Major Bleeding, Transfusions, and Anemia: The Deadly Triad of Cardiac Surgery

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Background. Postoperative bleeding is common after cardiac surgery. Major bleeding (MB) is a determinant of red blood cell (RBC) transfusion, especially in patients with preoperative anemia. Preoperative anemia and RBC transfusions are recognized risk factors for operative mortality. The present study investigates the role of MB as an independent determinant of operative mortality in cardiac surgery.

Methods. A single-center retrospective study based on the institutional database of cardiac surgery in the period 2000–2012 was conducted. Sixteen thousand one hundred fifty-four (16,154) consecutive adult patients undergoing cardiac surgery were analyzed. The impact of postoperative bleeding and MB on operative (30 days) mortality was analyzed univariately and after correction for preoperative anemia, RBC transfusions, and other confounders.

Results. Postoperative bleeding was significantly (p < 0.001) associated with operative mortality, both in univariate and multivariable models. The main complications associated with MB were thromboembolic complications, infections, and surgical reexploration. In a multivariable model, MB remained an independent predictor of operative mortality (odds ratio, 3.45; 95% confidence interval, 2.78 to 4.28). Preoperative anemia and RBC transfusions coexist in the model, acting with a multiplying effect when associated with MB.

Conclusions. Major bleeding is per se a risk factor for operative mortality. However, its deleterious effects are strongly enhanced by RBC transfusions and, to a lesser extent, preoperative anemia. Major bleeding is a partially modifiable risk factor, and adequate preemptive and treatment strategies should be applied to limit this event.

the patients was waived. At the time of hospital admission all patients gave written approval to the treatment of their data in an anonymous form and for scientific purposes.

**Patients**

We analyzed data routinely collected in our institutional database from the year 2000 through October 2012. The database includes all the patients receiving a cardiac surgery operation, with the exclusion of transplant operations that are not performed at our institution. The initial patient population included 18,456 patients. Patients younger than 18 years were excluded from the study population, leaving 16,154 patients.

**Data Collection and Definitions**

For each patient, the following data were collected and are available:

1. Preoperative: demographics; left ventricular ejection fraction; preoperative hematocrit (Hct, %); preoperative anemia (Hct < 36%); recent (within 30 days before surgery) myocardial infarction; congestive heart failure; cardiogenic shock; active endocarditis; unstable angina; serum creatinine value (mg/dL); chronic dialysis; chronic obstructive pulmonary disease; diabetes (on medication); previous cerebrovascular accident; previous cardiac surgery; urgent (to be operated on within 24 hours) or emergent (to be operated on immediately) procedures; use of anticoagulants (warfarin), low-molecular weight heparin, or antiplatelet agents (aspirin and/or thienopyridines, not withdrawn).

2. Operative: type of operation (including off-pump procedures and deep hypothermic cardiocirculatory arrest); CPB duration (minutes).

3. Postoperative: postoperative bleeding (drain blood collected in the first 12 postoperative hours); major bleeding, defined as blood loss greater than the tenth decile of the distribution or need for surgical revision owing to bleeding; allogeneic blood product transfusions (RBCs, fresh frozen plasma, platelet concentrates); need for intraaortic balloon pump; myocardial infarction (new Q waves plus enzymatic criteria); stroke; acute kidney injury (peak postoperative serum creatinine double the baseline value and >2 mg/dL); mesenteric infarction; mediastinitis; bloodstream infections (with positive cultures); length of intensive care unit (ICU) stay (days), operative (in-hospital or within 30 days after discharge) mortality.

**Surgical and Intensive Care Unit Management**

The median temperature during CPB was 32°C. Roller or centrifugal pumps were used, and the CPB circuit was primed with colloid solutions at variable volumes, ranging from 900 to 1,200 mL. No retrograde priming was used. Pump flow was set between 2.0 and 2.8 L · min⁻¹ · m⁻². Anticoagulation was achieved with unfractionated heparin according to our standard protocols, and heparin reversal was achieved with adequate doses of protamine sulfate.

All patients received tranexamic acid at a dose of 15 mg/kg before CPB and 15 mg/kg after protamine administration. No patient received aprotinin. A cell-saving device was used during the operation in selected cases.

After the operation and during the intensive care unit stay, mediastinal blood collected into a reservoir was not reinfused to the patients.

**Transfusion Policy and Bleeding Management Protocols**

In the years 2000 through 2007, no specific transfusion protocol was established. Since 2008, a specific transfusion protocol was adopted, considering a trigger value for RBC transfusions during CPB settled at an Hct of 18%, and after CPB at an Hct of 24%. These values could be higher in consideration of a number of patient-related conditions. However, RBC transfusions were not allowed for an Hct of 30% or greater.

Patients who demonstrated excessive postoperative bleeding were treated empirically until the year 2006. Subsequently, point-of-care tests became progressively available at our institution, including thromboelastography (TEG, Haemoscope Inc, Niles, IL) since 2006, platelet function analyzers (PFA-100, Siemens Healthcare Diagnostics Inc, Deerfield, IL) from 2006 to 2008, Multiplate (Hoffmann-La Roche Ltd, Basel, Switzerland) from 2008 until present, thromboelastometry (ROTEM, Pentapharm GmbH, Munich, Germany) from 2010 until present, and heparin monitoring system (HMS, Medtronic Inc, Minneapolis, MN) from 2006 until present.

Since 2008, bleeding patients are routinely treated according to a specific protocol previously published [2]. Pharmacologic interventions, guided by this algorithm, include additional doses of tranexamic acid and protamine, prothrombin complex concentrates, and fibrinogen concentrate (since 2011); in case of life-threatening, refractory bleeding, recombinant factor VIIa is considered. Substitution products include fresh frozen plasma and platelet concentrates. In case of bleeding without the evidence of coagulopathy at point-of-care testing, surgical reexamination is considered.

**Statistics**

All data are presented as number with percentage for categorical variables and mean with standard deviation for continuous variables.

The postoperative bleeding (mL/12 h) was analyzed in terms of distribution, and patients with a postoperative bleeding exceeding the 90th percentile were considered MB patients. Patients who required a surgical revision as a result of bleeding were included in the MB group.

Differences between groups were tested using the χ² test, the Student’s t test, and the Mann-Whitney test when appropriate.

The univariate association between postoperative bleeding and operative mortality was tested using a logistic regression analysis, generating an odds ratio with 95% confidence interval. After dichotomization (MB and non-MB patients), MB was tested for association within a multivariable model including all the other potential
confounders. We have included in the multivariable analysis all the factors being associated with MB at a probability value of less than 0.1. Owing to the large number of mortality events (604), no overfitting of the model was anticipated.

The crude and adjusted operative mortality rates in the presence or absence of MB, preoperative anemia, and RBC transfusion were calculated, and between-group differences were tested for statistical significance.

All tests were two-sided. A probability value of less than 0.05 was considered to be significant for all statistical tests. Statistical calculations were performed using a computerized statistical program (SPSS 13.0, Chicago, IL).

### Results

The operative mortality rate in the study population was 3.7% (95% confidence interval, 3.4 to 4.0). The mean postoperative bleeding was 473 ± 439 mL/12 h, with a median value of 350 mL/12h (interquartile range, 225 to 575 mL/12 h).

At univariate logistic regression analysis, postoperative bleeding was significantly ($p < 0.001$) associated with operative mortality. The odds ratio for operative mortality depending on postoperative bleeding is 1.0012 (95% confidence interval, 1.0010 to 1.0013). This accounts for a 12% relative risk increase per each incremental 100 mL/12 h of postoperative bleeding.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Total Patients (n = 16,154)</th>
<th>No Major Bleeding (n = 14,325)</th>
<th>Major Bleeding (n = 1,829)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>64.8 (13.0)</td>
<td>64.7 (13.0)</td>
<td>66.1 (13.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.4 (15.0)</td>
<td>73.5 (15.0)</td>
<td>72.7 (14.7)</td>
<td>0.025</td>
</tr>
<tr>
<td>Sex male</td>
<td>11,017 (68)</td>
<td>9,630 (67)</td>
<td>1,392 (76)</td>
<td>0.001</td>
</tr>
<tr>
<td>Preoperative laboratory data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.18 (0.83)</td>
<td>1.17 (0.83)</td>
<td>1.25 (0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>39.1 (4.8)</td>
<td>39.1 (4.7)</td>
<td>38.9 (5.4)</td>
<td>0.020</td>
</tr>
<tr>
<td>Anemia</td>
<td>3,384 (20.9)</td>
<td>2,933 (20.5)</td>
<td>450 (24.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiac conditions and comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.520 (0.118)</td>
<td>0.523 (0.116)</td>
<td>0.498 (0.130)</td>
<td>0.001</td>
</tr>
<tr>
<td>Recent (30 days) myocardial infarction</td>
<td>2,194 (13.6)</td>
<td>1,881 (13.1)</td>
<td>313 (17.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>845 (5.2)</td>
<td>719 (5.0)</td>
<td>126 (6.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>867 (5.4)</td>
<td>711 (5.0)</td>
<td>157 (8.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>111 (0.7)</td>
<td>78 (0.5)</td>
<td>34 (1.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Preoperative intraaortic balloon pump</td>
<td>134 (0.8)</td>
<td>103 (0.7)</td>
<td>30 (1.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Active endocarditis</td>
<td>161 (1.0)</td>
<td>137 (1.0)</td>
<td>27 (1.5)</td>
<td>0.042</td>
</tr>
<tr>
<td>Extracardiac comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic dialysis</td>
<td>131 (0.8)</td>
<td>114 (0.8)</td>
<td>16 (0.9)</td>
<td>0.677</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1,115 (6.9)</td>
<td>959 (6.7)</td>
<td>152 (8.3)</td>
<td>0.011</td>
</tr>
<tr>
<td>Previous cerebrovascular accident</td>
<td>654 (4.1)</td>
<td>567 (4.0)</td>
<td>87 (4.8)</td>
<td>0.113</td>
</tr>
<tr>
<td>Diabetes on medication</td>
<td>2,213 (13.7)</td>
<td>1,976 (13.8)</td>
<td>233 (12.7)</td>
<td>0.234</td>
</tr>
<tr>
<td>Preoperative therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>286 (1.8)</td>
<td>232 (1.6)</td>
<td>55 (3.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>2,840 (17.6)</td>
<td>2,530 (17.7)</td>
<td>310 (16.9)</td>
<td>0.472</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>3,764 (23.3)</td>
<td>3,248 (22.7)</td>
<td>518 (28.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Operation details</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonelective surgery</td>
<td>630 (3.9)</td>
<td>500 (3.5)</td>
<td>128 (7.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>175 (1.1)</td>
<td>117 (0.8)</td>
<td>53 (3.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Redo surgery</td>
<td>1,039 (6.4)</td>
<td>864 (6.0)</td>
<td>176 (9.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Nonisolated coronary operation</td>
<td>8,739 (54.1)</td>
<td>7,665 (53.5)</td>
<td>1,072 (58.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ascending aorta or arch operation</td>
<td>768 (4.8)</td>
<td>659 (4.6)</td>
<td>109 (6.0)</td>
<td>0.011</td>
</tr>
<tr>
<td>Deep hypothermic cardiac arrest</td>
<td>223 (1.4)</td>
<td>175 (1.2)</td>
<td>48 (2.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Off-pump operation</td>
<td>273 (1.7)</td>
<td>235 (1.6)</td>
<td>38 (2.1)</td>
<td>0.015</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>78.3 (40)</td>
<td>76.7 (37.1)</td>
<td>90.7 (55.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Surgery period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000–2003</td>
<td>5,535 (34.3)</td>
<td>4,965 (89.7)</td>
<td>569 (10.3)</td>
<td></td>
</tr>
<tr>
<td>2004–2007</td>
<td>5,600 (34.7)</td>
<td>4,741 (84.7)</td>
<td>859 (15.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>2008–2012</td>
<td>5,019 (31.1)</td>
<td>4,618 (92.0)</td>
<td>401 (8.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Data presented as mean (standard deviation) for continuous variables and counts (percentages) for categorical variables.*
Table 2. Outcome in Patients With and Without Major Bleeding

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>No Major Bleeding (n = 14,325)</th>
<th>Major Bleeding (n = 1,829)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative mortality</td>
<td>370 (2.6)</td>
<td>234 (12.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Transfusions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed red cells</td>
<td>5,657 (39.5)</td>
<td>1,438 (78.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>1,395 (9.7)</td>
<td>926 (50.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Platelet concentrates</td>
<td>488 (3.4)</td>
<td>402 (22.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Intensive care unit length of stay (d)</td>
<td>3.0 (4.7)</td>
<td>5.5 (8.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Intraaortic balloon pump</td>
<td>323 (2.3)</td>
<td>138 (7.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>73 (0.5)</td>
<td>18 (1.0)</td>
<td>0.018</td>
</tr>
<tr>
<td>Perioperative myocardial infarction</td>
<td>202 (1.4)</td>
<td>61 (3.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mesenteric infarction</td>
<td>26 (0.2)</td>
<td>9 (0.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>539 (3.8)</td>
<td>238 (13.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>15 (0.1)</td>
<td>8 (0.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Sepsis</td>
<td>268 (1.9)</td>
<td>84 (4.6)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

a Data presented as mean (standard deviation) for continuous variables and counts (percentages) for categorical variables.

According to the prestated definition, MB was settled at the upper 10th decile of the distribution, correspondent to 900 mL/12 h (1,704 patients). Additionally, 125 patients did not meet this inclusion criterion but were surgically revised owing to bleeding and were considered as MB patients. Overall, we had 1,829 (11.3%) patients included in the MB group.

Preoperative details and operative characteristics of the overall population, and of the non-MB and MB groups are shown in Table 1. Patients in the MB group had a more severe preoperative and intraoperative profile, with a number of factors being significantly different between groups.

Table 3. Multivariable Analysis for Operative Mortality

<table>
<thead>
<tr>
<th>Factor</th>
<th>Regression</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.047</td>
<td>1.048 (1.037–1.059)</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.241</td>
<td>1.272 (1.188–1.362)</td>
<td>0.001</td>
</tr>
<tr>
<td>Left ventricle ejection fraction</td>
<td>−3.993</td>
<td>0.961 (0.953–0.968)</td>
<td>0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.606</td>
<td>1.832 (1.407–2.385)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>0.723</td>
<td>2.061 (1.176–3.615)</td>
<td>0.012</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>0.423</td>
<td>1.526 (1.414–2.041)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes on medication</td>
<td>0.320</td>
<td>1.378 (1.082–1.755)</td>
<td>0.009</td>
</tr>
<tr>
<td>Low molecular weight heparin</td>
<td>0.274</td>
<td>1.316 (1.064–1.626)</td>
<td>0.011</td>
</tr>
<tr>
<td>Nonelective operation</td>
<td>0.892</td>
<td>2.440 (1.754–3.397)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time</td>
<td>0.015</td>
<td>1.015 (1.013–1.017)</td>
<td>0.001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.239</td>
<td>3.453 (2.785–4.282)</td>
<td>0.001</td>
</tr>
<tr>
<td>Packed red cells transfusion</td>
<td>1.070</td>
<td>2.916 (2.239–3.796)</td>
<td>0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.303</td>
<td>1.354 (1.099–1.668)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ascending aorta or arch operation</td>
<td>−1.205</td>
<td>0.300 (0.160–0.561)</td>
<td>0.011</td>
</tr>
<tr>
<td>Deep hypothermic cardiac arrest</td>
<td>0.951</td>
<td>2.589 (1.307–5.127)</td>
<td>0.006</td>
</tr>
<tr>
<td>Surgery in the years 2004–2007</td>
<td>−0.450</td>
<td>0.638 (0.514–0.791)</td>
<td>0.001</td>
</tr>
<tr>
<td>Constant</td>
<td>−7.593</td>
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</tr>
</tbody>
</table>

With respect to the outcome, the operative mortality was significantly (p < 0.001) higher in the MB group (12.8%) versus the non-MB group (2.6%), with a relative risk for operative mortality for MB patients of 5.53 (95% confidence interval, 4.66 to 6.57). Postoperative morbidity was significantly worse in MB patients, who received allogeneic blood products at a significantly higher rate, and demonstrated significantly higher rates of morbidity events and a longer intensive care unit stay (Table 2).

To investigate the association between MB and operative mortality, a multivariable logistic regression model (stepwise forward) was developed, including MB, RBC transfusion, and all the factors being associated with MB at the univariate analysis of Table 1. Additionally, other factors being univariately associated with operative mortality were included in the model: weight, previous cerebrovascular accident, and diabetes on medication.

The final model is shown in Table 3. In this model, MB, RBC transfusion, and anemia are all independent predictors of the operative mortality. According to this model, patients with MB or RBC transfusion have an operative risk almost three times higher than those without MB or RBC transfusion, whereas those with preoperative anemia have an operative mortality risk 35% higher than those without anemia, after adjustment for the other confounders.

Based on the observed and the predicted operative mortality rates, we could define the effect of MB, anemia, and transfusions, alone or combined, in crude and adjusted models.

In the crude model (Fig 1), there is an increased operative mortality rate depending on the combination of the three factors. Preoperative anemia acts as a multiplier of both MB and transfusion effects, with the greatest impact in patients without MB and transfusions (in whom the operative mortality rises from 0.7% to 3.0% in the presence of preoperative anemia; odds ratio, 4.8; 95%
confidence interval, 3.0 to 7.5; \( p < 0.001 \). In the other cases, the odds ratio ranges from 1.7 to 2.2, with a significant \( p < 0.001 \) effect in patients receiving transfusions with or without MB, and no significant effect in patients with MB not receiving transfusions, probably related to the limited size of this subgroup. The predicted mortality rates in the model adjusted for the other confounders listed in Table 3 are shown in Figure 2. These rates in the absence or presence of the three risk factors considered (anemia, transfusions, MB) are corrected for the mean value of the other 13 confounders observed in our patient population.

In Figure 3, the association between postoperative bleeding (as a continuous variable) in crude and adjusted (for the 15 confounding factors, including anemia and RBC transfusion) models is presented.

**Comment**

The main finding of our study is that MB is independently associated with operative mortality in cardiac surgery patients. Preoperative anemia and RBC transfusion are additional independent risk factors for operative mortality, with a multiplying effect in the presence of MB. Separately taken, these three factors have a well-known deleterious effect on cardiac surgery outcomes. However, it is certainly difficult to highlight the specific weight of each factor, given the great intercorrelation among them.

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**Fig 1.** Crude operative mortality according to the presence of major bleeding (MB), red blood cell (RBC) transfusions, and preoperative anemia.

**Fig 2.** Operative mortality according to the presence of major bleeding (MB), red blood cell (RBC) transfusions, and preoperative anemia, adjusted for the other confounders listed in Table 3.
Anemia of course is a trigger for RBC transfusion, as well as MB. Moreover, some anemic patients are at higher risk for MB when platelet count is low. Despite these intercorrelations, the three factors coexist in our multivariable model, being independently associated with the operative mortality risk.

There are several mechanisms by which MB, RBC transfusion, and preoperative anemia may exert deleterious effects.

Preoperative anemia has been recognized as a mortality risk factor in cardiac surgery in previous studies [3–6]. Preoperative anemia, unless corrected with RBC transfusions before the operation, is a major determinant of excessive hemodilution during CPB, and the nadir Hct on CPB is a well-recognized determinant of morbidity and mortality after cardiac operations [7–11]. The main interpretation for this association is that the oxygen delivery during CPB may be inadequate, leading to ischemic organ dysfunction, mainly at a renal level [10, 11]. Preoperative anemia, of course, is a major determinant of perioperative RBC transfusions; however, two recent studies demonstrated that preoperative anemia and nadir Hct value during CPB are determinants of increased morbidity even in the absence of transfusions [12, 13]. Our study confirms this finding: in an adjusted model, preoperative anemia has a 35% relative risk increase in operative mortality. However, it must be considered that in terms of absolute mortality risk, the effects of preoperative anemia are more clinically relevant in the presence of MB or RBC transfusions. In the absence of these conditions, the absolute risk difference is only 0.2% in the adjusted model. Conversely, in patients with MB and being transfused, the absolute risk difference owing to preoperative anemia rises to 1.9%.

Red blood cell transfusions are a well-recognized risk factor for morbidity and mortality in cardiac surgery [14–16], and our study confirms this finding, with a relative risk for mortality roughly three times higher in patients receiving RBC transfusions.

There are many possible mechanisms explaining the link between transfusions and bad outcomes in cardiac surgery, including storage lesion [17], and their analysis is outside the purposes of this study. However, it should always be considered that without clear data on the temporal link between transfusions and outcomes, the possibility that transfusions may be the consequence, rather than the cause, of morbid events is high.

The role of postoperative bleeding in determining bad outcomes after cardiac surgery has been explored in previous studies [18–22]. Postoperative bleeding is of course a major determinant of both surgical reexploration and RBC transfusions. Surgical reexploration is associated with an increased morbidity and mortality risk [18–24], and the same applies to RBC transfusions. However, little information exists with respect to the role of MB independently from RBC transfusions. In our series, MB is independently associated with a relative risk for operative mortality that is roughly three times higher than in patients without MB. Even in the absence of RBC transfusions, the operative mortality risk is about three times higher in patients with MB, in the adjusted model.

Our results offer some interpretative insights for the role of MB in increasing the operative mortality risk. Patients with MB are of course more likely to receive RBC transfusions and surgical reexploration. These two findings are probably the main determinants for an increased mortality rate. Additionally, we could identify other possible mechanisms leading to an increased mortality. Patients with MB had an increased rate of postoperative severe low cardiac output syndrome (significantly higher need for intraaortic balloon pump), and significantly higher rates of thromboembolic events (myocardial infarction, stroke, and mesenteric infarction) and infective complications (mediastinitis and sepsis).

Overall, the postoperative management of a severely bleeding patient requires a number of interventions. Maintaining a hemodynamic stability may be difficult, and the chronically reduced preload may lead to hypotension. The use of vasoconstrictors is common to counteract this pattern. Additionally, attempts to control bleeding include the use of specific drugs (tranexamic acid, desmopressin, prothrombin complex concentrates, and in the most severe cases, recombinant factor VIIa). Finally, specific allogeneic blood products are used to control bleeding (fresh frozen plasma and platelet concentrates were used at a significantly higher rate in patients with MB in our series). Therefore, it is not surprising that the combination of procoagulant blood products and drugs, together with the use of vasoconstrictors and a critical organ perfusion in case of low cardiac output, may create the ideal environment for thromboembolic events.

Additionally, the need for surgical reexploration and the exposure to allogeneic RBC, fresh frozen plasma, and platelet concentrates increase the risk for infective complications, as already demonstrated by other authors [25].

The management of bleeding in cardiac surgery is still a matter of concern. As highlighted by other authors [26], the genesis of this complication is multifactorial.
Control of fibrinolysis is more complex in the post-
aprotin era; however, in the modern scenario of car-
diac surgery, the focus should be placed on a number of
factors, including consumption coagulopathy that may
play a primary role in complex procedures, prolonged
CPB, aortic surgery, and implantation of mechanical
circulatory devices [26].

Within this scenario, a nonempirical approach to the
bleeding patient may offer some advantages. In our
series, the last period of observation (from 2008 to 2012)
differs from the previous ones being characterized by the
use of coagulation point-of-care tests to identify the re-
sidual effects of thienopyridines and to guide diagnosis
and treatment of postoperative bleeding. Of note, in this
period the rate of MB was significantly lower than in the
previous ones (8% versus 12.8%).

There are several limitations in our study. It is a single-
center study, and the definition of MB is appropriate in
this setting but may be different in other settings; the
definition of MB is based on postoperative events
(bleeding and surgical revision), and does not take into
account the operative bleeding before chest closure. The
large patient population included is a point of strength,
but the long period of observation (12 years) results in
a population that is heterogeneous with respect to the
techniques and strategies applied to contain hemo-
dilution, to control bleeding, and even with respect to
the transfusion policy. However, the surgery period has
been taken into account as a potential confounder.

Finally, we are lacking specific data with respect to
the use of procoagulant drugs to control bleeding in
each individual patient, and data regarding antiplatelet
drugs are incomplete in the first 10 years of observation
with respect to the exact agent and its discontinuation
time.

Altogether, our study has many clinical implications.
The most striking information is that patients without
preoperative anemia or MB and not being transfused
have a very low operative mortality rate of 0.6% to 0.7%.
This leads to the obvious consideration that controlling
these three risk factors may be of paramount importance
in cardiac surgery.

Actually, all these factors are potentially modifiable.
Preoperative anemia is not always inevitable, and
whenever the operation is not urgent, it can be hypothe-
sized that adequate treatments, including iron sup-
plementation and erythropoietin, may be beneficial.
Postoperative bleeding may be limited in different
ways: postponing the operation in patients taking anti-
platelet agents (thienopyridines) is an effective strategy
[27], and the use of point-of-care coagulation tests pro-
vided significant reductions in postoperative bleeding
and RBC transfusions in a recent randomized controlled
trial [28]. Finally, tolerance of postoperative anemia and
avoidance of liberal transfusion strategies is a sug-
gestion [29].

These and other strategies are included in the concept
of patient blood management [30], and the present study
contributes to the evidence that anemia and bleeding-
related complications, together with the deleterious
effects of RBC transfusions, are major determinants of
operative mortality in cardiac surgery.

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INVITED COMMENTARY

Despite advances in intraoperative management, measurement of the coagulation system, and transfusion medicine, major intraoperative and postoperative bleeding after cardiac operations remains a serious and perplexing problem. It remains to be established how much of the morbidity and mortality from operations that are complicated by major bleeding relates to the bleeding itself as opposed to the transfusions or to the underlying conditions that may have predisposed the patient to this problem. In this study, Ranucci and colleagues [1] provide new information from a large institutional database involving more than 16,000 consecutive adult patients who underwent cardiac operations. They confirm that patients who experienced major bleeding are at greater risk of operative mortality and morbid events, including thromboembolic complications, infections, and surgical reexploration. These associations persist even after adjustment for confounding variables such as preoperative anemia and packed red blood cell transfusions, although both of these factors appeared to exert a multiplier effect when associated with major bleeding.

The report also demonstrates the difficulties that arise in attempting to evaluate major bleeding in clinical studies. The authors defined major bleeding as patients who sustained blood loss in the upper decile of blood volume lost in the patient population, an amount that exceeded 900 mL in 12 hours. Other institutions with a different proportion of off-pump procedures, major aortic surgical procedures, emergency procedures, or left ventricular assist device implantations may experience a different spectrum of bleeding, making generalization of the results hazardous. Investigators can measure shed blood relatively reliably, but blood lost in the operating room in surgical sponges or in suction tubes that are not reinfused is harder to quantify. Transfusion management protocols and methods of assessing the coagulation profile change over time, and frequency of major bleeding can change (as evidenced by an observed decline in major bleeding rates in the most recent years in this study), making interpretation of study data more complicated.

Despite these issues, the data are convincing that major bleeding is a serious problem that warrants further efforts at reducing its incidence and effectively treating it when it occurs. Delays in surgical procedures when possible to treat preoperative anemia is one possible approach. Closer monitoring of the coagulation system during operations and formulating predefined transfusion strategies or targeted drug treatments (with agents such as desmopressin, recombinant factor VII, and others) may be another option. Clinical trials that assess these processes are needed but will require large numbers of patients subjected to well-defined protocols if we are to have an impact on this serious problem affecting patients undergoing cardiac procedures.

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Reference