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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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procedure. Pre-mixed acetylcholine in 3 concentrations (0.182, 1.82, and 18.2 μg/ml) was prepared within 3 h of the scheduled procedures.

Outpatient diagnostic coronary angiography was performed via the percutaneous femoral approach. A pigtail catheter was used to measure aortic and left ventricular pressures. Patients with significant CAD, coronary artery anomalies, or bridging were excluded. For borderline lesions, at the discretion of the interventionalist, intravascular ultrasound and/or fractional flow reserve were used to confirm absence of obstructive stenosis.

After angiography, women were given body weight–adjusted heparin for anticoagulation, and the activated clotting time was maintained above 250 s. CRT was performed by infusing vasoactive substances through a guiding catheter placed in the left main coronary artery. Doppler guidewire (0.014-inch diameter, FloWire, JOMED/Cardiometrics/Volcano, San Diego, California) was positioned in the proximal left anterior descending coronary artery (Fig. 1). The following coronary functions were tested:

1. Nonendothelial-dependent microvascular function determination: After an adequate flow reading was obtained by the ComboMap Pressure and Flow System (JOMED/Cardiometrics/Volcano), baseline average peak velocity was recorded (Fig. 2). Intracoronary (IC) bolus injections of incremental doses of adenosine (18 μg, 18 μg, and 36 μg) were administered to create maximal hyperemia. The catheter was flushed with saline after each adenosine injection, and an average peak velocity reading was obtained 5 s after the saline flush. Adenosine CFR was calculated by ComboMap as a ratio of average peak velocity to average baseline velocity. This process was repeated and recorded for each dose of adenosine after the peak velocity returned to baseline. A CFR ≤2.5 in response to adenosine was considered abnormal (14,19).
2. Endothelial-dependent microvascular and macrovascular dysfunction determination: Graded IC acetylcholine concentrations of 0.182 and 18.2 μg/ml were infused (2 ml over 3 min). An intermediate dose of 1.82 μg/ml was infused at the discretion of the angiographer if it was deemed unsafe to proceed directly to a higher dose of 18.2 μg/ml, based on the coronary reactivity from the lower dose (i.e., 0.182 μg/ml) of acetylcholine. Doppler measurement of peak velocity was obtained at the end of each acetylcholine infusion. Normal endothelial-dependent microvascular response was defined as a coronary blood flow increase >50% at the highest dose of acetylcholine. Post-acetylcholine cine image was obtained for each concentration for quantitative coronary angiography (QCA). We ensured that coronary flow returned to baseline before each infusion. Normal acetylcholine response, or endothelial-dependent macrovascular coronary function, was defined as coronary artery dilation >5%. Coronary blood flow response to acetylcholine was calculated from the Doppler-derived time-velocity integral and vessel diameter by the following equation: Coronary blood flow = π (average peak velocity/2) (vessel diameter/2)^2. Vessel diameter was calculated 5 mm distal to the Doppler wire.
3. Nonendothelial-dependent macrovascular function determination: After completion of acetylcholine infusions and the return of coronary flow velocity to baseline, IC nitroglycerin (200 μg) was injected to evaluate nonendothelial-dependent macrovascular function. Average baseline and peak velocity were recorded. A cine image within 30 s of IC nitroglycerin

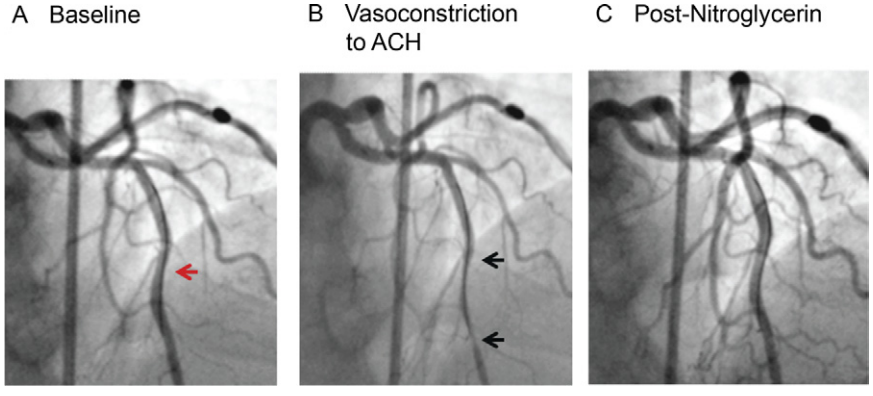

Figure 1. Coronary Angiogram and CRT

The figure shows Doppler flow wire in the left anterior descending artery **(red arrow) (A)**. In response to acetylcholine (ACH) infusion, there is abnormal coronary artery vasoconstriction **(black arrows)**, indicating endothelial dysfunction **(B)**. This is resolved by intracoronary nitroglycerin **(C)**. CRT = coronary reactivity testing.

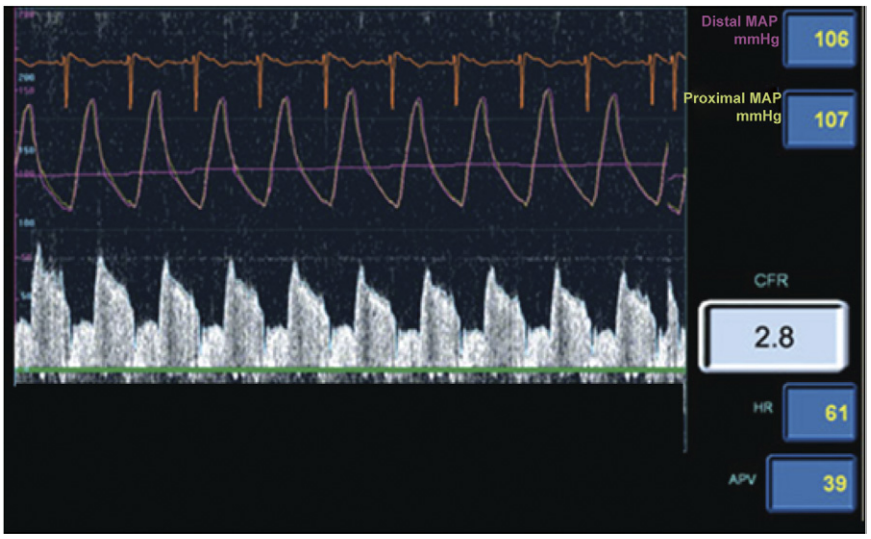

Figure 2. Example of Doppler Wire Tracing

The figure depicts a coronary flow velocity map showing an average peak velocity of 39 cm/s and a coronary flow reserve of 2.8 in response to adenosine, as determined by a Doppler flow wire in the coronary artery. Adenosine tests nonendothelial-dependent microvascular vasodilatory capacity. Coronary blood flow is calculated based on the change in diameter of the vessel and the change in velocity in response to acetylcholine. Acetylcholine tests endothelial-dependent vasomotor function.

was obtained for QCA. Normal nitroglycerin response was defined as a diameter increase >20%.

The angles, skew rotation, and table height were kept constant during the procedure. QCA measurements were made in the segment 5 mm distal to the tip of the Doppler wire. For each time interval, the diameter was measured in the same segment. Heart rate and blood pressure were recorded before and after administration of adenosine, acetylcholine, and nitroglycerin.

Periprocedural adverse events. Adverse events (AEs) and serious adverse events (SAEs) during and immediately post-CRT were recorded. SAEs were defined as those that required termination of the protocol and immediate hospitalization (hemodynamic instability, coronary artery dissection, MI, stroke, and death). AEs were defined as events related to the procedure that did not require hospitalization (such as deep venous thrombosis, transient coronary air embolism, nonsustained arrhythmias, and transient hypotension not requiring treatment). SAEs and AEs were adjudicated by a clinical events committee.

Table 1. Patient Demographics (N = 293)

White/Caucasian	247 (84%)
Age, yrs	54 ± 10
History of smoking	140 (48%)
Dyslipidemia	94 (32%)
Hypertensive	102 (35%)
Diabetic	29 (10%)

Values are n (%) or mean ± SD.

Outcomes during follow-up. As per WISE protocol, women were followed up for 6 weeks and then annually for death, nonfatal MI, nonfatal stroke, and hospitalization for heart failure. The MACE rate was calculated as the percentage of patients with a first event.

Results

The patient demographics are shown in Table 1. Results of CRT are reported in Table 2; not all patients underwent all aspects of reactivity testing, as this was site-dependent.

Table 2. Results of CRT

Abnormal nonendothelial microvascular function (CFR ≤2.5 in response to 18 μg of adenosine)	138/293 (47%)
Abnormal endothelial microvascular function (≤50% change in CBF in response to high-dose acetylcholine)	112/220 (51%)
bnormal endothelial macrovascular function (<5% increase in diameter in response to high-dose acetylcholine)	127/220 (58%)
AAbnormal smooth muscle function (nonendothelial macrovascular function (<20% increase in diameter to nitroglycerin)	136/225 (60%)
Coronary vasospasm (>50% reduction in diameter to high-dose acetylcholine compared with baseline)	11/220 (5%)
Coronary vasospasm (>70% reduction in diameter to high-dose acetylcholine compared with post-nitroglycerin diameter)	5/220 (2.3%)

Values are n/N (%).
CBF = coronary blood flow; CFR = coronary flow reserve; CRT = coronary reactivity testing.

Table 3. CRT-Related SAEs

Patient Age (Yrs)	Target Vessel	Complication	Treatment
53	LAD	Before initiation of protocol, a focal spasm in the LCX was visualized while the Doppler wire was in the LAD, causing an MI and prolonged chest pain.	Patient was given IC nitroglycerin and verapamil, as well as sublingual and intravenous nitroglycerin. She was admitted with a peak CPK of 532 and positive MB fraction.
58	LAD	A nonflow-limiting coronary dissection of the mid LAD resulted from advancement of the Doppler wire. Focal vasospasm and staining were visualized after the acetylcholine injection. IC nitroglycerin appropriately dilated the vessel.	TIMI flow grade 3 was present, and no intervention was needed. Patient was given clopidogrel and monitored overnight. She did not experience additional chest pain. There were no electrocardiographic changes.

CPK = creatine phosphokinase; CRT = coronary reactivity testing; IC = intracoronary; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; MB = myocardial band; MI = myocardial infarction; SAE = serious adverse event(s); TIMI = Thrombolysis In Myocardial Infarction.

CRT-related SAEs occurred in 2 women (0.7%) and included 1 coronary artery dissection (0.3%) and 1 ST-segment elevation MI due to coronary artery spasm (0.3%) (Table 3). CRT-related AEs occurred in 2 women (0.7%), and included 1 with transient air microembolism (0.3%) and 1 with deep venous thrombosis on the side of the groin access site (0.3%) >30 days after the CRT (Table 4). The combined CRT-related AE/SAE rate was 1.4%. There was no CRT-related mortality.

The prevalence of epicardial coronary vasospasm in our women was 5%, when vasospasm was defined as acetylcholine response of >50% coronary artery diameter reduction from baseline diameter (26). When defined as >70% coronary artery diameter reduction to acetylcholine from baseline, vasospasm occurred in 2 patients (0.9%). We also compared acetylcholine response to post-nitroglycerin diameter. Five patients (2.3%) had a >70% reduction in diameter due to acetylcholine compared with their post-nitroglycerin diameter.

The cohort was then followed for a period of 5.4 years, with 32 MACE observed in 24 women, including 5 deaths (1.7%), 8 nonfatal MIs (2.7%), 8 nonfatal strokes (2.7%), and 11 hospitalizations for heart failure (3.8%). The composite MACE rate to first event was 8.2% (24 of 293).

Discussion

Although invasive CRT is used to diagnose MCD in patients without obstructive CAD, the safety of CRT has not been well established, especially among women. The results of our study demonstrate that invasive CRT is relatively safe to evaluate MCD in symptomatic women with evidence of ischemia but no obstructive CAD. Compared with diagnostic coronary angiography, which carries a <2% risk of complications (26,27), addition of CRT does not appear to significantly raise procedural risk. Specifically, the combined CRT-related AE/SAE risk (1.4%) was substantially lower than the 5.4-year follow-up MACE rate (8.2%). Prior studies have documented that MCD is associated with an adverse cardiovascular prognosis compared with asymptomatic women (3,4,8–10). Although clinical trials testing whether medical therapy reduces MACE in patients with MCD are needed, existing intermediate outcome trials suggest that endothelial function improves with treatment (20–23), as do signs and symptoms of ischemia (28). Accordingly, establishment of the diagnosis of MCD in these patients is important for appropriate medical management.

Coronary blood flow is regulated by various endothelial-dependent and nonendothelial-dependent factors. Nonendothelial-dependent factors include myocardial metabolism, myocardial compressive forces, aortic pressure, and neurohumoral substances (29). We measured CFR directly by the Doppler wire in response to adenosine, a nonendothelial-dependent vasodilator (30). Acetylcholine was used to test endothelium-dependent function, as it stimulates nitric oxide release from the endothelial cells. Nitroglycerin response was used to test nonendothelial-dependent macrovascular function. Procedural success rates were high in our study, and one-half of patients in our patient population had an abnormal CRT (Table 2).

Table 4. CRT-Related AEs

Patient Age (Yrs)	Target Vessel	Complication	Treatment
66	LAD	An air microembolism to RCA was noticed during insertion of an infusion catheter, causing chest pain for 2 min.	Supplemental oxygen was delivered by face mask, with spontaneous recovery.
52	LAD	Patient was diagnosed with a deep venous thrombosis more than 30 days after her coronary reactivity study.	Anticoagulation was initiated as indicated.

AE = adverse event(s); RCA = right coronary artery; other abbreviations as in Table 3.

Safety of IC Doppler flow measurement. IC Doppler measurement currently has a Class IIb recommendation for assessment of the severity of coronary flow abnormalities in patients with angina, ischemia by stress testing, but no obstructive CAD (31). The Doppler wire used in our study is a 0.014-inch-diameter flexible, steerable guidewire with a piezoelectric ultrasound transducer integrated into the tip (32,33). The Doppler wire may cause coronary spasm, which was previously seen in 1% of patients undergoing IC Doppler examination (34). Wire-induced spasm was relieved by IC nitroglycerin, similar to our contemporary study findings. A smaller study of 44 patients reported that no Doppler wire–related complications occurred in patients with normal or mild CAD (35). In our study, there was 1 coronary artery dissection (0.3%) that may have been due to the Doppler wire. The dissection likely occurred during placement of the Doppler wire before reactivity testing. Focal vasospasm and staining of the mid left anterior descending coronary artery were then noted during acetylcholine injection. No intervention was needed as the dissection was stable, with no limitation of flow.

Safety of IC adenosine. The safety and use of IC boluses of adenosine is well established (36–38). In a study of 39 patients by Wilson et al. (39), IC boluses (2 to 16 μg) produced small, brief, dose-dependent reductions in mean arterial pressure and did not significantly change the PR, QRS, or QT intervals on the electrocardiogram, even when the drug was injected directly into the right coronary artery. However, in a study by Qian et al. (34) of 906 patients, 14 patients experienced arrhythmias (7 asystole, 4 second-degree atrioventricular block, 1 third-degree atrioventricular block, 1 severe sinus bradycardia, 1 ventricular fibrillation), all of whom received an IC bolus of 12 μg of adenosine in the right coronary artery. One patient experienced sinus bradycardia and hypotension after 18 μg of IC adenosine in the left anterior descending artery after stent implantation (34). In our study of 293 patients, neither the 18-μg nor the 36-μg dosages of adenosine resulted in any arrhythmias, and all cases were performed in the left coronary artery, showing that contemporary testing safety has improved and is safe.

Safety of IC acetylcholine. Acetylcholine has been used to evaluate coronary vasomotor function. Sueda et al. (40) performed 1,000 acetylcholine tests in Japanese men with and without obstructive CAD from 1991 to 2004. Incremental doses of 20/50/80 μg into the right coronary artery and 20/50/100 μg into the left coronary artery were injected over 20 s. They reported 17 of 1,000 patients (1.7%) who experienced a major adverse reaction during acetylcholine infusion, including 11 with nonsustained ventricular tachycardia (1.1%), 1 with sustained ventricular tachycardia (0.1%), 1 with ventricular fibrillation (0.1%), 3 with shock due to left main stem spasm (0.3%), and 1 with cardiac tamponade (0.1%). No serious complications, such as death, stroke, or acute MI, were observed in this study.

More recently, the CASPAR (Coronary Artery Spasm in Patients with Acute Coronary Syndrome) study investigators injected incremental doses of acetylcholine (2/20/100 μg over 3 min) into the left coronary artery and/or right coronary artery of 86 patients (15). Coronary vasospasm was detected in 42 patients (49%). Ischemic ST-segment changes were seen in 20 patients (17 ST-segment depressions, 3 ST-segment elevation), but there were no clinical adverse events. In a study of nifedipine's effect on endothelial dysfunction, investigators infused acetylcholine (0.36, 3.6, and 18 μg/ml at 2 ml/min for 3 min) in either the left anterior descending artery or circumflex artery of 641 patients (41). Transient electrocardiographic changes were reported in 5 patients, whereas diffuse coronary vasoconstriction with hemodynamic instability occurred in 5 patients (0.78%) (1 [0.16%] required resuscitation). One patient (0.16%) developed acute coronary syndrome and cardiac arrest in the catheterization laboratory, possibly related to acetylcholine.

In our similarly sized study, acetylcholine infusions were well tolerated, without significant hemodynamic changes, again suggesting that contemporary testing safety has improved. Although some patients did experience chest pain at higher doses of acetylcholine, we were careful in monitoring coronary flow throughout acetylcholine infusion to assess for significant spasm. Five patients (2.3%) developed acetylcholine-induced vasospasm, which immediately resolved after nitroglycerin injection, with no further sequelae. The higher doses of acetylcholine used in the CASPAR study (2/20/100 μg) likely caused more coronary vasospasm than the lower doses of acetylcholine used in our study (0.364/3.64/36.4 μg). Our case of coronary artery dissection was likely due to the Doppler wire rather than vasospasm from acetylcholine.

Study limitations. As per WISE protocol, CRT was performed in the left anterior descending coronary artery in all patients. Safety of CRT in the right coronary artery or left circumflex artery was not evaluated. Acetylcholine is not directly infused into the left anterior descending artery, but rather infused through the guiding catheter in the left main coronary artery, and thus the concentration of the acetylcholine may be diluted in the left anterior descending artery. Because vasoactive substances are infused in the left main artery, both the circumflex and the left anterior descending artery are susceptible to vasoconstrictive effects. The protocol stipulated for the Doppler wire to be maintained in the proximal left anterior descending coronary artery. Therefore, the safety of CRT when the Doppler wire is placed more distally is unknown. It is also difficult to accurately perform QCA in distal vessels due to their smaller diameter.

Conclusions

In women undergoing CRT for suspected MCD, contemporary testing is relatively safe with a low adverse event rate

when using standardized protocols for IC adenosine, acetylcholine, and nitroglycerin delivery in experienced centers. These results support the use of CRT by experienced operators for diagnostic and prognostic purposes in patients with persistent angina, evidence of myocardial ischemia, and no obstructive CAD. Prior studies investigating therapy directed at improvement of MCD have shown reduction of angina, vasospasm, heart failure, and stroke. Additional studies are needed to demonstrate improvement in cardiovascular outcomes.

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