

# Four Biomarkers Predict Event Risk in Women

BY BRUCE JANCIN  
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ORLANDO, FLA. — The presence of inflammatory markers, a low hemoglobin level, or both is superior to traditional cardiovascular risk factors for predicting adverse cardiovascular outcomes in women under evaluation for suspected myocardial ischemia, Christopher B. Arant, M.D., said at the annual meeting of the American College of Cardiology.

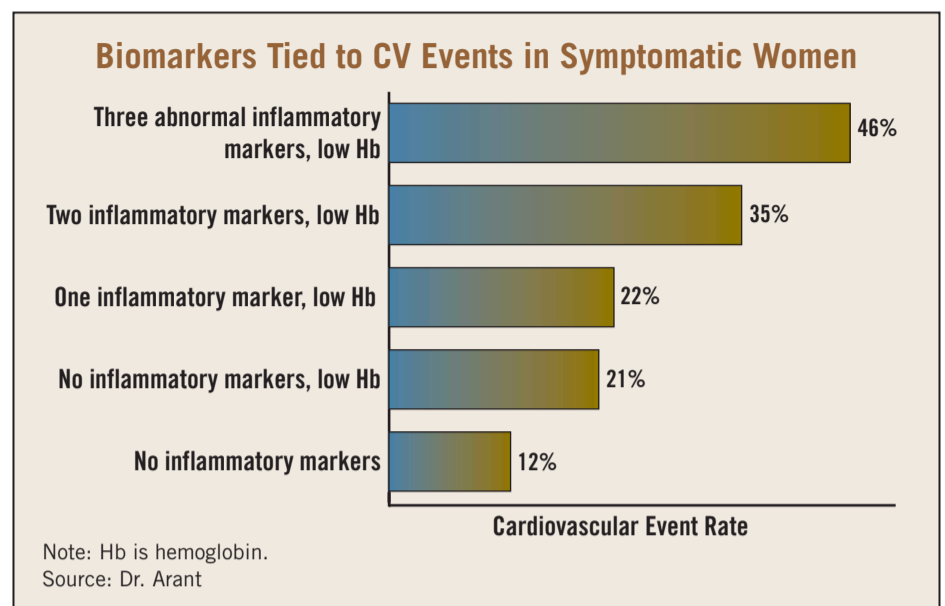
The standard cardiovascular risk factors appear to considerably underestimate the true risk of cardiovascular events in women presenting with chest pain, added Dr. Arant, a cardiologist at the University of Florida, Gainesville.

He reported on 595 women, mean age 58 years, who underwent coronary angiography as part of an evaluation for suspected myocardial ischemia in the National Heart, Lung, and Blood Institute-sponsored Women and Ischemia Syndrome Evaluation (WISE).

During a mean 3.6 years of follow-up, all-cause mortality among the women was 7%, and the rate of an MI, heart failure, stroke, another vascular event, or death was 20%. Yet their predicted 10-year risk of a cardiovascular event based on their Framingham risk score was just 4.6%. This underestimate emphasizes the need to develop better methods of recognizing women at high risk, which is the mission of WISE.

Inflammation plays a key role in atherosclerosis and its related complications, perhaps even more so in women than in men. Dr. Arant and his coinvestigators previously examined the predictive power of three inflammatory markers—C-reactive protein, interleukin-6, and serum amyloid A—and showed that they were strong predictors of cardiovascular risk in the WISE cohort. They separately established that hemoglobin level was an independent predictor of adverse cardiovascular outcomes.

In their new study, they showed that adding a hemoglobin concentration below 12 g/dL to the three inflammatory mark-



ers created a four-biomarker combination that incrementally and independently predicted cardiovascular events in the WISE study women. (See above.)

In a Cox multivariate regression analysis, the only traditional risk factors that predicted cardiovascular events were diabetes, which was associated with a 79% increase in risk, and obstructive coronary artery disease on angiography, which conferred a 65% increased risk.

In contrast, the presence of any one of the four biomarkers was associated with a 90% increased risk of cardiovascular events during follow-up. Two positive biomarkers conferred a 192% increased risk, and those with three had a 368% increased risk, and those with four abnormal biomarkers had a 550% increased risk.

The same graded relationship held true between abnormal biomarkers and all-cause mortality. The risk of death increased 4.5-fold in women with one abnormal biomarker, compared with those with none, and 19.2-fold in subjects with four biomarkers.

The mean hemoglobin in the WISE cohort was 12.9 g/dL. Why a modest reduction to below 12 g/dL was predictive of cardiovascular events in the WISE population remains speculative. Hemoglobin is not an obvious marker of inflammation. Yet physicians have known for some time that low hemoglobin is an independent predictor of

cardiovascular events in patients with heart failure, and more recent data suggest that the same applies in acute MI.

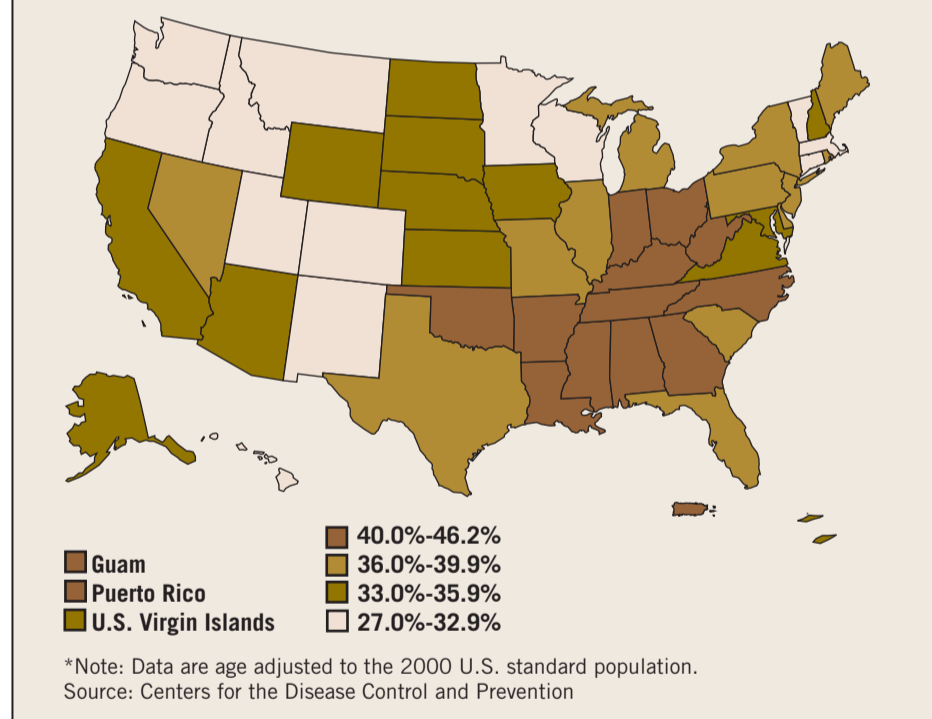
One possibility is that mild anemia may reflect bone marrow underproduction of red blood cells due to systemic inflammation. Thus, in that sense, a low hemoglobin may indeed be a surrogate marker for inflammation. However, the observation that adding hemoglobin to the three inflammatory markers yielded an incremental increase in event risk in WISE suggests a low hemoglobin may be acting directly to increase risk, Dr. Arant said.

Studies of sickle cell anemia patients suggest that hemoglobin may be important in the transport of nitric oxide, known to play a key role in endothelial function. Nearly two-thirds of women in WISE did not have obstructive coronary artery disease, instead presumably had what is often described as microvascular disease. Thus inadequate nitric oxide could exacerbate their endothelial dysfunction, which might explain the link between low hemoglobin and increased cardiovascular events, he said.

A clinical pearl from the WISE chest pain registry is that women with cardiac ischemia have a very high prevalence of atypical angina. "We like to say any pain above the waist in women who have risk factors requires a good history and physical exam and really needs to be considered as an anginal equivalent," he said. ■

## DATA WATCH

### Prevalence of Multiple Risk Factors for Heart Disease and Stroke Among Adults, 2003



# Half of ACS Patients Rehospitalized Within a Year for CVD

BY BRUCE JANCIN  
Denver Bureau

ORLANDO, FLA. — Nearly half of patients hospitalized for acute coronary syndrome at one large HMO were rehospitalized for cardiovascular disease within the next 12 months, Stephen Sidney, M.D., reported at the annual meeting of the American College of Cardiology.

Within 12 months, 29% of the patients were readmitted for acute coronary syndrome (ACS). Adding in admissions for other manifestations of coronary heart

disease along with those for heart failure and stroke, a total of 46% of patients were rehospitalized for cardiovascular disease (CVD) within 12 months of their index hospitalization for ACS.

Nearly 10% of patients were rehospitalized for coronary revascularization via coronary artery bypass graft surgery, and 7.4% were admitted for percutaneous intervention.

One-year mortality following the index hospitalization for ACS was 17.2%, and nearly two-thirds of the deaths were attributed to CVD, added Dr. Sidney of Kaiser

Permanente in Oakland, Calif.

Few data are available on 1-year outcomes after hospital discharge for ACS, so Dr. Sidney and his coinvestigators analyzed computerized records for 14,852 patients admitted for ACS to Kaiser Permanente of Northern California hospitals during 1999-2000. The hospitalization rate for ACS was 5.7 cases per 1,000 person-years among subscribers to the prepaid health plan, which provides coverage to 30% of the population in the San Francisco Bay Area.

At the index ACS hospitaliza-

tion, 31% of patients were hypertensive, 35% were diabetic, and 28% were hyperlipidemic. The relationships between these risk factors and the risks of rehospitalization for unstable angina and acute MI, respectively, differed in intriguing ways. For example, in a multivariate analysis, hyperlipidemic patients were 40% more likely to be rehospitalized for unstable angina within 12 months than were nonhyperlipidemic patients, but they were 32% less likely to experience MI.

In contrast, hypertension was associated with a 14% increased

risk of rehospitalization for unstable angina but no significantly increased risk of rehospitalization for MI. Patients aged 65 or older were 16% more likely than were younger ACS patients to be rehospitalized for MI, but 12% less likely to be rehospitalized for unstable angina.

Diabetic patients had a 26% greater likelihood of being rehospitalized for MI and a 14% increased risk of rehospitalization for unstable angina compared with nondiabetics.

The Kaiser study was funded by Eli Lilly & Co. ■