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Safety of Coronary Reactivity Testing in Women With No Obstructive Coronary Artery Disease

Results From the NHLBI-Sponsored WISE (Women's Ischemia Syndrome Evaluation) Study

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Objectives This study evaluated the safety of coronary reactivity testing (CRT) in symptomatic women with evidence of myocardial ischemia and no obstructive coronary artery disease (CAD).

Background Microvascular coronary dysfunction (MCD) in women with no obstructive CAD portends an adverse prognosis of a 2.5% annual major adverse cardiovascular event (MACE) rate. The diagnosis of MCD is established by invasive CRT, yet the risk of CRT is unknown.

Methods The authors evaluated 293 symptomatic women with ischemia and no obstructive CAD, who underwent CRT at 3 experienced centers. Microvascular function was assessed using a Doppler wire and injections of adenosine, acetylcholine, and nitroglycerin into the left coronary artery. CRT-related serious adverse events (SAEs), adverse events (AEs), and follow-up MACE (death, nonfatal myocardial infarction [MI], nonfatal stroke, or hospitalization for heart failure) were recorded.

Results CRT-SAEs occurred in 2 women (0.7%) during the procedure: 1 had coronary artery dissection, and 1 developed MI associated with coronary spasm. CRT-AEs occurred in 2 women (0.7%) and included 1 transient air microembolism and 1 deep venous thrombosis. There was no CRT-related mortality. In the mean follow-up period of 5.4 years, the MACE rate was 8.2%, including 5 deaths (1.7%), 8 nonfatal MIs (2.7%), 8 nonfatal strokes (2.7%), and 11 hospitalizations for heart failure (3.8%).

Conclusions In women undergoing CRT for suspected MCD, contemporary testing carries a relatively low risk compared with the MACE rate in these women. These results support the use of CRT by experienced operators for establishing definitive diagnosis and assessing prognosis in this at-risk population. (Women's Ischemia Syndrome Evaluation [WISE]; NCT00832702) (J Am Coll Cardiol Intv 2012;5:646–53) © 2012 by the American College of Cardiology Foundation

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In patients undergoing angiography for stable angina, the proportion of women and men with no obstructive coronary artery disease (CAD) is increasing over time (1). Compared with men, women have a higher incidence of signs and symptoms of myocardial ischemia, yet 30% to 50% of women who undergo coronary angiography do not have obstructive CAD (2–4). The absence of obstructive CAD is not benign, as 38% of women with acute myocardial infarction (MI) and no obstructive CAD have been found to have plaque rupture or ulceration using intravascular ultrasound (5). Women with angina in the absence of obstructive CAD are often inappropriately reassured and even dismissed without further investigation or treatment: yet angina among women, regardless of coronary angiographic findings, is associated with increased mortality (6,7). The National Heart, Lung, and Blood Institute–sponsored WISE (Women's Ischemia Syndrome Evaluation) studies have documented that approximately one-half of these symptomatic women with no obstructive CAD have microvascular coronary dysfunction (MCD), which produces ischemia and is associated with an adverse cardiovascular prognosis compared with asymptomatic women (3,4,8–11). Both coronary artery spasm and endothelial dysfunction have been shown to be predictors of morbidity and mortality in patients with angina (12–16). Coronary spasm may result in MI, ventricular arrhythmias, and sudden cardiac death (15,17,18). Recent data show that women without obstructive CAD who have a low coronary flow reserve (CFR) are at higher risk of major adverse cardiac events (MACE) compared with those with normal CFR (19). Treatment directed at endothelial function can reduce angina, coronary spasm, heart failure, and stroke (20–23); therefore, it is important to establish the diagnosis in order to institute appropriate medical management.

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Invasive coronary reactivity testing (CRT) using vasoactive agents to evaluate macrovascular and microvascular responses is considered the reference standard for a definitive diagnosis of MCD (24). However, it is not routinely performed for a variety of reasons, including a lack of standardized protocols and concerns over catheterization laboratory time. Furthermore, limited data exist on the safety of contemporary CRT in women suspected of having MCD. We evaluated the safety of CRT performed at 3 experienced centers in women with angina, evidence of myocardial ischemia by stress testing, and no obstructive CAD (3,25).

Methods

Women with angina and evidence of myocardial ischemia underwent CRT at 3 experienced clinical centers that participate in WISE: the University of Pittsburgh, the University of Florida, Gainesville, and Cedars-Sinai Medical Center. Inclusion criteria: women with angina, myocardial ischemia by stress testing, and absence of obstructive CAD (<50% luminal obstruction in 1 or more epicardial coronary arteries on angiography). Exclusion criteria: contraindications to angiography and invasive CRT (hypersensitivity to contrast media, active bleeding, bleeding diathesis, renal dysfunction); prior or planned percutaneous coronary intervention or coronary artery bypass grafting; acute MI within 30 days; primary valvular heart disease; cardiogenic shock or intra-aortic balloon pump; inability to withhold nitrates, calcium channel agents, and alpha- and beta-adrenergic blockers for 24 h before testing; New York Heart Association functional class III or IV heart failure; ejection fraction <40%; hypertrophic obstructive cardiomyopathy; severe lung, renal, or hepatic disease; life expectancy <6 months, age <21 years; or pregnancy. All study participants gave written informed consent before undergoing evaluation. Demographic data were recorded with standardized questionnaires. CRT data were read onsite (at the Cedars-Sinai Cardiovascular Intervention Center) or at the WISE Angiographic Core Laboratory (Brown University). The institutional review boards at each site approved the study.

Abbreviations and Acronyms

AE = adverse event(s)
CAD = coronary artery disease
CFR = coronary flow reserve
CRT = coronary reactivity testing
IC = intracoronary
MACE = major adverse cardiovascular event(s)
MCD = microvascular coronary dysfunction
MI = myocardial infarction
QCA = quantitative coronary angiography
SAE = serious adverse event(s)

CRT protocol. Patients fasted for 12 h and withheld caffeine, long-acting nitrates, and other vasoactive agents for 24 h before testing. Patients were instructed to discontinue nicotine and avoid sublingual nitroglycerin 4 h before the

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