ORIGINAL ARTICLE

Six-Month Outcomes after Restrictive or Liberal Transfusion for Cardiac Surgery

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ABSTRACT

BACKGROUND

We reported previously that, in patients undergoing cardiac surgery who were at moderate-to-high risk for death, a restrictive transfusion strategy 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 by hospital discharge or 28 days after surgery, whichever came first. We now report the clinical outcomes at 6 months after surgery.

METHODS

We randomly assigned 5243 adults undergoing cardiac surgery to a restrictive red-cell transfusion strategy (transfusion if the hemoglobin concentration was <7.5 g per deciliter intraoperatively or postoperatively) or a liberal red-cell transfusion strategy (transfusion if the hemoglobin concentration was <9.5 g per deciliter intraoperatively or postoperatively when the patient was in the intensive care unit [ICU] or was <8.5 g per deciliter when the patient was in the non-ICU ward). The primary composite outcome was death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis occurring within 6 months after the initial surgery. An expanded secondary composite outcome included all the components of the primary outcome as well as emergency department visit, hospital readmission, or coronary revascularization occurring within 6 months after the index surgery. The secondary outcomes included the individual components of the two composite outcomes.

RESULTS

At 6 months after surgery, the primary composite outcome had occurred in 402 of 2317 patients (17.4%) in the restrictive-threshold group and in 402 of 2347 patients (17.1%) in the liberal-threshold group (absolute risk difference before rounding, 0.22 percentage points; 95% confidence interval [CI], –1.95 to 2.39; odds ratio, 1.02; 95% CI, 0.87 to 1.18; P=0.006 for noninferiority). Mortality was 6.2% in the restrictive-threshold group and 6.4% in the liberal-threshold group (odds ratio, 0.95; 95% CI, 0.75 to 1.21). There were no significant between-group differences in the secondary outcomes.

CONCLUSIONS

In patients undergoing cardiac surgery who were at moderate-to-high risk for death, a restrictive strategy for 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 at 6 months after surgery. (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 Transfusion Requirements in Cardiac Surgery (TRICS) trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Restrictive strategies for red-cell transfusion (in which lower hemoglobin concentrations are used for transfusion) in patients undergoing cardiac surgery have been shown to result in the use of fewer units of allogeneic red cells than liberal strategies (in which higher hemoglobin concentrations are used for transfusion) and to produce short-term clinical outcomes that are noninferior to those with liberal strategies.[1,2] However, findings from observational and randomized studies have aroused concerns about the effects of transfusion strategies on longer-term outcomes, because both anemia and allogeneic transfusion can have effects that persist beyond hospitalization for surgery. Anemia can lead to tissue hypoxia in patients who are at high risk for perioperative complications, and persistent anemia-induced tissue hypoxia may be detrimental in such patients.[3] Allogeneic transfusion has short-term and long-lasting effects on the innate and adaptive immune system, which can potentially lead to poor clinical outcomes.[4-8] Therefore, although a short-term noninferiority between transfusion approaches may be shown, it is plausible that subacute or protracted anemia, immune modulation, or both may affect intermediate-term and long-term outcomes. Indeed, in the Transfusion Indication Threshold Reduction (TITRe2) randomized, controlled trial that compared postoperative restrictive transfusion thresholds with liberal transfusion thresholds, no significant difference in mortality was observed at 30 days, but by 90 days, mortality was significantly higher in the restrictive-threshold group than in the liberal-threshold group (4.2% vs. 2.6%; hazard ratio for death, 1.64; 95% confidence interval [CI], 1.00 to 2.67; P=0.045).[9]

We conducted the Transfusion Requirements in Cardiac Surgery (TRICS) III trial to compare a restrictive transfusion strategy with a liberal strategy in patients undergoing cardiac surgery with cardiopulmonary bypass who had at least a moderate risk of death. To overcome some of the limitations in previous trials, we conducted TRICS III in a wide range of hospitals and countries and enrolled more than 5000 patients. We found no significant differences in outcomes between the restrictive-threshold group and the liberal-threshold group within 28 days after surgery,[1] findings that are similar to those from the TITRe2 trial.[9] We prospectively evaluated and now report the 6-month clinical outcomes in the TRICS III trial.

Methods

Trial Design

The TRICS III trial was a randomized, open-label, noninferiority trial that compared a restrictive red-cell transfusion strategy with a liberal strategy in adult patients undergoing cardiac surgery with cardiopulmonary bypass who were at moderate-to-high predicted risk for death, as defined by an additive European System for Cardiac Operative Risk Evaluation (EuroSCORE) I score of 6 or higher (on a scale from 0 to 47, with higher scores indicating a higher risk of death after cardiac surgery); in-hospital primary outcomes were adjudicated in a blinded manner. The trial protocol and in-hospital results have been published previously.[1,10] The final 6-month statistical analysis plan is included in the current trial protocol, available with the full text of this article at NEJM.org.

The trial was designed by the executive committee and was carried out by the investigators (a complete list of investigators and sites is provided in the Supplementary Appendix, available at NEJM.org). The trial was funded by national peer-review organizations. The funders had no role in the design or conduct of the trial; in the collection, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript for submission. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Ethics approval was provided by all relevant local institutional review boards. An independent data and safety monitoring board provided trial oversight.

Patients

We enrolled patients who were scheduled to undergo cardiac surgery with cardiopulmonary bypass and who had a preoperative additive EuroSCORE I score of 6 or higher. We excluded patients who were unable to receive blood products, declined blood products, were participating in a preoperative autologous blood donation program, were undergoing heart transplantation, were having surgery solely for the insertion of a ventricular assist device, or were pregnant or lactating. All participants provided written informed consent.

The 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

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or postoperatively. The 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 when the patient was in the intensive care unit (ICU) or was less than 8.5 g per deciliter when the patient was in the non-ICU ward. The treating physicians followed the transfusion protocol until 28 days after surgery or hospital discharge, whichever came first.

OUTCOMES

The prespecified 6-month primary composite outcome included the same components of the primary composite outcome in our initial trial[1,10]: death from any cause, myocardial infarction, new focal neurologic deficit (stroke), or new-onset renal failure with dialysis occurring within 6 months after the index surgery. An expanded secondary composite outcome included all the components of the primary outcome as well as emergency department visit, hospital readmission, or coronary revascularization occurring within 6 months after the index surgery. The secondary outcomes included the individual components of the two composite outcomes.

STATISTICAL ANALYSIS

All analyses of the primary composite outcome and secondary outcomes were performed on a per-protocol basis and included all patients who had undergone randomization and underwent surgery with cardiopulmonary bypass, except those who had a protocol adherence of less than 90%, who were withdrawn from the trial by the treating physician, or who withdrew consent. The primary composite outcome was analyzed for noninferiority with the use of the same 3 percentage-point margin of noninferiority (at a one-sided alpha level of 0.025) that was defined for the primary outcome analysis in our initial trial. The trial was originally designed to have at least 85% power to detect noninferiority with the use of a noninferiority margin of 3 percentage points for the between-group difference in the percentage of patients who had a primary composite outcome event from the start of surgery until hospital discharge or 28 days after surgery, whichever came first.[1,10] Analyses of the primary composite outcome included an unadjusted comparison of the percentages of patients who had a primary composite outcome event against the noninferiority margin as well as calculation of an unadjusted odds ratio (for comparison with the adjusted analyses). In addition, the adjusted treatment effect on an odds-ratio scale (with 95% confidence intervals) was estimated with the use of logistic regression to control for age, sex, diabetes, type of surgery, preexisting pulmonary disease, baseline creatinine clearance and hemoglobin concentration, and left ventricular function at baseline.

The adjusted treatment effects (with two-sided 95% confidence intervals) for each of the remaining outcomes, including the expanded secondary composite outcome, were estimated with the same variables that were used in the adjusted analysis of the primary composite outcome. The time to death was summarized with the use of Kaplan–Meier curves, and the treatment groups were compared with the use of the log-rank test.

Subgroup analyses were performed to determine whether the effect of the transfusion strategy varied according to prespecified subgroups. Subgroup-specific estimates of the treatment effect and P values for interaction were derived from both unadjusted and adjusted models that included all the variables used to define the subgroups. Sensitivity analyses were performed in subgroups of patients that were defined according to protocol adherence, transfusion exposure, hemoglobin concentrations, and study site. Modified intention-to-treat analyses of the primary and secondary outcomes examined the consistency of the treatment effect. Because the widths of 95% confidence intervals of absolute risk differences and odds ratios of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects.

Data for this report may be shared in accordance with a data-sharing agreement. Analyses were performed with the use of the R statistical package, version 3.4.3 (R Core Team, November 2017; www.r-project.org).

RESULTS

PARTICIPANTS

A total of 5243 patients underwent randomization at 74 sites in 19 countries; 5092 of these patients were included in the modified intention-to-treat analysis, and 4860 (2430 in each treatment group) were included in the primary per-protocol analy-

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sis (Fig. S1 in the Supplementary Appendix). Six-month follow-up data on the primary outcome were available for 96% of the patients. The baseline characteristics were well balanced between groups (Table 1). Patients in the restrictive-threshold group received fewer units of red cells during transfusion and were less likely to receive a transfusion than those in the liberal-threshold group; they also had a lower mean predischarge hemoglobin concentration (Table 1).

CLINICAL OUTCOMES

At 6 months, a primary outcome event had occurred in 402 of 2317 patients (17.4%) in the restrictive-threshold group and in 402 of 2347 patients (17.1%) in the liberal-threshold group (absolute risk difference before rounding, 0.22 percentage points; 95% CI, –1.95 to 2.39; odds ratio, 1.02; 95% CI, 0.87 to 1.18) (Table 2). The upper bound of the 95% confidence interval of the absolute risk difference in the primary outcome was below the prespecified 3 percentage-point noninferiority margin (P=0.006). Similar results were obtained in the intention-to-treat population (absolute risk difference, 0.44 percentage points; 95% CI, –1.72 to 2.60; odds ratio, 1.03; 95% CI, 0.89 to 1.19; P=0.01 for noninferiority). There were no significant between-group differences in the individual components of the primary composite outcome in both the per-protocol analysis and the modified intention-to-treat analysis (Table 2, and Table S2 in the Supplementary Appendix).

At 6 months of follow-up, 141 of 2291 patients (6.2%) in the restrictive-threshold group had died, as compared with 149 of 2318 patients (6.4%) in the liberal-threshold group (odds ratio, 0.95; 95% CI, 0.75 to 1.21). Time to death is shown in Figure 1.

The expanded secondary composite outcome that included the components of the primary composite outcomes plus hospital readmission, emergency department visit, or coronary revascularization occurred in 43.8% of patients in the restrictive-threshold group and in 42.8% of patients in the liberal-threshold group (odds ratio, 1.04; 95% CI, 0.93 to 1.17). There were no significant between-group differences in the individual components of the expanded secondary composite outcome (Table 2).

Subgroup analyses of the primary outcome identified a qualitative interaction between transfusion strategy and age but not between transfusion strategy and other variables (Fig. 2). The restrictive transfusion strategy was associated with a lower risk of the primary composite outcome than the liberal strategy among patients 75 years of age or older, whereas the liberal strategy was associated with a lower risk of the primary composite outcome than the restrictive strategy among patients younger than 75 years of age. This effect was consistent in the analyses according to decades of age (Fig. 2) (P=0.004 for interaction), with dichotomization at age 75 years (P=0.001 for interaction), with age as a continuous variable with the use of restricted cubic splines (P=0.006 for interaction), after adjustment for all the variables used to define the subgroups (Figs. S2 and S3 in the Supplementary Appendix). Adjusted analyses in which logistic regression was used to control for age, sex, preoperative renal function, diabetes, left ventricular function, pulmonary disease, and type of surgery yielded results that were consistent with those of the primary analyses (Fig. S3 and Table S2 in the Supplementary Appendix). Sensitivity analyses that included only the populations with at least 70%, at least 80%, and 100% adherence to the transfusion protocol or that excluded patients who had a protocol suspension, who did not receive a red-cell transfusion during the first 28 days of hospitalization after the index surgery, or who had a hemoglobin concentration that was never measured below 9.5 g per deciliter during the trial also yielded results that were consistent with those of the primary analyses (Table S3 in the Supplementary Appendix).

DISCUSSION

The 6-month follow-up of the TRICS III trial showed that, in patients who had a moderate-to-high risk of death after cardiac surgery, a restrictive strategy of red-cell transfusion was noninferior to a liberal strategy in terms of the prespecified primary composite outcome of death from any cause, myocardial infarction, stroke, or renal failure with dialysis. At 6 months, there were no significant differences between the restrictive strategy and the liberal strategy in the individual components of the primary composite outcome and of the expanded composite outcome that included hospital readmission, emergency department visit, or coronary revascularization.

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Table 1. Baseline Characteristics of the Patients and In-Hospital Transfusion Outcomes.*

Variable	Restrictive Threshold (N=2430)	Liberal Threshold (N=2430)	Odds Ratio (95% CI)
Baseline characteristics			
Age — yr	72±10	72±10	NA
Male sex — no. (%)	1553 (63.9)	1586 (65.3)	NA
Body-mass index†	28.1±6.0	28.0±5.2	NA
EuroSCORE I score‡	7.9±1.8	7.8±1.9	NA
Previous cardiac surgery — no. (%)	307 (12.6)	280 (11.5)	NA
Myocardial infarction in past 90 days — no. (%)	562 (23.1)	601 (24.7)	NA
Diabetes mellitus — no. (%)	646 (26.6)	686 (28.2)	NA
Treated hypertension — no. (%)	1797 (74.0)	1803 (74.2)	NA
Emergency surgery — no. (%)	37 (1.5)	34 (1.4)	NA
Preoperative hemoglobin concentration — g/dl§	13.1±1.8	13.1±1.7	NA
CABG surgery only — no./total no. (%)	622/2429 (25.6)	645/2430 (26.5)	NA
CABG and valve surgery — no./total no. (%)	464/2429 (19.1)	472/2430 (19.4)	NA
CABG and other, nonvalve surgery — no./total no. (%)	205/2429 (8.4)	203/2430 (8.4)	NA
Valve surgery only — no./total no. (%)	703/2429 (28.9)	716/2430 (29.5)	NA
Other, non-CABG surgery — no./total no. (%)	433/2429 (17.8)	394/2430 (16.2)	NA
Duration of cardiopulmonary bypass — min¶	120±59	121±57	NA
Intraoperative tranexamic acid — no./total no. (%)	2219/2428 (91.4)	2235/2428 (92.1)	NA
Predischarge hemoglobin concentration — g/dl	9.4±1.3	10.2±1.2	NA
In-hospital transfusion outcomes			
≥1 Unit of red cells transfused after randomization — no. (%)	1271 (52.3)	1765 (72.6)	0.41 (0.37–0.47)
Protocol suspension at any time — no. (%)	348 (14.3)	270 (11.1)	1.34 (1.13–1.58)
Plasma transfusion — no. (%)	571 (23.5)	658 (27.1)	0.83 (0.73–0.94)
Platelet transfusion — no. (%)	700 (28.8)	716 (29.5)	0.97 (0.86–1.10)
Cryoprecipitate transfusion — no./total no. (%)	275/2334 (11.8)	275/2349 (11.7)	1.01 (0.84–1.20)
Prothrombin complex concentrate transfusion — no./total no. (%)	73/2334 (3.1)	61/2349 (2.6)	1.21 (0.86–1.71)

* Plus–minus values are means ±SD. There were no significant between-group differences in the listed baseline characteristics, with the exception of predischarge hemoglobin concentration, which was significantly lower in the restrictive-threshold group (P<0.001). Data are presented for 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). Details on baseline characteristics and transfusion outcomes of the intention-to-treat population are provided in Table S1 in the Supplementary Appendix. The restrictive transfusion threshold was a hemoglobin concentration of less than 7.5 g per deciliter intraoperatively and postoperatively, and the liberal transfusion threshold was a hemoglobin concentration of less than 9.5 g per deciliter intraoperatively or postoperatively when the patient was in the intensive care unit (ICU) or less than 8.5 g per deciliter when the patient was in the non-ICU ward. For all ratios, the restrictive-threshold group is in the numerator and the liberal-threshold group in the denominator. CABG denotes coronary-artery bypass graft, and NA not applicable.

† 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 additive European System for Cardiac Operative Risk Evaluation (EuroSCORE) I score 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 score 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.

§ Data on preoperative hemoglobin concentration were missing for one patient in the restrictive-threshold group and in two patients in the liberal-threshold group.

¶ Data on duration of cardiopulmonary bypass were missing for three patients in the restrictive-threshold group and in two patients in the liberal-threshold group.

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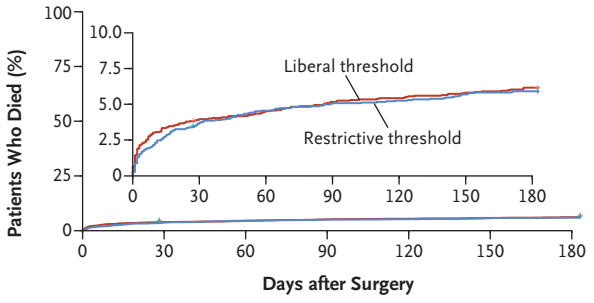
Table 2. Outcomes at 6 Months in the Per-Protocol Population.*

Outcome	Restrictive Threshold (N = 2430)	Liberal Threshold (N = 2430)	Odds Ratio (95% CI)
Primary outcome			
Composite-outcome event — no./total no. (%)	402/2317 (17.4)	402/2347 (17.1)	1.02 (0.87–1.18)
Secondary outcomes†			
Death from any cause — no./total no. (%)	141/2291 (6.2)	149/2318 (6.4)	0.95 (0.75–1.21)
Myocardial infarction — no./total no. (%)	162/2226 (7.3)	164/2237 (7.3)	0.99 (0.79–1.24)
Stroke — no./total no. (%)	88/2199 (4.0)	74/2222 (3.3)	1.21 (0.88–1.66)
New-onset renal failure with dialysis — no./total no. (%)	87/2222 (3.9)	94/2237 (4.2)	0.93 (0.69–1.25)
Expanded secondary composite-outcome event — no./total no. (%)	1015/2318 (43.8)	1006/2348 (42.8)	1.04 (0.93–1.17)
Coronary revascularization — no./total no. (%)	15/2199 (0.7)	19/2214 (0.9)	0.79 (0.40–1.57)
Hospital readmission or emergency department visit — no./total no. (%)	786/2216 (35.5)	746/2223 (33.6)	1.09 (0.96–1.23)
Hospital readmission — no./total no. (%)	577/2204 (26.2)	523/2216 (23.6)	1.12 (1.01–1.32)
No. of hospital readmissions per patient	0.38±0.76	0.34±0.74	
Emergency department visit — no./total no. (%)	579/2201 (26.3)	562/2211 (25.4)	1.07 (0.94–1.22)
No. of emergency department visits per patient	0.44±1.18	0.40±0.95	

* Plus–minus values are means ±SD. The primary composite outcome was death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis within 6 months after the index surgery. The expanded secondary composite outcome was death from any cause, myocardial infarction, stroke, new-onset renal failure with dialysis, coronary revascularization, hospital readmission, or emergency department visit within 6 months after the index surgery.

† None of the between-group differences in secondary outcomes were significant after Bonferroni correction that accounted for multiple comparisons. Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects.

Both transfusion and anemia have been associated with adverse short-term and long-term outcomes after surgery. Observational studies have shown an association between red-cell transfusion and increased mortality and major morbidity within 10 years after cardiac surgery.[4-7] This may be mediated in part by the immunomodulatory effects of red-cell transfusion, which can produce both immunosuppressive and proinflammatory effects and lead to the development of infection or organ dysfunction.[8] In addition, the perception that allogeneic red-cell transfusion is associated with risk is prevalent among patients, with 20% of patients perceiving that transfusion is very often or always risky.[11] Activation of adaptive hypoxic mechanisms has been shown in models of short-term, intermediate-term, and long-term anemia,[12,13] suggesting that prolonged, anemia-induced reductions in tissue oxygen delivery may place an ongoing hypoxic burden that could promote adverse outcomes, a finding that has been reported in observational studies and in patients with cardiovascular disease.[14-21]



No. at Risk

Liberal threshold	2429	2222	2209	2193	2187	2179	2170
Restrictive threshold	2427	2202	2181	2170	2165	2155	2150

Figure 1. Cumulative Incidence of Death from Any Cause.

Kaplan–Meier time-to-event curves show the cumulative incidence of death from any cause among patients who were randomly assigned to a restrictive transfusion strategy (transfusion if the hemoglobin concentration was <7.5 g per deciliter intraoperatively or postoperatively) or a liberal transfusion strategy (transfusion if the hemoglobin concentration was <9.5 g per deciliter intraoperatively or postoperatively when the patient was in the intensive care unit [ICU] or was <8.5 g per deciliter when the patient was in the non-ICU ward). The inset shows the same data on an enlarged y axis.

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Subgroup	No. of Patients	Restrictive Threshold	Liberal Threshold	Unadjusted Odds Ratio (95% CI)	P Value for Interaction
		no. of patients/total no. (%)			
Age					0.004
<45 yr	102	15/53 (28.3)	7/49 (14.3)	2.37 (0.87–6.43)	
45–54 yr	172	25/86 (29.1)	16/86 (18.6)	1.79 (0.88–3.67)	
55–64 yr	507	43/257 (16.7)	30/250 (12.0)	1.47 (0.89–2.44)	
65–74 yr	1556	146/772 (18.9)	129/784 (16.5)	1.18 (0.91–1.54)	
75–84 yr	2108	159/1040 (15.3)	192/1068 (18.0)	0.82 (0.65–1.04)	
≥85 yr	219	14/109 (12.8)	28/110 (25.5)	0.43 (0.21–0.87)	
Sex					0.82
Female	1631	145/824 (17.6)	143/807 (17.7)	0.99 (0.77–1.28)	
Male	3033	257/1493 (17.2)	259/1540 (16.8)	1.03 (0.85–1.24)	
Diabetes					0.31
No	3391	272/1706 (15.9)	276/1685 (16.4)	0.97 (0.81–1.16)	
Yes	1273	130/611 (21.3)	126/662 (19.0)	1.15 (0.87–1.51)	
Creatinine clearance					0.91
≥50 ml/min	3849	283/1927 (14.7)	274/1922 (14.3)	1.04 (0.87–1.24)	
<50 ml/min	813	118/388 (30.4)	128/425 (30.1)	1.01 (0.75–1.37)	
Chronic pulmonary disease					0.86
No	3888	332/1925 (17.2)	336/1963 (17.1)	1.01 (0.85–1.19)	
Yes	776	70/392 (17.9)	66/384 (17.2)	1.05 (0.72–1.52)	
Surgery category					0.74
CABG only	1218	90/598 (15.1)	91/620 (14.7)	1.03 (0.75–1.41)	
Non-CABG	2161	163/1083 (15.1)	169/1078 (15.7)	0.95 (0.75–1.20)	
CABG plus other	1285	149/636 (23.4)	142/649 (21.9)	1.09 (0.84–1.42)	
Left ventricular function					0.85
Good	2887	225/1416 (15.9)	242/1471 (16.5)	0.96 (0.79–1.17)	
Moderate	1378	135/696 (19.4)	124/682 (18.2)	1.08 (0.83–1.42)	
Poor	314	32/160 (20.0)	27/154 (17.5)	1.18 (0.67–2.08)	
Very poor	83	10/45 (22.2)	9/38 (23.7)	0.92 (0.33–2.57)	
Preoperative hemoglobin concentration					0.24
<10.0 g/dl	215	43/113 (38.1)	31/102 (30.4)	1.41 (0.80–2.48)	
10.0–12.0 g/dl	953	97/487 (19.9)	107/466 (23.0)	0.83 (0.61–1.14)	
>12.0 g/dl	3495	262/1716 (15.3)	264/1779 (14.8)	1.03 (0.86–1.24)	

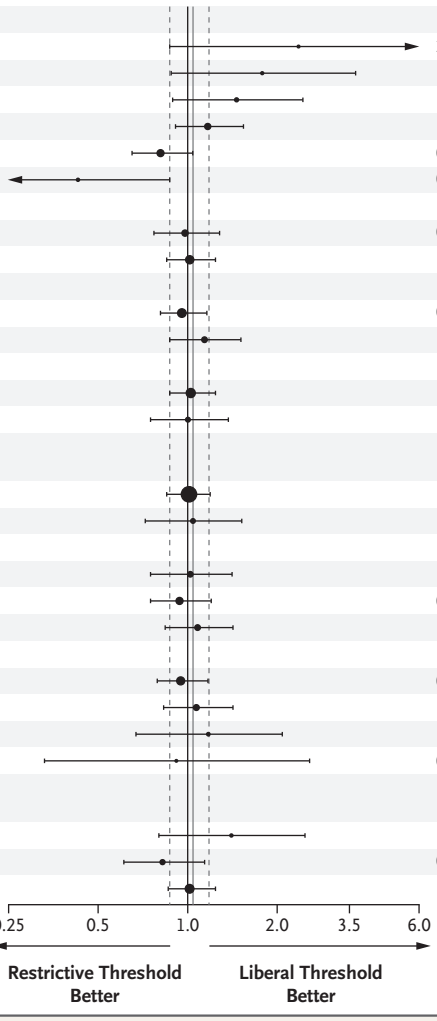

Figure 2. Unadjusted Subgroup Analyses of the Primary Outcome.

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. 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.

Randomized, controlled trials and meta-analyses of studies of cardiac surgery have reported no significant differences in short-term outcomes with restrictive transfusion as compared with liberal transfusion, but the long-term effects have not been well described.[1,2,9,22-25] Until the current analysis, the longest follow-up duration in a randomized, controlled trial was 90 days (in the TITRe2 trial). In that trial, there was no significant difference between the liberal-transfusion group and the restrictive-transfusion group in the primary outcome or in most of the secondary outcomes, although a significant difference in mortality at 90 days after surgery that favored liberal transfusion was observed (4.2% vs. 2.6%, P=0.045).[9] Because the number of patients enrolled in the TRICS III trial was more than double that in the TITRe2 trial, with a duration of fol-

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low-up that was twice as long, the findings provide new information about the long-term outcomes of perioperative transfusion strategies.

The rate of hospital readmission after cardiac surgery was consistent with the rates in other studies.[26,27] Predictors of hospital readmission have included age, chronic obstructive pulmonary disease, lower socioeconomic status, prolonged length of hospital stay, postoperative infection, postoperative renal failure, and left ventricular dysfunction.[27-29] The role of anemia in hospital readmission is unclear. Although a small study identified an association between a hematocrit of less than 30% at discharge and hospital readmission within 30 days,[30] we and others have reported previously that neither red-cell transfusion during the index hospitalization nor the last hemoglobin concentration measured before hospital discharge were associated with hospital readmission for any cause, readmission due to cardiac causes, or death after discharge.[27,31,32]

A significant interaction between transfusion threshold and age was found in our previous study of the 28-day outcomes, in which 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 but not among younger patients.[1] At 6 months, the interaction between age and transfusion threshold became qualitative, with a divergent effect of the restrictive strategy according to age; in patients 75 years or older, the restrictive strategy appeared to be superior to the liberal strategy, whereas in patients younger than 75 years, the liberal strategy was associated with a lower risk of the composite outcome than the restrictive strategy. The interaction was robust in a series of sensitivity analyses according to decades of age, with age as a continuous variable, with restricted cubic splines, and after adjustment for all the variables used to define subgroups. The findings in patients 75 years of age or older appear to contradict the current practice, in which a liberal transfusion strategy is used in older patients undergoing cardiac or noncardiac surgery who thus receive more red cell transfusions than do younger patients.[33,34] One could hypothesize that older patients may have unacceptable adverse effects related to transfusion (e.g., volume overload and inflammatory and infectious complications) or that there may be age-related differences in the adverse-effect profile of transfusion or anemia. Although not significant, the direction of this finding was also present in the TITRe2 trial.[9] The mechanisms underlying any potential differential effect of age on outcomes of transfusion must be further studied within the cardiac surgery population. Our findings suggest the value of incorporating long-term follow-up into studies of perioperative transfusion. Whether transfusion thresholds should differ according to age also needs to be determined in other populations at risk for anemia requiring transfusion.

This analysis has some limitations. First, we did not require physicians to follow the transfusion protocol after day 28 or hospital discharge and are unable to determine the degree to which the differences in hemoglobin concentrations or transfusions continued thereafter. Second, outcome data were obtained from a variety of sources, including telephone contact, hospital records, and database registries. It is possible that some follow-up visits were missed, although there is no reason to believe that missed visits would be more frequent in one treatment group than in the other. In addition, determination of cause of death was not possible. Primary outcome data were available for 96% of the patients; much of the missing data were for patients in the pilot study, in which long-term follow-up was not specified in the study design. Although the possibility of bias in an open-label trial cannot be ruled out, the findings from the various sensitivity analyses were consistent with those of the primary analysis and suggest that the results of our trial are robust.

In conclusion, we performed a large, multicenter, randomized trial comparing a restrictive red-cell transfusion strategy with a liberal strategy in patients undergoing cardiac surgery who had a moderate-to-high risk of death. Overall, the restrictive strategy was noninferior to the liberal strategy with respect to death from any cause, myocardial infarction, stroke, and new-onset renal failure with dialysis at 6 months after surgery.

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APPENDIX

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