ORIGINAL ARTICLE

# Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery

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## ABSTRACT

### BACKGROUND

The effect of a restrictive versus liberal red-cell transfusion strategy on clinical outcomes in patients undergoing cardiac surgery remains unclear.

### METHODS

In this multicenter, open-label, noninferiority trial, we randomly assigned 5243 adults undergoing cardiac surgery who had a European System for Cardiac Operative Risk Evaluation (EuroSCORE) I of 6 or more (on a scale from 0 to 47, with higher scores indicating a higher risk of death after cardiac surgery) to a restrictive red-cell transfusion threshold (transfuse if hemoglobin level was <7.5 g per deciliter, starting from induction of anesthesia) or a liberal red-cell transfusion threshold (transfuse if hemoglobin level was <9.5 g per deciliter in the operating room or intensive care unit [ICU] or was <8.5 g per deciliter in the non-ICU ward). The primary composite outcome was death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis by hospital discharge or by day 28, whichever came first. Secondary outcomes included red-cell transfusion and other clinical outcomes.

### RESULTS

The primary outcome occurred in 11.4% of the patients in the restrictive-threshold group, as compared with 12.5% of those in the liberal-threshold group (absolute risk difference, –1.11 percentage points; 95% confidence interval [CI], –2.93 to 0.72; odds ratio, 0.90; 95% CI, 0.76 to 1.07; P<0.001 for noninferiority). Mortality was 3.0% in the restrictive-threshold group and 3.6% in the liberal-threshold group (odds ratio, 0.85; 95% CI, 0.62 to 1.16). Red-cell transfusion occurred in 52.3% of the patients in the restrictive-threshold group, as compared with 72.6% of those in the liberal-threshold group (odds ratio, 0.41; 95% CI, 0.37 to 0.47). There were no significant between-group differences with regard to the other secondary outcomes.

### CONCLUSIONS

In patients undergoing cardiac surgery who were at moderate-to-high risk for death, a restrictive strategy regarding red-cell transfusion was noninferior to a liberal strategy with respect to the composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis, with less blood transfused. (Funded by the Canadian Institutes of Health Research and others; TRICS III ClinicalTrials.gov number, NCT02042898.)

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*A complete list of the TRICS investigators is provided in the Supplementary Appendix, available at NEJM.org.

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The avoidance of unnecessary blood transfusion is a high priority; therefore, determining safe thresholds for transfusion is imperative.[1,2] Among the highest recipients of red-cell transfusion are patients undergoing cardiac surgery,[2-6] with a substantial proportion of the total blood supply used by this group.[7,8] Whether a restrictive approach to intraoperative and postoperative transfusion in cardiac surgery safely achieves outcomes similar to those achieved by means of a more liberal approach remains unclear.[9-12]

The infectious and noninfectious risks associated with transfusion support a restrictive transfusion practice in several clinical settings.[13-15] However, anemia, particularly in the perioperative setting, may also be detrimental.[16-19] Patients who are at high perioperative risk may be more susceptible to anemia-induced tissue hypoxia,[20] potentially exposing them to an increased risk of complications and death if a restrictive approach is used.[21] We conducted a multicenter, randomized, controlled trial to determine whether a restrictive transfusion strategy applied throughout the perioperative period would be noninferior, in terms of major morbidities and mortality, to a liberal approach among patients undergoing cardiac surgery who had a moderate-to-high risk of death.

## Methods

### Trial Design and Oversight

The Transfusion Requirements in Cardiac Surgery (TRICS) III trial was an international, open-label, randomized, controlled, noninferiority trial that compared restrictive and liberal red-cell transfusion strategies in adults undergoing cardiac surgery with cardiopulmonary bypass who had a moderate-to-high predicted risk of death according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE I; scores are on a scale from 0 to 47, with higher scores indicating a higher risk of death after cardiac surgery).[22,23] An appropriately authorized ethics committee approved the trial in all the participating centers.

The trial was supported by the Canadian Institutes of Health Research, the Canadian Blood Services–Health Canada, the National Health and Medical Research Council of Australia, and the Health Research Council of New Zealand. The funders had no role in the trial design or conduct; in the collection, management, analysis, or interpretation of the data; or in the preparation or review of the manuscript or the approval of the manuscript for submission. The trial was designed by the executive committee and carried out by the TRICS investigators (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The first author and the last four authors vouch for the data and analyses and for the fidelity of the trial to the protocol (available at NEJM.org).

### Participants

We enrolled participants 18 years of age or older who were scheduled to undergo cardiac surgery with cardiopulmonary bypass and who had a preoperative additive EuroSCORE I of 6 or higher. The EuroSCORE I has been validated previously and has been shown to be predictive of an in-hospital mortality of 4% or more (see the Supplementary Appendix for a list of the EuroSCORE I components).[24,25] We excluded patients if they were unable to receive blood products, declined blood products, were involved in a preoperative autologous donation program, were undergoing heart transplantation, were having surgery solely for the insertion of a ventricular assist device, or were pregnant or lactating. Written informed consent was obtained from all the participants before enrollment.

### Randomization and Intervention

Before surgery, eligible patients were randomly assigned to one of two red-cell transfusion strategies, in a 1:1 ratio with the use of a concealed centralized, Web-based system, stratified according to center, with computer-generated random permuted blocks of varying sizes from two to six. Patients who were randomly assigned to the restrictive transfusion strategy received a red-cell transfusion if their hemoglobin concentration was less than 7.5 g per deciliter intraoperatively or postoperatively. Patients who were randomly assigned to the liberal transfusion strategy received a red-cell transfusion if their hemoglobin concentration was less than 9.5 g per deciliter intraoperatively or postoperatively in the intensive care unit (ICU) or if the hemoglobin concentration was less than 8.5 g per deciliter when the patient was in the non-ICU ward. Attending physicians had to follow the assigned transfusion strategy from induction of anesthesia for the index cardiac sur-

gical procedure until either hospital discharge or 28 days after surgery, whichever came first.

The hemoglobin level was to be measured at least at the following intervals: preoperatively, before cardiopulmonary bypass, during cardiopulmonary bypass, after cardiopulmonary bypass, on arrival in the ICU, and on days 1, 2, 3, 5, 7, 9, and 11 while the patient was still hospitalized. If the hemoglobin concentration fell below the appropriate threshold at any time, 1 unit of red cells was administered at a time and was followed with a reassessment of the hemoglobin concentration. Red-cell transfusion was to be administered as soon as possible after the threshold-related hemoglobin concentration was measured and had to be initiated within the following maximum time frames: 2 hours for patients during an operation; 18 hours in the ICU, including step-down units; or 40 hours on the non-ICU hospital ward. The protocol allowed physicians to recheck borderline measurements of the hemoglobin concentration before transfusion and to suspend the red-cell transfusion protocol temporarily in patients who had rapid blood loss or hemodynamic instability due to blood loss. The protocol was resumed as soon as hemostasis was achieved or at a maximum of 24 hours after suspension. Other blood products could be administered in accordance with published guidelines and local practice on the basis of the presence of ongoing bleeding and documented measurement of abnormal coagulation.

Nonadherence to the assigned red-cell transfusion strategy was considered to have occurred if a red-cell transfusion was given without a protocol-defined hemoglobin threshold being met; or if a red-cell transfusion was not initiated after a trigger was met, or a repeat hemoglobin value above the trigger was not measured, within the protocol-defined time period. All other aspects of care were left to the discretion of the attending clinicians. It was not possible to use formal blinding of the assigned transfusion strategy with regard to the participants and medical staff. However, participants were not actively informed about the treatment assignment, and outcome adjudicators were unaware of the trial-group assignments.

### OUTCOMES

The primary outcome was a composite of death from any cause, nonfatal myocardial infarction, stroke, or new-onset renal failure with dialysis, occurring during the index hospitalization from the start of surgery until either hospital discharge or 28 days after surgery, whichever occurred first. The prespecified secondary outcomes included the components of the primary outcome, blood-product (including red-cell) transfusion, lengths of stay in the ICU and in the hospital, duration of mechanical ventilation, prolonged state of low cardiac output, infection, bowel infarction, acute kidney injury, seizure, delirium, and encephalopathy. Definitions of the primary and secondary outcomes are provided in the Supplementary Appendix. All the deaths were verified centrally, and an adjudication committee whose members were unaware of the trial-group assignments evaluated all the other components of the primary outcome, as well as all reported instances of infection and bowel infarction.

### STATISTICAL ANALYSIS

The primary objective of the trial was to determine whether a restrictive transfusion threshold was noninferior to a liberal transfusion threshold. We initially planned that a sample of 3592 patients would provide the trial with 85% power to detect noninferiority at a one-sided alpha of 0.025, with the use of a noninferiority margin of 3 percentage points for the risk difference and assuming an event rate of the primary composite outcome of 10%, with one interim analysis with a Haybittle–Peto stopping rule ($P=0.0001$, one-sided). In November 2016, we increased the sample to 5000 participants without inspecting the accumulated data in order to increase the power to 90%. In addition, we planned to include in the analysis all the participants who had undergone randomization in our pilot trial (TRICS II; ClinicalTrials.gov number, NCT01484639), and we kept these data blinded until the completion of the TRICS III trial. Specific features of the TRICS II trial, such as the inclusion and exclusion criteria, hemoglobin-concentration triggers, and outcome definitions, are provided in the Supplementary Appendix.

The prespecified primary analysis of the primary outcome was a per-protocol analysis that included all the participants who had undergone randomization and who underwent surgery with cardiopulmonary bypass, except for patients who had a protocol adherence of less than 90%, patients who were withdrawn from the trial by the treating physician at any time, and patients who withdrew consent. We compared the risk differ-

ence for the primary outcome between groups against the noninferiority margin with a one-sided z-test at a one-sided alpha of 0.025. Confidence intervals for the primary and secondary outcomes are all two-sided 95% confidence intervals. We performed modified intention-to-treat and adjusted analyses of the primary and secondary outcomes to examine the consistency of the treatment effect. The modified intention-to-treat population included all the patients who underwent randomization except for those who did not undergo the planned surgical procedure and those who withdrew consent preoperatively.

For binary outcomes, analyses were adjusted with the use of a logistic-regression model that included age, sex, preoperative renal function, preexisting chronic pulmonary disease (defined as the long-term use of bronchodilators or glucocorticoids for lung disease), preoperative left ventricular function, history of diabetes, type of surgery (coronary-artery bypass grafting [CABG] only, CABG plus another procedure, or other, non-CABG procedure), and preoperative hemoglobin concentration. Outcomes regarding length of stay in both the ICU and the hospital were analyzed with the use of Cox proportional-hazards models. We undertook prespecified, exploratory subgroup analyses of the primary outcome to determine whether the effect of the transfusion strategy varied according to prespecified subgroups. Primary analyses were not stratified according to center. Additional sensitivity analyses aimed to determine whether specific subgroups of patients that were defined according to protocol adherence, transfusion exposure, and hemoglobin levels and the use of a mixed-effects model to account for variation between sites would yield similar results. Analyses were performed with the use of the R statistical package, version 3.2.4 (R Core Team [2016], www.r-project.org).

## RESULTS

### PARTICIPANTS

From January 20, 2014, to March 20, 2017, a total of 5035 patients underwent randomization at 73 sites in 19 countries (for a complete list, see the Supplementary Appendix). An additional 208 patients underwent randomization in the multicenter pilot trial. Of the total of 5243 patients who underwent randomization, 54 did not have surgery, 63 did not have cardiopulmonary bypass, and 34 withdrew before surgery or were excluded for other reasons, which left 5092 patients in the modified intention-to-treat population. A total of 4860 patients (2430 in each group) were included in the per-protocol analysis (Fig. S1 in the Supplementary Appendix).

The characteristics of the patients at baseline were similar in the two groups (Table 1); additional characteristics of the patients in the per-protocol population and the baseline characteristics of the patients in the intention-to-treat population are shown in Tables S1 and S2, respectively, in the Supplementary Appendix. The mean (±SD) age of the patients was 72±10 years, 35.4% of the patients were women, and the mean EuroSCORE I was 7.8±1.9. The distribution of type of surgery was CABG only (26.1%), CABG with another procedure (27.7%), and other, non-CABG procedure (46.2%).

### HEMOGLOBIN CONCENTRATIONS AND TRANSFUSIONS

Overall, the mean hemoglobin concentration of the patients at baseline was 13.1±1.8 g per deciliter. During surgery, the hemoglobin concentration decreased in each group. Postoperatively, the concentrations in the two groups separated by approximately 1 g per deciliter and remained separated from ICU admission through day 28 (Fig. 1).

In the restrictive-threshold group, 52.3% of the patients received a red-cell transfusion after randomization, as compared with 72.6% of those in the liberal-threshold group (odds ratio, 0.41; 95% confidence interval [CI], 0.37 to 0.47; P<0.001) (Table 2). Patients who had a transfusion received a median of 2 units (interquartile range, 1 to 4) of red cells after randomization in the restrictive-threshold group, as compared with 3 units (interquartile range, 2 to 5) in the liberal-threshold group (rate ratio, 0.85; 95% CI, 0.82 to 0.88) (Table 2).

### CLINICAL OUTCOMES

Table 3 presents the primary and secondary clinical outcomes according to the per-protocol analysis. The percentage of patients who had a primary composite outcome event was 11.4% in the restrictive-threshold group, as compared with 12.5% in the liberal-threshold group (absolute risk difference, –1.11 percentage points; 95% CI, –2.93 to 0.72; odds ratio, 0.90; 95% CI, 0.76 to 1.07). The upper limit of the 95% confidence interval for the

**Table 1. Baseline and Operative Characteristics.***

| Characteristic | Restrictive Threshold (N=2430) | Liberal Threshold (N=2430) |
|---|---|---|
| **Preoperative characteristics** | | |
| Age — yr | 72±10 | 72±10 |
| Male sex — no. (%) | 1553 (63.9) | 1586 (65.3) |
| Body-mass index† | 28.1±6.0 | 28.0±5.2 |
| EuroSCORE I‡ | 7.9±1.8 | 7.8±1.9 |
| Previous cardiac surgery — no. (%) | 307 (12.6) | 280 (11.5) |
| Myocardial infarction in previous 90 days — no. (%) | 562 (23.1) | 601 (24.7) |
| Left ventricular function — no./total no. (%)§ | | |
| Good | 1485/2430 (61.1) | 1523/2427 (62.8) |
| Moderately reduced | 733/2430 (30.2) | 710/2427 (29.3) |
| Poor | 166/2430 (6.8) | 156/2427 (6.4) |
| Very poor | 46/2430 (1.9) | 38/2427 (1.6) |
| Diabetes mellitus — no. (%) | 646 (26.6) | 686 (28.2) |
| Treated hypertension — no. (%) | 1797 (74.0) | 1803 (74.2) |
| Emergency surgery — no. (%) | 37 (1.5) | 34 (1.4) |
| Renal function — no./total no. (%)¶ | | |
| Normal | 1090/2332 (46.7) | 1071/2348 (45.6) |
| Moderately impaired | 857/2332 (36.7) | 866/2348 (36.9) |
| Severely impaired | 355/2332 (15.2) | 385/2348 (16.4) |
| Use of dialysis | 30/2332 (1.3) | 26/2348 (1.1) |
| Use of aspirin — no./total no. (%) | 1274/2428 (52.5) | 1293/2423 (53.4) |
| Hemoglobin — g/dl | 13.1±1.8 | 13.1±1.7 |
| **Operative characteristics** | | |
| Type of surgery — no./total no. (%) | | |
| CABG only | 622/2429 (25.6) | 645/2430 (26.5) |
| CABG and valve surgery | 464/2429 (19.1) | 472/2430 (19.4) |
| CABG and other, nonvalve surgery | 205/2429 (8.4) | 203/2430 (8.4) |
| Valve surgery only | 703/2429 (28.9) | 716/2430 (29.5) |
| Other, non-CABG surgery | 433/2429 (17.8) | 394/2430 (16.2) |
| Duration of cardiopulmonary bypass — min | 120±59 | 121±57 |
| Intraoperative tranexamic acid — no./total no. (%) | 2219/2428 (91.4) | 2235/2428 (92.1) |

* Plus–minus values are means ±SD. Data from the per-protocol population (all the participants who had undergone randomization and who underwent surgery with cardiopulmonary bypass, except for patients who had a protocol adherence of less than 90%, patients who were withdrawn from the trial by the treating physician at any time, and patients who withdrew consent) are presented here. Details on additional baseline characteristics of the per-protocol population and baseline characteristics of the intention-to-treat population are provided in Tables S1 and S2, respectively, in the Supplementary Appendix. The restrictive transfusion threshold was less than 7.5 g per deciliter intraoperatively and postoperatively, and the liberal transfusion threshold was less than 9.5 g per deciliter intraoperatively or postoperatively in the intensive care unit (ICU) or less than 8.5 g per deciliter on the non-ICU ward. There were no significant differences between the two groups in any of the baseline characteristics shown. Data on the preoperative hemoglobin concentration were missing for one patient in the restrictive-threshold group and for two in the liberal-threshold group; and data on the duration of cardiopulmonary bypass were missing for three and two, respectively. CABG denotes coronary-artery bypass graft.

† Data on the body-mass index (the weight in kilograms divided by the square of the height in meters) were missing for one patient in the liberal-threshold group.

‡ The European System for Cardiac Operative Risk Evaluation (EuroSCORE) I provides an estimate of the risk of death among patients undergoing cardiac surgery. The lowest risk is denoted by a score of 0, and the highest risk by a score of 47; a EuroSCORE I of 6 is predictive of increased risk. Data were missing for two patients in the restrictive-threshold group and for three in the liberal-threshold group.

§ Left ventricular function was defined according to the following categories: good (left ventricular ejection fraction, ≥51%), moderately reduced (31 to 50%), poor (21 to 30%), and very poor (≤20%).

¶ Renal function was defined according to the following categories: normal (creatinine clearance, >85 ml per minute), moderately impaired (50 to 85 ml per minute), severely impaired (<50 ml per minute), and use of dialysis (regardless of creatinine clearance).

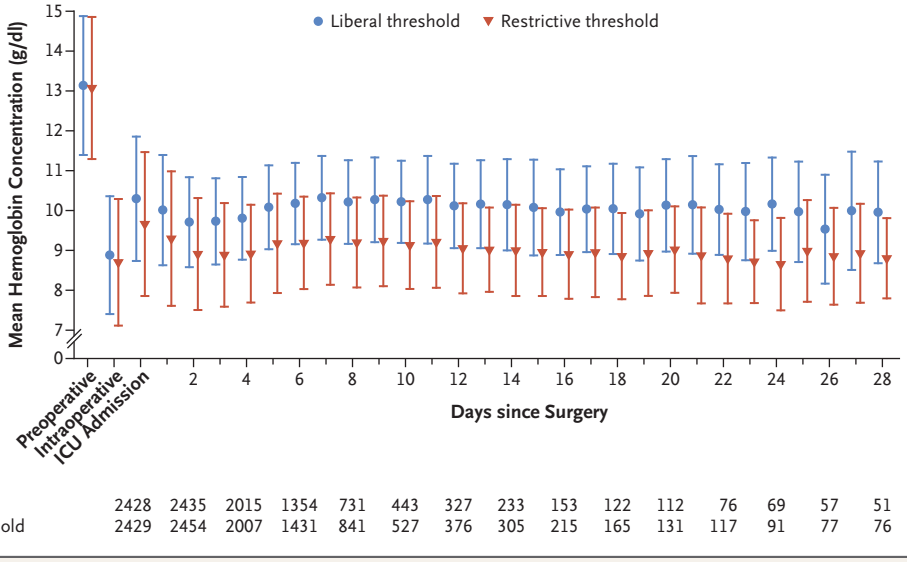


**Figure 1. Hemoglobin Concentration during the Trial Period.**

The restrictive transfusion threshold was less than 7.5 g per deciliter intraoperatively and postoperatively, and the liberal transfusion threshold was less than 9.5 g per deciliter intraoperatively or postoperatively in the intensive care unit (ICU) or less than 8.5 g per deciliter on the non-ICU ward. I bars indicate the standard deviation.

risk difference was within our noninferiority margin of 3 percentage points (P<0.001 for noninferiority). The modified intention-to-treat analysis confirmed the noninferiority of the restrictive transfusion threshold to the liberal transfusion threshold (12.3% in the restrictive-threshold group vs. 12.9% in the liberal-threshold group; absolute risk difference, −0.60 percentage points; 95% CI, −2.38 to 1.27; odds ratio, 0.95; 95% CI, 0.81 to 1.12). There were no significant differences between the treatment groups with regard to the individual components of the composite outcome in either the per-protocol analysis or the modified intention-to-treat analysis (Table 3, and Table S3 in the Supplementary Appendix).

Mortality was 3.0% in the restrictive-threshold group and 3.6% in the liberal-threshold group (absolute risk difference, −0.53 percentage points; 95% CI, −1.54 to 0.47; odds ratio, 0.85; 95% CI, 0.62 to 1.16). The causes of death are listed in Table S4 in the Supplementary Appendix.

Approximately 40% of the patients had a prolonged low-output state after surgery (40.9% in the restrictive-threshold group and 40.6% in the liberal-threshold group; odds ratio, 1.01; 95% CI, 0.90 to 1.14) (Table 3). The median duration of mechanical ventilation was 0.38 days (interquartile range, 0.22 to 0.75) in the restrictive-threshold group and 0.36 days (interquartile range, 0.22 to 0.71) in the liberal-threshold group (Table 3). The median length of stay in the ICU was 2.1 days (interquartile range, 1.0 to 4.0) in the restrictive-threshold group and 1.9 days (interquartile range, 1.0 to 3.9) in the liberal-threshold group, and the median hospital stay was 8.0 days (interquartile range, 7.0 to 13.0) and 8.0 days (interquartile range, 7.0 to 12.0), respectively. The rates of all the other outcomes were similar in the two groups (Table 3).

Subgroup analyses did not show a significant interaction with treatment, except with regard to age. The restrictive transfusion strategy was associated with a lower risk of the composite outcome than the liberal strategy among patients 75 years of age or older (odds ratio, 0.70; 95% CI, 0.54 to 0.89) but not among younger patients (odds ratio, 1.17; 95% CI, 0.91 to 1.50; P=0.004 for interaction) (Fig. 2). This effect was consistent in an analysis according to decades of age (beginning at age <45 years) or with age as a continuous variable with the use of restricted spline modeling (Fig. S2 in the Supplementary Appendix). Adjusted analyses with the use of logistic regression to control for age, sex, status with respect

**Table 2. Transfusion Outcomes in the Per-Protocol Population.**

| Characteristic | Restrictive Threshold (N = 2430) | Liberal Threshold (N = 2430) | Odds Ratio or Rate Ratio (95% CI) |
|---|---|---|---|
| **Red-cell transfusions after randomization** | | | |
| ≥1 Unit of red cells — no. (%) | 1271 (52.3) | 1765 (72.6) | 0.41 (0.37–0.47) |
| No. of units of red cells transfused | | | |
| Median | 2 | 3 | 0.85 (0.82–0.88)* |
| Interquartile range | 1–4 | 2–5 | |
| Distribution — no. (%) | | | |
| 0 | 1159 (47.7) | 665 (27.4) | |
| 1 | 383 (15.8) | 366 (15.1) | |
| 2 | 283 (11.6) | 367 (15.1) | |
| 3 | 174 (7.2) | 267 (11.0) | |
| 4 | 140 (5.8) | 225 (9.3) | |
| ≥5 | 291 (12.0) | 540 (22.2) | |
| Intraoperative red-cell transfusion | | | |
| No. of patients with transfusion (%) | 674 (27.7) | 1259 (51.8) | 0.36 (0.32–0.40) |
| Median no. of units transfused | 2 | 2 | 0.88 (0.82–0.95)* |
| Interquartile range | 1–3 | 1–3 | |
| Postoperative red-cell transfusion in ICU | | | |
| No. of patients with transfusion (%) | 867 (35.7) | 1253 (51.6) | 0.52 (0.46–0.58) |
| Median no. of units transfused | 2 | 2 | 0.98 (0.93–1.04)* |
| Interquartile range | 1–3 | 1–3 | |
| Postoperative red-cell transfusion not in ICU | | | |
| No. of patients with transfusion (%) | 278 (11.4) | 229 (9.4) | 1.24 (1.03–1.49) |
| Median no. of units transfused | 1 | 1 | 0.78 (0.60–1.03)* |
| Interquartile range | 1–1 | 1–2 | |
| Protocol suspension at any time — no. (%) | 348 (14.3) | 270 (11.1) | 1.34 (1.13–1.58) |
| **Other transfusions** | | | |
| Plasma — no. (%) | 571 (23.5) | 658 (27.1) | 0.83 (0.73–0.94) |
| Platelets — no. (%) | 700 (28.8) | 716 (29.5) | 0.97 (0.86–1.10) |
| Cryoprecipitate — no./total no. (%) | 275/2334 (11.8) | 275/2349 (11.7) | 1.01 (0.84–1.20) |
| Prothrombin complex concentrate — no./total no. (%) | 73/2334 (3.1) | 61/2349 (2.6) | 1.21 (0.86–1.71) |

* This value is a rate ratio. For all ratios, the restrictive-threshold group is in the numerator and the liberal-threshold group in the denominator.

to diabetes, left ventricular function, type of surgery, and statuses with respect to preoperative renal function, anemia, and pulmonary disease were consistent with the primary analyses (Table S3 in the Supplementary Appendix). Additional sensitivity analyses that included patients who had higher or lower adherence levels or that excluded patients who had a protocol suspension, who never received a red-cell transfusion, or whose hemoglobin concentration was never measured below 9.5 g per deciliter also yielded results that were consistent with those of the primary outcome (Table S5 in the Supplementary Appendix).

## DISCUSSION

In this randomized trial involving patients with an elevated perioperative risk of death who were undergoing cardiac surgery with cardiopulmonary bypass, a restrictive transfusion strategy was

**Table 3. Primary and Secondary Outcomes in the Per-Protocol Population.**

| Characteristic | Restrictive Threshold (N = 2430) | Liberal Threshold (N = 2430) | Odds Ratio or Hazard Ratio (95% CI) |
|---|---|---|---|
| **Primary outcome** | | | |
| Composite-outcome event — no./total no. (%) | 276/2428 (11.4) | 303/2429 (12.5) | 0.90 (0.76–1.07) |
| Death — no./total no. (%) | 74/2427 (3.0) | 87/2429 (3.6) | 0.85 (0.62–1.16) |
| Stroke — no./total no. (%) | 45/2428 (1.9) | 49/2429 (2.0) | 0.92 (0.61–1.38) |
| Myocardial infarction — no./total no. (%) | 144/2428 (5.9) | 144/2429 (5.9) | 1.00 (0.79–1.27) |
| New-onset renal failure with dialysis — no./total no. (%) | 61/2428 (2.5) | 72/2429 (3.0) | 0.84 (0.60–1.19) |
| **Secondary outcomes** | | | |
| Length of stay in ICU | | | |
| No. of patients with data | 2422 | 2418 | |
| Median — days | 2.1 | 1.9 | 0.89 (0.84–0.94)* |
| Interquartile range — days | 1.0–4.0 | 1.0–3.9 | |
| Length of stay in hospital | | | |
| No. of patients with data | 2419 | 2419 | |
| Median — days | 8.0 | 8.0 | 0.93 (0.88–0.99)* |
| Interquartile range — days | 7.0–13.0 | 7.0–12.0 | |
| Duration of mechanical ventilation | | | |
| No. of patients with data | 2416 | 2421 | |
| Median — days | 0.38 | 0.36 | 0.94 (0.89–1.00)* |
| Interquartile range — days | 0.22–0.75 | 0.22–0.71 | |
| Prolonged low-output state — no./total no. (%)† | 994/2429 (40.9) | 987/2430 (40.6) | 1.01 (0.90–1.14) |
| Infection — no./total no. (%) | 121/2428 (5.0) | 101/2429 (4.2) | 1.21 (0.92–1.58) |
| Bowel infarction — no./total no. (%) | 6/2428 (0.2) | 5/2429 (0.2) | 1.20 (0.37–3.94) |
| Acute kidney injury — no./total no. (%) | 792/2332 (34.0) | 797/2348 (33.9) | 1.00 (0.89–1.13) |
| Seizure — no./total no. (%) | 50/2428 (2.1) | 42/2429 (1.7) | 1.20 (0.79–1.81) |
| Delirium — no./total no. (%) | 306/2428 (12.6) | 264/2429 (10.9) | 1.18 (0.99–1.41) |
| Encephalopathy — no./total no. (%) | 26/2428 (1.1) | 22/2429 (0.9) | 1.18 (0.67–2.10) |

* This value is a hazard ratio. For all ratios, the restrictive-threshold group is in the numerator and the liberal-threshold group in the denominator.

† A prolonged low-output state was defined as the infusion of two or more inotropes for 24 hours or more, the use of an intraaortic balloon pump postoperatively, or the use of a ventricular assist device postoperatively, as described in the Supplementary Appendix.

noninferior to a liberal transfusion strategy with regard to the composite primary outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis. This finding was consistent in both the per-protocol and modified intention-to-treat analyses as well across subgroups and sensitivity analyses. Fewer patients in the restrictive-threshold group than in the liberal-threshold group received a red-cell transfusion, and patients in the restrictive-threshold group had fewer units of allogeneic red cells transfused.

Clinicians have been adopting restrictive transfusion strategies in cardiac surgery with increasing frequency, largely on the basis of the known risks of blood transfusions and of observational studies linking transfusion with increased mortality and major morbidity.[5,6,26,27] However, there has been some discrepancy between randomized trials on the one hand and observational studies on the other hand.[28,29] The Transfusion Indication Threshold Reduction (TITRe2) clinical trial, in which mortality at 90 days was higher with a restrictive postoperative transfusion threshold

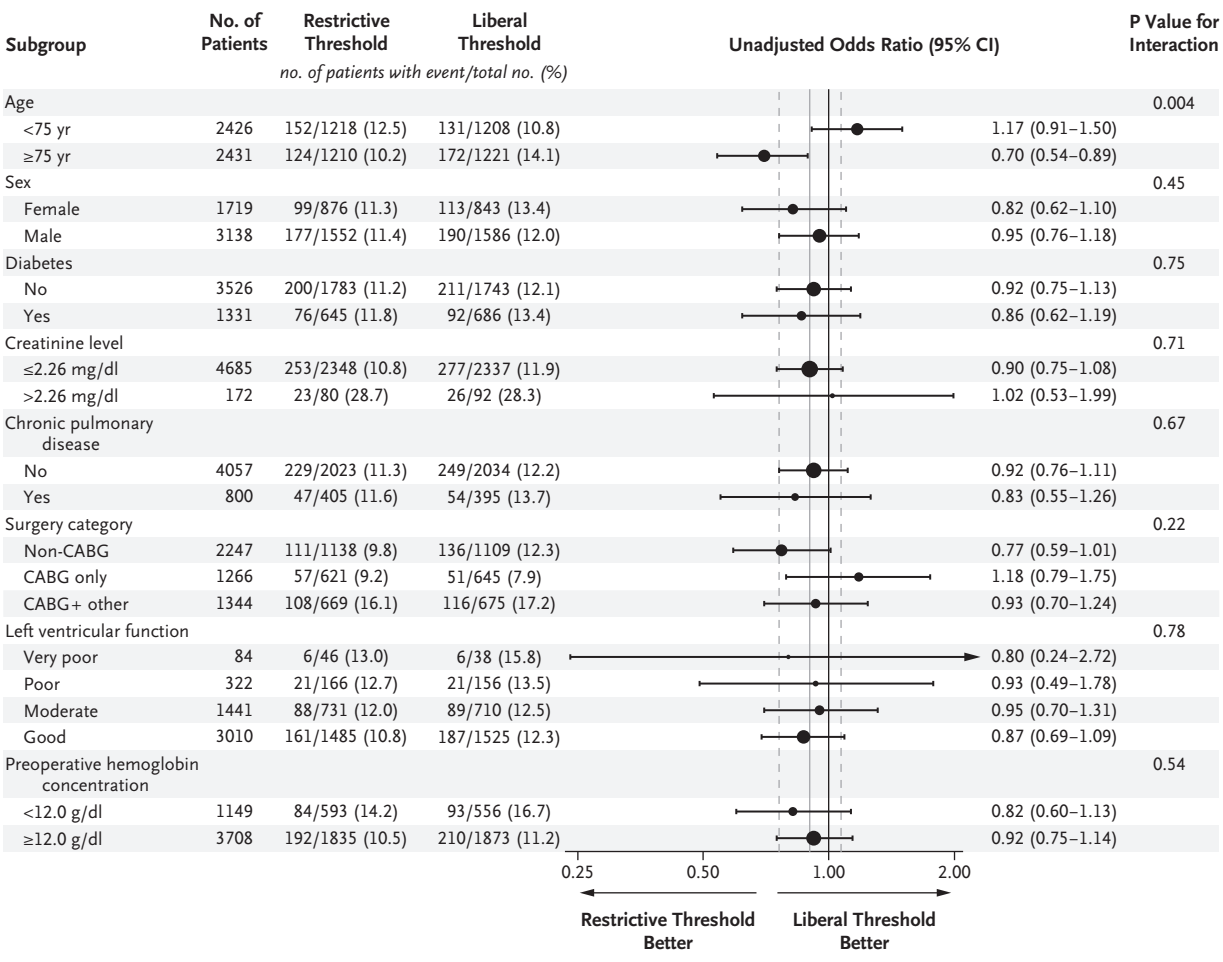


**Figure 2. Subgroup Analyses.**

The solid gray vertical line indicates the overall treatment estimate for the primary outcome in the primary analysis cohort (per-protocol population), and the dashed lines the 95% confidence interval. The size of the circles is proportional to the statistical precision of the estimates. An arrow indicates that the 95% confidence interval is outside the range shown. Data were missing for two patients in the restrictive-threshold group and for one in the liberal-threshold group. To convert the values for creatinine to micromoles per liter, multiply by 88.4. Chronic pulmonary disease was defined as the long-term use of bronchodilators or glucocorticoids for lung disease. Left ventricular function was defined according to the following categories: good (left ventricular ejection fraction, ≥51%), moderately reduced (31 to 50%), poor (21 to 30%), and very poor (≤20%). CABG denotes coronary-artery bypass grafting.

than with a liberal threshold, aroused concerns within the medical community over the adoption of a restrictive transfusion strategy.[30] Patients undergoing cardiac surgery have borderline cardiovascular reserve and are exposed to intraoperative hemodilution, which decreases the hemoglobin concentration, thus potentially increasing the risk of anemia-induced tissue hypoxia.[20] However, randomization in the TITRe2 trial did not occur until the postoperative period, and mortality was a secondary outcome.[30] The TRICS III trial provides compelling evidence that a restrictive transfusion strategy is as effective and safe as a liberal strategy in patients undergoing cardiac surgery.

Our findings are consistent with those observed in other fields of medicine. Restrictive transfusion strategies have been shown to be noninferior to liberal strategies in patients in the ICU,[31,32] patients having hip surgery,[28] and patients with gastrointestinal bleeding.[33] A meta-analysis involving patients undergoing noncardiac surgery showed

similar conclusions.[34] Uncertainty remains regarding appropriate transfusion thresholds in patients with acute coronary artery disease,[21,35] and a multicenter trial assessing transfusion thresholds in patients with acute coronary syndromes is currently ongoing (Myocardial Ischemia and Transfusion [MINT] trial, NCT02981407).

The TRICS III trial has limitations. Blinding is not feasible in a transfusion study; the lack of blinding could introduce bias in outcome detection and reporting. As has occurred in similar studies, the between-group difference in the hemoglobin concentration was lower than the difference in the triggers.[30,36,37] This situation could have been related to trial design, patients not reaching the specified threshold, protocol nonadherence, or an imbalance in protocol suspensions that may have minimized any potential differences between groups. The trial was designed to be pragmatic and reflective of standard practice in order to enhance its generalizability, but it did not include low-risk patients. Similarly, this trial does not answer the question of whether even lower transfusion thresholds might also be as safe as the thresholds used in this trial, nor did it specifically test the efficacy of transfusion. The trial design and unadjusted confidence intervals also do not allow us to draw definitive conclusions about the noninferiority of the restrictive strategy with regard to any of the secondary outcomes. Finally, we found an interaction with age that challenges current beliefs and that may be considered to be hypothesis-generating; at a minimum, it highlights that a restrictive transfusion strategy appears to be safe in elderly patients.

In conclusion, this trial showed that a restrictive red-cell transfusion strategy (hemoglobin threshold of <7.5 g per deciliter) was noninferior to a liberal strategy (hemoglobin threshold of <9.5 g per deciliter in the operating room or ICU and <8.5 g per deciliter on the non-ICU ward) with regard to death and major disability (including myocardial infarction, stroke, and new-onset renal failure with dialysis) among patients undergoing cardiac surgery who had a moderate-to-high risk of death. These outcomes were achieved with fewer units of blood being transfused.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

This article is dedicated to the memory of Dr. Charlie MacAdams.

## APPENDIX

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