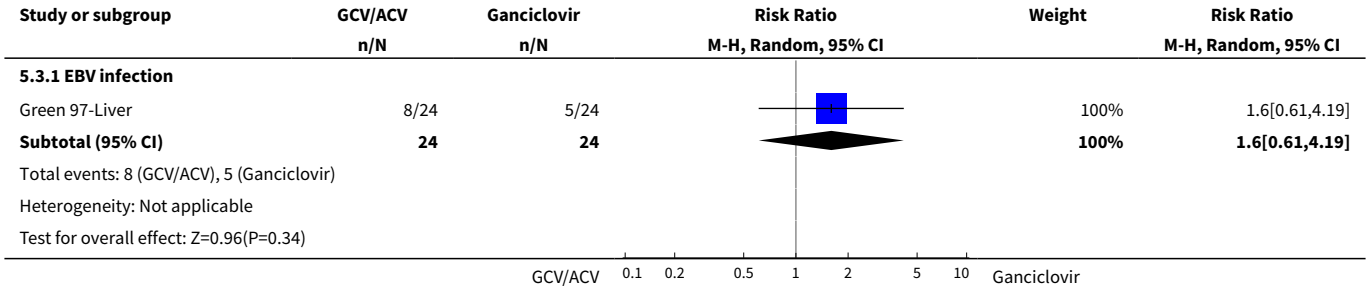




Analysis 5.2. Comparison 5 Ganciclovir / aciclovir versus ganciclovir, Outcome 2 Death.



Analysis 5.3. Comparison 5 Ganciclovir / aciclovir versus ganciclovir, Outcome 3 Additional outcomes.



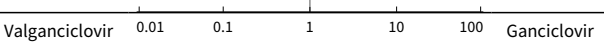
Comparison 6. Valganciclovir versus ganciclovir

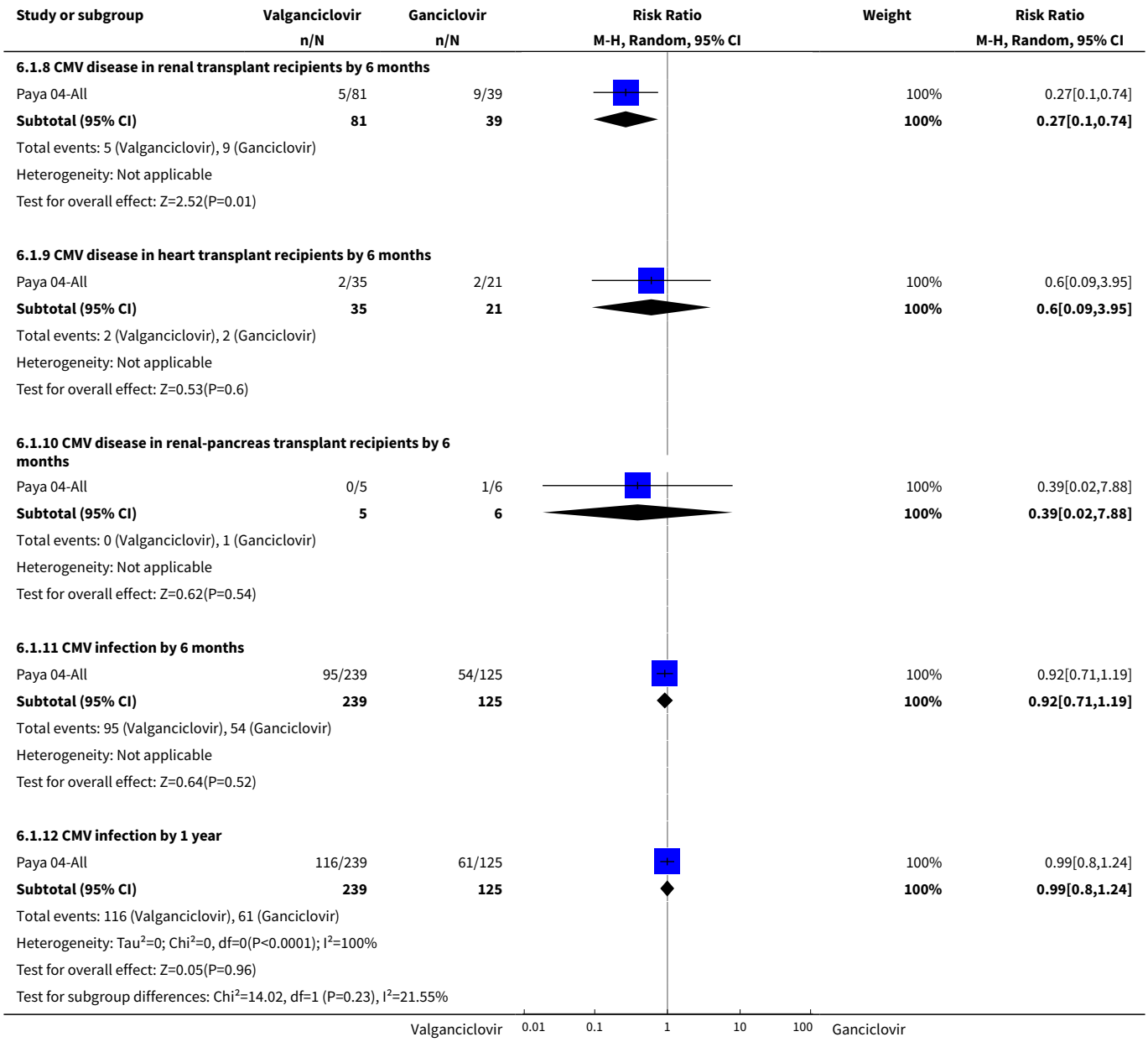
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease or infection in CMV donor +ve / recipient -ve	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 CMV disease by 6 months	1	364	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.47, 1.37]
1.2 CMV disease by 1 year	1	364	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.59, 1.48]
1.3 CMV syndrome by 6 months	1	364	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.23, 1.03]
1.4 CMV syndrome by 1 year	1	364	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.39, 1.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Tissue invasive CMV disease by 6 months	1	364	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.60, 3.66]
1.6 Tissue invasive CMV disease by 1 year	1	364	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.66, 3.14]
1.7 CMV disease in liver transplant recipients by 6 months	1	177	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.71, 3.47]
1.8 CMV disease in renal transplant recipients by 6 months	1	120	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.10, 0.74]
1.9 CMV disease in heart transplant recipients by 6 months	1	56	Risk Ratio (M-H, Random, 95% CI)	0.6 [0.09, 3.95]
1.10 CMV disease in renal-pancreas transplant recipients by 6 months	1	11	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.02, 7.88]
1.11 CMV infection by 6 months	1	364	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.71, 1.19]
1.12 CMV infection by 1 year	1	364	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.80, 1.24]
2 Death	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Death due to CMV disease	1	364	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.03, 8.29]
2.2 All-cause mortality	1	364	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.43, 2.25]
3 additional outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Acute rejection in all recipients	1	364	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.67, 1.22]
3.2 Graft loss	1	364	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.13, 4.63]
3.3 Opportunistic infections	1	364	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.42, 1.76]
3.4 Neutrophil count < 1000	1	370	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.81, 3.16]
3.5 Medications ceased because of neutropenia	1	370	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.21, 3.54]
3.6 Anaemia < 80 g/L	1	370	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.68, 3.55]
3.7 Platelet count < 100,000	1	370	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.88, 2.03]
3.8 Tremor	1	370	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.76, 1.57]

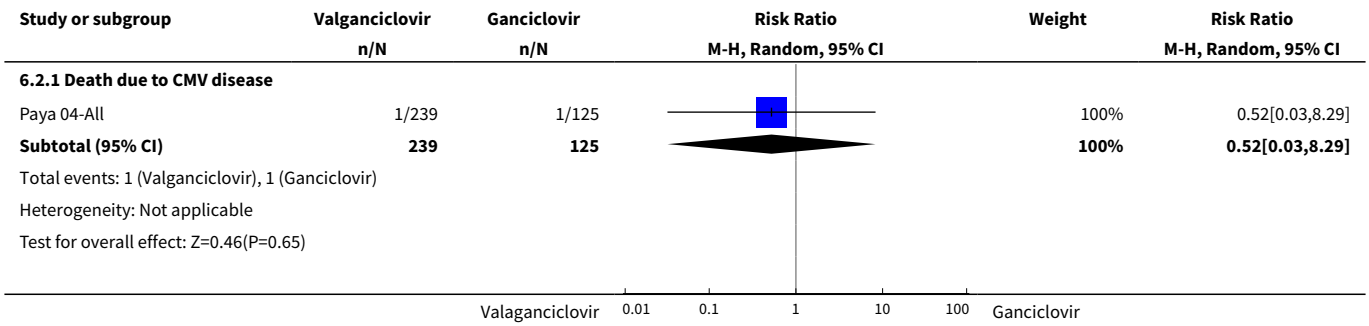
Analysis 6.1. Comparison 6 Valganciclovir versus ganciclovir, Outcome 1 CMV disease or infection in CMV donor +ve / recipient -ve.

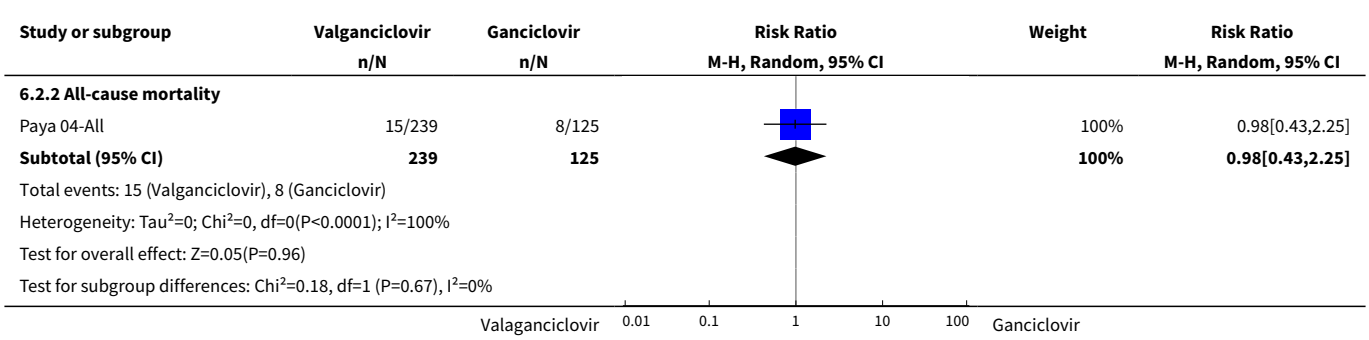
Study or subgroup	Valganciclovir n/N	Ganciclovir n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 CMV disease by 6 months					
Paya 04-All	29/239	19/125		100%	0.8[0.47,1.37]
Subtotal (95% CI)	**239**	**125**		**100%**	**0.8[0.47,1.37]**
Total events: 29 (Valganciclovir), 19 (Ganciclovir)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					
6.1.2 CMV disease by 1 year					
Paya 04-All	41/239	23/125		100%	0.93[0.59,1.48]
Subtotal (95% CI)	**239**	**125**		**100%**	**0.93[0.59,1.48]**
Total events: 41 (Valganciclovir), 23 (Ganciclovir)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.3(P=0.77)					
6.1.3 CMV syndrome by 6 months					
Paya 04-All	12/239	13/125		100%	0.48[0.23,1.03]
Subtotal (95% CI)	**239**	**125**		**100%**	**0.48[0.23,1.03]**
Total events: 12 (Valganciclovir), 13 (Ganciclovir)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.89(P=0.06)					
6.1.4 CMV syndrome by 1 year					
Paya 04-All	19/239	13/125		100%	0.76[0.39,1.5]
Subtotal (95% CI)	**239**	**125**		**100%**	**0.76[0.39,1.5]**
Total events: 19 (Valganciclovir), 13 (Ganciclovir)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.78(P=0.43)					
6.1.5 Tissue invasive CMV disease by 6 months					
Paya 04-All	17/239	6/125		100%	1.48[0.6,3.66]
Subtotal (95% CI)	**239**	**125**		**100%**	**1.48[0.6,3.66]**
Total events: 17 (Valganciclovir), 6 (Ganciclovir)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.85(P=0.39)					
6.1.6 Tissue invasive CMV disease by 1 year					
Paya 04-All	22/239	8/125		100%	1.44[0.66,3.14]
Subtotal (95% CI)	**239**	**125**		**100%**	**1.44[0.66,3.14]**
Total events: 22 (Valganciclovir), 8 (Ganciclovir)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.91(P=0.36)					
6.1.7 CMV disease in liver transplant recipients by 6 months					
Paya 04-All	22/118	7/59		100%	1.57[0.71,3.47]
Subtotal (95% CI)	**118**	**59**		**100%**	**1.57[0.71,3.47]**
Total events: 22 (Valganciclovir), 7 (Ganciclovir)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.12(P=0.26)					



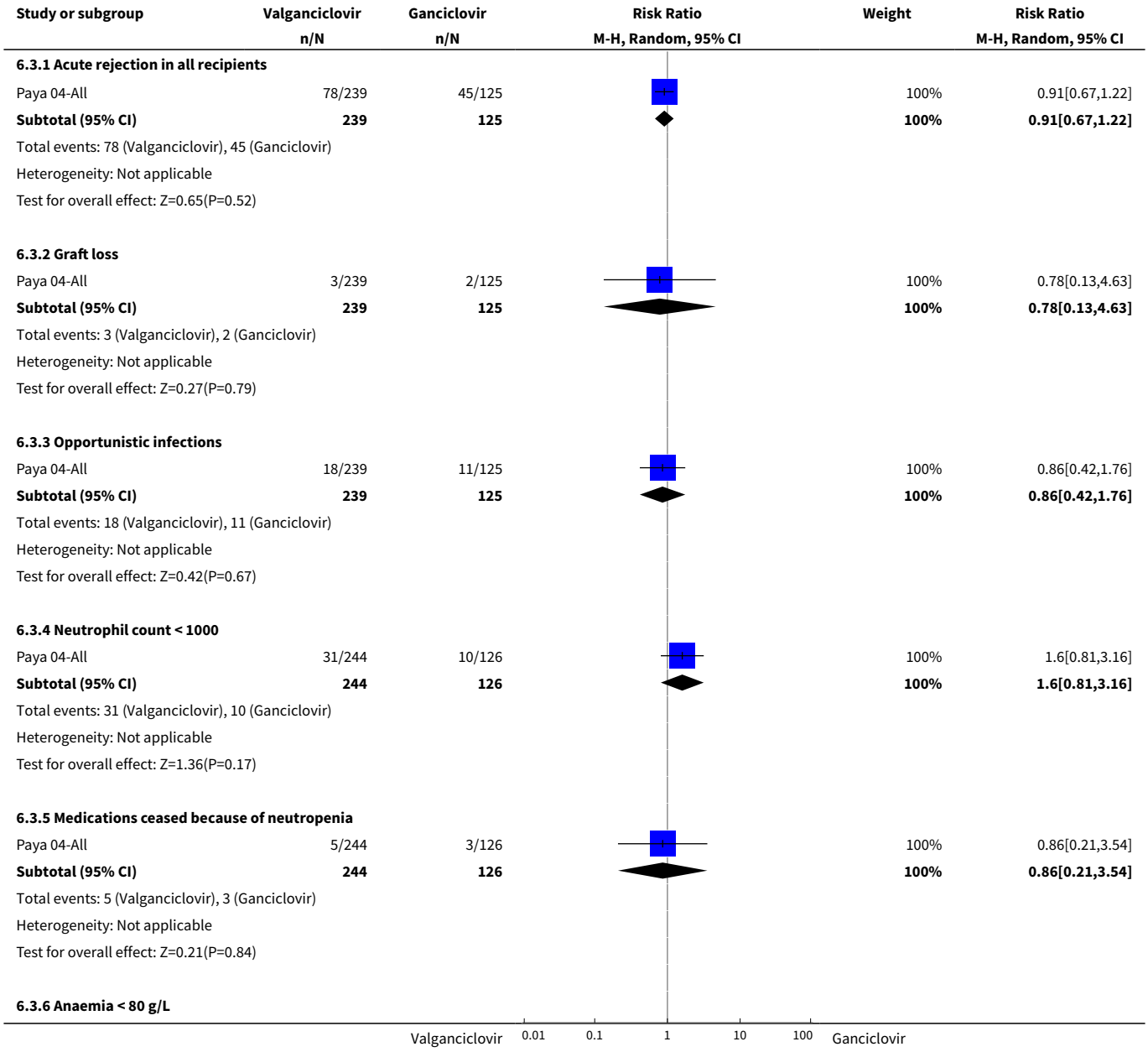


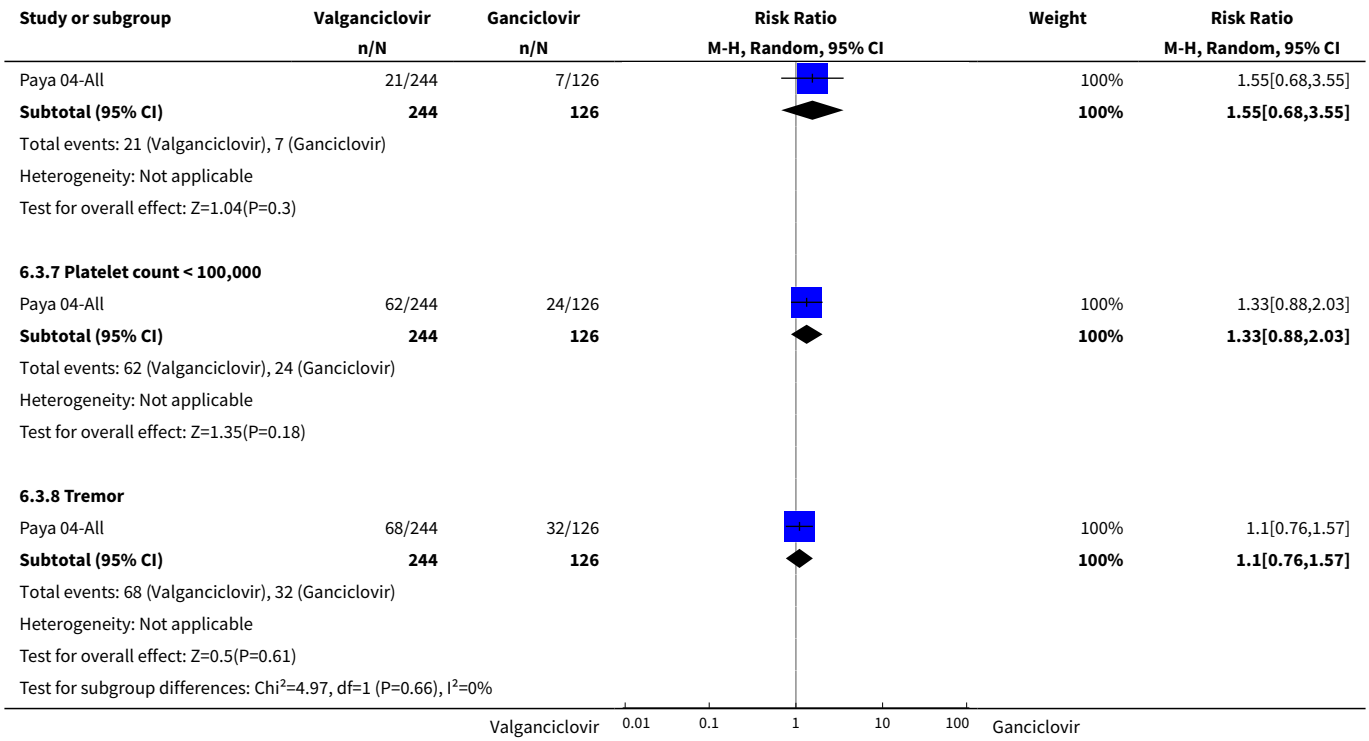
Analysis 6.2. Comparison 6 Valganciclovir versus ganciclovir, Outcome 2 Death.





Analysis 6.3. Comparison 6 Valganciclovir versus ganciclovir, Outcome 3 additional outcomes.



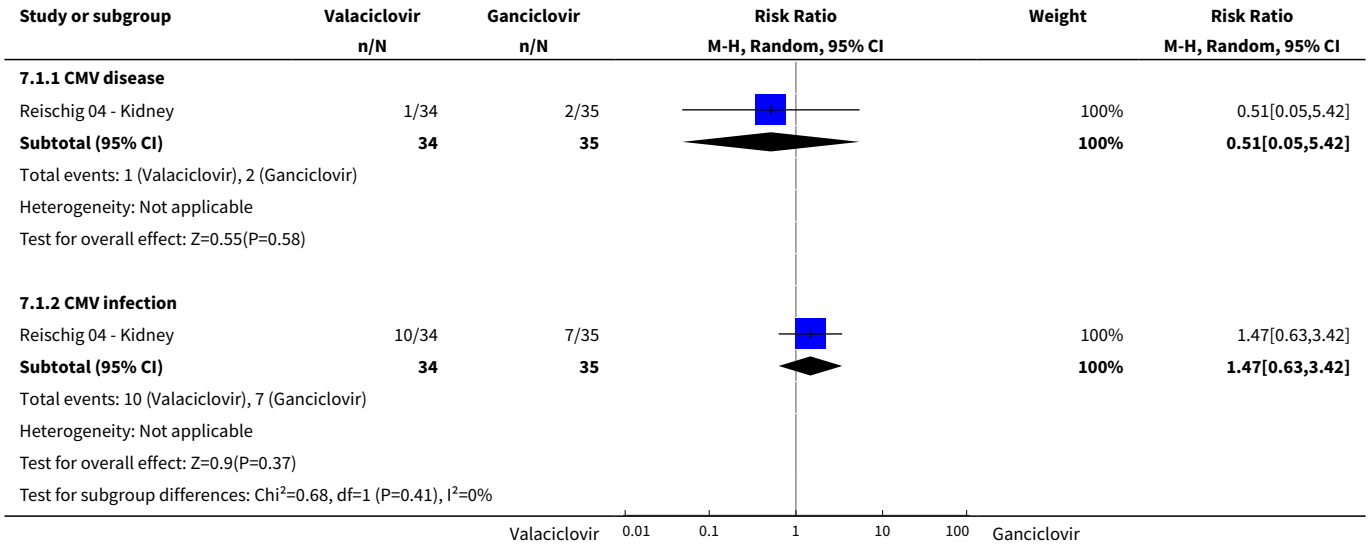


Comparison 7. Valaciclovir versus ganciclovir

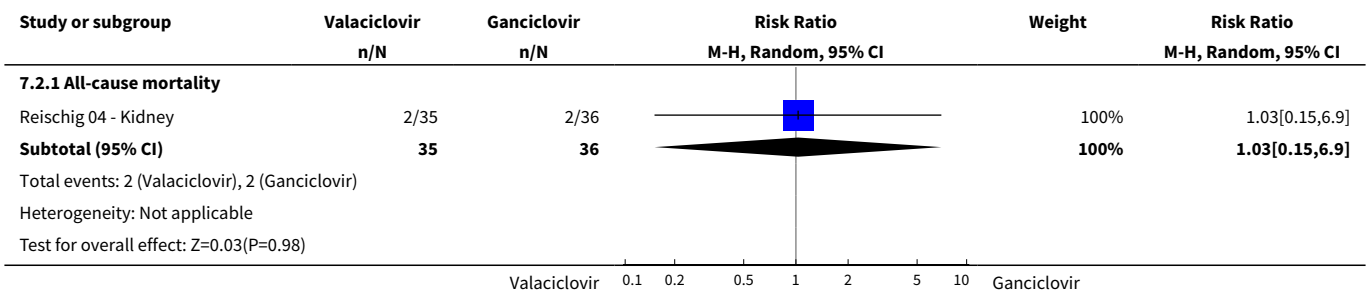
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 CMV disease and CMV infection in all treated patients	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 CMV disease	1	69	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.05, 5.42]
1.2 CMV infection	1	69	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.63, 3.42]
2 Death	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 All-cause mortality	1	71	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.15, 6.90]
3 Additional outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Acute rejection	1	69	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.12, 0.96]
3.2 Graft loss	1	71	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.14, 1.90]
3.3 Leucopenia	1	69	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.40, 2.62]
3.4 Thrombocytopenia	1	69	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.30, 1.33]
3.5 Anaemia	1	68	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.19, 1.31]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.6 Neurological dysfunction	1	69	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.62, 3.87]

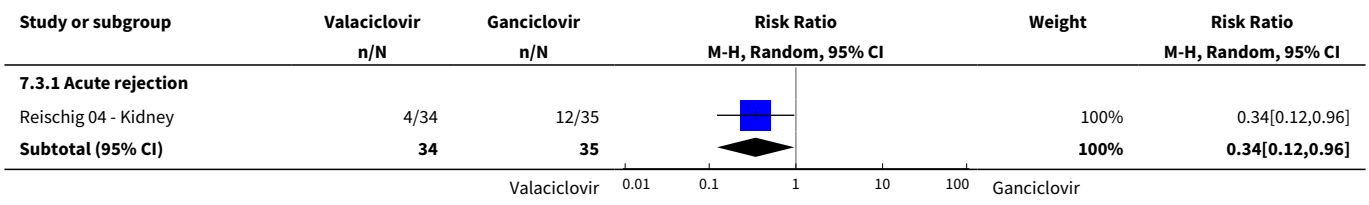
Analysis 7.1. Comparison 7 Valaciclovir versus ganciclovir, Outcome 1 CMV disease and CMV infection in all treated patients.

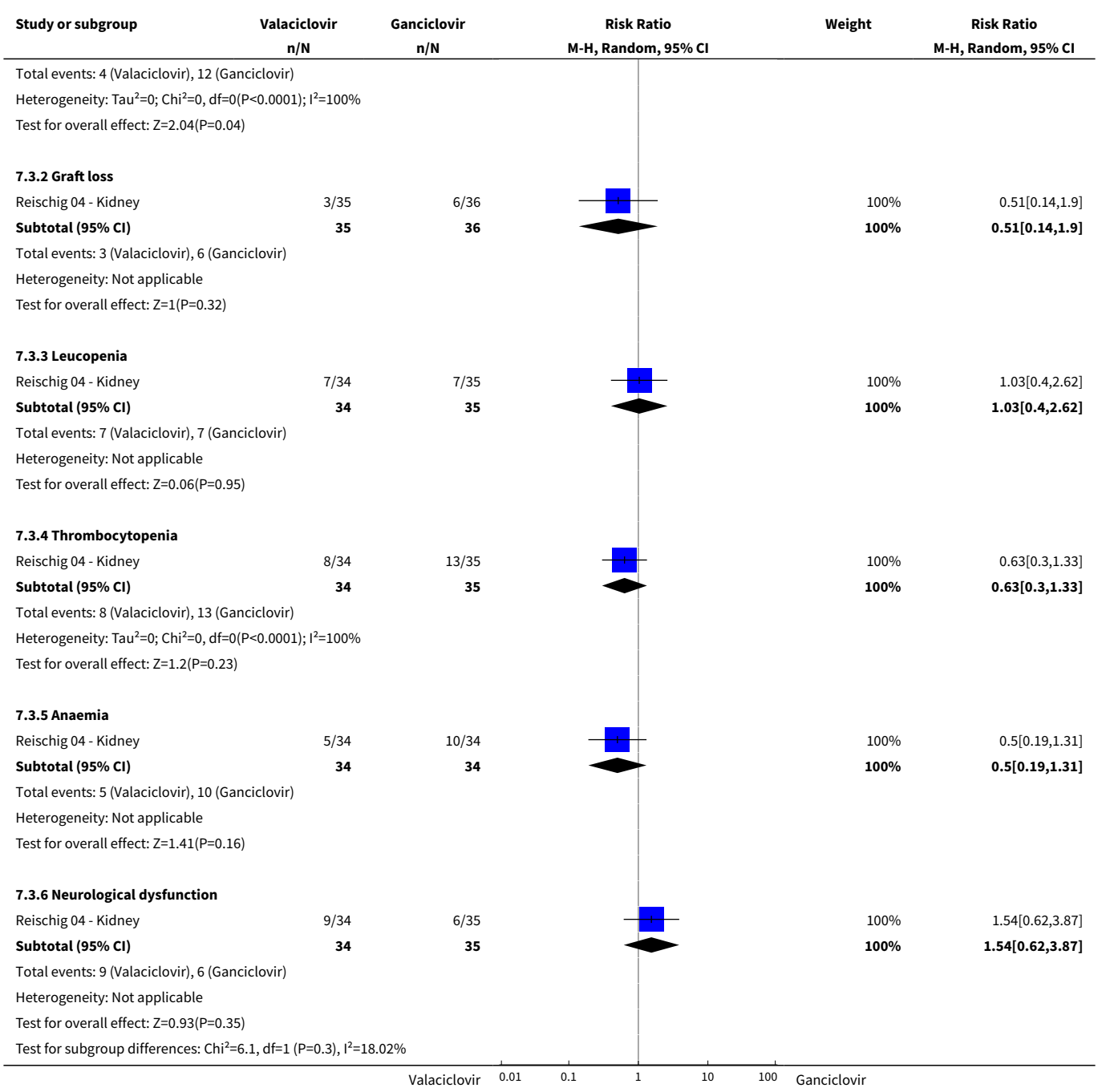


Analysis 7.2. Comparison 7 Valaciclovir versus ganciclovir, Outcome 2 Death.



Analysis 7.3. Comparison 7 Valaciclovir versus ganciclovir, Outcome 3 Additional outcomes.



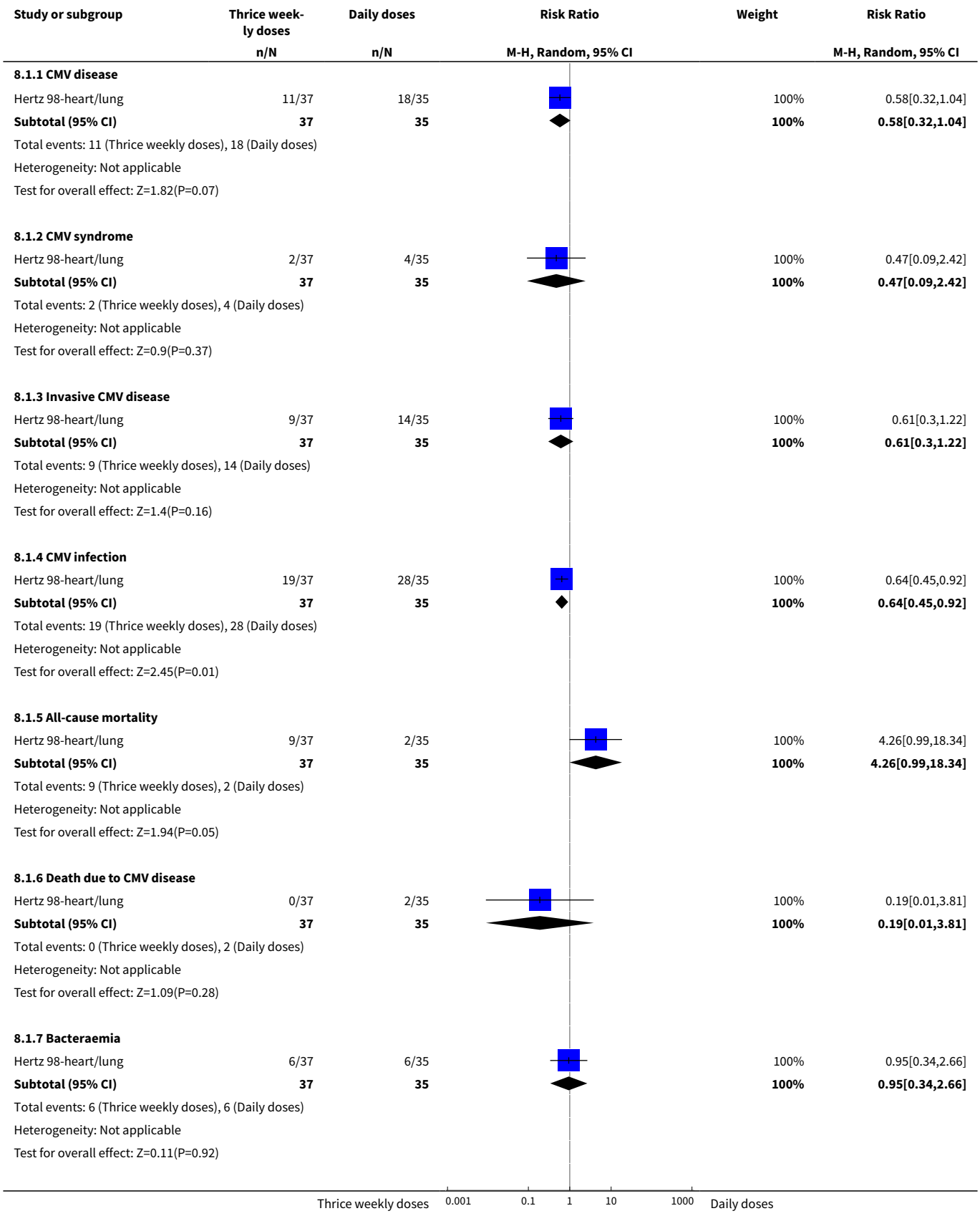


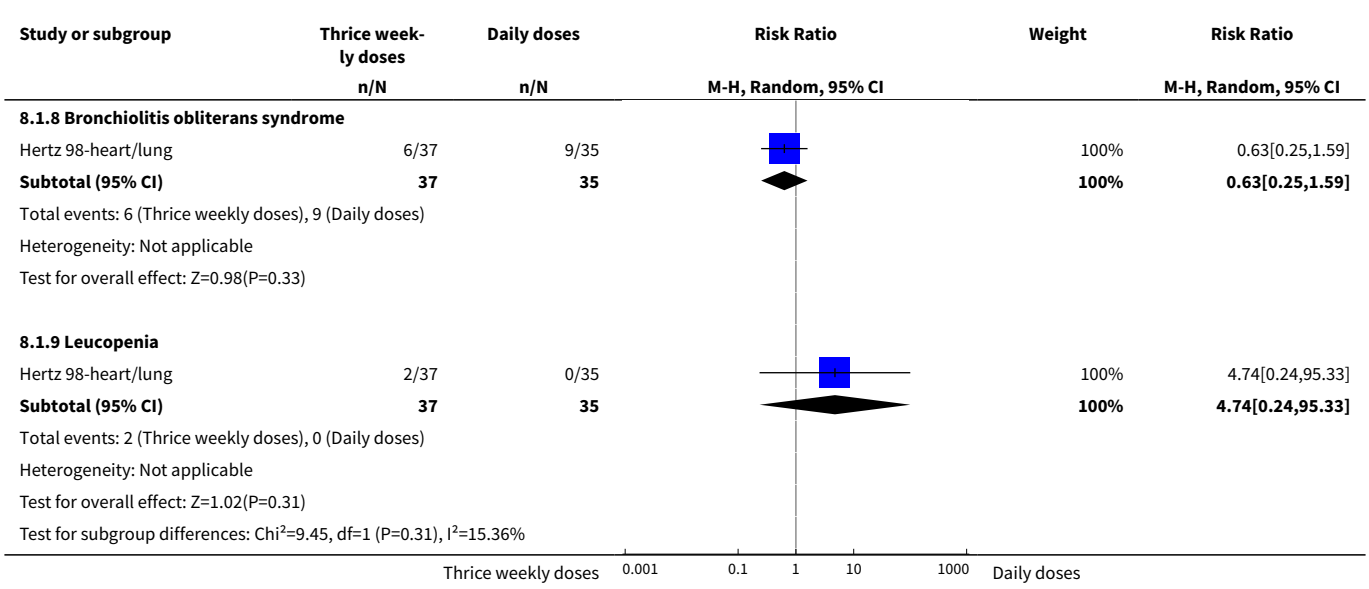
Comparison 8. Different ganciclovir regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 IV doses given at different frequencies	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

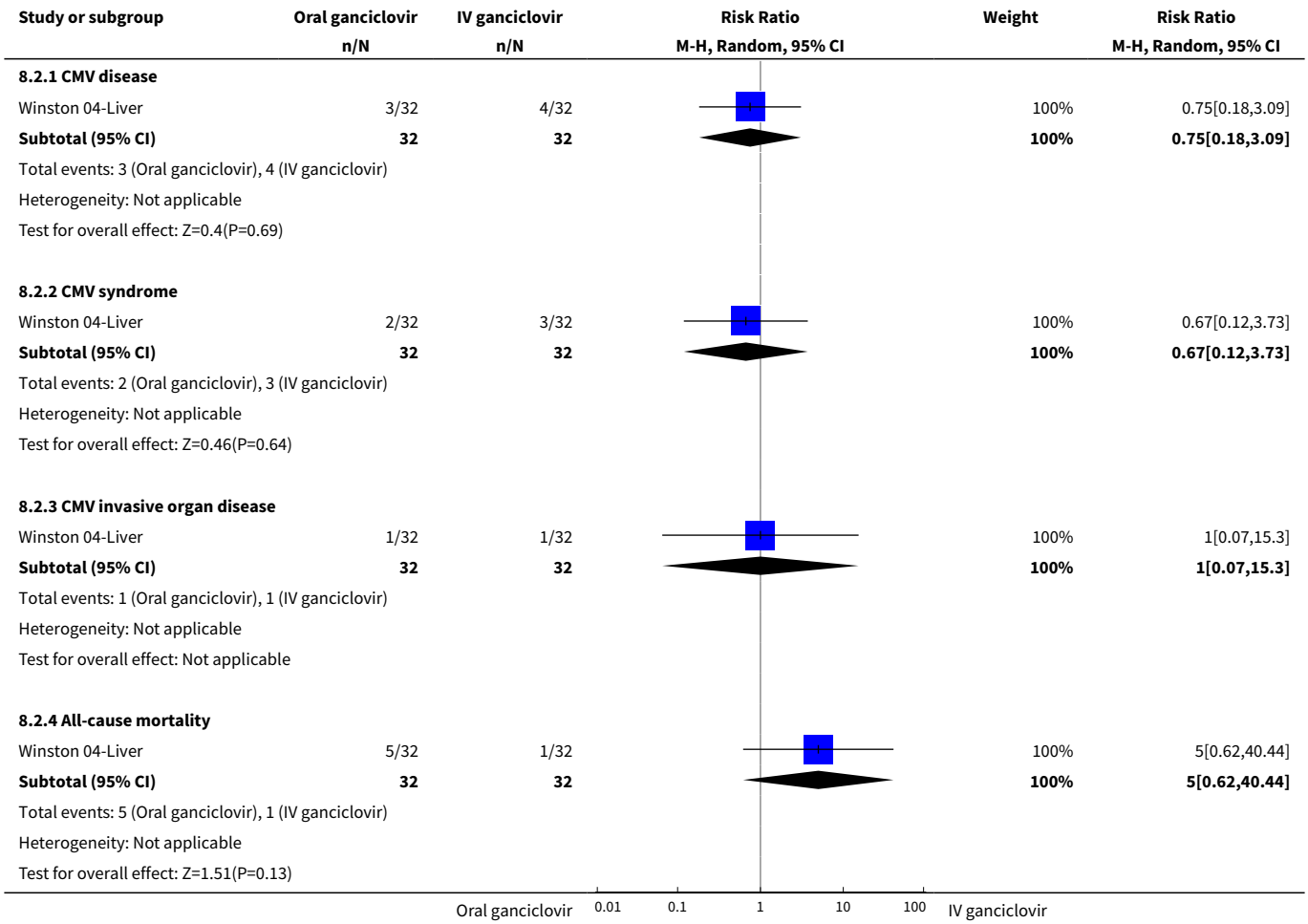
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 CMV disease	1	72	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.32, 1.04]
1.2 CMV syndrome	1	72	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.09, 2.42]
1.3 Invasive CMV disease	1	72	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.30, 1.22]
1.4 CMV infection	1	72	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.45, 0.92]
1.5 All-cause mortality	1	72	Risk Ratio (M-H, Random, 95% CI)	4.26 [0.99, 18.34]
1.6 Death due to CMV disease	1	72	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 3.81]
1.7 Bacteraemia	1	72	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.34, 2.66]
1.8 Bronchiolitis obliterans syndrome	1	72	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.25, 1.59]
1.9 Leucopenia	1	72	Risk Ratio (M-H, Random, 95% CI)	4.74 [0.24, 95.33]
2 Oral versus intravenous ganciclovir in donor +ve / -ve recipients	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 CMV disease	1	64	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.18, 3.09]
2.2 CMV syndrome	1	64	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.12, 3.73]
2.3 CMV invasive organ disease	1	64	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 15.30]
2.4 All-cause mortality	1	64	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.62, 40.44]
2.5 Leucopenia due to ganciclovir	1	64	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.35, 1.39]
2.6 Medications ceased due to leucopenia	1	64	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.27, 3.66]

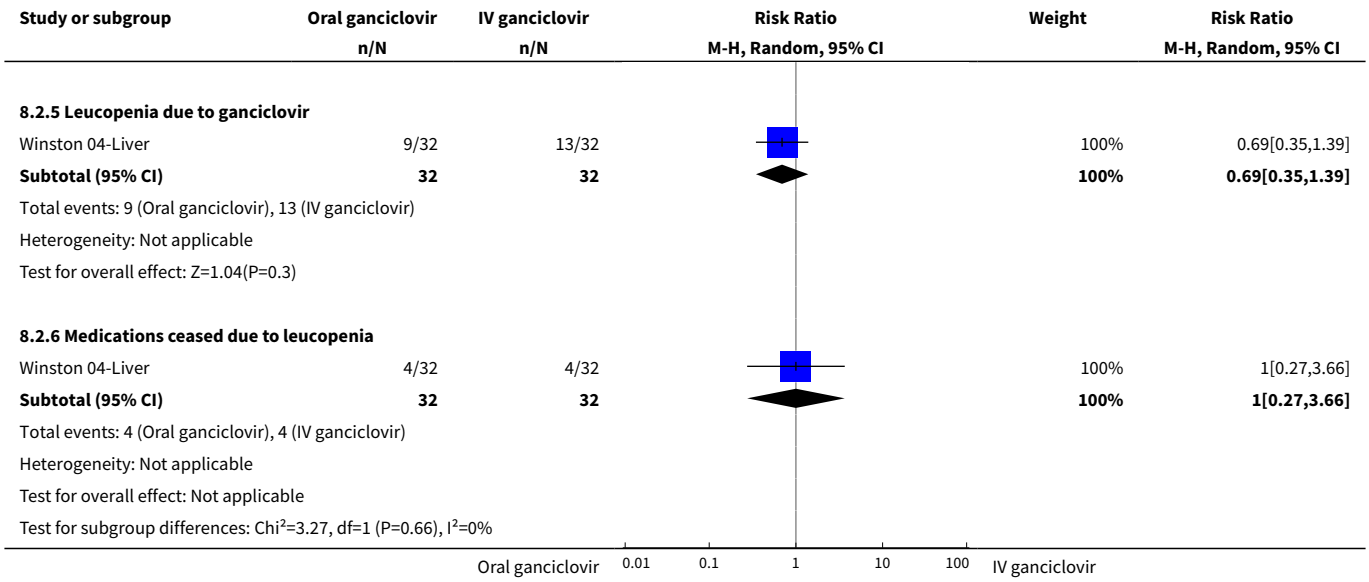
Analysis 8.1. Comparison 8 Different ganciclovir regimens, Outcome 1 IV doses given at different frequencies.





Analysis 8.2. Comparison 8 Different ganciclovir regimens, Outcome 2 Oral versus intravenous ganciclovir in donor +ve / -ve recipients.





ADDITIONAL TABLES

Table 1. Electronic search strategies

Database	Search terms
CENTRAL	1) cytomegalovirus 2) cytomegalovirus-infection 3) CMV 4) #1 or #2 or #3 5) transplantation (including organ-transplantation, kidney-transplantation, heart-transplantation, lung-transplantation, liver-transplantation, and pancreas-transplantation) 6) aciclovir 7) ganciclovir 8) valaciclovir 9) valganciclovir 10) cidofovir 11) immunoglobulin 12) vaccine and immunotherapy 13) #6 or #7 or #8 or #9 or #10 or #11 or #12 14) #4 and #5 and #13
MEDLINE	1) randomized controlled trial.pt. 2) controlled clinical trial.pt. 3) randomized controlled trials/ 4) random allocation/ 5) double blind method/ 6) single blind method/ 7) or/1-6 8) animal/ not (animal/ and human/) 9) 7 not 8 10) clinical trial.pt. 11) exp clinical trials/ 12) (clin$ adj25 trial$).ti,ab. 13) cross-over studies/ 14) (crossover or cross-over or cross over).tw.

Table 1. Electronic search strategies *(Continued)*

	15) ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 16) placebos/ 17) placebo$.ti,ab. 18) random$.ti,ab. 19) research design/ 20) or/10-19 21) 20 not 8 22) 21 or 9 23) exp cytomegalovirus/ or exp cytomegalovirus infection/ 24) exp organ transplantation/ 25) 24 not exp bone transplantation/ 26) 23 and 25 27) exp acyclovir/ or exp ganciclovir/ or exp antiviral agents/ 28) ac?clovir.tw./ or ganc?clovir.tw./ or valac?clovir.tw./ or valganc?clovir.tw./ or cidofovir.tw. 29) exp immunoglobulins/ or exp gamma-globulins/ or exp immunoglobulins, intravenous/ or exp immunotherapy/ 30) 27 or 28 or 29 31) 26 and 30 32) 22 and 31
EMBASE	1) exp clinical trial/ 2) evidence based medicine/ 3) outcomes research/ 4) crossover procedure/ 5) double blind procedure/ 6) single blind procedure/ 7) prospective study/ 8) major clinical study/ 9) exp comparative study/ 10) placebo/ 11) "evaluation and follow up"/ 12) follow up 13) randomization/ 14) or/1-13 15) controlled study/ not case control study 16) or/14-15 17) (clinic$ adj5 trial$).ti,ab. 18) ((single$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab. 19) (control$ or prospectiv$ or volunteer$).ti,ab. 20) random$.ti,ab. 21) placebo$.ti,ab. 22) or/17-21 23) 16 or 22 24) limit 23 to human 25) exp cytomegalovirus/ or exp cytomegalovirus infection 26) exp kidney transplantation/ or exp heart transplantation/ or exp lung transplantation/ or exp liver transplantation/ or exp pancreas transplantation 27) 25 and 26 28) exp aciclovir/ or exp ganciclovir/ or exp valaciclovir/ or valganciclovir/ or exp antiviral agents/ or exp immunoglobulin/ or exp immunotherapy 29) ac?clovir.tw./ or ganc?clovir.tw./ or valac?clovir.tw./ or valganc?clovir.tw./ or cidofovir.tw. 30) 28 or 29 31) 27 and 30 32) 24 and 31

Table 2. Potential sources of variability - CMV disease and all-cause mortality

Variable	CMV disease	CMV disease	CMV disease	All-cause mortality	All-cause mortality	All-cause mortality
	Number of trials	RR (95% CI)	P (for interaction)	Number of trials	RR (95% CI)	P (for interaction)
ANTIVIRAL MEDICATION - Aciclovir - Ganciclovir - Valaciclovir	6 11 2	0.45 (0.29 to 0.69) 0.44 (0.34 to 0.58) 0.30 (0.19 to 0.49)	0.43	5 10 2	0.67 (0.38 to 1.20) 0.69 (0.29 to 1.65) 0.50 (0.22 to 1.15)	0.85
TIME TO OUTCOME ASSESSMENT - Three to 6 months - nine to 12 months	11 8	0.46 (0.36 to 0.58) 0.36 (0.22 to 0.58)	0.37	7 10	0.63 (0.40 to 0.97) 0.64 (0.31 to 1.33)	0.83
RECIPIENT CYTOMEGALOVIRUS STATUS - Positive (donor positive or negative)* - Negative (donor positive)+	13 10	0.34 (0.24 to 0.50) 0.52 (0.37 to 0.74)	0.12	12 4	0.18 (0.09 to 0.36) 0.33 (0.11 to 0.95)	0.23
DONOR CYTOMEGALOVIRUS STATUS^ - Positive (recipients all positive) - Negative (recipients all positive)	5 5	0.18 (0.09 to 0.36) 0.33 (0.11 to 0.95)	0.37	No data No data	No data No data	No data
ORGAN TRANSPLANTED - Kidney - Liver - Heart	11 5 3	0.42 (0.31 to 0.57) 0.49 (0.29 to 0.84) 0.39 (0.25 to 0.63)	0.93	10 4 3	0.49 (0.24 to 1.00) 0.64 (0.39 to 1.00) 1.82 (0.39 to 8.51)	0.13
ANTIBODY THERAPY - Yes - No	11 6	0.43 (0.33 to 0.55) 0.47 (0.29 to 0.76)	0.74	10 5	0.81 (0.33 to 2.01) 0.63 (0.39 to 1.00)	0.93

Table 2. Potential sources of variability - CMV disease and all-cause mortality *(Continued)*

TREATMENT DURATION# - Six weeks or less - More than 6 weeks	7 4	0.49 (0.36 to 0.68) 0.33 (0.21 to 0.53)	0.72	6 4	0.91 (0.17 to 4.92) 0.62 (0.30 to 1.30)	0.15
ALLOCATION CONCEALMENT - Adequate - Unclear or inadequate	4 15	0.50 (0.31 to 0.79) 0.41 (0.33 to 0.51)	0.64	3 14	0.26 (0.06 to 1.20) 0.67 (0.45 to 0.99)	0.88
BLINDING - Yes - No	5 14	0.35 (0.25 to 0.48) 0.47 (0.37 to 0.59)	0.18	5 12	0.62 (0.39 to 0.98) 0.65 (0.33 to 1.27)	0.97
INTENTION-TO-TREAT ANALYSIS - Yes - No	10 9	0.38 (0.30 to 0.48) 0.47 (0.33 to 0.68)	0.37	9 8	0.62 (0.40 to 0.98) 0.65 (0.32 to 1.29)	0.57
* Trials in "positive" group included those in which recipients were positive for CMV with donor positive or negative for CMV						
+ Trials in "negative" group included those in which CMV negative recipients received CMV positive organs						
^ Trials in which recipients were CMV positive and the donors CMV positive (positive group) or negative (CMV negative group)						

Table 2. Potential sources of variability - CMV disease and all-cause mortality *(Continued)*

Ganciclovir studies only

Table 3. Summary of outcomes for antiviral medication versus placebo/no treatment

Outcome	Aciclovir	Ganciclovir	Valaciclovir	All medications
Acute rejection	4; 1.03 (0.78 to 1.36)*	7; 0.92 (0.70 to 1.21)	2; 0.81 (0.51 to 1.28)^	13; 0.90 (0.78 to 1.17)
Graft loss	4; 0.77 (0.35 to 1.68)	6; 0.73 (0.41 to 1.28)	No data	10; 0.74 (0.47 to 1.17)
Herpes simplex or zoster infections	3; 0.30 (0.14 to 0.62)	4; 0.25 (0.08 to 0.78)	2; 0.28 (0.20 to 0.40)	9; 0.27 (0.19 to 0.40)
Post-transplant lympho-proliferative disease	1; 2.90 (0.12 to 68.2)	1; 0.34 (0.01 to 8.33)	No data	2; 1.01 (0.11 to 9.51)
Bacterial infections	1; 0.67 (0.33 to 1.38)	1; 0.72 (0.44 to 1.17)	1; 0.27 (0.07 to 1.05)	3; 0.65 (0.44 to 0.96)
Fungal infections	1; 1.30 (0.31 to 5.39)	2; 0.28 (0.07 to 1.12)	No data	3; 0.58 (0.19 to 1.73)
Protozoal infections	No data	2; 0.31 (0.01 to 0.99)	No data	2; 0.31 (0.01 to 0.99)
Leucopenia [a]	No data	3; 0.99 (0.37 to 2.65)	1; 1.05 (0.62 to 1.78)	
Creatinine > 200 µmol/L [a]	2; 1.14 (0.27 to 4.70)	3; 2.36 (0.91 to 6.15)	No data	
Hallucinations [a]	1; 10.6 (0.62 to 183.3)	1; 1.59 (0.98 to 2.58)	1; 8.78 (2.69 to 28.7)	

[a] Placebo-controlled trials only

* number of trials contributing data; RR (95% CI)

^ Heterogeneity of trial results present

Table 4. Effects of antiviral medication on CMV disease and all-cause mortality

Recipient group	Without prophylaxis*	With prophylaxis+	Number prevented	Number with harms++
CMV DISEASE	7/100	3/100	4/100	7/100
- Kidney[a]	28/100	12/100	16/100	7/100
- Kidney[a]; liver^; heart[a]	59/100	25/100	39/100	7/100
- Liver, heart[a]; all^, antibody therapy included in immunosuppressive regimen				
ALL-CAUSE MORTALITY	6/100	4/100	2/100	7/100
- Kidney	20/100	13/100	7/100	7/100
- Liver	24/100	15/100	9/100	7/100
- Heart or lung				

Table 4. Effects of antiviral medication on CMV disease and all-cause mortality *(Continued)*

[a] Donor positive or negative for CMV; recipient negative ^ Donor positive recipient negative for CMV	* data from references	+ Calculated from summary estimates of RR (0.42 for prevention of CMV disease, 0.63 for all-cause mortality)	++ Based on proportion of patients, treated with valaciclovir, who developed hallucinations

WHAT'S NEW

Date	Event	Description
10 May 2017	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 4, 2005

Date	Event	Description
23 August 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

EMH identified and extracted data from included trials, contacted authors, analysed and interpreted the results and wrote the manuscript.
CAJ conceived, designed and developed the protocol and search strategy for the review, identified and extracted data from included trials and participated in revision of the manuscript.
ACW analysed and interpreted the results and participated in the revision of the manuscript.
GFMS checked the analysis and interpretation of the results and participated in the revision of the manuscript.
PGB and KK identified and extracted data from included trials and participated in revision of the manuscript.
DV developed the protocol and search strategy for the review.
JCC conceived, designed and developed the protocol, analysed and interpreted the results and edited the drafting and revision of the manuscript.

DECLARATIONS OF INTEREST

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PB is a member of Amgen Pharmacy Advisory Board, for which he receives an honorarium, and had received travel grants from Novartis Pharmaceuticals, Janssen-Cilag and Roche.
KK has received an educational grant from Amgen Australia and travel grants from Novartis Pharmaceuticals, Janssen-Cilag and Roche.
DV declares no conflicts of interest.

INDEX TERMS

Medical Subject Headings (MeSH)

*Organ Transplantation; Acyclovir [analogs & derivatives] [therapeutic use]; Antiviral Agents [adverse effects] [*therapeutic use]; Cytomegalovirus Infections [*prevention & control]; Ganciclovir [therapeutic use]; Randomized Controlled Trials as Topic; Valine [analogs & derivatives] [therapeutic use]

MeSH check words

Humans