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Coronary Microvascular Reactivity to Adenosine Predicts Adverse Outcome in Women Evaluated for Suspected Ischemia

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

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Objectives We investigated whether coronary microvascular dysfunction predicts major adverse outcomes during follow-up among women with signs and symptoms of ischemia.

Background Altered coronary reactivity occurs frequently in women evaluated for suspected ischemia, and the endothelium-dependent component is linked with adverse outcomes. Possible links between endothelium-independent microvascular coronary reactivity and adverse outcomes remain uncertain.

Methods As part of the National Heart, Lung and Blood Institute-sponsored WISE (Women's Ischemia Syndrome Evaluation), we investigated relationships between major adverse outcomes and baseline coronary flow reserve (CFR) after intracoronary adenosine in 189 women referred to evaluate suspected ischemia.

Results At a mean of 5.4 years, we observed significant associations between CFR and major adverse outcomes (death, nonfatal myocardial infarction, nonfatal stroke, or hospital stay for heart failure). An exploratory receiver-operator characteristic analysis identified CFR <2.32 as the best discriminating threshold for adverse outcomes (event rate 26.7%; and ≥ 2.32 event rate 12.2%; $p = 0.01$). Lower CFR was associated with increased risk for major adverse outcomes (hazard ratio: 1.16, 95% confidence interval: 1.04 to 1.30; $p = 0.009$). This held true among the 152 women without obstructive coronary artery disease (CAD) (hazard ratio: 1.20, 95% confidence interval: 1.05 to 1.38; $p = 0.008$). The CFR significantly improved prediction of adverse outcomes over angiographic CAD severity and other risk conditions.

Conclusions Among women with suspected ischemia and atherosclerosis risk factors, coronary microvascular reactivity to adenosine significantly improves prediction of major adverse outcomes over angiographic CAD severity and CAD risk factors. These findings suggest that coronary microvessels represent novel targets for diagnostic and therapeutic strategies to predict and limit adverse outcomes in women. (Women's Ischemia Syndrome Evaluation [WISE]; NCT00000554) (J Am Coll Cardiol 2010;55:2825–32) © 2010 by the American College of Cardiology Foundation

Women with chest discomfort and other findings suggesting myocardial ischemia are diagnostic and therapeutic challenges, due in part to low likelihood for obstructive coronary artery disease (CAD) and costs of care related to

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Abbreviations and Acronyms

CAD = coronary artery disease
CFR = coronary flow reserve
CHF = congestive heart failure
CI = confidence interval
CV = cardiovascular
HR = hazard ratio
LV = left ventricular
MBF = myocardial blood flow
MI = myocardial infarction
ROC = receiver-operator characteristic

repeated testing, hospital stay, and disability (1). Although knowledge of mechanisms explaining these findings is limited, impaired coronary reactivity (endothelium- and non–endothelium-dependent) has been proposed to contribute (2–10). The endothelium-dependent component has been linked to risk factors and proinflammatory processes promoting atherosclerosis (8,9) as well as adverse clinical outcomes (5,7,10). Although the non–endothelium-dependent component has received less attention, the concept that patients with risk factors might have evidence for reduced coronary flow reserve (CFR) is not new (11–17). There is increasing interest in this microvascular response, as recently reviewed elsewhere (18), and in particular the response among women (8). For example, hypercholesterolemia abolishes the voltage-dependent K+ channel contribution to adenosine-mediated smooth muscle relaxation, in both endothelium-intact and -denuded coronary arterioles, in a sex-specific manner (19,20). Vascular smooth muscle cells undergo alterations in phenotype in response to physiological and pathophysiological stimuli like hypertension and diabetes, which are highly prevalent in post-menopausal women, as well as estrogen receptor alpha expression (21,22).

Myocardial perfusion alterations during adenosine-induced vasodilation are not infrequent in the absence of significant epicardial CAD (23,24). Although there has been long interest in microvascular ischemia, most work has focused on the endothelium-dependent component (25–28), but adenosine-related vascular smooth muscle alterations do not necessarily correlate with dysfunctional endothelium (8,20,29). Thus, additional information on adenosine-related coronary microvascular reactivity would facilitate an improved understanding of processes underlying these vascular alterations in women. If these alterations contribute to adverse outcomes, they potentially offer an important target for risk stratification and evaluation of preventive treatments among these women, particularly now that coronary microvascular reactivity can be readily assessed noninvasively (30–32).

Accordingly, we investigated the relationship between adenosine-coronary reactivity at baseline and adverse outcomes during follow-up in women referred for coronary angiography.

Methods

The WISE (Women's Ischemia Syndrome Evaluation) study is a National Heart, Lung and Blood Institute-sponsored study aimed at improving diagnostic evaluation and understanding of pathological mechanisms of ischemic heart disease in women, and protocol details—including selection criteria—have been previously published (33). Site institutional review boards approved the study, and each participant provided written informed consent. Women ages 18 to 84 years undergoing clinically-indicated angiograms were enrolled, underwent a variety of testing, and were followed for clinical outcomes. A subgroup of 189 women from the Universities of Florida and Pittsburgh sites also had evaluation of coronary reactivity to adenosine. Their selection criteria also included informed consent for this additional testing, absence of stenosis warranting coronary revascularization, and an appropriate coronary segment for Doppler flow testing.

Baseline evaluation included physical examination and collection of clinical and laboratory data (Table 1). Inflammatory markers were measured in a subgroup of 134 women from blood frozen on site at −70°C and analyzed at a core laboratory with validated techniques. Qualitative and quantitative coronary angiographic analyses were done by a core laboratory masked to patient data (34). Any ≥50% diameter stenosis was defined as obstructive CAD, 20% to 49% as mild CAD, and <20% as no CAD. A CAD severity score was defined as an aggregate of percent stenosis, extent and location of stenosis, and degree of collateral vessels (34).

Coronary reactivity testing was performed in a stenosis-free area of the left anterior descending coronary artery (n = 138) when possible, with the left circumflex artery as a secondary choice. A Doppler-tipped guidewire (0.014-inch FloWire, JOMED/Cardiometrics, Mountain View, California) was advanced through the diagnostic catheter. Once a stable velocity signal was obtained, baseline recordings were made. Intracoronary bolus injections of 18 μg of adenosine (Adenocard, Fujisawa USA, Deerfield, Illinois), a predominantly non–endothelium-dependent microvascular dilator, were administered into the left main coronary artery (35). At least 3 injections were done to ensure that a stable average peak coronary flow velocity was obtained after adenosine, with return to baseline flow velocity documented before each bolus. Pulsed-wave Doppler flow spectra were used to calculate time-averaged peak velocity. Recordings were analyzed at a core laboratory (University of Florida) masked to all other data, and CFR was defined as the ratio of average peak velocity after adenosine to average baseline velocity just before adenosine. As this measure correlated closely ($r = 0.87$, $p < 0.001$) with volumetric flow (35), it was used to represent CFR.

To access the possible influence of left ventricular (LV) hypertrophy on CFR, 39 of these women without coronary stenosis had quantitative analysis of echocardiograms performed with a standardized protocol within several days of CFR measurements according to American Society of Echocardiography recommendations. These analyses included measurement of LV mass (2-dimensional echocardiography) determined by an anatomically validated short-axis area length method (36), mass index, and an index of