Hospital-Acquired Anemia in Patients With Cardiovascular Disease: Incidence, Outcomes, and Opportunities for Prevention

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Anemia is well recognized as a marker of poor prognosis in patients with cardiovascular disease. Despite increasing awareness that anemia is associated with higher mortality, more frequent hospitalization, and worse health status, it remains unclear whether treating chronic anemia improves patients' outcomes. The importance of studying hospital-acquired anemia (HAA), and recognizing which patients are at high risk for developing HAA early in the course of their hospitalization, is underscored by the potential opportunities for HAA prevention and management. This article reviews the incidence of HAA, risk factors for developing HAA, and its relationship with clinical outcomes.

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KEY WORDS

Hospital-acquired anemia • Cardiovascular disease • Acute myocardial infarction •Clinical outcomes

Anemia is well recognized as a marker of poor prognosis in patients with cardiovascular disease, including patients with stable coronary artery disease (CAD), acute myocardial infarction (AMI), and those with chronic heart failure.[1-4] Despite increasing awareness that anemia is associated with higher mortality, more frequent hospitalization, and worse health status, it remains unclear whether treating chronic anemia improves patients' outcomes. For example, treating severe anemia with blood transfusions transiently increases hemoglobin, but may also be associated with greater mortality.[5-9] Other treatments, such as erythropoietin analogues, appear to improve physical functioning but are also associated with clinically meaningful risks. Because these agents increase patients' risk

for thromboembolic complications, their current use for treatment of anemia in cardiac populations is limited.[10-13]

In contrast to chronic anemia, hospital-acquired anemia (HAA) develops during the course of hospitalization in patients with normal baseline hemoglobin. Because HAA is associated with in-hospital processes of care, it is preventable. Prior studies have found that it is common, and often develops in the absence of overt bleeding, suggesting that simply focusing on bleeding prevention to prevent in-hospital hemoglobin declines may result in substantial residual risk for HAA.[14-16] This multifactorial condition reflects the combined impact of underlying severity of illness (related to patients' age, chronic renal disease, acute and chronic inflammation, and other factors) but also potentially treatable risk factors (including periprocedural bleeding, diagnostic blood loss from laboratory testing, and unrecognized iron deficiency).

The importance of studying HAA, and recognizing which patients are at high risk for developing HAA early in the course of their hospitalization, is underscored by the potential opportunities for HAA prevention and management. In fact, some interventions, such as the use of low-volume pediatric blood tubes and limiting multiple daily blood draws could improve quality of care without adding cost. In an era of increasing tension created by rising costs and increased calls to improve quality, understanding how to prevent and manage HAA could provide a rare opportunity to improve patients' outcomes by applying low-cost, common sense clinical interventions. This novel and exciting area of research has received little attention from the cardiovascular community, but accumulating evidence suggests HAA may be an important target for quality improvement. Accordingly, we review the incidence of HAA, risk factors for developing HAA, and its relationship with clinical outcomes.

Definition of HAA

HAA is a new-onset anemia that develops during the course of hospitalization in patients whose admission hemoglobin is normal. Its incidence is strongly related to the definition of anemia selected. For example, in the Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients Health Status (TRIUMPH) study,[14] both chronic anemia (anemia at the time of patients' initial hemoglobin assessment upon hospitalization) and HAA were less common using the World Health Organization (WHO) anemia definition (833 and 1125 patients, respectively) than when using a more recently reported age-, sex-, and race-specific definition (950 and 1321 patients, respectively; Figure 1).[17,18] Although a host of definitions have been used to define anemia in the cardiovascular literature, in general, differences in these definitions largely influence the proportion of the population defined as having either mild chronic anemia or mild HAA. In contrast, the frequency of more significant grades of HAA, which appear to carry greater prognostic implications, is relatively stable across most anemia definitions.

Other key factors influencing the incidence of HAA should also be considered. Because anemia is particularly common after coronary artery bypass surgery, these patients have often been excluded from prior studies examining HAA.[14,15] Clearly, if these patients were included, the incidence of HAA would be even greater, particularly the proportion of the population with more significant grades of anemia. Whether HAA is identified using nadir hemoglobin, or hemoglobin at the time of discharge from the hospital, is also an important factor in understanding the incidence of HAA. Prior studies using these different strategies to define HAA have examined heterogeneous cohorts, but in general, a greater proportion of the population will have some degree of HAA when defined using nadir hemoglobin assessments.

Although HAA has only recently been studied as a separate entity, it was clear from earlier studies that in-hospital hemoglobin declines were common in cardiac patients.

Figure 1. Common anemia definitions in studies of hospital-acquired anemia in cardiovascular disease.

Beutler and Waalen Anemia Definition (g/dL)[18]			
	Men < 60 years	Men ≥ 60 years	Women
White	< 13.7	< 13.2	< 12.2
Non-White	< 12.9	< 12.7	< 11.5

World Health Organization Anemia Definition (g/dL)[17]		
	Men	Women
All races	< 13.0	< 12.0

TABLE 1

Incidence of HAA and Association With Clinical Outcomes in Prior Studies of HAA

Study	Sample Size (N)	Patient Population	HAA Definition	Incidence of HAA	Outcomes	Findings
Vaglio J et al[19]	604	ACS (UA, NSTEMI, STEMI) from 2 hospitals	Mild HAA: Hct decline from normal to < 39% at discharge Moderate-severe HAA: Hct decline from normal to < 33% at discharge	8.0% developed moderate-severe HAA, 34.9% developed mild HAA	2-year mortality	Mild HAA & mortality: HR 1.92 (95% CI, 0.82-4.51) Moderate-severe HAA & mortality: HR 3.05 (95% CI, 1.03-9.06)
Sattur S et al[15]	1415	Consecutive series of patients undergoing PCI at a single center	Hgb decline from normal to a nadir < 10.0 g/dL	8.8%	MACE and long-term mortality over a median follow-up of 1473 days	MACE: OR 2.4 (95% CI, 1.5-3.9) Mortality: OR 1.3 (95% CI, 1.1-1.6)
Salisbury AC et al[14]	2909	AMI patients enrolled in a 24-center observational registry	Mild HAA: Hgb decline from normal to discharge value < 13.7 g/dL in white men < 60, Hgb < 13.2 g/dL in white men ≥ 60, Hgb < 12.9 g/dL in black men < 60, Hgb < 12.7 g/dL in black men ≥ 60, Hgb < 12.2 g/dL in white women and Hgb < 11.5 g/dL in black women Moderate-severe HAA: Hgb decline from normal to < 11 g/dL at discharge	12.0% developed moderate-severe HAA, 34.4% developed mild HAA	1-year mortality and health status across 1 year	Mild HAA & mortality: HR 1.20 (95% CI, 0.75-1.90) Moderate-severe HAA & mortality: HR 1.82 (95% CI, 1.11-2.98) Mild HAA & SF-12 PCS over 1 year: + 0.52 points (95% CI, −0.27, 1.31) Moderate-severe HAA & SF-12 PCS over 1 year: −1.1 points (95% CI, −2.3, 0.1)
Valente S et al[16]	1122	Consecutive series of STEMI patients undergoing primary PCI at a single center	Hgb decline from normal to < 13 g/dL in men, < 12 g/dL in women	46.8%	In-hospital mortality	Unadjusted mortality rates: 10.7% with chronic anemia, 2.9% with HAA, 1.7% with no anemia ($P < .001$)
Salisbury AC et al[21]	17676	Consecutive AMI admissions to 57 hospitals	Mild HAA: Hgb decline from normal to a nadir value < 13.7 g/dL in white men < 60, Hgb < 13.2 g/dL in white men ≥ 60, Hgb < 12.9 g/dL in black men < 60, Hgb < 12.7 g/dL in black men ≥ 60, Hgb < 12.2 g/dL in white women and Hgb < 11.5 g/dL in black women Moderate HAA: Hgb decline from normal to a nadir value of 9-11 g/dL Severe HAA: Hgb decline from normal to < 9 g/dL	Severe HAA developed in 4.6%, moderate HAA in 15.5% and mild HAA in 37.4%	In-hospital mortality	Mild HAA & mortality: OR 0.92 (95% CI, 0.82-1.17) Moderate HAA & mortality: OR 1.38 (95% CI, 1.10-1.73) Severe HAA & mortality: OR 3.39 (95% CI, 2.59-4.44)

ACS, acute coronary syndromes; AMI, acute myocardial infarction; CI, confidence interval; HAA, hospital-acquired anemia; Hct, hematocrit; Hgb, hemoglobin; HR, hazard ratio; MACE, major adverse cardiac events; NSTEMI, non–ST-elevation myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; SF-12 PCS, Short Form-12 Physical Component Summary; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

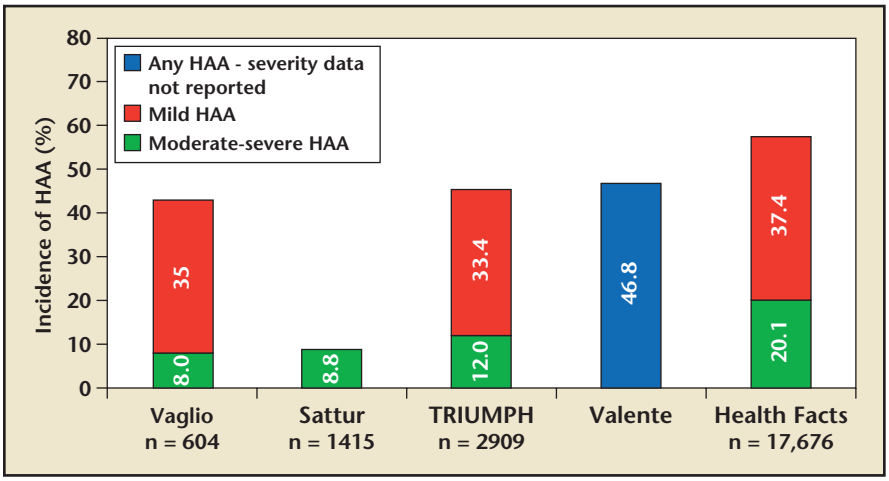


Figure 2. Incidence of hospital-acquired anemia (HAA) in prior studies. The incidence of HAA, by severity when reported, in prior studies. Studies examined cohorts with any acute coronary syndrome (Vaglio J et al[19]), patients undergoing percutaneous coronary intervention (PCI) for unstable coronary syndrome or electively (Sattur S et al[15]), acute myocardial infarction (Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients Health Status [TRIUMPH; Salisbury AC et al[14]] and Health Facts database [Salisbury AC et al[21]]) and patients managed with primary PCI for ST-elevation myocardial infarction (Valente S et al[16]).

Incidence of HAA and Bleeding in Patients With HAA

Although HAA has only recently been studied as a separate entity, it was clear from earlier studies that in-hospital hemoglobin declines were common in cardiac patients (Table 1). For instance, Vaglio and colleagues[19] reported that a greater proportion of patients were anemic at discharge than at the time of admission in an analysis of 1038 patients admitted with acute coronary syndromes (ACS). They also reported that anemia at discharge was a stronger predictor of long-term mortality after ACS than anemia at the time of admission. Similarly, Aronson and colleagues[20] found that anemia was markedly more common at discharge than at admission. In this study, the relationship between anemia at admission with mortality was attenuated by adjustment for potential confounders, whereas in-hospital hemoglobin declines, nadir hemoglobin during hospitalization, and discharge hemoglobin were independent predictors of long-term mortality.

The incidence of HAA has been reported in several cohorts of patients with CAD, each noting that HAA is common and often develops in the absence of overt bleeding (Figure 2). Sattur and coauthors[15] reported a single center series of 1512 patients who underwent percutaneous coronary intervention (PCI), of whom 1029 had PCI for management of an ACS. Defining both baseline anemia and new-onset anemia using a rather low hemoglobin threshold of $<$ 10 g/dL, they found that 8.8% of patients who did not undergo coronary artery bypass surgery (CABG) during their hospitalization became anemic before discharge. Of these patients, only 40% had recognized thrombolysis in myocardial infarction (TIMI) major or minor bleeding. The incidence of HAA was also examined in a larger cohort of patients admitted with AMI in the 24 US-center TRIUMPH registry.[14] Excluding patients who underwent CABG during their index hospitalization, 45.4% of patients developed some degree of HAA using age-, sex-, and race-specific diagnostic thresholds. Of these patients, over one in four developed moderate-severe HAA, defined as a hemoglobin decline from normal to $<$ 11 g/dL. In the setting of prospective collection of bleeding data using the TIMI classification, only 10.3% of patients with mild HAA (hemoglobin decline below diagnostic threshold but $>$ 11 g/dL), 16.8% with moderate HAA (hemoglobin decline from normal to 9-11 g/dL) and 51.8% of patients with severe HAA (Hgb decline from normal to $<$ 9 g/dL) had overt bleeding episodes. Examining a single-center, consecutive series of 1122 ST-elevation MI (STEMI) patients treated with PCI, Valente and associates[16] reported a similar incidence of HAA of 46.8% using the WHO anemia definition. Consistent with other reports, few patients who developed HAA in this series experienced major bleeding (14.9% using the Acute Catheterization and Urgent Intervention Triage Strategy [ACUITY] major bleeding definition). Finally, the largest study of HAA in AMI reported the incidence of HAA in an unselected cohort of 17,676 consecutive AMI patients from 57 US hospitals who were managed medically or with PCI in the Cerner Health Facts database.[21] This study included consecutive AMI admissions to these hospitals, with a greater acuity of illness than prior multicenter investigations owing to inclusion of all AMI patients in the database. This Health Facts database also included all hemoglobin values during the course of each patient's hospitalization, allowing identification of HAA incidence using nadir hemoglobin. Consequently, the proportion of patients with some degree of HAA (defined by nadir hemoglobin) was even higher than previous reports (57.5%), and one in five patients developed moderate-severe HAA (hemoglobin decline from normal to $<$ 11 g/dL).

HAA has yet to be studied in detail in patients admitted with decompensated heart failure. Anemia is known to be common in patients with heart failure, and prior studies have reported that new-onset anemia is common in ambulatory patients with systolic heart failure.[22] Studies are needed to describe the incidence of HAA during hospitalization with decompensated heart failure, because interventions, including limiting diagnostic blood loss from phlebotomy and treating unrecognized iron deficiency,[23-26] may also improve outcomes when applied to these patients.

Variability in the Incidence of HAA

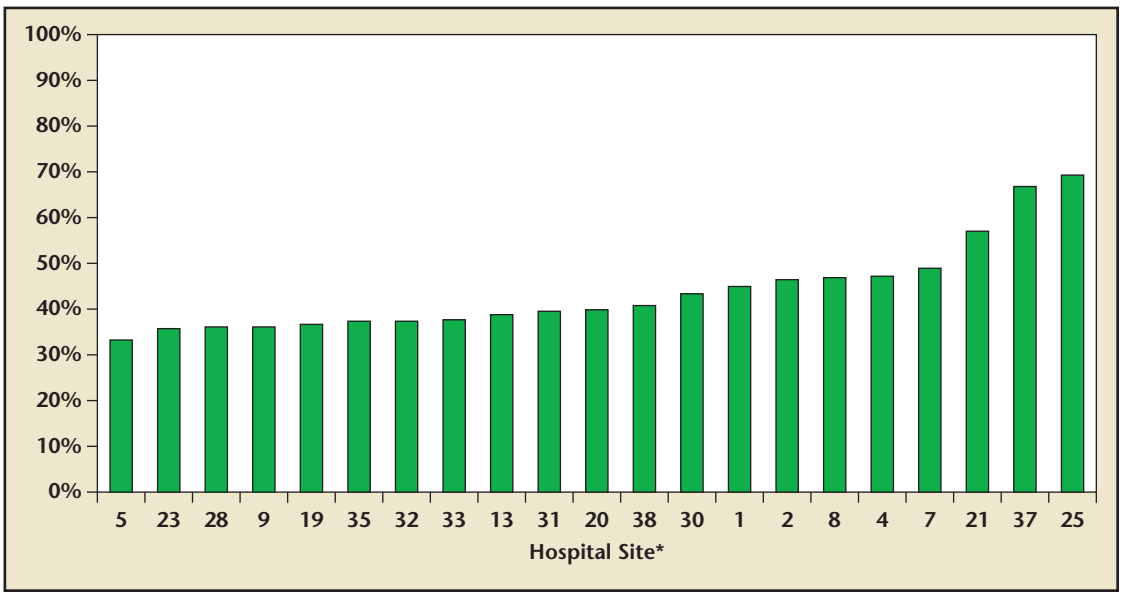
If HAA is related to differences in hospital-based processes of care, it follows that the incidence of HAA should vary across hospitals. Although few multicenter investigations have focused on HAA variability, a 24-center study of AMI patients found that the incidence of HAA varied between 33% and 69% across participating hospitals (Figure 3). Because much of this variation could reflect differences in case mix and patients' underlying disease severity, the authors calculated median rate ratios to identify the variation in HAA after adjusting for patient characteristics.[27] This statistic, which is the median value of the relative risk for HAA for two patients with identical covariates who present to all possible pairs of study hospitals, indicated a median 13% difference in the risk of HAA between pairs of identical patients presenting to participating hospitals (median rate ratio [mRR] 1.13; 95% confidence interval [CI], 1.12-1.18).[14] Emerging evidence indicates that there may be even greater variability in the risk for more severe grades of HAA.[28] In a study of consecutive AMI patients from 57 US hospitals, the shrinkage-adjusted incidence of moderate-severe HAA varied from 12.9% to 32%. There was substantial residual variability in the incidence of HAA across the hospitals after adjusting for demographic, clinical, and treatment characteristics (mRR 1.27; 95% CI, 1.19-1.39), which may indicate that unmeasured processes of care are driving the variation in HAA seen in this study. Although these data are intriguing, further studies are needed to compare processes of care at hospitals with low and high rates of HAA, and study how improving patterns of care might influence development of HAA.

Predictors of HAA

Several studies have reported independent predictors of HAA in cardiac patients. The risk factors for HAA represent a diverse collection of variables, some of which are nonmodifiable markers of underlying illness, and others that could be important targets for quality improvement (Figure 4). In patients with AMI, HAA shares several common risk factors with chronic anemia including age, female sex, and the presence of chronic renal disease.[14,16] Both

In patients with AMI, HAA shares several common risk factors with chronic anemia including age, female sex, and the presence of chronic renal disease.

Figure 3. Variability in the incidence of hospital-acquired anemia (HAA). Each bar represents the incidence of HAA for an individual hospital. *Site numbers reported on the *y*-axis were arbitrarily assigned to each hospital.



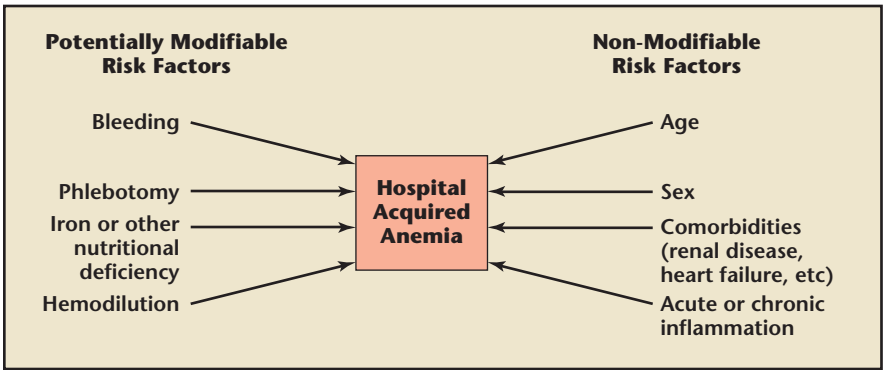


Figure 4. Risk factors for hospital-acquired anemia.

acute inflammation, in the setting of myocardial necrosis, and chronic inflammation may also blunt erythropoiesis.[29] Consistent with this hypothesis, Steinvil and colleagues reported that as time since symptom onset to coronary angiography increased in patients admitted with AMI, inflammatory markers (C-reactive protein [CRP] and fibrinogen) rose whereas hemoglobin declined in a single-center cohort of 677 patients. Moreover, both higher CRP and higher fibrinogen were independent correlates of a lower hemoglobin concentration. These risk factors may not be modifiable, but are important to recognize because they may predispose patients to hemoglobin declines during hospitalization with no blood loss or even minor bleeding and routine phlebotomy.

HAA is also associated with several hospital-based risk factors. Some of these reflect patients' disease severity and may not be influenced by changes to processes of care, such as cardiogenic shock and higher peak troponin.[14,16] Others may be amenable to quality improvement interventions. In-hospital bleeding has been shown to be an independent predictor of HAA,[14] and is highly actionable. Periprocedural bleeding can be prevented using a number of strategies, including radial access for coronary angiography and PCI,[31-33] using smaller sheaths with prompt sheath removal,[34] with use of alternative anticoagulants such as bivalirudin,[35-37] and potentially with closure devices.[38] Diagnostic blood loss from phlebotomy also holds promise as a target for HAA prevention and management. In an analysis of over 17,000 patients with AMI from 57 US hospitals, diagnostic blood loss was frequently substantial.[39] Among patients who developed moderate-severe HAA (a hemoglobin decline from normal to < 11 g/dL), the mean diagnostic blood loss was equivalent to nearly half a unit of whole blood and was significantly greater than in patients who did not develop moderate-severe HAA (173.8 $\pm$ 139.3 mL vs 83.5 $\pm$ 52.0 mL; $P < .001$). A significant proportion of patients with moderate-severe HAA experienced diagnostic blood loss > 300 mL (12.5%), and 3.8% had phlebotomy volumes > 500 mL during the course of their hospitalizations. After extensive multivariable adjustment, every 50 mL of diagnostic blood loss was associated with a 15% increased risk for moderate-severe HAA (relative risk = 1.15; 95% CI, 1.12-1.18). Acute renal failure is also associated with development of HAA.[14] Although it is unclear whether risk for HAA related to acute renal failure can be attenuated with intravenous hydration, more judicious use of diuretics, and intravenous contrast and other strategies, prevention of acute kidney injury may also prevent HAA.

There may be additional risk factors for HAA that have yet to be identified. Understanding the risk factors for HAA is an important step toward learning how to prevent and manage in-hospital anemia. Future studies should focus on identifying novel, potentially modifiable risk factors for HAA in cardiac patients that could be targets for quality improvement initiatives to prevent and manage HAA. It is likely that many predictors of HAA are generalizable to other patient populations, but further studies are needed in patients with heart failure or other acute cardiac disease.

HAA and Clinical Outcomes

The relationship between HAA and clinical outcomes has been reported in several cohorts of patients with CAD. In an analysis of 1038 ACS patients from two hospitals, Vaglio and colleagues[19] examined subgroups of patients anemic at discharge from the hospital including those without anemia at the time of admission but who were discharged with new-onset anemia. Patients who developed mild anemia (hematocrit 33%-39%) did not have significantly higher mortality in follow-up (hazard ratio [HR] 1.92; 95% CI, 0.82-4.51), whereas those with severe anemia (defined as a hematocrit $< 33\%$) had a greater risk for mortality over

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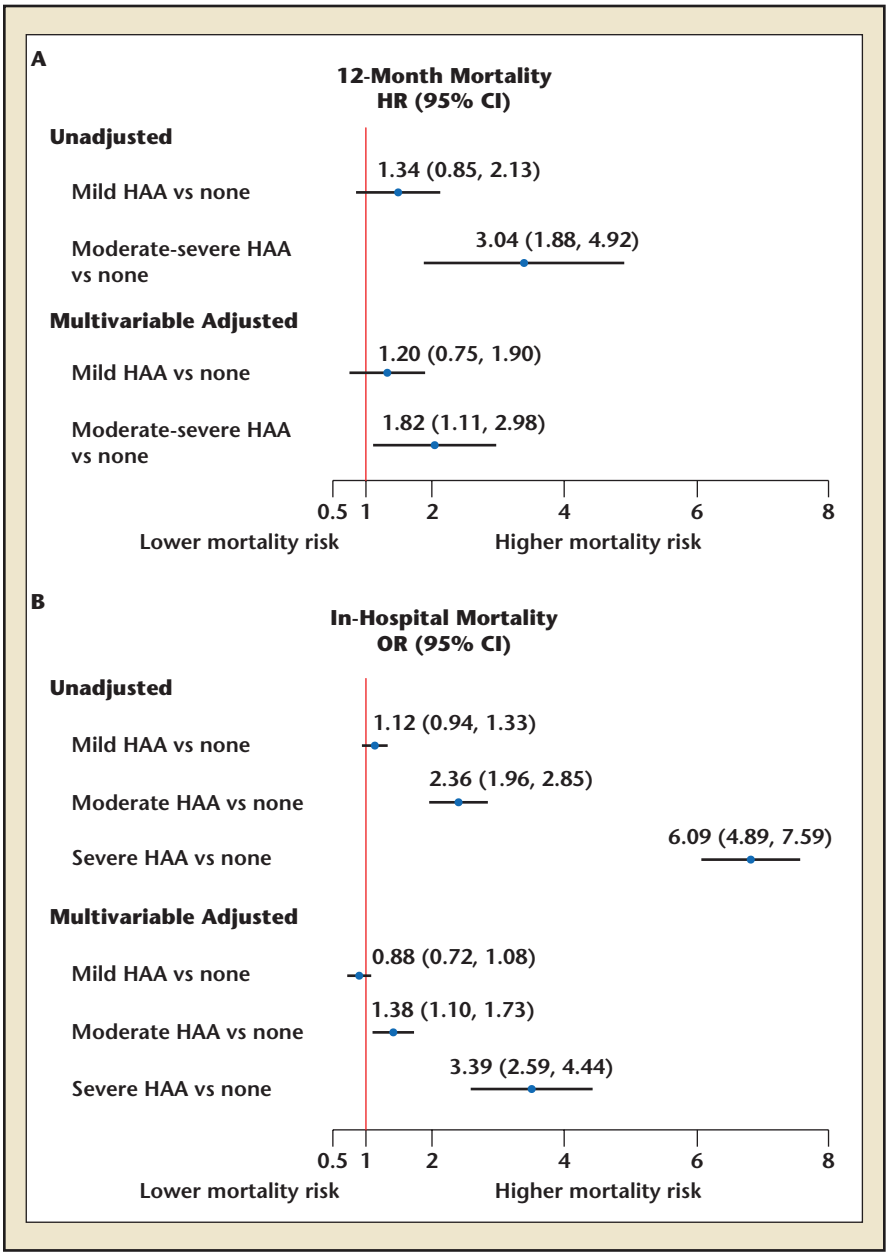

Figure 5. Relationship between HAA severity and mortality. Relationship between HAA and 12-month mortality in the 24-US hospital TRIUMPH registry (**A**) and among 57 US hospitals in the Health Facts database (**B**). CI, confidence interval; HAA, hospital-acquired anemia; HR, hazard ratio; OR, odds ratio; TRIUMPH, Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients Health Status. Data from Salisbury AC et al.[14,21]

24-month follow-up (HR 3.05; 95% CI, 1.03-9.06). Other studies have confirmed that outcomes appear to differ by severity of HAA in patients with AMI. In a 24-center study of AMI patients, mild HAA (hemoglobin < diagnostic thresholds but > 11 g/dL) was not associated with greater mortality or worse health status in follow-up. In contrast, after multivariable adjustment including adjustment for the presence and severity of bleeding, moderate-severe HAA (hemoglobin decline from normal to ≤ 11 g/dL) was associated with higher mortality over 1-year follow-up (HR 1.82; 95% CI, 1.11-2.98; Figure 5A). Patients with moderate-severe HAA also experienced, on average, worse health status over the course of the first year of recovery after AMI. These results were similar when using the WHO, rather than the Beutler and Waalen, anemia definition. In an analysis of another AMI cohort from 57 US hospitals, this graded relationship between severity of HAA and in-hospital mortality was further characterized. After extensive adjustment for patients' demographics, comorbidities, disease severity, in-hospital treatments, and in-hospital complications, mild HAA was not associated with higher in-hospital mortality (odds ratio [OR] 0.88; 95% CI, 0.72-1.88), whereas a graded association between moderate HAA (OR 1.38; 95% CI, 1.10-1.73) and severe HAA (3.39; 95% CI, 2.59-4.44) persisted after multivariable adjustment (Figure 5B).[21] Results were similar in a series of sensitivity analyses, including using alternative anemia definitions, excluding patients with known bleeding, and after excluding patients who were given blood transfusions.

Other studies examining the relationship between HAA and mortality did not examine whether the relationship between HAA and outcomes differed by HAA severity, but also found an association between HAA and outcomes. Using a diagnostic threshold of hemoglobin < 10 g/dL, a hemoglobin decline that would have been considered moderate-severe HAA in the previously discussed studies, Sattur and colleagues[15] also described an increased risk for mortality in patients with HAA. Individuals who developed HAA were more likely to experience major adverse cardiac events (MACE) over a 6-month follow-up (27.3% vs 14.5%; $P = .0006$) and experienced greater all-cause mortality over a median follow-up of nearly 4 years (35% vs 13%; $P < .001$). After multivariable adjustment, HAA was a significant

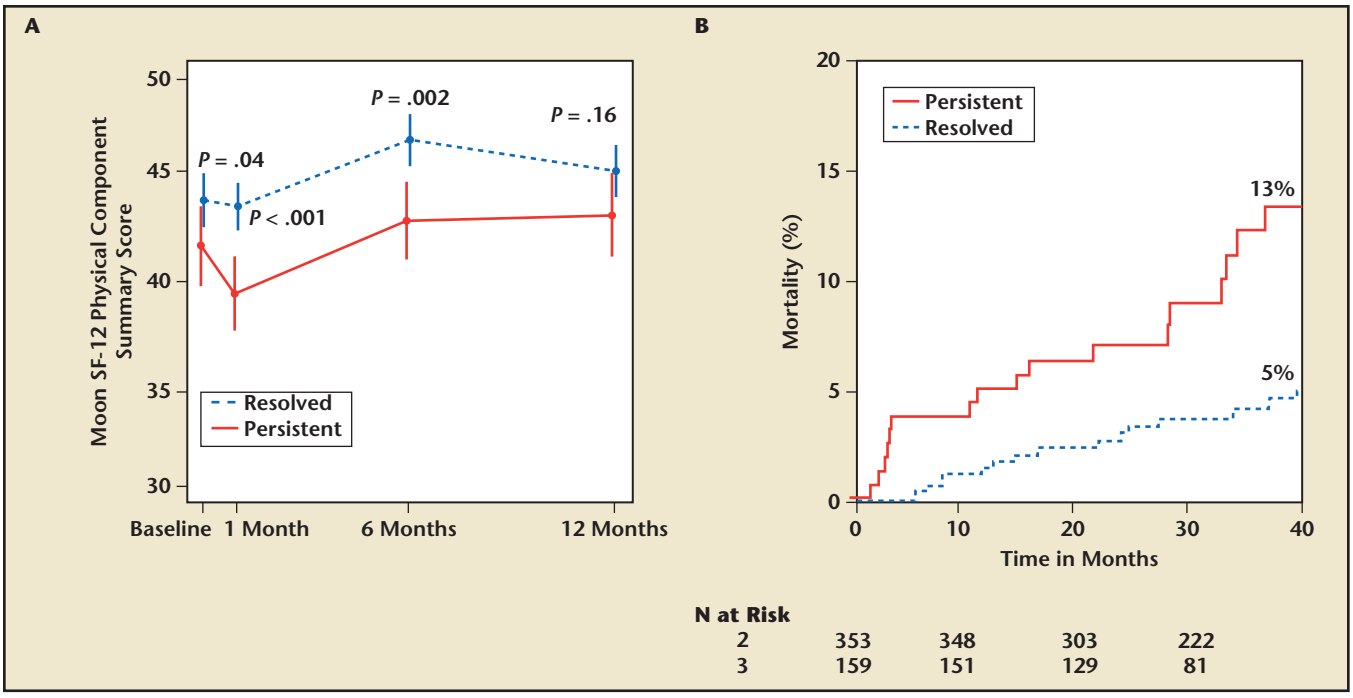

Figure 6. Association between hospital-acquired anemia (HAA) persistence 1 month after discharge and outcomes following acute myocardial infarction (AMI). **Panel A** shows SF-12 PCS scores, reflecting patient-reported general physical functioning, of patients with persistent versus resolved HAA 1 month after AMI throughout the first year after AMI. **Panel B** depicts the relationship between persistence versus resolution of HAA at 1 month and long-term mortality. SF-12 PCS, Short Form-12 Physical Component Summary.

predictor of both 6-month MACE and long-term all-cause mortality. They also reported that outcomes were similar among patients who did and did not experience TIMI major or minor bleeding. Similarly, Valente and colleagues,[16] in a single-center study of STEMI patients who underwent primary PCI, found that HAA was common and associated with greater in-hospital mortality.

Persistence of HAA in Follow-up and Relationship With Outcomes

Hemoglobin is not static across time, and frequently changes in follow-up after cardiovascular hospitalization. For example, Hasin and coauthors[40] reported that 43.8% of AMI patients with anemia at discharge had normalization of their hemoglobin anemia in follow-up. In their study, patients whose anemia resolved had similar outcomes to individuals who were not anemic, but persistently anemic patients experienced greater long-term mortality. Post-AMI patients who experience hemoglobin declines in follow-up are also at greater risk for mortality, as shown by Anker and colleagues in an analysis of the Optimal Trial in Myocardial Infarction With the Angiotensin II Antagonist Losartan (OPTIMAAL) study.[4] Similarly, a differential mortality risk by longitudinal hemoglobin trajectories has been reported in the heart failure literature. Studies by Tang and colleagues,[41] Kosiborod and colleagues,[42] and Peterson and colleagues[43] each reported higher mortality among anemic patients who remained persistently anemic in follow-up after heart failure hospitalization.

Because HAA results from a combination of short-term (bleeding and phlebotomy) and long-term (renal failure, heart failure, age) exposures, it is also important to understand whether it is commonly persistent in follow-up. In an analysis of the TRIUMPH registry data, 530 AMI patients discharged with HAA were studied and underwent protocol-driven hemoglobin assessment 1 month after hospital discharge.[44] Persistence of HAA at the follow-up assessment was common (31%). These patients experienced poorer physical functioning, as assessed using the Short Form-12 Physical Component Summary (SF-12 PCS) score, than patients whose HAA resolved by 1 month. Persistently anemic patients had particularly poor health status early in recovery after AMI at 1- and 6-month assessments (Figure 6A), and had a significantly lower SF-12 PCS score across 1-year follow-up than patients with resolved HAA (multivariable adjusted difference: −2.0 points [95% CI, −3.6, −0.3]; $P = .02$ across the follow-up period). Because patients may be most motivated to adopt lifestyle changes such as engaging in regular exercise early after MI, these impairments in physical functioning could limit participation with cardiac rehabilitation or delay

return to work among patients with persistent HAA. Moreover, patients with persistent HAA had a two-fold greater all-cause mortality over a nearly 3-year follow-up, even after adjusting for the severity of HAA at the time of discharge from the hospital (HR 2.08; 95% CI, 1.02-4.21; $P = .04$; Figure 6B). Although it is unclear whether early recognition and management of HAA could improve patients' outcomes, these findings identify a high-risk cohort of patients who may benefit from closer follow-up, additional diagnostic testing for treatable causes of anemia, and ongoing management of HAA. These findings are likely to generalize to other cardiovascular patients, but further studies are needed to identify whether HAA is commonly persistent in patients hospitalized with other acute cardiac conditions.

HAA Prevention and Management

The key clinical questions surrounding HAA are whether HAA prevention is feasible in practice and whether it improves clinical outcomes. Research conducted to date points to several promising opportunities for intervention. For example, bleeding is a strong risk factor for HAA. Several strategies might be leveraged to reduce periprocedural bleeding in patients undergoing urgent or elective coronary angiography or PCI. Radial access is a promising technique to reduce local bleeding complications.[31,32] An increasing number of centers are gaining expertise in radial access, and it is now being offered more frequently in the United States. Anticoagulation with bivalirudin, rather than heparin, has also been shown to reduce bleeding complications.[36,37] However, this is a more costly treatment option than heparin, and may be cost effective only for patients at high risk for bleeding in comparison with heparin.[45] Similarly, vascular closure devices can also reduce local bleeding complications,[38] but increase costs. Efficient use of these strategies requires targeting them to patients at the highest risk for bleeding and for HAA, for whom these measures are most likely to be effective. Unfortunately, higher-risk patients are less likely to receive these interventions in practice, and novel methods are needed to target these therapies to the most appropriate patients.[38]

One of the most common-sense targets for preventing HAA may be diagnostic blood loss from phlebotomy.

One of the most common-sense targets for preventing HAA may be diagnostic blood loss from phlebotomy. All AMI patients experience some degree of phlebotomy, and there is tremendous variability in the intensity of diagnostic phlebotomy.[39] Several key issues should be considered. First, diagnostic blood loss is most significant among patients who have complicated presentations requiring intensive care and/or prolonged hospitalization. For these individuals, a combination of interventions that even modestly reduce blood loss could be important. For example, smaller-volume (pediatric) blood tubes are available at many hospitals and could result in significant reductions in diagnostic blood loss, particularly for patients with long lengths of stay and those undergoing multiple daily blood draws.[24,25,39] Moreover, there may be opportunities to explore whether intentionally under-filling adult blood tubes is feasible.[46] If diagnostic accuracy was unaffected, and there was no increased risk for repeat sampling due to inadequate specimen volume, this could also be a promising intervention. Although these potential HAA prevention measures have not been prospectively studied, patients may also benefit from increased use of stored serum samples for appropriate tests, minimizing wasted blood when drawing from central venous catheters, grouped blood draws, and elimination of routine, scheduled phlebotomy when patients have achieved a more stable clinical status. Studies are currently underway to understand whether these common-sense strategies reduce in-hospital hemoglobin declines.

Additional research is needed to identify other potentially modifiable risk factors for HAA. One target may be unrecognized iron deficiency, because iron deficiency has been shown to be prevalent in patients with heart failure, and its treatment is associated with improved health status.[23,26,47] At the present time, the prevalence of iron deficiency in patients admitted with AMI is unknown, and it is unclear whether treating these patients with iron is useful to prevent HAA, limit its severity, and prevent progression to chronic anemia after discharge from the hospital. Other potentially modifiable risk factors are likely to be identified, and may be important components of a comprehensive program to address HAA.

Conclusions

HAA is common, potentially actionable, and is associated with poorer outcomes in patients with cardiovascular disease. Although HAA has been studied predominantly in AMI populations, risk factors for HAA and the prognostic implications of new-onset anemia are likely similar in other acutely ill patients. Studies are needed to understand whether preventing and treating

HAA improves patients' clinical outcomes, and to determine whether these interventions are feasible and cost effective. ■

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MAIN POINTS

- Hospital-acquired anemia (HAA) develops during the course of hospitalization in patients with normal baseline hemoglobin. Because HAA is associated with in-hospital processes of care, it may be preventable.
- Understanding the risk factors for HAA is an important step toward learning how to prevent and manage in-hospital anemia.
- Patients may benefit from increased use of stored serum samples for appropriate tests, minimizing wasted blood when drawing from central venous catheters, smaller-volume blood tubes, and elimination of routine, scheduled phlebotomy. Bleeding avoidance strategies should be used when appropriate at the time of invasive procedures.

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