Usefulness of Anemia in Men as an Independent Predictor of Two-Year Cardiovascular Outcome in Patients Presenting With Acute Coronary Syndrome

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Anemia has been shown to be an independent risk factor for the development of adverse cardiovascular outcomes in a variety of patient populations. In the case of patients presenting with acute coronary syndrome (ACS), anemia has been demonstrated to be a powerful and independent predictor of 30-day outcomes. However, there are limited and conflicting data about the long-term independent predictive value of anemia in patients with ACS. This is in contrast to non-ACS populations in which anemia has been shown to be an independent predictor of long-term outcomes. The present study investigated the long-term prognostic significance of anemia in a well-characterized cohort of 193 men with ACS who were referred for coronary angiography at a Veterans Affairs Medical Center. All patients were followed prospectively for the development of death or acute myocardial infarction (AMI), and follow-up data were available for all patients at 24 months. After controlling for a variety of baseline clinical, laboratory, and angiographic variables, hemoglobin (analyzed as a continuous variable and as a categorical variable using the World Health Organization cutoff of 13 g/dl for men) was a strong and independent predictor of the composite end point of death or AMI at 24 months when using a Cox proportional hazards model. At 24 months, the event-free survival was 64% in the group with a hemoglobin level <13 g/dl compared with 81% in the group with a hemoglobin level ≥13 g/dl ($p = 0.0065$ by log-rank test). In conclusion, these data demonstrate that baseline anemia is a strong and independent predictor of death or AMI at 2 years in patients with ACS. **(Am J Cardiol 2006;98:580–584)**

There are limited and conflicting data about the long-term independent predictive value of anemia in patients with acute coronary syndrome (ACS). Further, data with respect to the prognostic value of baseline hemoglobin levels beyond 1 year in such patients is completely lacking. Accordingly, the present study evaluated the effect of baseline anemia on 2-year cardiovascular outcomes in a cohort of prospectively followed patients with ACS in the context of other co-morbidities known to affect long-term prognosis.

Methods and Results

This study was conducted at a Veterans Administration Medical Center and was approved by the local institutional review board. Written informed consent was obtained from all patients. Between January 1999 and October 2002, 193 men who underwent diagnostic coronary angiography for the evaluation of ACS were enrolled in the study. Patients with active gastrointestinal bleeding were excluded from the study. Three groups of patients were categorized by type of ACS. (1) The group with ST-elevation acute myocardial infarction (AMI) included patients who had presented with ≥2-mm ST-segment elevation in ≥2 consecutive electrocardiographic leads. All such patients had enzymatically confirmed AMI. (2) The group with non–ST-elevation AMI consisted of patients with chest pain and enzymatic evidence of MI but without ST-segment elevation on the presenting electrocardiogram. (3) Unstable angina pectoris was defined according to the classification scheme based on guidelines of the American College of Cardiology/American Heart Association.[1] All patients had hemoglobin values obtained within 4 weeks of angiography. Patients were then followed prospectively for the next 24 months for the development of death or AMI.

Anemia was defined according to criteria of the World Health Organization, i.e., a hemoglobin level <13 g/dl in men.[2] Hemoglobin measurements were done with an automated system (Beckmann Coulter Automated CBC Analyzer; Beckman Coulter, Inc., Fullerton, California). Diabetes was defined as clinically known and treated diabetes mellitus. Patients were diagnosed as hypertensive if they were documented to have a blood pressure >140/90 mm Hg on ≥2 occasions or if they were already on antihypertensive therapy. Hyperlipidemia was diagnosed in patients who received lipid-lowering medication or had a history of total cholesterol levels >240 mg/dl.[3] Smoking was defined as the inhaled use of cigarettes, cigars, or pipes in any quantity. Obesity was defined as a body mass index ≥30 kg/m^2.

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0002-9149/06/$ – see front matter
doi:10.1016/j.amjcard.2006.03.031

Table 1
Baseline characteristics of the acute coronary syndrome population stratified by the World Health Organization definition of anemia for men (hemoglobin level <13 vs ≥13 g/dl)

Characteristics	Hemoglobin (g/dl)		p Value
	<13 (n = 80*)	≥13 (n = 111*)	
Age (yrs)	68 ± 9.6	63.1 ± 10.2	0.0010
	69.9 (63.3, 74.4)	64.4 (53.9, 70.8)	
Black	35 (44%)	35 (31%)	0.2237
Hispanic	21 (26%)	36 (32%)	
White	24 (30%)	40 (36%)	
Diabetes mellitus	42 (52%)	49 (44%)	0.2540
Hypertension	72 (90%)	89 (80%)	0.0657
Active tobacco use	22 (27%)	48 (43%)	0.0259
Hyperlipidemia	47 (59%)	57 (51%)	0.3111
Low-density lipoprotein cholesterol (mg/dl)	101.4 ± 32.9	111.1 ± 37.0	0.0502
	96.3 (75.4, 122.6)	108.8 (89.2, 127.6)	
High-density lipoprotein cholesterol (mg/dl)	39.1 ± 11.5	39.8 ± 9.7	0.7957
	38.5 (31.5, 46.5)	40.0 (33.0, 45.0)	
Triglycerides (mg/dl)	141.4 ± 99.2	152.9 ± 87.3	0.0827
	118 (78, 154)	138 (85, 191)	
Body mass index (kg/m^2)	27.7 ± 6.1	29.6 ± 5.6	0.0086
	26.5 (23.1, 31.0)	29.1 (25.8, 31.9)	
Body mass index ≥30 kg/m^2	26 (32%)	47 (42%)	0.1673
Congestive heart failure on presentation	29 (36%)	17 (15%)	0.0008
AMI on presentation	45 (56%)	62 (56%)	0.9568
Aspirin use	70 (87%)	104 (94%)	0.1380
β-Blocker use	62 (77%)	85 (77%)	0.8811
ACE inhibitor use	55 (69%)	64 (58%)	0.1186
Statin use	45 (56%)	55 (50%)	0.3603
No. of narrowed coronary arteries†			0.9218
0	10 (12%)	14 (13%)	
1	11 (14%)	18 (16%)	
2	19 (24%)	26 (23%)	
3	34 (42%)	48 (43%)	
4	6 (7%)	5 (4%)	
Left ventricular function			0.2433
Normal or mild decrease	40 (53%)	62 (61%)	
Moderate-severe decrease	36 (47%)	39 (39%)	
Troponin I (ng/ml)	18.7 ± 50.7	20.4 ± 73.3	0.8584
	1.1 (0.2, 10.5)	1.5 (0.3, 9.9)	
Serum creatinine (mg/dl)	1.78 ± 2.39	1.13 ± 0.86	0.0005
	1.1 (1.0, 1.5)	1.0 (0.9, 1.2)	

Data are presented as frequencies (percentages) for categorical variables and as means ± SD and medians (25th, 75th percentiles) for continuous variables.
* The total number is 191 due to missing hemoglobin values in 2 patients.
† Takes into account the left main, left anterior descending, left circumflex, and right coronary arteries.
ACE = angiotensin-converting enzyme.

Congestive heart failure on presentation was defined as the presence of radiographic or clinical evidence of pulmonary venous congestion within the preceding 24 hours of angiography. AMI on presentation was diagnosed by a history of chest discomfort and a troponin I level >1.0 ng/ml. AMI during follow-up (i.e., as a clinical outcome that was defined by a history of chest pain with an associated elevation of either troponin I >1.0 ng/ml or troponin T >0.1 ng/ml. Information regarding death was obtained via review of the Social Security Death Index, medical records, and conversation with the next of kin and/or primary physician.

All patients and their angiograms were graded as to the number of narrowed coronary arteries, taking into account the left main, left anterior descending, left circumflex, and right coronary arteries. A coronary artery was considered narrowed if there was any obstructive lesion ≥50% in diameter in that artery or 1 of its major branches (≥2.5 mm). Left ventricular systolic function was assessed by contrast ventriculography and categorized as normal (ejection fraction ≥55%), mildly decreased (ejection fraction 45% to 54%), moderately decreased (ejection fraction 31% to 44%), or severely decreased (ejection fraction ≤30%).

Patients were classified into 2 groups according to a baseline hemoglobin level (<13 versus ≥13 g/dl). Summary statistics for continuous variables were presented as means ± SDs and medians (interquartile ranges), and comparisons between groups were performed with Wilcoxon's rank-sum test. Categorical data were summarized as fre-

Table 2
Univariate Cox proportional hazards analyses for the composite outcome of death or acute myocardial infarction at 24 months

Baseline Variable	Hazards Ratio (95% CI)	p Value
Age/10 yrs	1.40 (1.04–1.88)	0.0262
Diabetes mellitus	1.73 (0.98–3.05)	0.0603
Congestive heart failure on presentation	1.65 (0.91–3.00)	0.0998
Hypertension	1.15 (0.52–2.55)	0.7367
Body mass index	0.88 (0.66–1.18)	0.3984
Obesity (body mass index ≥30 kg/m^2)	0.80 (0.45–1.44)	0.4615
Serum creatinine	1.13 (1.01–1.27)	0.0349
Troponin I	1.27 (0.99–1.63)	0.0604
Hyperlipidemia	0.80 (0.46–1.41)	0.4405
AMI on presentation	1.81 (1.00–3.30)	0.0508
Active tobacco use	0.96 (0.53–1.72)	0.8821
No. of diseased coronary arteries	2.42 (1.09–5.39)	0.0305
Left ventricular function*	2.02 (1.10–3.71)	0.0227
Hemoglobin (continuous)	0.66 (0.50–0.87)	0.0028
Hemoglobin ≥13 vs <13 g/dl	2.15 (1.22–3.79)	0.0079
Hemoglobin 10.5–12.5 vs >12.5 g/dl	1.80 (0.97–3.34)	0.0610
Hemoglobin <10.5 vs >12.5 g/dl	3.28 (1.42–7.58)	0.0056
β-Blocker use	1.42 (0.69–2.93)	0.3423
Aspirin use	0.63 (0.27–1.49)	0.2941
ACE inhibitor use	1.03 (0.57–1.84)	0.9295
Statin use	0.80 (0.46–1.40)	0.4391
Low-density lipoprotein	0.82 (0.63–1.08)	0.1636
High-density lipoprotein	1.16 (0.87–1.54)	0.3083
Triglycerides	0.88 (0.66–1.18)	0.3973

* Dichotomized as normal or mild decrease versus moderate to severe decrease.

CI = confidence interval; other abbreviation as in Table 1.

quencies and percentages, and comparisons between groups were performed with Pearson's chi-square test or Fisher's exact test. Predictors of the composite end point of death or AMI at 24 months were identified by univariate Cox regression. Multivariate Cox proportional hazards analyses were then performed as stepwise regressions with backward elimination to identify independent predictors. Time to event at 24 months was presented with Kaplan-Meier curves for the composite end point for the groups stratified by hemoglobin levels. Comparisons between groups identified by hemoglobin values were performed with the log-rank test. All analyses used 2-sided tests with overall significance level (α = 0.05).

In total, 193 men were enrolled in the study. Hemoglobin values were available for 191 of these patients. Two-year follow-up data were available for all patients. Baseline characteristics of the study population stratified by a hemoglobin value <13 versus ≥13 g/dl are presented in Table 1. At 24 months, 49 patients, or 26% of the cohort, developed ≥1 component of the composite end point of death or AMI (26 deaths and 37 fatal or nonfatal AMIs). Results of univariate analyses for the prediction of the composite outcome are presented in Table 2. Together with hemoglobin, all variables listed in Table 2 that were significant for their association with clinical outcomes with a p value <0.05 were entered in a backward stepwise multivariate Cox regression analysis. After adjustment for these factors, hemoglobin, analyzed as <13 versus ≥13 g/dl, was found to be a strong independent predictor of the composite outcome (Table 3), with a hazard ratio of 1.86 (95% confidence interval 1.02 to 3.40, p = 0.0429).

Table 3
Multivariate Cox proportional hazards analyses for the composite outcome of death or acute myocardial infarction at 24 months

Baseline Variable	Hazards Ratio (95% CI)	p Value
Model 1		
Left ventricular function*	2.05 (1.12–3.75)	0.0208
Hemoglobin <13 vs ≥13 g/dl	1.86 (1.02–3.40)	0.0429
Model 2		
Left ventricular function*	1.94 (1.05–3.59)	0.0338
Hemoglobin (continuous variable)	0.74 (0.55–0.99)	0.0411

* Dichotomized as normal or mild reduction versus moderate-to-severe reduction. Multivariate Cox proportional hazards analyses were performed as stepwise regressions with backward elimination. Twenty-five clinical, laboratory and angiographic variables were initially studied (see Table 2) by univariate analysis. Only those predictors with p <0.05 (age, number of diseased coronary arteries, left ventricular function, hemoglobin, serum creatinine) were subsequently entered into multivariate models, the results of which are displayed above.

Hemoglobin was also analyzed as a continuous variable and, when done so, was again found to be a strong independent predictor of the composite outcome of death or AMI (Table 3), with a hazard ratio of 0.74 (95% confidence interval 0.55 to 0.99, p = 0.0411). Finally, hemoglobin was also analyzed as a different categorical variable with thresholds of 10.5 and 12.5 g/dl. In this way, the hazard ratio of patients in the group with the lowest hemoglobin level could be compared with that in the group with the highest level. When analyzed in this manner, there was a strong trend toward an independent association between hemoglobin levels (analyzed as <10.5 vs >12.5 g/dl) and the presence of adverse cardiovascular outcomes (hazard ratio 2.37, 95% confidence interval 0.94 to 5.99, p = 0.0681).

When using a hemoglobin value of 13 g/dl as a prespecified cut-off point for the definition of anemia, Kaplan-Meier plots demonstrated a significant decrease in event-free survival with hemoglobin values <13 g/dl (Figure 1). Similarly, when using hemoglobin values of 10.5 and 12.5 g/dl as prespecified cut-off points, Kaplan-Meier plots demonstrated a graded and significant increase in death or AMI with progressively lower hemoglobin values (Figure 2).

Discussion

In a broad cohort of patients with ACS, we found a strong and statistically significant independent association between low hemoglobin concentrations and the adverse cardiovascular outcomes of death and AMI at 24 months. Although there are compelling data relating anemia to short-term clinical outcomes in ACS,[4] data for long-term outcomes are limited and conflicting. For example, in a study that examined a database of discharge abstract information in patients

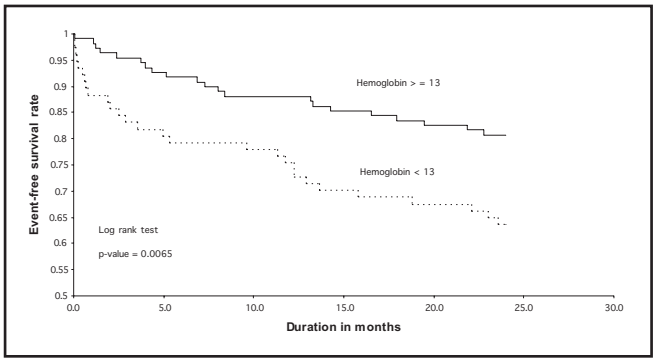

Figure 1. Kaplan-Meier curves for event-free survival according to baseline hemoglobin levels stratified by hemoglobin levels <13 and ≥13 g/dl. At 24 months, the event-free rate (for death or AMI) was 64% in the group with a hemoglobin level <13 g/dl compared with 81% in the group with a hemoglobin level ≥13 g/dl (p = 0.0065 by log-rank test).

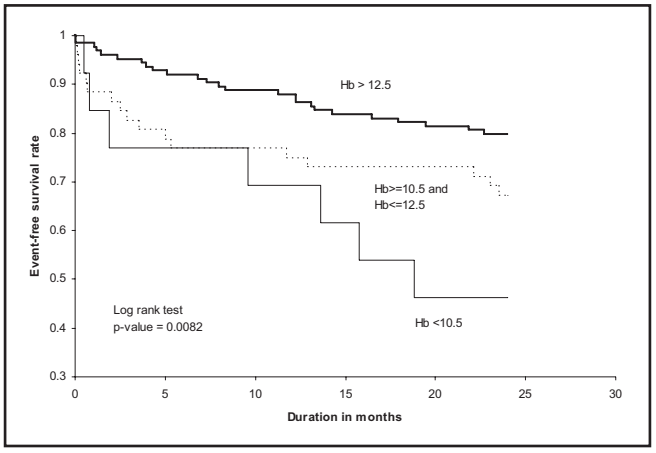

Figure 2. Kaplan-Meier curves for event-free survival according to baseline hemoglobin (Hb) levels stratified by Hb levels <10.5, 10.5 to 12.5, and >12.5 g/dl. At 24 months, the event-free rate (for death or AMI) was 46% in the group with a Hb level <10.5 g/dl, 67% in the group with a Hb level from 10.5 to 12.5 g/dl, and 80% in the group with a Hb level >12.5 g/dl (p = 0.0082 by log-rank test).

admitted with AMI, those identified as anemic on the basis of *International Classification of Disease, Ninth Revision* coding were not found to have a higher mortality at 1 year.[5] Although anemic patients in that study had significantly higher unadjusted risk for 1-year mortality, this association was no longer significant after controlling for a variety of co-morbidities known to affect long-term prognosis, such as left ventricular dysfunction. In contrast, Nikolsky et al[6] found baseline anemia in patients undergoing primary percutaneous coronary intervention for AMI to be an independent predictor of in-hospital and 1-year mortality.[6] Although the study by Nikolsky et al[6] involved a very defined subpopulation of patients with ACS (namely those with ST-elevation AMI undergoing primary angioplasty), the findings suggest that baseline anemia has long-term prognostic power in at least certain subgroups of patients with ACS.

Baseline anemia has also been shown to have long-term prognostic value in patients with non-ACS.[7,8] For example, Arant et al[7] found baseline anemia to be an independent predictor of adverse cardiovascular outcomes at a mean of 3.3 years in a cohort of women with suspected ischemia in the absence of AMI or heart failure. Similarly, in an even lower risk general population, the Atherosclerosis Risk in Communities (ARIC) investigators found baseline anemia to be an independent risk factor for cardiovascular outcomes during an average follow-up of 6.1 years.[8] We believe our findings extend the observations about the long-term predictive power of baseline hemoglobin in patients with non-ACS to those with ACS and extend the observations about the short-term predictive value of anemia in patients with ACS to the long term. Further, to our knowledge, our study is to first to relate anemia to outcomes beyond 1 year in patients with ACS.

There are several limitations to our study. Some studies of anemia have described a J- or U-shaped relation between baseline hemoglobin values and major adverse cardiovascular events.[4,9] That is, patients with low and high hematocrit have been demonstrated to be at increased risk of developing cardiovascular events. Because of our relatively small sample, the well-accepted cutpoint for the definition of anemia used in our study (hemoglobin level <13 g/dl in men), and the limited number of patients with high hemoglobin values, we were unable to demonstrate such a relation. Along the same lines, the size of our study also precluded further meaningful subanalyses of our ACS population. For example, it has been shown that the thresholds below which patients are at increased risk for major adverse cardiovascular events differ between ST-elevation and non–ST-elevation AMI.[4] Importantly, however, we believe that our inability to study these issues does not detract from the central message of our study, which is that low hemoglobin is associated with adverse long-term consequences in the full cohort of patients with ACS. Further, we believe that our limited sample is offset in part by the quality assurance that is possible in a smaller study. Specifically, our data were gathered prospectively and meticulously on a patient level rather than, e.g., from unconfirmed hospital discharge codes. In addition, our single-center study by its very nature did not have the so-called "center effect," whereby larger studies involving multiple centers are not able to control for differences in hemoglobin measurement among the different centers.[8] To this point, most of the AMIs in our study were captured in the Veterans Affairs system, with the same troponin reference standards applied to all patients.

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