

# Pro-Con session

Chair: Vernon Louw, Sarah Lessire

Thursday 18<sup>th</sup> of April, 2024

## 1. POST-OPERATIVE ANAEMIA: IV OR ORAL IRON?

Pro-IV: Rao Baikady Ravishankar

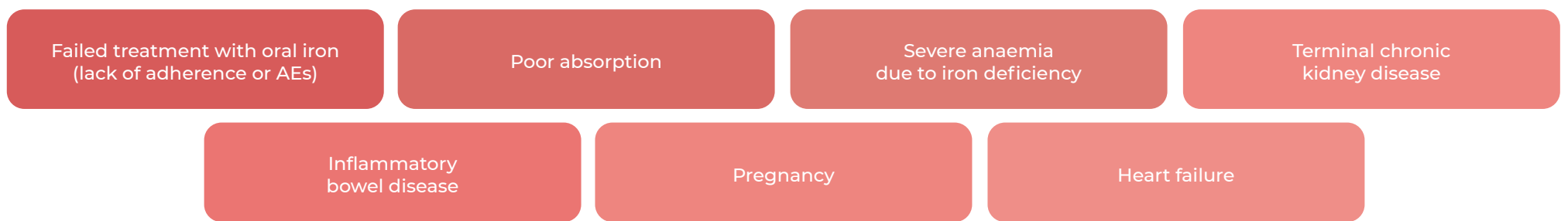
Post-operative anaemia occurs in over 90% of patients undergoing major surgery, and it is a poor-outcome non-dependent risk factor<sup>1</sup>. Thus, preventing and treating is essential. Anaemia management is approached in multiple clinical guidelines<sup>2-6</sup>.

Iron administration has certain limitations:



Furthermore, prescribing iron in the immediate post-operative period is not recommended, since the release of hepcidin in the inflammatory response after surgery decreases the intestinal absorption of iron<sup>9</sup>.

Currently, user-friendly intravenous iron preparations are available, and there is a series of conditions for which they are recommended<sup>10</sup>.



Post-operative administration of intravenous iron is effective for hemoglobin optimization. Optimization can be performed within 2-4 weeks<sup>11</sup>. In a retrospective review of patients undergoing oncological surgery who received intravenous iron during the COVID-19 pandemic, the following facts were observed:

- 459/728 were performed on women.
- 356/728 infusions were performed within 3 weeks of surgery.
- Post-operative administration of intravenous iron lead to a hemoglobin increase in patients undergoing major abdominal surgery.

It was also observed at the Royal Marsden Hospital, based on 2021 data, that the administration of intravenous iron is more common in women than men. Moreover, hemoglobin optimization within 2-4 weeks was higher in patients receiving iron after rather than before the surgery, and it was the same at 10-16 weeks.

In view of these results, further research is required going forward to obtain data on post-operative treatment with intravenous iron.

### Prospective comparisons

- Pre-operative vs post-operative iron (POSTVENTT): prospective audit in Australia and New Zealand, the main goal of which is to comply with anaemia peri-operative management guidelines in patient undergoing major abdominal surgery. It aims at better understanding current practices in anaemia peri-operative management and its impact on patient outcomes.

### Assessing outcome measurements

- Return to intended oncologic therapy (RIOT)
- Functional outcomes
- Readmission after surgery
- Hemoglobin optimization and transfusion

### Time of administration of post-operative intravenous iron

### Oral vs nutrition intravenous iron comparisons

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## 1.2 POST-OPERATIVE ANAEMIA: IV OR ORAL IRON?

Pro-oral: Elvira Bisbe

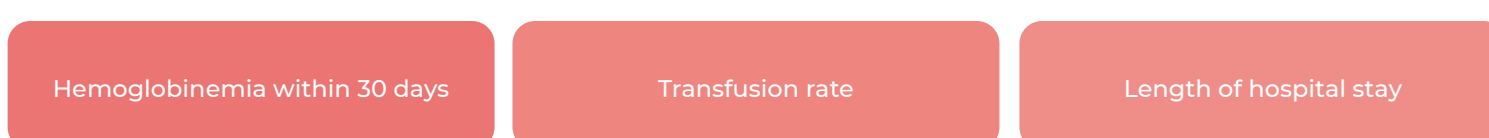
In view of the currently available data, post-operative anaemia should not be treated with iron in all patients. In fact, post-operative treatment with iron does not improve patient-centred outcomes. Given that current recommendations are based on low to moderate quality evidence, further data are required to support the use of intravenous iron in certain high-risk populations<sup>12</sup>.

The post-operative administration of intravenous iron is more beneficial than oral iron, and it may significantly increase hemoglobin and impact the quality of life of patients with moderate to severe anaemia and/or iron deficiency<sup>13</sup>:



It has been observed that the post-operative administration of intravenous iron compared to placebo increases serum hemoglobin and prevents anaemia within 4 weeks in patients with no pre-operative anaemia<sup>14</sup>. It also increases hemoglobin within 12 weeks in patients with isovolemic anaemia<sup>15</sup>.

However, the efficacy of intravenous iron has not yet been proved in the following variables<sup>15</sup>:



Regarding the dose that should be administered, no significant differences have been found as to the increase of hemoglobin within 30 days when using multiple fractionated doses of iron sucrose (500 mg) compared to a single dose of ferric carboxymaltose (1000 mg), even though multiple doses were associated to an increase in the infection rate<sup>16</sup>. Particular attention should be paid to the dose, especially in patients who received iron prior to the surgery.

Moreover, certain intravenous iron preparations can lead to a higher iron release and potential organ damage, as well as an increased oxidative stress<sup>17</sup>.

**At the moment, there is no further evidence on the use of intravenous iron to correct post-operative anaemia, and so the most appropriate way to prevent allogeneic transfusions is to correct anaemia or iron deficiency before surgery.**

**At present, studies are being conducted to generate further evidence<sup>18,19</sup>.**

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## 2. PATIENT BLOOD MANAGEMENT IS COST-EFFECTIVE

YES: Axel Hofmann

In 2021, a meta-analysis was published concluding that Patient Blood Management (PBM) does not provide relevant clinical benefits, except for the reduction of bleeding and the performance of transfusions in patients undergoing major surgery<sup>20</sup>. This conclusion is in contrast with the analysis of over a million surgery patients in the German Patient Blood Management Network, showing that the implementation of PBM results in a significant decrease in the use of packed red blood cells, and was not inferior in terms of safety when compared to standard care.

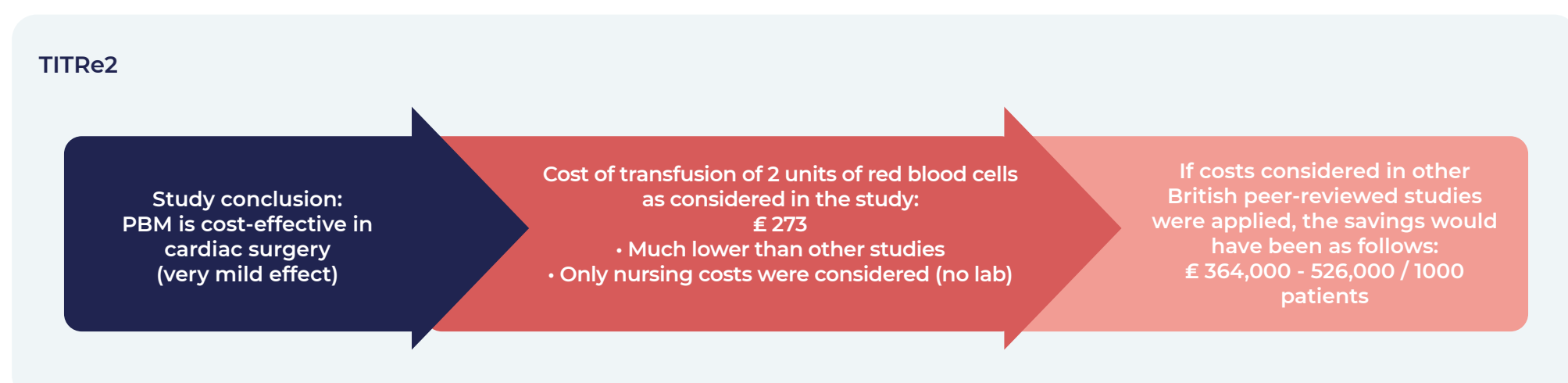
Still, a tendency to PBM effectiveness was observed in terms of mortality and other outcomes.

**This work did find a significant effect of PBM in terms of efficacy and cost reduction:**

Efficacy	Costs
<ul style="list-style-type: none"> <li>Transfusion risk</li> <li>Fresh frozen plasma transfusion</li> <li>Platelet transfusion</li> <li>Reoperation due to bleeding</li> <li>Number of red blood cell transfusions</li> <li>Blood loss</li> </ul>	<ul style="list-style-type: none"> <li>Length of ICU stay</li> <li>Length of hospital stay</li> </ul>

This meta-analysis should be reviewed and updated, since PBM cost-effectiveness was analysed in only one of the 393 works included — trial TITRe2<sup>21</sup>.

2007 patients were randomized in a restrictive group (transfusion if Hb < 7,5) or a liberal group (transfusion if Hb < 9). There were no differences in the composite primary outcome of serious infectious or ischemic events within three months. There were more deaths in the restrictive group after 30 days and after 90 days, 543.4% in the restrictive group and 92.2% in the liberal group received a transfusion. The average cost of transfusions was 287 pounds in the restrictive group, and 427 pounds in the liberal group, although the overall cost after 3 months was similar.



Several meta-analyses have found conflicting results in terms of the clinical benefits of different interventions considered in PBM, such as viscoelastic tests:

**Effect on mortality:**

	Outcome	Events/VET Total	Events/Control Total	RR (95% CI)
Wikkelslo, 2016 (treatment of hemostasis in bleeding patients) <sup>22</sup>	Mortality	14 / 364	26 / 353	0.52 (0.28 - 0.95)
Serraino, 2017 (treatment of coagulopathic bleeding in cardiac surgery) <sup>23</sup>	Mortality	12 / 350	23 / 339	0.55 (0.28 - 1.10)
Santos, 2020 (peri-operative period) <sup>24</sup>	Mortality	33 / 450	53 / 438	0.64 (0.43 - 0.96)
	Acute kidney damage	24 / 228	39 / 221	0.53 (0.34 - 0.83)

Cross-sectional studies have been conducted that allow the assessment of findings in RCTs:

Goodnough, 2014 - USA <sup>25</sup>	Leahy, 2017 - Australia <sup>26</sup>
N = 147,548	N = 605,046
14.3% decrease in mortality	28% decrease in mortality
5.9% decrease in the length of hospital stay	21% decrease in infections
\$6.4 million savings and major impact on total transfusion-related costs	31% decrease in infarction / stroke
	15% decrease in the length of hospital stay
	\$18.5 million in products and \$80-100 millions in activity
	Other benefits in key indicators and transfused units

In view of these results, PBM has a positive impact on health outcomes and is cost-effective. The expected aging of the population for the next few decades will add further weight to these results.

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## 2.1 PATIENT BLOOD MANAGEMENT IS COST-EFFECTIVE

NO: Gavin Murphy

**Why has PBM cost-effectiveness not been proven?**

- The existence of undeclared conflicts of interest, even from the pharma industry, may be having an impact on the results obtained in RCTs conducted with interventions included in the PBM<sup>27</sup>.
- The goals of PBM are focused on improving patient outcomes, and not decreasing the use of transfused units.

PILLAR 1	PILLAR 2	PILLAR 3
Optimization of blood flow	Minimization of bleeding	Optimization of tolerance to anaemia

Still, there is currently no unbiased research proving a clinical benefit of PBM beyond a decrease in red blood cell transfusion (RCT or high-quality RCT systematic reviews).

**Paradoxes around PBM**

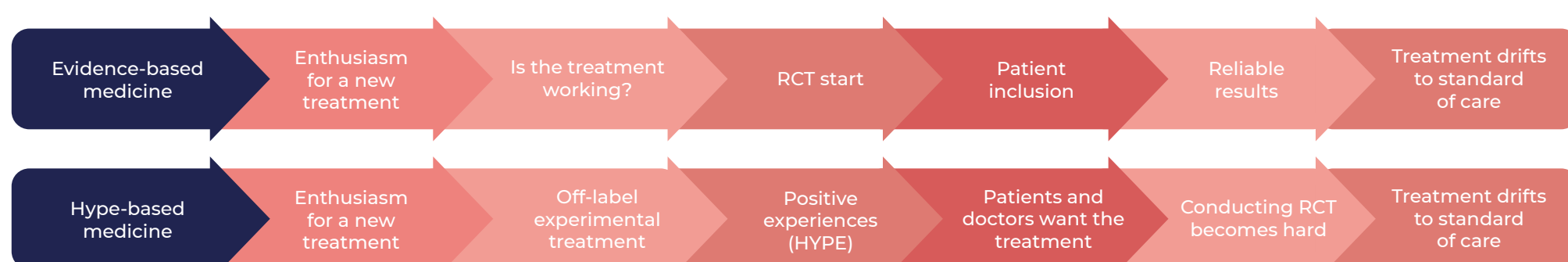
Optimization of red blood cell mass volume:	<ul style="list-style-type: none"> <li>The increase of pre-operative hemoglobin decreases mortality, but the treatment with iron does not decrease the risk of transfusion or death<sup>28-30</sup>.</li> </ul>
Minimization of bleeding	<ul style="list-style-type: none"> <li>Tranexamic acid causes reductions in the bleeding rate within 30 days, but it is not inferior to placebo in a composite safety variable including myocardial damage, non-hemorrhagic cerebrovascular accident, peripheral arterial thrombosis, or symptomatic proximal venous thromboembolism<sup>20,31</sup>.</li> <li>The precision of viscoelastic tests at the point of care has not been assessed in bleeding patients and show no clinical effectiveness<sup>23</sup>.</li> </ul>
Optimization of tolerance to anaemia	<ul style="list-style-type: none"> <li>In cardiac surgery, red blood cell transfusion entails a higher infection risk, post-operative morbidity, hospital stay and mortality, but restrictive transfusion strategies have not proven superior to the liberal ones in terms of morbidity or costs<sup>32,33</sup>.</li> </ul>

Furthermore, a secondary analysis to the TITRe2 trial suggested that the restrictive strategy is cost-effective, but this result was very uncertain, greatly due to the insignificant difference in the gained quality-adjusted life years.

After the instrumental variable analysis (consistent estimation when covariables are correlated to the error terms in a regression model) with the "post-randomization hemoglobin as a continuous variable" model, no significant differences were observed between the restrictive and liberal strategies in the composite variable of serious infection or ischemic event occurrence after 3 months<sup>34</sup>.

- There are no high-quality pharmaco-economic studies that have proven the cost-effectiveness of PBM.
- PBM is currently the standard of care, and therefore it cannot be assessed in an RCT.
- PBM is promoted by doctors with a motivation and focus on quality improvement.

**Is it then an evidence-based or hype-based medical practice?**





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