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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 ≥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.