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Liberal or Restrictive Transfusion after Cardiac Surgery

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ABSTRACT

BACKGROUND

Whether a restrictive threshold for hemoglobin level in red-cell transfusions, as compared with a liberal threshold, reduces postoperative morbidity and health care costs after cardiac surgery is uncertain.

METHODS

We conducted a multicenter, parallel-group trial in which patients older than 16 years of age who were undergoing nonemergency cardiac surgery were recruited from 17 centers in the United Kingdom. Patients with a postoperative hemoglobin level of less than 9 g per deciliter were randomly assigned to a restrictive transfusion threshold (hemoglobin level <7.5 g per deciliter) or a liberal transfusion threshold (hemoglobin level <9 g per deciliter). The primary outcome was a serious infection (sepsis or wound infection) or an ischemic event (permanent stroke [confirmation on brain imaging and deficit in motor, sensory, or coordination functions], myocardial infarction, infarction of the gut, or acute kidney injury) within 3 months after randomization. Health care costs, excluding the index surgery, were estimated from the day of surgery to 3 months after surgery.

RESULTS

A total of 2007 patients underwent randomization; 4 participants withdrew, leaving 1000 in the restrictive-threshold group and 1003 in the liberal-threshold group. Transfusion rates after randomization were 53.4% and 92.2% in the two groups, respectively. The primary outcome occurred in 35.1% of the patients in the restrictive-threshold group and 33.0% of the patients in the liberal-threshold group (odds ratio, 1.11; 95% confidence interval [CI], 0.91 to 1.34; P=0.30); there was no indication of heterogeneity according to subgroup. There were more deaths in the restrictive-threshold group than in the liberal-threshold group (4.2% vs. 2.6%; hazard ratio, 1.64; 95% CI, 1.00 to 2.67; P=0.045). Serious postoperative complications, excluding primary-outcome events, occurred in 35.7% of participants in the restrictive-threshold group and 34.2% of participants in the liberal-threshold group. Total costs did not differ significantly between the groups.

CONCLUSIONS

A restrictive transfusion threshold after cardiac surgery was not superior to a liberal threshold with respect to morbidity or health care costs. (Funded by the National Institute for Health Research Health Technology Assessment program; Current Controlled Trials number, ISRCTN70923932.)

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Perioperative anemia is common after cardiac surgery and is associated with significant increases in morbidity and mortality.[1-3] The transfusion of allogeneic red cells is the preferred treatment for acute anemia and is also used in patients undergoing cardiac surgery; typically, more than 50% of patients receive a perioperative transfusion,[4,5] which uses a substantial proportion of blood supplies.[6]

Observational studies suggest that transfusion is harmful after cardiac surgery; associations have been reported between transfusion and infection, low cardiac output, acute kidney injury, and death.[2,7,8] In contrast, randomized, controlled trials of red-cell transfusion with restrictive thresholds (i.e., transfusions at lower hemoglobin levels) versus more liberal thresholds (transfusions at higher hemoglobin levels) in a range of acute care and surgical settings have shown no significant differences between the two approaches with respect to adverse events or 30-day mortality.[9] These findings, combined with increasing demands on blood services[10] and the costs of storing, handling, and administering red-cell units,[11] have led to an emphasis on restrictive transfusion thresholds in contemporary blood-management guidelines[12-14] and in health policy statements.[15,16]

Nevertheless, uncertainty about a safe threshold for restrictive red-cell transfusion in cardiac surgery persists and is reflected in the wide range of transfusion rates in cardiac centers in the United Kingdom (25 to 75%)[5] and in the United States (8 to 93%).[4] Uncertainty persists because previous trials comparing liberal and restrictive thresholds in cardiac surgery lacked adequate statistical power,[17-21] and because other trials involved patients who have not undergone cardiac surgery and the results of those trials may not apply to patients with unstable cardiovascular disease.[9,22] To address this uncertainty, we performed the Transfusion Indication Threshold Reduction (TITRe2) trial to test the hypothesis that a restrictive threshold for red-cell transfusion, as compared with a liberal threshold, would reduce postoperative morbidity and health care costs.

Methods

Trial Design and Oversight

TITRe2 was a multicenter, parallel-group, randomized, controlled trial conducted at 17 cardiac surgery centers in the United Kingdom. Details of the methods have been reported previously.[23] The trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment program. A National Health Service research ethics committee approved the study, which was conducted in accordance with the principles of the International Conference on Harmonisation-Good Clinical Practice under the oversight of University Hospitals Bristol National Health Service Foundation Trust. The last author vouches for the data and the analyses and for the fidelity of this report to the study protocol (available with the full text of this article at NEJM.org).

Participants

Patients older than 16 years of age who were undergoing nonemergency cardiac surgery were eligible to participate; exclusion criteria[23] are described in Table S1 in the Supplementary Appendix, available at NEJM.org. Participants provided written informed consent before surgery. If the hemoglobin level dropped below 9 g per deciliter (or the hematocrit fell below 27%) at any time after surgery, the participant was randomly assigned to a study group. Thresholds were expressed in terms of hemoglobin level or hematocrit; hereinafter, hemoglobin threshold should be interpreted as a reference to either hemoglobin level or hematocrit.

Randomization

Patients were randomly assigned to either the liberal transfusion-threshold group (threshold hemoglobin level, 9 g per deciliter) or the restrictive transfusion-threshold group (threshold hemoglobin level, 7.5 g per deciliter) by means of a secure Internet-based system that concealed assignments and used cohort minimization to balance assignments according to center and type of surgery. Physicians and nurses were aware of the group assignments. We intended participants to be unaware of the group assignments and tested our success in keeping the study groups blinded by asking the patients if they were aware of the group they were in.

Interventions

Participants in the liberal-threshold group received a transfusion of 1 unit of red cells immediately after randomization. An additional unit was transfused if the patient's hemoglobin level

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remained below 9 g per deciliter or dropped below 9 g per deciliter again during postoperative hospitalization. In the restrictive-threshold group, 1 unit of red cells was transfused if the hemoglobin level dropped below 7.5 g per deciliter; a further unit was transfused if the level remained below 7.5 g per deciliter or dropped below 7.5 g per deciliter again during postoperative hospitalization.

Physicians could contravene the assigned threshold but had to document the reason for the contravention and record the hemoglobin level at the time of the contravention. Similarly, a physician could permanently discontinue adherence to the assigned treatment threshold. This discontinuation did not constitute withdrawal of the participant from the study, and we continued to collect outcome data in accordance with the protocol for all such participants and included them in the analysis population. Other aspects of postoperative care were carried out in accordance with the center's usual practice. Follow-up consisted of contact with the participants by mail or telephone 3 months after randomization to inquire whether a primary outcome event or some other serious adverse event had occurred, to find out about health resources used since discharge, and to ask questions about general health status and participants' awareness of their random assignment.

OUTCOMES

The primary outcome was a composite of a serious infection (sepsis or wound infection[24-26]) or an ischemic event (permanent stroke, myocardial infarction, infarction of the gut, or acute kidney injury[27]) within 3 months after randomization. Definitions and adjudication procedures are described in Table S2 in the Supplementary Appendix. An event was classified as "present" if it was recorded as having occurred, "absent" if it was confirmed that it had not occurred, and "missing" if it was not possible to confirm whether the event had occurred.

Several secondary outcomes were prespecified, including the number of units of red cells and other blood components transfused after randomization; the occurrence of an infection (either sepsis or wound infection, as for the primary outcome, but not including ischemic events); the occurrence of an ischemic event (permanent stroke, myocardial infarction, infarction of the gut, or acute kidney injury, as for the primary outcome, but not including infections); the duration of stay in the intensive care unit (ICU), a high-dependency unit (in which care is less intensive than in an ICU but more intensive than in a hospital ward), or the hospital; and all-cause mortality. The presence of a clinically significant pulmonary complication (defined according to the need for noninvasive ventilation, reintubation, or ventilation or a tracheostomy) was added as a secondary outcome in an amendment to the protocol dated December 2, 2012. All serious adverse events that occurred during follow-up were documented and coded in accordance with the *Medical Dictionary for Regulatory Activities*, version 14.1; adjudicators of adverse events were unaware of the group assignments.

General health status was assessed at 6 weeks and 3 months after surgery with the use of the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D).[28] The EQ-5D measure of health-related quality of life consists of a descriptive system, which can be converted into a single summary index score (ranging from −0.594 to 1), and a score on a visual-analogue scale (ranging from 0 to 100). For both the index score and the score on a visual-analogue scale, higher scores indicate better quality of life.

ADHERENCE TO THE PROTOCOL

Nonadherence was defined as either the failure to transfuse red cells within 24 hours after a patient's hemoglobin fell below the assigned threshold or the administration of a transfusion when the hemoglobin level was above the assigned threshold. Multiple instances of nonadherence could occur for one patient. An instance of nonadherence was considered to be severe when it changed the classification of a patient with respect to receipt of any transfusion (i.e., when a patient's hemoglobin level fell below the assigned threshold but the patient did not receive any transfusion or when a patient's hemoglobin level never fell below the assigned threshold but the patient did receive a transfusion).

COST ANALYSIS

We performed a cost analysis in accordance with guidelines established in the United Kingdom by the National Institute for Health and Care Excellence.[29] Resources used in the hospital and up to 3 months after surgery were documented, valued

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Table 1. Preoperative and Intraoperative Characteristics.*

Characteristic	Restrictive Transfusion Threshold (N=1000)	Liberal Transfusion Threshold (N=1003)
Preoperative		
Age — yr		
Median	69.9	70.8
Interquartile range	63.1–76.0	64.1–76.7
Male sex — no. (%)	693 (69.3)	680 (67.8)
Body-mass index†	28.2±5.0	28.2±4.9
EuroSCORE‡		
Median	5.0	5.0
Interquartile range	3.0–7.0	3.0–7.0
NYHA class — no./total no. (%)§		
I	235/977 (24.1)	258/974 (26.5)
II	445/977 (45.5)	440/974 (45.2)
III	268/977 (27.4)	257/974 (26.4)
IV	29/977 (3.0)	19/974 (2.0)
CCS angina class — no./total no. (%)¶		
No angina	365/982 (37.2)	353/980 (36.0)
I	169/982 (17.2)	193/980 (19.7)
II	273/982 (27.8)	253/980 (25.8)
III	139/982 (14.2)	142/980 (14.5)
IV	36/982 (3.7)	39/980 (4.0)
Coronary artery disease — no./total no. (%)		
None	310/993 (31.2)	310/998 (31.1)
Single-vessel	112/993 (11.3)	113/998 (11.3)
Double-vessel	132/993 (13.3)	150/998 (15.0)
Triple-vessel	403/993 (40.6)	402/998 (40.3)
Not investigated	36/993 (3.6)	23/998 (2.3)
Stenosis >50% in left main stem — no./total no. (%)	159/987 (16.1)	145/990 (14.6)
Urgent operative priority — no. (%)	126 (12.6)	119 (11.9)
Diabetes — no. (%)	198 (19.8)	201 (20.0)
Hemofiltration or dialysis — no./total no. (%)	7/999 (0.7)	12/1002 (1.2)
Cerebrovascular accident or transient ischemic attack — no. (%)	76 (7.6)	87 (8.7)
Hemoglobin — g/dl	13.3±1.5	13.3±1.5
Estimated GFR — ml/min/1.73 m^2		
Median	74.5	72.8‖
Interquartile range	57.2–92.9	56.4–93.2
Intraoperative		
Cardiac procedure — no. (%)		
CABG only	408 (40.8)	408 (40.7)
Valve only	307 (30.7)	304 (30.3)
CABG and valve	195 (19.5)	203 (20.2)
Major aortic procedure	54 (5.4)	62 (6.2)

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Table 1. (Continued.)

Characteristic	Restrictive Transfusion Threshold (N=1000)	Liberal Transfusion Threshold (N=1003)
Other procedure	36 (3.6)	26 (2.6)
Tranexamic acid used — no./total no. (%)	806/999 (80.7)	809/1002 (80.7)
Aprotinin used — no./total no. (%)	39/942 (4.1)	32/952 (3.4)
Blood-recovery system used — no./total no. (%)	481/999 (48.1)	503/1003 (50.1)

* Plus–minus values are means ±SD. The restrictive transfusion threshold was less than 7.5 g per deciliter, and the liberal transfusion threshold was less than 9 g per deciliter. There were no significant between-group differences at baseline. Details on other preoperative and intraoperative characteristics are provided in Table S3 in the Supplementary Appendix. CABG denotes coronary-artery bypass grafting, and GFR glomerular filtration rate.

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

‡ The European System for Cardiac Operative Risk Evaluation (EuroSCORE) allows the calculation of the risk of death after heart surgery. A score of 0 indicates the lowest level of risk and a score of 44 indicates the highest level of risk; a score of more than 5 is considered to indicate a high risk. Data are missing for 17 patients in the group with a restrictive transfusion threshold and 21 patients in the group with a liberal transfusion threshold.

§ New York Heart Association (NYHA) classes range from I to IV, with higher classes indicating worse condition.

¶ Canadian Cardiovascular Society (CCS) angina classes range from I to IV, with higher classes indicating greater limitations on physical activity owing to angina.

‖ Data were missing for two persons in this group.

in 2012–2013 pounds sterling with the use of national sources[30-33] (wherever possible the valuations were based on actual costs rather than on charges), and converted to U.S. dollars (£1=$1.67). Resources included blood products and any resources associated with complications (including diagnostic tests), length of hospital stay, and various levels of care up to 3 months after surgery; the costs of the index surgery were not included. Further details of the cost analysis are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Basing estimates on previous data[2] and allowing for anticipated nonadherence to the assigned thresholds,[23] we estimated that the frequency of the primary outcome in the group with the restrictive transfusion threshold would be approximately 11% and that the frequency in the group with the liberal threshold would be approximately 17%. We calculated that a sample size of 1468 would be required for the study to have 90% power to detect this difference in a two-sided test, at a 5% level of significance. The target sample size was increased to 2000 to account for uncertainty regarding the rate of nonadherence, since higher-than-expected rates of nonadherence would reduce the power.

All the analyses were performed on an intention-to-treat basis according to a prespecified analysis plan.[34] Continuous data are summarized as means and standard deviations or as medians and interquartile ranges if distributions are skewed. All the analyses were based on mixed-effects methods, with adjustment for the type of surgery as a fixed effect and center as a random effect (described as shared-frailty terms in time-to-event models). Binary outcomes were analyzed with the use of logistic regression. Time-to-event outcomes were analyzed with the use of Cox proportional-hazards models; data on duration of stay in the ICU, a high-dependency unit, and the hospital were censored at the time of a patient's death, and data on the time to death were censored at the time of the last follow-up for survivors. EQ-5D scores were analyzed with the use of mixed-effects, mixed-distribution models.[35]

We compared the frequency of the primary outcome in prespecified subgroups by estimating the interaction between group assignment and subgroup variable. Sensitivity analyses were performed for the primary outcome (as described in the Supplementary Appendix) and for mortality. A 5% significance level (two-sided) was used in the analysis of the main treatment effects and in subgroup analyses, and a 10% significance level was used in the analysis of interactions between assigned group and time in longitudinal

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models. Likelihood-ratio tests were performed. No formal adjustment was made for multiple testing or for an interim analysis.[23,34] All analyses were performed with the use of Stata software, version 12.1 or 13.1 (StataCorp), or SAS software, version 9.3 (SAS Institute).

RESULTS

STUDY POPULATION

Patients were screened for eligibility between July 2009 and February 2013; a total of 3565 consented to take part in the study (Fig. S1 in the Supplementary Appendix), of whom 2007 underwent randomization between July 15, 2009, and February 18, 2013. Four participants withdrew and requested that their data be excluded from the study. Therefore, the analysis population consisted of 2003 participants — 1000 in the restrictive-threshold group and 1003 in the liberal-threshold group.

The baseline characteristics were similar in the two groups (Table 1, and Table S3 in the Supplementary Appendix). The median age was 70.3 years (interquartile range, 63.5 to 76.4), and 68.5% were men. Most patients had undergone coronary-artery bypass grafting (40.7%) or valve surgery (30.5%). A total of 25.7% of the participants received a red-cell transfusion before randomization (Table 2). The baseline characteristics of patients who consented to participate but did not undergo randomization are shown in Table S4 in the Supplementary Appendix.

At discharge, 15.1% of patients believed that they knew which treatment they had received; 75.6% of those patients (115 patients) were correct (Table S13 in the Supplementary Appendix). At 3 months after surgery, a greater number of patients (27.5%) thought that they knew which treatment they had received, but fewer (56.6%) were correct.

HEMOGLOBIN LEVELS AND TRANSFUSIONS

After randomization, the mean nadir in the hemoglobin level was approximately 1 g per deciliter lower in the group assigned to the restrictive threshold than in the group assigned to the liberal threshold (Fig. 1); 53.4% of those in the restrictive-threshold group and 92.2% in the liberal-threshold group received one or more transfusions (risk ratio, 0.58; 95% confidence interval [CI], 0.54 to 0.62, P<0.001) (Table 2, and Table S5 and Fig. S2A in the Supplementary Appendix). A median of 1 unit of red cells (interquartile range, 0 to 2) was transfused in the restrictive-threshold group, and a median of 2 units (interquartile range, 1 to 3) were transfused in the liberal-threshold group. During the entire index admission, 63.7% of the patients in the restrictive-threshold group and 94.9% of those in the liberal-threshold group received transfusions. The use of other blood products was similar in the two groups (Table 2, and Table S5 and Fig. S2B in the Supplementary Appendix). The rate of severe nonadherence was 9.7% in the restrictive-threshold group and 6.2% in the liberal-threshold group, and the rates of any nonadherence were 30.0% and 45.2%, respectively (Table 2).

OUTCOMES

Outcome data at 3 months after randomization were not obtained for 25 participants (1.2%) (Fig. S1 in the Supplementary Appendix). The numbers of patients with data for each outcome analysis are shown in Table S6 in the Supplementary Appendix; for the primary outcome analysis overall, data were missing for 97 of 2003 participants (4.8%). The primary outcome was observed in 35.1% of the patients in the restrictive-threshold group and 33.0% of the patients in the liberal-threshold group (odds ratio, 1.11; 95% CI, 0.91 to 1.34; P=0.30) (Table 3, and Fig. S3 in the Supplementary Appendix). The majority of primary outcome events in each group occurred before hospital discharge (Table S7 in the Supplementary Appendix). The Supplementary Appendix includes additional details regarding the primary outcome, including the reasons for missing data (Table S6), the distribution of primary-outcome events before and after hospital discharge (Table S7), and a Kaplan–Meier plot of the time from randomization to the primary outcome (Fig. S3).

The duration of patient stay in the ICU or high-dependency unit did not differ significantly between the two groups, and the rates of clinically significant pulmonary complications were also similar (Table 3). There were significantly more deaths in the restrictive-threshold group than in the liberal-threshold group (4.2% vs. 2.6%; hazard ratio, 1.64; 95% CI, 1.00 to 2.67; P=0.045). Table S8 in the Supplementary Appendix shows the causes of death. Mortality at 30

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Table 2. Transfusions.*

Type of Transfusion	Restrictive Transfusion Threshold (N=1000)	Liberal Transfusion Threshold (N=1003)	Odds Ratio (95% CI)	P Value
	number (percent)			
≥1 Units of red cells transfused before randomization — no. of patients (%)†	250 (25.0)	264 (26.3)		
Units of red cells transfused after randomization‡				
Total units transfused — no.	1494	2494		
Median — no.	1.0	2.0		
Interquartile range	0–2.0	1.0–3.0		
Distribution — no. of patients (%)			0.58 (0.54– 0.62)§	<0.001
0 units	466 (46.6)	78 (7.8)		
1 unit	193 (19.3)	341 (34.0)		
2 units	152 (15.2)	262 (26.1)		
3 units	66 (6.6)	141 (14.1)		
4 units	50 (5.0)	62 (6.2)		
≥5 units	73 (7.3)	119 (11.9)		
Transfused red cells during entire index admission — no. of patients (%)¶	637 (63.7)	952 (94.9)		
Other transfusions — no. of patients (%)¶				
Fresh-frozen plasma	297 (29.7)	284 (28.3)	1.08 (0.88–1.33)	0.45
Platelets	376 (37.6)	362 (36.1)	1.08 (0.89–1.31)	0.42
Cryoprecipitate	99 (9.9)	102 (10.2)	0.99 (0.72–1.35)	0.95
Activated factor used — no. of patients (%)¶	7 (0.7)	5 (0.5)	1.41 (0.45–4.45)	0.56
Human blood coagulation factor IX used — no. of patients (%)¶	52 (5.2)	48 (4.8)	1.21 (0.73–2.03)	0.46
Severe nonadherence — no. of patients (%)‖	97 (9.7)	62 (6.2)		
Any nonadherence — no. of patients (%)**	300 (30.0)	453 (45.2)		

* Additional details regarding total units of red cells transfused after randomization and other transfusions that were performed are provided in Table S5 and Figure S2 in the Supplementary Appendix. CI denotes confidence interval.

† This category includes intraoperative transfusions (which were performed in 184 of 1000 patients [18.4%] in the restrictive-threshold group and in 180 of 1003 patients [17.9%] in the liberal-threshold group) and postoperative transfusions before randomization (which were performed in 98 of 1000 patients [9.8%] in the restrictive-threshold group and in 114 of 1003 patients [11.4%] in the liberal-threshold group).

‡ This category includes transfusions performed during a reoperation after randomization or after treatment had been discontinued.

§ This estimate is a risk ratio, rather than an odds ratio. The risk ratio reflects the comparison of any transfusion versus no transfusion. This statistic was calculated from an unadjusted logistic-regression model with a log-link function because a model adjusting for cardiac procedure or center would not converge.

¶ This category includes transfusions that were performed before and those that were performed after randomization.

‖ Severe nonadherence changed the classification of a patient as having or not having received a transfusion — that is, a transfusion was not performed in a patient whose hemoglobin level fell below the assigned threshold or a transfusion was performed in a patient whose hemoglobin level was above the assigned threshold.

** Any nonadherence includes instances such as red-cell transfusions performed outside the prescribed 24-hour window or 2 units given consecutively without the hemoglobin level being measured again.

days was 2.6% in the restrictive-threshold group and 1.9% in the liberal-threshold group. Kaplan–Meier curves are shown in Figure S4 in the Supplementary Appendix. EQ-5D scores were similar in the two groups (Table S9 in the Supplementary Appendix). The rate of serious postoperative complications (excluding primary-outcome events) was 35.7% in the restrictive-threshold group and 34.2% in the liberal-threshold group (Table S10 in the Supplementary Appendix).

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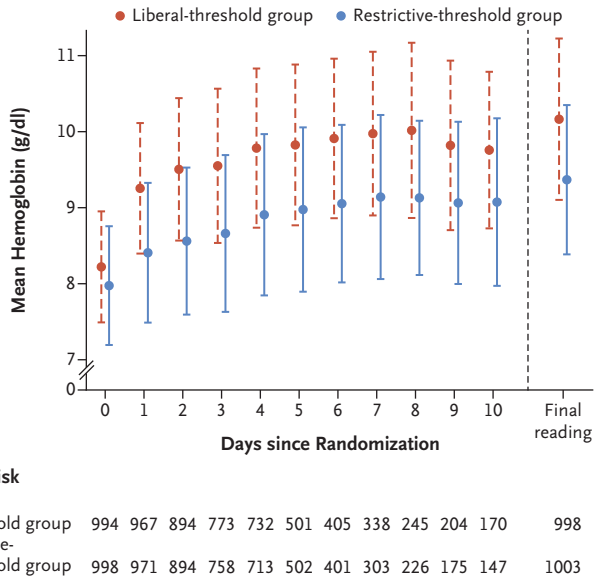

Figure 1. Mean Daily Nadir in Hemoglobin Level.
I bars indicate standard deviations, which were calculated independently at each time point.

SENSITIVITY AND SUBGROUP ANALYSES

When additional acute kidney injury events, identified by means of routinely collected data on creatinine level, were included in the primary outcome, there was a trend toward higher risk in the restrictive-threshold group than in the liberal-threshold group (odds ratio, 1.20; 95% CI, 1.00 to 1.44; P=0.04) (Table S11 in the Supplementary Appendix). A similar trend was seen when patients who received a transfusion before randomization were excluded from the primary-outcome analysis (odds ratio, 1.23; 95% CI, 0.97 to 1.54; P=0.08). When the primary outcome was restricted to serious events, there was no significant difference between the two groups (odds ratio, 0.99; 95% CI, 0.77 to 1.27; P=0.94) (Tables S11 and S12 in the Supplementary Appendix). A further sensitivity analysis showed no significant heterogeneity among sites (P=0.65) and no trend toward a null effect with increases in severe nonadherence (Fig. S5 in the Supplementary Appendix). There was no indication of significant heterogeneity with respect to the primary outcome according to subgroup (Fig. 2).

COSTS

Mean costs associated with red-cell units were £287 ($479) in the restrictive-threshold group and £427 ($713) in the liberal-threshold group (P<0.001). Other cost components and total mean costs up to 3 months after surgery were similar in the two groups (£10,636 [$17,762] in the restrictive-threshold group and £10,814 [$18,059] in the liberal-threshold group) (Table S14 in the Supplementary Appendix).

DISCUSSION

In the TITRe2 trial, we tested the hypothesis that the use of a restrictive threshold, as compared with a liberal threshold, for the transfusion of red cells after cardiac surgery in adults would reduce postoperative morbidity and costs. We observed no significant between-group difference with respect to the primary composite outcome. This finding cannot be explained by the possibility that the study did not have adequate power, since the power of the study was greater than that planned because of the higher-than-expected frequency of the outcome. There were also no significant differences in outcome according to hemoglobin threshold in prespecified subgroup analyses, a finding that is inconsistent with the view that the thresholds for hemoglobin in red-cell transfusions should be adjusted according to the patient's level of risk. More patients in the restrictive-threshold group than in the liberal-threshold group died (4.2% vs. 2.6%). There were no significant differences in other secondary outcomes, including total costs, between the two strategies.

Our results differ from those of observational analyses of transfusion in patients undergoing cardiac surgery,[36] which have uniformly showed that red-cell transfusion is associated with an increased risk of death and other serious adverse outcomes. The difference is probably due to the fact that observational analyses are confounded by prognostic factors that influence the decision to transfuse red cells. In contrast, our results are consistent with findings of a Cochrane review of randomized, controlled trials involving surgical patients and critically ill patients,[9] in which the clinical outcomes in patients who received transfusions with restrictive thresholds for hemoglobin level were similar to those in patients who received transfusion with liberal thresholds.

A restrictive threshold for transfusion is likely to be favored because it requires the use of fewer units of allogeneic red cells. However, the results of our secondary analyses create new

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Table 3. Outcomes.

Outcome	Restrictive Transfusion Threshold (N=1000)	Liberal Transfusion Threshold (N=1003)	Estimated Treatment Effect	
			Odds Ratio or Hazard Ratio (95% CI)	P Value
Serious infection or ischemic event: primary outcome				
Overall	331/944 (35.1)	317/962 (33.0)	1.11 (0.91–1.34)*	0.30
Infectious event†	238/936 (25.4)	240/954 (25.2)	1.02 (0.83–1.26)*	0.83
Sepsis	210/982 (21.4)	214/983 (21.8)		
Wound infection	55/921 (6.0)	46/936 (4.9)		
Ischemic event	156/991 (15.7)	139/991 (14.0)	1.16 (0.90–1.49)*	0.26
Permanent stroke	15/989 (1.5)	17/985 (1.7)		
Myocardial infarction	3/987 (0.3)	4/981 (0.4)		
Gut infarction	6/987 (0.6)	1/982 (0.1)		
Acute kidney injury	140/989 (14.2)	122/989 (12.3)		
Stage 1	49/989 (5.0)	40/989 (4.0)		
Stage 2	39/989 (3.9)	35/989 (3.5)		
Stage 3	50/989 (5.1)	46/989 (4.7)		
Secondary outcomes				
No. of hours in ICU or high-dependency unit‡				
Median	49.5	45.9	0.97 (0.89–1.06)§	0.53
Interquartile range	21.9–99.7	20.1–94.8		
No. of days in hospital¶				
Median	7.0	7.0	1.00 (0.92–1.10)§	0.94
Interquartile range	5.0–10.0	5.0–10.0		
All-cause mortality at 90 days	42/1000 (4.2)	26/1003 (2.6)	1.64 (1.00–2.67)§	0.045
Clinically significant pulmonary complications	127/979 (13.0)	116/982 (11.8)	1.11 (0.85–1.45)*	0.45
All-cause mortality at 30 days	26/1000 (2.6)	19/1003 (1.9)		

* This value is an odds ratio.
† Since the amount of missing data was greater than 5% (owing primarily to missing data on posthospital discharge), a separate treatment estimate was estimated for infections that occurred before hospital discharge (according to the rules regarding missing data outlined in the statistical analysis plan in the study protocol). For this treatment effect, we estimated an odds ratio of 1.07 (95% CI, 0.85 to 1.36; P=0.55).
‡ The duration of stay in the intensive care unit (ICU) or high-dependency unit after randomization was 0 days for 63 patients in the restrictive-threshold group and 61 patients in the liberal-threshold group; data were censored for 23 patients in the restrictive-threshold group and 15 patients in the liberal-threshold group. In addition, 37 patients in the restrictive-threshold group and 32 patients in the liberal-threshold group had more than one admission to the ICU or high-dependency unit.
§ This value is a hazard ratio.
¶ The duration of hospital stay after randomization was 0 days for 4 patients in the restrictive-threshold group and 2 patients in the liberal-threshold group; data were censored for 25 patients in the restrictive-threshold group and 17 patients in the liberal-threshold group.

uncertainty regarding the use of a restrictive threshold for transfusion after cardiac surgery. It is challenging to interpret the results of secondary analyses when several statistical tests are performed,[37] but the higher frequency of death in the restrictive-threshold group, which per-

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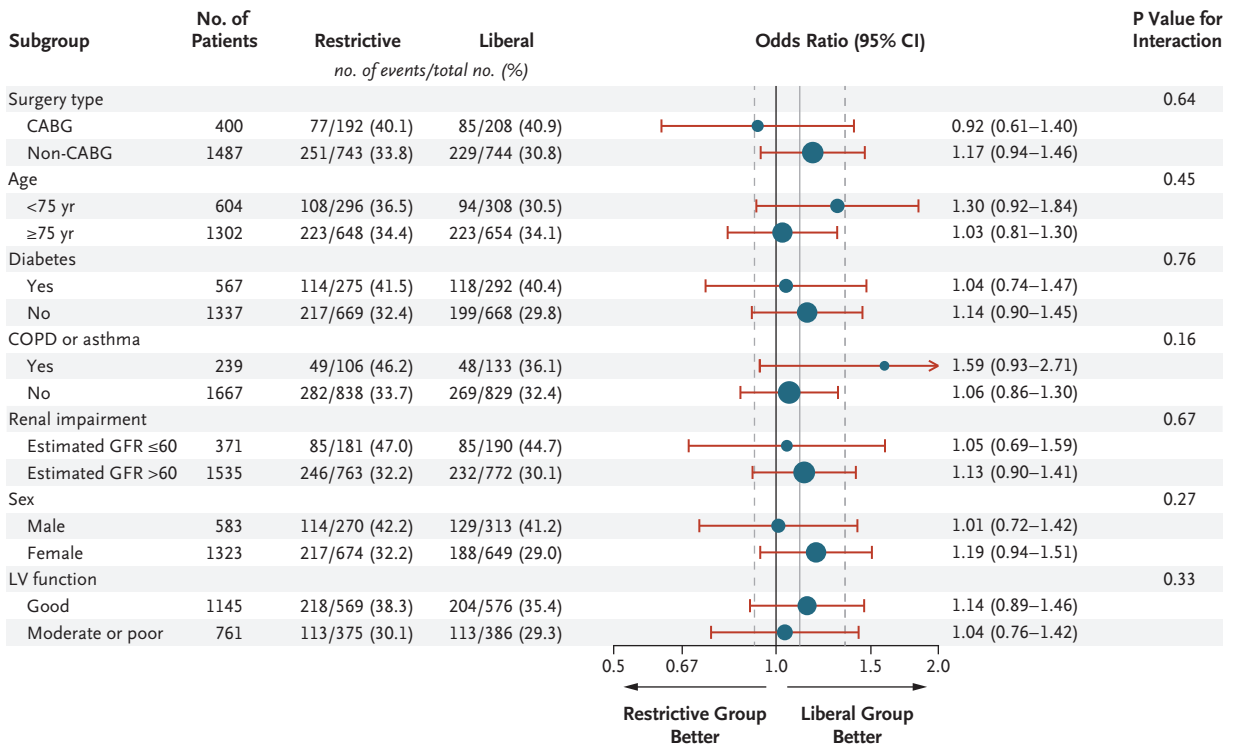

Figure 2. Subgroup Analyses.

The gray vertical lines represent the overall treatment estimate (solid line) and the 95% confidence interval (dashed lines) for the primary outcome as calculated for the entire analysis cohort. The sizes of the circles designating the point estimates reflect the sizes of the subgroups. The restrictive transfusion threshold for hemoglobin was less than 7.5 g per deciliter, and the liberal transfusion threshold was less than 9 g per deciliter. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, GFR glomerular filtration rate, and LV left ventricular.

sisted in sensitivity analyses (Table S11 in the Supplementary Appendix), is a cause for concern. It is not clear in what way anemia that was attributable to the restrictive threshold may have resulted in an increased number of deaths. The difference in hemoglobin level between the groups was modest (1 g per deciliter), and an assessment of causes of death or of severe adverse events that preceded death did not suggest a cause-and-effect relationship, although establishing a cause-and-effect relationship may have been an unrealistic expectation given the small number of deaths that occurred and given a medical setting (cardiac surgery) in which death typically occurs after a sequence of adverse events. A benefit from transfusion with a more liberal hemoglobin threshold was also suggested in two sensitivity analyses of the primary outcome, one in which patients who had received a transfusion before randomization were excluded and one in which additional acute kidney injury events, as determined on the basis of serial data on creatinine levels, were included. These findings seem to support a hypothesis that the use of a more liberal hemoglobin threshold may be beneficial in patients with a hemoglobin level of less than 9 g per deciliter after cardiac surgery.

This hypothesis is clinically plausible. The TITRe2 trial differs from previous large trials of transfusion thresholds in that all the participants had cardiovascular disease[38,39]; in addition, a substantial proportion of participants are likely to have been dependent on oxygen supplementation in the immediate postoperative period.[40,41] Therefore, patients undergoing cardiac surgery are often at the limits of their cardiovascular reserve and may benefit from higher hemoglobin levels. Such patients were excluded

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from the only contemporary trial we could find that showed restrictive transfusion to be beneficial, a trial that assessed transfusion thresholds in patients with acute upper gastrointestinal bleeding.[42] In contrast, a large trial involving patients with hip fracture,[43] in which 63% of the participants had cardiovascular disease, showed no benefit from restrictive transfusion, and a more recent feasibility trial of transfusion thresholds in patients with unstable coronary disease (myocardial infarction) showed a reduced risk of death among patients who received transfusions at a more liberal hemoglobin threshold.[44] Patients with cardiovascular disease may represent a specific high-risk group for which more liberal transfusion thresholds are to be recommended. This hypothesis should be tested in future pragmatic trials.

The main limitation of our trial was our inability to keep health care staff unaware of the group assignments. However, the use of objective end points and the adjudication of end points by personnel who were unaware of the group assignments protected against detection bias. The nature of nonadherence to protocol differed according to group but affected the overall transfusion rate in only a small percentage of participants. This percentage was similar in the two groups. Another limitation was that prospective data collection failed to identify acute kidney injury events that were apparent on the basis of the routinely collected data on serial creatinine levels. We attribute this discrepancy to differences among centers in the baseline creatinine value used to define acute kidney injury.[45] Finally, we cannot exclude the possibility that other transfusion thresholds, or a wider differential between the two transfusion thresholds, could have altered the results.

In conclusion, the TITRe2 trial compared a restrictive transfusion threshold with a liberal transfusion threshold after cardiac surgery. The restrictive threshold was not superior to the liberal threshold with respect to postoperative morbidity or total costs.

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

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