

Unfortunately, their statistical methods are so complex, "an extension of multivariable Bayesian hierarchical random effects models for mixed multiple treatment comparisons" that many are mystified by whether the conclusions make sense. Their webtable of data by trial enables the following explanation by use of simple statistics.

I concentrate on Stettler and colleagues' finding of significantly fewer myocardial infarctions for sirolimus-eluting stents compared with both paclitaxel-eluting and bare-metal stents. Since all trials had 1:1 randomisation, a sensible start is to add up the numbers of patients who had a myocardial infarction in head-to-head comparisons. For the 17 trials comparing sirolimus-eluting stents with paclitaxel-eluting stents there were 170 versus 203 myocardial infarctions. The approximate risk ratio is $170/203=0.84$. The simplest statistical test comparing these two counts² is reliable when event rates are low and gives $p=0.09$.

This result agrees with that of Stettler and colleagues' conventional meta-analysis: hazard ratio 0.84 (95% CI 0.69–1.02). So why does their main approach—the "network" meta-analysis—push this finding to a stronger level of significance?

For sirolimus-eluting stents versus bare-metal stents (15 trials) there were 119 versus 142 myocardial infarctions (hazard ratio 0.86, $p=0.12$) and for paclitaxel-eluting stents versus bare-metal stents (eight trials) there were 135 versus 129 myocardial infarctions (hazard ratio 1.06, $p=0.7$). The network meta-analysis uses this indirect evidence that (1) bare-metal stents and paclitaxel-eluting stents had similar myocardial infarction risks, and (2) there is a non-significant trend towards fewer myocardial infarctions with sirolimus-eluting stents versus bare-metal stents, to reinforce the non-significant trend of fewer myocardial infarctions with sirolimus-eluting stents versus paclitaxel-eluting stents. As if by

magic, the complex modelling in the network meta-analysis pushes the sirolimus-eluting stents versus paclitaxel-eluting stents comparison to $p=0.045$ and the sirolimus-eluting stents versus bare-metal stents comparison to $p=0.03$.

This might be squeezing the data too hard. Virtually all other meta-analyses stick to head-to-head comparisons of treatments, which seems inherently wise. Use of indirect comparisons entails strong assumptions—ie, it ignores the fact that the bare-metal stent comparators in the sirolimus-eluting stents trials and paclitaxel-eluting stents trials are different.

I am concerned about the increasing reliance on random-effects methods for meta-analyses. As they try to capture statistical heterogeneity between studies, they perversely increase the amount of weight given to small studies, so one small outlying trial can have undue influence.

Fixed-effect methods avoid this problem and are more readily accessible to non-specialists (eg, adding up the numbers of myocardial infarctions gives meaningful insight). By all means do both if space allows, and I would encourage Stettler and colleagues to publish a fixed-effect head-to-head version of all their findings.

Another concern is that any such meta-analysis combines evidence from trials that are substantially different in their design. For instance, we are including trials of primary percutaneous coronary intervention after myocardial infarction with trials in stable coronary disease, the definition of myocardial infarction across studies will be inconsistent, as will the angiographic eligibility criteria. These issues all raise concerns as to the extent to which the meta-analysis conclusions can be trusted³ and to whom the findings apply.

I have served on data monitoring committees of studies sponsored by Boston Scientific and Johnson and Johnson, and consulted with Abbott Vascular.

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Asthma guidelines on house dust mites are not evidence-based

In your Sept 8 Editorial (p 802),¹ you describe the new US guidelines for asthma control² as being rigorous and evidence-based. This is not correct for the recommendations on house dust mites.

On p 171 of the guidelines, the expert panel recommends various interventions pertaining to house dust mites, including encasing mattresses in allergen-impermeable covers. The panel quotes 10 papers in support of this recommendation, but not our Cochrane review, even though it contains 49 randomised trials (2733 patients) in its last update,³ 22 of which had studied the effect of mattress covers. We could not find any effect of physical or chemical interventions against house dust mites.

We have previously shown substantial reference bias in this area.⁴ The most quoted trial in 70 reviews had only seven patients per group, its claimed significant result was probably erroneous, and it did not report a clinical outcome. Furthermore, recommendations were often based on non-randomised studies, and the most quoted non-randomised study included only 10 patients per group but claimed very positive results.

Of the 10 papers quoted by the panel, one is an editorial, one is a review, one is a before-and-after study, one is about rhinitis, one was excluded from our review because only some of the patients were allergic



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to mites and because no outcome data were provided for this group, and one is not relevant because it involved multiple interventions and allergens (no effect was found for peak flow). What remains are only five trials and these did not show an effect of mattress encasings.³

I declare that I have no conflict of interest.

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- 1 New guidelines for better asthma control. *Lancet* 2007; **370**: 802.
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Lamotrigine and the risk of fulminant hepatic failure

I refer to a letter by Debbie Shawcross and colleagues (July 28, p 314),¹ written in response to the SANAD study,² in which a case of fatal hepatic failure is attributed to lamotrigine. As the consultant neurologist involved in the care of this patient, I would like to add some relevant information that seems to have been either omitted or neglected: continuous exposure to valproate before the liver failed, and a concomitant acute cytomegalovirus infection.

The patient, as described by Shawcross and colleagues, had initially come to the clinic to seek preconception advice before she made an informed decision to change from valproate to lamotrigine. Within 2 weeks of starting lamotrigine, she developed a mononucleosis

syndrome characterised by sore throat, cervical lymphadenopathy, and pyrexia followed by a maculopapular rash. She was found to have deranged liver enzymes and lamotrigine was discontinued; she was admitted to a local hospital and kept on valproate.

During her hospital stay, IgM and IgG against cytomegalovirus were found and the patient was then started on ganciclovir. Unfortunately, 3 weeks later she developed a fulminant hepatic failure that led to her death, despite liver transplantation.

Although Shawcross and colleagues suggest that the hepatic failure was caused by lamotrigine, valproate might have also had a significant role. Furthermore, even after autopsy, it remains unclear as to whether an antiepileptic drug or cytomegalovirus was the ultimate cause of the hepatic failure.

I am grateful to A G Marson and A Gil-Nagel for their useful comments. I would also like to acknowledge D McCorry for his initial encouragement in reporting this case. I declare that I have no conflict of interest.

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- 1 Shawcross D, Knighton S, Bernal W, Sizer E, Auzinger G. Old versus new antiepileptic drugs: the SANAD study. *Lancet* 2007; **370**: 314–15.
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A framework convention on alcohol control

I am writing to express unhappiness at your Sept 29 Editorial (p 1102).¹ Your support for the development of a framework convention on alcohol control is of course extremely welcome, but it is the detail building up to this to which I object.

In particular you state that, “at country level, ineffective control strategies (warning labels, education in schools) have been adopted”. In the USA, warning labels on alcohol products were adopted in the early 1990s and were associated with a change in behaviour of those drinking.² In Britain, from 2008, after a 4-year campaign by the British Society of Gastroenterology and British Association for the Study of the Liver, health information is to be included on alcohol product labels, giving details of the alcohol unit content coupled with the safe daily limits for consumption in men and women. This is the first time that the public will be provided with the necessary information required to make sensible drinking choices and is comparable to product information which has been provided on foods for many years. Warning labels are well established on tobacco products and indeed an announcement has recently been made that picture versions are shortly to be introduced.³

Alcohol education in schools has been studied by the UK's National Institute for Health and Clinical Excellence and their recommendations, which endorse an alcohol education programme in schools, were published in November, 2007.⁴

It takes a wide range of measures to change behaviour in society and the provision of health information on alcohol products is only one. However, the provision of such information is a human right and is the backbone of the other measures which are required to change behaviour. To state that such information is an ineffective control measure is unhelpful and plays into the hands of the alcohol industry.

The adoption of effective health information on alcohol products was achieved with the greatest of difficulty and even now, despite being included in the Alcohol Harm Reduction Strategy for England in 2004,⁵ there is no movement on the provision of