Prognostic Impact of Blood Transfusion After Primary Angioplasty for Acute Myocardial Infarction

Analysis From the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) Trial

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Objectives We sought to determine the relationship between red blood cell (RBC) transfusion and clinical outcomes in patients undergoing primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI).

Background The implications of RBC transfusion in patients undergoing primary PCI for AMI have not been evaluated.

Methods Clinical outcomes of patients from the prospective, randomized CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial were analyzed by administration of in-hospital RBC transfusion not related to coronary artery bypass surgery.

Results Of 2,060 randomized patients, 82 (3.98%) received RBC transfusion during the index hospitalization, including 33 (1.60%) with moderate/severe bleeding and 49 (2.38%) without overt major bleeding. Transfusion was independently associated with baseline anemia (odds ratio [95% confidence interval]: 4.44 [2.60 to 7.58], p < 0.0001), older age (1.03 [1.01 to 1.06], p = 0.002), triple-vessel disease (2.54 [1.47 to 4.38], p = 0.0008), and female sex (1.04 [1.02 to 1.06], p = 0.0008). Patients transfused versus not transfused had significantly higher rates of 1-year mortality (23.9% vs. 3.4%), disabling stroke (2.5% vs. 0.5%), reinfarction (7.0% vs. 2.2%), and composite major adverse cardiac events (41.0% vs. 16.6%) (all p values < 0.01). After multivariable adjustment for potential confounders including transfusion propensity, RBC transfusion was independently associated with mortality at 30 days (hazards ratio: 4.71, p = 0.0005) and 1 year (hazards ratio: 3.16, p = 0.0005).

Conclusions An RBC transfusion after primary PCI in AMI may be harmful, which is consistent with the findings from other studies after PCI in the noninfarct setting. Alternatively, RBC transfusion may be a marker of markedly increased risk. Randomized studies are warranted to determine the optimal threshold for RBC transfusion in patients with AMI undergoing mechanical reperfusion therapy. (J Am Coll Cardiol Intv 2009;2:624–32) © 2009 by the American College of Cardiology Foundation

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Despite the widespread use of blood product transfusions in patients with chronic anemia and active hemorrhage, there are limited data to guide transfusion decisions in patients with coronary artery disease (CAD). Improved survival in patients with CAD after red blood cell (RBC) transfusions has not been prospectively demonstrated. The majority of available data examining outcomes after RBC transfusions are from retrospective studies, the results of which have been conflicting. In 3 series of patients with acute myocardial infarction (AMI), the prognostic impact of RBC transfusion varied, possibly due to differences in the baseline hemoglobin level (1–3). However, in 3 other reports (4–6), patients with acute coronary syndromes had markedly higher rates of death, MI, and recurrent ischemia after RBC transfusion. Among 4,131 patients with ST-segment elevation myocardial infarction (STEMI) in the GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) IIb trial treated with pharmacological reperfusion, blood transfusion was associated with more than 2-fold increase in 30-day and 1-year mortality and remarkably increased rates of reinfarction (6). In the same analysis, as well in the study on patients in the setting of nonemergency percutaneous coronary intervention (PCI), blood transfusion was found to be an independent predictor of in-hospital and 1-year mortality (6,7).

The clinical implications of blood transfusion in patients undergoing primary PCI for AMI have not been evaluated. We therefore sought to determine the relationship between RBC transfusions and clinical outcomes from a large, prospective, multicenter, randomized trial of patients undergoing primary PCI for AMI.

Methods

Patient population and protocol. In the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial, a total of 2,082 patients of any age with AMI within 12-h onset undergoing primary PCI in a native coronary artery eligible for stent implantation were randomized to 1 of 4 mechanical reperfusion strategies: percutaneous transluminal coronary balloon angioplasty with or without abciximab (Centocor, Malvern, Pennsylvania) versus stenting with the Multilink stent (Guidant Corp., Santa Clara, California) with or without abciximab. The design and principal results of the CADILLAC trial have been reported previously (8). Major clinical inclusion criteria were age >18 years and symptoms consistent with MI lasting >30 min but <12 h in duration. With regard to hemorrhagic risk, patients were excluded who had a history of bleeding diathesis, major surgery within the preceding 6 weeks, gastrointestinal or genitourinary bleeding within 6 months, cerebrovascular event within 2 years or any permanent residual neurological defect, a history of leukopenia, thrombocytopenia, hepatic or renal dysfunction, or recent administration of a thrombolytic agent. Other exclusion criteria were cardiogenic shock, allergy or intolerance to study medications (including aspirin, unfractionated heparin, abciximab, thienopyridines, or contrast media), hepatic or renal dysfunction, and noncardiac illness with life expectancy <1 year.

Prior to catheterization, patients received 325 mg of aspirin, ticlopidine 500 mg or clopidogrel 300 mg, a 5,000–IU heparin bolus, and intravenous beta-blockade in the absence of contraindications. Abciximab was administered as a bolus of 0.25 mg/kg, followed by a 12-h infusion at 0.125 µg/kg/min (10 µg/min maximum). Heparin dosing was guided by nomogram to achieve an activated clotting time ≥350 s in the absence of abciximab and 200 to 300 s if randomized to abciximab. Heparin infusion after primary angioplasty was permitted for patients treated without abciximab as per operator discretion, but not in patients receiving abciximab. Following PCI, medical therapy included aspirin 325 mg daily, beta-blockers and angiotensin-converting enzyme inhibitors if not contraindicated. Patients receiving stents were treated with oral ticlopidine 250 mg twice daily or clopidogrel 75 mg daily for 4 weeks. Clinical follow-up was performed at 1, 6, and 12 months.

Analysis plan, end points, and definitions. Clinical outcomes during the index hospitalization, at 30 days and at 1 year were examined according to administration of in-hospital RBC transfusion. Furthermore, to explore the impact of the indication for blood transfusions, patients were stratified into 3 groups: 1) patients administered 1 or more units of RBC transfusions due to moderate or severe bleeding; 2) patients administered RBC transfusions in the absence of overt major bleeding; and 3) patients that did not receive RBC transfusions. Patients undergoing coronary artery bypass graft (CABG) surgery during index hospitalization were excluded from the present analysis.

The primary composite end point of the CADILLAC trial included death from any cause, reinfarction, target vessel revascularization as a result of ischemia, or disabling stroke, as previously defined (8). Moderate bleeding was a clinically evident hemorrhage requiring transfusion, and severe bleeding was defined as clinically evident hemorrhage resulting in hemodynamic compromise or hemorrhagic

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Abbreviations and Acronyms

AMI = acute myocardial infarction
CABG = coronary artery bypass graft
CAD = coronary artery disease
MI = myocardial infarction
PCI = percutaneous coronary intervention
RBC = red blood cell
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction
stroke. Anemia was defined using the World Health Organization criteria as a hematocrit value at initial presentation of <39% for men and <36% for women (9). Chronic renal insufficiency was defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m² (Levey modified modification of diet in renal disease [MDRD] formula) (10). The study was approved by the institutional review board at each center. Written informed consent was obtained from each patient before enrollment.

Statistical analysis. Categorical variables were compared using the Fisher exact test. Continuous variables are presented as medians with interquartile ranges and were compared using the nonparametric Kruskal-Wallis test. Clinical outcomes data were estimated by the Kaplan-Meier method and compared by log-rank test.

Multivariable analysis of predictors of mortality was performed using time-dependent Cox proportional hazards regression with stepwise selection using alpha entry and exit criteria of <0.10 and <0.15, respectively. An RBC transfusion was treated as a time-dependent covariate and the additional candidate variables entered in the model included age, sex, diabetes mellitus, hypertension, hypercholesterolemia, current smoking, history of prior MI or CAGB surgery, Killip class ≥2, baseline anemia, creatinine clearance, left anterior descending artery as an infarct vessel, triple vessel disease, treatment with abciximab or stent, baseline reference vessel diameter, minimal luminal diameter, final Thrombolysis In Myocardial Infarction (TIMI) flow grade, time from the symptom onset to the first balloon inflation, admission medications, and moderate/severe bleeding as a time-dependent covariate. To account for the confounding effect between transfusions and clinical outcomes, a propensity score for RBC transfusions was constructed and included in the multivariable model. The propensity model was developed using a multivariable logistic model; its discrimination was assessed by the goodness of fit with the Hosmer-Lemeshow statistic, and its predictive performance was assessed with the C statistic.

Results

Incidence of blood transfusion after primary angioplasty. During the index hospitalization, of 2,060 randomized patients not treated with CAGB surgery, 82 patients (3.98%) received RBC transfusions, including 33 patients (1.60%) in whom a transfusion was administered in the setting of moderate or severe bleeding, and 49 patients (2.38%) who were transfused in the absence of moderate or severe bleeding. The RBC transfusions were administered to 75 of 1,681 patients (4.5%) enrolled in the U.S. as compared with 7 of 379 patients (1.8%) enrolled in other countries (p = 0.015). One RBC unit was transfused in 8.5% of patients, 2 U in 54.9%, and ≥3 U in 36.6% (median [interquartile range] = 2 [2 to 4]).

Correlates of blood transfusion. As seen in Table 1, patients who received RBC transfusions were older, more frequently female, had a higher prevalence of prior gastrointestinal bleeding, chronic renal insufficiency, multivessel disease, and lower body mass index. Baseline values of hemoglobin and hematocrit were lower, and as such, anemia at baseline was more frequent in patients receiving RBC transfusions. Patients who received RBC transfusions more frequently were treated with calcium-channel blockers and angiotensin-converting enzyme inhibitors before admission, and less frequently with beta-blockers. Time from AMI onset to the first balloon inflation was longer in patients who received RBC transfusions. As shown in Table 2, longer procedure duration, post-procedure TIMI flow grade 0/2, smaller post-procedure reference vessel diameter, and lower rates of procedural success were also associated with subsequent RBC transfusion. Administration of abciximab per randomization did not differ significantly between the 2 groups; however, more patients in the transfusion group received abciximab for bail-out indication.

Hematological indices and blood product use. Patients who received RBC transfusions associated with moderate or severe bleeding versus those without overt major bleeding versus those not transfused had significantly lower nadir hematocrit values (28.5% [26.3% to 30.6%] vs. 30.4% [26.9% to 33.0%] vs. 37.0% [33.9% to 40.0%], respectively, p < 0.0001) and significantly lower nadir hemoglobin values during the index hospitalization (9.6 [9.0 to 10.5] g/dl vs. 10.2 [8.6 to 11.4] g/dl vs. 12.6 [11.5 to 13.7] g/dl, respectively, p < 0.0001). A histogram of nadir hematocrit values in patients administered RBC transfusion is shown in Figure 1. In more than one-half of the patients, the nadir hematocrit of transfused patients was >30% (44 of 82 patients; 53.7%). At hospital discharge, patients who received RBC transfusions associated with moderate or severe bleeding versus those without moderate or severe bleeding versus those not transfused had a significantly lower hematocrit (32.8% [29.7% to 33.9%] vs. 33.0% [29.6% to 36.1%] vs. 37.7% [34.1% to 40.7%], respectively, p < 0.0001) and hemoglobin (11.0 [9.7 to 11.7] g/dl vs. 10.9 [10.1 to 12.3] g/dl vs. 12.7 [11.6 to 13.8] g/dl, respectively, p < 0.0001). Thrombocytopenia during the index hospitalization (nadir platelet count <100 × 10⁹/l) was also more common in patients receiving versus those not receiving RBC transfusions [7.3% vs. 3.2%, p = 0.05], as was transfusion of platelets (6.1% vs. 0.2%, p < 0.0001) and fresh frozen plasma (6.1% vs. 0.1%, p < 0.0001).

Clinical outcomes. Infarct size, as estimated by the peak post-procedural creatine phosphokinase level, tended to be larger in patients with versus those without RBC transfusion (2,022 [753 to 2,838] U/l vs. 1,386 [599 to 2,582] U/l, respectively; p = 0.06).

Clinical outcomes are presented in Figure 2. Patients receiving versus those not receiving RBC transfusions dur-
ing the index hospitalization had markedly higher rates of 30-day and 1-year mortality, disabling stroke, reinfarction, and composite major adverse cardiac events. Patients who received blood transfusions without associated moderate or severe bleeding tended to have higher rates of 30-day and 1-year death, target vessel revascularization, and composite major adverse cardiac events than did patients who received transfusions in the setting of clinically evident hemorrhage (Table 3).

**Multivariable analysis.** The propensity model for RBC transfusion during the index hospitalization included baseline anemia (odds ratio [95% confidence interval]: 4.44 [2.60 to 7.58], p < 0.0001), older age (1.03 [1.01 to 1.06], p = 0.002), triple-vessel disease (2.54 [1.47 to 4.38], p = 0.0008), and female sex (1.04 [1.02 to 1.06], p = 0.0008), but not randomization to abciximab. The C statistic of 0.76 from the model and the p value of 0.54 from the Hosmer-Lemeshow goodness of fit test indicated good model fit.

### Table 1. Baseline Clinical Characteristics and Angiographic Features According to Blood Transfusion Administration

<table>
<thead>
<tr>
<th></th>
<th>Red Blood Cell Transfusion (n = 82)</th>
<th>No Transfusion (n = 1,978)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>47.6%</td>
<td>74.1%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>67.5 [58–74]</td>
<td>59 [50–68]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23.2%</td>
<td>24.3%</td>
<td>0.13</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57.3%</td>
<td>47.7%</td>
<td>0.09</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>42.7%</td>
<td>37.6%</td>
<td>0.35</td>
</tr>
<tr>
<td>Current smoking</td>
<td>34.1%</td>
<td>43.7%</td>
<td>0.09</td>
</tr>
<tr>
<td>Prior myocardal infarction</td>
<td>7.3%</td>
<td>14.0%</td>
<td>0.10</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention</td>
<td>6.1%</td>
<td>11.4%</td>
<td>0.15</td>
</tr>
<tr>
<td>Prior coronary bypass surgery</td>
<td>3.7%</td>
<td>1.9%</td>
<td>0.21</td>
</tr>
<tr>
<td>Prior stroke or transient ischemic attack</td>
<td>4.9%</td>
<td>2.9%</td>
<td>0.30</td>
</tr>
<tr>
<td>History of peripheral vascular disease</td>
<td>6.1%</td>
<td>2.6%</td>
<td>0.07</td>
</tr>
<tr>
<td>History of gastrointestinal bleeding</td>
<td>6.1%</td>
<td>0.9%</td>
<td>0.002</td>
</tr>
<tr>
<td>History of genitourinary bleeding</td>
<td>0.0%</td>
<td>0.2%</td>
<td>1.00</td>
</tr>
<tr>
<td>Killip class ≥2</td>
<td>17.1</td>
<td>10.4%</td>
<td>0.07</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.9 [25.8–28.7]</td>
<td>27.3 [28.8–30.5]</td>
<td>0.005</td>
</tr>
<tr>
<td>Baseline anemia</td>
<td>36.6%</td>
<td>10.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline hematocrit,%</td>
<td>38.7 [34.4–43.0]</td>
<td>43.1 [40.1–45.9]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline creatinine clearance, ml/min</td>
<td>64 [46–92]</td>
<td>89 [67–113]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic renal insufficiency,%</td>
<td>38.0%</td>
<td>17.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ST-segment elevation or left bundle branch block</td>
<td>86.8%</td>
<td>88.0%</td>
<td>0.72</td>
</tr>
<tr>
<td>Symptom to balloon inflation, h</td>
<td>4.4 [3.4–7.8]</td>
<td>4.0 [2.9–6.1]</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Angiographic features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-vessel disease</td>
<td>43.9%</td>
<td>52.0%</td>
<td>0.17</td>
</tr>
<tr>
<td>Double-vessel disease</td>
<td>28.0%</td>
<td>33.3%</td>
<td>0.34</td>
</tr>
<tr>
<td>Triple-vessel disease</td>
<td>28.0%</td>
<td>14.7%</td>
<td>0.002</td>
</tr>
<tr>
<td>Left ventricle ejection fraction,%</td>
<td>45 [35–55]</td>
<td>50 [40–56]</td>
<td>0.07</td>
</tr>
<tr>
<td>Infarct-related artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>37.8%</td>
<td>36.7%</td>
<td>0.91</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>19.5%</td>
<td>17.2%</td>
<td>0.55</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>42.7%</td>
<td>45.8%</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Medications on admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>23.2%</td>
<td>27.4%</td>
<td>0.45</td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>2.4%</td>
<td>2.6%</td>
<td>1.0</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>18.3%</td>
<td>9.0%</td>
<td>0.01</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>7.3%</td>
<td>15.1%</td>
<td>0.06</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>34.1%</td>
<td>14.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Statin</td>
<td>17.1%</td>
<td>11.6%</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Data are presented as percentages and as median (interquartile range).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.
After multivariable adjustment for potential confounders, RBC transfusion was identified as an independent predictor of mortality at 30 days and at 1 year (Table 4).

**Discussion**

The principal findings of this analysis, the first such investigation examining the relationship between blood transfusion and outcomes in patients undergoing primary PCI for AMI, are the following: 1) RBC transfusion was administered to 3.9% of patients, despite the absence of clinically overt moderate or severe bleeding in more than one-half of these cases; 2) baseline anemia represented the strongest independent predictor of RBC transfusion; 3) patients receiving RBC transfusion had worse clinical and angiographic features at baseline, longer times from symptom onset to balloon inflation and PCI duration, worse procedural outcomes, and larger infarct sizes; 4) after adjustment for potential confounders including baseline anemia and transfusion propensity, RBC transfusion (but not anemia) remained a powerful independent predictor of 30-day and 1-year mortality; and 5) the prognosis following RBC transfusions tended to be worse among those patients without an associated moderate or severe hemorrhagic event than in those who were transfused due to clinically evident major bleeding.

**Threshold for blood transfusion.** The observed 3.9% rate of RBC transfusions not related to CABG surgery after primary PCI in patients with AMI enrolled in the CADIL-LAC trial is similar to that previously reported from the Cooperative Cardiovascular Project in patients with AMI treated either medically or with PCI (4.7%) (1). Notably, however, in the present study, the rates of RBC transfusion were 2.5-fold higher at U.S. sites than at non-U.S. sites (4.5% vs. 1.8%). This is consistent with pooled analysis from 3 international randomized trials of 23,096 patients with non-STEMI in which non-U.S. compared with U.S. patients had significantly lower adjusted hazards for blood transfusion (11). According to the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Table 2. Procedural Results According to Blood Transfusion Administration

<table>
<thead>
<tr>
<th></th>
<th>Red Blood Cell Transfusion</th>
<th>No Transfusion</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TIMI flow</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>70.4%</td>
<td>67.8%</td>
<td>0.71</td>
</tr>
<tr>
<td>Grade 2</td>
<td>7.4%</td>
<td>10.2%</td>
<td>0.57</td>
</tr>
<tr>
<td>Grade 3</td>
<td>22.2%</td>
<td>22.0%</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Final</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0 or 1</td>
<td>6.3%</td>
<td>1.1%</td>
<td>0.003</td>
</tr>
<tr>
<td>Grade 2</td>
<td>7.5%</td>
<td>2.8%</td>
<td>0.03</td>
</tr>
<tr>
<td>Grade 3</td>
<td>86.3%</td>
<td>96.1%</td>
<td>0.0004</td>
</tr>
<tr>
<td><strong>Reference diameter, mm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.8 [2.5–3.3]</td>
<td>3.0 [2.6–3.3]</td>
<td>0.06</td>
</tr>
<tr>
<td>Final</td>
<td>2.9 [2.5–3.2]</td>
<td>3.0 [2.6–3.4]</td>
<td>0.048</td>
</tr>
<tr>
<td><strong>Minimal luminal diameter, mm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0 [0–0.8]</td>
<td>0 [0–0.7]</td>
<td>0.64</td>
</tr>
<tr>
<td>Final</td>
<td>2.6 [2.5–2.9]</td>
<td>2.7 [2.4–3.0]</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Diameter stenosis, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>100 [71–100]</td>
<td>100 [75–100]</td>
<td>1.0</td>
</tr>
<tr>
<td>Final</td>
<td>10 [0–19]</td>
<td>11 [4–18]</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Stent implanted</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Per randomization</td>
<td>48.8%</td>
<td>49.8%</td>
<td>0.91</td>
</tr>
<tr>
<td>As bail-out for complications</td>
<td>7.3%</td>
<td>8.1%</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Abciximab administered</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per randomization</td>
<td>57.6%</td>
<td>50.5%</td>
<td>0.26</td>
</tr>
<tr>
<td>As bail-out for complications</td>
<td>9.8%</td>
<td>2.6%</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Volume of contrast media, ml</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>300 [240–360]</td>
<td>295 [211–375]</td>
<td>0.79</td>
</tr>
<tr>
<td>Final</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Procedural success</strong></td>
<td>76.9%</td>
<td>92.8%</td>
<td></td>
</tr>
<tr>
<td><strong>Procedure duration, h</strong></td>
<td>1.20 [0.90–1.80]</td>
<td>1.02 [0.78–1.35]</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Data are presented as percentages and as median (interquartile range).
TIMI = Thrombolysis In Myocardial Infarction.
Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines National Quality Improvement Initiative Registry, despite remarkable variability in rates of blood transfusion among the U.S. sites, nadir hematocrit of transfused patients was constant (3). No data exist whether there is a difference in transfusion threshold between the U.S. and the non-U.S. sites. Also of note, in the CADIL-LAC trial, more than one-half of RBC transfusions were administered in the absence of moderate or severe bleeding (presumably in the setting of baseline anemia secondary to comorbidities and/or mild bleeding, with or without clinical deterioration). The nadir hematocrit values that triggered blood transfusion in the present analysis varied greatly, with more than one-half of the patients receiving a blood transfusion with a nadir hematocrit value >30%. These observations reflect the lack of a uniform standard to guide the appropriateness of blood product usage (12). Although most would agree that blood transfusion is indicated in the patient with CAD and active bleeding with either hemodynamic deterioration due to hypovolemia or ischemia from diminished oxygen delivery, whether blood transfusions are beneficial or harmful in other settings is controversial.

**Impact of blood transfusion on subsequent mortality and adverse cardiovascular events.** Previous studies examining the utility of blood product transfusions in patients with CAD have reported conflicting results. In a retrospective study in 78,974 Medicare beneficiaries with AMI, RBC transfusion was associated with lower 30-day mortality among patients whose admission hematocrit values were \( \geq 30.0\% \), but with increased 30-day mortality in those with an admission hematocrit of \( \geq 36.1\% \) (1). In a study of 4,470 critically ill patients, transfusion in a subgroup of anemic patients with cardiac disease was associated with improved survival (13). However, in the multicenter randomized Transfusion Requirement in Critical Care (TRICC) trial, 30-day mortality did not differ significantly in a subgroup of critically ill normovolemic patients with known cardiovascular disease assigned to a restrictive transfusion strategy (transfusion only for hemoglobin <7 g/dl, with hemoglobin maintained between 7 and 9 g/dl) versus a liberal transfusion strategy (transfusion for hemoglobin <10 g/dl, with hemoglobin maintenance of 10 to 12 g/dl) (14). Two retrospective studies (4,5) also failed to show a survival benefit in patients with known CAD treated with RBC transfusion. Other studies have suggested RBC transfusions may be harmful. In a pooled analysis of 3 large international trials comprising 24,112 patients with acute coronary syndromes, RBC transfusion was an independent predictor of 30-day mortality after adjustment for baseline characteristics, bleeding and transfusion propensity, and nadir hematocrit (3). Other studies have also reported higher early and late mortality and MI rates after blood transfusion in patients with acute coronary syndromes and in those undergoing PCI (5–7).

The impact of blood transfusion in patients treated with primary PCI in AMI has not been previously examined. In the propensity-matched analysis of 316 patients with STEMI treated with thrombolytic therapy in the GUSTO IIb trial, transfusion as a time-dependent variable was a strong and independent predictor of all-cause mortality (6). In a pooled analysis from 16 TIMI trials treated primarily with pharmacologic reperfusion therapies, the impact of RBC transfusion appeared to be different for patients with STEMI versus patients with non-STEMI (2). Among 25,419 STEMI patients, RBC transfusion was associated with a decreased risk of cardiovascular death when the baseline hemoglobin was <12 g/dl (adjusted odds ratio: 0.42), but not when the hemoglobin was \( \geq 12 \) g/dl (adjusted odds ratio: 1.42). Among 14,503 patients with non-STEMI, RBC transfusion correlated with an increased risk of the composite end point of death, MI, and recurrent ischemia (adjusted odds ratio: 1.54), regardless of the baseline hemoglobin (2). Finally, in the analysis from the CRUSADE registry, transfusion was associated with lower in-hospital mortality in patients with nadir hematocrit \( \leq 24\% \) and higher in-hospital mortality in patients with nadir hematocrit >30%, whereas there was no effect of transfusion on in-hospital mortality in the middle group (3). Fairly small sample size in this study does not allow analyzing in detail the impact of transfusion on outcomes of patients with different values of nadir hematocrit transfused in the setting of moderate to severe bleeding or in its absence.
In the CADILLAC trial, RBC transfusion after primary PCI in AMI was associated with significantly greater rates of short-term and long-term mortality, disabling stroke, reinfarction, and composite adverse ischemic events. An RBC transfusion was a powerful independent predictor of mortality at both 30 days and 1 year after multivariable adjustment for potential confounders, suggesting a possible primary deleterious effect of blood transfusion. This likelihood is made more credible by the observation that adverse events occurred more frequently when RBC transfusions were administered in the absence of clinically evident moderate or severe hemorrhagic events. We earlier reported that in the CADILLAC trial by multivariable analysis (accounting for blood product transfusion but not for propensity score for transfusions), baseline anemia and not transfusion was an independent predictor of in-hospital and

Figure 2. Kaplan-Meier Estimates of Adverse Events at 1 Year
Cumulative adverse event rates during 1 year of follow-up in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction stratified by red blood cell transfusion. (A) Death; (B) reinfarction; (C) target vessel revascularization; (D) disabling stroke; and (E) composite major adverse cardiovascular events (MACE).
1-year mortality after primary PCI (15). In the present analysis, after accounting for the transfusion propensity in the multivariable model, baseline anemia and female sex no longer predicted early or late mortality. This is likely due to the powerful relationships among baseline anemia, sex, and transfusion. Not surprisingly, in this study both anemia and female sex were strongest independent predictors of transfusion. Still, the data of the present analysis do not allow clarifying what is the precise mechanism of worse outcomes of patients treated with blood transfusion. Future prospective studies should provide the answer whether anemia, blood product transfusion or both contribute to reduced survival in this patient cohort.

The mechanisms through which RBC transfusion might increase cardiovascular risk are undetermined. An RBC transfusion may increase the level of systemic inflammation (16). Transfusion of aged RBCs may be high in lactate content and have reduced oxygen carrying capacity due to depletion of 2,3-diphosphoglycerate, thereby shifting the oxygen dissociation curve to the left (17). Nitric oxide levels are also known to be significantly depleted in stored erythrocytes, which may impair vasodilation and result in RBC capillary sludging (18,19). Functional capillary density, blood flow, and oxygen distribution in microvascular networks are also reduced after stored RBC transfusions (20). Withdrawal of medications known to prolong survival after AMI poses additional risk in patients with anemia (15) and probably after transfusion.

**Study limitations.** This analysis was necessarily post hoc and should therefore be considered hypothesis generating. The relatively young median age (59 years) of the patients in the CADILLAC trial as well as fairly preserved baseline me-

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**Table 3. Clinical Outcomes at 30 Days and 1 Year in Patients Receiving Red Blood Cell Transfusions According to Whether Overt Moderate or Severe Bleeding Was Present**

<table>
<thead>
<tr>
<th></th>
<th>Transfusion in the Setting of Major Bleeding (n = 33)</th>
<th>Transfusion Without Major Bleeding (n = 49)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td>6.1%</td>
<td>18.4%</td>
<td>0.11</td>
</tr>
<tr>
<td>1 yr</td>
<td>19.0%</td>
<td>29.3%</td>
<td>0.26</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td>3.1%</td>
<td>2.3%</td>
<td>0.83</td>
</tr>
<tr>
<td>1 yr</td>
<td>3.0%</td>
<td>2.3%</td>
<td>0.83</td>
</tr>
<tr>
<td>Reinfection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td>0.0%</td>
<td>4.4%</td>
<td>0.23</td>
</tr>
<tr>
<td>1 yr</td>
<td>7.9%</td>
<td>7.2%</td>
<td>0.90</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td>0.0%</td>
<td>8.9%</td>
<td>0.05</td>
</tr>
<tr>
<td>1 yr</td>
<td>7.9%</td>
<td>17.3%</td>
<td>0.19</td>
</tr>
<tr>
<td>Composite adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td>9.1%</td>
<td>30.6%</td>
<td>0.02</td>
</tr>
<tr>
<td>1 yr</td>
<td>28.6%</td>
<td>45.0%</td>
<td>0.09</td>
</tr>
</tbody>
</table>

**Table 4. Multivariable Predictors of Mortality at 30 Days and 1 Year**

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>5.96 (2.73–13.03)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left anterior descending artery infarct vessel</td>
<td>5.06 (2.32–11.02)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>4.71 (1.97–11.26)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Propensity to transfusion</td>
<td>1.60 (1.04–2.45)</td>
<td>0.032</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.91 (1.24–6.81)</td>
<td>0.014</td>
</tr>
<tr>
<td>1-year mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>3.16 (1.66–6.03)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Left anterior descending artery infarct vessel</td>
<td>2.41 (1.47–3.96)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2.60 (1.42–4.74)</td>
<td>0.002</td>
</tr>
<tr>
<td>Killip class 2 or 3</td>
<td>2.28 (1.30–4.02)</td>
<td>0.004</td>
</tr>
<tr>
<td>Baseline minimal luminal diameter</td>
<td>0.44 (0.24–0.81)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.01–1.06)</td>
<td>0.015</td>
</tr>
<tr>
<td>Propensity to transfusion</td>
<td>1.43 (1.03–1.99)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

**Conclusions and Clinical Implications**

The limitations notwithstanding, the present study, derived from a large, multicenter clinical trial, suggests that at least some RBC transfusions after primary PCI in AMI may be harmful. In this regard, the current study contributes to a growing body of published data suggesting that the liberal administration of blood products in patients with AMI may be deleterious. Additional studies are required to confirm these results and explore the underlying mechanisms of adverse impact of transfusion on clinical outcomes. Moreover, randomized studies are warranted and required to establish the optimal threshold for RBC transfusion in patients undergoing PCI in the AMI and noninfarct settings and to evaluate the safety of blood transfusion versus...
alternative treatments (e.g., erythropoietin or artificial oxygen carriers).

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REFERENCES


Key Words: transfusion ■ primary angioplasty ■ myocardial infarction ■ bleeding.