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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 half of women with suspected myocardial ischemia have no obstructive CAD, and abnormal coronary reactivity (CR) is commonly found.

Objectives: We 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 Women's Ischemia Syndrome Evaluation (WISE).

Methods: Women (n=224) with signs and symptoms of ischemia underwent CR testing. Coronary flow reserve (CFR) and coronary blood flow (CBF) were obtained to test microvascular function, while epicardial CR was tested by coronary dilation response to intracoronary (IC) acetylcholine and IC-nitroglycerine. All-cause mortality, major adverse cardiovascular events

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(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: We identified 129 events during the follow-up period. Low CFR was predictor of increased MACE rate (HR 1.06; 95% CI 1.01–1.12, $p=0.021$), while low CBF was associated with increased risk of mortality (HR=1.12; 95% CI 1.01–1.24, $p=0.038$) and MACE (HR= 1.11; 95% CI 1.03–1.20, $p=0.006$) 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 1.02–1.07, $p<0.0001$). There was no association between epicardial IC-nitroglycerine 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.

Condensed abstract: Currently as many as half of women with suspected myocardial ischemia undergoing clinically indicated coronary angiography have no obstructive CAD, yet abnormal epicardial and microvascular coronary reactivity is commonly found. In this study, we investigated the relationship between microvascular, epicardial coronary reactivity and clinical cardiovascular outcome. We found impaired coronary microvascular function predicts adverse cardiovascular outcomes in women with signs and symptoms of ischemia. Evaluation of coronary reactivity can identify those at higher risk of adverse outcomes in the absence of significant CAD.

Keywords

coronary reactivity; endothelial function; microvasculature; coronary flow reserve; cardiovascular outcome

Introduction

Prior work that included predominantly men with obstructive coronary artery disease (CAD), abnormal coronary reactivity testing in a non-obstructed epicardial coronary artery predicted adverse outcomes (1). Currently as many as 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).

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 (3–5 year) adverse outcomes, predominantly angina hospitalization, compared to 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 with signs and symptoms of ischemia but no obstructive CAD incurred similar short-term health care costs compared to patients with obstructive CAD (13).

The original WISE study includes up to 10-yr follow-up, therefore we prospectively investigated epicardial and microvascular coronary reactivity 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 Women's Ischemia Syndrome Evaluation (WISE).

Methods

We studied women with signs and symptoms of ischemia who were enrolled in the National Heart, Lung, and Blood Institute (NHLBI) - Women's Ischemia Syndrome Evaluation (WISE) from 1996 to 2000, as previously described(14). The WISE 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.

Coronary Reactivity Testing

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

1. Non-endothelium dependent microvascular reactivity was assessed using intracoronary bolus injections of incremental doses of adenosine (18 mcg and 36 mcg). 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 intracoronary acetylcholine infusion (IC-Ach) 0.182 $\mu\text{g/ml}$ (10⁻⁶ mol/L) at 2mL/min for 3 minutes. This was followed by infusion of 18.2 $\mu\text{g/ml}$ (10⁻⁴mol/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 $\mu\text{g/ml}$ IC-Ach was used for safety purposes to make sure no significant coronary spasm in response to IC-Ach occurs. Therefore, only the 18.2 $\mu\text{g/ml}$ IC-Ach data are reported. Coronary angiography was obtained after the infusion completed. Endothelium-dependent epicardial coronary reactivity was assessed by calculating the percentage in coronary cross-sectional area change in response to IC-Ach (change in epicardial cross-sectional area >0% is considered normal), while endothelium-dependent microvascular reactivity was evaluated by calculating the

change in coronary blood flow (CBF) (change in CBF \geq 50% is considered normal).

3. Non-endothelium-dependent epicardial coronary reactivity was assessed using intra-coronary nitroglycerin (IC-NTG) injection. Coronary angiography was obtained after each injection to measure coronary artery diameter and calculate coronary cross-sectional area (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 coronary diameter measured 5 mm distal to the tip of the Doppler wire. CBF was calculated using the equation $CBF = CSA \times AV \times 0.5$ (16) at rest and in response to IC-Ach. Change in CBF was calculated as: $(CBF_{peak} - CBF_{rest} / CBF_{rest}) \times 100$. 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 one investigator masked to all other patient data at the WISE angiographic core laboratory (Rhode Island Hospital, Providence, RI) 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 (NDI) 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 two 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.

Statistical Analysis

Clinical variables were summarized using mean \pm standard deviation 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 three event types: (1) overall mortality, (2) 4-component MACE, (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 coronary reactivity testing variables alone, as well as separate models to adjust the association of coronary reactivity 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, NC).

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 median follow-up duration of 9.7 years. Two-hundred (89%) subjects underwent CFR evaluation, 126 (56%) underwent evaluation of endothelium-dependent epicardial coronary reactivity testing using coronary cross-sectional area change in response to IC-Ach, 113 (50%) subjects underwent endothelium-dependent microvascular reactivity testing using CBF change in response to IC-Ach and 131 (58%) subjects received IC-NTG for evaluation of non-endothelium-dependent epicardial coronary reactivity. Most women underwent evaluation of multiple coronary reactivity pathways (Figure 1), related to testing feasibility, vasoactive medication tolerance and safety. We identified 77 (38%) women with abnormal CFR, 55 (49%) with abnormal CBF, while 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 $20\%–50\%$); and 19% had significant CAD (defined as $>50\%$). During follow-up, there were 32 deaths, eighteen (56%) of them 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 Intracoronary Adenosine

Mean CFR was 2.56 ± 0.76 and 123 out of 200 (62%) subjects had normal CFR (> 2.32). There was no difference in medication regimen between women with CFR > 2.32 ; and those with CFR < 2.32 (S1. supplemental table). There was no difference in all-cause mortality rate between normal and abnormal CFR (13% versus 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 to 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 (HR 1.06; 95% CI 1.01–1.12, $p=0.021$). This association remained significant after adjusting for age, history of hypertension, dyslipidemia, smoking status, diabetes, and CAD status (HR=1.06; 95% CI 1.004–1.12, $p=0.035$). Following adjustment, low CFR was not significantly associated with the 3-component MACE (HR 1.06; 95% CI 0.99–1.14, $p=0.064$).

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 to those with normal CFR (23% versus 12%; $p=0.03$). After adjusting 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 1.01–1.16, p=0.036).

Endothelium-dependent Coronary Microvascular Reactivity in Response to Intracoronary Acetylcholine

Mean CBF change was $79 \pm 107\%$. Compared to resting CBF, change in CBF was normal (i.e. increase by $\geq 50\%$) in response to IC-Ach in 58 women (51%) and abnormal in 55 women (49%). Medication regimen at baseline was not different in women with abnormal CBF response versus women with normal response (S1. supplemental table). 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 to those with normal CBF (24% versus 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% versus 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 1.01–1.24, p=0.038), 11% increase in the 4-component MACE (HR=1.11; 95% CI 1.03–1.20, p=0.006), and 12% increase in the 3-component MACE (HR=1.12; 95% CI 1.03–1.22, 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 1.04–1.45, p=0.015), a 16% excess risk for both the 4-component MACE (HR = 1.16; 95% CI 1.06–1.27, p=0.001), and 3-component MACE (HR = 1.16; 95% CI 1.05–1.28, p=0.003).

Endothelium-dependent Epicardial Coronary Reactivity in Response to Intracoronary Acetylcholine

Mean coronary artery cross-sectional area change in response to IC-Ach was $2.68 \pm 24.5\%$. Fifty-seven women (45%) had normal response (i.e. epicardial vasodilatation), while 69 women (55%) had abnormal response (i.e. epicardial vasoconstriction) in response to IC-Ach. Although there was no association between change in cross-sectional area in response to IC-Ach and mortality or MACE, abnormal response (change in cross-sectional area <0%) was associated with an increased rate of hospitalizations due to angina [for each 1% decrease in cross-sectional area in response to IC-Ach, there is an estimated 5% higher hazard of angina hospitalization (HR=1.05; 95% CI 1.02–1.07, 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 1.02–1.07, p=0.0002) (Figure 3).

Non-Endothelium Dependent Epicardial Coronary Reactivity in Response to Intracoronary Nitroglycerine—Mean coronary artery cross-sectional area change in response to IC-NTG was $20.13 \pm 24.51\%$. In 43% (56 out of 131 subjects) of the women who received IC-NTG, coronary artery cross-sectional area increased $>20\%$. Changes in coronary artery cross-sectional area in response to nitroglycerine was not predictive of death, MACE or angina hospitalization (Figure 4).

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 coronary reactivity 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 coronary reactivity on long-term outcomes. Given the relatively young age of this cohort, identifying patients who are at higher risk due to impaired compared to normal reactivity becomes of paramount importance, specifically in women with no obstructive CAD (Central Illustration). Our study extends the findings in previous publications that coronary blood flow regulation might contribute to development and progression of CAD (1,11,18) and that impaired endothelium and non-endothelium dependent coronary reactivity 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 coronary reactivity 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 coronary reactivity is associated with rapid progression of atherosclerosis, increased plaque burden and rupture (19,21–24). This may be in part due to decrease in bioavailability of nitric oxide (NO) and increase in endothelial adhesion molecules for monocytes which could lead to inflammation of the vasculature wall, loss of vascular 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 non-obstructive 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%–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 to 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 coronary reactivity 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 coronary reactivity and to appropriately follow and treat these patients to avoid recurrent hospitalizations.

The predominant effect of nitroglycerine 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 nitroglycerine to its active metabolite) (33). We did not find an association between endothelium-independent epicardial coronary reactivity response to nitroglycerine 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. showed that pathway specific medical therapy guided by invasive coronary reactivity testing led to reduction in angina severity and significant improvement in quality of life compared to patients received standard care (34). The main clinical implication of our findings is to endorse efforts towards reliably identifying patients who have angina due to impaired coronary reactivity. In current practice, efforts towards routine invasive assessment of coronary reactivity 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 non-invasive 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 to previous studies which 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 coronary reactivity and adverse outcomes in low risk patients with no significant CAD. Furthermore, despite the relative small sample size for the number of co-variates required in the adjustment model, we performed comprehensive adjustments in our comparisons, which add confidence to our findings. There are several limitations which should be noted. First, the cohort is limited to patients pre-determined to undergo coronary angiography based on inclusion and exclusion criteria. Second, coronary reactivity 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 pathways, it is unknown which testing modality is best predictor of adverse cardiovascular events. In this study, among the women with non-obstructive CAD, only a minority were treated, the women with events conversely had higher use of calcium channel blockers, nitrates and statin, but not ACE/ARB, aspirin or beta blocker, perhaps related to therapeutic uncertainty in the group (S2 and S3. supplemental tables). Medication use in 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 non-obstructive CAD (34). Additionally, we were limited by the absence of advanced intra-coronary imaging techniques to assess extent of atherosclerosis. And lastly, coronary reactivity testing is an invasive procedure that requires experienced operators. It is usually performed in centers specialized in vascular function testing.

In conclusion, when evaluating longer-term outcomes, impaired coronary microvascular reactivity predicts adverse cardiovascular outcomes. While abnormal endothelium-dependent epicardial coronary reactivity 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 coronary reactivity can identify those at higher risk of adverse outcomes in the absence of significant CAD. Future research should evaluate feasible, preferably non-invasive, and cost-effective strategies to assess coronary reactivity in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CAD	Coronary artery disease
CFR	Coronary flow reserve
CBF	Coronary blood flow
IC	Intra-coronary
MACE	Major adverse cardiovascular events
WISE	Women's Ischemia Syndrome Evaluation

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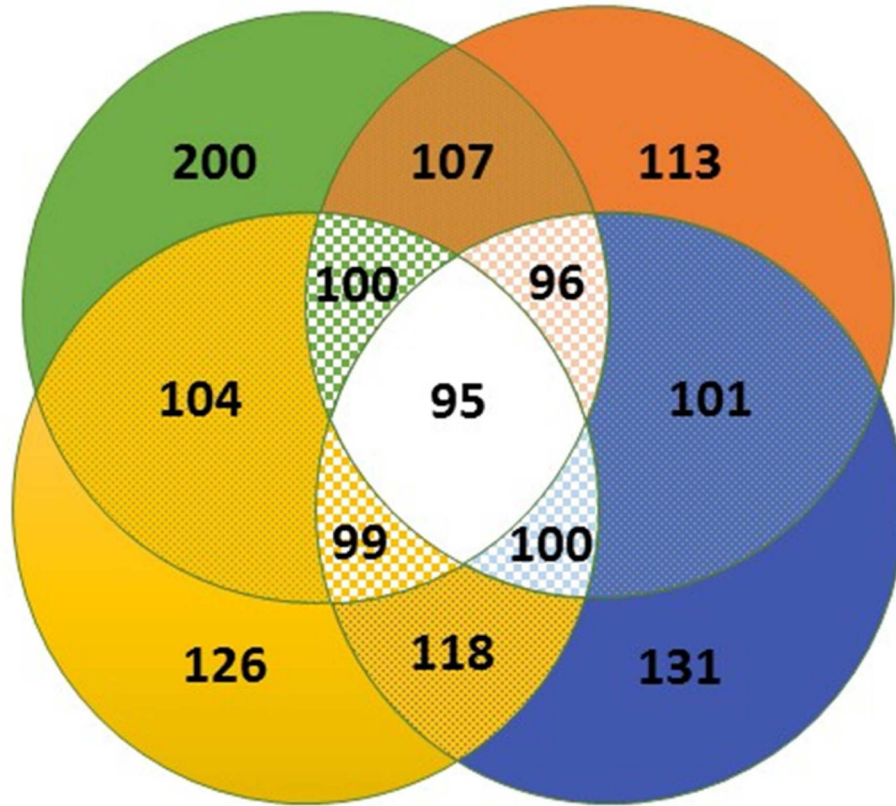
CLINICAL PERSPECTIVES

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.



- Coronary Flow Reserve (CFR) (N=200)**
- Coronary Blood Flow (CBF) (N= 113)**
- Change in CSA in response to (IC-Ach) (N=126)**
- Change in CSA in response to (IC-NTG) (N=131)**

Figure 1. Distribution of selected coronary reactivity testing in 224 women with signs and symptoms of ischemia.
 Most women underwent evaluation of more than one coronary reactivity pathway. Green color represents women who underwent evaluation of non-endothelium dependent microvascular reactivity using coronary flow reserve (CFR); orange color represents women who underwent evaluation of endothelium dependent microvascular reactivity using coronary blood flow (CBF); yellow color represents women who underwent evaluation of endothelium dependent epicardial coronary reactivity using change in coronary artery cross sectional area in response to intracoronary acetylcholine (IC-Ach); while blue color represents women who underwent evaluation of non-endothelium dependent epicardial coronary reactivity using change in coronary artery cross sectional area in response to intracoronary nitroglycerine (IC-NTG).

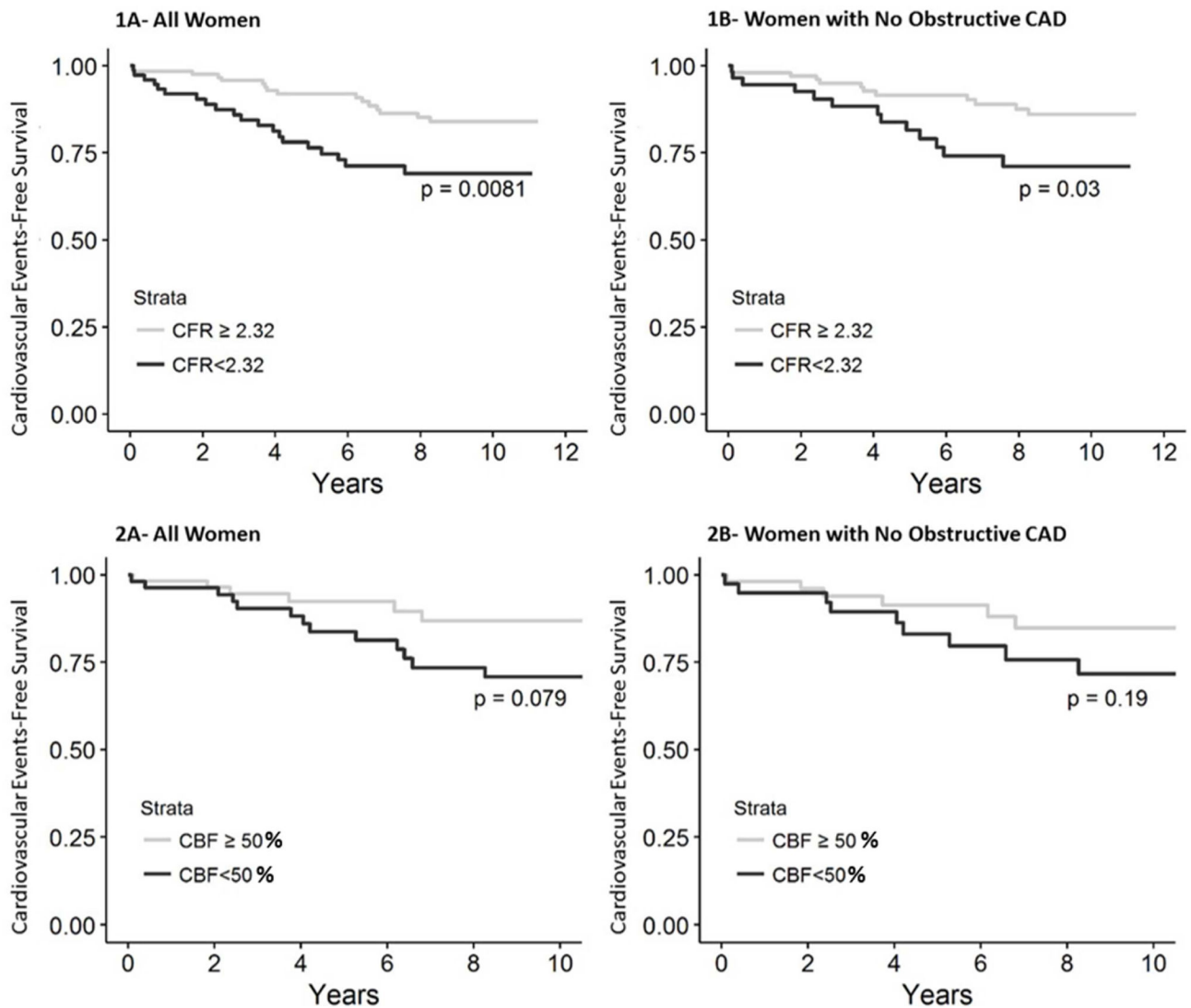


Figure 2: Relationship between coronary microvascular function and cardiovascular events. (1A) Kaplan-Meier analysis showing percentage of women surviving free from the 4-component major adverse cardiovascular event (MACE) including cardiovascular death, nonfatal MI, nonfatal stroke and HF during long-term follow-up stratified by coronary flow reserve (CFR). (1B) Kaplan-Meier analysis showing percentage of women with no obstructive coronary artery disease stratified by CFR surviving free from the 4-component MACE during long-term follow-up. (2A) 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. (2B) Kaplan-Meier analysis showing percentage of women with no obstructive coronary artery disease stratified by CBF surviving free from the 4-component MACE during long-term follow-up.

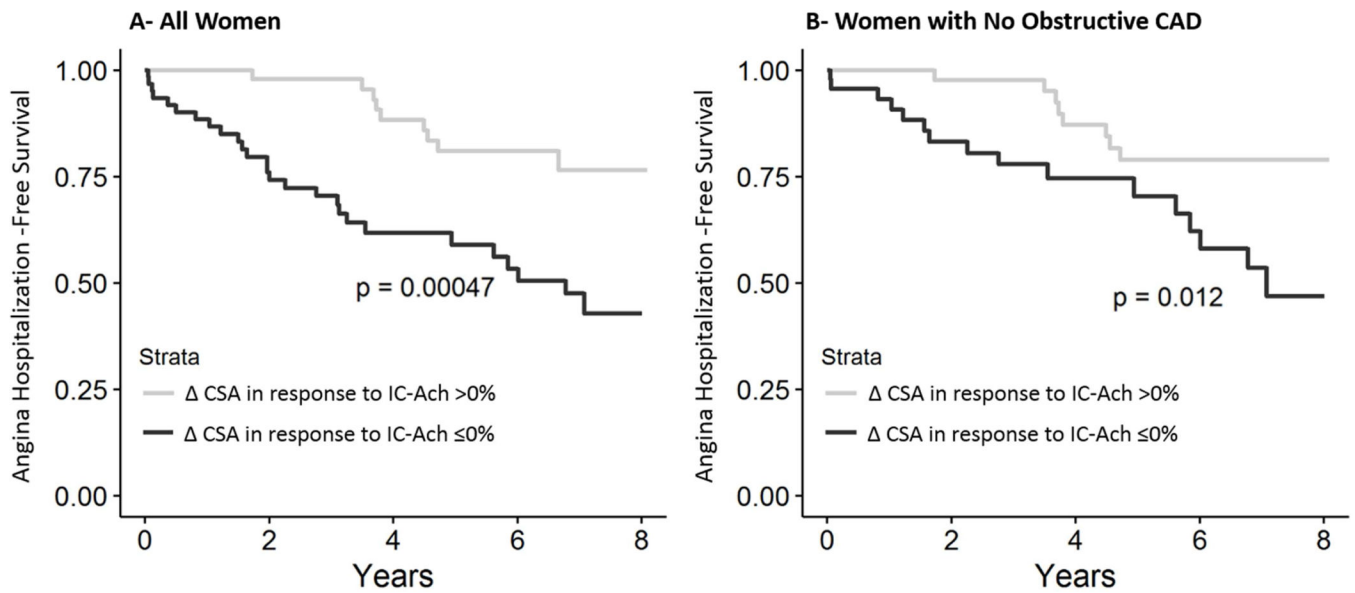


Figure 3. Relationship between endothelium-dependent epicardial coronary function stratified by change in coronary artery cross-sectional area (CSA) in response to intra-coronary acetylcholine (IC-Ach) and cardiovascular events.

(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.

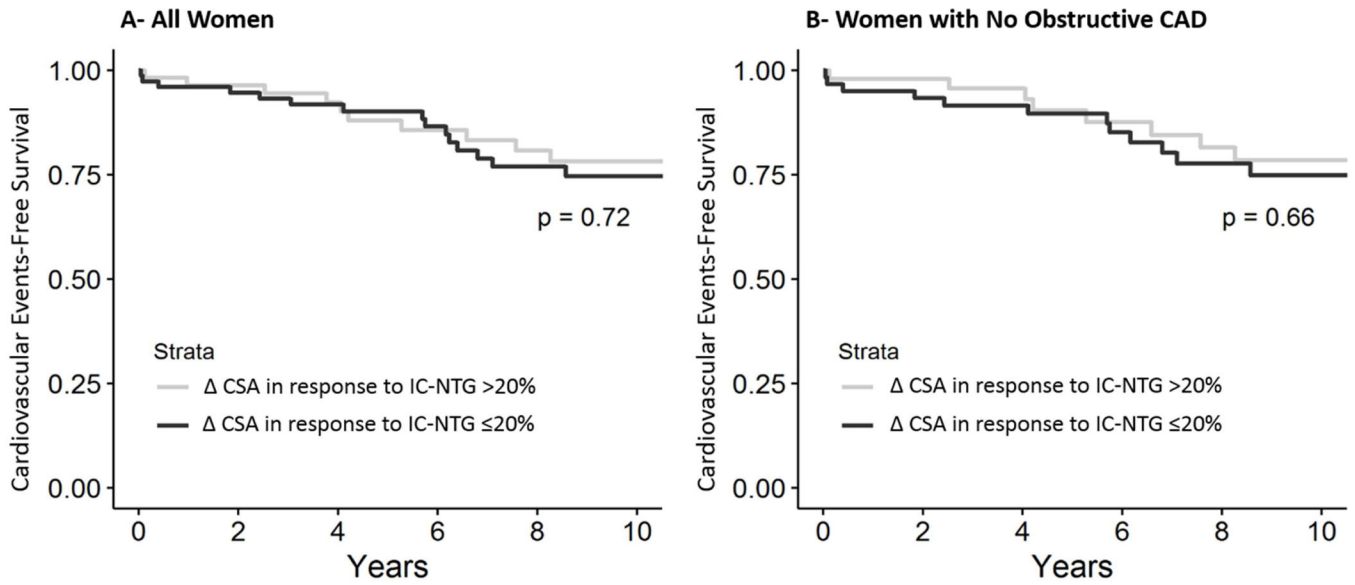
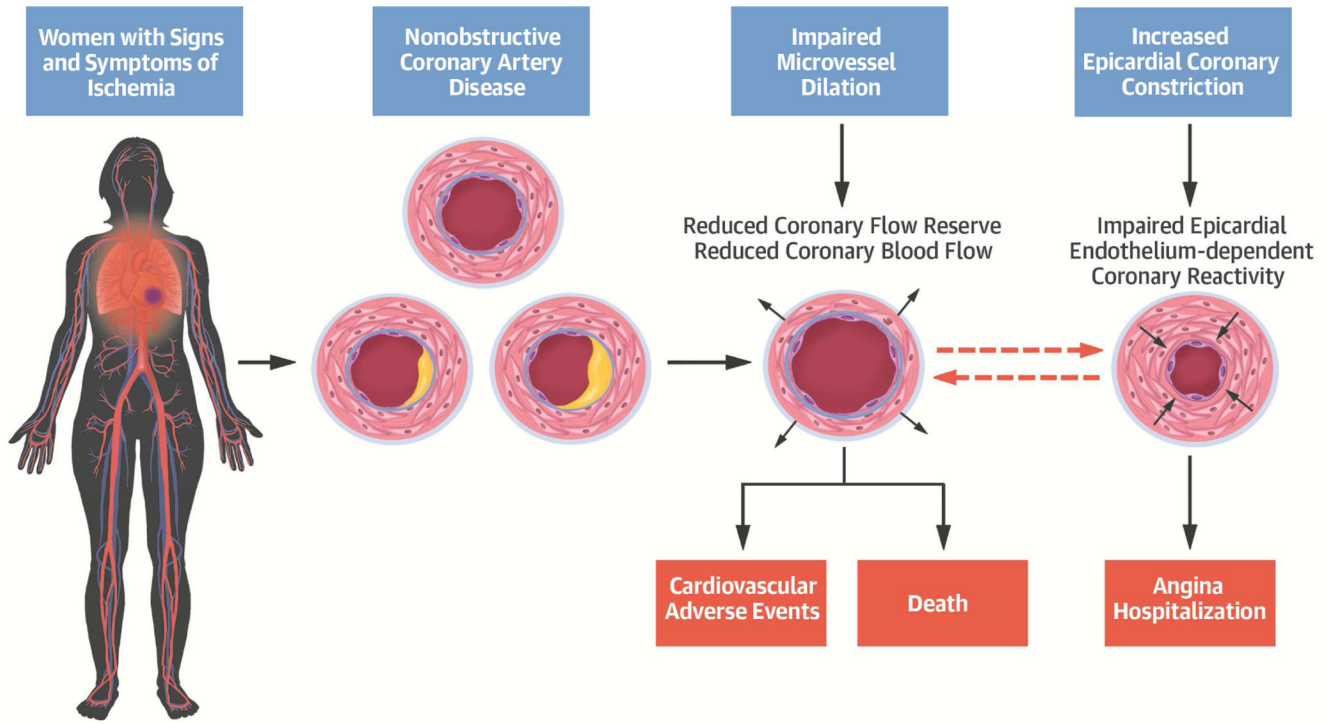


Figure 4. Relationship between endothelium-independent epicardial coronary function stratified by change in coronary artery cross-sectional area (CSA) in response to intra-coronary nitroglycerin (IC-NTG) and cardiovascular events.

(A) Kaplan-Meier analysis showing percentage of women surviving free from the 4-component MACE during long-term follow-up. (B) Kaplan-Meier analysis showing percentage of women with no obstructive coronary artery disease surviving free from the 4-component MACE during long-term follow-up.



Central Illustration. Women with signs and symptoms of ischemia with no obstructive coronary artery disease and the potential role of coronary reactivity testing. women with no obstructive coronary artery disease (CAD) and potential role of coronary reactivity testing to identify those at higher risk for adverse events. CFR: coronary flow reserve, CBF: coronary blood flow.

Table 1:

Baseline Characteristics of the Women (N=224)

Age, years (mean±SD)	55±11
Race	
White, n (%)	181 (81%)
African-American, n (%)	40 (18%)
Others, n (%)	3 (1%)
History of Diabetes, n (%)	49 (22%)
History of Hypertension, n (%)	125 (56%)
Family History Coronary Disease, n (%)	142 (66%)
Dyslipidemia, n (%)	105 (52%)
CAD minimal or none, n (%)	179 (81%)
Current smoking, n (%)	44 (20%)
Coronary Hemodynamics	
CFR, mean±SD (N=200)	2.56 0.76
CBF (%) (N=113)	79 ± 107%
CSA (IC-Ach) (%) (N=126)	2.68 ± 24.45%
CSA (IC-NTG) (%) (N=131)	20.13 ± 24.51%
Baseline Medications	
ACE-I/ARB	54 (24%)
Beta Blockers	65 (29%)
CCD	58 (26%)
Nitrates	47 (21%)
Statins	38 (17%)
Aspirin	110 (50%)
Vasodilators	15 (7%)

CAD: coronary artery disease, CFR: coronary flow reserve, CBF: coronary blood flow, CSA: coronary cross-sectional area, IC-Ach: intra-coronary acetylcholine infusion, IC-NTG: intra-coronary nitroglycerine, ACE-I: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, CCB: Calcium channel blockers.

Table 2:

Total Adverse Events during Median Follow-Up of 9.7 years

Events	Number of Events (n=224)	Number of 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

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