**Keywords:** anaemia; haemoglobin; myocardial injury; noncardiac surgery; risk adjustment

Editor—Kehlet[1] asserts that procedure type may have confounded our analysis of anaemia and myocardial injury published recently in the *British Journal of Anaesthesia*.[2] In our published analysis, we adjusted for elective, emergency, and urgent classification, but not type of surgery.

We therefore conducted a sensitivity analysis adjusted for type of surgery categorised by the Clinical Classifications Software for Services and Procedures of the Agency for Healthcare Research and Quality (categories with <10 events were aggregated into one group). With this adjustment, the adjusted hazard ratio of myocardial injury after noncardiac surgery was 1.29 (95% confidence interval: 1.17; 1.43) for a 1 g $dl^{-1}$ decrease in haemoglobin ($P<0.001$), which was identical to our original analysis. The strong association we report between anaemia and myocardial injury remains the same.

## Declarations of interest

The authors declare that they have no conflicts of interest.

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# Surgeons' view of the PREVENTT trial. Comment on *Br J Anaesth* 2021; 126: 9–11

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**Keywords:** anaemia; colorectal surgery; intravenous iron; iron deficiency anaemia; postoperative complications

Editor—We read with great interest the editorial by Meybohm and colleagues[1] commenting on the PREVENTT trial[2] and would like to bring the surgeon's point of view to the discussion.

In abdominal surgery, the most feared complications are death and septic complications such as surgical site infection and anastomotic leak.[3] Anaemia was identified by retrospective cohort studies as a risk factor for both surgical site infection[4] and anastomotic leak.[5] Further, perioperative blood transfusion is a risk factor for surgical site infection (including organ space surgical site infection, which includes anastomotic leak).[4,6,7] In its guidelines for optimised perioperative care in colorectal surgery, the Enhanced Recovery After Surgery (ERAS) Society recommends screening for preoperative anaemia and to correct it if found (strong level of recommendation).[8] Therefore, the results of the PREVENTT trial were awaited.

The trial was ambitious, involving 46 UK tertiary centres and including 487 patients.[2] Richards and colleagues[2] chose a composite primary outcome grouping of death or perioperative blood transfusion of one or more units of any blood product from randomisation until 30 days after surgery. However, we would like to express some concerns that prevent us from reaching a definitive conclusion regarding preoperative correction of anaemia using intravenous iron.

As a first concern, we believe that blood transfusion is not a good indicator of perioperative surgical complications caused by anaemia. Intraoperative blood transfusion may reflect difficult surgery (e.g. as a result of a locally advanced tumour or vascular reconstruction) and not necessarily be associated with the effects of preoperative anaemia causing poor tissue perfusion, ultimately leading to medical and surgical complications, such as anastomotic leak. In other words,

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perioperative blood transfusion may not constitute a good measure of the effects of preoperative anaemia as it constitutes the treatment of anaemia and does not reflect the effect of anaemia causing organ hypoperfusion. Further, despite its immunomodulatory effects, blood transfusion after surgery is not the best indicator for overall postoperative complications, except for haemorrhage. Difficult surgery may constitute a confounding factor for the postulated effect of blood transfusion.[9,10] In addition, the indication for blood transfusion has been shown to be subject to considerable surgeon- and hospital-dependent variation[7] and may be subject to interpretation by the treating physician and not necessarily respond to an objective requirement or predefined study criterion. It is regrettable that Richards and colleagues[2] did not report preoperative coagulation parameters of the patients included in their RCT, despite the outcome they have designed included an intervention (transfusion of any blood products, including platelet concentrates and plasma), which may aim at correcting such coagulation issues, their consequences, or both. Indeed, transfusion of blood products (which is the primary outcome of the trial) may not only be a therapeutic response to anaemia, but could also aim at correcting deficits in platelets or coagulation factors just before or at the beginning of the surgical procedure in non-anaemic patients. Therefore, we think that either reporting coagulation parameters of included patients, restricting the outcome to red blood cell transfusion, or both would have been preferable. We note that previous trials aiming at correcting preoperative anaemia have used haemoglobin as a primary outcome and have reported improved 5-year survival in colorectal cancer patients with correction of preoperative anaemia.[11] We note that the PREVENTT trial[2] also showed improved haemoglobin concentrations in the intravenous iron group at 8 weeks and at 6 months after intervention, therefore questioning the chosen trial outcome.

A second point of concern is that the authors did not report the incidence of surgical site infection. This is unfortunate, as both anaemia and blood transfusion (through immunomodulatory effects) have been identified as risk factors for poor healing.[4–7] Richards and colleagues[2] therefore assessed the effect of their intervention on one of the many risk factors for surgical complications (blood transfusion) instead of incorporating an important outcome for surgeons and patients.

A third, and our main, point of concern, which was also raised by Meybohm and colleagues,[1] is that the aetiology of anaemia was not taken into account when selecting the study population. An alternative aetiology for the anaemia may explain why a majority of the patients did not correct anaemia after iron transfusion. In that regard, Richards and colleagues[2] reported in Table 1 proportions of iron-deficient patients of 28% and 29%, depending on the group. Not selecting the subgroup of patients prone to respond to the trial intervention might only reduce the effect of the intervention (intravenous iron) on the intervention group and lead to a type 2 statistical error, as the trial was not powered on the subgroup of patients with iron deficiency anaemia. The importance of appropriate selection of the study population was previously outlined.[12] Therefore, this limitation does not allow a definitive conclusion regarding the effect of preoperative intravenous iron in correcting anaemia before abdominal surgery when considering the PREVENTT trial. A previous trial targeting iron deficiency anaemia patients showed reduced incidence of allogeneic blood transfusion in patients undergoing abdominal surgery and treated with intravenous iron.[13]

To conclude, considering the limitations of the present trial, further evidence should be obtained before revising the NICE NG24[14] or the ERAS[8] guidelines regarding management of preoperative anaemia. Future RCTs should aim at determining if preoperative correction of iron deficiency anaemia using intravenous iron allows reduction in the incidence of clinically important surgical complications, such as surgical site infection (including anastomotic leak), and ideally include a cost-benefit analysis of intravenous iron.

## Declarations of interest

The authors declare that they have no conflicts of interest.

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# Bleeding Independently associated with Mortality after noncardiac Surgery (BIMS). Comment on *Br J Anaesth* 2021; 126: 163–71

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**Keywords:** anaemia; mortality; perioperative bleeding; risk assessment; transfusion

Editor—We wish to congratulate Roshanov and colleagues[1] for their important study on Bleeding Independently associated with Mortality after noncardiac Surgery (BIMS). The authors identified three diagnostic bleeding criteria that were independently associated with postoperative 30 day mortality after noncardiac surgery: postoperative haemoglobin <70 g $L^{-1}$, transfusion of ≥1 unit of red blood cells, or bleeding judged to be the cause of death, requiring at least one of the aforementioned diagnostic criteria for BIMS.[1] We believe there is additional information that will help address some concerns and better put their findings into clinical perspective.

First, the authors studied candidate criteria in a subgroup of patients (Supplementary Fig. S1)[1] that was enrolled in the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) prospective international cohort study.[2] The population used for selecting variables, including threshold to predict BIMS, overlaps with the population used afterwards for estimating the prognostic importance of BIMS. This approach might lead to a performance bias caused by overfitting, which could be reduced using a standard internal validation approach such as bootstrapping, split sample, or cross-validation for model derivation and validation.[3]

Second, the list of adjustment variables and candidate diagnostic criteria for BIMS (Supplementary Table S1)[1] requires 31 degrees of freedom in total. A total of 167 events (30 day mortality) were observed in the cohort for deriving the BIMS definition, leading to a total of 5.4 events per predictor parameter (EPP), again raising concern regarding overfitting.[4,5]

Lastly, we recognise the selection and ranking of the candidate criteria with consideration of their pragmatic value by the authors. Nonetheless, haemoglobin itself or haemoglobin-derived parameters are overrepresented (Supplementary Table S1) and limit the power to test their associations with mortality, as discussed by the authors.[1] We are concerned that multicollinearity was not assessed. Multicollinearity might lead to inflated standard errors and therefore coefficients wrongly determined to be non-statistically significant. Moreover, collinear coefficients cannot be interpreted independently.[6] The authors should provide the variation inflation factor for each variable of the multivariable prediction model used for deriving the BIMS definition.

Prospective diagnostic studies of patients undergoing noncardiac surgery have proven to be an important source for evaluating and identifying risk factors for perioperative mortality.[2,7–9] Approaches such as the ones undertaken by Roshanov and colleagues[1] are critical to reducing perioperative morbidity and mortality.

## Declarations of interest

The authors declare that they have no conflicts of interest.

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