Clearly, Drs Ho, Wills, and Cranshaw have provided a very important addition to this subject, and their data suggest that we must be cautious in accepting such mathematical indices and in extrapolating their use into untested scenarios. In particular, we would advise caution in the use of our novel formula outside of the conditions in which it was tested.

On a positive note, it seems that the bias and precision found by Drs Ho, Wills, and Cranshaw may still be acceptable for clinical use, albeit with slightly less optimism than we had conveyed in our original paper, and possibly with greater caution in patients with severe gas exchange defects. We remain confident that its bias and precision will still be better than existing methods (e.g. use of the $P_{A/O}_2/F_{I/O}_2$ ratio), although such confidence is, admittedly, largely based on our knowledge that existing methods are very poor.

**Declaration of interest**

None declared.

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**Tranexamic acid in open cardiac surgery with cardiopulmonary bypass, convulsive seizures, and in-hospital mortality**

Editor—We read with great interest the paper by Koster and colleagues which is topical and of clinical relevance to cardiac anaesthetists. Existing evidence suggests that tranexamic acid reduces bleeding and mortality both in trauma and surgical patients. After the removal from the market of aprotonin, tranexamic acid is routinely used as a first-line anti-fibrinolytic at moderate-to-high doses in cardiac surgery using cardiopulmonary bypass in order to reduce bleeding. Koster and colleagues concluded that in patients who had open-heart procedures, moderate tranexamic acid doses were associated with a doubled rate of convulsive seizures and in-hospital mortality. As Koster and colleagues point out with regard to their observational study, bias cannot be eliminated only reduced. However, there are a couple of points we wished to make. First, we felt it was unlikely that every neurological event could be
observed, especially as a doctor had to be called to corroborate the event. Often these episodes can be very transient and could go unwitnessed, for example, during night shifts or when the bedside nurse is busy. This bias would however be expected to affect both the group of patients equally. Secondly, there are a multitude of other acute perioperative causes for convulsive seizures that are not specifically mentioned such as ischaemia, embolic phenomena, drugs, and hypoglycaemia, which might be expected to occur with a higher frequency in the tranexamic acid group due to this group being older having more chronic health problems, including arterial occlusive disease, a longer cardiopulmonary bypass time and cross-clamp time, and a greater number of open-heart procedures. Also no mention is made in the data collection of whether the patients had been screened for a history of seizures or epilepsy in the past. Thirdly, although reasonably high number of patients was included in this study, there is no mention whether a power analysis was used in order to detect a clinical difference. As the authors rightly stated in their paper, we cannot conclude any causal relationship between tranexamic acid and convulsive seizures or mortality based on observational studies. However, in following on from recent papers with similar findings, we should exercise caution with tranexamic acid at these doses until the definitive prospective randomized controlled trials have been conducted.

Declaration of interest

None declared.

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Reply from the authors

Editor—We thank Dehghani and Trenfield for their critical review of our article. The numbers of investigations using the statistical method of propensity scoring (PS) have increased dramatically over the last years. However, the value of this method in comparison with the established ‘golden standard’ of clinical investigation, the prospective ‘randomized controlled trial’ (RCT), is still a matter of ongoing discussion. We agree with the points outlined by them and had mentioned this in our limitations of the study section. However, there are two aspects which we would like to point out. First, in a prospective RCT, clear and distinct inclusion and exclusion criteria for patient selection are formulated so that a possible effect of a drug or intervention can most probably be attributed to this action. The data harvested from the ‘rougher’ clinical databases usually lack this distinction in the detail. For example, the database of a specialized cardiac surgical institution will indicate that the patient had previous neurological events. However, it will most likely not differentiate, whether the patient had convulsive seizures and whether these seizures may be attributed to a former stroke or other reasons. Secondly, as they pointed out, in an RCT, sophisticated methods for detection of the primary and secondary endpoints will be established so that these events will be recognized in nearly 100%. As they have already pointed out, this particularly applies for transient clinical events such as clinical convulsive seizures. However, with regard to our second endpoint of ‘in-hospital mortality’, we consider having a 100% documentation of this definitive event rate. Viewing these limitations of PS, we strongly believe that observational studies such as ours are useful, to test if there are possible relationships between an intervention and patient outcome. Based on the data of such trials, power calculations for well-designed prospective RCT can be performed. In the case of our observation, we would highly appreciate further prospective trials. However, slight pessimism is indicated. As most pharmacological trials are industry-sponsored, who will pay the costs for such an expensive trial considering the fact that the drug is well established, but however inexpensive?

Declaration of interest

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