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Individualised or liberal red blood cell transfusion after cardiac surgery: a randomised controlled trial

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Short title: Individualised red blood cell transfusion based on central venous oxygen saturation

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Editor's Key Points

- Whether haemoglobin levels are a justified trigger for red blood cell (RBC) transfusion in cardiac surgery is under discussion.
- This randomised study evaluated transfusion guided by central venous oxygen saturation (ScVO₂) as alternative for haemoglobin-guided transfusion.
- A transfusion strategy based on ScVO₂ reduced the number of patients receiving at least one RBC transfusion versus a strategy based solely on haemoglobin levels.
- ScVO₂-guided transfusion was not associated with an increase in hospital morbidity or mortality.
- This study is supportive for a more physiological approach for RBC transfusion in perioperative care.

Abstract

Background: Current practice guidelines for red blood cell (RBC) transfusion in intensive care units are based on the haemoglobin threshold, without consideration of oxygen delivery or consumption. We aimed to evaluate an individual physiological threshold guided by central venous oxygen saturation (ScVO₂).

Methods: In a randomised bicentric study in two French academic hospitals, 164 patients who were admitted in an intensive care unit following cardiac surgery with postoperative haemoglobin < 9 g dl⁻¹ were assigned to receive a transfusion with one unit of RBCs (haemoglobin group) or only if the ScVO₂ was < 70% (individualised group). The primary outcome was the number of patients receiving at least one unit of RBCs. The secondary composite outcome was acute kidney injury, stroke, myocardial infarction, acute heart failure, mesenteric ischemia, or in-hospital mortality. One- and six-month mortality were evaluated during the follow-up.

Results The primary outcome was observed for 80 of 80 patients (100%) in the haemoglobin group and in 61 of 77 patients (79%) in the individualised group (absolute risk -21% [-32.0; -14.0] *P* < 0.001). There was no significant difference in the secondary outcome between the two groups. The follow-up showed a nonsignificant difference in mortality at one and six months.

Conclusion An individualised strategy based on a ScVO₂ threshold of 70% allows for a more restrictive RBC transfusion strategy with no incidence on postoperative morbidity or six-month mortality.

Keywords: cardiac surgery, red blood cell transfusion, outcomes, haemoglobin, central venous oxygen saturation

Introduction

Red blood cell (RBC) transfusion is widely used in various settings in medicine to increase oxygen delivery to tissues but is associated with adverse reactions.¹ Among the most frequent recipients of RBC transfusions are patients scheduled for cardiac surgery. Large high-evidence trials have shown the non-inferiority of a restrictive strategy relative to a generalised strategy in terms of postoperative mortality.^{2,3} However, no haemoglobin threshold is mentioned in the latest European guidelines of blood management in cardiac surgery, which, nonetheless, highlight the necessity of considering the condition of the patient and the balance between O₂ delivery and O₂ consumption.⁴

Indeed, the application of an arbitrary threshold using the haemoglobin value for all patients is questionable, as it does not consider the O₂ consumption (VO₂)-to-delivery (DO₂) ratio. This ratio can be determined from blood samples obtained from a central venous catheter by measuring central venous oxygen saturation (ScVO₂), as $ScVO_2 = SaO_2 - (VO_2/DO_2)$. Thus, ScVO₂, as a component of goal-directed therapy, has been shown to improve early outcomes in septic-shock patients.⁵ After optimization of oxygenation and cardiac output, ScvO₂ records individual metabolic tolerance to anaemia and could be used as an individualised and physiological transfusion indicator.⁶ In spite of a physiological rationale, the clinical utility of RBC transfusion using individual ScVO₂ threshold has been scarcely reported in randomized study.⁷

The main endpoint of this study was to assess the feasibility of such a strategy in decreasing the incidence of patients receiving at least one RBC transfusion. The secondary endpoints were to assess the safety of such a strategy in terms of clinical outcomes and mortality.

Materials and methods

Ethics and population study

The postoperative individualised transfusion threshold trial was an open-label, randomised, controlled, superiority trial conducted in two French academic hospitals (Amiens University Hospital and Caen University Hospital). The PITT trial was approved by the local institutional review board (CPP Nord Ouest II, Amiens, France; IRB identifier: 2016-A00880-51, clinicaltrials.gov registration NCT 02963883) in accordance with the Declaration of Helsinki and French law on clinical research.⁸ Each participant provided written consent.

Participants

Participants were at least 18 years of age, underwent cardiac surgery with cardiopulmonary bypass (CPB), and had a postoperative haemoglobin measurement $< 9 \text{ g dl}^{-1}$. The exclusion criteria were active postoperative bleeding, defined as chest tube production over $1.5 \text{ ml kg}^{-1} \text{ h}^{-1}$ for six consecutive hours or necessitating reintervention within 24 h for persistent bleeding, implantation of mechanical circulatory support, complex aortic surgery, emergency surgery, sepsis, patient refusal to be transfused (religious belief), patients under guardianship, renal failure with dialysis treatment, minor patients or those under court protection, and pregnant or breastfeeding woman.

Intra operative transfusion

The management of transfusion during surgery was at the discretion of the physician and independent of the study.

Postoperative management

Postoperative care was delivered within the first hours after surgery to ensure normothermia (temperature over 36.5°C), including mechanical ventilation, assessment of surgical blood loss, and coagulation tests (anti-Xa heparin activity < 0.2 UI ml⁻¹, fibrinogen level > 2 g l⁻¹, platelet count > 50,000 mm⁻³, activated partial thromboplastin time > 50%, and activated clotting time < 240 s).

Circulatory support using fluid therapy, vasopressor, and inotrope drugs was delivered to ensure a mean arterial pressure > 65 mmHg, a cardiac index > 2.5 ml min⁻¹ m⁻², diuresis > 0.5 ml kg⁻¹ min⁻¹, and arterial lactate < 2 mmol l⁻¹.

Interventions

All patients were screened for haemoglobin values as soon as the haemoglobin value fell < 9 g dl⁻¹ throughout the intensive care unit stay following surgery. In the haemoglobin group, the patient systematically received a transfusion with one unit of RBCs. If haemoglobin remained < 9 g dl⁻¹, the patient received another unit of RBCs until the haemoglobin value was > 9 g dl⁻¹.

In the individualised group, the patient received a transfusion with one unit of RBCs according to the ScVO₂ value. If the ScVO₂ was < 70%, after exclusion of hypoxemia and hypovolemia (a new ScVO₂ measurement was performed after correction for these parameters if necessary), the

participant received one unit of RBCs. If the ScVO₂ was $\geq 70\%$, the participant did not receive one unit of RBCs, unless the haemoglobin value was $< 7.5 \text{ g dl}^{-1}$, for safety concerns.

The patient was weaned from the protocol at ICU discharge once the central venous line was removed.

Clinical and biological monitoring was performed for 24 h for both groups and included arterial blood pressure monitoring, haemoglobin, and ScVO₂ control and screening for complications, as defined in the data collection section. ScvO₂ was determined by point-of-care blood gas analysis (ABL800 FLEX; Radiometer, Copenhagen, Denmark).

Physicians were aware of the ScVO₂ in both groups. Physicians could contravene the allocated group but had to document the reason for contravention. Similarly, physicians could permanently discontinue adherence to the assigned group, but such discontinuation did not constitute withdrawal of the participant from the study and the data were continuously collected, in accordance with the intention-to-treat analysis.

Endpoints

Primary endpoint

The main outcome was the number of patients receiving a transfusion with at least one unit of RBCs from inclusion to hospital discharge.

Secondary endpoints

The secondary endpoints were the presence of the following complications from inclusion to hospital discharge: acute kidney injury, stroke, myocardial infarction, acute heart failure,

mesenteric ischemia, 15-day mortality, one-month mortality, six-month mortality, intensive care unit stay (days), and hospital stay (days).

Endpoint definition and data collection

The primary endpoint was the total number of patients receiving a transfusion with at least one unit of RBCs per group. The secondary endpoints were defined according to standard definitions of postoperative outcomes established by the European Society of Anesthesia.⁹ Acute kidney injury was defined according to kidney improving global outcomes (KDIGO) criteria as an increase in serum creatinine of $> 27 \mu\text{mol l}^{-1}$ within 48 h or diuresis $< 0.5 \text{ ml kg}^{-1} \text{ h}^{-1}$.¹⁰ Stroke was defined as an embolic, thrombotic, or haemorrhagic cerebral event with persistent residual motor, sensory, or cognitive dysfunction (e.g., hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory) diagnosed by cerebral CT. Myocardial infarction was defined as an elevation in cardiac troponin above the 99th percentile combined with at least one of the following symptoms of acute myocardial ischemia: new ischemic electrocardiographic changes, development of pathological waves, imaging evidence of the new loss of viable myocardium or a pattern of new regional wall motion abnormality consistent with an ischemic aetiology, and identification of a coronary thrombus by angiography, including intracoronary imaging or by autopsy.¹¹ Acute heart failure was defined as evidence of fluid accumulation in the alveoli due to poor cardiac function. Mesenteric ischemia was defined as necrosis of the small intestine during laparotomy. Mortality was screened during the hospital stay and at the one- and six-month follow-ups.

The following preoperative data were included: age, body-mass index, male sex, medical history, chronic medications, logistic Euroscore, preoperative left ventricular ejection fraction, and preoperative creatinine and haemoglobin levels. The following intraoperative data were

collected: type of surgery, duration of CPB, duration of aortic clamp, and number of RBC transfusions during CPB. The following data were included at inclusion: heart rate, systolic arterial pressure, diastolic arterial pressure, proportion of patients receiving norepinephrine, proportion of patients receiving dobutamine, ScVO₂, cardiac troponin level, PaO₂, haemoglobin level, platelet count, and activated partial thromboplastin time.

Follow up

Follow-up consisted of contact with the participants by telephone six months following randomization to inquire whether a secondary outcome or another serious adverse event had occurred and to determine the health resources used since discharge.

Randomisation

Patients were randomly assigned to one of two groups at a 1:1 ratio using a concealed centralized, web-based system stratified according to centre and haemoglobin value at the time of inclusion using the minimization method. Randomisation was performed on the day that the participant met the inclusion criteria and after checking for the absence of exclusion criteria.

Sample size and statistical analysis

We expected to show a difference in absolute risk of 15% for patients receiving at least one RBC transfusion. In total, 73 patients in each group (individualised and liberal groups) were required with a power of 90% and a two-tailed alpha risk of 5%. Considering a 10% loss to follow-up, 164 patients were enrolled in the study. The prespecified primary analysis of the primary

outcome was intention-to-treat analysis, which included all participants who had undergone randomisation, except for patients who withdrew consent, in accordance with French laws. No intermediate analysis was planned in the trial. Data are presented as means (standard deviations), medians [interquartile range], or numbers (percentage). The primary endpoint was assessed using Fisher's exact test. Stratification of the centre and haemoglobin value was performed using logistic regression. Secondary endpoints were assessed using chi-2 or Fisher's exact tests for qualitative variables and the Wilcoxon rank sum test for quantitative variables. Differences in absolute risk were calculated with a 95% confidence interval. To assess if RBC transfusion at a threshold of 8 g dl⁻¹ is beneficial for the patients, we performed a sensitivity analysis with the selection of patients with a postoperative haemoglobin < 8 g dl⁻¹ and applied the study protocol with the same value of ScVO₂. All analyses were performed using SAS software, version 9.4 (SAS Institute) and R software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org) through the R Studio Interface Version 1.3.1093 – © 2009-2020. The statistical test results were considered significant if $P < 0.05$ for primary and secondary endpoints.

Results

Participants

In total, 2,536 patients underwent cardiac surgery at the two centres between January 30, 2017, and October 4, 2019. Among them, 164 patients were included, and 160 were analysed: 77 in the individualised group and 80 in the haemoglobin group (Fig. 1). A protocol violation concerned one patient in the individualised group.

Baseline characteristics

The baseline characteristics were similar for the two groups in terms of preoperative data, surgical risk, and type of surgery. The intraoperative characteristics, including the duration of CPB and the aortic clamp, were also similar (Tables 1 and 2).

Haemoglobin concentrations

The haemoglobin concentrations of patients before surgery were 12.3 (0.4) and 12.2 (0.5) g dl⁻¹ for the haemoglobin and individualised groups, respectively (Table 1). At inclusion, the mean haemoglobin value was similar for both groups (8.2 (0.4) g dl⁻¹ for the haemoglobin group and 8.2 (0.5) g dl⁻¹ for the individualised group; $P = 0.990$). Baseline ScVO₂ did not differ between the groups: 63 (11) % for the haemoglobin group and 62 (11) % ($P = 0.895$) for the individualised groups. The number of patients with an ScVO₂ < 70% did not differ between the two groups (Table 2).

Primary endpoint

The number of patients receiving at least one RBC transfusion was significantly lower in the individualised than haemoglobin group (61 [79%] vs 80 [100%]), absolute risk reduction -21%, 95% CI: -32.0 to -14.0, $P < 0.001$) (Table 3). Kaplan-Meier analysis was used to estimate the risk of receiving RBC transfusion units (Fig. 2). In total, 198 units were administered: 108 for the haemoglobin group and 90 for the individualised group. The median number of units transfused was 1 [1-2] for the haemoglobin group and 1 [1-1] ($P = 0.028$) for the individualised group.

Secondary endpoints

The occurrence of acute kidney injury, stroke, myocardial infarction, acute heart failure, and mesenteric ischemia did not significantly differ between the two groups during the hospitalization period. The in-hospital mortality rates were 2.7% (2 patients) for the haemoglobin group and 1.4% (1 patient) for the individualised group (absolute risk reduction -1.28%, 95%CI: -5.82 to 3.26, $P = 0.584$). The length of the ICU and hospital stays did not differ between the two groups. The mortality rates at the one and six-month follow-ups were similar between the two groups (Table 3).

Sensitivity analysis

We performed sensitivity analysis to assess the number of patients receiving RBCs if the threshold value was 8 g dl⁻¹ instead of 9 g dl⁻¹. Adapting the same trial protocol (haemoglobin < 8 g dl⁻¹ and ScVO₂ < 70%), 22 patients would have received one unit of RBCs in the haemoglobin group and 15 patients in the individualised group ($P < 0.001$).

Discussion

In this randomised trial involving patients following cardiac surgery, an individualised transfusion strategy based on ScVO₂ reduced the number of patients receiving at least one RBC transfusion versus a strategy based solely on haemoglobin levels, without an increase in hospital morbidity or mortality. The six-month follow-up showed similar mortality rates between the two groups.

RBC transfusion is one of the most frequently used therapies worldwide and is associated with clinical benefits, as well as risks and high overall costs. In the cardiac surgery setting, two large studies compared liberal and restrictive transfusion and showed the non-inferiority of a restrictive strategy in terms of postoperative mortality versus a liberal strategy.^{2,3} Guidelines are not comparable across the globe; the 2018 Frankfurt consensus conference recommended a haemoglobin concentration threshold of 7.5 g dl⁻¹,¹² for RBC transfusion, whereas the American Association of Blood Banks recommends a value of 8 g dl⁻¹,¹³ and the French guidelines a value of 7 g dl⁻¹ or 10 g dl⁻¹ if acute coronary disease or cardiac insufficiency is present or if beta-blockers are used.¹⁴ Indeed, patients administered β-blockers who experienced severe bleeding in the perioperative setting were shown to have a higher mortality and an increased frequency of multiorgan dysfunction syndrome, explaining the higher suggested RBC threshold value.¹⁵ Moreover, a liberal transfusion strategy was shown to be associated with a trend towards fewer major cardiac events and deaths than a more restrictive strategy for patients with symptomatic coronary disease.¹⁶

Our study had several strengths. The study population showed stable hemodynamic parameters and oxygenation in the ICU for both groups. A correction for hypovolemia and hypoxemia was performed for the individualised group using ScVO₂ before again measuring ScVO₂ to guide

RBC transfusion if the value remained $< 70\%$. No patients showed sepsis, which could modify the interpretation of ScVO₂. Finally, the follow-up to ascertain survival was six months following cardiac surgery.

Hence, the results of our study favour a more restrictive RBC transfusion strategy, along with a reduction in the administration of units, while considering oxygen demand based on ScVO₂. Thus, patients who may poorly tolerate anaemia or are at risk of organ damage could be screened through ScVO₂ monitoring. Approaches guided by ScVO₂ have not been reported until publication of the very recent study of Zeroual et al.⁷ In a closed design study setting, the authors also demonstrated a reduction in RBC transfusions of 32% when targeting a ScVO₂ of 65%.

Other potential physiological triggers should be considered. Initially, clinical symptoms of anaemia could be used, such as cardiac symptoms (angina or electrocardiographic modifications), pulmonary signs (dyspnoea, polypnea), and neurological disorders (confusion, stroke). However, such symptoms may appear too late to be safely used. Other indicators of metabolic triggers are available, such as blood lactate levels or the veno-arterial CO₂ gap, but little data are available concerning their utility as transfusion triggers and they should be interpreted with caution, especially in septic shock patients. A multiparametric approach based on more than one universal transfusion trigger could be used by physicians at the bedside, based on both the clinical context (disease and clinical tolerance) and biological data (i.e., haemoglobin value, ScVO₂, and lactate level, for example).

Our study had several limitations. First, our threshold haemoglobin value in the haemoglobin group was higher than that recommended in recent guidelines, which suggest a value of 8 g dl⁻¹

rather than the 9 g dl⁻¹ used in our study. However, at the time we designed the trial, a haemoglobin value of 9 g dl⁻¹ was the consensual indicator for the need of a RBC transfusion. Moreover, we completed a sensitivity analysis with a haemoglobin value at 8 g dl⁻¹. The number of RBC administered remained lower when combined to ScVO₂ use with a value under 70%. However, we believe that a lower value of ScVO₂ could be tolerated before RBC transfusion. Zeroual et al. chose a value of 65% for ScVO₂ before transfusing postsurgical patients and confirmed the safety of such a decision.⁷ In our study, the value of 70% came from a previous report of Vallet et al. showing that critically ill patients would receive the most benefit from transfusion in terms of metabolic demand at this value.⁶

The choice of the primary endpoint may have also not been ideal, as it did not assess a robust outcome, such as mortality or clinical outcomes. However, we initially intended to demonstrate the feasibility of ScVO₂ as the RBC transfusion trigger without increasing adverse outcomes. Further large studies are required to assess the clinical outcomes of using an individualised ScVO₂-guided strategy versus one based on a haemoglobin value threshold before recommending this strategy.

Finally, the current application of ScVO₂ appears to be limited to cardiac surgery, given the necessity of having a central venous line during the early postoperative period. It could be informative to study such an RBC transfusion strategy in a perioperative setting or in non-cardiac surgery or a medical ICU.

Our findings and those of Zeroual et al.⁷ suggest that ScVO₂ may be appropriate for critically ill patients to reduce the frequency of RBC transfusion and potentially reduce associated adverse reactions.

Conclusion

The PITT trial compared an individualised threshold-based transfusion strategy with one based on a haemoglobin threshold and assessed the length of ICU and hospital stay following cardiac surgery. A transfusion strategy based on ScVO₂ allowed a reduction in the number of RBC transfusions and appears to be safe in terms of postoperative outcomes.

Author contribution: Study conception and manuscript drafting: OAA, PGG, and MOF. Clinical data collection: PH, CB, MG, KB, and SD. Patient follow up: TC and GB. Statistical analysis: MD. Revision of the manuscript: JLH, HD, and EL. All the authors approved the final version of the manuscript.

Declaration of interest

The authors declare that they have no conflicts of interest.

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References

1. Carson JL, Triulzi DJ, Ness PM. Indications for and Adverse Effects of Red-Cell Transfusion. Longo DL, editor. *N Engl J Med* 2017; **377**: 1261–72
2. Murphy GJ, Pike K, Rogers CA, et al. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med* 2015; **372**: 997–1008
3. Mazer CD, Whitlock RP, Fergusson DA, et al. Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery. *New England Journal of Medicine* 2017; **377**: 2133–44
4. Boer C, Meesters MI, Milojevic M, et al. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia* 2018; **32**: 88–120
5. Rivers E, Nguyen B, Havstad S, et al. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. *N Engl J Med* 2001; **345**: 1368–77
6. Vallet B, Robin E, Lebuffe G. Venous oxygen saturation as a physiologic transfusion trigger. *Crit Care* 2010; **14**: 213
7. Zeroual N, Blin C, Saour M, et al. Restrictive Transfusion Strategy after Cardiac Surgery. *Anesthesiology* 2021; 10.1097/ALN.0000000000003682
8. Toulouse E, Lafont B, Granier S, Mcgurk G, Bazin J-E. French legal approach to patient consent in clinical research. *Anaesthesia Critical Care & Pain Medicine* 2020; **39**: 883–5
9. Jammer I, Wickboldt N, Sander M, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. *Eur J Anaesthesiol* 2015; **32**: 88–105
10. Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care* 2013; **17**: 204
11. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *European Heart Journal* 2019; **40**: 237–69
12. Mueller MM, Van Remoortel H, Meybohm P, et al. Patient Blood Management: Recommendations From the 2018 Frankfurt Consensus Conference. *JAMA* 2019; **321**: 983
13. Carson JL, Guyatt G, Heddle NM, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. *JAMA* 2016; **316**: 2025
14. HAS. French national health authority guideline for red blood cell transfusion [Internet].

2014. Available from: https://www.has-sante.fr/upload/docs/application/pdf/2015-02/transfusion_de_globules_rouges_homologues_-_hematologie_oncologie_-_argumentaire.pdf
15. Le Manach Y, Collins GS, Ibanez C, et al. Impact of perioperative bleeding on the protective effect of β -blockers during infrarenal aortic reconstruction. *Anesthesiology* 2012; **117**: 1203–11
16. Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. *Am Heart J* 2013 ; **165** : 964-971.e1

Tables and figure legends

Table 1. Preoperative and intraoperative characteristics.

ACEI: angiotensin converting enzyme inhibitor, **ARB:** angiotensin II receptor blocker, **BMI:** body mass index, **COPD:** chronic obstructive pulmonary disease, **LVEF:** left ventricular ejection fraction, **CABG:** coronary artery bypass graft, **CPB:** cardiopulmonary bypass. Data are presented as means \pm standard deviations, medians [interquartile ranges], or numbers (percentages).

Table 2. Patient characteristics.

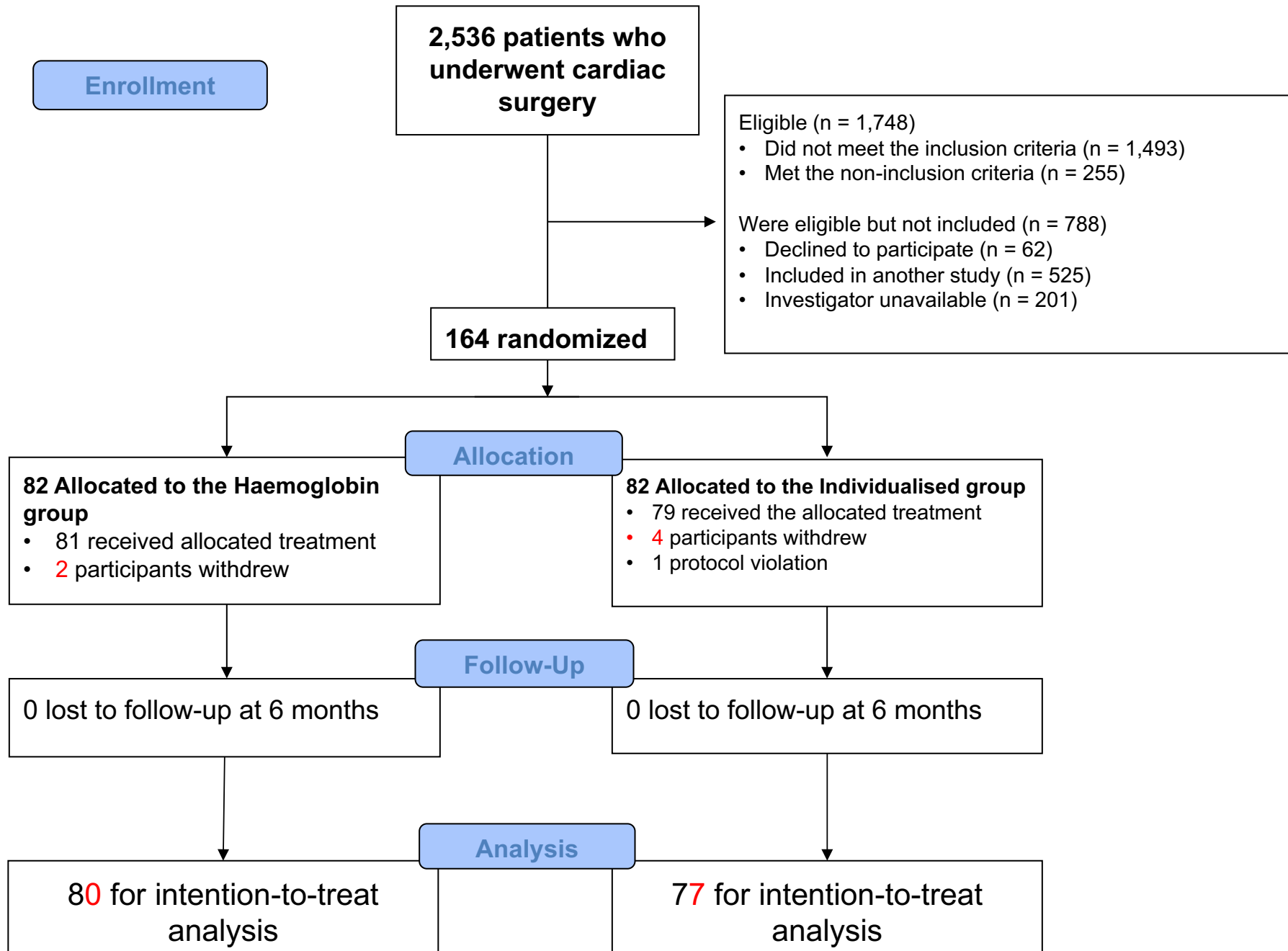
HR: heart rate, **SAP:** systolic arterial pressure, **DAP:** diastolic arterial pressure, **ScVO₂:** central venous saturation in oxygen, **aPTT:** activated partial thromboplastin time, **SOFA:** sequential organ failure assessment. Data are presented as means \pm standard deviations, medians [interquartile ranges] or numbers (percentages).

Table 3. Primary and secondary endpoints.

RCT: red cell transfusion, **AKI:** acute kidney injury, **ICU:** intensive care unit, **NA:** non-applicable

Fig. 1 Flow chart of the study

Fig. 2 Kaplan-Meier analysis to estimate the risk of patients receiving red blood cells for the haemoglobin group (red) and individualised-ScVO₂ group (blue) following surgery.



Probability of transfusion

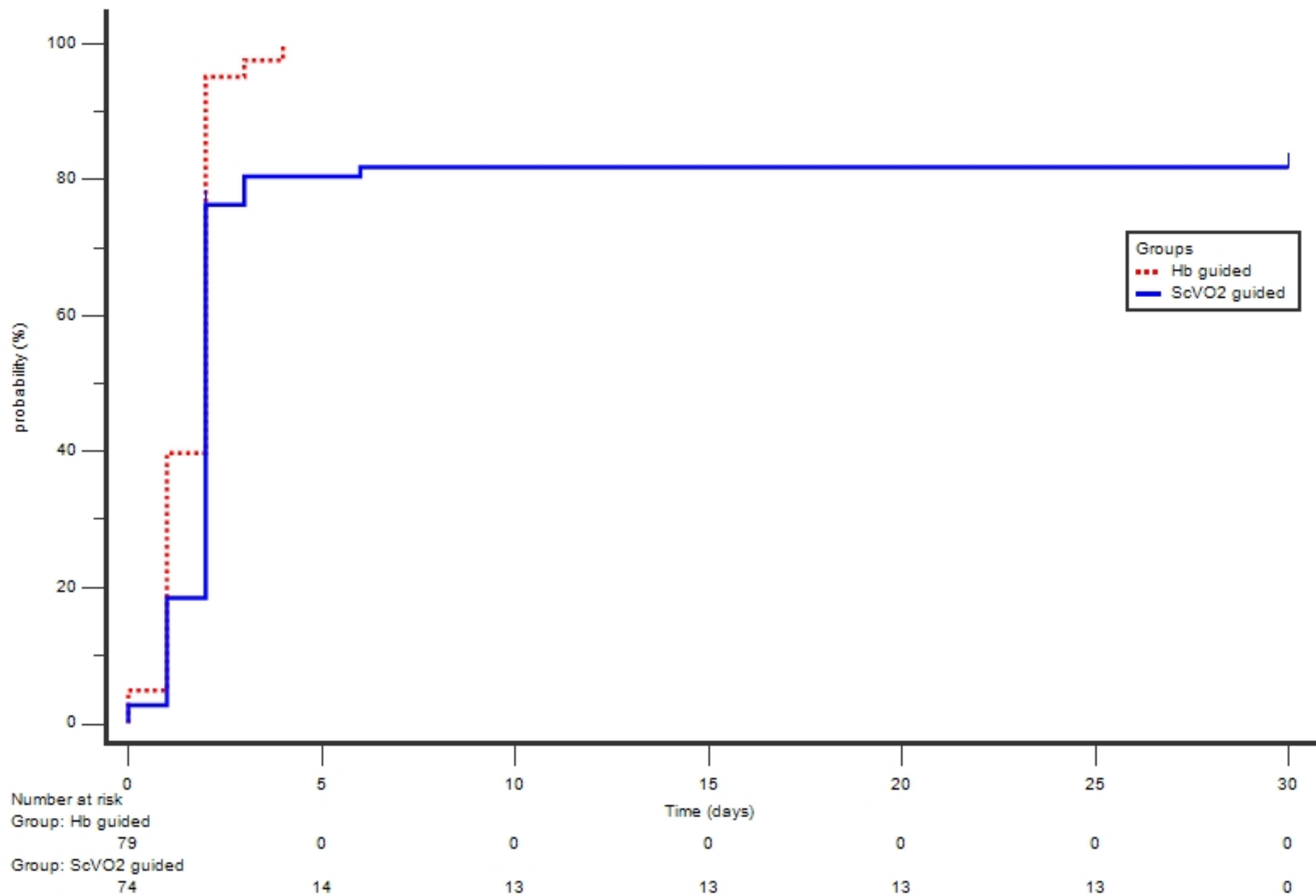


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Characteristics	Haemoglobin group (n = 80)	Individualised group (n = 77)
Preoperative		
Age, years	67 \pm 12	67 \pm 11
BMI, kg m ⁻²	27.30 \pm 5.16	28.13 \pm 4.70
Male gender, n (%)	46 (58)	48 (62)
Medical history, n (%)		
COPD	3 (4)	8 (10)
Coronary disease	40 (50)	37 (48)
Peripheral vascular disease	13 (16)	11 (14)
Hypertension	49 (61)	47 (61)
Smoking (active or former)	11 (14)	15 (19)
Diabetes	21 (26)	25 (32)
Dyslipidaemia	33 (41)	33 (43)
Chronic renal disease	6 (8)	15 (19)
Stroke	9 (11)	9 (12)
Medications, n (%)		
Aspirin	50 (63)	43 (56)
Clopidogrel	11 (14)	13 (17)
ACEIs	32 (40)	36 (47)
ARB	16 (20)	12 (16)
Statin	56 (70)	47 (61)
Vitamin K antagonist	8 (10)	5 (6)
Beta blocker use	45 (56)	47 (61)
Logistic Euroscore, %	4.3 [2.9 – 7.6]	5.2 [2.8 – 9.7]
LVEF, %	57 \pm 11	52 \pm 14
Haemoglobin, g dl ⁻¹	12.3 \pm 0.4	12.2 \pm 0.5
Creatinine, μ mol l ⁻¹	70 [46 - 94]	78 [33 - 123]
Intraoperative		
Cardiac procedure (n, %)		
Valve repair/replacement	43 (53)	42 (53)
CABG	37 (46)	35 (44)
Combined	8 (10)	19 (24)

Others	8 (10)	6 (7)
Duration of CPB, <i>min</i>	91 ± 42	103 ± 48
Duration of aortic clamp, <i>min</i>	67 ± 33	74 ± 36
RBC units during CPB, <i>n (%)</i>	28 (35)	21 (27)

Table 2. Patient characteristics at inclusion and following RBC transfusion.

HR: heart rate, **SAP:** systolic arterial pressure, **DAP:** diastolic arterial pressure, **ScVO₂:** central venous saturation in oxygen, **aPTT:** activated partial thromboplastin time, **RBC:** red blood cells, **SOFA:** sequential organ failure assessment. Data are presented as mean ± standard deviation, median [interquartile range] or number (percentage).

Characteristics	Haemoglobin group (n = 80)	Individualised group (n = 77)	P value
At inclusion time			
Hemodynamic data			
HR, <i>bpm</i>	86 ± 17	85 ± 15	0.625
SAP, <i>mmHg</i>	120 ± 14	121 ± 14	0.715
DAP, <i>mmHg</i>	58 ± 9	58 ± 10	0.813
Cardiac output, <i>l min⁻¹</i>	4.8 ± 1.6	5.2 ± 1.8	0.276
Catecholamine use, n (%)			
Dobutamine	3 (4)	4 (5)	0.661
Norepinephrine	24 (30)	15 (20)	0.127
SOFA	2 [1-4]	2 [1-4]	0.856
ScVO ₂ , %	63 ± 11	62 ± 11	0.895
ScVO ₂ <70%, n (%)	64 (80)	59 (77)	0.635
Arterial lactate, <i>mmol l⁻¹</i>	1.3 ± 0.8	1.2 ± 0.7	0.521
Creatinine, <i>μmol l⁻¹</i>	80 ± 39	104 ± 72	0.011
Cardiac troponin, <i>ng ml⁻¹</i>	1.20 [0.63 - 3.15]	1.72 [0.80 - 3.15]	0.250
PaO ₂ , <i>mmHg</i>	103 ± 36	101 ± 33	0.677
Haemoglobin, <i>g dl⁻¹</i>	8.2 ± 0.4	8.2 ± 0.5	0.990
Haemoglobin between 8 and 9 <i>g dl⁻¹</i> and ScVO ₂ < 70%	51 of 61 (84)	45 of 57 (79)	0.004
Platelet count, <i>10³ mm⁻³</i>	155 ± 63	158 ± 58	0.077
aPTT, %	70 ± 13	73 ± 15	0.259
Day of RBC transfusion from surgery	2 [1-3]	2 [2-3]	0.420

Following RBC transfusion

ScVO ₂ following RBC transfusion, %	60 ± 11	63 ± 9	0.156
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Haemoglobin following inclusion

Day 1	9.0 ± 1.3	9.0 ± 0.7	0.629
Day 2	9.2 ± 0.7	9.0 ± 0.8	0.721
Day 7	9.6 ± 1.0	9.2 ± 0.8	0.752

Table 3. Primary and secondary endpoints.

RBC: red blood cell, AKI: acute kidney injury, ICU: intensive care unit, NA: non-applicable

Variables	Haemoglobin group (n = 80)	Individualised group (n = 77)	Absolute risk difference (Individualised haemoglobin) (%)	P value
Primary endpoint				
RBC units, <i>n</i> (%)	80 (100)	61 (79)	-21 [-32.0; -14.0]	<0.001
Secondary endpoint, <i>n</i> (%)				
AKI	2 (2.7)	2 (2.8)	0.11 [-5.15 – 5.37]	0.967
Stroke	0 (0)	1 (1.4)	1.43 [-1.35 – 4.21]	0.312
Myocardial infarction	1 (1.4)	2 (2.9)	1.45 [-3.32 – 6.22]	0.551
Acute heart failure	1 (1.3)	0 (0)	-1.33 [-3.93 – 1.26]	0.326
Mesenteric ischemia	2 (2.7)	1 (1.4)	-1.28 [-5.82 – 3.26]	0.584
In hospital mortality	2 (2.7)	1 (1.4)	-1.28 [-5.82 – 3.26]	0.584
1-month mortality	2 (2.7)	1 (1.4)	-1.28 [-5.82 – 3.26]	0.584
6-months mortality	2 (2.7)	1 (1.4)	-1.28 [-5.82 – 3.26]	0.584
ICU stay (days)	4 [3-6]	5 [3-6]	NA	0.526
Hospital stay (days)	12 [10-17]	11 [10-17]	NA	0.671