The beneficial effect of patient blood management relies not only on the reduction of transfusion, but on how multimodal perioperative patient-specific interventions synergistically improve clinical outcomes. The implementation of patient blood management targets more than mortality, which thankfully is a very rare endpoint, but any perioperative complications, such as hospital-acquired infection and hospital-acquired anaemia, that could affect patients' perioperative course, resource utilisation (not only cost), and long-term health. Because patient blood management is a clinical 'bundle' promoting implementation of a patient-centred and multimodal strategy,[3] it does not lend itself to being studied in the same manner as a single therapy (such as preoperative treatment of anaemia, restrictive transfusion protocol, tranexamic acid, cell salvage, or point-of-care tests of coagulopathy) in the context of a network meta-analysis. Although, RCTs are important to assess the efficacy of a specific treatment in a specific population (e.g. can restrictive transfusion thresholds 'work' under a specific set of circumstances), alternatives are required to assess the effectiveness of a comprehensive bundle of clinical strategies in real-world circumstances. The effectiveness and cost-effectiveness of the implementation of patient blood management have been demonstrated in several analyses of data obtained from institutional or national programs.[4–8] Those results might not be based on randomised designs, but described real-life effects of implementing a bundle of perioperative patient-specific interventions. None of those real-life experiences were considered in Roman and colleagues'[1] network meta-analysis.

The results reported by Roman and colleagues[1] should be interpreted with caution as they highlight the numerous limitations of the network meta-analysis design. We disagree with the authors' conclusion that patient blood management interventions do not have important clinical benefits beyond reducing bleeding and transfusion in people undergoing major surgery, clinical benefits that have been shown with a design more appropriate to studying patient blood management. We believe patient blood management interventions have a synergistic effect such that the effectiveness of patient blood management interventions on outcome (beyond mortality) and resource utilisation (beyond costs) can only be studied through patient-centred analysis of multimodal interventions.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Interpretation of network meta-analysis of isolated patient blood management interventions. Response to *Br J Anaesth* 2021; 126: e1–2

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Editor—Faraoni and colleagues[1] have commented on the interpretation of our recent network meta-analysis.[2] Our network meta-analysis investigated transfusion-related outcomes and important clinical outcomes for key patient blood management (PBM) interventions targeting anaemia and bleeding: preoperative treatment using iron supplementation, restrictive transfusion protocols, and use of tranexamic acid, cell salvage, or point-of-care testing.

Faraoni and colleagues[1] have highlighted the potential limitations of pooling studies where there is potentially heterogeneity between trial cohorts with respect to clinical setting, tolerance of anaemia, implementation of transfusion strategies, or other components of PBM. However, the evidence from our review of all the published trials of five PBM interventions, in which we performed detailed subgroup analyses stratified by cohort, indication, setting, and intervention type, suggested that these factors did not contribute to heterogeneity of outcomes. In fact, we showed almost no heterogeneity for clinical outcomes across all our analyses, with no analysis indicating any clinical benefit. Specifically, our analyses, and no previous trial of which we are aware, have definitively identified a patient subgroup with different tolerance to anaemia than patients in general. There are uncertainties as to the role of patient age and the presence of cardiovascular disease on transfusion thresholds, and we hope this will be addressed by ongoing trials including the MINT (Myocardial Ischemia and Transfusion)[3] and the TRICS IV (Transfusion Requirements in Cardiac Surgery) trials. No RCT identified in our review has shown that heterogeneity in transfusion regimens affects clinical outcomes. Finally, large high-quality trials have evaluated the effects of transfusion protocol adherence, nadir haemoglobin, number of units transfused per transfusion, or volume of red cells transfused before randomisation, and demonstrated that these factors did not interact significantly with the overall treatment effects of the evaluated PBM interventions.[4–7]

In their second point, the authors draw attention to the potential synergistic effects of PBM interventions leading to improved clinical outcomes. No trial in our review showed synergism between the five studied PBM interventions. The design of the network meta-analysis aimed to address the potential synergism between individual interventions and evaluate the additive effect of combined PBM interventions. Notwithstanding its limitations, this network meta-analysis did not show evidence of synergy when evaluating clinical benefits.

In their third point, Faraoni and colleagues[1] rightfully acknowledge that other clinical outcomes besides mortality are important when assessing PBM interventions. Our manuscript evaluated multiple important clinical outcomes including infection, myocardial infarction, acute brain injury, acute kidney injury, and low cardiac output, as reported in the online supplement. No analysis showed a clinical benefit for these outcomes. The small number of trials of PBM interventions identified in our review that evaluated longer-term outcomes did not show any treatment effects of PBM interventions for longer-term clinical outcomes.[7,8]

The fourth point of the authors is that PBM is a clinical care bundle and does not lend itself to being studied in the same manner as a single therapy in the context of a network meta-analysis. We politely disagree with this statement for the following reasons.

1. RCTs are the best available method to demonstrate safety, efficacy, and cost-effectiveness of a complex intervention or group of interventions. We have shown that observational analyses of PBM interventions are characterised by multiple sources of bias including bias by indication, lead-time bias, reporting bias, and unmeasured confounders.[9] RCTs, on the other hand, can demonstrate cause and effect. In our analysis of more than 350 trials involving more than 50 000 patients, reductions of red cell transfusion of 30–40% had no significant effect on important clinical outcomes.
2. Using regression analysis, two high-quality trials[5,10] demonstrated significant associations between red cell transfusion and adverse outcomes in their trial cohorts, despite both trials demonstrating no cause and effect between more liberal transfusion and adverse outcome. In the TITRE2 trial, a further analysis using instrumental variables analysis, a statistical technique that adjusts for the most common confounders identified in observational data, demonstrated no significant association.[4] This is further evidence that observational analyses of PBM interventions are subject to confounding and bias that produce misleading results.

Finally, it is erroneous to suggest that complex interventions cannot be evaluated in randomised trials, while well-established frameworks are designed for this purpose.[11,12] Mixed methods evaluations of complex interventions have now become routine in clinical trials in the UK. The most significant barrier to conducting such a trial is the claim that PBM represents the standard of care. Our analysis acknowledges the value of PBM interventions. However, our analyses and conclusion question the value of treatment recommendations for multimodal PBM to be considered the standard of care, in the absence of evidence of clinical benefit or cost-effectiveness from RCTs. Intuitively, the next step would be to conduct a large pragmatic trial of multimodal PBM. We invite those who are sceptical of the results of our review to join with us to undertake such a trial.

Declarations of interest

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Patient blood management interventions lead to important benefits for major surgery. Comment on *Br J Anaesth* 2021; 126: 149–56

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Editor—Systematic reviews and meta-analyses provide clinicians and policymakers with valuable, simple, and reliable summary measures to guide decisions on various conditions and treatments. In our opinion, the recent meta-analysis by Roman and colleagues[1] on certain patient blood management (PBM) interventions misses the mark. We have concerns about potentially far-reaching negative impacts of the conclusions that are not wholly supported by the evidence.

In their meta-analysis,[1] the authors focused on three outcome domains and clearly showed the effectiveness of the studied PBM measures in two (measures of transfusion/bleeding and measures of resource use). Conversely, they failed to detect efficacy in the domain of clinical effectiveness, led by mortality.[1] Finally, the authors were only able to identify a single RCT addressing cost-effectiveness of a PBM modality that showed significant cost reduction, but the results were not fully consistent with four other model-based studies.[1] Consequently, the authors concluded that 'PBM interventions did not lead to important clinical benefits or cost-effectiveness' as indicated in the title of their manuscript and highlighted in the abstract.[1] Titles and abstracts are often the first (and sometimes, only) parts of a paper seen by many clinicians, and the message conveyed, that PBM does not work, cannot be any more clear. That message is inconsistent with their findings.

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