RACE611 CLINICAL EPIDEMIOLOGY AND EVIDENCE-BASED MEDICINE

Systematic Review

Master of Science Program in Medical Epidemiology and Doctor of Philosophy Program in Clinical Epidemiology
Section for Clinical Epidemiology & Biostatistics
Faculty of Medicine Ramathibodi Hospital
Mahidol University
www.ceb-rama.org/
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Semester 1

REFERENCES

1. Fletcher RH, Fletcher SW, Wagner EH. Clinical Epidemiology. The Essentials. 4th Ed.Baltimore: Lippincott Williams & Wilkins, 2005:205-20.

2. Haynes RB, Sackett DL, Guyatt GH, Tugwell P. Clinical epidemiology. How to do clinical practice research, 3rd Ed. Philadephia: Lippincott Williams & Wilkins, 2006:15-48.

3. Heneghan C, Badenoch D. Evidence-based medicine toolkit. 2nd Ed. Massachusetts: Blackwell Publishing, 2006:27-33.

4. Levine M, Haslan D, Walter S, et al. Harm. Guyatt G, Rennie D. Users' guides to the medical literature. Essentials of evidence-based clinical practice. Chicago: AMA Press, 2002:241-70.

Critical appraisal for systematic review

Scenario

You are a clinical fellowship of nephrology at the school of medicine, where kidney transplantation is often performed. Antiviral prophylaxis for Cytomegalovirus infection is routinely prescribed in this centre. However, the prophylaxis regimens are varied between physicians. You are wondering which regimen should be prescribed, and whether the prophylaxis can prevent cytomegalovirus disease?

ASSIGNMENTS

A. What is your clinical question?

   P:

   I:

   C:

   O:

B. What are your search term?

C. Read the article and critically appraise its validity using the Appraisal Guides for an Article on systematic review (Appendix 1).

D. Appraise the results of the study, discussing the rationale for each in worksheet for systematic review (Appendix 2).

E. Create critical appraisal topic (CAT) from this study (Appendix 3).

READING

1. Haynes RB, Sackett DL, Guyatt GH, Tugwell P. Clinical epidemiology. How to do clinical practice research, 3rd Ed. Philadephia: Lippincott Williams & Wilkins, 2006: 15-48.

2. Levine M, Haslan D, Walter S, et al. Harm. Guyatt G, Rennie D. Users' guides to the medical literature. Essentials of evidence-based clinical practice. Chicago: AMA Press, 2002:241-70.

Appendix (include articles assign for reading)

Appendix 1: Guideline for Critical Appraisal on Systematic review

Levine M, Haslan D, Walter S, et al. Harm. Guyatt G, Rennie D. Users' guides to the medical literature. Essentials of evidence-based clinical practice. Chicago: AMA Press, 2002: 241-70.

Appendix 2: Systematic review worksheet

Systematic review

A. Are the results valid?	
* Did the Review Explicitly Address a Sensible Clinical Question?	
* Was the Search for Relevant Studies Detailed and Exhaustive?	
* Were the Primary Studies of High Methodologic Quality?	
* Were Assessments of Studies Reproducible?	
B. What are the results?	
* Were the Results Similar From Study to Study?	
* What Are the Overall Results of the Review?	
* How Precise Were the Results?	

C. How can I apply the results to patient care?	
* How Can I Best Interpret the Results to Apply Them to the Care of Patients in My Practice?	
* Were All Clinically Important Outcomes Considered?	
* Are the Benefits Worth the Costs and Potential risks?	

Appendix 3: Critical appraisal topic (CAT) for systematic review

Clinical Question:

Citation:

A. Study Characteristics:

1. Studies included –
2. Intervention compared -
3. Outcome -

B. Validity Criteria:

1. Explicitly address a sensible clinical question?
2. Methods for searching the literature explicit & reasonably thorough?
3. Appropriate criteria used to select studies for inclusion?
4. Validity of included studies assessed?
5. Were assessments of studies reproducible?
6. Was it appropriate to combine results (for meta-analysis)?

C. Results [adjust the number of rows as needed]:

Outcome	No. of Studies	No. of Patients	Point Estimate	95% Confidence Interval
1.				
2.				
3.				
4.				
5.				
6.				
Total				

D. Applicability:

E. Author's Conclusion:

F. Reviewer's Conclusion:

Reviewer: **Date:**

Appendix 4:

Reading article

Antiviral medications to prevent cytomegalovirus disease and early death in recipients of solid-organ transplants: a systematic review of randomised controlled trials

Elisabeth M Hodson, Cheryl A Jones, Angela C Webster, Giovanni F M Strippoli, Peter G Barclay, Kathy Kable, Dushyanthi Vimalachandra, Jonathan C Craig

Summary

Background **Antiviral prophylaxis is commonly used in recipients of solid-organ transplants with the aim of preventing the clinical syndrome associated with cytomegalovirus infection. We undertook a systematic review to investigate whether this approach affects risks of cytomegalovirus disease and death.**

Methods **Randomised controlled trials of prophylaxis with antiviral medications for cytomegalovirus disease in solid-organ-transplant recipients were identified. Data were combined in meta-analyses by a random-effects model.**

Findings **Compared with placebo or no treatment, prophylaxis with aciclovir, ganciclovir, or valaciclovir significantly reduced the risks of cytomegalovirus disease (19 trials, 1981 patients; relative risk 0·42 [95% CI 0·34–0·52]), cytomegalovirus infection (17 trials, 1786 patients; 0·61 [0·48–0·77]), and all-cause mortality (17 trials, 1838 patients; 0·63 [0·43–0·92]), mainly owing to lower mortality from cytomegalovirus disease (seven trials, 1300 patients; 0·26 [0·08–0·78]). Prophylaxis also lowered the risks of disease caused by herpes simplex or zoster virus, bacterial infections, and protozoal infections, but not fungal infection, acute rejection, or graft loss. Meta-regression showed no significant difference in the risk of cytomegalovirus disease or all-cause mortality by organ transplanted or cytomegalovirus serostatus; no conclusions were possible for cytomegalovirus-negative recipients of negative organs. In trials of direct comparisons, ganciclovir was more effective than aciclovir in preventing cytomegalovirus disease. Valganciclovir and intravenous ganciclovir were as effective as oral ganciclovir.**

Interpretation **Prophylaxis with antiviral medications reduces the risk of cytomegalovirus disease and associated mortality in recipients of solid-organ transplants. This approach should be used routinely in cytomegalovirus-positive recipients and in cytomegalovirus-negative recipients of organs positive for the virus.**

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Introduction

Cytomegalovirus infection is common in recipients of solid-organ transplants; more than 50% of recipients have laboratory evidence of primary or reactivated cytomegalovirus infection in the first year after transplantation.[1] Clinical sequelae of cytomegalovirus infection have been divided into the direct effects of viral replication (fever, leucopenia, and thrombocytopenia with or without specific organ dysfunction) and indirect effects resulting from the influence of the virus on the host's immune response. The indirect effects include acute rejection of the transplanted organ,[2] reduced long-term graft function,[3,4] and increased risk of other opportunistic infections.[5] Before prophylaxis was widely used, cytomegalovirus disease occurred in 7–32% of recipients of solid-organ transplants; the risk was lowest in kidney recipients and highest in heart-lung recipients.[6]

After the initial infection, cytomegalovirus persists throughout life in the host, with periodic reactivation. In general, primary infection is associated with the highest risk of disease. De-novo infection with a new cytomegalovirus strain can also occur in a cytomegalovirus-positive individual. Cytomegalovirus-negative recipients of organs from donors positive for the virus[2,4,7] and recipients being treated with antibodies to lymphocyte antigens are at higher risk of developing symptomatic cytomegalovirus disease.[8]

The high risk of sequelae from cytomegalovirus infection in recipients of solid-organ transplants has resulted in the widespread use of antiviral prophylaxis or pre-emptive therapy to prevent cytomegalovirus disease, but many questions remain unanswered. Does cytomegalovirus prophylaxis reduce mortality or the indirect effects of cytomegalovirus infection? What is the best regimen to prevent cytomegalovirus disease? Which recipients should be given prophylaxis? In this systematic review we aimed to answer these questions.

Methods

Design

We included randomised controlled trials comparing antiviral medications with placebo or no treatment, comparing different combinations of antiviral medications, or comparing different dosing regimens of the same antiviral medication to prevent cytomegalovirus disease in recipients of solid-organ transplants. Other interventions were excluded from this study because they are less commonly used (cytomegalovirus immunoglobulin), are experimental only (cytomegalovirus vaccines and interferon), or warrant a separate systematic

review (pre-emptive therapy on detection of cytomegalovirus viraemia). The primary outcomes of interest were cytomegalovirus disease and death (all-cause mortality and death from cytomegalovirus disease). Secondary outcomes sought were cytomegalovirus infection (cytomegalovirus disease and asymptomatic infection), time to development of cytomegalovirus disease, graft loss, acute rejection, other infections, and adverse effects of medications.

In the trials included, cytomegalovirus infection was defined as: the isolation of cytomegalovirus from the blood (buffy coat), urine, or organ biopsy sample by conventional culture or by "shell-vial" rapid culture; the presence of pp65 antigenaemia (with the threshold of positivity defined by study investigators); seroconversion in recipients who were cytomegalovirus negative before transplantation; a four-fold rise in antibody titre in cytomegalovirus-positive recipients; or the detection of cytomegalovirus DNA in the blood (viraemia). Cytomegalovirus disease was defined as infection with the virus plus cytomegalovirus syndrome, tissue-invasive cytomegalovirus disease, or both. Cytomegalovirus syndrome comprised fever, leucopenia, thrombocytopenia, and malaise. Tissue-invasive cytomegalovirus disease was defined by: the presence of organ-specific symptoms or signs plus the detection of cytomegalovirus in organ biopsy samples by histopathology or immunostaining; isolation of the virus from bronchoscopic lavage in a patient with otherwise unexplained pneumonia; or fundoscopic changes of chorioretinitis.

Randomised and quasi-randomised controlled trials were identified from MEDLINE (1966 to February, 2004), EMBASE (1988 to February, 2004), the Cochrane Central Register (Cochrane Library Issue 1, 2004), and the Cochrane Renal Group Trials Register, without language restriction. The most sensitive strategies of the Cochrane Collaboration to identify randomised controlled trials were used for MEDLINE and EMBASE searches.[9,10] They were combined with subject headings and textwords for cytomegalovirus infection and disease, solid-organ-transplant recipients (kidney, liver, heart, lung, combined liver and kidney, combined kidney and pancreas, and combined heart and lung), and antiviral medications including aciclovir, valaciclovir, ganciclovir, valganciclovir, and foscarnet (full details in web-appendix). Reference lists of review articles and relevant trials and abstracts of scientific meetings were also searched. Two reviewers independently reviewed trials for study eligibility and extracted trial data.

See Lancet Online for webappendix

Two reviewers assessed study quality without masking of author or source, using standard criteria for allocation concealment, intention-to-treat analysis, completeness of follow-up, and masking of participants, investigators, and outcome assessment. Discrepancies were resolved through discussion between reviewers. Information on allocation methods was sought from the original authors when it was not available in the published report.

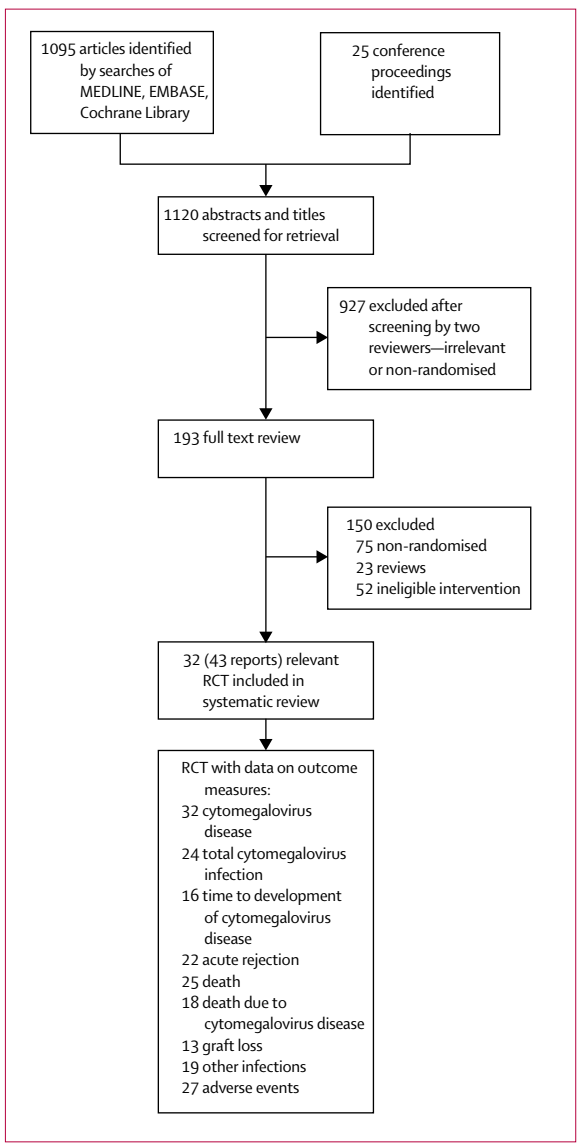

Figure 1: **Literature search flow diagram**
RCT=randomised controlled trials.

Statistical analysis

For dichotomous outcomes, relative risks with 95% CI were calculated in Review Manager (version 4.2.3, Cochrane Collaboration, 2003) for individual studies; the summary statistics were calculated with a random-effects model. This model takes into account variability between studies as well as within studies. Heterogeneity was analysed by Cochran's Q statistic with $\alpha=0{\cdot}05$ for statistical significance and by the statistic I^2, which is derived from Q and describes the proportion of total variation that is due to heterogeneity beyond chance.[11] To explore clinical differences between trials that might be expected to influence the size of the treatment effect for the primary outcomes of cytomegalovirus disease and all-cause mortality, subgroup analyses and univariate meta-

Drug, organ, and study	Cytomegalovirus status, donor/recipient			n	Experimental group, total dose per day	Control group	Treatment duration, days	Follow-up, months
	Either/positive	Positive/negative	Negative/negative					
Aciclovir, kidney								
12	Yes	Yes	Yes	104	2400 mg orally	Placebo	84	12
13	No	Yes	No	36	3200 mg orally	No treatment	84	12
14	Yes	No	No	37	6 mg/kg intravenously for 3 days, 3200 mg orally	No treatment	84	6
Aciclovir, liver								
15	Yes	Yes	Yes	55	3200 mg orally	Placebo	84	3
16	Yes	No	No	73	2000 mg orally	No treatment	106	12
17	Yes	No	No	120	500 mg/m^2 intravenously for 10 days, 3200 mg orally	No treatment	84	3
Ganciclovir, kidney								
18	Yes	Yes	No	44	1500 mg orally	No treatment	84	9
19	Yes	Yes	No	42	3000 mg orally	No treatment*	84	6
20	Yes	No	No	40	5 mg/kg intravenously	No treatment	10†	12
21	Yes	No	No	113	2·5 mg/kg intravenously	No treatment	9†	6
22	No	Yes	No	23	10 mg/kg intravenously	No treatment	14	3
23	Yes	Yes	Yes	50	5 mg/kg for 14 days, aciclovir 3200 mg orally	Placebo	84	6
24	Yes	No	No	32	10 mg/kg intravenously	No treatment	14	3
Ganciclovir, liver								
25	Yes	Yes	No	65	10 mg/kg intravenously	No treatment	14	18
26	Yes	Yes	Yes	304	3000 mg orally	Placebo	88	12
Ganciclovir, heart								
27	Yes	Yes	No	56	5 mg/kg intravenously for 3 days/week	Placebo	42	12
28	Yes	Yes	No	149	10 mg/kg for 14 days, 6 mg/kg intravenously 5 days/week	Placebo	28	4
Valaciclovir, kidney								
29	Yes	Yes	No	616	8000 mg orally	Placebo	87	12
Valaciclovir, heart								
30	Yes	No	No	27	8000 mg orally	No treatment*	87	6

*Control group given aciclovir 400 mg/day to prevent herpes simplex disease. †Median duration of treatment during administration of antithymocyte globulin.

Table 1: **Characteristics of included studies comparing antiviral medications with placebo or no treatment for prevention of cytomegalovirus infection in recipients of solid-organ transplants**

regression were done by use of STATA software (version 8.2) with restricted maximum likelihood to estimate the between-study variance. The potential sources of variability defined a priori were: organ transplanted, antiviral medication used, use of immunosuppressive regimen including antibody therapy, treatment duration, donor's and recipient's cytomegalovirus status at transplantation, the time from transplantation when the outcomes were measured, and methodological quality. Multivariate meta-regression was used to investigate whether the results changed after allowance for the differences in drug used, organ transplanted, and recipient's cytomegalovirus serostatus at the time of transplantation.

Role of the funding source

The funding sources had no role in the study design; the collection, analysis, or interpretation of data; or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 1120 articles initially identified, 193 reports were reviewed in full and 32 trials were included (figure 1). 19 trials (table 1)[12–30] compared aciclovir, ganciclovir, or valaciclovir with placebo or no treatment. 15 trials excluded cytomegalovirus-negative recipients of cytomegalovirus-negative donors.[13,14,16–22,24,25,27–30] 11 trials compared different antiviral medications,[1,3,31–40] and two[41,42] compared different regimens of ganciclovir administration (table 2). No trials comparing treatment with placebo or no treatment and only three comparison trials included recipients of organs other than heart, kidney, and liver (tables 1 and 2).

Ten (31%) trials reported adequate allocation concealment, one trial[19] had inadequate allocation concealment, and the information was not available for 21 trials. Six (19%) trials reported masking of investigators and participants, and three (9%) trials reported masking of outcome assessors. 19 (63%) trials carried out intention-to-treat analysis, and more than 95% of participants completed the trial in 31 (97%) trials.

The average risk of cytomegalovirus disease in the groups assigned placebo or no treatment for all trials was 30% (range 11–72) and that of cytomegalovirus infection was 49% (36–100). Prophylaxis with all agents significantly reduced the risk of cytomegalovirus disease (19 trials, 1981 patients; relative risk 0·42 [95% CI 0·34–0·52], figure 2), cytomegalovirus infection (17 trials, 1786 patients; 0·61 [0·48–0·77]), cytomegalovirus syndrome (11 trials, 1570 patients; 0·41 [0·29–0·57]), and cytomegalovirus invasive organ disease (12 trials, 1628 patients; 0·34 [0·21–0·55]) compared with placebo or no

Antiviral agents and organ	Study	Cytomegalovirus status, donor/recipient			n	Medication 1, total dose per day	Medication 2, total dose per day	Treatment duration, days	Follow-up, months
		Either/positive	Positive/negative	Negative/negative					
Ganciclovir *vs* aciclovir									
Kidney	31	Yes	Yes	No	79	Ganciclovir 3000 mg orally	Aciclovir 3200 mg orally	84	12
Liver	32	Yes	Yes	Yes	167	Ganciclovir 10 mg/kg intravenously for 14 days, aciclovir 3200 mg orally	Aciclovir 3200 mg orally	119	12
Liver	33	Yes	Yes	Yes	48	Ganciclovir 10 mg/kg intravenously for 14 days, aciclovir 3200 mg/m^2 orally	Ganciclovir 10 mg/kg intravenously for 14 days	365	12
Liver	34	Yes	Yes	Yes	139	Ganciclovir 10 mg/kg intravenously for 14 days, aciclovir 3200 mg orally	Aciclovir 3200 mg orally	84	6
Liver	35	Yes	Yes	Yes	104	Ganciclovir 5 mg/kg intravenously as inpatient, aciclovir 5 mg/kg orally	Aciclovir 5 mg/kg intravenously as inpatient, 5 mg/kg orally	84	3
Liver	36	Yes	Yes	Yes	99	Ganciclovir 6 mg/kg intravenously	Aciclovir 60 mg/kg intravenously as inpatient, 3200 mg orally	100	4
Liver	37	Yes	No	No	219	Ganciclovir 6 mg/kg intravenously for 14 days, 3000 mg orally	Ganciclovir 6 mg/kg intravenously for 14 days, aciclovir 3200 mg orally	100	12
Lung	3	Yes	Yes	No	25	Ganciclovir 20 mg/kg intravenously for 21 days, 5 mg/kg 5 times/week	Ganciclovir 20 mg/kg intravenously for 21 days, aciclovir 3200 mg orally	90	12
Kidney, liver, heart	1	No	Yes	No	155	Ganciclovir 5 mg/kg intravenously for 10 days, 3000 mg orally	Ganciclovir 5 mg/kg intravenously for 10 days, aciclovir 1200 mg orally	94	12
Valganciclovir *vs* ganciclovir									
Kidney, liver, heart, kidney-pancreas	38	No	Yes	No	364	Valganciclovir 900 mg orally	Ganciclovir 3000 mg orally	90	12
Valaciclovir *vs* ganciclovir									
Kidney	39,40	Yes	Yes	No	71	Valaciclovir 8000 mg orally	Ganciclovir 3000 mg orally	81	6
Ganciclovir doses									
Liver	41	Yes	No	No	64	Ganciclovir 6 mg/kg intravenously for 14 days, 3000 mg orally	Ganciclovir 6 mg/kg intravenously for 14 days, 5 mg/kg intravenously 5 times/week	100	12
Lung, heart-lung	42	Yes	Yes	No	72	Ganciclovir 10 mg/kg intravenously for 14 days, 5 mg/kg intravenously 3 times/week	Ganciclovir 10 mg/kg intravenously for 14 days, 5 mg/kg daily	90	12

Table 2: **Characteristics of included studies comparing different antiviral medications or different regimens of one antiviral medication for prevention of cytomegalovirus infection in recipients of solid-organ transplants**

treatment. No significant heterogeneity between studies was detected in the effect of prophylaxis on cytomegalovirus disease, syndrome, or invasive organ disease. There was substantial heterogeneity between studies for cytomegalovirus infection (I^2=76%), with no explanation apparent, but the point estimates for individual trials favoured prophylaxis in 15 of the 17 trials. Time to onset of cytomegalovirus disease was reported in 11 trials. In nine, prophylaxis significantly increased the time from transplantation to the onset of cytomegalovirus disease. Different methods of reporting precluded combination of these data in a meta-analysis.

When analysed separately, aciclovir, ganciclovir, and valaciclovir significantly reduced the risk of cytomegalovirus disease compared with placebo or no treatment (figure 2). Subgroup analysis by prophylactic drug used showed no significant difference in the beneficial treatment effects between the drugs in preventing cytomegalovirus disease (table 3). Further subgroup analyses, in which trials were stratified by methodological quality and features of trial design specified a priori, showed that treatment efficacy did not vary significantly among trials (table 3). Multivariate meta-regression showed no significant difference in cytomegalovirus disease after allowance for potential confounding or effect modification by prophylactic drug used, organ transplanted, or recipient serostatus in cytomegalovirus-positive recipients and cytomegalovirus-negative recipients of cytomegalovirus-positive donors. Insufficient data were available for us to assess the efficacy in cytomegalovirus-negative recipients of cytomegalovirus-negative donors.

The average all-cause mortality rate reported at 1 year or less after transplantation in the placebo or no-treatment groups of all trials was 7·1% (range 0–37). Prophylaxis significantly reduced all-cause mortality (17 trials, 1838 patients; relative risk 0·63 [95% CI 0·43–0·92], figure 3). In seven trials that reported all-cause mortality and the number of deaths from cytomegalovirus disease, the average mortality rate from cytomegalovirus disease in the groups assigned placebo or no treatment was 2·3% (range 0·3–7·4) and that from non-cytomegalovirus causes was 5·7% (0–15·6). Prophylaxis significantly reduced the risk of death from cytomegalovirus disease but not the risk of death from non-cytomegalovirus causes (figure 3). Subgroup analysis did not show any difference in this observed effect of treatment, after stratification of trials by methodological quality and features of trial design (table 3). Multivariate meta-regression showed that allowance for differences in organ transplanted, drug used, and recipient serostatus did not significantly affect the summary effect estimate.

There was no significant reduction in the risk of acute rejection or graft loss with prophylaxis for all solid-organ transplants (table 4). The risk of acute rejection did not differ on subgroup analysis between trials that used biopsy diagnosis (five trials; 0·97 [0·71–1·31]) and those that used clinical criteria (eight trials; 0·91 [0·76–1·08]; p for interaction 0·92). In one trial[29] with subgroups prespecified according to cytomegalovirus serostatus, prophylaxis significantly reduced the risk of acute rejection in cytomegalovirus-negative recipients of cytomegalovirus-positive kidneys (0·51 [0·35–0·74]) compared with cytomegalovirus-positive recipients (0·84 [0·63–1·10]; test of interaction p=0·04). This difference is the cause of the heterogeneity shown between valaciclovir trials (table 4).

Prophylaxis with aciclovir, ganciclovir, or valaciclovir reduced the risk of clinical disease caused by herpes simplex and herpes zoster (table 4). Data on bacterial, protozoal, or fungal infections in all patients were reported in three or fewer trials. Combination of the trials of different medications showed that the risks of bacterial and protozoal infections but not fungal infections were significantly reduced by prophylaxis (table 4).

16 trials reported data on adverse effects of medications. Except for six placebo-controlled trials, we could not assess baseline-adjusted effects of medications on leucocyte counts, renal function, and neurological dysfunction because the numbers of patients with abnormalities in these features were not reported for the no-treatment groups. In placebo-controlled trials, valaciclovir significantly increased the risk of hallucinations (8·5% *vs* 0·97%); no significant differences were identified for leucopenia or reduced renal function (table 4).

In trials with direct comparisons (seven trials; 1113 patients; table 2), ganciclovir was more effective than aciclovir in preventing cytomegalovirus disease in

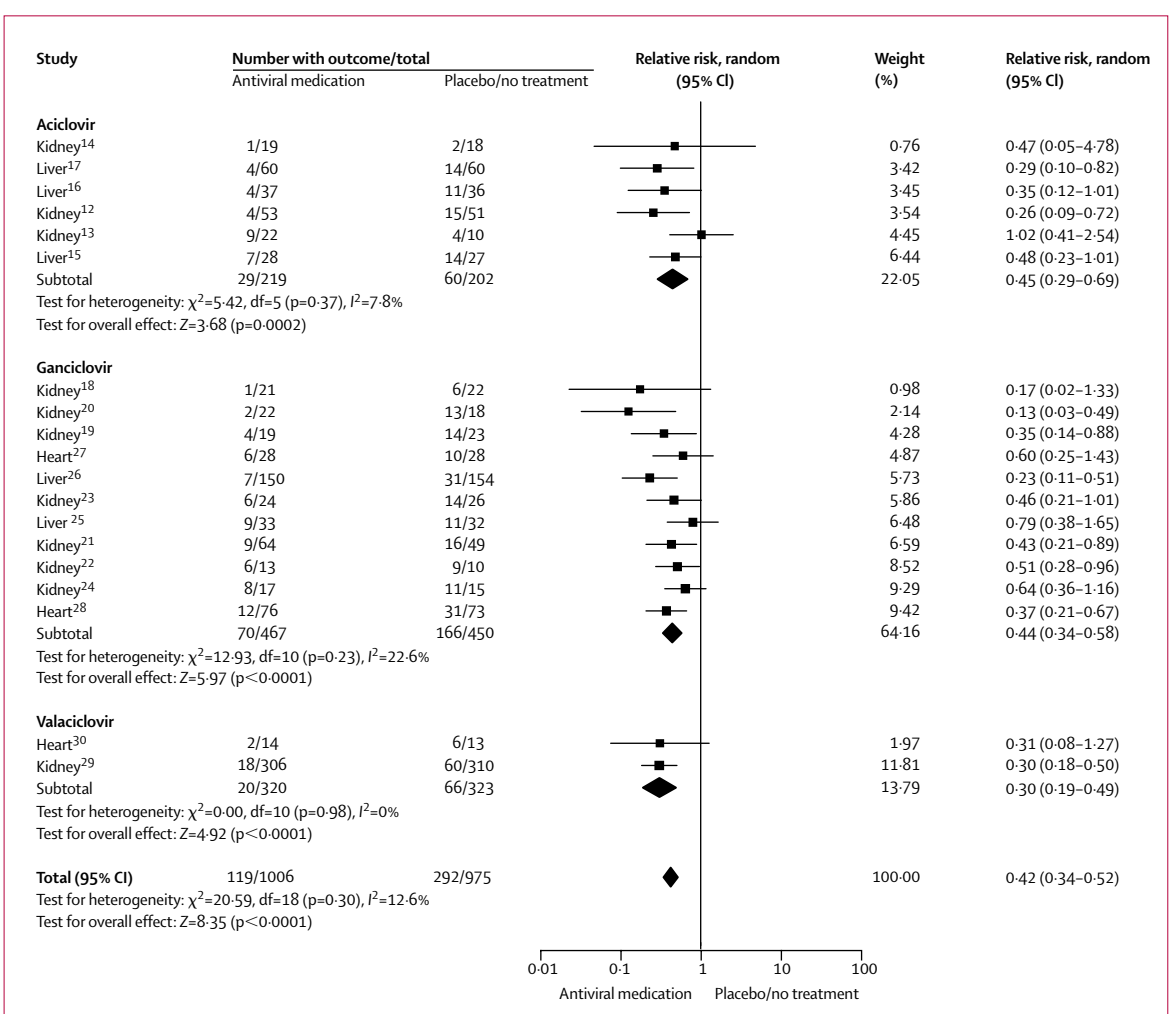

Figure 2: **Meta-analysis of randomised controlled trials examining the numbers of solid-organ-transplant recipients with cytomegalovirus disease in trials of prophylaxis with aciclovir, ganciclovir, or valaciclovir versus placebo or no treatment**

Variable	Cytomegalovirus disease			All-cause mortality		
	Number of trials	Relative risk (95%CI)	p*	Number of trials	Relative risk (95% CI)	p*
Antiviral medication						
Aciclovir	6	0·45 (0·29–0·69)	0·43	5	0·67 (0·38–1·20)	0·85
Ganciclovir	11	0·44 (0·34–0·58)		10	0·69 (0·29–1·65)	
Valaciclovir	2	0·30 (0·19–0·49)		2	0·50 (0·22–1·15)	
Time to outcome assessment						
3–6 months	11	0·46 (0·36–0·58)	0·37	7	0·63 (0·40–0·97)	0·83
9–12 months	8	0·36 (0·22–0·58)		10	0·64 (0·31–1·33)	
Recipient cytomegalovirus status†						
Positive (donor positive or negative)	13	0·34 (0·24–0·50)	0·12	12	0·18 (0·09–0·36)	0·23
Negative (donor positive)	10	0·52 (0·37–0·74)		4	0·33 (0·11–0·95)	
Donor cytomegalovirus status (recipients all positive)‡						
Positive	5	0·18 (0·09–0·36)	0·37		NA	NA
Negative	5	0·33 (0·11–0·95)			NA	
Organ transplanted						
Kidney	11	0·42 (0·31–0·57)	0·93	10	0·49 (0·24–1·00)	0·13
Liver	5	0·49 (0·29–0·84)		4	0·64 (0·39–1·00)	
Heart	3	0·39 (0·25–0·63)		3	1·82 (0·39–8·51)	
Antibody therapy						
Yes	11	0·43 (0·33–0·55)	0·74	10	0·81 (0·33–2·01)	0·93
No	6	0·47 (0·29–0·76)		5	0·63 (0·39–1·00)	
Treatment duration§						
≤6 weeks	7	0·49 (0·36–0·68)	0·72	6	0·91 (0·17–4·92)	0·15
>6 weeks	4	0·33 (0·21–0·53)		4	0·62 (0·30–1·30)	
Allocation concealment						
Adequate	4	0·50 (0·31–0·79)	0·64	3	0·26 (0·06–1·20)	0·88
Unclear or inadequate	15	0·41 (0·33–0·51)		14	0·67 (0·45–0·99)	
Masking						
Yes	5	0·35 (0·25–0·48)	0·18	5	0·62 (0·39–0·98)	0·97
No	14	0·47 (0·37–0·59)		12	0·65 (0·33–1·27)	
Intention-to-treat analysis						
Yes	10	0·38 (0·30–0·48)	0·37	9	0·62 (0·40–0·98)	0·57
No	9	0·47 (0·33–0·68)		8	0·65 (0·32–1·29)	

NA=no available data. *For interaction. †Trials in "positive" group included those in which recipients were positive for cytomegalovirus (donor positive or negative); trials in "negative" group included those in which cytomegalovirus-negative recipients received cytomegalovirus-positive organs. ‡Trials in which all recipients were cytomegalovirus positive and the donors were either positive (positive group) or negative (negative group). §Ganciclovir studies only.

Table 3: **Potential sources of variability in the efficacy of antiviral medications to prevent cytomegalovirus disease and all-cause mortality in recipients of solid-organ transplants**

all recipients (0·37 [0·23–0·60]), in cytomegalovirus-positive recipients (0·27 [0·13–0·55]), and in cytomegalovirus-negative recipients of cytomegalovirus-positive organs (0·64 [0·41–0·99]). In subgroup analyses, no differences in efficacy were found between studies in which the experimental group received ganciclovir followed by aciclovir (three trials; 0·38 [0·22–0·64]) and those in which the experimental group received ganciclovir for 3 months (four trials; 0·28 [0·09–0·82]; p for interaction 0·96). Ganciclovir was also more effective than aciclovir in reducing cytomegalovirus infection (0·45 [0·29–0·69]) but there was significant heterogeneity among studies. Valganciclovir and ganciclovir did not differ significantly in the prevention of cytomegalovirus disease (0·93 [0·59–1·48]) or cytomegalovirus infection (0·99 [0·80–1·24]). Similarly, the risks of cytomegalovirus disease (0·51 [0·05–5·42]) and cytomegalovirus infection (1·47 [0·63–3·42]) did not differ significantly between valaciclovir and ganciclovir prophylaxis. No significant differences were reported in all-cause mortality, mortality due to cytomegalovirus disease, graft loss, acute rejection, or other infections in trials comparing ganciclovir and aciclovir or valganciclovir and ganciclovir. Acute rejection was significantly less common with valaciclovir than with ganciclovir (0·34 [0·12–0·96]). Leucopenia was more common with ganciclovir than with aciclovir (3·28 [1·48–7·25]). Neutrophil counts below 1×10^9/L occurred in 13% of patients assigned valganciclovir compared with 8% of those assigned ganciclovir, but the difference was not significant. There were no significant differences in the risk of cytomegalovirus disease with different frequencies of intravenous doses or between oral or intravenous routes of administration of ganciclovir.

Discussion

Our study shows that the antiviral medications ganciclovir, valaciclovir, and aciclovir improve outcomes for recipients of solid-organ transplants far beyond the primary indication for use. In addition to reducing the risk of cytomegalovirus disease by 60%, these medications lowered all-cause mortality by 40% predominantly as a result of reduced mortality from cytomegalovirus disease, clinical disease caused by herpes simplex and herpes zoster by 70%, bacterial infections by 35%, and protozoal infections by 70%. For cytomegalovirus disease and mortality, the relative benefits of aciclovir, ganciclovir, and valaciclovir were consistent across recipients of heart, kidney, and liver transplants, occurred in both cytomegalovirus-positive and cytomegalovirus-negative recipients of organs positive for cytomegalovirus, occurred irrespective of whether immunosuppression included antibody therapy against lymphocytes, and did not depend on the time of outcome assessment.

Are these results relevant to current clinical practice, in which valganciclovir is the most commonly prescribed antiviral medication for cytomegalovirus prophylaxis?[43] This systematic review of 19 trials (1981 patients) published between 1989 and 2002 has shown a consistent reduction in cytomegalovirus disease and all-cause mortality with aciclovir, ganciclovir, or valaciclovir compared with placebo or no treatment. Therefore examination of the efficacy of valganciclovir or future antiviral medications in placebo-controlled trials can no longer be considered ethical. In the only published trial[38] comparing valganciclovir (the prodrug of ganciclovir) and ganciclovir, there were no significant differences in the risk of cytomegalovirus disease, all-cause mortality, or other outcomes between ganciclovir and valganciclovir, which suggests that outcomes demonstrated in this systematic review in placebo or no-treatment trials can be extrapolated to valganciclovir.

There was no clear effect on graft loss or acute rejection, although a small but clinically important benefit has not been excluded. The summary relative

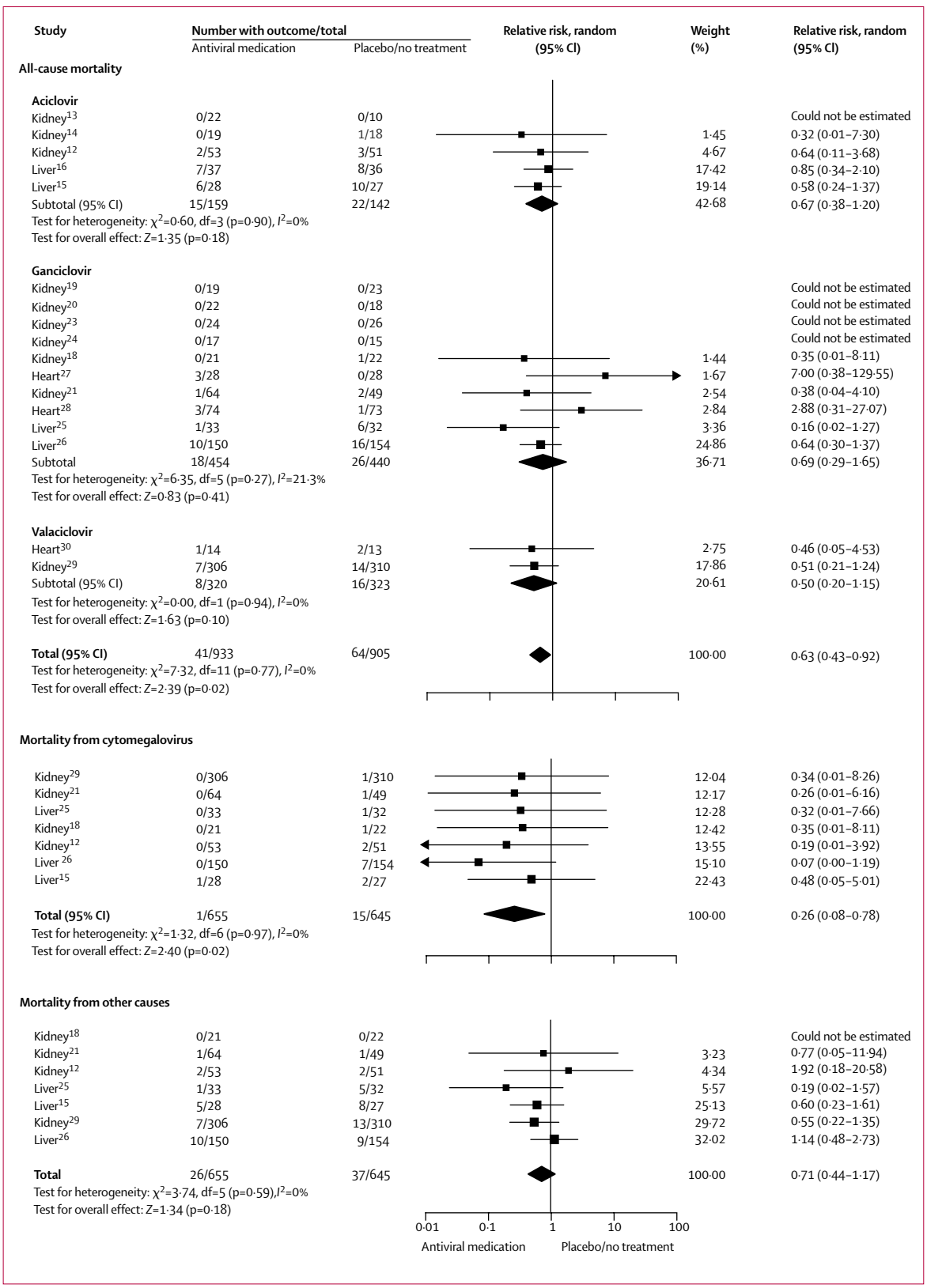

Figure 3: **Meta-analysis of randomised controlled trials examining the numbers of recipients of solid-organ transplants dying from any cause, from cytomegalovirus, or from other causes in trials of prophylaxis with aciclovir, ganciclovir, or valaciclovir versus placebo or no treatment**

Outcome	Aciclovir		Ganciclovir		Valaciclovir		All medications	
	Number of trials	Relative risk (95% CI)	Number of trials	Relative risk (95% CI)	Number of trials	Relative risk (95% CI)	Number of trials	Relative risk (95% CI)
Acute rejection	4	1·03 (0·78–1·36)	7	0·92 (0·70–1·21)	2*	0·81 (0·51–1·28)	13	0·90 (0·78–1·05)
Graft loss	4	0·77 (0·35–1·68)	6	0·73 (0·41–1·28)	0	No data	10	0·74 (0·47–1·17)
Herpes simplex or zoster infections	3	0·30 (0·14–0·62)	4	0·25 (0·08–0·78)	2	0·28 (0·20–0·40)	9	0·27 (0·19–0·40)
PTLD	1	2·90 (0·12–68·2)	1	0·34 (0·01–8·33)		No data	2	1·01 (0·11–9·51)
Bacterial infections	1	0·67 (0·33–1·38)	1	0·72 (0·44–1·17)	1	0·27 (0·07–1·05)	3	0·65 (0·44–0·96)
Fungal infections	1	1·30 (0·31–5·39)	2	0·28 (0·07–1·12)		No data	3	0·58 (0·19–1·73)
Protozoal infections	0	No data	2	0·31 (0·01–0·99)		No data	2	0·31 (0·01–0·99)
Leucopenia†	0	No data	3	0·99 (0·37–2·65)	1	1·05 (0·62–1·78)		
Creatinine >200 μmol/L†	2	1·14 (0·27–4·70)	3	2·36 (0·91–6·15)		No data		
Hallucinations†	1	10·6 (0·62–183·3)	3	1·59 (0·98–2·58)	1	8·78 (2·69–28·7)		

PTLD=post-transplant lymphoproliferative disease.*Heterogeneity of trial results present. † Placebo-controlled trials only.

Table 4: **Effects of prophylaxis against cytomegalovirus with different antiviral medications compared with placebo or no treatment on risk of acute rejection, graft loss, other infections, and adverse events**

risks for both outcomes favoured antiviral medication but the 95% CI were wide and were consistent with there being no effect. The exception was in a predefined subgroup in a single trial,[29] in which cytomegalovirus prophylaxis reduced the risk of biopsy-proven acute rejection in cytomegalovirus-negative recipients of cytomegalovirus-positive renal transplants by 50%.

Valaciclovir significantly increased the risk of hallucinations, on the basis of data from a single large trial.[29] There was no significant increase in adverse effects with aciclovir or ganciclovir although the CI were wide. Very few trials adequately reported harms, so 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 cytomegalovirus antiviral prophylaxis prevents cytomegalovirus disease and all-cause mortality, irrespective of organ transplanted and cytomegalovirus 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). 19 eligible studies were identified, and the relative risks in 18 trials favoured antiviral medication for the outcome prevention of cytomegalovirus disease. 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 in heart-transplant patients[27,28] had relative risks suggesting increased mortality from cytomegalovirus prophylaxis. Unlike the outcome of cytomegalovirus disease, no individual trial showed a significant reduction in all-cause mortality with antiviral medication; the effect was evident only from the meta-analytic estimate. The overall I^2 was 12·6% for cytomegalovirus disease and zero for all-cause mortality, showing very low heterogeneity beyond chance, despite the clear differences in groups of patients (table 1). Supporting this contention, as shown in table 3, no predefined 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, masking, and analysis by intention to treat. We cannot exclude a difference in the magnitude of the effect of antiviral medication in recipients of solid-organ transplants. However, any difference is likely to be clinically unimportant since data from 19 trials and about 2000 patients were insufficient to demonstrate any difference. In addition, the consistency in results across all trials suggests that any undetected difference would be in magnitude and not direction of effect.

The data were relatively sparse in three areas, and further research is still needed. For the outcome of all-cause mortality in heart-transplant recipients, there were few relevant trials (two), patients (205), and events (seven), so the effects of antiviral agents in these patients remain very uncertain. Both trials had higher death rates in the active-treatment groups but the CI were very wide, the results are consistent with other groups of patients (liver and kidney recipients), and the likely pathway for benefit—reduction in cytomegalovirus disease—is evident in this group.

Second, there were very few data on transplants from cytomegalovirus-negative donors to cytomegalovirus-negative recipients, though a recent review reported that 43% of this group receive antiviral medications to prevent cytomegalovirus disease.[43] These patients are rarely enrolled in trials, because event rates are low and there is no biological mechanism by which cytomegalovirus disease could be prevented in patients not exposed to the disease.

Third, our conclusions on the other benefits of antiviral medications and the adverse effects of these drugs (table 4) must be interpreted more cautiously because the summary estimates are imprecise and because many eligible trials did not report these outcomes; these results therefore could be biased. The direction of the bias cannot be assessed unless

additional data are obtained from the study investigators about these outcomes.

Having shown that antiviral medications as a drug class reduce all-cause mortality and risks of cytomegalovirus disease, we then sought to find out which antiviral regimen was the most beneficial. Indirect comparisons showed no difference between antiviral medications administered. However, ganciclovir was significantly more effective than aciclovir in preventing cytomegalovirus disease in direct comparison trials, which emphasises the importance of assessing the relative effects of medications in such trials. This difference could be explained by differences in duration of therapy in the indirect trials. Aciclovir was given for 84 days or longer, whereas ganciclovir was given for a shorter time (9–42 days) in seven of the 11 ganciclovir trials; thus, agent and duration were investigated rather than agent alone, as in direct comparison trials.

One large trial[38] showed no significant difference in efficacy between ganciclovir and its prodrug, valganciclovir. Although one small trial found no difference in efficacy to prevent cytomegalovirus disease between ganciclovir and valaciclovir[39,40] the wide CI of the summary estimate (relative risk 0·51 [95% CI 0·05–5·42)] suggests that a significant difference in efficacy cannot be excluded. From existing trial data, aciclovir is inferior to ganciclovir, and no clear superiority has been shown between ganciclovir and valganciclovir.

The results of this review confirm and expand the findings of three previous systematic reviews,[44–46] which included 12, ten, and nine trials comparing antiviral medications with placebo or no treatment for prevention of cytomegalovirus disease. All found that prophylaxis reduced the risk of cytomegalovirus disease in recipients of solid-organ transplants. One review[44] found no effect on mortality (ten trials, 992 patients; relative risk 0·69 [95% CI 0·41–1·18]) and a second,[45] which included two studies that used immunoglobulin and antiviral agents, found that prophylaxis with aciclovir or valaciclovir significantly reduced all-cause mortality (ten trials, 1321 patients; odds ratio 0·60 [95% CI 0·40–0·90]). Our systematic review differs from previous studies in the larger number of trials, the focus on antiviral medications only, and the inclusion of comparisons of different antiviral medications so that conclusions on the comparative effects of agents can be made. Furthermore, our study included a detailed exploration of potential heterogeneity. The finding of a reduction in all-cause mortality is largely explained by the lower mortality from cytomegalovirus disease (figure 3), although a reduction in mortality from other causes cannot be totally excluded. The latter is biologically plausible because cytomegalovirus disease leads to an increase in other opportunistic infections in recipients of heart and liver transplants,[5,47] which suggests a mechanism by which the prevention of cytomegalovirus disease could prevent other infectious complications that contribute to overall mortality.

What are the implications of this study for clinical practice? Current treatment guidelines[48,49] recommend cytomegalovirus prophylaxis for cytomegalovirus-negative recipients of cytomegalovirus-positive organs and for cytomegalovirus-positive recipients who receive immunosuppression with antibodies targeted against lymphocytes. In recipients of liver and heart transplants, prophylaxis is also recommended for all cytomegalovirus-positive recipients because of the higher risk of cytomegalovirus disease. Prophylaxis is not generally recommended for cytomegalovirus-positive renal-transplant recipients or for donor-negative/recipient-negative patients,[48] owing to the low frequency of cytomegalovirus disease in these groups. Our data suggest that the recommendations for use are too narrow because the benefits for survival of patients and the constant relative benefits for cytomegalovirus disease, irrespective of cytomegalovirus serostatus, have not been recognised previously. The absolute effects of antiviral medications on the prevention of cytomegalovirus disease and all-cause mortality are shown quantitatively in groups of patients at different

Recipient group	Number with outcome per 100 patients			Number with harm‡ per 100 patients
	Without prophylaxis*	With prophylaxis†	Number prevented	
Cytomegalovirus disease				
Kidney§	7	3	4	7
Kidney§; liver¶; heart§	28	12	16	7
Liver, heart§; all¶, antibody therapy included in immunosuppressive regimen	59	25	39	7
All-cause mortality				
Kidney	6	4	2	7
Liver	20	13	7	7
Heart or lung	24	15	9	7

*Data from references[2,6–8,50] for cytomegalovirus disease and from references[4,51–55] for all-cause mortality. †Calculated from summary estimates of relative risk (0·42 for prevention of cytomegalovirus disease and 0·63 for all-cause mortality). ‡Based on proportion of patients, treated with valaciclovir, who developed hallucinations.[29] §Donor positive or negative for cytomegalovirus; recipient positive. ¶Donor positive, recipient negative for cytomegalovirus.

Table 5: **Effects of antiviral medications on cytomegalovirus disease and all-cause mortality in recipients of solid-organ transplants**

baseline risk of these outcomes in table 5. The primary determinants for cytomegalovirus disease are organ transplanted and serostatus, whereas organ transplanted is the most important determinant for all-cause mortality. Thus, benefit exceeds harm for all but the lowest risk groups on the assumption of equal importance of the outcomes. However, since all-cause mortality and cytomegalovirus disease might be seen as being much more clinically important than the adverse effects of medications, most patients and clinicians provided with this information will be likely to use cytomegalovirus prophylaxis with antiviral medications across all risk categories, except in the group of seronegative donors and recipients, for whom there are few data.

Future research is required in the group of seronegative donors and recipients and in heart-transplant recipients, on the optimum duration of prophylaxis, and on the comparative effects, including harms, of antiviral medications in clinical use, particularly valaciclovir and valganciclovir. 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 affect the risk of acute rejection or graft loss. Further information is needed for assessment of whether prophylaxis can reduce the risk of rejection in particular groups of patients, whether it affects the number or severity of rejection episodes, and whether it reduces graft loss at periods beyond 1 year.

Contributors

E M Hodson identified and extracted data from included trials, contacted authors, and analysed and interpreted the results. C A Jones conceived, designed, and developed the protocol and search strategy for the review and identified and extracted data from included trials. A C Webster analysed and interpreted the results. G F M Strippoli checked the analysis and interpretation of the results. P G Barclay and K Kable identified and extracted data from included trials. D Vimalachandra developed the protocol and search strategy for the review. J C Craig conceived, designed, and developed the protocol and analysed and interpreted the results. E M Hodson wrote the report, J C Craig edited the drafting and revision, and all the other authors contributed to revision.

Conflict of interest statement

The Cochrane renal group (EMH, ACW, GFMS, JCC) receives financial support from several sources including government and industry. The general fund is managed by the Children's Hospital at Westmead and is used to support key activities including hand-searching, the development of a trials registry, training and support for reviewers conducting reviews, and consumer participation in the group. Those contributing funds have no rights of authorship or publication. The authors of the review retain the right to interpret the results and to publish. Past or current funding sources are: Amgen Australia, Amgen Inc, Aventis Pharma (past), Janssen-Cilag, Novartis Pharmaceuticals, Servier (past), Wyeth Australia, Australian Department of Health and Ageing, Kidney Health Australia, Australian and New Zealand Society of Nephrology, National Health and Medical Research Council of Australia. CAJ has received a Sylvia and Charles Viertel Clinical Investigator Award, National Health and Medical Research Council of Australia for unrelated research. ACW receives indirect support for infrastructure costs associated with unrelated research with ANZDATA, the Dialysis and Transplant Registry of Australia and New Zealand, in the form of an unrestricted educational grant from Novartis Pharmaceuticals Australia. PGB is a member of Amgen Pharmacy Advisory Board, for which he receives an honorarium, and has 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 conflict of interest.

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References

1 Rubin RH, Kemmerly SA, Conti D, et al. Prevention of primary cytomegalovirus disease in organ transplant recipients with oral ganciclovir or oral acyclovir prophylaxis. *Transpl Infect Dis* 2000; **2:** 112–17.

2 Waiser J, Budde K, Schreiber M, et al. Effectiveness of deferred therapy with ganciclovir in renal allograft recipients with cytomegalovirus disease. *Transplant Proc* 1998; **30:** 2083–85.

3 Duncan SR, Grgurich WF, Iacono AT, et al. A comparison of ganciclovir and acyclovir to prevent cytomegalovirus after lung transplantation. *Am J Respir Crit Care Med* 1994; **150:** 146–52.

4 Schnitzler MA, Lowell JA, Hardinger KL, Boxerman SB, Bailey TC, Brennan DC. The association of cytomegalovirus sero-pairing with outcomes and costs following cadaveric renal transplantation prior to the introduction of oral ganciclovir CMV prophylaxis. *Am J Transplant* 2003; **3**: 445–51.

5 George MJ, Snydman DR, Werner BG, et al. The independent role of cytomegalovirus as a risk factor for invasive fungal disease in orthotopic liver transplant recipients. *Am J Med* 1997; **103:** 106–13.

6 Ho M. Advances in understanding cytomegalovirus infection after transplantation. *Transplant Proc* 1994; **26:** 7–11.

7 Smith SR, Butterly DW, Conlon PJ, Harland RC, Emovon OE. Incidence of cytomegalovirus disease in renal transplantation without antilymphocyte induction: is prophylaxis necessary? *Transplant Proc* 1998; **30:** 2097–99.

8 Hibberd PL, Tolkoff-Rubin NE, Cosimi AB, et al. Symptomatic cytomegalovirus disease in the cytomegalovirus antibody seropositive renal transplant recipient treated with OKT3. *Transplantation* 1992; **53:** 68–72.

9 Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994; **309:** 1286–91.

10 Lefebvre C, McDonald S. Development of a sensitive search strategy for reports of randomized controlled trials in EMBASE. Proceedings of the 4th International Cochrane Colloquium, Oct 20–24, 1996, Adelaide, Australia.

11 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327:** 557–60.

12 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. *N Engl J Med* 1989; **320:** 1381–87.

13 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. *J Am Soc Nephrol* 1996; **7:** 325–30.

14 Rostaing L, Crespin A, Icart J, et al. Cytomegalovirus (CMV) prophylaxis by acyclovir in pre-transplant CMV-positive renal transplant recipients. *Transplant Int* 1994; **7** (suppl 1)**:** S331–35.

15 Barkholt L, Lewensohn-Fuchs I, Ericzon BG, Tyden G, Andersson J. High-dose acyclovir prophylaxis reduces cytomegalovirus disease in liver transplant patients. *Transpl Infect Dis* 1999; **1:** 89–97.

16 Gavalda J, De Otero J, Murio E, et al. Two grams daily of oral acyclovir reduces the incidence of cytomegalovirus disease in CMV-seropositive liver transplant recipients. *Transplant Int* 1997; **10:** 462–65.

17 Saliba F, Eyraud D, Samuel D, et al. Randomized controlled trial of acyclovir for the prevention of cytomegalovirus infection and disease in liver transplant recipients. *Transplant Proc* 1993; **25:** 1444–45.

18 Ahsan N, Holman MJ, Yang HC. Efficacy of oral ganciclovir in prevention of cytomegalovirus infection in post-kidney transplant patients. *Clin Transplant* 1997; **11:** 633–39.

19 Brennan DC, Garlock KA, Singer GG, et al. Prophylactic oral ganciclovir compared with deferred therapy for control of cytomegalovirus in renal transplant recipients. *Transplantation* 1997; **64:** 1843–46.

20 Conti DJ, Freed BM, Singh TP, et al. Preemptive ganciclovir therapy in cytomegalovirus-seropositive renal transplants recipients. *Arch Surg* 1995; **130:** 1217–22.

21 Hibberd PL, Tolkoff-Rubin NE, Conti D, et al. Preemptive ganciclovir therapy to prevent cytomegalovirus disease, in cytomegalovirus antibody-positive renal transplant recipients: a randomized controlled trial. *Ann Intern Med* 1995; **123:** 18–26.

22 Leray H, Mourad G, Chong G, Segondy M, Mion C. Prophylactic treatment of cytomegalovirus primary infection with ganciclovir in renal transplant recipients. *Transplant Proc* 1995; **27:** 2448.

23 Pouteil-Noble C, Megas F, Chapuis F, et al. Cytomegalovirus prophylaxis by ganciclovir followed by high-dose acyclovir in renal transplantation: a randomized, controlled trial. *Transplant Proc* 1996; **28:** 2811.

24 Rondeau E, Bourgeon B, Peraldi MN, et al. Effect of prophylactic ganciclovir on cytomegalovirus infection in renal transplant recipients. *Nephrol Dial Transplant* 1993; **8:** 858–62.

25 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. *J Med Virol* 1993; **40:** 5–9.

26 Gane E, Saliba F, Valdecasas GJ, et al. Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. *Lancet* 1997; **350:** 1729–33.

27 Macdonald PS, Keogh AM, Marshman D, et al. A double-blind placebo-controlled trial of low-dose ganciclovir to prevent cytomegalovirus disease after heart transplantation. *J Heart Lung Transplant* 1995; **14:** 32–38.

28 Merigan TC, Renlund DG, Keay S, et al. A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. *N Engl J Med* 1992; **326:** 1182–86.

29 Lowance D, Neumayer HH, Legendre CM, et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. *N Engl J Med* 1999; **340:** 1462–70.

30 Egan JJ, Carroll KB, Yonan N, Woodcock A, Crisp A. Valacyclovir prevention of cytomegalovirus reactivation after heart transplantation: a randomized trial. *J Heart Lung Transplant* 2002; **21:** 460–66.

31 Flechner SM, Avery RK, Fisher R, 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:** 1682–88.

32 Badley AD, Seaberg EC, Porayko MK, et al. Prophylaxis of cytomegalovirus infection in liver transplantation: a randomized trial comparing a combination of ganciclovir and acyclovir to acyclovir. *Transplantation* 1997; **64:** 66–73.

33 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. *Clin Infect Dis* 1997; **25:** 1344–49.

34 Martin M, Manez R, Linden P, 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:** 779–85.

35 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. *Transplant Proc* 1993; **25:** 1935–37.

36 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:** 69–74.

37 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:** 229–33.

38 Paya C, Humar A, Dominguez E, et al. Efficacy and safety of valganciclovir vs oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2004; **4:** 611–20.

39 Reischig T, Opatrny K Jr, Bouda M, Treska V, Jindra P, Svecova MT. Trial of oral ganciclovir versus oral valacyclovir for prophylaxis of cytomegalovirus disease after renal transplantation: a randomized prospective controlled trial. *Transpl Int* 2002; **15:** 615–22.

40 Reischig T, Jindra P, Mares J, et al. Valacyclovir for cytomegalovirus prophylaxis reduces the risk of acute renal allograft rejection: a randomized comparison of oral ganciclovir and valacyclovir. *Am J Transplant* 2004; **4:** 493.

41 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:** 305–08.

42 Hertz MI, Jordan C, Savik SK, et al. Randomized trial of daily versus three-times-weekly prophylactic ganciclovir after lung and heart-lung transplantation. *J Heart Lung Transplant* 1998; **17:** 913–20.

43 Baliga RS, Kadambi PV, Javaid B, et al. A nationwide survey of cytomegalovirus prophylaxis and treatment in the transplant community. *Am J Transplant* 2004; **4:** 495.

44 Couchoud C. Cytomegalovirus prophylaxis with antiviral agents for solid organ transplantation. *Cochrane Database Syst Rev* 2000; CD001320.

45 Fiddian P, Sabin CA, Griffiths PD. Valacyclovir provides optimum acyclovir exposure for prevention of cytomegalovirus and related outcomes after organ transplantation. *J Infect Dis* 2002; **186** (suppl 1): S110–15.

46 Gourishankar S, Wong W, Dorval M. Meta-analysis of prophylaxis of CMV disease in solid organ transplantation: is ganciclovir a superior agent to acyclovir? *Transplant Proc* 2001; **33:** 1870–72.

47 Valantine HA. Role of CMV in transplant coronary artery disease and survival after heart transplantation. *Transpl Infect Dis* 1999; **1** (suppl 1): 25–30.

48 Jassal SV, Roscoe JM, Zaltzman JS, et al. Clinical practice guidelines: prevention of cytomegalovirus disease after renal transplantation. *J Am Soc Nephrol* 1998; **9:** 1697–708.

49 Van der BW, Speich R. Management of cytomegalovirus infection and disease after solid-organ transplantation. *Clin Infect Dis* 2001; **33** (suppl 1): S32–37.

50 Falagas ME, Snydman DR, Griffith J, Ruthazer R, Werner BG. Effect of cytomegalovirus infection status on first-year mortality rates among orthotopic liver transplant recipients. *Ann Intern Med* 1997; **126:** 275–79.

51 Falagas ME, Paya C, Ruthazer R, et al. Significance of cytomegalovirus for long-term survival after orthotopic liver transplantation: a prospective derivation and validation cohort analysis. *Transplantation* 1998; **66:** 1020–28.

52 Singh N, Gayowski T, Falagas ME, Snydman DR. Cytomegalovirus and death in liver transplantation. *Ann Intern Med* 1997; **127:** 412–13.

53 Shapiro R, Jordan ML, Scantlebury VP, et al. A prospective, randomized trial of tacrolimus/prednisone versus tacrolimus/prednisone/mycophenolate mofetil in renal transplant recipients. *Transplantation* 1999; **67:** 411–15.

54 Bonet LA. Predictors of mortality following heart transplantation: Spanish Registry of Heart Transplantation 1984–2001. *Transplant Proc* 2003; **35:** 1946–50.

55 Trulock EP, Edwards LB, Taylor DO, et al. The registry of the international society for heart and lung transplantation: twentieth official adult lung and heart-lung transplant report 2003. *J Heart Lung Transplant* 2003; **22:** 625–35.