

Hemoglobin Level Is an Independent Predictor for Adverse Cardiovascular Outcomes in Women Undergoing Evaluation for Chest Pain

Results From the National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation Study

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OBJECTIVES	This study was designed to investigate the relationship between hemoglobin level (Hgb) and adverse cardiovascular outcomes in women with suspected ischemia.
BACKGROUND	Low Hgb levels correlate with increased cardiovascular morbidity and mortality in patients presenting with acute myocardial infarction (MI) or congestive heart failure (CHF). However, the prognostic significance of Hgb in women with suspected ischemia is unclear.
METHODS	As part of the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Women's Ischemia Syndrome Evaluation (WISE), we prospectively studied 936 women referred for coronary angiography to evaluate suspected ischemia. We compared Hgb levels with cardiovascular risk factors, core lab interpreted angiograms, inflammatory markers, and adverse cardiovascular outcomes.
RESULTS	Of women enrolled, 864 (mean age 58.4 ± 11.6 years) had complete Hgb, angiogram, and follow-up (mean 3.3 ± 1.7 years) data. The mean Hgb was 12.9 g/dl (range 7.7 to 16.4 g/dl) and 184 women (21%) were anemic (Hgb <12 g/dl). Anemic women had higher creatinine and were more likely to be nonwhite and have a history of diabetes, hypertension, and CHF ($p < 0.05$). However, we found no difference in EF or severity of coronary artery disease. Anemic women had a higher risk of death from any cause (10.3% vs. 5.4%; $p = 0.02$) and total adverse outcomes (26% vs. 16%, $p < 0.01$). In a multivariable model, decreasing Hgb was associated with significantly higher risk of adverse outcomes (hazard ratio = 1.20, $p = 0.002$). Also, anemic women had shorter survival time free of adverse outcome ($p < 0.001$).
CONCLUSIONS	Our findings extend previous reports, linking lower hemoglobin levels with higher risk for adverse cardiovascular outcomes, to women evaluated for suspected ischemia in the absence of acute MI or CHF. (J Am Coll Cardiol 2004;43:2009-14) © 2004 by the American College of Cardiology Foundation

Ischemia-related chest pain is due to an imbalance between myocardial oxygen supply and demand, primarily related to epicardial coronary flow limitations caused by atherosclerosis. In patients without significant epicardial coronary artery obstruction, endothelial and/or microvascular dysfunction also have the potential to limit blood flow and have been

suggested as an underlying mechanism for chest pain in women with angiographically normal coronary arteries (1). Decreased hemoglobin levels (Hgb) with subsequent impaired oxygen-carrying capacity in the setting of limited coronary flow by either mechanism have the potential to worsen ischemia and associated symptoms. Furthermore, recent research suggests that decreased Hgb is an independent predictor of increased morbidity and mortality in patients presenting with acute myocardial infarction (MI) and patients with hematocrit $<33\%$ who received transfusions had improved outcomes (2-4). In addition, several studies in patients with heart failure (HF) primarily from ischemic heart disease showed that anemia was independently associated with worsened symptoms and increased morbidity and mortality (5-7). Also, smaller studies have shown that treating anemia in patients undergoing dialysis is associated with regression of left ventricular dysfunction and improved outcomes (8-10). Table 1 summarizes some

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Abbreviations and Acronyms

CAD	= coronary artery disease
CHF	= congestive heart failure
EF	= ejection fraction
HF	= heart failure
Hgb	= hemoglobin
hs-CRP	= high sensitivity C-reactive protein
IL	= interleukin
MI	= myocardial infarction
TNF	= tumor necrosis factor
WISE	= Women's Ischemia Syndrome Evaluation study

of the studies evaluating the relationship between anemia and cardiovascular disease.

The National Center for Health Statistics reported that approximately 3.4 million Americans have anemia, with a much higher prevalence in women than in men (11). Although anemia is a well-known inciter of myocardial ischemia in patients with cardiovascular disease and seems to contribute to increased mortality and morbidity in patients with acute MI or HF, the prognostic importance of decreased hemoglobin in women presenting for evaluation of chest pain has not been studied. The aim of our study was to determine the impact of hemoglobin level on the adverse outcomes of women enrolled in the Women's Ischemia Syndrome Evaluation (WISE).

METHODS

The WISE study, a National Heart, Lung, and Blood Institute (NHLBI)-sponsored four-center study, aims to improve diagnostic testing in the evaluation of ischemic heart disease in women. Between 1996 and 2000, 936 women age 18 to 83 years were enrolled. The institutional review board at each site approved the study, and all data were monitored by an independent Data and Safety Monitoring Committee appointed by the NHLBI. Participant consent was obtained. Women referred for clinically indicated angiograms to further evaluate the basis for suspected ischemia were included in the study. Major exclusion

criteria for the WISE study were comorbidity that would compromise one-year follow-up, pregnancy, contraindications to provocative diagnostic testing, cardiomyopathy, New York Heart Association functional class III to IV congestive heart failure (CHF), recent MI, significant valvular or congenital heart disease, and a language barrier to questionnaire testing. Details of the protocol and design of the WISE study are published elsewhere (12).

Baseline evaluation included a physical examination and collection of clinical and laboratory data (Table 2). Qualitative and quantitative coronary angiographic analyses were carried out by core lab according to methodology published from the WISE study (12,13). Severity of coronary artery disease (CAD) was determined by angiographic assessment of luminal diameter narrowing. Obstructive CAD was defined as $\geq 50\%$ reduction, minimal as 20% to 49% reduction, and no stenosis as $< 20\%$ reduction of luminal diameter. A CAD severity score was defined as an aggregate of percent luminal stenosis, extent and location of stenosis, and degree of collateral vessels. Hemoglobin levels were analyzed on site, and anemia was defined using World Health Organization criteria of Hgb < 12 g/dl (14). Other components of the complete blood count were not recorded. Standardized forms containing demographic, clinical, angiographic, and follow-up information were collected at the site and then sent to the WISE study data coordinating center in Pittsburgh for processing.

An experienced nurse and/or physician collected follow-up data in person or by telephone interview at six weeks and then yearly. Each woman was queried for the occurrence of adverse outcomes. When an adverse outcome was identified, the referring physician was contacted for confirmation, dates, and documentation. In the event of death, a death certificate was obtained and an event committee reviewed available information to determine the likelihood of a cardiovascular etiology.

Measurements of inflammatory markers were available in 602 women and analyzed at a core lab. Measurement of these markers was added to the project after recruitment had begun, so previously enrolled patients did not have adequate stored serum to measure these levels. Plasma sampled at

Table 1. Summary of Studies Evaluating Anemia and Cardiovascular Disease

Patient Condition	n	Results
General population (2)	14,410 (57% women)	Anemia was a risk factor for MI, revascularization, or CV death
Hospitalized for acute MI (3)	78,974 (54% women)	After MI, patients with lower Hct had a higher 30-day mortality
Left ventricular dysfunction (5)	6,635 (14% women)	Impaired kidney function and anemia were risk factors for increased mortality
Advanced heart failure (6)	1,061 (23% women)	Anemia was associated with worsened functional status and was independent predictor of mortality
New onset heart failure (7)	12,065 (51% women)	Anemia was an independent risk factor for mortality
Renal failure requiring dialysis (8)	100 (46% women)	Showed that regression of left ventricular wall mass was possible with optimal management, including correction of anemia
Renal failure requiring dialysis (9)	22	Treating anemia with recombinant erythropoietin (epo) was associated with partial regression of ventricular hypertrophy
Advanced heart failure (10)	40	Correction of anemia with epo and iron was associated with improved cardiac function, decreased hospitalizations and stabilization of renal function

CV = cardiovascular; Hct = hematocrit; MI = myocardial infarction.

Table 2. Baseline Characteristics

	All Women (n = 864)	Women With Inflammatory Marker Levels (n = 602)
	Mean ± SD	
Age (yrs)	58.4 ± 11.6	58.0 ± 11.7
Total cholesterol (mg/dl)	194 ± 45	191 ± 43
HDL cholesterol (mg/dl)	54 ± 13	53 ± 12
LDL cholesterol (mg/dl)	111 ± 39	109 ± 37
Triglycerides (mg/dl)	155 ± 123	154 ± 130
Fasting blood sugar (mg/dl)	117 ± 55	115 ± 54
Creatinine (mg/dl)	0.9 ± 0.5	0.9 ± 0.5
Systolic blood pressure (mm Hg)	137 ± 22	137 ± 22
Diastolic blood pressure (mm Hg)	77 ± 11	76 ± 11
Pulse (beats/min)	74 ± 13	74 ± 13
BMI (kg/m ²)	29.7 ± 6.6	29.7 ± 6.9
Waist circumference (in)	36.8 ± 7.3	36.5 ± 7.3
Waist hip ratio	0.85 ± 0.11	0.87 ± 0.11
CAD severity score	15.0 ± 14.8	13.7 ± 13.3
Ejection fraction (%)	65.2 ± 10.8	65.3 ± 10.8
Percent With Characteristic		
Nonwhite	18.8	18.1
More than high school education	38.4	39.7
History of diabetes	25.2	25.6
Diabetes, using insulin	47.7	43.5
History of dyslipidemia	54.7	54.5
Current smoking	20.2	19.8
History of hypertension	59.6	57.6
History of congestive heart failure	8.6	8.3
Family history of premature CAD	66.4	65.9
Postmenopausal	75.9	74.9
S/P hysterectomy	53.7	53.4
Current HRT (postmenopausal only)	46.0	48.4
Obese (BMI ≥30)	41.7	41.3
Angiographic CAD stenosis ≥50%	39.2	35.1
Angiographic CAD stenosis 20% to 49%	24.7	24.9
Medication Use		
	Percent Reporting Use	
ACE inhibitors	26.4	26.3
Aspirin	60.6	60.5
Beta-blockers	39.5	40.9
Statins	25.0	27.4
Thyroid medication	13.9	15.0

ACE = angiotensin-converting enzyme; BMI = body mass index; CAD = coronary artery disease; HDL = high-density lipoprotein; HRT = hormone replacement therapy; HS = high school; LDL = low-density lipoprotein; S/P = status post.

baseline was frozen at -70°C for subsequent measurement of inflammatory markers. Levels of high-sensitivity C-reactive protein (hs-CRP) were measured by a high-sensitivity method using validated techniques (15). Interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha levels were measured from plasma using a commercially available enzyme-linked immunosorbent assay kit.

The primary analysis focused on adverse outcome, defined as a composite of hospitalization for nonfatal MI, CHF, stroke, other vascular events, or death. Myocardial infarction was defined by creatine kinase-MB isoenzyme elevation at least five times the upper limit of normal. Other vascular events included primarily peripheral atherosclerosis-related events.

Statistical analyses. Data are summarized as mean and standard deviation for continuous variables and frequencies for categorical variables. Tests for normality were performed

using the Shapiro-Wilk test. Comparisons of characteristics of women with anemia (hemoglobin levels <12 g/dl) and those without anemia were done by Wilcoxon tests for continuous variables and chi-square tests for discrete data. Spearman rank correlations coefficients were used to assess relationships between hemoglobin values and severity scores as well as hemoglobin values and inflammatory markers. Coronary artery disease is defined as a categorical variable (obstructive CAD/no obstructive CAD) and as a continuous variable called the severity score. Because the CAD severity score, ejection fraction (EF), and creatinine do not follow a normal distribution (Shapiro-Wilk test), the Wilcoxon test was used to compare values of women with anemia and those without anemia. A general linear model was used to assess relationships between hemoglobin and inflammatory markers while adjusting for variables found to

be significantly different between the cohort of women with inflammatory markers and those without. In these analyses, a log transformation of the inflammatory markers was used. Univariate and multivariable Cox regression models were used to identify predictors of mortality and adverse outcomes. Variables were chosen for entry into the model based on previous univariate associations. Multivariable Cox regression models were run as a forward step selection procedure. For the Cox proportional hazards model, the hazard ratio and 95% confidence intervals were calculated. The Kaplan-Meier method was used to estimate cumulative incidence rates of adverse events, with the log-rank statistic used to assess differences by level of hemoglobin. Adjusted estimates of event-free survival were based on the Cox model. All tests were two-sided and values of $p < 0.05$ were considered statistically significant. All statistics were analyzed using SAS version 8.2 (Cary, North Carolina).

RESULTS

Baseline clinical characteristics. Of 936 women enrolled in the WISE, 864 (mean age 58.4 ± 11.6 years) had complete data (Table 2). They were followed prospectively for a mean of 3.3 ± 1.7 years (2,831 patient-years) after entry. Baseline characteristics reveal that 60% had a history of hypertension, 55% dyslipidemia, 25% diabetes, 20% currently smoking, and 60% with a family history of premature heart disease. Of the women enrolled, 19% were non-white. Only 184 (21%) women were anemic (Hgb < 12 g/dl). Despite the high proportion of women with traditional CAD risk factors, only 39% had any coronary atherosclerotic stenoses $\geq 50\%$ diameter reduction by angiography, and 64% had any stenoses $\geq 20\%$. We found no correlation between Hgb level and presence of or severity of coronary atherosclerosis. The mean EF was $65.2 \pm 11\%$, and $< 3\%$ had an EF $< 40\%$.

Clinical outcomes. Over the follow-up period, 155 (18%) women had an adverse outcome. Thirty-five had more than one event. Fifty-six women died, with 29 (52%) of these deaths cardiovascular in etiology. Of 184 women with anemia, 11 (6%) had a cardiovascular-related death compared with 18 (2.6%) of 680 non-anemic women ($p = 0.03$). Anemic women had a significantly higher rate of first adverse outcome (Fig. 1) ($p < 0.001$), risk of death from any cause (10.3% vs. 5.4%, $p = 0.02$), and total adverse outcomes (26% vs. 16%, $p < 0.01$). Furthermore, anemic women were more likely to be non-white and to have a history of diabetes mellitus, hypertension, CHF, and currently not smoking (all $p < 0.01$). However, we found no difference in EF (66% vs. 64%, $p = \text{NS}$) or the presence or severity of CAD in anemic compared to non-anemic women. Anemic women did have a significantly higher creatinine level (mean 1.1 vs. 0.8 mg/dl, $p < 0.01$). Otherwise, we found no significant difference between anemic and non-anemic women regarding other characteristics and risk factors.

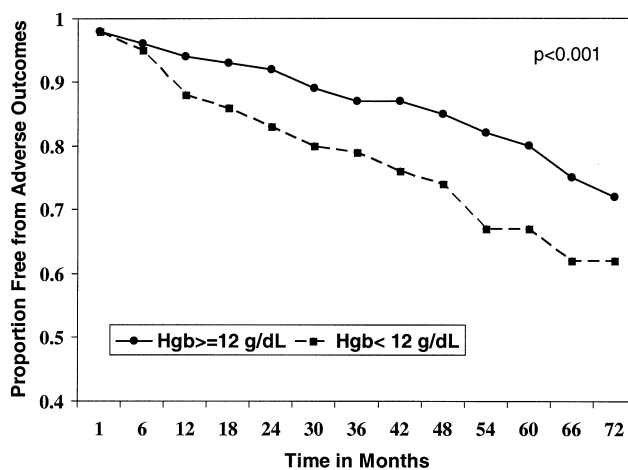


Figure 1. Adjusted estimate of survival free from adverse outcomes by level of hemoglobin (Hgb). Survival curves were generated using Kaplan-Meier methods. See text for definition of adverse outcomes. Note the decreased survival free from adverse outcomes for women with anemia.

On univariate analysis, each g/dl decrease in Hgb was associated with a 27% increase in all-cause mortality (hazard ratio = 1.27, $p = 0.01$). Also on univariate analyses, age, diabetes, dyslipidemia, hypertension, creatinine, use of statins, and any CAD stenosis $\geq 20\%$ diameter narrowing were each associated with adverse outcomes. In a multivariable Cox model, a lower Hgb level was associated with significantly higher risk of adverse outcomes (hazard ratio = 1.20, $p = 0.002$). Therefore, a decrease in Hgb of only 1 g/dl was associated with a 20% increase in adverse outcomes. Furthermore, after controlling for factors thought to contribute to or confound the observed deleterious effects of anemia on cardiovascular disease, Hgb independently predicted adverse outcomes. Figure 2 shows the significant independent predictors of adverse outcomes from Cox multivariable model.

Serum inflammatory markers, including hs-CRP, IL-6, and TNF-alpha, were available in 64% of the women (Table 2). When compared with women without inflammatory

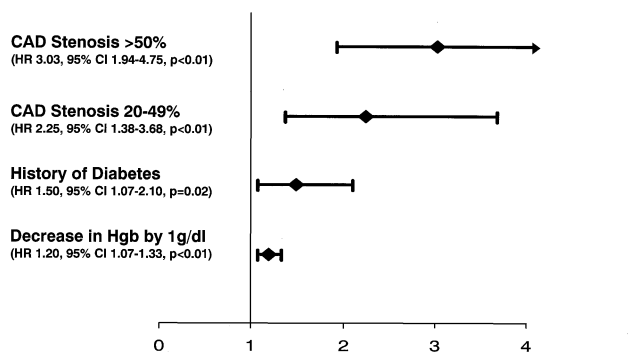


Figure 2. Risk factors found to be significant with hazard ratios (HR) independent predictor of any adverse outcome in multivariate analysis, and 95% confidence intervals (CI) for any adverse outcome. Hemoglobin is modeled as a continuous variable. Note the significantly increased risk of adverse outcomes associated with decreased hemoglobin levels. CAD = coronary artery disease.

measurements, women with inflammatory marker measurements had lower waist:hip ratio (mean 0.85 vs. 0.87, $p = 0.002$), greater statin use (27% vs. 19%, $p = 0.01$), lower CAD severity score (mean 13.7 vs. 17.7, $p = 0.002$), and lower prevalence of any CAD stenosis $>50\%$ (35% vs. 49%, $p = 0.001$). Anemic women had higher levels of CRP ($p = 0.02$), IL-6 ($p < 0.001$), and TNF-alpha ($p = 0.006$). After adjusting for the differences in variables listed above, anemia was associated with increased levels of CRP ($p = 0.07$), IL-6 ($p < 0.001$), and TNF-alpha ($p = 0.005$).

DISCUSSION

An association between hemoglobin level and ischemic heart disease in women has not been well recognized. We found that hemoglobin level was an independent predictor of adverse outcomes in women presenting with suspected ischemia. Our study primarily found that women with lower hemoglobin levels had higher risk of adverse outcomes. In addition, the all-cause and cardiovascular mortality of women with anemia was significantly increased. Furthermore, differences in traditional risk factors, CAD, renal impairment, thyroid disease, and cardiovascular medication use did not account for the differences observed in adverse outcomes. In multivariable analysis, decreased hemoglobin was also a stronger predictor of adverse outcomes than many traditional cardiovascular risk factors such as increasing age, history of hypertension, current smoking, and family history. Despite the univariate association, multivariable analysis did not show a significant independent relationship between statin use and adverse outcomes. Epicardial CAD and a history of diabetes were the only variables that were stronger predictors of adverse outcomes in this group of women.

We also found that women with anemia had significantly higher levels of inflammatory markers. Even after adjusting for variables known to decrease or be associated with these markers, anemia remained inversely related to inflammatory marker levels. Furthermore, women without inflammatory marker measurements had a higher waist:hip ratio, less statin use, and more severe CAD than the women with marker measurements. Therefore, women without inflammatory marker measurements could have higher levels of these markers, making it possible that we are underestimating the association between hemoglobin level and inflammatory marker levels in this population.

The basis for a link between hemoglobin level and adverse cardiovascular events in these women is not known. Historically, explanations for anemia-related cardiovascular dysfunction have included left ventricular dilation with remodeling as well as an increase in cardiac output through various mechanisms such as decreased blood viscosity, hypoxia-induced vasodilation, or altered nitric oxide activity with subsequent development of cardiac failure (16,17). Although compensated HF cannot be completely excluded as a contributor to the adverse outcomes seen in this study,

EF was not significantly associated with hemoglobin level or with risk of adverse outcome. In addition, $<3\%$ of patients had an EF $<40\%$.

A possible link could be the relationship of inflammation to both anemia and cardiovascular disease. Although the etiology of low hemoglobin levels could not be determined from the data available in our study, epidemiologic studies have shown that anemia in older men and women is most likely secondary to anemia of chronic disease or iron deficiency anemia (18). In this study, 76% of the patients were postmenopausal and thus less likely to have iron deficiency anemia due to menorrhagia. Anemia of chronic disease is associated with chronic inflammatory states and the effects of various cytokines, such as TNF, ILs, and interferons, which are also known to be associated with vascular disease and death (19). These inflammatory mediators may play a role in the lower hemoglobin levels, coronary microvascular dysfunction, and adverse outcomes seen in this population of women (1). In addition, 20% of the anemic women were nonwhite. Some women with anemia and adverse events may have a form of occult hemoglobinopathy, which may be associated with impaired delivery and metabolism of nitric oxide leading to coronary vascular dysfunction (20).

In contrast to previous studies (2–7), the adverse event rates in this study were significantly increased even in women with only mild to moderate decreases in hemoglobin level. Several studies have shown that correcting anemia improves outcomes (3,8–10,21), but previous analyses of anemia are primarily limited to patients with MI or HF or patients requiring hemodialysis. To our knowledge, no studies have been published regarding anemia in men evaluated for suspected ischemia without HF or MI. Because of the known differences between men and women, including genotype, hormones, and delays in manifestations of ischemic heart disease, extending our findings to a similar population of men would be speculative. In addition, women 18 years of age and older were enrolled with signs or symptoms warranting invasive investigation for suspected ischemia. This resulted in a population of women with a mean age of 58 years. This and further analyses of the WISE study cohort outcomes may show that the age or other characteristics of women at risk for ischemic heart disease are different from our current perceptions.

Study limitations. This prospective observational study has the inherent limitations of such a design. In addition, this study also has a relatively small population of women with Hgb levels measured only at baseline and without other red blood cell indices or serum iron studies available that may help determine the etiology of anemia. Correction of anemia at follow-up was also not captured by our database; thus, we are unable to determine the duration of anemia or the effect of changes in hemoglobin or treatment on outcomes. Finally, women may have been lost to follow-up as a result of an adverse event (e.g., survival bias); therefore, an underestimation of the long-term adverse events rates is possible.

Conclusions. Our findings suggest that lower Hgb is significantly and independently associated with adverse cardiovascular outcomes in women presenting with ischemic-type symptoms, regardless of the presence or severity of CAD. Furthermore, this association is seen with only modest reductions in Hgb during intermediate-term follow-up. These results extend previous reports linking lower Hgb with higher risk for adverse cardiovascular outcomes to women evaluated for suspected ischemia in the absence of acute MI or CHF.

The prevalence and prognostic importance of Hgb levels in this population necessitate further confirmation and investigation of the underlying pathophysiologic mechanisms as well as the potential benefits of therapeutic intervention in women with low Hgb being evaluated for suspected ischemia. Further thought should also be given to the clinical relevance of the current definition of anemia in this population, and further recognition of clinically important hemoglobin levels should be based on well-designed research of clinical and epidemiologic outcomes.

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