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Bleeding, anaemia, and transfusion: an ounce of prevention is worth a pound of cure

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This editorial accompanies the following articles:

Association between postoperative haemoglobin concentrations and composite of non-fatal myocardial infarction and all-cause mortality in noncardiac surgical patients: post hoc analysis of the POISE-2 trial by Turan et al., *Br J Anaesth* 2021;126:87–93, doi: [10.1016/j.bja.2020.08.054](https://doi.org/10.1016/j.bja.2020.08.054)

Association between postoperative haemoglobin and myocardial injury after noncardiac surgery: a retrospective cohort analysis by Turan et al., *Br J Anaesth* 2021;126:94–101, doi: [10.1016/j.bja.2020.08.056](https://doi.org/10.1016/j.bja.2020.08.056)

Bleeding Independently associated with Mortality after noncardiac Surgery (BIMS): an international prospective cohort study establishing diagnostic criteria and prognostic importance by Roshanov et al., *Br J Anaesth* 2021;126:163–171, doi: [10.1016/j.bja.2020.06.051](https://doi.org/10.1016/j.bja.2020.06.051)

Preoperative prediction of Bleeding Independently associated with Mortality after noncardiac Surgery (BIMS): an international prospective cohort study by Roshanov et al., *Br J Anaesth* 2021;126:172–180, doi: [10.1016/j.bja.2020.02.028](https://doi.org/10.1016/j.bja.2020.02.028)

Keywords: anaemia; bleeding; cardiovascular outcomes; mortality; transfusion

Bleeding is bad, anaemia is bad, and transfusion is bad. On the surface, that is how one might summarize the findings in two pairs of companion papers^{1–4} published in this issue of the *British Journal of Anaesthesia*. It's not often you are asked to write an editorial covering four publications in the same issue of a journal. But it was actually easier than one might think since they all basically have the same findings, that bleeding, anaemia, and red blood cell (RBC) transfusion are all associated with adverse outcomes, specifically myocardial injury, myocardial infarction, and death.

To quote Jeffrey Carson and Paul Hebert, two founding fathers of transfusion research, "Here we go again – blood transfusion kills patients?".⁵ That was the title of their editorial in 2013 about a meta-analysis showing that blood transfusion was associated with an almost 3-fold greater risk ratio for all-cause mortality in patients with acute myocardial infarction.⁶ The take-home message from the editorial is that transfusion is indeed associated with bad outcomes in virtually all retrospective studies, but such analyses are confounded by indication, meaning the transfused patients are sicker and have more complicated procedures, so the real impact of transfusion itself is best determined by prospective randomised trials. Association is not causation. This is an important consideration when interpreting the results of all four of the studies discussed here.

Turan and colleagues^{1,2} and Roshanov and colleagues^{3,4} each published a pair of papers that are summarized in Table 1. The first by Turan and colleagues¹ is a sub-analysis from the POISE-2 trial,⁷ originally designed to assess aspirin and clonidine in a randomised trial in patients having noncardiac surgery with a

composite outcome of 30-day mortality or non-fatal myocardial infarction. Using the lowest (nadir) haemoglobin (Hb) concentration over the course of hospital stay, they assessed the relationship between anaemia and the adverse outcome. In the cohort with a nadir Hb < 80 g L⁻¹, adverse events occurred 10-fold more frequently than those with a nadir Hb > 130 g L⁻¹ (20% vs. 2%). In fact, the odds ratio was 1.46 for each 10 g L⁻¹ decrease in nadir Hb in patients with a lowest Hb < 110 g L⁻¹. As might be expected, the more anaemic cohort also had a lower baseline Hb, longer surgeries, and more intraoperative hypotension. The authors did not report the percentage of patients transfused or the number of RBC units given, so they don't comment on any relation between transfusion and outcomes. It is entirely possible, or even likely, that when these patients were enrolled between 2010 and 2013, transfusion strategy was more liberal than current practice, since five large randomised trials supporting a restrictive transfusion strategy have since been published.^{8–12} Nonetheless, the authors concluded that anaemia is associated with cardiac events and mortality, however whether this relationship is causal or amenable to treatment remains unknown. Association is the key concept in this study. It is entirely plausible that the anaemia reflects a more severe postoperative course and is not the cause of the cardiac events. The authors adjusted for potential confounding variables, but all values were baseline or surgical demographics, plus intraoperative hypotension. There was no adjustment for major events that may have occurred intraoperatively or postoperatively.

The second paper by Turan and colleagues² included a heterogeneous group of patients from five major randomised

Table 1 Summary of four studies relating bleeding, anaemia, and transfusion to adverse outcomes.

Study	Sample size, n	Source of patients	Main outcome and findings
Turan and colleagues ¹	7,227	POISE-2 study	30-day postoperative composite of non-fatal myocardial infarction or all-cause mortality 1.46 odds ratio for each 10 g dL ⁻¹ decrease in nadir Hb
Turan and colleagues ²	4,403	Five different studies: Cleveland Clinic, POISE 2, ENIGMA, VISION, BALANCED trials	3-day postop myocardial injury after noncardiac surgery (MINS) 1.29 hazard ratio for each 10 g dL ⁻¹ decrease in nadir Hb
Roshanov and colleagues ³	16,079	VISION study	30-day BIMS and all-cause mortality 17.3% had BIMS, 1.87 hazard ratio for mortality associated with BIMS
Roshanov and colleagues ⁴	16,079	VISION study	risk calculator predicting BIMS * website calculator predicts 29% risk of BIMS for 70 yr old male total knee arthroplasty * website predicts 79% risk of BIMS for 70 yr old female total knee arthroplasty

POISE-2 – Perioperative Ischemic Evaluation-2 Trial.

ENIGMA-II – Addition of nitrous oxide to general anesthesia in at-risk patients having major noncardiac surgery.

VISION – Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study.

BALANCED – Balanced Anesthesia Study.

Hb, haemoglobin; RBC, red blood cell.

BIMS - Bleeding independently associated with mortality after noncardiac surgery (defined as postoperative Hb < 70 g L⁻¹ or ≥ 1 u RBC transfused or bleeding judged to be cause of death).

* (<http://perioperativerisk.com/BIMS>)¹⁴ with preoperative haemoglobin 130 g L⁻¹ and creatinine 1.2 mg dL⁻¹.

trials, again designed to assess other interventions (not anaemia or transfusion). This study assessed risk for myocardial injury after noncardiac surgery (MINS) over a 3-day postoperative time period, using routine (not symptom driven) troponin T monitoring. As in their other paper, a lower nadir Hb was strongly associated with adverse outcomes, with a 1.29 hazard ratio for each 10 g L^{-1} decrease in the postoperative nadir Hb. Again, the most anaemic group (nadir Hb $< 80 \text{ g L}^{-1}$) had a rougher perioperative course with a 9-fold greater amount of intraoperative hypotension (time-weighted area under curve – mean arterial pressure $< 65 \text{ mm Hg}$), and a much greater incidence of RBC transfusion compared to the nadir Hb $> 130 \text{ g L}^{-1}$ cohort (23% vs. 0%). As expected, the most anaemic group also had a 10-fold greater median estimated intraoperative blood loss (300 vs. 30 mL). They concluded that there was a strong association between lower postoperative Hb and myocardial injury, again with no evidence of causation, and no evidence that treatment (transfusion) improves outcome.

The third paper is by Roshanov and colleagues,³ which is a sub-analysis of their previous VISION study¹³ designed to assess myocardial injury by 4th generation troponin T levels and subsequent 30-day mortality. These patients were enrolled between 2007 and 2011 at 12 centres in 8 countries on 5 continents. The current study evaluates what the authors call “bleeding independently associated with mortality” after noncardiac surgery (BIMS). Although the title of the paper and the acronym include the word “bleeding”, and the abstract contains “bleeding” seven times, it is fascinating that there are no data showing blood loss or estimated blood loss in this or in the parent (VISION study) paper. They first screened for suspected bleeding looking for a decrease in Hb concentration by 30 g L^{-1} , transfusion of either RBCs, plasma, platelets, or cryoprecipitate, a reoperation for bleeding, or suspected bleeding as a cause of death. After screening, a BIMS event was defined as a postoperative Hb $< 70 \text{ g L}^{-1}$, ≥ 1 unit RBC transfused, or bleeding judged to be the cause of death. Of the 16,079 included patients, there was a 17.3% rate of BIMS, with a 1.87 hazard ratio for 30-day mortality associated with a BIMS event. The majority of BIMS episodes were designated as BIMS due to receipt of RBC transfusion, as 99.2% of BIMS event patients received an RBC transfusion. The second most commonly attributed event causing BIMS was a postoperative Hb $< 70 \text{ g L}^{-1}$ (in 15.9% of BIMS event patients), while only 0.5% had bleeding as a cause of death as a reason for BIMS. The 30-day mortality with BIMS was 5.8%, while mortality without BIMS was 1.1–1.3%. Using relatively complicated statistics, the authors conclude that BIMS may account for a quarter of deaths after noncardiac surgery, which sounds somewhat scary, as if this is the chance of bleeding to death, which luckily is not the case.

Finally, the fourth paper, also by Roshanov and colleagues,⁴ uses the identical patient population from the VISION study¹³ to create a risk calculator for preoperative prediction of BIMS. Variables such as type of surgery, age, sex, risk of kidney or coronary disease and diagnosis of cancer were used to create the risk index calculator, which was internally validated using sophisticated statistical models. Most interesting is the website referenced in the paper where the investigators have created a risk calculator available to all,¹⁴ with a disclaimer that it is intended for use by healthcare professionals. Out of curiosity, we entered some theoretical patients into the risk calculator. For example, a 70-year old male with a preoperative Hb of 130 g L^{-1} and normal kidney function, having a total knee

arthroplasty, a common surgery. The risk of BIMS (bleeding impacting mortality after noncardiac surgery, as it reads on the website) was 29%. The same exact patient but female, has a BIMS risk of 79%, which seems incredibly high for a routine surgery. One must consider the emotional impact on web-savvy patients who after visiting this website and using its calculator may imagine bleeding to death during surgery, while the fact is that many centres now have transfusion rates under 5% for total joint replacements. The patients from the VISION study were all enrolled at least a year before the FOCUS trial¹⁵ was published, a study which showed that a restrictive transfusion strategy in orthopaedic surgery results in the same outcomes as a liberal strategy. In the papers by Roshanov and colleagues, however, the Hb thresholds for transfusion are not given, and thus receiving ≥ 1 RBC unit may in fact not reflect bleeding during surgery, but rather may represent what we now consider to be inappropriate transfusions. In fact, since 2011 when the last VISION trial patient was enrolled, there have been seven large trials published, showing that patients do as well or better when given less blood.^{8–12,15,16} The fact that the definition of a bleeding event included any RBC transfusion in the Roshanov and colleagues articles, and the outcome, BIMS (bleeding impacting mortality after noncardiac surgery event), is also defined by transfusion, making it somewhat of a self-fulfilling prophecy.

There is no doubt that bleeding, anaemia, and transfusion are all incredibly strong markers of coexisting disease, and also markers of more complicated or extensive surgical procedures. Even using the most sophisticated statistical methods, it may be impossible to adjust for confounding variables when we are comparing apples to oranges, e.g. a knee replacement to a meniscectomy, or a 5-level revision spinal fusion to a 1-level discectomy. Bleeding, anaemia, and transfusion seem to be inextricably linked to coexisting disease and complexity of procedures. Nonetheless, many retrospective transfusion studies have shown that bleeding and anaemia are associated with bad outcomes, and transfusion looks like a toxic poison hastening death when examined retrospectively. Ten large randomised trials,^{8–12,15–19} however, have shown that giving extra blood (liberal transfusion) does not improve outcomes, and in four of these studies liberal transfusion was associated with a worse outcome,^{9,11,16,17} at least in some subgroups of patients. So, bleeding and anaemia may be bad, but transfusion has not by any means been clearly shown to fix the problem. One clinical parameter not measured, reported or discussed in any of the four studies is the impact of intravascular volume. Bleeding and anaemia are more likely to be tolerated as long as cardiac output is maintained by volume expanders (crystalloid or colloid). With normovolaemia and adequate cardiac output, oxygen delivery can be optimised in anaemic patients, so these studies all have an additional limitation of not reporting relevant data on intravascular volume status.

Perhaps the best lesson learned from these four studies combined is that if bleeding, anaemia and transfusion are all bad, why not use preventive medicine to avoid all three? Even if there was confounding in these studies, there is no evidence that bleeding and anaemia are good for you, so we should try hard to prevent them. Hospital acquired anaemia is an incredibly common problem.²⁰ The vast majority of inpatients have declining Hb levels each day in the hospital, and rarely does Hb increase, except maybe with intense diuresis.²¹ Of course, sicker patients have lower starting Hb levels, and more complicated or prolonged hospital courses, and thus are predisposed to more profound anaemia. The four reasons for

hospital-acquired anaemia are: 1) bleeding, which does not always stop when the patient leaves the operating room, 2) haemodilution, from intravenous fluids and remobilised ‘third-spaced’ fluids, 3) phlebotomy blood loss for laboratory tests, and 4) decreased erythropoiesis from inflammation and increased hepcidin levels.²² Two potential fixes for this problem are preoperative treatment of anaemia, and “keeping the blood in the patient” throughout the hospital stay. Meticulous surgical technique, smaller phlebotomy tubes, antifibrinolytic drugs, normothermia, controlled hypotension, topical haemostatic agents, newer cautery devices, and cell salvage are methods to reduce hospital-acquired anaemia by keeping blood in the patient.²³

In Roshanov and colleague’s study,³ RBC transfusion was the reason for a BIMS event in the vast majority who had BIMS. As we describe above, it is possible that these patients may have had what we now consider to be unnecessary transfusions at Hb levels that would not trigger transfusion today. As such, liberal (unnecessary) transfusions can be prevented with a strong patient blood management program.²³ Even when transfusion is indicated, experts in the field have crafted *Choosing Wisely* aims to advocate single-unit RBC transfusions instead of the historical default of a 2-unit transfusion.²⁴ Preventive medicine for transfusion can also be accomplished with best practice advisories triggered on recent Hb values, which alert clinicians to potential unnecessary transfusions before they are ordered.²⁵ Another aim of good patient blood management is to avoid unnecessary “yellow products”. Plasma, platelets and cryoprecipitate are often given without clear indication, in fact the guidelines are much less clear on when these are indicated given the paucity of randomised trials for these products compared to RBCs. Transfusing these other products can further complicate the need for RBC transfusion by contributing to dilutional anaemia and morbidities of their own.

With four new studies in the *Journal* all focused on bleeding, anaemia, transfusion and outcomes, what can we conclude? For the studies themselves, each used complicated statistical models, and the conclusions presented have yet to be externally validated, so we should be cautious given their retrospective designs. More broadly and in simple terms, keeping the blood in the patient can prevent anaemia and transfusion, so whatever methods can be used effectively to accomplish this aim (some of which are listed above) are always welcome. For transfusion, as in many other aspects of medicine, not too much and not too little is likely the answer. There is no doubt that blood saves lives when needed, but only increases risks and costs when not, so eliminating unnecessary transfusions should be a primary goal. By adopting a preventive medicine approach to bleeding, anaemia, and transfusion, we can improve outcomes and provide high-value care to our patients.

Declaration of interests

SMF has been on scientific advisory boards for Haemonetics, Medtronic, and Baxter.

MMC is a consultant for Octapharma and Instrumentation Laboratories.

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Intravenous iron administered to anaemic patients before surgery and hospital readmission in the PREVENTT study: one answer, a potentially important health benefit, and new questions

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Keywords: abdominal surgery; anaemia; hospital readmission; iron deficiency; outcome; patient blood management; transfusion

In recent observational studies encompassing thousands of surgical patients, the prevalence of preoperative anaemia varied between 10% and 50%,¹ and was associated with increased morbidity and mortality. Trials investigating more liberal allogeneic red blood cell (RBC) transfusion to reverse anaemia have failed to demonstrate substantial clinical benefits.² In this respect, an increasing number of guidelines recommend that patients undergoing major surgery should be screened for anaemia and treated preoperatively to improve erythropoiesis. In patients with iron-deficiency anaemia, iron substitution would ideally reduce the allogeneic blood transfusion rate and side-effects associated with blood transfusion including fluid overload, infection, and transfusion errors.

From a practical point of view, patients undergoing surgical procedures with expected blood loss >500 ml or a ≥10% probability of RBC transfusion should be screened for anaemia.^{2–4} Early treatment of anaemia using an easy-to-follow diagnostic algorithm is desirable.⁵ Intravenous iron is efficacious, safe⁶ and should be used in patients in whom oral iron is not tolerated, or if surgery is planned within 4–6 weeks after the diagnosis of iron deficiency (anaemia).

Only a few well-designed, adequately powered RCTs assessing the effect of i.v. iron to treat anaemia in patients undergoing abdominal surgery are available. Froessler and colleagues⁷ randomised 72 patients with iron-deficiency

anaemia undergoing major abdominal surgery to receive either i.v. iron or usual care. Administration of perioperative i.v. iron reduced the need for allogeneic blood transfusion by 60% (31.2% vs 12.5%), was associated with a shorter hospital stay (9.7 vs 7.0 days), enhanced restoration of iron stores, and resulted in a higher increase of mean haemoglobin concentrations 4 weeks after surgery (0.9 vs 1.9 g dl⁻¹).

To evaluate further the clinical effectiveness of i.v. iron therapy (ferric carboxymaltose, 1000 mg) vs placebo (saline) in anaemic patients undergoing major open elective abdominal surgery, Richards and colleagues⁸ conducted the double-blind, parallel-group, placebo-controlled, randomised PREVENTT trial at 46 centres in the UK.

Co-primary endpoints were the rate of blood transfusion or death and the number of blood transfusions from randomisation to 30 days postoperatively. Among 487 participants randomised between January 2014 and September 2018, death or blood transfusion occurred in 67/243 subjects in the placebo group (28.3%) and 69/244 subjects in the i.v. iron group (29.1%). Death (1% vs 1%), postoperative complications (11% vs 9%), hospital stay, or days alive and out of the hospital at 30 days did not differ among groups. However, both haemoglobin concentrations at the time of surgery and postoperative haemoglobin concentrations were higher in the i.v. iron treatment group, and may have led to improved postoperative recovery.