Incidence, Correlates, and Outcomes of Acute, Hospital-Acquired Anemia in Patients With Acute Myocardial Infarction

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Background—Anemia is common among patients hospitalized with acute myocardial infarction and is associated with poor outcomes. Less is known about the incidence, correlates, and prognostic implications of acute, hospital-acquired anemia (HAA).

Methods and Results—We identified 2909 patients with acute myocardial infarction who had normal hemoglobin (Hgb) on admission in the multicenter TRIUMPH registry and defined HAA by criteria proposed by Beutler and Waalen. We used hierarchical Poisson regression to identify independent correlates of HAA and multivariable proportional hazards regression to identify the association of HAA with mortality and health status. At discharge, 1321 (45.4%) patients had HAA, of whom 348 (26.3%) developed moderate-severe HAA (Hgb <11 g/dL). The incidence of HAA varied significantly across hospitals (range, 33% to 69%; median rate ratio for HAA, 1.13; 95% confidence interval, 1.07 to 1.23, adjusting for patient characteristics). Although documented bleeding was more frequent with more severe HAA, fewer than half of the patients with moderate-severe HAA had any documented bleeding. Independent correlates of HAA included age, female sex, white race, chronic kidney disease, ST-segment elevation myocardial infarction, acute renal failure, use of glycoprotein IIb/IIIa inhibitors, in-hospital complications (cardiogenic shock, bleeding and bleeding severity), and length of stay. After adjustment for GRACE score and bleeding, patients with moderate-severe HAA had higher mortality rates (hazard ratio, 1.82; 95% confidence interval, 1.11 to 2.98 versus no HAA) and poorer health status at 1 year.

Conclusions—HAA develops in nearly half of acute myocardial infarction hospitalizations among patients treated medically or with percutaneous coronary intervention, commonly in the absence of documented bleeding, and is associated with worse mortality and health status. Better understanding of how HAA can be prevented and whether its prevention can improve patient outcomes is needed. (Circ Cardiovasc Qual Outcomes. 2010;3:00-00.)

Key Words: myocardial infarction ■ anemia ■ hemoglobin ■ outcomes
subsequent mortality and health status outcomes in the Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients’ Health Status study (TRIUMPH), a prospective 24-center observational registry of AMI treatment and outcomes. TRIUMPH provided an ideal opportunity to address these important questions, as it collected detailed patient data on in-hospital hemoglobin, hospital-based treatments, complications and processes of care, as well as serial assessments of patient outcomes after discharge.

WHAT IS KNOWN

- Prior literature has described a strong association between chronic anemia and poor outcomes after acute myocardial infarction including higher mortality rates and worse health-related quality of life, but the prognostic implications of acute, hospital-acquired anemia (HAA) are unclear.

WHAT THE STUDY ADDS

- HAA develops in nearly half of acute myocardial infarction patients treated medically or with percutaneous coronary intervention, and its incidence varies across hospitals.
- Inpatient bleeding is a strong independent predictor of HAA, but many patients with HAA do not have a documented bleeding event during hospitalization, suggesting that HAA is not simply a surrogate for in-hospital bleeding.
- Moderate-severe HAA is associated with greater mortality rates and worse health status in the first year after acute myocardial infarction.

Methods

TRIUMPH Study

A total of 4340 patients were enrolled in TRIUMPH between April 11, 2005, and December 31, 2008. Patients were ≥18 years of age, with elevated cardiac biomarkers (troponin or creatine kinase-MB fraction assessed within 24 hours of admission) and supporting evidence of AMI (ECG ST-segment changes or prolonged ischemic signs/symptoms). Participants were required to either present to the enrolling institution or to have been transferred within 24 hours of evidence of AMI (ECG ST-segment changes or prolonged ischemic signs/symptoms). Participants were required to either present to the enrolling institution or to have been transferred within 24 hours of admission value. Discharge hemoglobin was defined as the last hemoglobin value obtained within 48 hours of discharge from the hospital. HAA was defined as absence of anemia on admission but development of anemia at discharge. For our primary analyses, anemia was defined using age-, sex-, and race-specific criteria was described by Beuter and Waelen as a hemoglobin value ≤13.7 g/dL for white men ages 20 to 59 years, 13.2 g/dL for white men ≥60 years, 12.9 g/dL for black men ages 20 to 59, 12.7 g/dL for black men ≥60 years, 12.2 g/dL for white women, and 11.5 g/dL for black women. This classification has been previously shown to be more accurate than the World Health Organization definition (WHO). In light of its common use in prior cardiovascular literature, we also conducted sensitivity analyses using WHO diagnostic criteria for anemia (Hgb <13.0 g/dL in men, Hgb <12.0 g/dL in women). HAA was defined as absence of anemia on admission but development of anemia at discharge using these criteria. Anemia was further categorized as severe (Hgb <9.0 g/dL), moderate (Hgb 9.1 to 11.0 g/dL), or mild (Hgb >11.0 g/dL). Data regarding in-hospital blood transfusions were systematically collected by the data abstractors. Because using discharge hemoglobin to define anemia severity could result in misclassification of a patient’s anemia severity among those who received a blood transfusion during hospitalization, we subtracted the number of units transfused (1 g/dL Hgb per unit transfused) from the discharge hemoglobin and used this derived value to assign patients to the appropriate anemia severity category. All transfused patients were categorized as having HAA.

Bleeding episodes were also systematically recorded by data abstractors using the Thrombolysis In Myocardial Infarction (TIMI) classification. TIMI major bleeding was defined as intracranial hemorrhage, retroperitoneal hemorrhage, or a Hgb decline ≥5 g/dL. TIMI minor bleeding was assigned if the drop in Hgb was 3 to 5 g/dL in the setting of observed bleeding. Any bleeding episode with a decline in Hgb <3 g/dL was classified as TIMI minor bleeding. All TIMI categories accounted for blood transfusion, with adjustment of Hgb values by 1 g/dL per unit transfused. Bleeding site was recorded as cardiac catheterization site, gastrointestinal, retroperitoneal, or other.

Health status was assessed using the Short Form-12 Physical Component Summary score (SF-12 PCS). The SF-12 is a valid and reliable instrument with scores ranging from 0 to 100, with higher scores representing better health status. A score of 50 is normalized to the mean health status of the US population, and each 10 points represents 1 standard deviation from that mean.
Statistical Analyses

Baseline characteristics, in-hospital treatments, in-hospital complications, and laboratory values of patients who developed HAA were compared with those who did not have anemia at either admission or discharge. We also compared the frequency of in-hospital bleeding among those with and without HAA, as well as within categories of HAA severity. For the 12-month outcome analyses, we divided HAA into mild and moderate-severe anemia, comparing each HAA category to a reference category of no anemia. We also included patients with chronic anemia at admission in outcome analyses, comparing

| Table 1. Characteristics of AMI Patients With and Without Hospital-Acquired Anemia |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| Demographic                                 | Hospital-Acquired Anemia | No Hospital Acquired-Anemia | P Value |
| Age, y                                       | 59.8 ± 12.2      | 55.7 ± 11.5      | < 0.001         |
| Sex, % men                                   | 846 (64.0)       | 1127 (71.0)      | < 0.001         |
| Race, % white                                | 928 (70.4)       | 1041 (65.8)      | 0.009           |
| Medical history                              |                  |                  |                 |
| Body mass index, kg/m²                       | 29.3 ± 6.4       | 30.1 ± 6.1       | 0.002           |
| Atrial fibrillation                          | 61 (4.6)         | 49 (3.1)         | 0.03            |
| Diabetes mellitus                            | 376 (28.5)       | 376 (23.7)       | 0.003           |
| Chronic heart failure                        | 94 (7.1)         | 91 (5.7)         | 0.13            |
| LVEF < 40%                                   | 244 (18.5)       | 235 (14.8)       | 0.007           |
| Dyslipidemia                                 | 653 (49.4)       | 727 (45.8)       | 0.05            |
| Hypertension                                 | 867 (65.6)       | 962 (60.6)       | 0.005           |
| Chronic kidney disease                       | 70 (5.3)         | 57 (3.6)         | 0.03            |
| Peripheral arterial disease                  | 52 (3.9)         | 43 (2.7)         | 0.06            |
| Prior stroke                                 | 53 (4.0)         | 52 (3.3)         | 0.29            |
| Prior MI                                     | 238 (18.0)       | 300 (18.9)       | 0.55            |
| Prior PCI                                    | 233 (17.6)       | 292 (18.4)       | 0.60            |
| Prior CABG                                   | 140 (10.6)       | 129 (8.1)        | 0.02            |
| Medical history                              |                  |                  |                 |
| Admission medications                        |                  |                  |                 |
| Warfarin                                     | 42 (3.2)         | 53 (3.3)         | 0.81            |
| Aspirin                                      | 516 (39.1)       | 560 (35.3)       | 0.04            |
| Thienopyridine                               | 155 (11.7)       | 147 (9.3)        | 0.03            |
| β-Blocker                                    | 417 (31.6)       | 424 (26.7)       | 0.004           |
| ACE inhibitor/ARB                            | 461 (34.9)       | 442 (27.8)       | < 0.001         |
| Statin                                       | 419 (31.7)       | 441 (27.8)       | 0.02            |
| Admission characteristics and in-hospital complications |                  |                  |                 |
| Heart rate                                   | 82.1 ± 22.7      | 81.0 ± 19.9      | 0.15            |
| Systolic blood pressure                      | 143.1 ± 31.5     | 146.8 ± 28.7     | 0.001           |
| MI diagnosis, % STEMI                        | 677 (51.2)       | 738 (46.5)       | 0.01            |
| Acute noncardiac condition on admission      | 31 (2.3)         | 22 (1.4)         | 0.05            |
| Length of stay, median, IQR                  | 4.0 (3.0, 5.0)   | 3.0 (2.0, 4.0)   | < 0.001         |
| Acute renal failure                          | 43 (3.3)         | 23 (1.2)         | 0.001           |
| Cardiogenic shock                            | 51 (3.9)         | 17 (1.1)         | < 0.001         |
| Inpatient treatments                         |                  |                  |                 |
| Aspirin                                      | 1274 (96.4)      | 1534 (96.6)      | 0.82            |
| Fibrinolytic                                 | 94 (7.1)         | 85 (5.4)         | 0.05            |
| Glycoprotein IIb/IIla inhibitor              | 930 (70.4)       | 1037 (65.3)      | 0.003           |
| Thienopyridine                               | 1012 (76.6)      | 1167 (73.5)      | 0.05            |
| Anticoagulant                                | 1222 (92.5)      | 1453 (91.5)      | 0.32            |
| Antithrombin                                 | 64 (4.8)         | 68 (4.3)         | 0.47            |
| PCI in hospital                              | 1007 (76.2)      | 1145 (72.1)      | 0.01            |

Values are expressed as mean ± SD or n (%).

In-hospital medication variables include the following individual medications: GP IIb/IIa inhibitor (abciximab, eptifibatide, tirofiban); thienopyridine (clopidogrel, ticlopidine); anticoagulant (intravenous heparin, low-molecular-weight heparin such as enoxaparin or dalteparin, or other heparinoid); and antithrombin (bivalirudin, lepirudin).

LVEF indicates left ventricular ejection fraction; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; STEMI, ST-segment elevation myocardial infarction; and IQR, interquartile range.
However, in this study the event being modeled (HAA) was not rare, due to its skewed distribution, and results are reported as the median and interquartile range. We used hierarchical modified Poisson regression within hospital to identify patient characteristics independently associated with HAA. Typical analyses use logistic regression to estimate adjusted odds ratios, which are then generally interpreted as relative risks. However, in this study the event being modeled (HAA) was not rare, in which case odds ratios are poor estimates of relative risk. To address this issue, we estimated adjusted relative risks directly using a modified Poisson regression model with a robust error variance. Variables included in the model were identified as being clinically important or differed between the groups in bivariate comparisons (P<0.05). These included enrollment hospital, age, sex, race (white versus other), diabetes, hypertension, chronic kidney disease, history of chronic heart failure, left ventricular ejection fraction <40%, prior CABG, prehospital use of aspirin or clopidogrel, acute non-Q-wave myocardial infarction, heart failure, MI type (ST-segment elevation versus non-ST-segment elevation), in-hospital percutaneous coronary intervention, in-hospital treatment with GP IIb/IIIa inhibitor, antiplatelet agents or anti-coagulants, cardiogenic shock, in-hospital bleeding in each TIMI category, and length of stay. Missing covariate data in the predictors of HAA model were minimal and included 1 missing value for race, 1 missing value for length of stay, and 1 missing value for left ventricular ejection fraction. Additionally, these models were repeated after including baseline Hgb as a continuous variable to understand the influence of initial Hgb on identification of independent correlates of anemia.

We calculated the proportion of patients with HAA at each hospital using shrinkage estimation from a hierarchical model including site as a random effect (with no additional covariates), which accounts for sites with small enrollments by pulling their rates toward the overall mean. To further describe variation in HAA, rates across hospitals were quantified by the median rate ratio. This is the median value of the relative risk for HAA development for 2 patients with identical characteristics admitted to 2 randomly selected hospitals. To evaluate the association between HAA and long-term outcomes, we used log-rank tests and generated Kaplan–Meier curves for crude morality analyses and compared crude SF-12 PCS scores using 1-way ANOVA. Mortality was defined as time to event and was censored at 12-months after hospital discharge among patients surviving at 12-months. To better understand the contribution of in-hospital bleeding on HAA-associated mortality risk, Kaplan–Meier curves were also generated for the subgroups of patients with HAA who did and did not have documented bleeding, and their 12-month mortality was compared using log-rank test. We then used multivariable proportional hazards regression models for 12-month mortality and tested the proportional hazards assumption in the fully adjusted model using Schoenfeld residuals. To assess changes in health status, we used a multivariable repeated measures linear regression model with a random effect for patient and an autoregressive within-patient covariance structure for Short Form-12 physical component scores (SF-12 PCS) that incorporated 1-, 6-, and 12-month health status assessments. The use of full-data maximum likelihood methods, accounting for within-patient correlation, corrects for missing-data biases that are attributable to other observed patient characteristics.

### Table 2. Hemoglobin by Severity of Hospital-Acquired Anemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>All HAA (n=1321)</th>
<th>No HAA (n=1588)</th>
<th>Mild HAA (n=973)</th>
<th>Moderate HAA (n=292)</th>
<th>Severe HAA (n=56)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin: admit, g/dL</td>
<td>14.4±1.3</td>
<td>15.2±1.4</td>
<td>14.6±1.2</td>
<td>13.6±1.2</td>
<td>13.6±1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin: discharge, g/dL</td>
<td>11.7±1.3</td>
<td>14.2±1.3</td>
<td>12.4±0.7</td>
<td>10.4±0.5</td>
<td>8.1±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin change, g/dL</td>
<td>−2.6±1.4</td>
<td>−1.0±1.3</td>
<td>−2.3±1.1</td>
<td>−3.2±1.3</td>
<td>−5.5±2.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P values presented are for comparison of no HAA, mild HAA, moderate HAA, and severe HAA.*

### Table 3. In-Hospital Bleeding by Hospital-Acquired Anemia Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>All HAA (n=1321)</th>
<th>No HAA (n=1588)</th>
<th>Mild HAA (n=973)</th>
<th>Moderate HAA (n=292)</th>
<th>Severe HAA (n=56)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital bleeding, n (%)</td>
<td>178 (13.5)</td>
<td>71 (4.5)</td>
<td>100 (10.3)</td>
<td>49 (16.8)</td>
<td>29 (51.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI bleeding, n (%)</td>
<td>26 (2.0)</td>
<td>3 (0.2)</td>
<td>5 (0.5)</td>
<td>8 (2.7)</td>
<td>13 (23.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI major</td>
<td>73 (5.5)</td>
<td>14 (0.9)</td>
<td>40 (0.4)</td>
<td>23 (7.9)</td>
<td>10 (17.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI minimal</td>
<td>79 (6.0)</td>
<td>54 (3.4)</td>
<td>55 (5.7)</td>
<td>18 (6.2)</td>
<td>6 (10.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding location, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheterization site</td>
<td>105 (59.0)</td>
<td>55 (77.5)</td>
<td>67 (67.0)</td>
<td>29 (59.2)</td>
<td>9 (31.0)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>22 (12.4)</td>
<td>2 (2.8)</td>
<td>9 (9.0)</td>
<td>4 (8.2)</td>
<td>9 (31.0)</td>
<td></td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>16 (9.0)</td>
<td>0 (0.0)</td>
<td>3 (3.0)</td>
<td>8 (16.3)</td>
<td>5 (17.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>35 (19.7)</td>
<td>14 (19.7)</td>
<td>21 (21.0)</td>
<td>8 (16.3)</td>
<td>6 (20.7)</td>
<td></td>
</tr>
<tr>
<td>PRBC transfusion, n (%)</td>
<td>69 (5.2)</td>
<td>0</td>
<td>9 (0.9)</td>
<td>19 (6.5)</td>
<td>41 (73.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRBC units transfused in patients receiving transfusion, mean units ±SD</td>
<td>2.4±1.4</td>
<td>n/a</td>
<td>2.1±1.0</td>
<td>1.8±0.4</td>
<td>2.8±1.8</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*P values presented are for comparison of no HAA, mild HAA, moderate HAA, and severe HAA. PRBC indicates packed red blood cells.*
These models were adjusted for hospital site and the GRACE discharge to 6-month mortality risk score, which is strongly predictive of long-term mortality and incorporates important potential confounders. Variables included in GRACE score are age, heart rate, systolic blood pressure, creatinine, history of congestive heart failure, prior MI, in-hospital PCI or CABG, ST-segment depression on the initial ECG, and elevated cardiac biomarkers. Presence and severity of bleeding were also included in the models, using dummy variables for TIMI major, minor and minimal bleeding to understand whether the prognostic impact of HAA is independent of bleeding presence and severity. The models evaluating the relationship between SF-12 PCS scores and HAA also adjusted for baseline SF-12 PCS. Finally, several sensitivity analyses were conducted. First, models were repeated using the WHO definition of anemia. Second, analyses were repeated after excluding patients who received blood transfusions. Finally, we examined the association between HAA and 12-month mortality after adjusting for baseline Hgb. All analyses were conducted with SAS version 9.1.3 (SAS Institute, Cary, NC) and R version 2.7.2 (R Development Core Team (2006)–R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3 to 900051-07 to 0, http://www.R-project.org).

Results

HAA Incidence, Severity, and Baseline Patient Characteristics

Among 2909 AMI patients without anemia at admission, 1321 (45.4%) developed HAA. Baseline demographics, co-morbidities, in-hospital characteristics, and treatments of patients with and without HAA are compared in Table 1. Hemoglobin at admission, discharge, and change during hospitalization are presented in Table 2. Hgb declined by a mean of 2.6±1.4 g/dL during hospitalization among patients with HAA but also declined modestly (by 1.0±1.3 g/dL) in those who did not develop HAA (P<0.001). The majority of cases of HAA were mild (973, 73.7%), whereas 292 (22.1%) had moderate anemia and 56 (4.24%) had severe anemia. There were important clinical differences between patients with and without HAA, as detailed in Table 1.

Bleeding and HAA

Although documented in-hospital bleeding was more common in patients with HAA as compared with those without HAA, the majority (1143 of 1321 patients, 86.5%) of patients with HAA did not have any documented in-hospital bleeding (Table 3). The mean hemoglobin decline in patients with recorded bleeding was 3.1±1.9 g/dL, as compared with
1.6±1.4 in those who did not have a bleeding episode. As the severity of HAA increased among patients with documented bleeding, a greater proportion of bleeding events were classified as TIMI major and TIMI minor bleeds. Although in-hospital bleeding was significantly more common in patients with severe HAA than those with less severe or no HAA, nearly half of patients with severe HAA still had no significant bleeding episode.

Independent Correlates of HAA

Independent correlates of HAA are presented in Figure 1. In-hospital bleeding was associated with a greater likelihood of developing HAA (TIMI minimal bleeding: relative risk [RR] of 1.36; 95% confidence interval [CI], 1.25 to 1.48; TIMI minor: RR of 1.72; 95% CI, 1.39 to 2.13; TIMI major bleeding RR of 1.72; 95% CI, 1.46 to 2.02). Additional patient characteristics associated with developing HAA included age, female sex, white race, and chronic kidney disease as well as development of cardiogenic shock, acute renal failure, presentation with ST-segment elevated myocardial infarction, and treatment with glycoprotein IIb/IIIa inhibitors. Longer length of stay was also associated with HAA.

We also repeated this model with the addition of baseline Hgb, which was strongly associated with HAA (RR, 0.70; 95% CI, 0.66 to 0.75) per 1 g/dL increase in baseline Hgb. Because we used diagnostic thresholds for anemia that were age-, sex-, and race-specific and thus accounted for the lower normal Hgb values in African Americans, older patients, and women, the inclusion of baseline Hgb in the models artificially altered the point estimates for these demographic variables as predictors of HAA (eg, female sex was associated with less risk of HAA whereas white race was more strongly associated with HAA after inclusion of baseline Hgb; data not presented). The addition of baseline Hgb to the model did not substantially alter point estimates for any other HAA correlates.

Variability in HAA Across Hospitals

The unadjusted incidence of HAA across all TRIUMPH hospitals varied between 33% and 69%. After generating shrinkage estimates, the incidence ranged from 35% to 66% (Figure 2). The median rate ratio for site was 1.13 (95% CI, 1.07 to 1.23), indicating that 2 patients with identical demographic and clinical characteristics presenting to 2 randomly selected hospitals can be 13% more or less likely to develop HAA.

Outcomes Associated With HAA

To assess the prognostic significance of HAA, we compared outcomes across HAA severity categories to patients with no anemia and chronic anemia at the time of admission. Important differences in 12-month survival were associated with
the development and severity of HAA. Mortality was lowest in those without HAA (40 of 1581, 2.6%), rising progressively in those with mild HAA (34 of 966, 3.6%), moderate-severe HAA (29 of 345, 8.4%), and chronic anemia (117 of 945, 12.6%) ($P<0.001$; Figure 3A). Among patients who developed HAA, survival did not differ on the basis of presence or absence of documented bleeding (Figure 3B).

Using no anemia as the reference group, there was no unadjusted or multivariable-adjusted association between mild HAA and mortality (Figure 4). In contrast, moderate-severe HAA and chronic anemia were strongly associated with mortality. Even after adjusting for GRACE 6-month mortality score and the presence and severity of bleeding, patients with moderate-severe HAA had an increased risk of death as compared with those without anemia (HR, 1.82; 95% CI, 1.11 to 2.98). Similarly, chronic anemia was strongly and independently associated with 12-month mortality (HR, 2.31; 95% CI, 1.57 to 3.40). The proportional hazards assumption was met for the fully adjusted mortality model ($P=0.233$).

At baseline, the SF-12 PCS scores were higher in those without anemia and in patients with mild HAA and lower in those with moderate-severe HAA and chronic anemia (no anemia: 44.9±11.6; mild HAA: 44.2±11.6; moderate-severe HAA: 40.1±12.6; chronic anemia: 37.3±12.8; $P<0.001$). Adjusting for baseline health status and incorporating 1-, 6-, and 12-month SF-12 scores, mean follow-up SF-12 PCS scores were lower in those with chronic anemia with a trend toward lower scores in those with moderate-severe HAA in comparison to those without anemia (Figure 5). Patients with mild HAA and no anemia had similar SF-12 PCS scores.

We conducted a series of sensitivity analyses to assess the robustness of our primary analysis. Using the WHO definition of anemia, excluding those who received blood transfusion, and adjusting the outcomes models for baseline Hgb all resulted in similar findings (data not shown).

**Discussion**

We found that almost half of patients who had normal hemoglobin at admission developed anemia by hospital discharge in this large, prospective, multicenter AMI cohort. Although inpatient bleeding was a strong independent predictor of HAA, most patients with HAA did not have a documented bleeding event during hospitalization, suggesting that HAA is not simply a surrogate for in-hospital bleeding events. Importantly, moderate-severe HAA was associated with increased long-term mortality, independent of AMI severity and regardless of the presence and extent of bleeding, suggesting that HAA is prognostically important in its own right and may represent a target for prevention efforts. Supporting that there is opportunity to minimize the risk of developing HAA, we observed significant variability in incidence of HAA across hospital sites.

Prior studies have established the short- and long-term prognostic significance of chronic anemia, and more recent reports have examined the association between changes in Hgb during hospitalization and outcomes. Aronson et al found that declines in Hgb during AMI hospitalization were independently associated with mortality; however, their analyses included both patients with baseline anemia and new-onset anemia during hospitalization. Because patients with...
chronic anemia presumably have poorer hematopoietic re-
serve or greater baseline comorbidity, potentially predispos-
ing them to large Hgb declines. It is unclear from these data
whether the relationship between inpatient Hgb decline and
survival is present among those with normal baseline Hgb.
Our work extends these insights by defining a population
with acute anemia, a potentially preventable condition, and
observing that moderate-severe HAA is associated with an
increased risk of mortality of similar magnitude to those with
chronic anemia, even after adjustment for the presence and
severity of bleeding. Our findings also extend prior observa-
tions by Sattur et al,17 who reported, in a single-center study,
that incident anemia in PCI patients was independently
associated with long-term mortality. The anemia threshold
used in that study (Hgb <10 g/dL) was relatively low,
potentially leading to overestimation of the association be-
 tween anemia and outcomes. Our study provides new insights
by examining a large, contemporary, multicenter cohort,
focusing on patients with AMI and using standard definitions
of anemia. Moreover, our analyses include a broad range of
outcomes (including health status), and provide important
new data about the variability of HAA across hospitals.
Our findings have important clinical implications. Several
of the correlates of HAA are also associated with chronic
anemia and bleeding in AMI patients (such as age, female
sex, acute heart failure, and chronic kidney disease)2,7,18,19
and probably identify a high-risk population with poor
hematopoietic reserve. On the other hand, some independent
correlates are hospital-based processes and complications
(use of glycoprotein IIb/IIIa inhibitors and bleeding) and
could be targets for prevention efforts. Several of these
variables are associated with bleeding,18–20 and the use of
bleeding avoidance measures, such as radial artery access for
percutaneous coronary intervention, closure devices, smaller
sheaths, or alternative antithrombotic agents such as bivaliru-
din in place of heparin and a glycoprotein IIb/IIIa inhibitor,
present potential opportunities for improvement.21–24 Addi-
tionally, the strong association between moderate-severe
HAA and 12-month mortality, even after adjusting for the
presence and severity of bleeding, indicates that HAA is
distinct from bleeding and is clinically important in its own
right. Although the major causes of HAA among those
without documented bleeding remain unclear, it is possible
that it is related to subclinical blood loss (such as frequent
phlebotomy), undetected minor periprocedural bleeding
(“nuisance bleeding”), inadequate hematopoietic response, or
a combination of processes. Our findings indicate that addi-
tional emphasis on prevention of HAA, a process distinct
from overt bleeding in many cases, could be just as important
as prevention of major bleeding. Further studies are needed to
better define specific causes of HAA, to develop the tools that
can prospectively identify patients at high risk for HAA at the
time of admission, and to study the feasibility, comparative
clinical effectiveness and cost effectiveness of various HAA
prevention strategies (such as reducing phlebotomy and the
use of bleeding avoidance strategies), so that the most

Figure 5. Association of mild HAA, moderate-severe HAA, and chronic ane-
mia with physical functioning over 12
months of follow-up. Repeated-measures
health status scores, comparing mean
difference in SF-12 PCS scores in each
anemia category over 12 months of
follow-up controlling for baseline SF-12
PCS score. Results are presented as
mean points difference in SF-12 PCS
score comparing each anemia category
to the reference group without anemia
(95% CI).
effective and least costly measures can be adopted. The first step in this process, however, is to raise awareness about the incidence and prognostic importance of HAA, which is the main objective of our study.

Our findings should be interpreted in the context of several potential limitations. We used discharge hemoglobin values to define HAA since nadir hemoglobin values were not available. This approach may underestimate the prevalence of HAA; however, given the relatively short duration of hospitalization (median, 3.0 days; interquartile range, 2.0 to 4.0) it is unlikely that a substantial proportion of HAA cases were missed. More importantly, our goal was to examine prognosis after discharge, and discharge Hgb is the most accurate assessment of patients’ anemia status at that time. It is also possible that unrecognized, minor bleeding episodes (ie, “nuisance bleeding”) were not detected despite careful prospective collection of bleeding data. Even if this were the case, however, the association between bleeding and adverse outcomes has only been demonstrated for more severe categories of bleeding, and not for mild bleeding. These “nuisance” bleeding events are currently considered by many to be unimportant and are not systematically tracked either clinically or as end points in clinical trials.25 Our data highlight the need to better understand if HAA may in part be caused by “nuisance” bleeding and whether minor bleeding events have a greater impact on patient outcomes than previously thought. Another possible limitation is that some misclassification of anemia severity occurred in patients with HAA who received blood transfusions before discharge hemoglobin assessment. However, we adjusted the discharge hemoglobin values for in-hospital blood transfusion to minimize this issue and performed sensitivity analyses excluding patients who received a blood transfusion. It is also possible that frequent scheduled phlebotomy was associated with HAA; however, data on blood draws were not collected in this registry. Our definition of chronic anemia was any anemia present at admission, which could have captured subacute cases in addition to those with long term anemia. Finally, these observational data do not allow us to draw conclusions about causal relationships between HAA and mortality, and it remains unclear whether HAA is a marker for, or a mediator of, poor outcomes.

In conclusion, we found that HAA is common in AMI patients who are treated medically or with percutaneous coronary intervention and varies significantly across hospitals. Development of moderate-severe HAA is associated with higher mortality and worse health status in the first year after AMI, independent of documented in-hospital bleeding. Better understanding of whether prevention of HAA is feasible and can improve patient outcomes is needed.

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References


Incidence, Correlates, and Outcomes of Acute, Hospital-Acquired Anemia in Patients With Acute Myocardial Infarction

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Conclusions—Les récidives d’IDM et les ruptures cardiaques forment une fraction élevée des morts subites qui se produisent au tout début de la période qui suit un IDM aigu, alors que, par la suite, le décès semble davantage susceptible d’être secondaire à un trouble du rythme cardiaque. Ces données pourraient en partie expliquer l’absence d’effet bénéfique de la pose précoce d’un défibrillateur automatique implantable. (Traduit de l’anglais : Pathogenesis of Sudden Unexpected Death in a Clinical Trial of Patients With Myocardial Infarction and Left Ventricular Dysfunction, Heart Failure, or Both. Circulation. 2010;122:597–602.)

Mots clés : mort, subite ■ autosie ■ infarctus du myocarde ■ insuffisance cardiaque ■ rupture cardiaque

Incidence, facteurs favorisants et pronostic clinique de l’anémie aiguë nosocomiale chez les patients atteints d’un infarctus du myocarde aigu

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Contexte—L’anémie est une complication fréquente chez les patients hospitalisés pour un infarctus du myocarde aigu et constitue un élément de mauvais pronostic. Nous ne possédons toutefois que peu de données sur l’incidence, les facteurs favorisants et les implications pronostiques de l’anémie aiguë nosocomiale (AAN).

Méthodes et résultats—Dans le registre multicentrique TRIUMPH (Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients’ Health status [Etude translationnelle visant à identifier les disparités sous-jacentes d’état de santé des patients victimes d’un infarctus du myocarde]), nous avons recensé 2 909 patients hospitalisés pour un infarctus du myocarde en phase aiguë qui présentaient un taux d’hémoglobine (Hb) normal à leur admission, l’AAN ayant été défini en utilisant les critères proposés par Beutler et Waalen. Nous avons eu recours à une analyse par régression hiérarchique de Poisson pour rechercher les facteurs indépendants favorisant la survenue d’une AAN et à une analyse multivariée par régression des risques proportionnels pour identifier les liens unissant ce trouble à la mortalité et à l’état de santé. A leur sortie d’hôpital, 1 321 patients (45,4 %) présentaient une AAN qui, chez 348 (26,3 %) d’entre eux, était de degré modéré à sévère (Hb <11 g/dl). L’incidence de ces AAN variait fortement selon les hôpitaux (extrêmes : 33 à 69 % ; rapport médian des risques d’AAN : 1,13 ; intervalle de confiance [IC] à 95 % : 1,07 à 1,23 après ajustement en fonction des caractéristiques des patients). Bien que les AAN de sévérité accrue aient eu tendance à être plus fréquentes chez les patients ayant présenté un saignement avéré, moins de la moitié des patients atteints d’une AAN modérée à sévère avaient été sujets à un épisode hémorragique documenté. Les facteurs indépendants qui se sont révélés favoriser la survenue d’une AAN ont été l’âge, le sexe féminin, la race blanche, la néphropathie chronique, l’infarctus du myocarde avec sus-décalage du segment ST, l’insuffisance rénale aiguë, l’administration d’inhibiteurs des récepteurs à la glycoprotéine IIb/IIIa, les complications intrahospitalières (choc cardiogénique, hémorragie et sévérité de cette dernière) ainsi que la durée d’hospitalisation. Après ajustement pour le score GRACE et la survenue d’un épisode hémorragique, il est apparu que, un an après leur sortie d’hôpital, les patients qui avaient contracté une AAN de degré modéré à sévère avaient présenté un taux de mortalité plus élevé (rapport de risques : 1,82 ; IC à 95 % : 1,11 à 2,98 par rapport aux patients n’ayant pas acquis d’AAN) ainsi qu’un état de santé plus médiocre.


Mots clés : infarctus du myocarde ■ anémie ■ hémoglobine ■ pronostic