Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases?*

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**Objective:** To compare a restrictive red blood cell transfusion strategy with a more liberal strategy in volume-resuscitated critically ill patients with cardiovascular disease.

**Setting:** Twenty-two academic and three community critical care units across Canada.

**Study Design:** Randomized controlled clinical trial.

**Study Population:** Three hundred fifty-seven critically ill patients with cardiovascular diseases from the Transfusion Requirements in Critical Care trial who had a hemoglobin concentration of <90 g/L within 72 hrs of admission to the intensive care unit.

**Interventions:** Patients were randomized to a restrictive strategy to receive allogeneic red blood cell transfusions at a hemoglobin concentration of 70 g/L (and maintained between 70 and 90 g/L) or a liberal strategy to receive red blood cells at 100 g/L (and maintained between 100 and 120 g/L).

**Results:** Baseline characteristics in the restrictive (n = 160) and the liberal group (n = 197) were comparable, except for the use of cardiac and anesthetic drugs (p < .02). Average hemoglobin concentrations (85 ± 6.2 vs. 103 ± 6.7 g/L; p < .01) and red blood cell units transfused (2.4 ± 4.1 vs. 5.2 ± 5.0 red blood cell units; p < .01) were significantly lower in the restrictive compared with the liberal group. Overall, all mortality rates were similar in both study groups, including 30-day (23% vs. 23%; p = 1.00), 60-day, hospital, and intensive care unit rates. Changes in multiple organ dysfunction from baseline scores were significantly less in the restrictive transfusion group overall (0.2 ± 4.2 vs. 1.3 ± 4.4; p = .02). In the 257 patients with severe ischemic heart disease, there were no statistically significant differences in all survival measures, but this is the only subgroup where the restrictive group had lower but nonsignificant absolute survival rates compared with the patients in the liberal group.

**Conclusion:** A restrictive red blood cell transfusion strategy generally appears to be safe in most critically ill patients with cardiovascular disease, with the possible exception of patients with acute myocardial infarcts and unstable angina. (Crit Care Med 2001; 29:227–234)

**Key Words:** critical care; cardiovascular disease; red blood cell transfusion practice; oxygen delivery; transfusion trigger; anemia; ischemic heart disease; hemoglobin; cardiac surgery; vascular surgery

Although approximately 31% of critically ill patients receive allogeneic red blood cell transfusions (1), there remain divergent views regarding the risks and benefits of treating anemia in anemic patients with cardiovascular diseases. On one hand, laboratory-based studies suggest that patients with cardiovascular disease may require higher hemoglobin concentrations to maintain oxygen delivery in occluded or diseased coronary arteries (2, 3). On the other hand, the transfusion of red blood cells is postulated to induce clinically important immune suppression (4), increasing nosocomial infections in recipients. In addition, the storage of red blood cells may decrease the ability of the red cell to transport, release, or deliver oxygen through an abnormal microcirculation (5).

Recently, we published a randomized clinical trial demonstrating that a restrictive transfusion strategy was at least as safe as, and possibly superior to, a more liberal approach to red blood cell transfusion in a diverse group of critically ill patients (6). This study, however, provided limited data about patients with cardiovascular diseases, a group at considerable risk for complications associated with moderate anemia and transfusion. Few clinical trials have examined the consequences of anemia and transfusion practice in patients who have cardiovascular disease. Two small, randomized, controlled trials (7, 8) examined transfusion practice in patients undergoing coronary artery bypass grafting and concluded that a conservative approach to the administration of red cells may be safe. However, two recent cohort studies suggested that anemia may increase the risk of mortality in patients with cardiovascular disease after surgery (9) and critical illness (1). The consequences of moderate anemia are therefore of particular concern in patients with cardiovascular disease. To better understand the potential adverse effects of anemia and transfusion in this high-risk population, we compared clinical outcomes after the implementation of either a restrictive or a liberal transfusion strategy in patients with...
cardiovascular disease who participated in recently published Transfusion Requirements in Critical Care (TRICC) trial (6).

METHODS

Brief Description of the TRICC Trial

The TRICC trial was a randomized, controlled, clinical trial that enrolled 838 critically ill patients who had a hemoglobin concentration of ≤90 g/L within 72 hrs of intensive care unit (ICU) admission and were considered volume resuscitated by the attending staff. Physicians caring for patients who were allocated to the restrictive red blood cell transfusion strategy were instructed to transfuse one red blood cell unit when hemoglobin concentrations decreased below 70 g/L and maintain concentrations between 70 and 90 g/L. In the liberal red blood cell group, hemoglobin concentrations were maintained between 100 and 120 g/L, and a red blood cell unit was administered when hemoglobin values decreased below 100 g/L. Hemoglobin concentrations were measured after each red blood cell unit transfused in all study patients. The protocol directed transfusion regimens only during the patients’ ICU stay. Upon their discharge to a hospital ward, a copy of the patient's guidelines was attached to the patient's chart with a request that the guidelines be followed as much as possible.

In Canada, red blood cell units were provided by the Canadian Red Cross Society and were transfused at no charge to the patients. Red cell concentrate was stored in a citrate/phosphate/dextrose/adenine anticoagulant solution. During the study, units were not leukodepleted.

The primary outcome in the TRICC study was 30-day all-cause mortality. Secondary outcomes included other mortality rates and rates of organ failure. For the present report, we identified a subgroup of patients within the trial who were considered at increased risk of morbidity or mortality from anemia because they had a diagnosis related to coronary artery disease. We included all patients with a cardiac or vascular diagnosis as either the primary or secondary diagnosis and all patients with known acute or chronic coronary artery disease. A detailed description of the TRICC trial protocol and overall results were reported previously (6).

The TRICC study protocol was approved by the institutional review board of each participating institution, and informed consent was obtained from either the patient or the closest family member before enrollment in the study.

Establishing the Patient's Diagnosis

In this subgroup analysis, we identified all patients at risk for anemia because of heart disease. Therefore, we selected all patients with a primary or secondary ICU admission diagnosis of a cardiovascular disease, as well as those patients with cardiac disease as an important comorbid illness defined as New York Heart Association class III or IV. As a second step, we examined all patients who were known to have ischemic heart disease. The diagnosis most responsible for the patient’s ICU admission was recorded. As many as three secondary diagnoses and up to eight separate comorbid conditions were identified. All diagnoses were adjudicated by two of four critical care physicians who were members of the TRICC trial Executive Committee. Adjudicators were blinded to patient outcomes. Disagreements were resolved through consensus.

In postoperative patients, the procedure performed and the responsible diagnosis were recorded. The cardiovascular disease category included all diagnoses related to ischemic heart disease (myocardial infarct, angina, congestive heart failure, and cardiogenic shock), rhythm disturbances, cardiac arrest, other forms of shock, uncontrolled hypertension, and cardiac and vascular surgical procedures such as abdominal aortic aneurysm repair and peripheral vascular surgical procedures. All data were coded by an expert data analyst who used the International Classification of Diseases, Ninth Edition.

Statistical Analyses

The final analysis was conducted on an intention-to-treat basis. Hemoglobin concentrations over time were compared by using repeated measures analysis of variance, followed by Tukey's honestly significant difference test for pairwise comparisons. Mortality rates and the number of organs failing per patient were compared by using the Fisher's exact test. Stepwise logistic regression was used to adjust raw mortality proportions in two stages: first by using covariates with p < .10, and second by forcing potential confounders—including patient age, acute Physiology and Chronic Health Evaluation (APACHE) II score, comorbid illness, diagnostic category, and the center—into the logistic model. Kaplan-Meier survival curves, describing the survival experience for each transfusion strategy, were compared by using a log rank test statistic. Multiple organ dysfunction (MOD) scores and MOD scores adjusted for death were analyzed with an independent Student's t-test. Complications were compared by using a Fisher’s exact test. Lengths of ICU and hospital stay were analyzed with the Wilcoxon rank sum test for independent samples. Comparisons involving primary outcomes were considered statistically significant with an overall two-sided alpha of .05. No adjustments were made for multiple comparisons. Absolute p values and 95% confidence intervals (CI) are reported.

RESULTS

Study Population

Of the total of 838 patients who fulfilled all eligibility requirements and were enrolled in the TRICC trial, 357 (43%) patients had cardiovascular disease: 160 in the restrictive red blood cell transfusion group and 197 in the liberal red blood cell transfusion group. All patients in this subgroup analysis completed the clinical trial and were followed for 30 days. One patient was lost to follow-up at 60 days.

All baseline characteristics except for the use of cardiac medications (75% vs. 85%; p = .02) and anesthetic agents (17% vs. 7%; p < .01) were balanced equally among the patients with cardiovascular disease. Patients were allocated randomly to either the restrictive or liberal allogeneic transfusion strategies (p > .05) (Table 1). Less frequent diuretic use in the restrictive group (43% vs. 58%; p < .01) accounted for the observed difference in cardiac medications between groups, whereas the use of epidural anesthetic medications was greater in the restrictive group (8% vs. 2%; p < .01). Overall, study participants with cardiovascular disease had an elevated APACHE II score averaging 23, and >85% were mechanically ventilated.

Were Transfusion Protocols Appropriately Implemented?

Average daily hemoglobin concentrations were 85 ± 6.2 g/L in the restrictive transfusion group and 103 ± 6.7 g/L in the liberal transfusion group (p < .01). Hemoglobin concentrations were significantly different over time as shown in Figure 1. Once randomized, there was a 53% relative decrease in the number of red blood cell units transfused per patient in the restrictive group compared with the liberal transfusion group (2.4 ± 4.1 vs. 5.2 ± 5.0 red blood cell units per patient; p < .01). Physician nonadherence, defined as measured hemoglobin concentrations outside of prespecified ranges for at least 48 hrs, occurred in 4.1% (8 of 197) of patients in the liberal
Table 1. Baseline characteristics in the 357 patients with cardiovascular diseases

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Restrictive Group (n = 160)</th>
<th>Liberal Group (n = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean ± SD</td>
<td>64.0 ± 14.1</td>
<td>65.6 ± 13.7</td>
</tr>
<tr>
<td>APACHE II score, mean ± SD</td>
<td>22.7 ± 7.6</td>
<td>23.1 ± 8.2</td>
</tr>
<tr>
<td>MOD score, means ± SD</td>
<td>8.4 ± 3.6</td>
<td>7.8 ± 3.9</td>
</tr>
<tr>
<td>No. organs failing (MSOF) (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>35 (22)</td>
<td>55 (28)</td>
</tr>
<tr>
<td>One</td>
<td>66 (41)</td>
<td>84 (43)</td>
</tr>
<tr>
<td>Two</td>
<td>38 (24)</td>
<td>33 (17)</td>
</tr>
<tr>
<td>Three</td>
<td>16 (10)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>More than three</td>
<td>5 (3)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Primary cardiac diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease (no CABG)</td>
<td>20 (13)</td>
<td>27 (14)</td>
</tr>
<tr>
<td>Ischemic heart disease (with CABG)</td>
<td>11 (7)</td>
<td>19 (10)</td>
</tr>
<tr>
<td>Pulmonary embolism/RV failure</td>
<td>9 (6)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>36 (23)</td>
<td>34 (17)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>19 (12)</td>
<td>26 (13)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>9 (6)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>10 (6)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>8 (5)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (6)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>26 (16)</td>
<td>36 (18)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Transfusions (units per patient) before ICU admission</td>
<td>2.3 ± 3.9 (n = 158)</td>
<td>2.5 ± 4.6 (n = 195)</td>
</tr>
<tr>
<td>ICU interventions, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation, n (%)</td>
<td>136 (85)</td>
<td>175 (89)</td>
</tr>
<tr>
<td>Pulmonary artery flotation catheter, n (%)</td>
<td>82 (51)</td>
<td>108 (55)</td>
</tr>
<tr>
<td>Noninvasive pressure ventilation</td>
<td>5 (3)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>13 (8)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Vascular catheters</td>
<td>149 (94)</td>
<td>187 (94)</td>
</tr>
<tr>
<td>Nutrition</td>
<td>75 (47)</td>
<td>90 (46)</td>
</tr>
</tbody>
</table>

APACHE II, Acute Physiology and Chronic Health Evaluation II; MOD, multiple organ dysfunction; MSOF, multiple system organ dysfunction; CABG, coronary artery bypass graft; RV, right ventricle; ICU, intensive care unit.

**Figure 1.** Mean daily hemoglobin concentration in patients in the restrictive and liberal allogeneic red blood cell transfusion groups. Hemoglobin concentration (g/L) in each cardiac patient was measured at least once daily. Error bars represent srs. Daily hemoglobin means were significantly greater in the liberal group (dashed line) than in the restrictive group (solid line) during the 30-day period (p < .0001 using analysis of variance).
discernible differences in 30- and 60-day as well as ICU mortality rates (see Table 4). However, we noted a nonsignificant ($p = 0.3$) decrease in overall survival rate in the restrictive group (Fig. 3) in the patient group with confirmed ischemic heart disease, severe peripheral vascular disease, or severe comorbid cardiac disease.

**DISCUSSION**

We evaluated whether anemic, ill patients with cardiovascular disease might be at increased risk of adverse outcomes from the anemia. In this subgroup analysis from the TRICC trial, mortality among patients with cardiovascular diseases was not significantly increased in the cohort randomized to the restrictive red blood cell transfusion strategy. There were also no clinically important mortality differences in the subgroup of 257 patients with known coronary artery disease. Complication rates including new myocardial infarction were not significantly different after the use of the restrictive red blood cell transfusion strategy.

As a measure of morbidity, the degree of MOD was comparable between the two groups. Therefore, the use of a transfusion threshold as low as 70 g/L combined with maintenance of hemoglobin concentrations between 70 and 90 g/L was as safe as the more liberal red blood cell transfusions strategy in volume-resuscitated critically ill patients with cardiovascular disease. This suggests that in patients with heart disease, the restrictive strategy should be considered the approach of choice for the critically ill patient, not only because of an inability to detect harm but also because the maintenance of hemoglobin concentrations between 70 and 90 g/L decreased the average number of red blood cell units transfused by 53%.

Because the myocardium extracts near-maximal concentrations of oxygen from blood under resting conditions, the heart muscle increases coronary blood flow as a primary adaptive response to increased oxygen demand or decreased oxygen supply (11, 12). Thus, it has been hypothesized that when anemia results in limited oxygen delivery, the myocardium is at increased risk of ischemic injury. Laboratory studies have examined the effects of normovolemic anemia on the coronary circulation (11–17). The available data suggest minimal consequences with hemoglobin concentrations as low as 70 g/L, when the coronary circulation is free from occlusion (11, 12). However, myocardial dysfunction and ischemia either occur earlier or are more noteworthy in anemic animals with moderate to high-grade coronary stenosis compared with controls with normal hemoglobin concentrations (13–15, 17). In addition, hypermetabolism, increased cardiac output, and myocardial dysfunction observed in patients with severe sepsis and septic shock (18, 19) may further increase the risk of significant morbidity and mortality from a restrictive red blood cell transfusion strategy in critically ill patients with concomitant coronary artery disease. Inferences from many of these studies in experimental animals should be

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**Table 2. Outcomes in the 357 patients with cardiovascular disease**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Restrictive Group ($n = 160$)</th>
<th>Liberal Group ($n = 197$)</th>
<th>Difference</th>
<th>95% CI of Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality rates, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day</td>
<td>36 (23)</td>
<td>45 (23)</td>
<td>0.3%</td>
<td>-8.4% to 9.1%</td>
</tr>
<tr>
<td>60-day ($n = 356$)</td>
<td>42 (26)</td>
<td>53 (27)</td>
<td>0.8%</td>
<td>-8.4% to 10.0%</td>
</tr>
<tr>
<td>ICU</td>
<td>31 (19)</td>
<td>32 (16)</td>
<td>-3.1%</td>
<td>-4.8% to 11.1%</td>
</tr>
<tr>
<td>Hospital</td>
<td>43 (27)</td>
<td>56 (28)</td>
<td>1.9%</td>
<td>-6.9% to 10.9%</td>
</tr>
<tr>
<td>Organ failure and dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MODS ($n = 351$)</td>
<td>8.6 ± 4.9</td>
<td>9.0 ± 4.4</td>
<td>0.4</td>
<td>-0.6 to 1.4</td>
</tr>
<tr>
<td>ΔMODS ($n = 351$)</td>
<td>0.2 ± 4.2</td>
<td>1.28 ± 4.4</td>
<td>1.1</td>
<td>0.1 to 2</td>
</tr>
<tr>
<td>MODS* ($n = 357$)</td>
<td>11.1 ± 7.6</td>
<td>11.9 ± 7.9</td>
<td>0.7</td>
<td>-0.8 to 2.4</td>
</tr>
<tr>
<td>ΔMODS* ($n = 357$)</td>
<td>2.7 ± 6.9</td>
<td>4.0 ± 7.3</td>
<td>1.3</td>
<td>-0.2 to 2.8</td>
</tr>
<tr>
<td>Length of stay (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU (days)</td>
<td>9.2 ± 9.1</td>
<td>11.3 ± 11.6</td>
<td>2</td>
<td>-0.2 to 4.3</td>
</tr>
<tr>
<td>Hospital (days)</td>
<td>33.0 ± 19.6</td>
<td>35.1 ± 19.5</td>
<td>2.2</td>
<td>-2 to 6.2</td>
</tr>
</tbody>
</table>

CI, confidence interval; ICU, intensive care unit; MODS, multiple organ dysfunction score; ΔMODS, change in multiple organ score from baseline values.

*Nonsurvivors are considered to have all organs failing on date of death.
viewed with some skepticism, given that most studies used isolated coronary occlusion models rather than diffuse ath- erosclerotic coronary models.

Two small, randomized, clinical trials compared transfusion strategies in patients undergoing coronary artery bypass grafting (7, 8). Although the sample sizes were small, neither study documented increased rates of postoperative complications after the maintenance of normovol- emic anemia. Among other relevant reports, there are numerous observational studies of severe anemia being well tolerated in perioperative and critical care settings (1, 9, 20, 21). In an obser-

vational study examining the association between transfusion practice and mortality, critically ill patients (9) with cardiovascular disease were more likely to die when hemoglobin concentrations decreased below 95 g/L (55% vs. 42%; \( p = .09 \)) compared with anemic patients with other diagnoses. In this same study, patients with anemia, a high APACHE II score (>20), and a cardiovascular diagnosis had a significantly lower mortality rate when transfused with either 1–3 or 4–6 red blood cell units. The ICU mor-
tality rate was 55% if patients were not given any red blood cells vs. 35% when given 1–3 red blood cell units or 32% when administered 4–6 red blood cell units, respectively \( (p = .01) \) (9).

In their trial examining postoperative infection and mortality in cardiac surgery patients, van de Watering et al. (22) noted that there was no difference in mortality in patients receiving 1–3 units of buffy coat-depleted red cells, fresh-filtered red cells, or stored-filtered red cells. How-

ever, in patients receiving more than three units, there was a statistically signif-
ificant difference between those patients transfused with buffy coat-depleted red cells and patients transfused with filtered red cell units \( (p = .005) \). As well, the infection rate in patients receiving buffy coat-depleted cells was higher than in patients receiving filtered red cells, although the difference was not statistically significant. In Jehovah’s Witness patients undergoing surgical interventions (9), the adjusted odds of death increased from 2.3 (95% CI, 1.4–4.0) to 12.3 (95% CI, 2.5–62.1) as preoperative hemoglobin concentrations declined from a range of 100–109 to 60–69 g/L in patients with cardiovascular disease. In noncardiovas-
cular patients with comparable levels of anemia, there appeared to be no impact from anemia on 30-day mortality. Differ-
ences between the present study and the two observational studies may be due to biases and confounding affecting the ob-
servational designs.

The inability to document differences in outcomes in patients with cardiac dis-
 ease also may result from a small sample size, the heterogeneity of patients, or the diversity of therapeutic interventions in this subgroup analysis. In addition, coro-

nary artery disease was documented in

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Restrictive Group ((n = 111))</th>
<th>Liberal Group ((n = 146))</th>
<th>Difference</th>
<th>95% CI of Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality rates, n (%)</td>
<td></td>
<td></td>
<td>-4.9%</td>
<td>-15.3% - 5.6%</td>
</tr>
<tr>
<td>30-day</td>
<td>29 (26)</td>
<td>31 (21)</td>
<td>-4.0%</td>
<td>-14.9% - 6.9%</td>
</tr>
<tr>
<td>60-day</td>
<td>32 (29)</td>
<td>36 (25)</td>
<td>-6.3%</td>
<td>-16.2% - 3.5%</td>
</tr>
<tr>
<td>ICU</td>
<td>26 (23)</td>
<td>25 (17)</td>
<td>-2.1%</td>
<td>-13.2% - 8.9%</td>
</tr>
<tr>
<td>Hospital</td>
<td>32 (29)</td>
<td>39 (27)</td>
<td>-3.4%</td>
<td>-12.3% - 5.5%</td>
</tr>
<tr>
<td>Organ failure and dysfunction</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MODS</td>
<td>9.1 ± 5.0</td>
<td>9.1 ± 4.5</td>
<td>0.1</td>
<td>-1.2 - 1.2</td>
</tr>
<tr>
<td>ΔMODS</td>
<td>0.31 ± 4.3</td>
<td>1.00 ± 4.3</td>
<td>0.7</td>
<td>-0.4 - 1.8</td>
</tr>
<tr>
<td>MODS*</td>
<td>11.8 ± 8.2</td>
<td>11.6 ± 7.5</td>
<td>-0.3</td>
<td>-2.2 - 1.7</td>
</tr>
<tr>
<td>ΔMODS*</td>
<td>3.0 ± 7.1</td>
<td>3.4 ± 6.7</td>
<td>0.4</td>
<td>-1.3 - 2.2</td>
</tr>
<tr>
<td>Length of stay (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU (days)</td>
<td>9.3 ± 9.7</td>
<td>10.4 ± 10.3</td>
<td>1.1</td>
<td>-1.4 - 3.6</td>
</tr>
<tr>
<td>Hospital (days)</td>
<td>28.7 ± 19.5</td>
<td>30.6 ± 18.8</td>
<td>1.9</td>
<td>-6.7 - 2.8</td>
</tr>
</tbody>
</table>

\*Non-survivors are considered to have all organs failing on date of death.

Table 3. Description of the 257 patients with ischemic heart disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Restrictive ((n = 111))</th>
<th>Liberal ((n = 146))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>79 (46)</td>
<td>92 (54)</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>66.1 ± 12.6</td>
<td>66.6 ± 13.1</td>
</tr>
<tr>
<td>APACHE II score (mean ± SD)</td>
<td>7.69 ± 0.73</td>
<td>7.87 ± 0.65</td>
</tr>
<tr>
<td>APACHE II &lt; 20, n (%)</td>
<td>36 (32)</td>
<td>50 (34)</td>
</tr>
<tr>
<td>APACHE II &gt; 20, n (%)</td>
<td>73 (68)</td>
<td>96 (66)</td>
</tr>
<tr>
<td>Primary diagnoses, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease (no CABG)</td>
<td>17 (15)</td>
<td>19 (13)</td>
</tr>
<tr>
<td>Ischemic heart disease (with CABG)</td>
<td>8 (7)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>26 (23)</td>
<td>36 (25)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>33 (30)</td>
<td>33 (23)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4 (4)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1 (1)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>2 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>5 (5)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Any comorbid illness, n (%)</td>
<td>63 (41)</td>
<td>92 (59)</td>
</tr>
<tr>
<td>Cardiac comorbidity, n (%)</td>
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</tr>
<tr>
<td>Ischemic heart disease (NYHA class III/IV)</td>
<td>8 (7)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Congestive heart failure (NYHA class III/IV)</td>
<td>3 (3)</td>
<td>6 (4)</td>
</tr>
</tbody>
</table>

APACHE II, Acute Physiology and Chronic Health Evaluation II; CABG, coronary artery bypass graft; NYHA, New York Heart Association.

Table 4. Outcomes in the 257 patients with ischemic heart disease

Table 5. Description of the 257 patients with ischemic heart disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Restrictive ((n = 111))</th>
<th>Liberal ((n = 146))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>79 (46)</td>
<td>92 (54)</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>66.1 ± 12.6</td>
<td>66.6 ± 13.1</td>
</tr>
<tr>
<td>APACHE II score (mean ± SD)</td>
<td>7.69 ± 0.73</td>
<td>7.87 ± 0.65</td>
</tr>
<tr>
<td>APACHE II &lt; 20, n (%)</td>
<td>36 (32)</td>
<td>50 (34)</td>
</tr>
<tr>
<td>APACHE II &gt; 20, n (%)</td>
<td>73 (68)</td>
<td>96 (66)</td>
</tr>
<tr>
<td>Primary diagnoses, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease (no CABG)</td>
<td>17 (15)</td>
<td>19 (13)</td>
</tr>
<tr>
<td>Ischemic heart disease (with CABG)</td>
<td>8 (7)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>26 (23)</td>
<td>36 (25)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>33 (30)</td>
<td>33 (23)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4 (4)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1 (1)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>2 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>5 (5)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Any comorbid illness, n (%)</td>
<td>63 (41)</td>
<td>92 (59)</td>
</tr>
<tr>
<td>Cardiac comorbidity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease (NYHA class III/IV)</td>
<td>8 (7)</td>
<td>14 (10)</td>
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<tr>
<td>Congestive heart failure (NYHA class III/IV)</td>
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</tbody>
</table>
Based on the results of this subgroup analysis, we suggest that most hemodynamically stable, critically ill patients with cardiovascular disease may receive a transfusion safely when hemoglobin concentrations decrease to below 70 g/L and may be maintained at hemoglobin concentrations between 70 and 90 g/L.

Figure 3. Thirty-day survival in patients with ischemic heart disease in the restrictive and liberal allogeneic red blood cell transfusion strategy groups. This graph illustrates Kaplan-Meier survival curves for all patients with ischemic heart disease in both study groups. There was no difference in mortality in patients in the restrictive group compared with the liberal group (p = .30).

only 257 of the 357 patients with cardiovascular diseases, and even then it was not the primary reason for ICU admission in a significant proportion of patients. There also may have been selection bias by physicians who excluded patients with cardiac disease from participation in the TRICC trial. As documented in the original publication of the trial, patients with cardiac disease represented 26% of patients excluded, compared with 20% of patients enrolled in the trial (6).

We also should emphasize that the present report represents a subgroup analysis of a larger clinical trial and therefore should be considered as an explanatory analysis given that unknown prognostic variables may not be balanced completely between groups. Despite this concern, an adjusted analysis did not yield significant changes in the direction or magnitude of the odds ratio.

Finally, if the results indeed represent the truth, then why did red blood cell transfusions fail to improve outcomes in a population of patients at risk of cardiac ischemia? It is conceivable that red blood cell transfusions did not augment oxygen delivery as expected. Indeed, age-related changes in red blood cell units during storage (23–25) and/or changes caused by diseases such as sepsis (26, 27) may have contributed to decreased tissue oxygen delivery in multitransfused patients compared with similar patients who were transfused more conservatively. Recently, Mariak and Sibbald (23) observed a decrease in oxygen delivery in the gastrointestinal tract measured by using gastric tonometry in critically ill patients transfused with red blood cell units stored for ≥15 days, compared with patients who received red blood cell units stored for <15 days. In the full TRICC study analysis, patients simply may have experienced more acute life-threatening complications after red blood cell transfusions. Although not detected in this subgroup analysis, a greater number of myocardial infarcts and episodes of pulmonary edema might contribute to an increased mortality rate in the liberal group. It is also conceivable that the greater number of allogeneic red blood cell units transfused in the liberal group significantly depressed host immune responses (22, 28), increasing mortality rates from nosocomial infections and multisystem organ dysfunction. However, this was not detectable in our study because approximately 30% of patients had an infection at baseline. It is also possible that our results may be explained by a beneficial effect of hemodilution, such as less organ failure attributable to improved oxygen delivery (29) at the microcirculatory level, or fewer thrombotic complications as a consequence of less platelet aggregation (30).

Based on the results of this subgroup analysis, we suggest that most hemodynamically stable, critically ill patients with cardiovascular disease may receive a transfusion safely when hemoglobin concentrations decrease to below 70 g/L and may be maintained at hemoglobin concentrations between 70 and 90 g/L. One possible exception may be patients with unstable coronary ischemic syndromes, such as acute myocardial infarction and unstable angina.

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