

# Transfusion Requirements After Cardiac Surgery

## The TRACS Randomized Controlled Trial

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CARDIAC SURGERY IS ASSOCIATED with a high rate of allogeneic blood transfusion, varying from 40% to 90% in most reports.<sup>1-3</sup> The rationale for perioperative red blood cell (RBC) transfusion is based on the observation that anemia is an independent risk factor for morbidity and mortality after cardiac operations.<sup>4,5</sup> However, transfusions have been associated with high rates of morbidity and mortality in critically ill patients,<sup>6</sup> and some recent studies have shown worse outcomes, including increased occurrence of renal failure and infection, as well as respiratory, car-

**Context** Perioperative red blood cell transfusion is commonly used to address anemia, an independent risk factor for morbidity and mortality after cardiac operations; however, evidence regarding optimal blood transfusion practice in patients undergoing cardiac surgery is lacking.

**Objective** To define whether a restrictive perioperative red blood cell transfusion strategy is as safe as a liberal strategy in patients undergoing elective cardiac surgery.

**Design, Setting, and Patients** The Transfusion Requirements After Cardiac Surgery (TRACS) study, a prospective, randomized, controlled clinical noninferiority trial conducted between February 2009 and February 2010 in an intensive care unit at a university hospital cardiac surgery referral center in Brazil. Consecutive adult patients (n=502) who underwent cardiac surgery with cardiopulmonary bypass were eligible; analysis was by intention-to-treat.

**Intervention** Patients were randomly assigned to a liberal strategy of blood transfusion (to maintain a hematocrit  $\geq 30\%$ ) or to a restrictive strategy (hematocrit  $\geq 24\%$ ).

**Main Outcome Measure** Composite end point of 30-day all-cause mortality and severe morbidity (cardiogenic shock, acute respiratory distress syndrome, or acute renal injury requiring dialysis or hemofiltration) occurring during the hospital stay. The noninferiority margin was predefined at  $-8\%$  (ie, 8% minimal clinically important increase in occurrence of the composite end point).

**Results** Hemoglobin concentrations were maintained at a mean of 10.5 g/dL (95% confidence interval [CI], 10.4-10.6) in the liberal-strategy group and 9.1 g/dL (95% CI, 9.0-9.2) in the restrictive-strategy group ( $P < .001$ ). A total of 198 of 253 patients (78%) in the liberal-strategy group and 118 of 249 (47%) in the restrictive-strategy group received a blood transfusion ( $P < .001$ ). Occurrence of the primary end point was similar between groups (10% liberal vs 11% restrictive; between-group difference, 1% [95% CI,  $-6\%$  to  $4\%$ ];  $P = .85$ ). Independent of transfusion strategy, the number of transfused red blood cell units was an independent risk factor for clinical complications or death at 30 days (hazard ratio for each additional unit transfused, 1.2 [95% CI, 1.1-1.4];  $P = .002$ ).

**Conclusion** Among patients undergoing cardiac surgery, the use of a restrictive perioperative transfusion strategy compared with a more liberal strategy resulted in noninferior rates of the combined outcome of 30-day all-cause mortality and severe morbidity.

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diac, and neurologic complications, in transfused compared with nontransfused patients after cardiac surgery.<sup>7,8</sup>

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There is a lack of evidence regarding optimal blood transfusion practice in patients undergoing cardiac surgery.<sup>9</sup> On

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the basis of past clinical observations, some authors have suggested that hematocrit should be maintained at around 30% and hemoglobin concentration at 10 g/dL.<sup>10</sup> Recently, however, this hemoglobin threshold has been reconsidered because of recognized risks associated with transfusion and greater appreciation of the importance of individual physiological responses to anemia.<sup>11</sup> In a comparative trial of 428 patients undergoing elective coronary artery bypass graft (CABG) surgery, Bracey et al reported that reducing the hemoglobin trigger to 8 g/dL did not adversely affect patient outcomes and resulted in lower costs.<sup>12</sup>

An important multicenter Canadian study by Hébert et al that included a large number of critically ill patients (but not those undergoing cardiac surgical procedures) revealed that a restrictive transfusion strategy (hemoglobin concentration maintained between 7.0 and 9.0 g/dL) may be superior to a liberal strategy (hemoglobin concentration between 10 and 12 g/dL) in terms of reducing organ dysfunction and mortality.<sup>13</sup> There currently are no data from prospective randomized trials to guide transfusion decisions in patients undergoing cardiac surgery. We therefore conducted the Transfusion Requirements After Cardiac Surgery (TRACS) study, a prospective, randomized, controlled clinical trial to elucidate whether a restrictive perioperative strategy of RBC transfusion was as safe as a liberal strategy in patients undergoing elective cardiac surgery.

## METHODS

### Study Design and Treatment Strategies

The TRACS study was designed as a prospective, randomized, noninferiority controlled trial. Consecutive patients scheduled for elective cardiac surgery with cardiopulmonary bypass at the Heart Institute of the University of São Paulo, São Paulo, Brazil, between February 9, 2009, and February 1, 2010, were enrolled. We included patients who were undergoing CABG surgery or cardiac valve replacement or repair, alone or in combination. Patients were excluded for any of the following reasons: younger than 18 years; surgery without cardiopulmonary bypass; emergency procedure; ascending and de-

scending thoracic aortic procedures; left ventricular aneurysm resection; inability to receive blood products; enrollment in another study; chronic anemia (preoperative hemoglobin concentration less than 10 g/dL); low platelet count (preoperative platelet count less than  $150 \times 10^3/\mu\text{L}$ ); coagulopathy (previous history or prothrombin time longer than 14.8 seconds); pregnancy; neoplasm; endocarditis; congenital heart defect; hepatic dysfunction (total bilirubin value higher than 1.5 mg/dL [to convert to  $\mu\text{mol/L}$ , multiply by 17.104]); end-stage renal disease (receiving chronic dialysis therapy); and refusal to consent.

The study was approved by the Heart Institute Ethics Committee, Clinics Hospital, University of São Paulo, and written informed consent was obtained from all patients before enrollment.

Patients were randomly assigned to a liberal or a restrictive transfusion strategy. Opaque envelopes arranged using a random-number table were prepared by the chief statistician and opened sequentially to determine the patient's treatment group. The research coordinator enrolled the participants and obtained informed consent. Information about the treatment strategy was given to the anesthesiologist and to health care workers in the intensive care unit (ICU). The patient and outcome assessors were blinded to group assignment.

Transfusion triggers for the study groups were determined from information obtained from previous studies that showed that hematocrit values as low as 22% are safe in cardiac surgery with cardiopulmonary bypass.<sup>14,15</sup> Patients assigned to the liberal-strategy group received RBC transfusions if the hematocrit was less than 30% at any time from the start of surgery until discharge from the ICU. Patients assigned to the restrictive-strategy group received RBC transfusions if hematocrit values were less than 24%.

Physicians were instructed to administer transfusions one unit at a time and to measure hematocrit after each transfused unit. In both groups, no further units were given if the goal hematocrit was obtained (24% for the restrictive strategy and 30% for the liberal strat-

egy). Hematocrit levels were measured at least 3 times in the operating room and twice daily in the ICU for each patient. Attending physicians could administer RBC transfusions outside the rules of the protocol if they considered the patient's status to be life-threatening, as in hemorrhagic or other forms of circulatory shock; such an event was considered a protocol deviation. Patients were analyzed in their originally assigned groups on an intention-to-treat basis.

At the Heart Institute, RBCs are separated from whole blood and stored in a citrate solution without leukodepletion. The volume of an RBC unit ranges from 250 to 350 mL, with a hematocrit of 80%. In our hospital, blood bank policy is to use blood with short-duration storage in patients undergoing cardiac surgery.

### Surgical Procedure and ICU Admission

Preoperative medication consisted of midazolam (0.1 to 0.2 mg/kg given orally 30 minutes before surgery). Anesthesia was induced with fentanyl (3–5  $\mu\text{g/kg}$ ), midazolam (0.05 mg/kg), etomidate (0.2–0.3 mg/kg), and pancuronium bromide (0.1 mg/kg). Anesthesia was maintained with isoflurane in oxygen and fentanyl as needed. During cardiopulmonary bypass, additional doses of midazolam and pancuronium were administered as required. All patients were monitored with an arterial and central venous catheter; some also received a pulmonary artery catheter. After tracheal intubation, all patients received invasive mechanical ventilation with intermittent positive pressure with a tidal volume of 8 mL/kg, positive end-expiratory pressure of 5 to 8 cm H<sub>2</sub>O, and fraction of inspired oxygen of 0.6 to 1 to keep arterial oxygen saturation above 95%. Nitroglycerin and sodium nitroprusside were administered intravenously as vasodilators, dobutamine as an inotrope, and norepinephrine and epinephrine as vasopressors. In all patients, blood glucose levels were kept below 160 mg/dL (to convert to mmol/L, multiply by 0.0555), using continuous intravenous insulin if needed. Methylprednisolone (10 mg/kg) and cefurox-

ime (750 mg) were administered intravenously at induction of anesthesia. All surgical procedures were undertaken through a median sternotomy.

In all patients, clopidogrel and oral anticoagulants were stopped at least 5 days before surgery. All patients received 5 g of  $\epsilon$ -aminocaproic acid, an antifibrinolytic, at induction of anesthesia and an additional 1 g/h until the end of surgery. Anticoagulation was established with an initial dose of 500 IU/kg of heparin injected into the central venous line before initiation of bypass, with a target activated clotting time of 480 seconds. Additional heparin was given intermittently to titrate clotting times during bypass. At the end of bypass, heparin was reversed by protamine chloride in a 1:1 ratio, with additional protamine given as required to return the activated clotting time to preoperative values. A coagulation profile and platelet count were obtained after heparin reversal. Significant intraoperative bleeding associated with platelet disorders or coagulopathy could be treated using platelets, fresh frozen plasma, or cryoprecipitate. Surgeons performed a hemostasis review. Cell salvage was not used.

A centrifugal pump (Medtronic Biomedicus; Medtronic, Minneapolis, Minnesota) was used for bypass. An extracorporeal circuit containing a microporous polypropylene membrane oxygenator (Braile; São José do Rio Preto, São Paulo, Brazil) with an integrated venous cardiotomy reservoir was used. The oxygenator was primed with 1500 mL of lactated Ringer solution, 20% (1 g/kg) mannitol, and 2500 units of unfractionated heparin. During bypass, a mild hypothermic temperature management strategy (32°C to 34°C) with  $\alpha$ -stat blood gas management was used in all patients. During bypass, nonpulsatile flow was maintained at 2.0 to 2.4 L/min per square meter, and mean arterial pressure varied from 60 to 90 mm Hg. Myocardial preservation was achieved by intermittent antegrade cold crystalloid cardioplegia. Cardioplegia was repeated every 30 minutes during the cross-clamping period. Fluid manage-

ment was accomplished with lactated Ringer solution and adjusted according to filling pressures, diuresis, and cardiac output. Albumin or hydroxyethyl starch (130/0.4) could be administered if considered necessary.

Patients were transferred to the ICU before recovery from anesthesia while still receiving mechanical ventilation. Patients were weaned from the ventilator after exhibiting complete recovery from anesthesia, hemodynamic stability with no evidence of significant bleeding, core temperature higher than 36°C, and adequate blood gas values. Patients were discharged from the ICU on the second postoperative day if they met institutional discharge criteria.

### Baseline Assessment and Data Collection

At the time of randomization, demographic and clinical data as well as the information needed to calculate the predicted risk of surgery using the standard EuroSCORE (European System for Cardiac Operative Risk Evaluation)<sup>16</sup> were obtained for each patient. Preoperative laboratory values, collected up to 48 hours before surgery, were recorded and included hemoglobin, hematocrit, prothrombin time, activated partial thromboplastin time, creatinine level, bilirubin level, and platelet counts.

During surgery, hemoglobin levels and hematocrit were measured at baseline (just after induction of anesthesia), during bypass, and at the end of the procedure. Central venous oxygen saturation (ScvO<sub>2</sub>) and lactate concentration were measured at the beginning and end of the procedure. Information was also collected on the type of surgical procedure, number and type of grafts used, duration of bypass, duration of cross-clamping, number of RBC units transfused, administration of other blood products, amount and type of fluids administered, and clinically important events such as bleeding or hemodynamic instability.

During the ICU stay, clinical data were collected daily by 2 blinded assessors, both trained physicians with more than 3 years' experience caring for

patients in the cardiac ICU. Hemoglobin and hematocrit were measured every 12 hours until ICU discharge. Levels of serum creatinine, creatine kinase MB, troponin, electrolytes, lactate, blood gases, and bilirubin were measured once daily. Clinical and laboratory data for the Simplified Acute Physiology Score II<sup>17</sup> and for the Acute Physiology and Chronic Health Evaluation II score<sup>18</sup> were recorded using the worst value within the first 24 hours after ICU admission. Data were also recorded regarding hemodynamic status, need for vasoactive drugs and other medications, need for mechanical ventilation, need for dialysis, and other forms of organ dysfunction. During the hospital stay, data were collected regarding the use of RBC transfusion, hematocrit goals, and complications. After discharge from the ICU, clinical outcomes were evaluated on the regular ward, still in a blinded fashion.

Respiratory complications were defined as prolonged need for mechanical ventilation (>48 hours) and development of pneumonia or acute respiratory distress syndrome (ARDS) defined by standard criteria.<sup>19</sup> Pneumonia was diagnosed if the patient had a new, persistent, or progressive lung infiltrate on chest radiograph and if at least 2 of the following criteria were present: temperature 38°C or greater, leukocytosis greater than 12 000 cells/ $\mu$ L or leukopenia less than 3000 cells/ $\mu$ L, or purulent endotracheal secretions with a Gram stain showing more than 25 neutrophils and fewer than 10 epithelial cells per field.<sup>20</sup> In patients receiving mechanical ventilation and with clinical suspicion of nosocomial pneumonia, bronchial secretions for cultures were obtained with a protected pulmonary specimen brush introduced by fiberoptic bronchoscopy through the endotracheal tube.

Cardiac complications included cardiogenic shock, tachyarrhythmia, or perioperative cardiac ischemia. Cardiogenic shock was defined as the presence of tachycardia, hypotension, and poor perfusion associated with ScvO<sub>2</sub> less than 65% or metabolic acidosis (de-

crease in base deficit  $>4$ ) or an increase in lactate level ( $>18.02$  mg/dL [to convert to mmol/L, multiply by 0.111]) in the absence of a cause other than heart failure.<sup>21</sup> An electrocardiogram was performed twice daily during the ICU stay and once daily on the regular ward. Perioperative cardiac ischemia was considered if creatine kinase MB level was elevated to at least 5 times the upper limit of normal ( $>30$  ng/mL), if troponin I values were greater than 5 ng/mL during the first 72 hours, if new pathological Q waves appeared, if coronary artery occlusion was angiographically documented, or if there was imaging evidence of new loss of viable myocardium.<sup>22</sup>

Renal function was evaluated daily using the RIFLE (renal risk, injury, failure, loss, end-stage kidney disease) classification.<sup>23</sup> The need for renal replacement therapy was recorded.

Neurologic complications were diagnosed if the patient presented with delirium (the Confusion Assessment Method in the ICU scale<sup>24</sup> was applied daily) or stroke, which was characterized by a new focal deficit with a compatible image on computed tomography.

Infectious complications included septic shock, defined by standard criteria<sup>25</sup>; mediastinitis, defined as a superficial or deep infection of the sternotomy wound with positive findings on cultures obtained from the wound; and pneumonia as described above. Inflammatory complications were diagnosed if the patient had vasodilatory shock, associated with a cardiac index greater than 4.0 L/min per square meter. Bleeding was defined as clinically important when blood loss exceeded 100 to 300 mL/h after ICU admission and patients needed reoperation.<sup>26</sup> Operative mortality was considered as death from all causes in the 30 days after surgery. Telephone contact was used to evaluate this outcome.

### Outcome Measures

The primary outcome was a composite end point that included 30-day all cause mortality and severe morbidity (cardiogenic shock, ARDS, or acute renal injury requiring dialysis or hemo-

filtration) occurring during the hospital stay. These clinical complications were selected because of the established association between these complications and blood transfusion and their known association with mortality.<sup>5,9,12,13</sup> Secondary outcomes included all respiratory, cardiac, neurologic, and infectious complications; inflammatory complications; bleeding requiring reoperation; and ICU and hospital lengths of stay. We also evaluated the incidence of RBC transfusions and the number of units transfused, predictive factors for RBC transfusions, and the effects of transfusion on patient outcomes.

### Statistical Analysis

This was a noninferiority trial, and we estimated a 10% incidence of the primary outcome.<sup>12,13</sup> Based on previous studies,<sup>12,13</sup> we predicted there would be no difference between groups for the primary outcome event rate and set the noninferiority margin at  $-8\%$  (minimal clinically important difference of  $8\%$ ). To obtain 90% statistical power with a 1-sided  $\alpha = .05$ , at least 482 patients needed to be enrolled. Considering the probability of subject attrition, we added 6% to the sample size, yielding a final required number of 512 patients. An interim analysis was conducted by the monitoring committee after 250 patients had been enrolled, and the monitoring board advised that the trial should be continued.

We compared baseline characteristics, follow-up measures, and clinical outcomes on an intention-to-treat basis according to the randomized study group assignment. Continuous variables were compared using a *t* test or Mann-Whitney U test and categorical variables using Pearson  $\chi^2$  or Fisher exact or likelihood ratio test. Logarithmic transformation was performed to normalize the distribution of variables so parametric tests could be used. Comparisons of hemoglobin concentration over time were made using analysis of variance with repeated measures, followed by the least-squares difference test to discriminate differences.

Results are expressed as means with 95% confidence intervals (CIs) or medians with interquartile ranges (IQRs). A multiple logistic regression analysis was performed to estimate predictive factors for primary and secondary outcomes and predictive factors for red blood cell transfusion, including variables significant in the univariate model, ie, age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), comorbid conditions, left ventricular ejection fraction and EuroSCORE, type of surgery, duration of cardiopulmonary bypass, initial and final hemoglobin level, hematocrit, lactate concentration,  $ScVO_2$ , and number of RBC units transfused. We calculated unadjusted 30-day Kaplan-Meier survival estimates, dividing patients by transfusion strategy and by number of transfused RBC units, using a log-rank test. To determine the risk of death at 30 days according to the number of transfused RBC units, we built a multivariate Cox proportional hazard model in the overall population with death as the dependent factor, using the variables above.

A 1-sided *P* value less than .05 was considered statistically significant. Statistical analyses were performed using SPSS version 18.0 (SPSS Inc, Chicago, Illinois).

## RESULTS

### Study Population

A total of 1765 patients were assessed for eligibility (FIGURE 1). After exclusions for various medical reasons and lack of consent, 512 patients were enrolled in the study: 257 assigned to the liberal transfusion strategy group and 255 to the restrictive transfusion strategy group. Of these, 10 patients (1.9%) (4 in the liberal-strategy group and 6 in the restrictive-strategy group) were excluded after consent because surgery was performed without cardiopulmonary bypass, leaving 502 (253 in the liberal-strategy group and 249 in the restrictive-strategy group) in the intention-to-treat analysis. In the liberal-strategy group, there were no cases of protocol deviation. Four of the pa-



tients in the restrictive-strategy group were considered to have deviated from protocol because they received 1 RBC unit outside the protocol trigger to address hemodynamic instability.

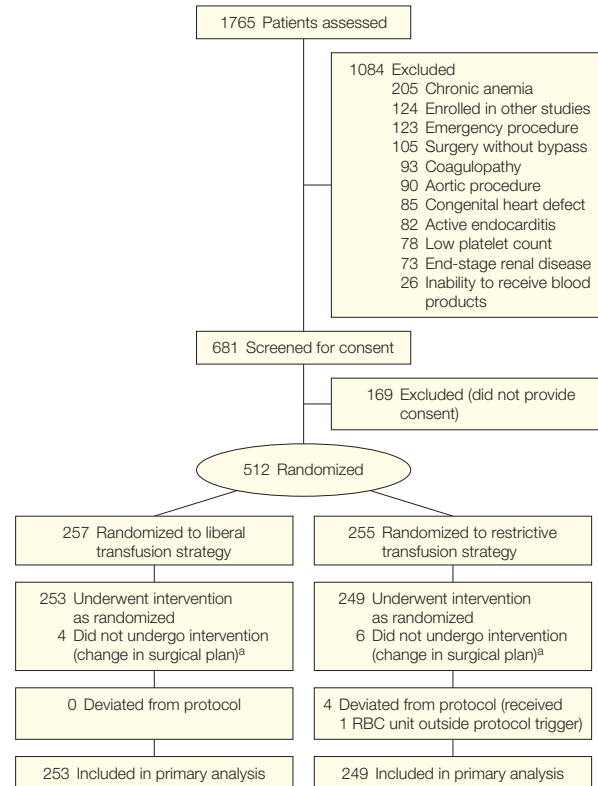
Baseline characteristics were well balanced between the study groups (TABLE). Hemoglobin concentrations at the time of randomization were similar in the liberal- and restrictive-strategy groups (mean, 13.1 g/dL [SD, 1.6] vs 13.4 g/dL [SD, 1.8],  $P=.18$ ). Procedure-related variables in the intraoperative period were similar between groups, with the exception of RBC transfusion (eTable 1, available at <http://www.jama.com>).

### Intervention

Hemoglobin concentrations were significantly higher in the liberal-strategy group than in the restrictive-strategy group intraoperatively (final hemoglobin level), immediately postoperatively, and at days 1, 2, 3, and 7 after ICU admission (FIGURE 2). The mean hemoglobin concentrations were 10.5 g/dL (95% CI, 10.4-10.6) in the liberal-strategy group and 9.1 g/dL (95% CI, 9.0-9.2) in the restrictive-strategy group ( $P<.001$ ). Hematocrit concentrations were maintained above or at the threshold for 95% of the time; overall average hematocrit values in the ICU were 31.8% (95% CI, 31.5%-32.1%) in the liberal-strategy group and 28.4% (95% CI, 27.9%-28.9%) in the restrictive-strategy group ( $P<.001$ ).

As expected, more patients in the liberal-strategy group received a blood transfusion than in the restrictive-strategy group (78% vs 47%,  $P<.001$ ). The total number of transfused RBC units was 613 in the liberal-strategy group and 258 in the restrictive-strategy group ( $P<.001$ ). Most transfusions were given in the operating room or in the first 3 days after surgery. The liberal-strategy group received a median of 2 RBC units (IQR, 1-3), while the restrictive-strategy group received a median of 0 RBC units (IQR, 0-2) ( $P<.001$ ) (eFigure 1). There was no difference in the median storage age of RBC units between the liberal- vs restrictive-strategy

**Figure 1. Study Flow**



RBC indicates red blood cell.

<sup>a</sup>Patients excluded after consent because of a change in surgical plan such that surgery was performed without cardiopulmonary bypass.

groups (median, 3 [IQR, 2-3] vs 3 [IQR, 2-3] days;  $P=.28$ ). During the hospital stay, there were no differences between the groups in the use of fresh frozen plasma (27% [95% CI, 16%-26%] vs 21% [95% CI, 13%-22%],  $P=.11$ ), platelets (10% [95% CI, 3%-9%] vs 9% [95% CI, 4%-10%],  $P=.92$ ), or cryoprecipitate (4% [95% CI, 1%-4%] vs 4% [95% CI, 0%-4%],  $P=.97$ ).

### Outcome Measures

The primary composite end point—all-cause 30-day mortality, cardiogenic shock, ARDS, or acute renal injury requiring dialysis or hemofiltration during the hospital stay—occurred in 10% (95% CI, 6%-13%) of patients in the liberal-strategy group and in 11% (95% CI, 7%-15%) in the restrictive-strategy group (between-group difference, 1% [95% CI, -6% to 4%];  $P=.85$ )

(eFigure 2). The lower limit of the between-group difference CI is above the -8% predefined noninferiority threshold, confirming the primary hypothesis of noninferiority between the groups. There was no significant difference between the strategies in 30-day mortality rates (5% [95% CI, 2%-7%] vs 6% [95% CI, 3%-9%], respectively;  $P=.93$ ) (FIGURE 3) or rates of cardiogenic shock (5% [95% CI, 2%-7%] vs 9% [95% CI, 5%-12%],  $P=.42$ ), ARDS (1% [95% CI, 0%-2%] vs 2% [95% CI, 0%-4%],  $P=.99$ ), or acute renal failure requiring dialysis or hemofiltration (5% [95% CI, 2%-9%] vs 4% [95% CI, 2%-6%],  $P=.99$ ) (eFigure 2).

There were no significant differences in the occurrence of cardiac complications (21% [95% CI, 16%-26%] vs 24% [95% CI, 18%-29%],  $P=.27$ ), res-

piratory complications (11% [95% CI, 7%-14%] vs 11% [95% CI, 7%-15%],  $P = .82$ ), neurologic complications (6% [95% CI, 3%-9%] vs 6% [95% CI, 3%-9%],  $P = .96$ ), infectious complications (10% [95% CI, 6%-14%] vs 12% [95% CI, 8%-16%],  $P = .58$ ), or severe bleeding requiring reoperation (4% [95% CI, 2%-7%] vs 5% [95% CI, 2%-8%],  $P = .97$ ) (eFigure 2). During the ICU stay, there was no difference between the liberal- and restrictive-strategy groups in mean lactate levels (27.03 mg/dL [95% CI, 26.13-27.93] vs

26.13 mg/dL [95% CI, 24.32-27.93],  $P = .49$ ). There were also no differences in lengths of ICU stay (median, 3 days [IQR, 2-6] vs 3 days [IQR, 2-6];  $P = .94$ ) or hospital stay (median, 9 days [IQR, 7-14] vs 9 days [IQR, 7-15];  $P = .45$ ).

### RBC Transfusion: Predictive Factors and Effects on Outcomes

In total, 316 patients (63%) received an RBC transfusion. Patients who received RBC transfusions were older (mean, 61 years [95% CI, 59.6-62.4] vs 58 years

[95% CI, 55.9-59.2];  $P = .003$ ), more likely to be women (48 vs 22%,  $P < .001$ ), and less likely to be smokers (39% vs 56%,  $P < .001$ ) (eTable 2). They had a lower body mass index (25.8 [95% CI, 25.3-26.3] vs 27 [95% CI, 26.3-27.6],  $P = .004$ ), higher EuroSCORE values (median, 5 [IQR, 3-7] vs 3 [IQR, 2-5];  $P < .001$ ), lower preoperative hemoglobin levels (12.7 g/dL [95% CI, 12.5-12.9] vs 14.2 g/dL [95% CI, 13.9-14.4],  $P < .001$ ) and hematocrit (38.3% [95% CI, 37.8%-38.8%] vs 42.2% [95% CI, 41.6%-42.9%],  $P < .001$ ), longer cardiopulmonary bypass duration (96.4 minutes [95% CI, 93.0-99.9] vs 90.5 minutes [95% CI, 86.5-94.5],  $P = .03$ ), and higher lactate values at the end of surgery (43.24 mg/dL [95% CI, 40.54-45.95] vs 36.94 mg/dL [95% CI, 33.33-39.64],  $P = .003$ ), and more received fresh frozen plasma intraoperatively (24% vs 11%,  $P < .001$ ) (eTable 3). After admission to the ICU, patients who received an RBC transfusion had higher Acute Physiology and Chronic Health Evaluation II scores (9 [95% CI, 8.5-9.5] vs 7.4 [95% CI, 6.9-7.9],  $P < .001$ ) and Simplified Acute Physiology Score II values (21.7 [95% CI, 20.5-22.9] vs 18.6 [95% CI, 17.3-20.0],  $P < .001$ ) compared with those who did not. Patients who received RBC transfusions had longer lengths of ICU stay (median, 4 [IQR, 2-7] days vs 3 [IQR, 2-4] days;  $P < .001$ ) and hospital stay (median, 10 [IQR, 7-17] days vs 8 [IQR, 7-12] days,  $P < .001$ ) compared with nontransfused patients.

In the multivariate model, previous cardiac surgery (odds ratio [OR], 8.92 [95% CI, 1.05-76.1];  $P = .04$ ), female sex (OR, 1.81 [95% CI, 1.03-3.18];  $P = .04$ ), final lactate levels (OR, 1.02 [95% CI, 1.01-1.04];  $P = .001$ ), duration of bypass (OR, 1.01 [95% CI, 1.00-1.02];  $P = .03$ ), and baseline hemoglobin level (OR, 0.51 [95% CI, 0.43-0.62];  $P < .001$ ) were predictive of RBC transfusion (eTable 4).

To determine the effect of the number of transfused RBC units on clinical complications, we performed a multiple logistic regression analysis. The number of transfused RBC units was an independent risk factor for the occur-

**Table.** Baseline Characteristics of Study Patients

Variable	No. (%)		P Value
	Liberal Strategy (n = 253)	Restrictive Strategy (n = 249)	
Age, mean (SD), y	60.7 (12.5)	58.6 (12.5)	.06
Men	161 (64)	149 (60)	.38
Body mass index, mean (SD) <sup>a</sup>	26.1 (4.3)	26.3 (4.4)	.65
Comorbid conditions			
Hypertension	201 (79)	192 (77)	.53
Diabetes	79 (31)	86 (35)	.45
Dyslipidemia	139 (55)	147 (60)	.33
Renal disease	26 (11)	26 (11)	.50
Smoking	34 (14)	38 (16)	.74
COPD	6 (2)	8 (3)	.55
Unstable angina	79 (31)	76 (31)	.87
Previous myocardial infarction	86 (34)	89 (36)	.61
Heart failure, NYHA classification			
I	8 (6)	8 (7)	.50
II	42 (34)	48 (41)	
III	65 (52)	49 (42)	
IV	10 (8)	11 (10)	
LVEF, %			
30-39	32 (13)	37 (15)	.75
40-59	76 (30)	75 (30)	
≥60	145 (57)	137 (55)	
Reoperation	11 (4)	13 (5)	.65
EuroSCORE, median (IQR)	5 (3-6)	4 (3-7)	.07
Preoperative laboratory values, mean (SD)			
Hemoglobin, g/dL	13.1 (1.6)	13.4 (1.8)	.18
Hematocrit, %	39.5 (4.3)	39.9 (5.2)	.65
Prothrombin time, s	11.3 (1.1)	11.3 (2.2)	.54
Platelet count, ×10 <sup>3</sup> /μL	222 (67)	225 (66)	.83
Creatinine level, mg/dL	1.12 (0.4)	1.12 (0.3)	.99
Leukocyte count/μL	7600 (2100)	7700 (2000)	.56
Preoperative drug exposure			
Aspirin	103 (41)	94 (38)	.52
Heparin	3 (1)	2 (1)	>.99

Abbreviations: COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

SI conversion factor: To convert creatinine values to μmol/L, multiply by 88.4.

<sup>a</sup>Calculated as weight in kilograms divided by height in meters squared.

rence of several clinical complications. For each transfused unit, the risk of occurrence increased for respiratory complications (OR, 1.27 [95% CI, 1.12-1.45];  $P < .001$ ), cardiac complications (OR, 1.28 [95% CI, 1.14-1.45];  $P < .001$ ), renal complications (OR, 1.26 [95% CI, 1.08-1.46];  $P = .004$ ), infectious complications (OR, 1.20 [95% CI, 1.05-1.37];  $P = .007$ ), and the composite end point (OR, 1.25 [95% CI, 1.09-1.42];  $P < .001$ ) (eTable 5).

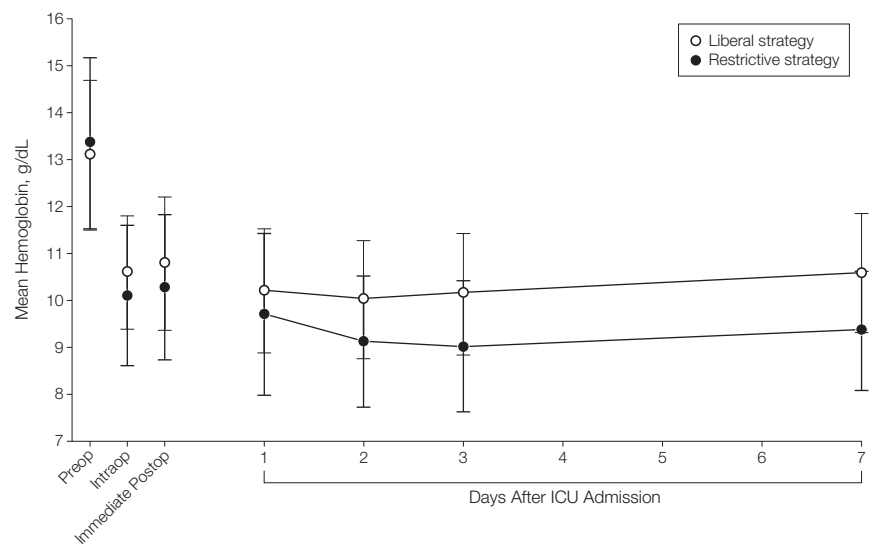
Transfusion of 5 or more RBC units was associated with higher mortality (FIGURE 4). In a multivariate Cox regression analysis that included age and sex, type of surgery, left ventricular ejection fraction, previous cardiac surgery, initial and final operative hemoglobin level and hematocrit, lactate level, and  $ScvO_2$ , the number of transfused RBC units was independently associated with an increased risk of death at 30 days in the entire population (hazard ratio, 1.2 [95% CI, 1.1-1.4];  $P = .002$ ) (eTable 6).

## COMMENT

To our knowledge, this is the first prospective, controlled, randomized clinical trial to compare a liberal with a restrictive transfusion strategy in patients undergoing cardiac surgery. Our data suggest that a restrictive transfusion strategy targeting a hematocrit of 24% is as safe as a liberal strategy targeting a hematocrit of 30%, with respect to a composite end point of 30-day mortality and inpatient clinical complications. Moreover, regardless of the treatment strategy, the number of transfused RBC units was an independent risk factor for worse outcomes, including mortality.

Patients in this study experienced slightly higher rates of serious complications than those in other studies,<sup>27,28</sup> likely because our population was a higher-risk group, with a median EuroScore of 4 to 5 and with some patients undergoing valve surgery alone or combined with CABG surgery. In addition, our hospital is a referral center for cardiac surgery, and some patients were severely ill. Although there were no significant differences in the mor-

**Figure 2.** Mean Hemoglobin Levels During the Study According to Transfusion Strategy



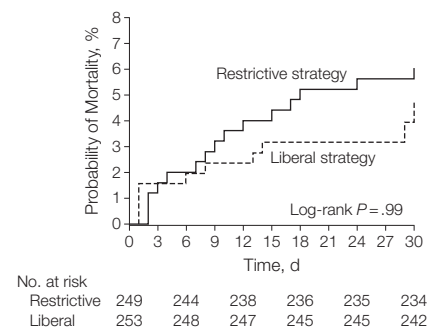
$P < .05$  between the groups at all points following preop. Error bars indicate 95% confidence intervals. ICU indicates intensive care unit.

tality rates and rates of inpatient complications between our 2 groups, there was a trend toward an increased incidence of cardiogenic shock in patients treated using the restrictive compared with the liberal strategy.

In a randomized controlled clinical trial of 838 critically ill patients (not including patients undergoing cardiac surgery), Hébert et al showed that a restrictive strategy of red blood cell transfusion was as effective as and possibly superior to a liberal transfusion strategy.<sup>13</sup> However, in cardiac surgery, there have been no similar large randomized controlled trials. Two small studies in patients undergoing CABG surgery suggested that different transfusion strategies gave similar outcomes<sup>29,30</sup>; however, the small numbers of patients in those studies did not allow for definitive conclusions to be drawn. Guidelines from the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists emphasize the lack of evidence on transfusion triggers after cardiac surgery.<sup>31</sup>

The rationale for implementing a restrictive transfusion strategy is based on many studies that have shown a lack of benefit and, at the same time, substantially

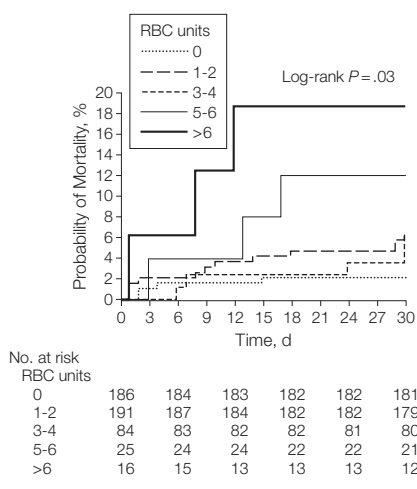
**Figure 3.** Kaplan-Meier Estimates of 30-Day Survival by Transfusion Strategy



Time zero was just after randomization (12 hours before surgery). Hazard ratio, 1.28 (95% confidence interval, 0.60-2.73) ( $P = .99$ ) for restrictive strategy vs liberal strategy.

increased costs and adverse effects associated with RBC transfusion.<sup>32,33</sup> These adverse effects include acute hemolytic and nonhemolytic reactions, transmission of viral and bacterial diseases, transfusion-related acute lung injury, and transfusion-associated circulatory overload. Immunosuppression has also been associated with transfusion and may explain the higher risk of infection and recurrence of neoplastic diseases observed in transfused patients.<sup>34,35</sup> Evidence from retrospective

**Figure 4.** Kaplan-Meier Estimates of 30-Day Survival Based on Number of Red Blood Cell (RBC) Units Transfused



Time zero was just after randomization (12 hours before surgery). With 0 RBC units as the reference category, the hazard ratio was 2.97 (95% confidence interval [CI], 0.96-9.21) ( $P = .06$ ) for 1 to 2 RBC units; 2.78 (95% CI, 0.75-10.35) ( $P = .13$ ) for 3 to 4 units; 5.82 (95% CI, 1.30-26.02) ( $P = .02$ ) for 5 to 6 units; and 9.70 (95% CI, 2.17-43.34) ( $P = .003$ ) for more than 6 units.

studies has pointed to worse early, mid-term, and long-term outcomes related to transfusion in patients undergoing cardiac surgery.<sup>36,37</sup> In a retrospective analysis of 11 963 patients who underwent isolated CABG surgery, Koch et al showed that perioperative RBC transfusion was associated with a dose-dependent increased risk of postoperative cardiac complications, serious infection, renal failure, neurologic complications, overall morbidity, prolonged ventilator support, and in-hospital mortality.<sup>38</sup> In a similar retrospective study, Murphy et al<sup>39</sup> showed that RBC transfusion was strongly associated with infection and with postoperative ischemic morbidity, hospital stay, increased early and late mortality, and hospital costs.

However, there has been concern about the adverse effects of anemia in patients with cardiovascular disease.<sup>4,5</sup> One retrospective cohort study of 1958 surgical patients reported that increased severity of anemia was associated with a disproportionate increase in mortality rates among patients with cardiovascular disease.<sup>4</sup> Moreover, some studies in patients with

anemia and myocardial infarction seem to suggest that transfusion may be beneficial (OR for mortality, 0.42 [95% CI, 0.20-0.89]),<sup>40</sup> particularly for patients older than 65 years (OR for mortality, 0.69 [95% CI, 0.53-0.89]; hematocrit range, 30-33).<sup>41</sup> In our study, patients with cardiovascular disease did not have adverse outcomes when a hematocrit threshold of 24% was used. This apparent discrepancy may be the result of confounding or because the hemoglobin concentrations of our patients during the study were not less than 9 g/dL.

Sixty-three percent of our study population received an RBC transfusion. A similar rate was reported in a retrospective study of 8724 patients presenting a lower number of risk factors for transfusion, such as older age, heart failure, on-pump surgery, and valve procedures.<sup>40</sup> Reoperation, female sex, high final lactate level in the operating room, long bypass duration, and low baseline hemoglobin level were independently associated with transfusion. These observations are similar to those reported in previous retrospective studies.<sup>42-44</sup>

As expected, the restrictive-strategy patients received fewer RBC units than the liberal-strategy patients and, consequently, had lower mean hemoglobin levels during the study. Interestingly, this did not result in a higher incidence of clinical complications. Presumably this occurred because the restrictive strategy did not result in reduced oxygen availability to the cells. This is supported by the lack of difference in lactate levels between the 2 groups during the study period.

In our study, independent of the treatment strategy, patients who received an RBC transfusion had higher rates of complications after surgery, including 30-day mortality. The number of transfused RBC units was a predictive factor for 30-day mortality. As already suggested by Koch et al<sup>38</sup> for adult cardiac procedures and by Gauvin et al<sup>45</sup> for pediatric cardiac operations, we showed that the higher the number of transfused RBC units, the higher the mortality. Regardless of the trans-

fusion strategy, transfusing even a single RBC unit was associated with a significantly increased risk of serious postoperative morbidity and mortality. RBC transfusion was independently associated with a 1.2-fold increased risk of death at 30 days for each unit transfused. These findings suggest that the primary strategy in patients undergoing cardiac surgery should be to avoid giving RBC transfusion solely to correct low hemoglobin levels. The increased risk of mortality related to the number of transfused RBC units supports a restrictive therapy in cardiac surgery. In addition, clinicians caring for patients after cardiac surgery should administer only 1 RBC unit at a time, because this may result in less exposure to risks but similar benefits.

Limitations of our study include that it was performed in a single referral center for cardiac surgery, which could compromise the generalizability of our findings. Another limitation is the lack of blood leukodepletion in our study, which reflects current practice in Brazil but again could limit generalizability. Some studies,<sup>46,47</sup> but not all,<sup>48</sup> have suggested better outcomes in critically ill patients who receive transfusions of leukodepleted RBCs. The potential higher risk associated with use of nonleukodepleted blood in our study may be compensated for by the relatively young age of the RBCs, with a median of only 3 days of storage in both groups, the result of routine active selection of fresh blood (stored less than 10 days) for patients undergoing cardiac surgery at our institution. In one study, transfusions with blood stored for more than 14 days were associated with a significant increase in morbidity and mortality in patients undergoing cardiac surgery.<sup>49</sup>

In conclusion, using a noninferiority margin of -8% among patients undergoing elective cardiac surgery, the use of a restrictive perioperative transfusion strategy compared with a more liberal strategy resulted in noninferior rates of the combined outcome of 30-day all-cause mortality and severe morbidity.



**Author Contributions:** Dr Hajjar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Hajjar, Vincent, Galas, Auler. **Acquisition of data:** Hajjar, Galas, Nakamura, Silva, Santos, Sierra, Lopes, Roquim, Leão, Dallan.

**Analysis and interpretation of data:** Hajjar, Vincent, Galas, Fukushima, Kalil Filho, Mauad, Sundin, Almeida, Pomerantzeff, Jatene, Stolf, Auler.

**Drafting of the manuscript:** Hajjar, Vincent, Nakamura, Almeida.

**Critical revision of the manuscript for important intellectual content:** Vincent, Galas, Silva, Santos, Fukushima, Kalil Filho, Sierra, Lopes, Mauad, Roquim, Sundin, Leão, Pomerantzeff, Dallan, Jatene, Stolf, Auler. **Statistical analysis:** Fukushima.

**Administrative, technical, or material support:** Nakamura, Silva, Santos, Kalil Filho, Sierra, Lopes, Roquim, Sundin, Leão, Almeida, Pomerantzeff, Dallan, Jatene, Stolf, Auler.

**Study supervision:** Hajjar, Vincent, Galas, Mauad, Auler.

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**Online-Only Material:** eTables 1 through 6 and eFigures 1 and 2 are available at <http://www.jama.com>.

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