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Impact of Abnormal Coronary Reactivity on Long-Term Clinical Outcomes in Women

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ABSTRACT

BACKGROUND Currently as many as one-half of women with suspected myocardial ischemia have no obstructive coronary artery disease (CAD), and abnormal coronary reactivity (CR) is commonly found.

OBJECTIVES The authors prospectively investigated CR and longer-term adverse cardiovascular outcomes in women with and with no obstructive CAD in the National Heart, Lung, and Blood Institute–sponsored WISE (Women's Ischemia Syndrome Evaluation) study.

METHODS Women (n = 224) with signs and symptoms of ischemia underwent CR testing. Coronary flow reserve and coronary blood flow were obtained to test microvascular function, whereas epicardial CR was tested by coronary dilation response to intracoronary (IC) acetylcholine and IC nitroglycerin. All-cause mortality, major adverse cardiovascular events (MACE) (cardiovascular death, myocardial infarction, stroke, and heart failure), and angina hospitalizations served as clinical outcomes over a median follow-up of 9.7 years.

RESULTS The authors identified 129 events during the follow-up period. Low coronary flow reserve was a predictor of increased MACE rate (hazard ratio [HR]: 1.06; 95% confidence interval [CI]: 1.01 to 1.12; p = 0.021), whereas low coronary blood flow was associated with increased risk of mortality (HR: 1.12; 95% CI: 1.01 to 1.24; p = 0.038) and MACE (HR: 1.11; 95% CI: 1.03 to 1.20; p = 0.006) after adjusting for cardiovascular risk factors. In addition, a decrease in cross-sectional area in response to IC acetylcholine was associated with higher hazard of angina hospitalization (HR: 1.05; 95% CI: 1.02 to 1.07; p < 0.0001). There was no association between epicardial IC-nitroglycerin dilation and outcomes.

CONCLUSIONS On longer-term follow-up, impaired microvascular function predicts adverse cardiovascular outcomes in women with signs and symptoms of ischemia. Evaluation of CR abnormality can identify those at higher risk of adverse outcomes in the absence of significant CAD. (Women's Ischemia Syndrome Evaluation [WISE]; NCT00000554)
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Prior work that included predominantly men with obstructive coronary artery disease (CAD), abnormal coronary reactivity (CR) testing in a nonobstructed epicardial coronary artery predicted adverse outcomes (1). Currently, as many as one-half of women with suspected myocardial ischemia undergoing clinically indicated coronary angiography have no angiographic evidence of obstructive epicardial CAD (2). We have demonstrated that women with no obstructive CAD are at increased risk of major cardiovascular events (e.g., death, myocardial infarction [MI], stroke, or heart failure [HF] hospitalization) during follow-up (3–5). These findings have been confirmed by others and have been extended to apply to men (2,6,7).

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We have further documented that abnormal coronary endothelium and non-endothelium-dependent reactivity is common in women with signs and symptoms of ischemia, but no obstructive CAD (8–11). We also noted that women with reduced coronary flow reserve (CFR) and abnormal epicardial coronary endothelium dilation are at higher risk of relatively short-term (3-year to 5-year) adverse outcomes, predominantly angina hospitalization, compared with those with normal response (9,11). The presence of coronary microvascular dysfunction, ischemia on stress testing, and persistent angina >1 year, identified women at higher risk for adverse outcomes (4,12). Cost analyses demonstrated WISE (Women's Ischemia Syndrome Evaluation) women with signs and symptoms of ischemia but no obstructive CAD incurred similar short-term health care costs compared with patients with obstructive CAD (13).

The original WISE study includes up to 10-year follow-up; therefore, we prospectively investigated epicardial and microvascular CR and longer-term adverse cardiovascular outcomes in women with signs and symptoms of ischemia including those with no obstructive CAD in the National Heart, Lung, and Blood Institute–sponsored WISE study.

METHODS

We studied women with signs and symptoms of ischemia who were enrolled in the WISE study from 1996 to 2000, as previously described (14). The WISE study protocol, approved by the relevant institutional review boards, has been described in detail previously (14), and all subjects gave written informed consent before study participation.

CR TESTING. Women were asked to hold vasoactive medications for 48 h before the procedure. CR testing was performed in an epicardial coronary artery free of obstructive CAD (<50% diameter stenosis). The left anterior descending coronary artery was the preferred vessel, followed by the left circumflex coronary artery if anatomic issues prohibited safe access to the left anterior descending coronary artery. To assess blood flow velocity, a Doppler-tipped guidewire (0.014-inch FloWire, Volcano Corporation, San Diego, California) was advanced through the diagnostic catheter. Recordings were made once a stable Doppler signal in the proximal or mid-vessel was obtained. During CR testing, the following pathways were evaluated:

1. Non-endothelium-dependent microvascular reactivity was assessed using intracoronary (IC) bolus injections of incremental doses of adenosine (18 μg and 36 μg). CFR was calculated as a ratio of average peak velocity to average baseline (rest) velocity. CFR in response to each bolus was recorded, and a CFR of ≥2.32 was considered normal (9).
2. Endothelium-dependent reactivity was assessed using IC acetylcholine infusion (IC-Ach) 0.182 μg/ml (10^{-6} mol/l) at 2 ml/min for 3 min. This was followed by infusion of 18.2 μg/ml (10^{-4} mol/l) over 3 min, and then blood flow and pressure recordings were made and angiography was repeated to assess coronary vessel diameter. The 0.182 μg/ml IC-Ach was used for safety purposes to make sure no significant coronary spasm in response to IC-Ach

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
CBF = coronary blood flow
CFR = coronary flow reserve
CI = confidence interval
CR = coronary reactivity
CSA = cross-sectional area
HF = heart failure
HR = hazard ratio
IC = intracoronary
IC-Ach = intracoronary acetylcholine
IC-NTG = intracoronary nitroglycerin
MACE = major adverse cardiovascular events
MI = myocardial infarction

Los Angeles, California, the Barbra Streisand Women's Cardiovascular Research and Education Program, Cedars-Sinai Medical Center, Los Angeles, The Society for Women's Health Research (SWHR), Washington, DC, The Linda Joy Pollin Women's Heart Health Program, and the Erika Glazer Women's Heart Health Project, Cedars-Sinai Medical Center, Los Angeles, California. This work is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or National Institutes of Health. Dr. Bairey Merz has been a speaker for Abbott Diagnostics and served on the board of directors for iRhythm. Dr. Bittner has received institutional contracts to serve as a steering committee member for Sanofi; as a national trial coordinator for AstraZeneca, DalCor, and Esperion; as a trial coinvestigator for Amgen; and as a site principal investigator for AstraZeneca and Bayer; and has served on advisory boards for Sanofi. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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occurs. Therefore, only the 18.2 μg/ml IC-Ach data are reported. Coronary angiography was obtained after the infusion was completed. Endothelium-dependent epicardial CR was assessed by calculating the percentage in coronary cross-sectional area (CSA) change in response to IC-Ach (change in epicardial CSA >0% is considered normal), whereas endothelium-dependent microvascular reactivity was evaluated by calculating the change in coronary blood flow (CBF) (change in CBF ≥50% is considered normal).

3. Non-endothelium-dependent epicardial CR was assessed using IC nitroglycerin (IC-NTG) injection. Coronary angiography was obtained after each injection to measure coronary artery diameter and calculate coronary CSA (change in CSA >20% is considered normal) (15).

Quantitative coronary angiography and blood flow recordings. All angiography was done in a standardized oblique projection to minimize overlapping and better visualization of coronary vessels. Angiograms and average blood flow velocity (AV) recordings were made at baseline and after administration of each vasoactive drug. CSA was calculated from the coronary diameter measured 5 mm distal to the tip of the Doppler wire. CBF was calculated using the equation CBF = CSA × AV × 0.5 (16) at rest and in response to IC-Ach. Change in CBF was calculated as: (CBFpeak − CBFrest/CBFrest) × 100. Epicardial coronary artery responses to IC-Ach were assessed by measuring coronary diameter at baseline and after IC-Ach infusion by quantitative coronary angiography. For quantitative coronary angiography, angiograms were analyzed by 1 investigator masked to all other patient data at the WISE angiographic core laboratory (Rhode Island Hospital, Providence, Rhode Island) as described previously (17).

FOLLOW-UP, MORTALITY, AND ADVERSE OUTCOMES. A standardized protocol-directed follow-up was conducted by experienced site nurses or physicians through direct, telephone, and/or mail contact at 6 weeks, 1 year, and annually thereafter. Women were provided with questionnaires asking about their symptoms, medication use, hospitalizations, and diagnostic or revascularization procedures since last contact. All the reports were reviewed by the study committee and classified as death, cardiovascular death, nonfatal MI, nonfatal stroke, and HF hospitalization up to December 2005. In addition, a National Death Index search was conducted for all women thought to be alive up to December 2007. Furthermore, because persistent angina predicts cardiovascular events in women with no obstructive CAD (3), we monitored hospitalization due to angina as well. We evaluated 2 composite outcomes for major adverse cardiovascular events (MACE): 1) a 4-component MACE of cardiovascular death, nonfatal MI, nonfatal stroke, or HF hospitalization; and 2) a 3-component MACE of cardiovascular death, nonfatal MI, and nonfatal stroke. We analyzed angina hospitalization separately from MACE outcome; specifically, we did not combine angina and cardiovascular composite outcome in any model.

TABLE 1 Baseline Characteristics of the Women (N = 224)

Age, yrs	55 ± 11
Race	
White	181 (81)
African-American	40 (18)
Other	3 (1)
History of diabetes	49 (22)
History of hypertension	125 (56)
Family history coronary disease	142 (66)
Dyslipidemia	105 (52)
CAD minimal or none	179 (81)
Current smoking	44 (20)
Coronary hemodynamics	
CFR (n = 200)	2.56 ± 0.76
ΔCBF, % (n = 113)	79 ± 107
Δ CSA, IC-Ach, % (n = 126)	2.68 ± 24.45
Δ CSA, IC-NTG, % (n = 131)	20.13 ± 24.51
Baseline medications	
ACE inhibitor/ARB	54 (24)
Beta-blockers	65 (29)
CCD	58 (26)
Nitrates	47 (21)
Statins	38 (17)
Aspirin	110 (50)
Vasodilators	15 (7)

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CBF = coronary blood flow; CCB = calcium channel blockers; CFR = coronary flow reserve; CSA = coronary cross-sectional area; IC-Ach = intracoronary acetylcholine infusion; IC-NTG = intracoronary nitroglycerin.

STATISTICAL ANALYSIS. Clinical variables were summarized using mean ± SD or using count (%) for categorical variables. Follow-up time was summarized using medians and ranges. Kaplan-Meier analysis was used for stratified analysis of time-to-event for 3 event types: 1) overall mortality; 2) 4-component MACE; and 3) 3-component MACE and hospitalization due to angina. Cox proportional hazards regression was used to analyze hazard for these events with each of the continuous CR testing variables alone, as well as separate models to adjust the association of CR variables for clinical factors of age, and binary indicators for history of hypertension, dyslipidemia, smoking status, diabetes, and CAD status. A significance level of 0.05 was used for all analyses. Analysis

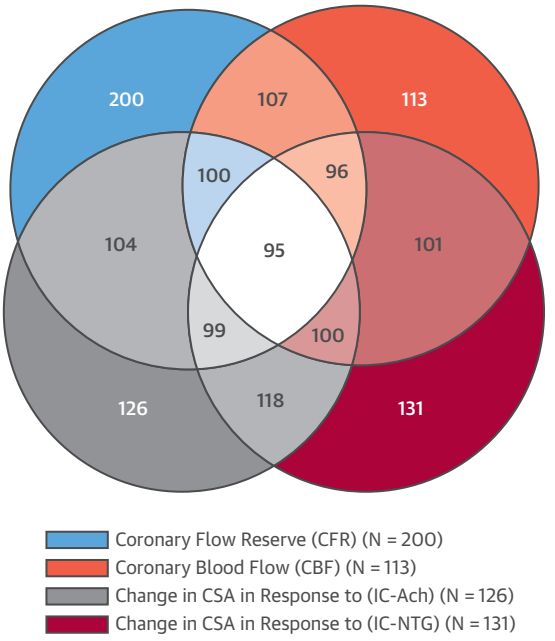
was carried out using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENT CHARACTERISTICS AND ADVERSE OUTCOME. The baseline characteristics of the 224 subjects are summarized in Table 1. Mean age was 55 ± 11 years with a median follow-up duration of 9.7 years. Two-hundred subjects (89%) underwent CFR evaluation, 126 (56%) underwent evaluation of endothelium-dependent epicardial CR testing using coronary CSA change in response to IC-Ach, 113 subjects (50%) underwent endothelium-dependent microvascular reactivity testing using CBF change in response to IC-Ach, and 131 subjects (58%) received IC-NTG for evaluation of non-endothelium-dependent epicardial CR. Most women underwent evaluation of multiple CR pathways (Figure 1), related to testing feasibility, and vasoactive medication tolerance and safety. We identified 77 women (38%) with abnormal CFR, 55 (49%) with abnormal CBF, whereas we identified 69 (55%) with abnormal change in CSA in response to IC-Ach and 75 (57%) with abnormal change in CSA in response to IC-NTG. In this cohort, 51% had no CAD (defined as <20% stenosis); 30% had minimal CAD (defined as 20% to 50%); and 19% had significant CAD (defined as >50%). During follow-up, there were 32 deaths, 18 of them (56%) were related to cardiovascular cause. There were 57 4-component MACE events, 37 3-component MACE events, and 58 hospitalizations related to angina (Table 2).

NON-ENDOTHELIUM-DEPENDENT CORONARY MICROVASCULAR REACTIVITY IN RESPONSE TO IC ADENOSINE. Mean CFR was 2.56 ± 0.76, and 123 of 200 subjects (62%) had normal CFR (≥2.32). There was no difference in medication regimen between women with CFR ≥2.32 and those with CFR <2.32 (Online Table 1). There was no difference in all-cause mortality rate between normal and abnormal CFR (13% vs. 16%; p = 0.48). Both the 4-component and 3-component MACE rates were higher in the group of women with CFR <2.32 compared with those with CFR ≥2.32 (26% vs. 13%; p = 0.008, 19% vs. 10%; p = 0.028, respectively) (Figure 2). Low CFR was an independent predictor of the 4-component MACE rate (hazard ratio [HR]: 1.06; 95% confidence interval [CI]: 1.01 to 1.12; p = 0.021). This association remained significant after adjusting for age, history of hypertension, dyslipidemia, smoking status, diabetes, and CAD status (HR: 1.06; 95% CI: 1.004 to 1.12; p = 0.035). Following adjustment, low CFR was not significantly associated with the 3-component MACE (HR: 1.06; 95% CI: 0.99 to 1.14; p = 0.064).

FIGURE 1 Distribution of Selected CR Testing in 224 Women With Signs and Symptoms of Ischemia



Most women underwent evaluation of >1 coronary reactivity (CR) pathway. **blue** represents women who underwent evaluation of non-endothelium-dependent microvascular reactivity using coronary flow reserve (CFR); **orange** represents women who underwent evaluation of endothelium-dependent microvascular reactivity using coronary blood flow (CBF); **gray** represents women who underwent evaluation of endothelium-dependent epicardial CR using change in coronary artery cross-sectional area (CSA) in response to intracoronary acetylcholine (IC-Ach); whereas **red** represents women who underwent evaluation of non-endothelium-dependent epicardial CR using change in coronary artery CSA in response to intracoronary nitroglycerin (IC-NTG).

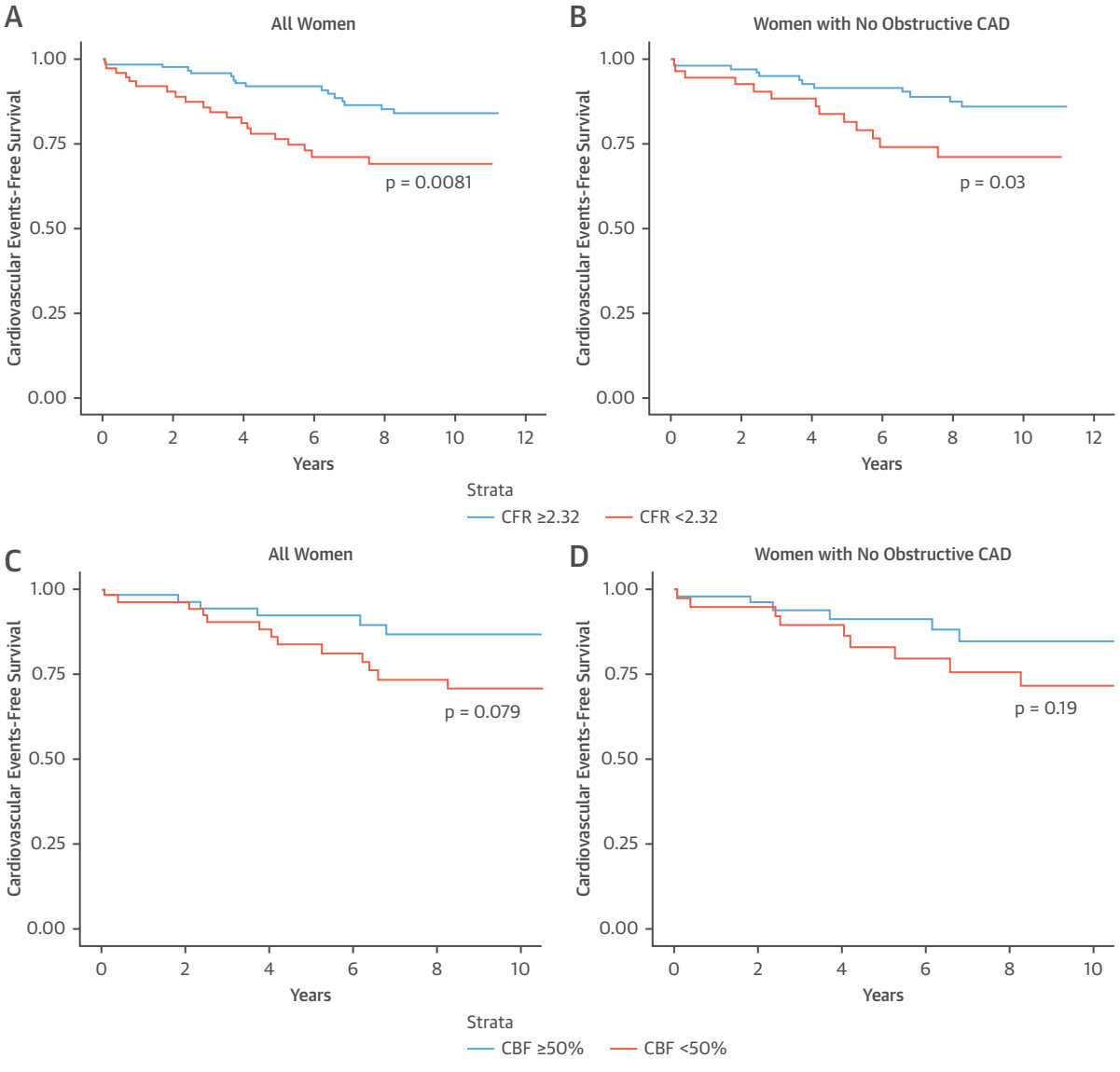
Women with no obstructive CAD (defined as epicardial coronary artery stenosis <50%) and abnormal CFR (57 [36%]) had higher rates of 4-component MACE compared with those with normal CFR (23% vs. 12%; p = 0.03). After adjusting

TABLE 2 Total Adverse Events During Median Follow-Up of 9.7 Years

	Total Events (N = 224)	Events in Women With No Obstructive CAD (n = 179)
Death	32	22
Cardiovascular death	18	11
Myocardial infarction	8	6
Stroke	11	9
Heart failure hospitalization	20	13
Angina hospitalization	58	41

CAD = coronary artery disease.

FIGURE 2 **Relationship Between Coronary Microvascular Function and Cardiovascular Events**

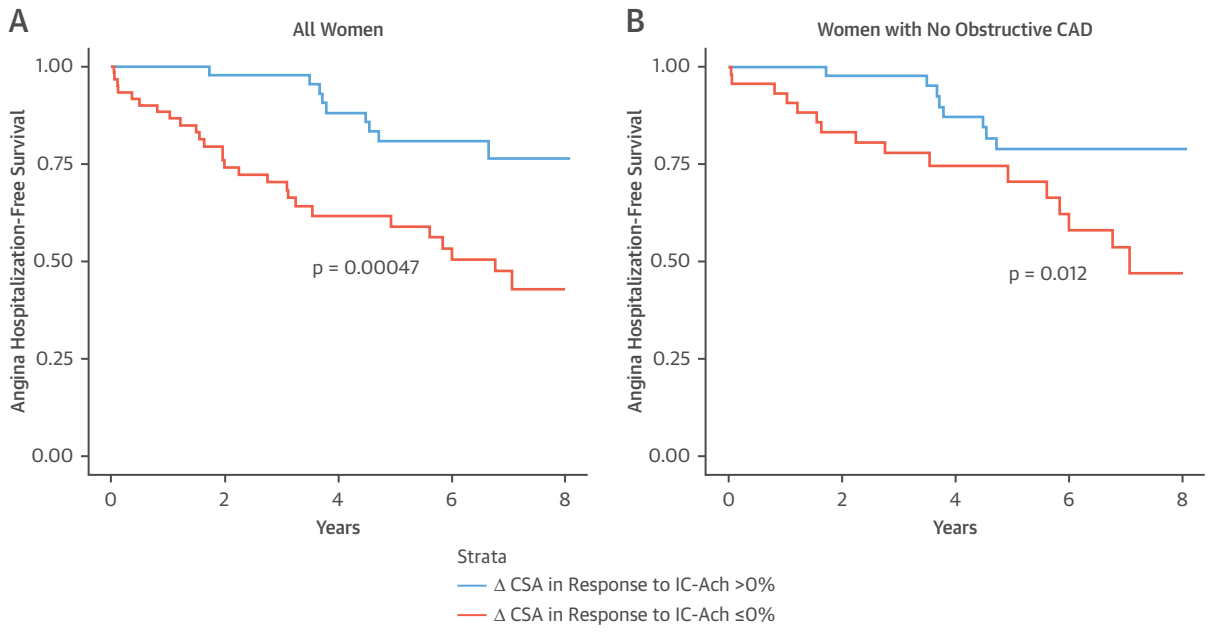


(A) Kaplan-Meier analysis showing percentage of women surviving free from the 4-component major adverse cardiovascular event (MACE) including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and heart failure during long-term follow-up stratified by coronary flow reserve (CFR). **(B)** Kaplan-Meier analysis showing percentage of women with no obstructive coronary artery disease (CAD) stratified by CFR surviving free from the 4-component MACE during long-term follow-up. **(C)** Kaplan-Meier analysis showing percentage of women stratified by coronary blood flow (CBF) surviving free from the 4-component MACE during long-term follow-up. **(D)** Kaplan-Meier analysis showing percentage of women with no obstructive CAD stratified by CBF surviving free from the 4-component MACE during long-term follow-up.

for traditional cardiovascular risk factors including age, history of hypertension, dyslipidemia, smoking status, and diabetes, a decrease of 0.1 in CFR was associated with an 8% increase in hazard of adverse cardiovascular events (HR: 1.08; 95% CI: 1.01 to 1.16; p = 0.036).

ENDOTHELIUM-DEPENDENT CORONARY MICROVASCULAR REACTIVITY IN RESPONSE TO IC-ACH. Mean CBF change was 79 ± 107%. Compared with resting CBF, change in CBF was normal (i.e., increased by ≥50%) in response to IC-Ach in 58 women (51%) and abnormal in 55 women (49%). Medication regimen at

FIGURE 3 Relationship Between Endothelium-Dependent Epicardial Coronary Function Stratified by Change in Coronary Artery CSA in Response to IC-Ach and Cardiovascular Events



(A) Kaplan-Meier analysis showing percentage of women surviving free from angina hospitalization during long-term follow-up. **(B)** Kaplan-Meier analysis showing percentage of women with no obstructive coronary artery disease surviving free from angina hospitalization during long-term follow-up. Abbreviations as in Figure 1.

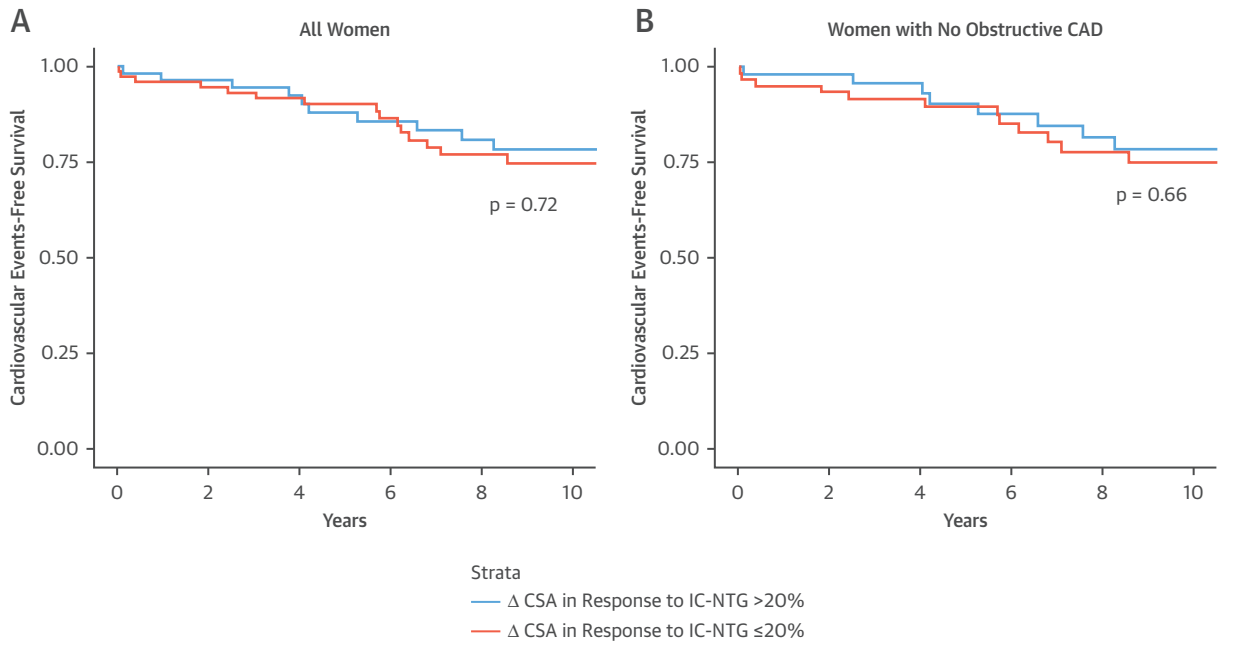
baseline was not different in women with an abnormal CBF response versus women with a normal response (Online Table 1). In unadjusted models, there was no association between CBF change and all-cause mortality. However, there was a trend toward higher rates of MACE in the abnormal group compared with those with normal CBF (24% vs. 10% events; p = 0.078) (Figure 2). Similarly, there was trend toward higher rates of the 3-component MACE in women with low CBF response versus those with normal response (20% vs. 7%; p = 0.055). After adjusting for age, history of hypertension, dyslipidemia, smoking status, diabetes, and CAD status, for each 10% reduction in CBF there was a 12% significant increased risk of all-cause mortality (HR: 1.12; 95% CI: 1.01 to 1.24; p = 0.038), 11% increase in the 4-component MACE (HR: 1.11; 95% CI: 1.03 to 1.20; p = 0.006), and 12% increase in the 3-component MACE (HR: 1.12; 95% CI: 1.03 to 1.22; p < 0.01).

When evaluating women with no obstructive disease, every 10% decrease in CBF was associated with a 23% increase in risk of all-cause mortality (HR: 1.23; 95% CI: 1.04 to 1.45; p = 0.015), a 16% excess risk for both the 4-component MACE (HR: 1.16; 95% CI: 1.06 to 1.27; p = 0.001), and 3-component MACE (HR: 1.16; 95% CI: 1.05 to 1.28; p = 0.003).

ENDOTHELIUM-DEPENDENT EPICARDIAL CR IN RESPONSE TO IC-ACH. Mean coronary artery CSA change in response to IC-Ach was 2.68 ± 24.5%. Fifty-seven women (45%) had a normal response (i.e., epicardial vasodilation), whereas 69 women (55%) had an abnormal response (i.e., epicardial vasoconstriction) in response to IC-Ach. Although there was no association between change in CSA in response to IC-Ach and mortality or MACE, abnormal response (change in CSA <0%) was associated with an increased rate of hospitalizations due to angina (for each 1% decrease in CSA in response to IC-Ach, there is an estimated 5% higher hazard of angina hospitalization [HR: 1.05; 95% CI: 1.02 to 1.07; p < 0.0001]). Similarly, epicardial vasoconstriction in response to IC-Ach in women with no obstructive CAD was associated with higher rates of hospitalization due to angina (HR: 1.05; 95% CI: 1.02 to 1.07; p = 0.0002) (Figure 3).

Non-endothelium-dependent epicardial CR in response to IC-NTG. Mean coronary artery CSA change in response to IC-NTG was 20.13 ± 24.51%. In 43% of the women who received IC-NTG (56 of 131 subjects), coronary artery CSA increased >20%. Changes in coronary artery CSA in response to nitroglycerin was not predictive of death, MACE, or angina hospitalization (Figure 4).

FIGURE 4 Relationship Between Endothelium-Independent Epicardial Coronary Function Stratified by Change in Coronary Artery CSA in Response to IC-NTG and Cardiovascular Events



(A) Kaplan-Meier analysis showing the percentage of women surviving free from the 4-component MACE during long-term follow-up. **(B)** Kaplan-Meier analysis showing the percentage of women with no obstructive CAD surviving free from the 4-component MACE during long-term follow-up. Abbreviations as in **Figures 1 and 2**.

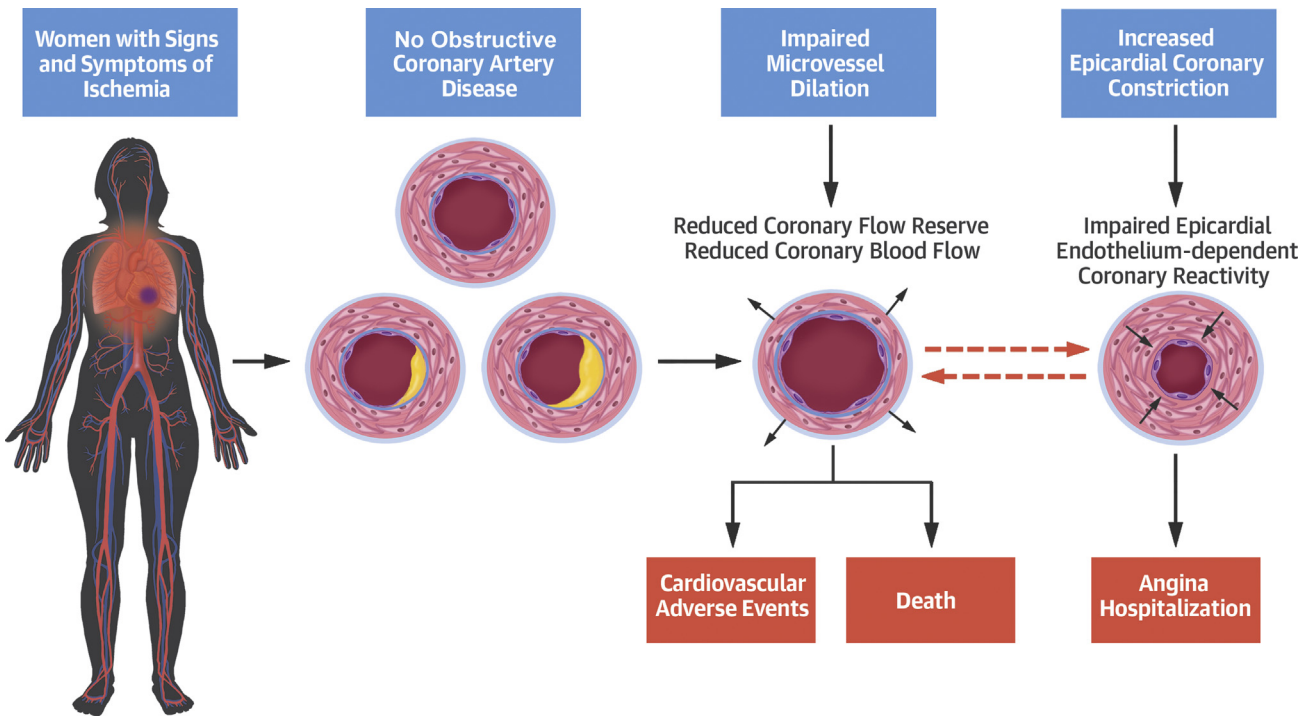
DISCUSSION

On longer-term follow-up among women with signs and symptoms of ischemia, we found that impaired endothelium and non-endothelium-dependent coronary microvascular reactivity predicts adverse cardiovascular events. Abnormal response to endothelium-dependent pathways in the microvasculature also predicts increased mortality on long-term follow-up when adjusted for various cardiovascular risk factors. In addition, impaired epicardial endothelium-dependent CR was associated with increased angina hospitalizations. Lastly, we noted no relationship between response to IC-NTG and outcomes.

These data highlight the prognostic importance of impaired CR on long-term outcomes. Given the relatively young age of this cohort, identifying patients who are at higher risk due to impaired compared with normal reactivity becomes of paramount importance, specifically in women with no obstructive CAD (**Central Illustration**). Our study extends the findings in previous publications that CBF regulation might contribute to development and progression of CAD (1,11,18) and that impaired endothelium and non-endothelium-dependent CR predicts MACE beyond angiographic CAD severity and traditional cardiovascular risk factors (9,11). We add to the existing knowledge base by showing an association between coronary endothelium-dependent microvascular reactivity as assessed by CBF and long-term MACE and its robust association among women with no evidence of obstructive CAD.

The relationship between impaired endothelium-dependent CR and adverse cardiovascular events has been demonstrated previously, including in patients with no obstructive CAD (1,11,18-20). The mechanism of this relationship is complex. Based on in vitro and animal models of atherosclerosis, impaired endothelium-dependent CR is associated with rapid progression of atherosclerosis, and increased plaque burden and rupture (19,21-24). This may be in part due to a decrease in bioavailability of nitric oxide and an increase in endothelial adhesion molecules for monocytes, which could lead to inflammation of the vasculature wall, loss of vascular

CENTRAL ILLUSTRATION **Women With Signs and Symptoms of Ischemia With No Obstructive Coronary Artery Disease and the Potential Role of Coronary Reactivity Testing**



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Women with no obstructive coronary artery disease and the potential role of coronary reactivity testing to identify those at higher risk for adverse events.

function, progression of atherosclerosis, and plaque rupture (25–27). In our cohort of women, after adjusting for traditional cardiovascular risk factors, we found impaired endothelium-dependent microvascular reactivity predicts all-cause mortality and MACE. Our results are similar to Suwaidi et al. (18), which suggested impaired coronary blood flow in response to IC-Ach as a measure of endothelium-dependent microvascular reactivity is associated with development of adverse cardiovascular events.

Several studies have assessed the impact of abnormal CFR on prognosis in both obstructive and nonobstructive CAD patients (28–31). From the WISE study, we reported that among women undergoing invasive assessment of CFR, a value of <2.32 is associated with increased risk of cardiovascular death, MI, stroke, and HF hospitalization over an average of 5.4 years of follow-up (9). Our current analysis shows a persistent relationship between abnormal CFR and major adverse cardiovascular events over longer-term follow-up.

Hospitalizations for recurrent angina carry morbidity and are associated with significant health care costs (13). We previously found that 20% of 883 WISE participants with no obstructive CAD and 38% to 55% with 1-vessel to 3-vessel CAD were hospitalized for chest pain through 5 years of follow-up. Angina hospitalization was around 2-fold higher in women with no obstructive CAD compared with those with 1-vessel disease after 1-year follow-up (13). In the current study, we showed a significant association between impaired endothelium-dependent epicardial CR in response to IC-Ach and hospitalization due to angina. These findings highlight the need for identifying patients with an objective cause for symptoms of angina such as abnormal CR and to appropriately follow and treat these patients to avoid recurrent hospitalizations.

The predominant effect of nitroglycerin is on the smooth muscles in the epicardial coronary arteries (32), likely due to lack of sulfhydryl groups in small coronary arterioles (sulfhydryl groups are required

for conversion of nitroglycerin to its active metabolite) (33). We did not find an association between endothelium-independent epicardial CR response to nitroglycerin and cardiovascular adverse events. This is in line with multiple previous reports which also failed to show an association (11,20).

Recently, Ford et al. (34) showed that pathway-specific medical therapy guided by invasive CR testing led to reduction in angina severity and significant improvement in quality of life compared with patients who received standard care. The main clinical implication of our findings is to endorse efforts toward reliably identifying patients who have angina due to impaired CR. In current practice, efforts toward routine invasive assessment of CR are hampered by time, expertise, and cost. Though these procedures are relatively safe, they require experienced operators familiar with the protocols and techniques. Validation of simpler invasive protocols and noninvasive tools would be needed to appropriately diagnose the majority of these patients.

Our study should be interpreted in the context of strengths and limitations. The strength of this study is the long-term follow-up in relatively low-risk patients compared with previous studies that included higher-risk patients with significant CAD (1,30). In addition, previous studies included few women (18,35). The current study is an extension of previous studies addressing the relationship between CR and adverse outcomes in low-risk patients with no significant CAD. Furthermore, despite the relative small sample size for the number of covariates required in the adjustment model, we performed comprehensive adjustments in our comparisons, which add confidence to our findings.

STUDY LIMITATIONS. First, the cohort is limited to patients pre-determined to undergo coronary angiography based on inclusion and exclusion criteria. Second, CR testing results were from a single testing period, which may not necessarily reflect the status of the coronary artery over time. In addition, most of the women in our cohort underwent testing for multiple reactivity pathways. In women with >1 impaired pathway, it is unknown which testing modality is the best predictor of adverse cardiovascular events. In this study, among the women with no obstructive CAD, only a minority were treated, the women with events conversely had higher use of calcium channel blockers, nitrates, and statin, but not angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, aspirin, or beta-blockers, perhaps related to therapeutic uncertainty in the group (Online Tables 2 and 3). Medication use in an observational study is always confounded, challenging to present concisely, and difficult to interpret. Recently, a stratified medical therapy guided by diagnostic procedure showed improvement in angina and quality of life in patients with nonobstructive CAD (34). Additionally, we were limited by the absence of advanced IC imaging techniques to assess the extent of atherosclerosis. And lastly, CR testing is an invasive procedure that requires experienced operators. It is usually performed in centers specialized in vascular function testing.

CONCLUSIONS

When evaluating longer-term outcomes, impaired coronary microvascular reactivity predicts adverse cardiovascular outcomes. Abnormal endothelium-dependent epicardial CR was associated with increase rate of angina hospitalizations in women with signs and symptoms of ischemia, including those with no angiographic evidence of obstructive coronary artery disease. Evaluation of CR can identify those at higher risk of adverse outcomes in the absence of significant CAD. Future research should evaluate feasible, preferably noninvasive, and cost-effective strategies to assess CR in clinical practice.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In women with symptoms and signs of myocardial ischemia, impaired coronary microvascular function is associated with adverse cardiovascular outcomes.

TRANSLATIONAL OUTLOOK: Further studies are needed to better understand the therapeutic implications of abnormal coronary reactivity in women with myocardial ischemia.

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KEY WORDS cardiovascular outcome, coronary flow reserve, coronary reactivity, endothelial function, microvasculature

APPENDIX For supplemental tables, please see the online version of this paper.