

LETTER

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# Tetrastarch in cardiac surgery: error, confounding and bias in a meta-analysis of randomized trials

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See related research by Jacob et al., <http://ccforum.com/content/18/6/656>

In a meta-analysis of cardiac surgery trials, we showed that hydroxyethyl starch increases postoperative blood loss, blood product transfusion and reoperation for bleeding [1]. Citing that meta-analysis, the US Food and Drug Administration determined excess bleeding to be a class effect of hydroxyethyl starch solutions and issued a safety warning [2].

Jacob and colleagues report a new meta-analysis suggesting lower perioperative blood loss with tetrastarch than albumin across three trials [3]. However, postoperative blood loss was in the opposite direction (Figure 1). By imputing key unreported data instead of contacting the trial investigators, Jacob and colleagues introduced major errors favoring tetrastarch; for example, inflating the blood loss difference in one trial by 2.3-fold. Furthermore, the other two trials were confounded by exposure of one group to both test fluids. The potential distortion is highlighted by a randomized trial in which coadministration of low-dose albumin with tetrastarch reduced blood loss by 21% ( $P < 0.05$ ) versus tetrastarch alone [4]. Without confounding the blood loss differences would almost certainly have been larger, and any meta-analysis incorporating the confounded trials is likely to be biased in favor of tetrastarch.

Their finding of lower blood loss with tetrastarch than pentastarch is attributable to publication bias, since an unpublished trial with higher blood loss and more frequent reoperation for bleeding after tetrastarch was omitted [1,5]. The omitted trial had been submitted to the US Food and Drug Administration in a New Drug Application by the same tetrastarch manufacturer who commissioned the new meta-analysis. That trial was included in two previous meta-analyses [1,5].

#### Competing interests

RJN and MMW have received previous unrestricted research grant support from Baxter, CSL Behring and Grifols. GRH has served as a consultant to Covidien Inc.

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#### Authors' contributions

All authors participated in the conceptualization and composition of the letter. All authors revised the letter and read and approved the final manuscript.

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This work is solely that of the authors. No other individual or organization contributed substantially to the conception of the letter or to manuscript preparation and revision.

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