

- 1 van Wijk I, Kappelle LJ, van Gijn J, et al, for the LiLAC study group. Long-term survival and vascular event risk after transient ischaemic attack or minor ischaemic stroke: a cohort study. *Lancet* 2005; **365**: 2098–104.
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I van Wijk and colleagues¹ assess the long-term risk of death and vascular events in patients with transient ischaemic attack or minor stroke of arterial origin. However, among the predictors factors of future events, they have not considered the baseline concentrations of C-reactive protein (CRP). This marker of systemic inflammation has been shown to be higher in patients with symptomatic carotid artery disease than in those with asymptomatic disease,² suggesting that systemic inflammatory status could be a marker for patients with an exaggerated inflammatory response that might accelerate atheroma progression and facilitate plaque instability.

Since an increased concentration of CRP after a first ischaemic neurological event seems to be associated with a worse prognosis,^{3,4} C-reactive protein could be added to conventional risk factors in the secondary prevention of cerebrovascular events.⁵

We declare that we have no conflict of interest.

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Antiviral treatment after solid organ transplantation

We were interested to read the comprehensive systematic review by E M Hodson and colleagues (June 18, p 2105)¹ but are concerned over the interpretation of the results. Specifically, the statements: "prophylaxis with antiviral medications reduces the risk of cytomegalovirus disease and associated mortality in recipients of solid-organ transplants" and "this approach should be used routinely in cytomegalovirus-positive recipients and in cytomegalovirus-negative recipients of organs positive for the virus" are not fully supported by the data presented.

Limaye and colleagues² have shown that, although antiviral prophylaxis prevented cytomegalovirus disease in recipients of liver transplants during the prophylaxis period, a significant number of patients developed late disease once antivirals were stopped. In the study by Paya and colleagues,³ in which patients were randomised to receive 100 days of prophylaxis with oral ganciclovir three times a day or once daily valganciclovir, a quarter of the patients who developed cytomegalovirus disease in the valganciclovir group did so 6–12 months after transplantation. Late-onset disease has also been independently associated with post-transplant mortality.² Because studies with follow-up phases as short as 3 months are included in the systematic review, one cannot draw conclusions about the risk of cytomegalovirus disease or associated mortality for the whole period that patients are known to be at risk.

Furthermore, a recommendation for routine use of prophylaxis should only be made after comparison with all alternative management approaches—a task that was outside the limited objective of the review. An alternative approach to the prevention of post-transplant cytomegalovirus disease is pre-emptive therapy (ie, administration of antiviral drugs once active surveillance has detected evidence of cytomegalovirus infection by PCR or antigenaemia laboratory assays). The use of a pre-emptive approach is supported by the findings of a randomised placebo-controlled trial.⁴

The incidence of late disease in transplant recipients, coupled with evidence of antiviral resistance with prolonged use of ganciclovir,⁵ urges caution in the use of prophylaxis. The strategy of pre-emptive therapy is an effective way of preventing cytomegalovirus disease and may not be so susceptible to these disadvantages. We believe, therefore, that the decision as to how to prevent cytomegalovirus disease in solid organ transplant recipients is currently best made locally at each transplant centre.

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Authors' reply

B Caplin and colleagues are concerned that cytomegalovirus prophylaxis for 6–12 weeks after transplantation does not prevent disease occurring during the complete period of risk. This point is self-evident, but has only become relevant because antiviral prophylaxis has increased the number of survivors at risk of late cytomegalovirus disease compared with patients not on routine prophylaxis. As we show in table 3 of the original paper, the effects of antiviral prophylaxis are no different 3–6 months after transplantation and 9–12 months after transplantation. There are significant reductions in cytomegalovirus disease and all-cause mortality extending to 12 months after transplantation, and we could find no evidence for a waning or “rebound” effect which would be expected if there was an excess risk of late cytomegalovirus in the treated group. Indeed, given the expected survival bias in the treated group, estimates for cytomegalovirus disease are likely to be an underestimate of the true benefit of prophylaxis. Caplin and colleagues cite only two studies, which highlights the potential pitfalls of selective data reporting compared with formal systematic reviews. However, as we emphasised in our paper, we agree that additional trials are needed to determine the optimum duration of antiviral medications to prevent cytomegalovirus disease after transplantation.

Caplin and colleagues also suggest that routine antiviral prophylaxis should be compared with other strategies such as pre-emptive therapy before superiority can be claimed. We agree and have recently completed a systematic review.¹ There are striking differences in

the quantity, quality, and results of randomised controlled data on pre-emptive therapy compared with prophylaxis. For antiviral prophylaxis, there are 19 published trials involving 1981 patients. By contrast, only six trials (288 patients) have compared pre-emptive therapy with placebo or no treatment, and only three trials (151 patients) have compared the two strategies. Pre-emptive treatment reduced the risk of cytomegalovirus disease but not mortality. Also, around 20% of patients developed cytomegalovirus disease after screening and before randomisation and were excluded from the trials, so the true benefit of the pre-emptive strategy is likely to be less than that reported by the trials. A direct comparison of pre-emptive therapy with prophylaxis was uninformative due to lack of power.

We agree that ganciclovir resistance should prompt caution in the long-term use of the drug. However, we tested this hypothesis by using year of study and duration of treatment as explanatory covariates and found no empirical evidence of resistance.

Caplin and colleagues finish with an intriguing sentence: “We believe, therefore, that the decision as to how to prevent cytomegalovirus disease in solid organ transplant recipients is currently best made locally at each transplant centre”. We would agree if they had shown that the benefit-harm trade-off for routine antiviral prophylaxis and for pre-emptive therapy varied significantly by centre through case-mix differences in absolute risks of cytomegalovirus disease or adverse effects. As researchers, it is not our role to decide local practice but simply to inform clinicians, patients, and policymakers. On the basis of our data, we would suggest that routine prophylaxis (except in donor-negative or recipient-negative patients) or participation in randomised controlled trials of pre-emptive therapy versus prophylaxis or of different durations of therapy should be local practice.

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Intelligence and socioeconomic inequalities in health

David Batty and Ian Deary raise an interesting point in their Correspondence (May 21, p 1765)¹ based on our paper about educational inequalities in cause-specific mortality.² They state that researchers should examine the possibility that education is a proxy for intelligence in its association with mortality. We agree that the role of intelligence in the association between socioeconomic position and health should be assessed because it may help us to explain part of the association.

We saw that the association between education and mortality was present in men and women, in all age-groups, and all countries.² This finding means that, besides country-specific explanations for inequalities in mortality, we also need to look for generic explanations, and intelligence may be one. However, after examining the findings of several pieces of research, we believe that it is still premature to accept that this is the case.