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Diagnostic Blood Loss From Phlebotomy and Hospital-Acquired Anemia During Acute Myocardial Infarction

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Background: Hospital-acquired anemia (HAA) during acute myocardial infarction (AMI) is associated with higher mortality and worse health status and often develops in the absence of recognized bleeding. The extent to which diagnostic phlebotomy, a modifiable process of care, contributes to HAA is unknown.

Methods: We studied 17 676 patients with AMI from 57 US hospitals included in a contemporary AMI database from January 1, 2000, through December 31, 2008, who were not anemic at admission but developed moderate to severe HAA (in which the hemoglobin level declined from normal to <11 g/dL), a degree of HAA that has been shown to be prognostically important. Patients' total diagnostic blood loss was calculated by multiplying the number and types of blood tubes drawn by the standard volume for each tube type. Hierarchical modified Poisson regression was used to test the association between phlebotomy and moderate to severe HAA, after adjusting for site and potential confounders.

Results: Moderate to severe HAA developed in 3551 patients (20%). The mean (SD) phlebotomy volume was higher in patients with HAA (173.8 [139.3] mL) vs those without HAA (83.5 [52.0 mL]; $P < .001$). There was significant variation in the mean diagnostic blood loss across hospitals (moderate to severe HAA: range, 119.1-246.0 mL; mild HAA or no HAA: 53.0-110.1 mL). For every 50 mL of blood drawn, the risk of moderate to severe HAA increased by 18% (relative risk [RR], 1.18; 95% confidence interval [CI], 1.13-1.22), which was only modestly attenuated after multivariable adjustment (RR, 1.15; 95% CI, 1.12-1.18).

Conclusions: Blood loss from greater use of phlebotomy is independently associated with the development of HAA. These findings suggest that HAA may be preventable by implementing strategies to limit blood loss from laboratory testing.

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BOTH CHRONIC ANEMIA, PRESENT at the time of admission to the hospital, and hospital-acquired anemia (HAA), which develops during hospitalization in patients with a normal hemoglobin level at admission, are associated with greater mortality and worse health status in patients with acute myocardial infarction (AMI).¹⁻⁵ However, in

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contrast to chronic anemia, HAA could potentially be prevented by implementing strategies to reduce blood loss in high-risk patients. Although in-hospital bleeding is a risk factor for HAA and is already recognized as an important target for quality improvement, HAA seems to be multifactorial and commonly develops in the absence of bleeding.^{4,6}

Several factors other than bleeding might be associated with HAA, including blunted hematopoietic response and phlebotomy.

*See Invited Commentary
at end of article*

Impaired hematopoiesis, resulting from pre-existing and nonmodifiable factors, such as inflammation, chronic renal disease, or congestive heart failure, could impair recovery from even minor blood loss during hospitalization.^{7,8} It is important to note that blood loss from diagnostic phlebotomy has been linked to in-hospital declines in hemoglobin level and requirement for blood transfusion in other patient populations and may be a risk factor for HAA in patients hospitalized with AMI.⁹⁻¹¹ Furthermore, blood loss from phlebotomy could be an actionable target for intervention. Limiting scheduled phlebotomy, use of pediatric blood

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tubes, and more frequent use of stored serum specimens in high-risk patients may all minimize diagnostic blood loss (DBL)¹²⁻¹⁴ and could reduce the incidence and severity of HAA.

To our knowledge, the relationship between diagnostic phlebotomy and the risk of HAA has not been previously explored in patients with AMI. Accordingly, we used Cerner Corp's (Kansas City, Missouri) Health Facts, an electronic medical record database, to evaluate the association between DBL and HAA in an unselected cohort of patients with AMI hospitalized in 57 medical centers. Health Facts provided an ideal opportunity to address this hypothesis since the database contains detailed information on the frequency and type of laboratory testing, as well as patients' hemoglobin levels, across diverse group of US hospitals.

METHODS

DATA SOURCE

To identify the association between phlebotomy and HAA, we used the Cerner Corp's Health Facts database (see the "Methods" section of the eAppendix; <http://www.archinternmed.com>).^{15,16} The database captured deidentified data from the Cerner electronic medical record for patients admitted to participating hospitals from January 1, 2000, through December 31, 2008. Data included hospital characteristics; patients' demographic characteristics, medical history, and comorbidities (using the *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICM-9-CM] codes); laboratory studies (venous and arterial blood draws and time of phlebotomy); medications; procedures; and complications. All data were deidentified before they were provided to the investigators, and an exemption from review was provided by the Saint Luke's Hospital (Kansas City, Missouri) institutional review board.

DEFINITIONS

We defined anemia using age-, sex-, and race-specific criteria described by Beutler and Waalen¹⁷ as a hemoglobin level lower than 13.7 g/dL for white men aged 20 to 59 years, lower than 13.2 g/dL for white men 60 years or older, lower than 12.9 g/dL for black men aged 20 to 59 years, lower than 12.7 g/dL for black men 60 years or older, lower than 12.2 g/dL for white women, and lower than 11.5 g/dL for black women. (To convert hemoglobin to grams per liter, multiply by 10.0.) This classification is based on large, contemporary cohorts and identifies anemia more accurately than the World Health Organization (WHO) definition.^{17,18} In the absence of race-specific data for patients of other racial backgrounds (<5% of patients), we applied diagnostic criteria for white patients. Patients were classified as having HAA if their initial hemoglobin level was higher than the diagnostic thresholds but their lowest (nadir) hemoglobin level during hospitalization fell below the diagnostic threshold for anemia. Consistent with prior work, HAA was classified as mild if the nadir hemoglobin level was 11.0 g/dL or greater and moderate to severe if the nadir hemoglobin level was lower than 11.0 g/dL.⁴ The outcome for this study was the development of moderate to severe HAA, since only moderate to severe HAA has been shown to be prognostically important.⁴

PATIENT POPULATION

We included all patients hospitalized with a primary discharge diagnosis of AMI as determined by ICM-9-CM diagnos-

tic codes 410.xx, and further confirmed AMI by requiring that patients had at least 1 elevated cardiac biomarker (troponin or creatine kinase MB) and were not discharged within the first 24 hours. The inclusion and exclusion criteria are listed in detail in the eAppendix and eFigure 1; key exclusions were patients who underwent coronary bypass grafting during hospitalization (etiology and outcomes of anemia are different in these patients) and those already anemic at admission to the hospital.⁴ The analytic cohort included 17 676 patients with AMI and no anemia on admission from 57 hospitals.

DIAGNOSTIC BLOOD LOSS

The date and time of every phlebotomy event, and results from the laboratory tests collected with each blood draw, were included in Health Facts. We identified the number and types of blood tubes that would be needed to run the laboratory tests recorded in the medical record. Several conservative assumptions were made when calculating phlebotomy volumes. With each blood draw, all laboratory tests that could be processed from a particular type of blood tube were assumed to have been run from a single tube. We further assumed that with each blood draw, only the minimal blood volume needed to run the required tests was drawn and that no blood was wasted at the time of blood draws. Hematology tubes were assigned a volume of 5 mL; coagulation laboratory tubes, 4.5 mL; chemistry/miscellaneous laboratory tubes, 5 mL; arterial blood gas tubes, 2 mL; and blood cultures, 10 mL, based on estimates from prior literature.¹¹ For each patient, these blood volumes were multiplied by the number of blood tubes of each type collected during their hospitalization to arrive at the total blood volume drawn for diagnostic tests during the entire hospitalization. We also calculated the mean blood volume drawn per 24 hours of hospitalization. Finally, we calculated the mean phlebotomy volumes on each of days 1 to 10 of hospitalization. For example, we calculated the mean blood volume drawn on hospital day 1 among the entire cohort, whereas only patients who remained hospitalized 5 days after admission were included in the calculation of mean phlebotomy volumes drawn on hospital day 5.

STATISTICAL ANALYSIS

Baseline patient characteristics, laboratory values, in-hospital treatments, and complications of patients who developed moderate to severe HAA were compared with those who did not. For descriptive purposes, we presented categorical data as frequencies and compared groups using χ^2 tests. Continuous variables were reported as means (SDs), and differences were compared using *t* tests. We used the Wilcoxon rank-sum test to compare length of stay owing to its skewed distribution, and results are reported as the median [interquartile range].

When comparing DBL across hospitals in the Health Facts database, we generated shrinkage estimates to account for lower enrollment from small hospitals. This approach pulls estimates from smaller hospitals toward the overall mean. Estimates were generated using a generalized linear model, regressing site as a random effect on diagnostic blood volume as the dependent variable.

We used hierarchical multivariable Poisson regression with robust error variance, with hospital as a random variable, to account for clustering within hospitals.¹⁹ To identify the independent association between phlebotomy volume and development of moderate to severe HAA, we adjusted for variables that were identified a priori based on clinical experience and prior literature. These included demographics (age, sex, race [white vs other]), clinical characteristics (chronic kidney disease, heart failure, hypertension, diabetes mellitus, prior myo-

cardial infarction [MI]) and MI type and treatments (ST-elevation MI vs non-ST-elevation MI; thrombolytic drugs; in-hospital cardiac catheterization or percutaneous coronary intervention; use of aspirin, thienopyridines, glycoprotein IIb/IIIa inhibitors, heparin, and bivalirudin), and in-hospital complications (acute renal failure, mechanical ventilation, and cardiogenic shock).

Missing data for model covariates were minimal. The initial creatinine level was the variable that was most often missing (in 247 patients [1.4%]). These data were assumed to be missing at random and were imputed using sequential regression imputation with IVEware software (Survey Methodology Program, Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor).²⁰

SENSITIVITY ANALYSIS

We pursued several sensitivity analyses to confirm the robustness of our findings and to further investigate the time course of moderate to severe HAA development (eAppendix). First, to understand when patients developed moderate to severe HAA, we calculated the proportion of patients who developed new moderate to severe HAA on each of the first 10 hospital days. Second, we tested an interaction between length of stay and DBL and repeated our analyses after stratifying by length of stay. We then repeated our analyses after excluding patients with known bleeding events and after using the WHO anemia definition.¹⁸ Finally, we repeated the analyses using several alternative assumptions for standard adult blood tube volumes and using volumes reported to fill pediatric blood tubes.^{9,11,13,21,22} All statistical analyses were evaluated at a 2-sided significance level of $P = .05$ and performed using SAS (version 9.2; SAS Institute Inc, Cary, North Carolina) and R (version 2.0; Vienna, Austria) software.

RESULTS

DEVELOPMENT OF MODERATE TO SEVERE HAA AND BASELINE PATIENT CHARACTERISTICS

One of every 5 patients with AMI developed moderate to severe HAA (3551 patients [20.1%]). The baseline characteristics of patients who did and did not develop moderate to severe HAA are compared in **Table 1**. The mean (SD) hemoglobin values declined during hospitalization in both groups, with greater declines in those with moderate to severe HAA compared with those without moderate to severe HAA (3.9 [1.6] g/dL vs 1.6 [1.1] g/dL; $P < .001$).

DIAGNOSTIC BLOOD LOSS

The mean, median, and range of DBL during the entire hospitalization and per 24 hours in the hospital are presented in **Table 2**, as well as the phlebotomy volume per type of blood tube drawn. The estimated mean (SD) blood loss from phlebotomy was nearly 100 mL higher over the course of hospitalization among patients who developed moderate to severe HAA compared with those who did not (173.8 [139.3] mL vs 83.5 [52.0] mL; $P < .001$); the mean (SD) blood loss per 24 hours of hospitalization was modestly higher with greater variability in those with moderate to severe HAA compared with those without moderate to severe HAA (24.4 [34.1] mL vs 22.8 [20.9] mL; $P < .001$). Particularly large DBL over the entire hospitalization was relatively common in pa-

tients who developed moderate to severe HAA (>300 mL: 444 patients [12.5%]; >500 mL: 136 patients [3.8%]) and was infrequent in patients who did not develop moderate to severe HAA (>300 mL: 117 patients [0.8%]; >500 mL: 12 patients [0.08%]). When DBL was estimated for each hospital day, the mean DBL was highest on the first 2 hospital days and declined subsequently (**Figure 1**).

CENTER VARIATION IN DBL

There was significant variability in the average volume of blood drawn for laboratory testing across Health Facts hospitals. Shrinkage estimates of mean DBL for the entire cohort ranged from 53.0 mL (95% confidence interval [CI], 47.7-58.3 mL) to 109.6 mL (95% CI, 104.5-114.6 mL). There was even greater hospital variability among patients with moderate to severe HAA (**Figure 2**) (119.1 mL [95% CI, 92.1-146.1 mL] to 246.0 mL [95% CI, 219.2-272.7 mL]). There was a significant association between greater incidence of moderate to severe HAA at a hospital and higher mean DBL ($P < .001$; eFigure 2).

DBL AND MODERATE TO SEVERE HAA

The volume of diagnostic blood drawn was associated with moderate to severe HAA. In unadjusted analyses, each 50 mL of blood drawn was associated with an 18% increase in risk of moderate to severe HAA (relative risk [RR], 1.17; 95% CI, 1.14-1.21; $P < .001$). After adjusting for site and potential confounders, the relationship between greater DBL and higher risk of moderate to severe HAA persisted (per 50 mL: RR, 1.15; 95% CI, 1.12-1.18; $P < .001$; eTable 1).

SENSITIVITY ANALYSES

The risk of moderate to severe HAA was highest on the first hospital day (10.5%), followed by a daily risk ranging between 2.8% and 4.5% on hospital days 2 through 10 (eFigure 3). The results of sensitivity analyses, including stratifying by length of stay, excluding patients with known bleeding, using the WHO anemia definition and calculating DBL with alternative tube volumes (**Table 3**), were all consistent with the primary analysis (see the "Results" section of the eAppendix).

Hypothetically, if low-volume pediatric blood tubes were used in place of standard tubes for all blood draws, the mean (SD) estimated DBL volume in the overall cohort could decline dramatically to 35.5 (39.0); for moderate to severe HAA, it would decline to 65.3 (62.2) mL; and for mild HAA or no HAA, it would decline to 28.0 (25.5) mL.

COMMENT

To our knowledge, our study is the first to directly assess the association between DBL and HAA in a large, unselected cohort of patients with AMI from hospitals across the United States. Diagnostic blood loss was substantial, particularly among individuals with HAA, and varied widely across hospitals, suggesting that process-of-care differ-

Table 1. Patient Characteristics by Moderate to Severe Hospital-Acquired Anemia (HAA) Status

Characteristic	Moderate to Severe HAA, No. (%)		P Value
	Yes (n=3551)	No (n=14 125)	
Demographics			
Age, mean (SD), y	71.9 (13.0)	64.5 (14.5)	<.001
White race	2933 (82.6)	12 314 (87.2)	<.001
Female sex	2481 (69.9)	4651 (32.9)	<.001
Medical history			
Dyslipidemia	1054 (29.7)	7056 (50.0)	<.001
Heart failure	1377 (38.8)	2995 (21.2)	<.001
Hypertension	1793 (50.5)	7833 (55.5)	<.001
History of PCI	109 (3.1)	923 (6.5)	<.001
Chronic kidney disease	454 (12.8)	648 (4.6)	<.001
Peripheral arterial disease	101 (2.8)	293 (2.1)	.005
Diabetes mellitus	1134 (31.9)	3566 (25.2)	<.001
History of CABG	97 (2.7)	642 (4.5)	<.001
Prior MI	131 (3.7)	909 (6.4)	<.001
Current smoking	483 (13.6)	4635 (32.8)	<.001
History of stroke/TIA	167 (4.7)	320 (2.3)	<.001
Creatinine level at admission, mean (SD), mg/dL	1.4 (1.2)	1.2 (0.7)	<.001
MI type and in-hospital complication			
ST-elevation MI	1547 (43.6)	6127 (43.4)	.84
Length of stay, median [IQR], d	6.5 [4.1-10.1]	3.5 [2.5-5.0]	<.001
Acute renal failure	513 (14.4)	510 (3.6)	<.001
Cardiogenic shock	336 (9.5)	305 (2.2)	<.001
In-hospital mechanical ventilation	390 (11.0)	422 (3.0)	<.001
Bleeding event	499 (14.1)	436 (3.1)	<.001
Bleeding event type (from ICD-9-CM diagnosis codes)			
Miscellaneous site	290 (58.1)	301 (69.0)	<.001
GI tract bleeding	196 (39.3)	100 (22.9)	
Intracranial	13 (2.6)	35 (8.0)	
In-hospital management			
Thienopyridine	2379 (67.0)	9924 (70.3)	<.001
ACE inhibitor/ARB	2431 (68.5)	9242 (65.4)	<.001
Aspirin	3091 (87.1)	12 304 (87.1)	.95
β-Blockers	3049 (85.9)	11 957 (84.7)	.07
Diuretics	1935 (54.5)	4376 (31.0)	<.001
Glycoprotein IIb/IIIa inhibitor	1702 (47.9)	7213 (51.1)	<.001
Intravenous heparin	1957 (55.1)	7224 (51.1)	<.001
Bivalirudin	129 (3.6)	656 (4.6)	.01
Thrombolytic drugs	184 (5.2)	575 (4.1)	.003
Warfarin	507 (14.3)	1295 (9.2)	<.001
In-hospital cardiac catheterization	2253 (63.4)	10 230 (72.4)	<.001
In-hospital PCI	1719 (48.4)	7970 (56.4)	<.001
Hemoglobin level, g/dL, mean (SD)			
Initial	13.64 (1.15)	14.71 (1.26)	<.001
Minimum	9.78 (1.14)	13.09 (1.22)	<.001
Final	10.67 (1.05)	13.41 (1.30)	<.001
Time from admission to moderate to severe HAA, mean (SD), d	2.7 (2.6)	NA	NA

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; GI, gastrointestinal; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IQR, interquartile range; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; to convert hemoglobin to grams per liter, multiply by 10.0.

ences may influence DBL. It is important to note that DBL was independently associated with a higher risk of HAA and that this association remained robust after multivariable adjustment and in several sensitivity analyses.

Prior studies have shown that HAA is common and associated with higher mortality and worse health status after AMI.^{4,6,24} In our study, 1 in 5 patients who did not have baseline anemia (and did not undergo coronary bypass surgery) developed moderate to severe HAA.

Several factors contribute to development of HAA. Some of these are not modifiable (age, sex, chronic kidney disease, acute inflammation from AMI),^{4,25} but 2 are clearly under the control of health care providers: prevention of periprocedural bleeding and minimization of phlebotomy. Alternative anticoagulants such as bivalirudin, closure devices, and radial access for coronary angiography all reduce the incidence of periprocedural bleeding.²⁶⁻²⁹ However, no clear bleeding event is identified in

many patients with HAA.^{4,6} Although phlebotomy has been suggested as a cause of in-hospital hemoglobin level declines in patients with AMI,³⁰ to our knowledge, our study is the first to identify DBL as an independent predictor of HAA in a contemporary cohort reflecting real-

world patient care and highlights phlebotomy as a potentially modifiable risk factor.

Our findings have important clinical implications. Among patients who developed HAA, the mean esti-

Table 2. Diagnostic Blood Loss (DBL) Estimates During Hospitalization With Acute Myocardial Infarction

DBL	Moderate to Severe Hospital-Acquired Anemia, Mean (SD)	
	Yes (n=3551)	No (n=14 125)
Total DBL, mL	173.8 (139.3)	83.5 (52.0)
Median [IQR]	132.0 [88.5-209.0]	69.5 [51.0-99.5]
DBL per 24 h, mL	24.4 (34.1)	22.8 (20.9)
Median [IQR]	21.1 (16.0-28.8)	20.5 (15.6-26.7)
Type of tests obtained ^b		
Arterial blood gas	18.3 (19.7)	7.7 (6.9)
Serum chemistries and other serum studies	69.6 (63.3)	35.8 (23.5)
Coagulation laboratory test	26.6 (28.5)	15.3 (16.8)
Hematology laboratory test	47.4 (38.7)	21.3 (12.5)
Blood cultures	12.0 (20.1)	3.4 (9.5)

Abbreviation: IQR, interquartile range.

^a $P < .001$ for all comparisons.

^b Reported values represent the mean (SD) values in milliliters among patients who had the respective laboratories drawn during the course of their hospitalization.

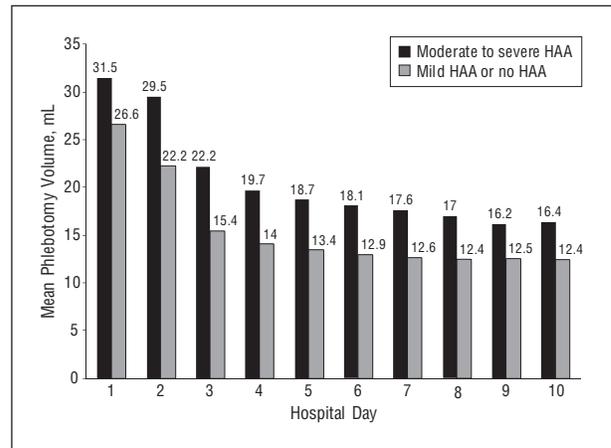


Figure 1. Mean volume of diagnostic blood drawn on each day from hospital days 1 through 10. Mean blood drawn for laboratory tests on each of the first 10 hospital days, comparing patients who developed moderate to severe hospital-acquired anemia (HAA) with those who did not. The denominator on each hospital day included all patients who remained in the hospital on each respective day hospital day (hospital day 1: 17 676; hospital day 2: 13 632; hospital day 3: 11 403; hospital day 4: 8261; hospital day 5: 5263; hospital day 6: 3339; hospital day 7: 2183; hospital day 8: 1475; hospital day 9: 1060; hospital day 10: 753).

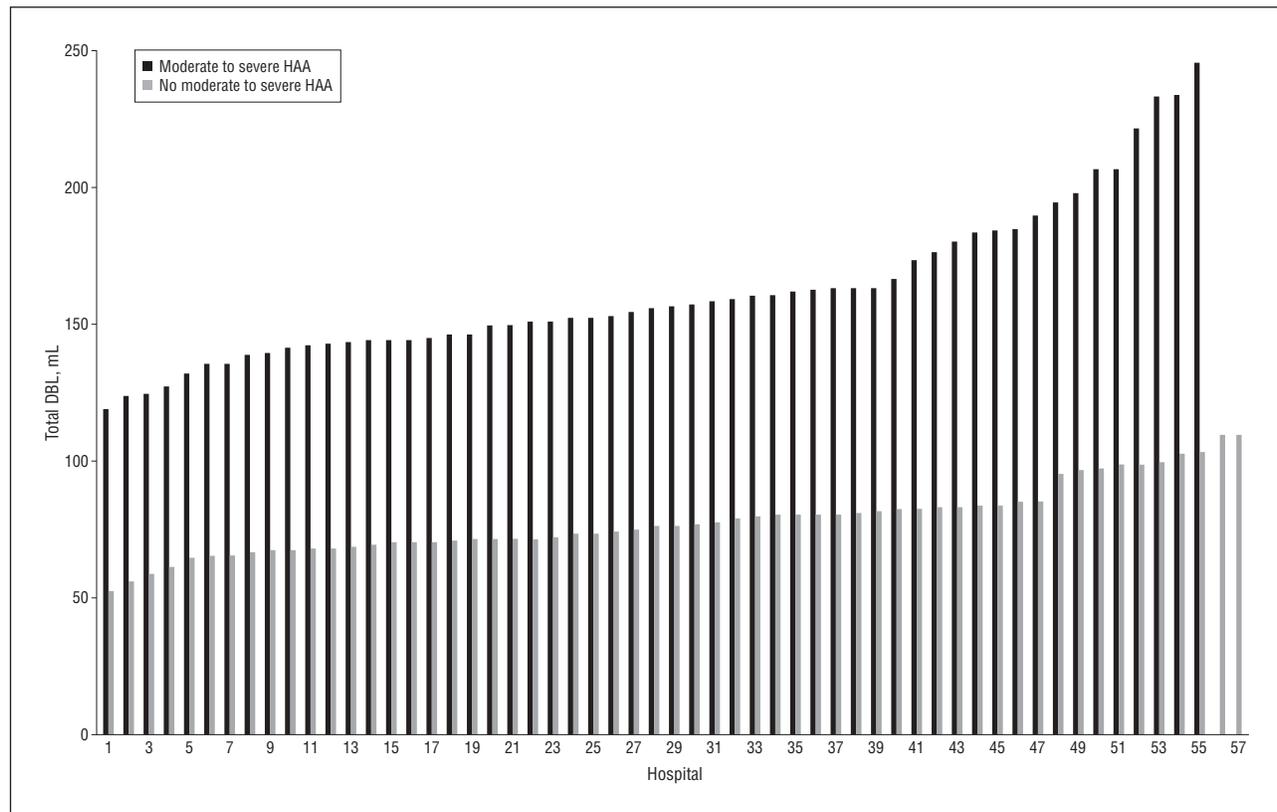


Figure 2. Variation in mean diagnostic blood loss (DBL) across the 57 hospitals included in a contemporary acute myocardial infarction database (Cerner Corp's Hospital Facts database.) Bars represent shrinkage estimates of the mean DBL for patients' entire hospitalizations across each hospital. Black bars represent the mean value for patients with moderate to severe hospital-acquired anemia (HAA), and gray bars present the mean value for patients without moderate to severe HAA. Hospitals are plotted on the x-axis from the hospital with the smallest mean blood loss to the hospital with the largest, ranked separately among those with moderate to severe HAA and without moderate to severe HAA.

mated phlebotomy volume was 173.8 mL, which is equivalent to nearly half a unit of whole blood, and over 12% had more than 300 mL of blood drawn over the course of hospitalization. Diagnostic blood loss remained relatively constant throughout the course of hospital stay after the first 2 days of hospitalization and was particularly high among patients with long lengths of stay. Since most diagnostic evaluation and therapeutic interventions often occur early during AMI hospitalization, it is likely that much of the blood taken later during hospitalization represents routine, scheduled laboratory draws that could lead to ongoing blood loss. Our findings are likely generalizable to other populations of seriously ill medical patients. In this regard, further studies that establish whether minimizing DBL can prevent HAA and improve patient outcomes could have broad implications for hospitalized patients.

Our findings also indicate that reduction of blood loss from phlebotomy could be important to limit development and severity of HAA.¹²⁻¹⁴ For example, we found that estimates of phlebotomy volumes were dramatically lower with pediatric tubes, highlighting a promising intervention to limit DBL. It might be possible to reduce DBL with no additional cost to hospitals (using pediatric tubes or stored serum samples) or even potential cost savings (reducing unnecessary, scheduled blood draws). Although the universal use of pediatric tubes may not be possible at some hospitals where smaller tubes are not compatible with analytic equipment, a potential alternative in these cases may be to fill standard adult tubes with less blood. For example, Xu et al³¹ reported similar diagnostic accuracy for automated hematology testing when filling standard 4-mL tubes with only 1 or 2 mL of blood. Nevertheless, while DBL may be a key factor in HAA development, is likely not the only contributor. Future HAA prevention efforts are most likely to be effective if they incorporate multimodal interventions that both minimize unnecessary DBL and prevent bleeding.

Several limitations of our study should be considered. First, calculation of phlebotomy volume relied on estimates of the amount of blood required for each tube. We included several conservative assumptions, such as assuming that only 1 tube of each type was drawn with each phlebotomy event, and not including an estimate of wasted blood to avoid overestimating DBL. Accordingly, estimates presented in this article likely represent the minimum amount of DBL that could have occurred. Moreover, we conducted sensitivity analyses in which we used alternative volumes for the amount of blood required for each tube and found that DBL was substantial regardless of which estimates were used. Second, we were unable to assess the impact of hemodilution from intravenous fluids or fluid retention; however, since large hemoglobin level declines were required to develop HAA, hemodilution is an unlikely culprit for HAA in our patient population. Third, hemoglobin assessments were not performed at regular intervals because the Health Facts database reflects routine clinical practice. Although there was variability in the number and timing of hemoglobin assessments, these data are generalizable to real-world clinical practices in which these tests are obtained at the discretion of the treating physician. Fourth, we used a single threshold for moderate

Table 3. Diagnostic Blood Loss (DBL) Estimated Using Alternative Tube Volumes From Prior Literature

Study Reporting Blood Tube Volumes	DBL, Mean (SD), mL		Adjusted Risk of Moderate to Severe HAA, per 50 mL, RR (95% CI)
	Moderate to Severe HAA	Mild HAA or No HAA	
Smoller and Kruskal ⁹ 1986	233.0 (187.0)	114.5 (69.6)	1.11 (1.08-1.14)
Wisser et al, ²¹ 2003	144.5 (122.4)	67.8 (46.5)	1.17 (1.13-1.21)
Shaffer, ²² 2007	140.1 (115.7)	66.6 (45.7)	1.19 (1.15-1.23)
Pabla et al, ²³ 2009 ^a	155.8 (128.6)	73.0 (48.8)	1.17 (1.13-1.20)

Abbreviations: CI, confidence interval; HAA, hospital-acquired anemia; RR, relative risk.

^aNo reported blood volume for arterial blood gas tubes; 2 mL were used for each arterial blood gas tube when generating these estimates.

to severe HAA of hemoglobin levels lower than 11 g/dL. Using this threshold, an African American woman required a smaller (>0.5 g/dL) hemoglobin decline to be classified as having HAA. Ideally, age-, sex-, and race-specific thresholds would be used to define moderate to severe HAA; however, there are no reports in the literature that describe different thresholds for anemia severity by sex, race, or age. Moreover, regardless of race, a prior study (using the same definition of anemia as the present study) demonstrated that hemoglobin level declines from normal levels to less than 11 g/dL are associated with greater long-term mortality.⁴ In addition, using the WHO anemia definition¹⁸ (which is not race specific) did not change our results. Finally, patients with HAA had greater disease severity and more comorbidities than patients who did not, as indicated by their demographics, comorbidities, and in-hospital complications. Given the retrospective nature of these analyses, residual and unmeasured confounding cannot be excluded, and no causal inference can be drawn from these observational data. Randomized trials are needed to test the hypothesis that reducing phlebotomy prevents HAA and improves patients' outcomes.

In conclusion, blood loss from phlebotomy is substantial in patients with AMI, varies across hospitals, and is independently associated with the development of HAA. Studies are needed to test whether strategies that limit both the number of blood draws and the volume of blood removed for diagnostic testing can prevent HAA and improve clinical outcomes in patients with AMI.

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Online-Only Material: The online-only eAppendix and eFigures 1, 2, and 3 are available at <http://www.archinternmed.com>.

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INVITED COMMENTARY

ONLINE FIRST

Hazards of Hospitalization

More Than Just “Never Events”

Hospitalization can be a hazardous time for patients. Complications that occur as a result of hospitalization, such as venous thromboembolism, nosocomial infections, and medication errors, result in considerable morbidity and mortality.¹ In this issue of *Archives*, Salisbury et al² suggest that hospital-acquired anemia (HAA) may be yet one more potentially preventable complication associated with hospitalization. Anemia has been associated with worse clinical outcomes in the setting of acute myocardial infarction (AMI).³ The authors evaluated the association between HAA and blood loss from diagnostic phlebotomy in patients with AMI hospitalized in 57 US hospitals. Increased blood loss from phlebotomy was an independent predictor of HAA. Of particular interest was the finding that the mean phlebotomy volume in patients varied widely across individual hospitals, suggesting that some blood tests may have been simply “routine” and implying that reduction in the variability of care could potentially lead to reductions in HAA.

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According to a recent report from the Department of Health and Human Services,⁴ an estimated 1 in 7 Medicare beneficiaries experienced an adverse event in the hospital, and an additional 13.5% had events causing temporary harm. Of these, 44% were considered preventable and resulted in estimated costs of \$4.4 billion in a given year. Adverse events were commonly related to medications (31%), but there were also not insignificant rates of urinary catheter-associated infections (3.9%), vascular catheter-associated infections (3.1%), venous thromboembolic events (3.9%), and health care-associated pneumonia (3.1%). Direct consequences of adverse events included increased hospital length of stay, permanent harm, additional interventions, and death.

Particularly since the publication of the Institute of Medicine report “To Err Is Human: Building a Safer Health System,”⁵ there has been increased attention focused on improving the safety of patients during hospitalization. Recent efforts to raise awareness of and motivate hospitals to re-

duce preventable adverse conditions have included consumer, regulatory, and funding agencies. For example, the National Quality Forum designates a number of conditions “serious reportable events,”^{6(p1)} commonly referred to as “never events,” including wrong-site surgery and severe hospital-acquired pressure ulcers. The Centers for Medicare and Medicaid Services subsequently announced that it will not reimburse hospitals for the additional costs incurred by some of these conditions.⁷

The increased attention on patient safety has led hospitals to test and implement system-wide interventions, some of which have been found to be effective in reducing the rates of hospital-acquired complications. Institutions effective in improving hospital quality share several key features: an interest in promoting a culture of safety, involvement of local champions and multidisciplinary teams, adopting evidence-based standards of practice, rigorously measuring performance, and improving health system processes and infrastructure, including through the use of technology.⁸ Some of these interventions have shown dramatic results. The Michigan Health and Hospital Association Keystone intensive care unit project was a multicenter quality improvement initiative aimed at reducing catheter-associated bloodstream infections and ventilator-associated pneumonia.⁹ The project used a multimodal approach, including promoting teamwork and communication, checklists, monitoring with alerts, standardized forms, regular audits with feedback, and collaboration with hospital-based, infection-control practitioners. The intervention resulted in a remarkable 77% and 66% reduction in ventilator-associated pneumonia and bloodstream infection rates, respectively, as well as a subsequent reduction in hospital mortality.

A group of patients particularly vulnerable to hospital-acquired complications is older adults. Elderly individuals face unique challenges in the hospital setting and are at elevated risk for functional decline, falls, immobility and pressure ulcers, and acute delirium during hospitalization.¹⁰ Effective interventions that reduce the adverse consequences of hospitalization in elderly persons have often incorporated team-based and patient-centered strategies. For example, delirium in elderly patients has been