Red blood cell transfusion is a determinant of neurological complications after cardiac surgery

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Abstract

OBJECTIVES: The aim of this study was to evaluate the impact of red blood cell (RBC) transfusions on the occurrence of stroke and transient ischaemic attack (TIA) after cardiac surgery.

METHODS: Data on 14 956 patients undergoing coronary artery bypass grafting (CABG) and valve surgery (with or without concomitant CABG) were retrieved at three European University Hospitals. The prognostic impact of RBC transfusion on postoperative stroke and TIA was investigated by logistic regression and multilevel propensity score analysis.

RESULTS: Postoperative stroke was observed in 147 (1.0%) patients and combined stroke/TIA in 238 (1.6%). Of the total population, 6439 (43%) patients received RBC transfusion with a median of 2 units (25th–75th percentile, 2–4 units). When adjusted for other significant risk factors, RBC transfusion was an independent predictor of stroke [odds ratio (OR) 1.14; 95% confidence interval (CI) 1.11–1.17 per unit] and stroke/TIA (OR 1.12; 95% CI 1.09–1.15 per unit). Increase in the amount of transfused RBC units was associated with higher rates of stroke (no RBC transfusion: 0.8%, 1 RBC units: 1.0%, OR 1.42; >2 RBC units: 2.7%, OR 3.10) and stroke/TIA (no RBC transfusion: 0.8%, 1 RBC units: 1.8%, OR 1.49; >2 RBC units: 4.0%, OR 2.72). Multilevel propensity score analysis confirmed these findings and showed a very high risk of stroke (3.9% OR 3.85; 95% CI 2.30–6.45) and stroke/TIA (5.9% OR 3.30; 95% CI 2.17–5.02) associated with transfusion of ≥6 units of RBCs.

CONCLUSIONS: Transfusion of more than 6 units of RBCs after cardiac surgery is associated with a significantly increased risk of postoperative stroke and TIA.

Keywords: Stroke • Transient ischaemic attack • Blood transfusion • Cardiac surgery • Coronary artery bypass • Aortic valve • Mitral valve

INTRODUCTION

Red blood cell (RBC) transfusion has been reported to be associated with increased early and late mortality and additional indirect hospital expenditures in patients undergoing cardiac surgery [1–5]. Recent studies suggest that RBC transfusions may be associated with postoperative stroke and such a risk is increased even after transfusion of 1 or 2 units of RBCs [4–8]. Plausible causative mechanisms refer to the prothrombotic status induced by blood transfusions because of the reduced deformability and the high free haemoglobin concentrations of stored RBCs, which may result in the occlusion of the microcirculation and vasoconstriction due to the potent nitric oxide scavenging ability of the free haemoglobin [9–12].

However, the role and association of RBC transfusion with cerebrovascular complications in cardiac surgery are poorly defined [4–8]. The present study aimed to investigate in a multicentre registry the impact of RBC transfusions on the risk of stroke and transient ischaemic attack (TIA) in patients undergoing cardiac surgery.

MATERIALS AND METHODS

Patient population

Between July 1999 and December 2011, all patients undergoing coronary artery bypass grafting (CABG) and valve surgery (with or without concomitant CABG) at three European University Hospitals (Bristol Heart Institute, UK: 7450 patients, 52.6% isolated CABG; Varese University Hospital: 3282 patients, 73.7% isolated CABG; Centro Cardiologico Monzino IRCCS, Italy: 4224 patients,
50.7% isolated CABG) with completed data on received RBC units were reviewed. Elective, urgent or emergency procedures were all included. The patient population comprised a total of 14 956 patients with complete data on postoperative neurological complications as well as other pre-, peri- and postoperative variables. Data used in this analysis were retrieved from institutional databases, which remained consistent over the study period. All data were prospectively collected, and information about demographics, comorbidities, medical and surgical history, operative details and postoperative events during the hospital stay were all recorded. In all the three hospitals, a similar data collection form is present and entered in a database (Patient Analysis & Tracking System; Dendrite Clinical Systems, London, UK) and includes five sections that are filled in consecutively by anaesthesiologists, surgeons, intensive care unit (ICU), high-dependency unit and ward nurses. The study protocol was in compliance with the local Institutional Review Boards and received full approval. Patient consent was waived.

**Patient management**

Preoperative management, anaesthetic and surgical techniques followed routine methods and remained consistent during the study period among the centres [1, 13]. Generally, antiplatelet and anticoagulation therapies were discontinued on the day of hospitalization, whereas other medications were routinely omitted on the day of operation and restarted after the operation, unless clinically contraindicated [1, 13]. The anaesthetic technique consisted of propofol infusion (5 mg/kg/h) combined with sufentanil (0.75 µg/kg). Neuromuscular blockade was achieved by pancuronium bromide or vecuronium and the lungs were ventilated to normocapnia with air and oxygen (45–50%). Intravenous heparin (2.5–4.0 mg/kg) was administered after sternotomy to maintain an activated clotting time of more than 400 s. At the end of the procedure, the circulating heparin was reversed with protamine (3.0 mg/kg). The decision to perform off-pump or on-pump CABG technique was based on individual surgeon preference. At the end of surgery, patients were transferred to the ICU. The lungs were ventilated with 60% oxygen with volume-controlled ventilation and a tidal volume of 10 ml/kg with 5–10 cmH2O of positive end-expiratory pressure. Adjustments in FiO2 and respiratory rate were made according to routine blood gas analysis to maintain PaO2 between 80 and 100 mmHg and PaCO2 between 35 and 40 mmHg. Forced air warming was used until a stable nasopharyngeal temperature of 37°C was reached. Generally, patients were extubated as soon as they met the following criteria: hemodynamic stability, no excessive bleeding (<80 ml/h), normothermia and consciousness with pain control. Potassium and magnesium deficiencies were treated as necessary to maintain electrolyte balance within the normal range. Perioperative need for blood products was determined on an individual, patient-by-patient basis. In general, homologous red cells were given intraoperatively to maintain a haemoglobin concentration >7 g/dl, or a haematocrit (Htc) >20% during cardio-pulmonary bypass, or given postoperatively when haemoglobin was <8 g/dl. Additional blood product transfusions were, however, at the discretion of the individual surgeon or anaesthesiologist. Units of RBCs transfused were documented from the blood bank databases, and any RBC transfusion versus none was the a priori exposure of interest. At the end of surgery, patients were transferred to a dedicated ICU and managed according to the unit protocol [1, 13].

**Outcome end-points and their definition criteria**

The present study is a retrospective, observational, multicentre cohort study of prospectively collected data from consecutive patients. The primary outcome end-point of this study was stroke and combined stroke/TIA. Postoperative stroke was defined as any new persistent neurological deficit on physical examination, tomographic scan or magnetic resonance imaging, while TIA as any new transient neurological deficit [6–8]. Stroke and TIA were confirmed by independent neurologists. In patients with a previous history of cerebrovascular events, new stroke and TIA were diagnosed if they developed new neurological clinical and radiological deficits [6–8].

**Statistical analysis**

Statistical analysis was computed using SPSS v. 22.0 statistical software (IBM SPSS, Inc., Chicago, IL, USA). No attempt to replace missing values was made. Group differences were evaluated by the Mann–Whitney U-, Pearson’s χ2 and Fisher’s exact tests. Logistic regression was performed to identify independent predictors of postoperative cerebrovascular events. Only variables with a P < 0.05 at univariate analysis were included in the regression models in order to avoid overfitting. The model was calibrated by the Hosmer–Lemeshow goodness-of-fit test as well as residual diagnostics (deviance and dfBetas). Model discrimination was evaluated by using the area under the receiver-operating characteristic (ROC) curve. Ordinal regression including all available pre- and perioperative variables was used to estimate the multilevel propensity score of being assigned to one of the seven main study groups, i.e. patients who received none to ≥6 units of RBCs. The obtained six propensity scores were employed as covariates for adjusted analysis in the logistic regression. Adjusted analysis was performed also by considering the seven classes of the transfused RBC units along with all risk factors, which were independent predictors of stroke and stroke/TIA. All tests were two-sided with the α level set at 0.05 for statistical significance.

**RESULTS**

Baseline and operative characteristics of 14 956 patients are presented in Table 1. Hospital mortality was observed in 307 (2.1%) patients, stroke in 147 (1.0%) and combined stroke/TIA in 238 (1.6%). The incidence of cerebrovascular complications significantly differed between institutions (Bristol Heart Institute, UK: stroke rate 0.6%, stroke/TIA 1.2%; Varese University Hospital: stroke 1.5%, stroke/TIA 2.5%; Centro Cardiologico Monzino IRCCS, Italy: stroke 1.3%, stroke/TIA 1.6%), but these were rather low in all participating centres.

Of the total population, 6419 (43%) patients received RBC transfusions, of whom 786 (12%) received ≥6 RBC units. The mean number of transfused RBC units was 1.3 ± 2.4 RBC units (among transfused patients: mean 3.1 ± 2.9, median, 2 RBC units: 25th–75th percentile, 2–4 units). Patients receiving RBC transfusions were older (69.2 ± 9.8 vs 64.6 ± 10.4, P < 0.001), with a lower left ventricular ejection fraction (54.5 ± 12.0 vs 56.1 ± 10.9, P < 0.001)
and a more severe profile of comorbidities (additive EuroSCORE: 5.8 ± 3.2 vs 3.6 ± 2.6, P < 0.001). They also had lower preoperative haemoglobin levels (12.6 ± 1.8 vs 14.0 ± 1.5, P < 0.001) and underwent more frequently an emergency operation (6.9 vs 2.1%, P < 0.001). Patients receiving RBC transfusions when compared with patients not transfused had a higher incidence of stroke (1.6 vs 0.5%, P < 0.001) and stroke/TIA 2.6 vs 0.8%, P < 0.001), along with a higher hospital mortality (3.9 vs 0.6%, P < 0.001). The incidence of neurological complications increased along with the number of transfused RBC units (Fig. 1). Furthermore, transfused patients had a longer ICU stay [48 h (25th–75th percentile: 24–72 h) vs 24 h (25th–75th percentile: 24–48 h), P < 0.001] and length of hospital stay [8 days (25th–75th percentile: 7–11 days) vs 7 days (25th–75th percentile: 6–8 days), P < 0.001].

### Multivariate analysis

Logistic regression showed that RBC transfusion was an independent predictor of postoperative stroke [Hosmer–Lemeshow’s test: P = 0.185, area under the ROC curve: 0.75; 95% confidence interval (CI) 0.71–0.79, Table 2]. When included in the same regression model as a continuous variable, RBC transfusion was associated with an odds ratio (OR) of 1.14 (95% CI 1.11–1.17) per unit. Peripheral vascular disease, prior cerebrovascular event, type of procedure, use of cardiopulmonary bypass and preoperative use of intra-aortic balloon pump (IABP) were other independent predictors of postoperative stroke (Table 2). RBC transfusion was an independent predictor also of postoperative stroke/TIA (Hosmer–Lemeshow’s test: P = 0.319, area under the ROC curve: 0.76; 95% CI 0.73–0.79, Table 2). When included in the same regression model as a continuous variable, RBC transfusion was associated with an OR of 1.12 (95% CI 1.09–1.15) per unit. Patient’s age, peripheral vascular disease, prior cerebrovascular event, type of procedure, use of cardiopulmonary bypass, postoperative atrial fibrillation and preoperative IABP use were other independent predictors of postoperative stroke/TIA (Table 3).

There was a significant correlation between preoperative haemoglobin level and the amount of RBC transfusions (Spearman rho: −0.398, P < 0.001). However, multivariate analysis adjusted for other

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**Table 1**: Baseline characteristics and operative variables and their impact on postoperative neurological events on univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>No. (%)</th>
<th>Stroke</th>
<th>P-value</th>
<th>Stroke/TIA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66.6 ± 10.4</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>Female gender</td>
<td>4052 (27.2)</td>
<td>0.001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>3101 (20.8)</td>
<td>0.054</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>1018 (6.8)</td>
<td>0.050</td>
<td>0.080</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1658 (11.1)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1140 (7.7)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>Prior myocardial infarction</td>
<td>5085 (34.1)</td>
<td>0.075</td>
<td>0.012</td>
<td></td>
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<tr>
<td>Prior cardiac surgery</td>
<td>724 (4.9)</td>
<td>0.001</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>66 ± 18</td>
<td>0.011</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>78 (0.5)</td>
<td>0.791</td>
<td>0.824</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td>608 (4.1)</td>
<td>0.012</td>
<td>0.001</td>
<td></td>
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</tr>
<tr>
<td>Preoperative IABP</td>
<td>157 (1.1)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>Left ventricular ejection fraction</td>
<td>3470 (23.3)</td>
<td>0.025</td>
<td>0.001</td>
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<td>30–50%</td>
<td>529 (3.5)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Type of operation</td>
<td></td>
<td></td>
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<tr>
<td>Isolated CABG</td>
<td>9341 (62.6)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
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<tr>
<td>Isolated valve procedure</td>
<td>3796 (25.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG plus valve procedure</td>
<td>1786 (12.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>OPCAB</td>
<td>3612 (24.2)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC transfusion</td>
<td>6419 (43.0)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive EuroSCORE</td>
<td>4.5 ± 3.0</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

Nominal variables are reported as counts and percentages (in parentheses); continuous variables are reported as the mean ± standard deviation. P-values are from univariate analysis. IABP: intra-aortic balloon pump; eGFR: estimated glomerular filtration rate; CABG: coronary artery bypass grafting; OPCAB: off-pump coronary surgery; RBC: red blood cell; TIA: transient ischaemic attack.
Multilevel propensity score-adjusted analysis

Propensity scores were estimated by ordinal regression (14 793 patients included in the analysis). Multivariate analysis adjusted for these propensity scores showed that the risk of stroke and stroke/TIA was significant in patients receiving >2 units of RBCs (Table 4). The risk of stroke (3.9%; OR 3.85; 95% CI 2.30–6.45) and stroke/TIA (5.9%; OR 3.30; 95% CI 2.17–5.02) was particularly high among patients who received ≥6 units of RBCs (Table 4). When participating centres were included in multivariate analysis, this was not associated with a significantly different risk of stroke (P = 0.804) or stroke/TIA (P = 0.204), but RBC transfusion was still an independent predictor of such cerebrovascular complications.

**DISCUSSION**

Cerebrovascular events are vexing complications of cardiac surgery [14]. Although several studies have attempted to determine aetiological factors in their pathogenesis, stroke and TIA are the consequence of an interplay of different pathophysiological mechanisms, mainly including embolic events and circulatory disturbances as hazards of surgical manipulation, use of cardiopulmonary bypass and perioperative arrhythmic events [14].

However, recent evidence also suggest an adverse neurological impact exerted by RBC transfusions in patients undergoing cardiac surgery [5–8]. Karkouti et al. [6], investigating the morbidity role of low Htc during cardiopulmonary bypass, observed an independent association between the amount of RBC transfusions and the development of postoperative stroke. Paone et al. [5] recently observed an increased risk of stroke even after a transfusion of as little as 1 or 2 RBC units. Koch et al. [15] highlighted a dose-response effect between the transfused amount of RBCs and postoperative morbidity, including neurological complications (OR, 1.37/unit).

Our study strongly corroborated this negative impact of RBC transfusion, demonstrating a striking association between excessive amount of RBC transfusions with the development of postoperative neurological complications. Patients receiving RBC transfusions revealed a three- to four-fold increased risk of postoperative stroke or TIA, and this negative effect was independent of typical predictors for stroke (peripheral vascular disease and prior cerebrovascular disease) or type of surgical procedures even when adjusted by the multilevel propensity score. The use of 1–2 RBC units was also associated with a slightly higher risk of
neurological complications, even if such a difference failed to reach statistical significance (Table 4).

Although the specific mechanisms for these neurological events associated with RBC transfusion have not yet been clearly identified, the most plausible ones include impairment of oxygen delivery at the cellular level, prothrombotic events promoted by morphological abnormalities of packed RBCs and release of deleterious substances from these cells [9–12].

Packed RBCs are commonly transfused aimed at increasing oxygen delivery to tissues, although, during their storage, morphological and biochemical changes adversely affect this ability [9–12, 16–18]. Depletion of 2,3-diphosphoglycerate enhances haemoglobin affinity, and shifting the oxyhaemoglobin dissociation curve to the left reduces RBC ability to unload oxygen to the cellular level [16]. In addition, the combination with anaemia due to surgical blood loss and cardiopulmonary bypass-related haemodilution exacerbates hypoperfusion, favouring cerebral injury [6, 7]. This anaemia-transfusion interaction has been recently demonstrated to considerably contribute to stroke after cardiac operations [2, 4–7]. Loor et al. [2], in 9942 patients undergoing surgical procedures requiring cardiopulmonary bypass, observed that neurological complications occurred in 2.3% of patients with exposure to both anaemia (Htc <25%) and intraoperative RBC transfusion, compared with 1% for those without anaemia (Htc ≥25) and with no transfusion. Interestingly, patients without anaemia (Htc ≥25) who received RBC transfusions had a neurological complication rate of 1.6%, thus suggesting that blood transfusions may independently contribute to postoperative neurological complications [2].

Packed RBCs also present morphological deteriorations with reduced ability to transverse the microcirculatory bed, favouring thrombotic phenomena because of the consequent increased adhesiveness and aggregability in the microvascular blood flow [9, 10]. In addition, stored RBCs present lower adenosine triphosphate (ATP) levels with an impaired ability to release it in the microcirculation, therefore preventing the potent ATP-related vasodilatory effect [18]. The high free haemoglobin concentrations measured in stored blood may further affect microcirculation because free haemoglobin has a strong NO scavenging ability, inducing vasoconstriction and worsening these mechanisms for these neurological events [12]. The above-mentioned changes occurring during RBC storage, referred to as ‘storage lesions’, are especially evident when RBCs have been stored for more than 14 days [19].

Finally, RBC transfusions elicit an inflammatory response by direct infusion of inflammatory mediators, and inflammation has been clearly demonstrated to contribute to neuronal injury [20, 21]. These processes are further amplified by the intense inflammatory response registered during surgical trauma, use of cardiopulmonary bypass and haemodilution itself [20, 21]. Leucocyte migration occurring as a result of inflammatory cell activation and increased adhesion molecule expression, results in transmigration of activated leucocytes into specific organs, including the brain [22].

Interestingly, in the present study, preoperative anaemia was not associated with an increased risk of neurological complications. This observation is in consonance with previous studies, although preoperative anaemia has been repeatedly associated with an increased hazard of other postoperative complications and mortality [3, 4]. Mikkola et al. [8], in a Finnish multicentre registry, did not observe a significant association between preoperative anaemia and the risk of stroke after CABG, a finding confirmed by Karkouti et al. [4]. It remains distinctly possible that the potential negative effect of preoperative anaemia on cerebral function due to the unavoidable cerebral hypoperfusion could have been overcome by the stronger negative effect of RBC transfusions and other complex events that occur during cardiac operations such as haemodilution with the consequent low postoperative Htc. As a matter of fact, Bahrainwala et al. [7] did not observe a significant impact of preoperative anaemia on the risk of postoperative stroke, whereas an independent prognostic effect of postoperative haemoglobin levels along with intraoperative RBC transfusions was detected. In addition, even the poorly defined data on the cause or duration of preoperative anaemia could have been contributed to confound its detrimental neurological impact, and preoperative haemoglobin levels have been demonstrated to have relevant prognostic implications on postoperative outcome [4].

There are a number of limitations associated with the present study. Firstly, this is an observational study with possible confounding effects and unmeasured factors affecting the role of RBC transfusions on neurological complications. Data on the temporal relationship between RBC transfusion and neurological event occurrence were not available in the present registry, a limitation shared with other similar studies [1–6]. Furthermore, we do not have data on intra- and postoperative levels of haemoglobin or Htc, which could have clarified their possible interaction with RBC transfusions, and also confirm the independent role of blood transfusion on cerebral events. However, the relationship between Htc and perioperative morbidity had conflicting results with respect to stroke [4, 23, 24]. Van Wermeskerken et al. [23] first addressed the above-mentioned issue by enrolling 2862 CABG patients, demonstrating no evidence that the lowest Htc was associated with major adverse neurological outcomes. DeFoe et al. [24] subsequently confirmed that Htc had no impact on intra- and postoperative stroke in a consecutive multicentre series of 6980 CABG patients. In addition, our database does not account for fresh frozen plasma (FFP) or aprotinin data, preventing further analyses on the impact of this blood product on cerebrovascular complications. However, several studies investigating the role of blood product transfusion in patient outcome have not entered FFP in the analysis, and patients receiving multiple RBC transfusions often receive FFP transfusions as well [1–7, 15, 20–25]. Whether plasma transfusions contribute to postoperative complications or are just a surrogate marker for the need for a higher number of RBC transfusions is unknown. As a matter of fact, previous retrospective studies yielded conflicting results concerning the association between plasma transfusions and outcome in cardiac surgery. Similarly, our study did not investigate the potential role of aprotinin in neurological outcome following cardiac surgery, although its use was limited to the very early phase of the study and its neurological effect reveal controversial results. Finally, we do not have data on the duration of RBC storage, although the effect of RBC age on adverse events has been questioned [25].

In conclusion, the present study adds further evidence on the detrimental role of RBC transfusion in the development of stroke and TIA after cardiac surgery. Although the mechanisms underlying the development of cerebrovascular complications after RBC transfusion are still elusive, the present findings strengthen the importance of optimizing haemoglobin levels before surgery and of avoiding significant perioperative bleeding in order to reduce the risk of stroke and TIA after cardiac surgery.

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