Association of Hemoglobin Levels With Clinical Outcomes in Acute Coronary Syndromes

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Background—In the setting of an acute coronary syndrome (ACS), anemia has the potential to worsen myocardial ischemia; however, data relating anemia to clinical outcomes in ACS remain limited.

Methods and Results—We examined the association between baseline hemoglobin values and major adverse cardiovascular events through 30 days in 39,922 patients enrolled in clinical trials of ACS. After adjustment for differences in baseline characteristics and index hospitalization treatments, a reverse J-shaped relationship between baseline hemoglobin values and major adverse cardiovascular events was observed. In patients with ST-elevation myocardial infarction, when those with hemoglobin values between 14 and 15 g/dl were used as the reference, cardiovascular mortality increased as hemoglobin levels fell below 14 g/dl, with an adjusted OR of 1.21 (95% CI 1.12 to 1.30, P<0.001) for each 1-g/dL decrement in hemoglobin. At the other end of the range of hemoglobin, patients with hemoglobin values >17 g/dl also had excess mortality (OR 1.79, 95% CI 1.18 to 2.71, P=0.007). In patients with non–ST-elevation ACS, with those with hemoglobin 15 to 16 g/dl used as the reference, the likelihood of cardiovascular death, myocardial infarction, or recurrent ischemia increased as the hemoglobin fell below 11 g/dl, with an adjusted OR of 1.45 (95% CI 1.33 to 1.58, P<0.001) for each 1-g/dL decrement in hemoglobin. Patients with hemoglobin values >16 g/dl also had an increased rate of death or ischemic events (OR 1.31, 95% CI 1.03 to 1.66, P=0.027).

Conclusions—Anemia is a powerful and independent predictor of major adverse cardiovascular events in patients across the spectrum of ACS. (Circulation. 2005;111:2042-2049.)

Key Words: anemia ■ coronary disease ■ hemoglobin ■ myocardial infarction ■ risk factors

Methods

Patient Populations
The study cohort eligible for these analyses consisted of 41,637 patients with ACS from the following 16 Thrombolysis In Myocardial Infarction (TIMI) trials: IIIB,15 4,16 9A,17 9B,18 10A,19 10B,20 11A,21 11B,22 12,23 14,24 16 (OPUS),25 17 (InTIME II),26 18 (TACTICS),27 20 (INTEGRITI),28 23 (ENTIRE),29 and 24 (FAST-ER),30 the details for which have been published. Patients with active cancer, significant liver or renal disease (typically a creatinine ≥2.0 mg/dl), active or recent internal bleeding, known bleeding diathesis, and other significant comorbidities were excluded from these trials.

Baseline Data and Clinical Outcomes
Baseline characteristics were recorded by the local investigators. Baseline hemoglobin values were available in 96% of patients (39,922). For patients with ST-elevation MI (STEMI), the clinical end points were cardiovascular mortality and congestive heart failure through 30 days. For patients with non–ST-elevation ACS (NSTEMI), the clinical end points were cardiovascular mortality, MI, and recurrent myocardial ischemia through 30 days. Major bleeding was defined as intracranial bleeding or any clinically overt sign of hemorrhage that was associated with a fall in hemoglobin of ≥5 g/dl.31
Statistical Analyses

Patients were initially divided into categories based on 1-g/dL hemoglobin increments. Univariate associations between hemoglobin categories and other baseline demographic and clinical variables were evaluated with ANOVA and \( \chi^2 \) tests. Unadjusted event rates for the aforementioned cardiovascular end points were compared across hemoglobin categories with the \( \chi^2 \) test for trend across ordered groups. To evaluate the independent relationship between hemoglobin and cardiovascular end points at 30 days, multivariable logistic regression was used. Hemoglobin was coded as a multicategory predictor in 1-g/dL increments, and the hemoglobin category that demonstrated association with baseline known clinical importance were included in the final model.32 This comprehensive search for potential confounders was conducted. Specifically, candidate variables for which we had data in patients and that either demonstrated association with baseline hemoglobin levels (at a significance threshold of \( P<0.05 \)) or were of known clinical importance were included in the final model.32 This approach yielded the following covariates: age; gender; race; hypertension; diabetes; smoking history; creatinine clearance; prior MI; prior congestive heart failure; prior percutaneous coronary intervention; prior CABG; cerebrovascular disease; peripheral arterial disease; prior aspirin, \( \beta \)-blocker, ACE inhibitor, angiotensin receptor blocker, or hypolipidemic use; index hospitalization aspirin, \( \beta \)-blocker, ACE inhibitor, angiotensin receptor blocker, or hypolipidemic use; index revascularization; and, for STEMI patients, anterior location of the index MI.

Results

There were a total of 25 419 patients with STEMI and 14 503 patients with NSTE ACS in whom baseline hemoglobin data were available. These patients were divided into categories based on 1-g/dL hemoglobin increments, and their baseline characteristics are shown in Tables 1 and 2, respectively. Across the spectrum of ACS, those with lower baseline hemoglobin levels were more likely to be older and female, were less likely to be a current smoker, had lower estimated creatinine clearances, and were less likely to undergo revascularization during their index hospitalization.

Indicators of Severity of Acute Ischemic Insult

In patients with STEMI, the likelihood of hypotension, tachycardia, and Killip class II to IV was significantly related to baseline hemoglobin (Figures 1A through 1C, \( P<0.001 \) for each), with patients at either end of the hemoglobin spectrum being more likely to have hemodynamic disarray. Similarly, among patients with NSTE ACS, the presence of ST deviation was related to the baseline hemoglobin (\( P<0.001 \)), again with a J-shaped pattern (Figure 2).
Given imbalances in important baseline characteristics, multivariable logistic regression was used to evaluate the independent relationship between hemoglobin and clinical outcomes after adjustment for a wide range of covariates, including demographics, cardiac risk factors, prior cardiac disease, medications and revascularization procedures, location of STEMI, and index medications and revascularization (C-statistics for models were 0.84 for STEMI and 0.71 for NSTE ACS). Figure 3 shows a plot of the adjusted OR and 95% CI for 30-day cardiovascular mortality in patients with STEMI categorized by 1-g/dL hemoglobin increments. A nonmonotonic, reverse J-shaped relationship is evident. With patients with hemoglobin values of 14 to 15 g/dL as the reference, cardiovascular mortality increased as hemoglobin levels fell below 14 g/dL, with an adjusted OR of 1.21 (95% CI 1.11 to 1.29), and a highly significant trend for their composite (P<0.001). In both STEMI and NSTE ACS patients, the rate of adverse events started to increase in those with very high hemoglobin values (>16 to 17 g/dL). The rates of TIMI major bleeding were low (≈5%) and were not associated with hemoglobin levels in either STEMI (P=0.49) or NSTE ACS (P=0.19) patients.

**Adjusted ORs**
Given imbalances in important baseline characteristics, multivariable logistic regression was used to evaluate the independent relationship between hemoglobin and clinical outcomes after adjustment for a wide range of covariates, including demographics, cardiac risk factors, prior cardiac disease, medications and revascularization procedures, location of STEMI, and index medications and revascularization (C-statistics for models were 0.84 for STEMI and 0.71 for NSTE ACS). Figure 3 shows a plot of the adjusted OR and 95% CI for 30-day cardiovascular mortality in patients with STEMI categorized by 1-g/dL hemoglobin increments. A nonmonotonic, reverse J-shaped relationship is evident. With patients with hemoglobin values of 14 to 15 g/dL as the reference, cardiovascular mortality increased as hemoglobin levels fell below 14 g/dL, with an adjusted OR of 1.21 (95% CI 1.11 to 1.29), and a highly significant trend for their composite (P<0.001). In both STEMI and NSTE ACS patients, the rate of adverse events started to increase in those with very high hemoglobin values (>16 to 17 g/dL). The rates of TIMI major bleeding were low (≈5%) and were not associated with hemoglobin levels in either STEMI (P=0.49) or NSTE ACS (P=0.19) patients.
similar relationship was seen between baseline hemoglobin and the risk of heart failure. Those with a hemoglobin <14 g/dL were at increased risk of developing heart failure (adjusted OR 1.20, 95% CI 1.05 to 1.38, \(P<0.001\)) for each 1-g/dL decrement in hemoglobin. When in-hospital medications were excluded from the model, the adjusted OR was identical (OR 1.45, 95% CI 1.33 to 1.58). For all patients with a baseline hemoglobin <11 g/dL, the adjusted OR of the composite end point was 2.26 (95% CI 1.83 to 2.79, \(P<0.001\)). Directionally consistent associations were seen between hemoglobin and the individual components of the composite end point, including cardiovascular death (adjusted OR 1.35, 95% CI 0.74 to 2.45), MI (adjusted OR 1.63, 95% CI 1.07 to 2.48), and recurrent ischemia (adjusted OR 2.60, 95% CI 2.08 to 3.26). Again, reflecting the J-shaped relationship, patients with baseline hemoglobin values >16 g/dL were also at an increased risk for the composite end point (adjusted OR 1.31, 95% CI 1.03 to 1.66, \(P=0.027\)).

**Transfusion**

A total of 4.6% of patients with STEMI and 2.7% percent of patients with NSTE ACS received transfusions with whole blood or packed red blood cells. Approximately 80% of these transfusions were in the setting of bleeding. In STEMI patients, when transfusion, interaction terms between transfusion and hemoglobin, and bleeding were added to the aforementioned multivariable model, transfusion was associated with a decreased risk of cardiovascular death when the baseline hemoglobin was <12 g/dL (adjusted OR 0.42, 95% CI 0.20 to 0.89) but not when hemoglobin was ≥12 g/dL (adjusted OR 1.42, 95% CI 0.94 to 2.17). In NSTE ACS, transfusion appeared to be associated with an increased risk of the composite end point (adjusted OR 1.54, 95% CI 1.14 to 2.09), regardless of the hemoglobin concentration.

**Discussion**

In a broad cohort of patients with ACS, we found large, highly statistically significant, and independent associations between low hemoglobin concentrations and adverse cardiovascular outcomes. Among patients with STEMI, there was a progressive increase in cardiovascular mortality and heart failure as the baseline hemoglobin dropped below 14 g/dL. In patients with NSTE ACS, an increased odds of cardiovascular death, MI, or recurrent ischemia became apparent when the baseline hemoglobin fell below 11 g/dL.

To this point, data linking anemia and adverse outcomes in ACS have been limited. In one study that examined a database of discharge abstract information in patients admitted with MI, those identified as anemic on the basis of the International Classification of Diseases, 9th Revision (ICD-9) coding were not found to have a higher mortality. In contrast, in a large database study of elderly Medicare beneficiaries with acute MI in which actual hematocrit data were used, a powerful, albeit unadjusted, relationship between hematocrit on admission and all-cause 30-day mortal-
ity was found. Similar to the present study, there was a dose-response effect, with progressively lower survival rates with more profound degrees of anemia.\(^2\) In a small study of 444 consecutive patients with NSTE ACS admitted to the coronary unit of a single medical center, those with hemoglobin concentrations below 12.8 g/dL were at significantly increased risk of death or MI.\(^2\) In a study of 936 women undergoing evaluation for chest pain, hemoglobin was an independent predictor of adverse cardiovascular outcomes, with a 20% increased risk for each 1-g/dL decrement in hemoglobin.\(^3,4\) Among patients undergoing percutaneous coronary intervention for ACS, anemia was associated with an increased risk of periprocedural MI and major adverse cardiovascular events through 30 days.\(^5,6\)

After careful adjustment for a broad array of baseline characteristics, we found a striking dose-response relationship across the spectrum of ACS. Anemia has been shown to significantly decrease oxygen delivery to myocardium downstream of coronary stenoses.\(^3\) Anemia also increases myocardial oxygen demand through necessitating a higher stroke volume and heart rate to maintain adequate systemic oxygen delivery.\(^4\) The combination of these processes may explain the pathophysiology underlying the progressively worse outcomes we observed in patients with ACS with lower baseline hemoglobin concentrations. Interestingly, the thresholds below which patients were at increased risk for major adverse cardiovascular events differed between STEMI and NSTE ACS. This may reflect differences in the mechanisms by which anemia predisposes to adverse cardiovascular events in the 2 types of ACS. In STEMI, even mildly reduced hemoglobin concentrations at the abrupt onset of the coronary occlusion may significantly attenuate the ability of collateral flow from nearby patent vessels to limit the extent of myocardial necrosis and peri-infarct ischemia. We did not have scintigraphic or core laboratory biochemical measurements of infarct size in the present cohort to test this theory directly; however, consistent with this hypothesis is our finding that worsening degrees of anemia were associated with progressively higher rates of hypotension, tachycardia, and heart failure. For NSTE ACS, coronary occlusion is usually subtotal, and the likelihood of death and recurrent ischemic events over the ensuing days may reflect a delicate balance between myocardial oxygen supply and demand. In the setting of aggressive antiischemic pharmacological therapy, a more profound degree of anemia may be necessary to predispose a patient to recurrent ischemic events.

In both types of ACS, patients with very high baseline hemoglobin (>16 to 17 g/dL) also were at greater risk for adverse cardiovascular events, a finding supported by observations from other studies.\(^3,4\) The pathophysiological basis for these observations may be that high hemoglobin concentrations can increase blood viscosity. This, in turn, can increase coronary vascular resistance and decrease coronary blood flow,\(^3,5\) predispose to thrombosis,\(^3,6\) and increase myocardial work.\(^3,7\)

Potential limitations of this study should be considered. The present study population was derived from clinical trials rather than unselected community cohorts; however, the inclusion and exclusion criteria differed between these 16 trials, thus potentially strengthening the generalizability of our findings. Moreover, the use of clinical trials allowed us to gather data prospectively on important baseline characteristics and clinical outcomes from dedicated case report forms rather than, for example, unconfirmed ICD-9 coding on discharge summaries. Furthermore, we used actual hemoglobin values, thereby minimizing misclassification and permitting a quantitative approach to the definition of anemia. The cause of anemia in patients in the present study was unknown.

### TABLE 3. Clinical Outcomes Through 30 Days in STEMI Patients Stratified by Baseline Hemoglobin

<table>
<thead>
<tr>
<th>Hemoglobin on Admission, g/dL</th>
<th>End Point</th>
<th>&lt;8 (n=137)</th>
<th>8–9 (n=306)</th>
<th>9–10 (n=342)</th>
<th>10–11 (n=343)</th>
<th>11–12 (n=976)</th>
<th>12–13 (n=2331)</th>
<th>13–14 (n=3520)</th>
<th>14–15 (n=3390)</th>
<th>15–16 (n=2130)</th>
<th>16–17 (n=812)</th>
<th>&gt;17 (n=216)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, % (954 events)</td>
<td>3.7</td>
<td>2.3</td>
<td>2.3</td>
<td>3.8</td>
<td>2.4</td>
<td>1.8</td>
<td>1.7</td>
<td>1.5</td>
<td>1.3</td>
<td>1.5</td>
<td>0.9</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Myocardial (re)infarction, % (591 events)</td>
<td>5.1</td>
<td>2.9</td>
<td>5.3</td>
<td>5.8</td>
<td>4.7</td>
<td>4.0</td>
<td>3.9</td>
<td>4.4</td>
<td>3.2</td>
<td>4.5</td>
<td>3.7</td>
<td>0.191</td>
<td></td>
</tr>
<tr>
<td>Recurrent ischemia, % (1879 events)</td>
<td>37.2</td>
<td>25.8</td>
<td>27.1</td>
<td>15.6</td>
<td>12.8</td>
<td>12.8</td>
<td>11.7</td>
<td>11.7</td>
<td>12.0</td>
<td>13.6</td>
<td>16.7</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Composite, % (2217 events)</td>
<td>40.2</td>
<td>27.5</td>
<td>29.2</td>
<td>19.2</td>
<td>16.8</td>
<td>15.5</td>
<td>14.8</td>
<td>15.0</td>
<td>14.5</td>
<td>17.0</td>
<td>19.9</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 4. Clinical Outcomes Through 30 Days in NSTE ACS Patients Stratified by Baseline Hemoglobin

<table>
<thead>
<tr>
<th>Hemoglobin on Admission, g/dL</th>
<th>End Point</th>
<th>&lt;8 (n=962)</th>
<th>10–11 (n=2502)</th>
<th>11–12 (n=5077)</th>
<th>12–13 (n=6926)</th>
<th>13–14 (n=5702)</th>
<th>14–15 (n=2783)</th>
<th>15–16 (n=968)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, % (1086 events)</td>
<td>14.7</td>
<td>11.9</td>
<td>10.1</td>
<td>7.1</td>
<td>4.8</td>
<td>3.3</td>
<td>2.8</td>
<td>2.8</td>
<td>4.2</td>
</tr>
<tr>
<td>Congestive heart failure, % (248 events)</td>
<td>12.7</td>
<td>12.5</td>
<td>12.5</td>
<td>10.8</td>
<td>8.8</td>
<td>6.8</td>
<td>7.1</td>
<td>6.8</td>
<td>8.9</td>
</tr>
<tr>
<td>Composite, % (2744 events)</td>
<td>21.6</td>
<td>19.2</td>
<td>18.4</td>
<td>15.1</td>
<td>12.2</td>
<td>9.0</td>
<td>8.8</td>
<td>8.7</td>
<td>11.2</td>
</tr>
</tbody>
</table>

End Point values are expressed as % (n events).
although patients with recent bleeding, known bleeding
diathesis, or significant renal or hematologic-oncological
diseases (all important potential confounders) were excluded
from these trials. We did not measure erythropoietin levels in
these patients. In addition to stimulating erythrocyte precursors,
erthropoietin has multiple cardiovascular effects that
range from myocardial protection and angiogenesis to activa-
tion of platelets and upregulation of plasminogen activator
inhibitor-1. Thus, some of our observations may be due to
low or high erythropoietin levels rather than anemia per se.
Lastly, comorbidities associated with hemoglobin and prog-
nosis or differences in treatment influenced by the baseline
hemoglobin had the potential to confound our analyses;
however, we conducted a comprehensive search for potential
confounders and included a broad group of prognostic and
treatment-related variables in our multivariable analyses.
Although incompletely or unmeasured comorbidities could
cause residual confounding, given the breadth of covariates
adjusted for in the present analyses, the impact is likely to be
small.

If the association between hemoglobin levels and adverse
cardiovascular events is, in fact, causal, the present findings
would support the current practice guidelines from the Amer-
ican College of Cardiology/American Heart Association that
suggest screening for and correcting anemia in ACS. The
guidelines, however, do not specify what hemoglobin level to
target. Studies of transfusion thresholds have provided some
data relevant to patients with coronary disease. In a random-
ized clinical trial in critical illness, there was no apparent
benefit to a more liberal transfusion strategy (hemoglobin
target 10 to 12 g/dL) versus a more restrictive strategy (target
7 to 9 g/dL); however, in an analysis specifically restricted
to those with ischemic heart disease, there was a trend toward
higher mortality in those who were randomized to a restric-
tive strategy. Two recent nonrandomized studies have
yielded conflicting results. In a study of patients with ACS,
transfusion was associated with an increased risk of 30-day
mortality, although this effect was no longer apparent if the
nadir hematocrit was below 25%. In contrast, elderly
patients with acute MI, transfusion appeared to be beneficial

Figure 3. Unadjusted and adjusted ORs and 95% CIs for association between
baseline hemoglobin concentration and cardiovascular mortality through 30
days in patients with STEMI. Adjusted for age; gender; race; hypertension; diabetes;
smoking history; renal disease; prior MI; prior heart failure; prior percutaneous
coronary intervention; prior CABG; cerebrovascular disease; peripheral arterial
disease; prior aspirin, β-blocker, ACE inhibitor or angiotensin receptor blocker,
and hypolipidemic use; anterior MI; index hospitalization aspirin, β-blocker, ACE
inhibitor or angiotensin receptor blocker, and hypolipidemic use; and index revas-
cularization. CV indicates cardiovascular; Hgb, hemoglobin; and n, number of
patients.

Figure 4. Unadjusted and adjusted ORs and 95% CIs for association between
baseline hemoglobin concentration and cardiovascular death, MI, or recurrent
ischemia through 30 days in patients with NSTE ACS. Adjusted for age; gender;
race; hypertension; diabetes; smoking history; renal disease; prior MI; prior heart
failure; prior percutaneous coronary intervention; prior CABG; cerebrovascular
disease; peripheral arterial disease; prior aspirin, β-blocker, ACE inhibitor or
angiotensin receptor blocker, and hypolipidemic use; index hospitalization aspirin,
β-blocker, ACE inhibitor or angiotensin receptor blocker, and hypolipidemic use;
and index revascularization. CVD indicates cardiovascular death; Hgb, hemoglobin;
and n, number of patients.
if the hematocrit was <33%. The present data show a reduction in cardiovascular mortality with transfusion in STEMI patients with a hemoglobin <12 g/dl (approximately equivalent to a hematocrit <36%) but an increased risk of cardiovascular death, MI, or recurrent ischemia in patients with NSTE ACS who were transfused; however, we would underscore that all nonrandomized comparisons must be viewed with caution because, despite multivariable analyses, there can be residual confounding by indication, with physicians more likely to transfuse sicker patients. Only randomized trials can definitely resolve the benefit of transfusions in ACS.

In conclusion, we have found that in 39,922 patients with ACS enrolled in clinical trials, anemia was a powerful predictor of cardiovascular mortality and ischemic events. The graded relationship between hemoglobin levels and clinical outcomes persisted after adjustment for a wide array of baseline prognostic factors and in-hospital treatments. Given these data, a prospective, randomized clinical trial may be warranted to determine whether precise targeting of hemoglobin levels improves outcomes in patients with ACS.

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