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Design, Methodology and Baseline characteristics of the Women's Ischemia Syndrome Evaluation Coronary Vascular Dysfunction (WISE-CVD)

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Abstract

Background: A significant number of women with signs and symptoms of ischemia with no obstructive coronary artery disease (INOCA) have coronary vascular dysfunction, detected by invasive coronary reactivity testing (CRT). However, the noninvasive assessment of coronary vascular dysfunction has been limited.

Methods: The Women's Ischemia Syndrome Evaluation - Coronary Vascular Dysfunction (WISE-CVD) was a prospective study of women with suspected INOCA, aimed to investigate whether: 1) cardiac magnetic resonance imaging (CMRI) abnormalities in left ventricular morphology and function and myocardial perfusion predicted CRT measured coronary microvascular dysfunction; 2) these persistent CMRI abnormalities at 1-year follow-up predict persistent symptoms of ischemia; and 3) these CMRI abnormalities predict cardiovascular outcomes. By design a sample size of 375 women undergoing clinically indicated invasive coronary angiography for suspected INOCA was projected to complete baseline CMRI, *a priori* subgroup of 200 clinically indicated CRT, and *a priori* subgroup of 200 repeat 1-year follow-up CMRI.

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Results: A total of 437 women enrolled between 2008 to 2015, 374 completed baseline CMRI, 279 completed CRT, and 214 completed 1-year follow-up CMRI. Mean age was 55 ± 11 years, 93% had 20-50% coronary stenosis and 7% had <20% stenosis by angiography.

Conclusions: The WISE-CVD study investigates the utility of noninvasive CMRI to predict coronary vascular dysfunction in comparison to invasive coronary reactivity testing (CRT), and the prognostic value of CMRI abnormalities for persistent symptoms of ischemia and cardiovascular outcomes in women with INOCA. WISE-CVD will provide new understanding of a non-invasive imaging modality for future clinical trials.

Background

Individuals with signs and symptoms of ischemia and no obstructive coronary artery disease (INOCA) are increasingly recognized, with an estimated prevalence of 3 to 4 million, with women making up about 70% of this population in the US.¹⁻⁵ Women experience more frequent angina, more office visits, more avoidable hospitalizations, higher healthcare costs, and higher rates of heart failure hospitalization, myocardial infarction (MI), and mortality compared to men despite a lesser extent and severity of obstructive CAD.⁶⁻⁸

The Women's Ischemia Syndrome Evaluation - Coronary Vascular Dysfunction (WISE-CVD) ([NCT00832702](#)) study design builds on important findings from the original NHLBI-Women's Ischemia Syndrome Evaluation (WISE) ([NCT00832702](#)) cohort and addresses critical new research needs defined in the WISE/NHLBI 2002 workshop.^{9, 10} The original WISE cohort documented a high prevalence (47%) of coronary microvascular dysfunction (CMD) in women with INOCA,¹¹⁻¹³ defined as macrovascular or microvascular nonendothelial or endothelial dysfunction that limits myocardial perfusion.¹⁴ The diagnosis of CMD in women with INOCA is associated with higher rates of cardiovascular events, including MI, hospitalization for heart failure, and cardiac death compared to INOCA without evidence of CMD.^{13, 15-28}

Invasive and noninvasive modalities can be used to diagnose CMD. Invasive coronary reactivity testing (CRT) is considered the clinical gold-standard to assess coronary vascular function, where acetylcholine is used to assess endothelial dependent coronary function and adenosine and nitroglycerin are used to assess non-endothelial dependent function. A decrease in coronary flow reserve (CFR) in response to adenosine during CRT has been found to predict adverse outcomes in women with INOCA.¹¹⁻¹³ Echocardiographic-Doppler of the left anterior descending artery and myocardial positron emission tomography (PET) can be used to noninvasively measure CFR velocity. However, echocardiographic-doppler is technically challenging and limited to lean patients, and PET although it provides more definitive data requires exposure to ionizing radiation and is limited by availability of tracers.^{20, 27, 29-32} Myocardial perfusion cardiac magnetic resonance imaging (CMRI) with first-pass gadolinium enhancement overcomes many of these limitations (minimally invasive, relatively body habitus independent, free of ionizing radiation), and can be used to noninvasively detect myocardial hypoperfusion and semi-quantitatively measure myocardial perfusion reserve index (MPRI).³³⁻³⁷ In addition, CMRI's excellent spatial resolution provides additive insight into ventricular morphology and function, as well as late-

gadolinium enhancement (LGE) myocardial scar detection; providing critical pathophysiologic insight. However, studies on the use of this noninvasive imaging modality in the INOCA population are limited.

Study Aims

The WISE-CVD study aims to investigate whether: 1) cardiac magnetic resonance imaging (CMRI) abnormalities in left ventricular morphology and function and myocardial perfusion predicts coronary vascular dysfunction measured invasively 2) these persistent CMRI abnormalities at 1-year follow-up predict persistent symptoms of ischemia; and 3) these CMRI abnormalities predict cardiovascular outcomes in a cohort of women with suspected INOCA. In this report, we present the study design, methodology and baseline characteristics from the WISE-CVD study.

Methods

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I. Study Design

The WISE-CVD ([NCT00832702](#)) is a prospective cohort study of women with suspected INOCA undergoing clinically indicated invasive coronary angiography at Cedars-Sinai Medical Center (CSMC), Los Angeles, and the University of Florida (UF), Gainesville. The protocol was approved by the IRBs each site and all participants provided written informed consent.

Women were enrolled after clinically indicated invasive coronary angiography ordered by treating physician demonstrated no obstructive CAD (defined as <50% diameter stenosis in epicardial arteries). The protocol was designed with a total sample size of 375 women with INOCA to complete baseline CMRI and be followed longitudinally. From this primary cohort, *a priori* subgroup analysis was planned with a target sample size of at least 200 women to undergo clinically indicated invasive CRT. Women were selected for and the CRT

subgroup based on clinical judgment by treating physician due to persistent angina, angina refractory to empiric therapy, hospitalization for angina, and/or myocardial infarction after coronary angiography. A second *a priori* subgroup analysis was planned with a sample size of at least 200 women to undergo repeat CMRI at 1-year follow-up. Repeat CMRI at 1-year follow-up was offered to all participants and performed consecutively until target was reached. The study schema in Figure 1 illustrates the actual number of participants that were enrolled and completed baseline CMRI, CRT and repeat 1-year follow-up CMRI.

II. Study Inclusion and Exclusion Criteria

Inclusion criteria: women with signs and symptoms of ischemia undergoing clinically indicated coronary angiography; age ≥ 21 years and competent to give informed consent.

Exclusion criteria: acute coronary syndrome (defined by the ACC/AHA criteria),³⁸ acute MI; participants with concurrent cardiogenic shock or requiring inotropic or intra-aortic balloon support; prior or planned percutaneous coronary intervention or CABG; primary valvular heart disease clearly indicating need for valve repair or replacement; chest pain with a non-ischemic etiology (e.g. pericarditis, pneumonia, esophageal spasm); and conditions that preclude accurate or safe testing, or prognostic follow-up, specifically: contraindications to CMRI (e.g., implantable cardioverter defibrillator, pacemaker, untreatable claustrophobia, known angioedema, severe renal impairment (eGFR <45 mL/min)); prior non-cardiac illness with an estimated life expectancy <4 years. Women with obstructive CAD defined as $>50\%$ luminal diameter stenosis in ≥ 1 epicardial coronary artery, assessed visually at the time of angiography were not included.

III. Data Collection Procedures

The schedule of data collection and study procedures at enrollment and follow-up are shown in Table 1. At enrollment baseline data collected included demographics, socioeconomic status, medical history, cardiac risk factors, and medications. Data was not collected on the reasons/indications for performing coronary angiography by the treating physicians.

Detailed information on chest pain symptoms included the 19-item Seattle Angina Questionnaire (SAQ) which measures health status across 5 domains including physical limitation, angina stability, angina frequency, treatment satisfaction and quality of life.^{39–42} Psychosocial questionnaires administered included: environmental stress, trait anxiety, anger expression, social support, Cardiac Anxiety Questionnaire, Center for Epidemiological Studies Depression Scale, Positive Health Expectations, Life Orientation Test.^{43–48} Quality of life was measured by the Medical Outcomes Study-Short Form-12 Health Survey, Postmenopausal Estrogen-Progestin Intervention questionnaire (PEPI-Q) scores and the Duke Activity Status Inventory (DASI).^{49, 50} These were completed at baseline and 6-weeks and will be collected annually indefinitely. Physical examination at baseline visit included weight, height, waist-hip ratio, body mass index, blood pressure, heart rate, 12-lead ECG. Blood serum, plasma, and urine samples were also collected at baseline visit.

IV. Invasive Coronary Reactivity Testing Protocol

Long-acting nitrates, ranolazine, short-acting calcium-channel blockers, α -blockers, β -blockers, aldosterone inhibitors and angiotensin-converting enzyme-II/angiotensin-II-receptor antagonists were held for 24 hours, and long-acting calcium-channel blockers were

held for 48 hours before CRT. Sublingual nitroglycerin was held for 4 hours before testing, and participants were caffeine-free and nicotine-free for 24 hours before CRT.

All cases were done through femoral approach. Baseline angiogram was performed before Doppler wire was inserted in preselected oblique projection that minimized overlap and foreshortening of left anterior descending coronary artery (LAD). A Judkins or pigtail 6 or 7 French catheter was inserted into the left ventricle through femoral venous access and the aortic valve was crossed to measure end-diastolic pressure at rest, prior to initiation of CRT. Participants were heparinized to achieve an activating clotting time greater than 200 seconds and a Doppler guidewire (0.014-inch FlowWire, Volcano Corporation, California, USA) was positioned in the midportion of the LAD as the preferred vessel, followed by the left circumflex coronary artery. Figure 2 illustrates coronary reactivity tests performed and pathways tested as per our previously established protocol which includes: ^{24, 37}

(1) Non-endothelial dependent microvascular function: Assessed from coronary flow response to sequential boluses of intracoronary adenosine (18-36 µg), used to achieve maximal hyperemia. CFR was derived from the ratio of the average peak velocity (APV) of blood flow at hyperemia and the APV at rest for each bolus since we had previously shown that this velocity ratio closely predicted volumetric CFR.¹² Abnormal CFR was defined as CFR <2.5 in response to adenosine.¹²

(2) Endothelial dependent micro- and macro-vascular function: Assessed by the administration of the intra-coronary acetylcholine (ACH) at increasing concentrations of 0.182 µg/ml (10^{-6}) and 18.2 µg/mL (10^{-4}) infused over 3 minutes intracoronary. The 10^{-6} mol/L was used for safety purposes to ensure no significant coronary spasm in response to intracoronary acetylcholine. Blood flow recordings were made after acetylcholine 10^{-4} infusion and angiography was repeated to assess diameter change. Pulse-wave Doppler flow spectra dose was used to calculate APV. Vessel diameter was calculated 5 mm distal to the tip of the Doppler wire. Coronary blood flow (CBF) response to acetylcholine was calculated from APV and vessel diameter by the ratio of CBF after maximum dose of ACH and CBF at baseline using the following equation: $CBF = \pi (APV/2)(\text{vessel diameter}/2)^2$. Abnormal microvascular endothelial dysfunction was defined as an increase in CBF 50% in response to acetylcholine (CBF). Abnormal macrovascular endothelial coronary function was measured as the percentage change in epicardial coronary artery diameter in response to a maximum dose of ACH, where ACH 0% (no change or constriction of vessel) was considered abnormal.⁵¹

(3) Endothelial-dependent coronary vascular function in response to cold pressor testing was performed by wrapping an ice pack around the hand and forearm or the forehead for 2 minutes after documenting 4°C. Change in epicardial coronary diameter and CBF in response to cold pressor testing was assessed as described above. Normal response to cold pressor test is $12.0 \pm 1.0\%$ increase in coronary vessel diameter by angiographic assessment,⁵² however there are no clear cutoff for abnormal response.

(4) Non-endothelial dependent macrovascular function: Intracoronary nitroglycerin (200 µg) was injected. Abnormal non-endothelial macrovascular function was defined as a change in epicardial coronary artery diameter $\geq 20\%$ in response to nitroglycerin (NTG).

Hemodynamic data was obtained before and after each coronary reactivity test. Coronary angiogram for quantitative coronary angiography (QCA) were obtained after each coronary reactivity test. A return of coronary flow velocity to baseline was documented before proceeding to next coronary reactivity test.

V. Coronary Angiography and CRT Core Laboratory Analyses

Angiograms were analyzed by an experienced investigator (R. David Anderson) masked to all other participant data at the WISE angiographic core laboratory at University of Florida, Gainesville. The core laboratory quantitatively assessed the extent and severity of CAD and classified each coronary artery as no CAD ($<20\%$ stenosis), no obstructive CAD (20-50% stenosis), obstructive CAD ($\geq 50\%$), and “not analyzable”. Additionally, quantitative assessment of the presence, severity and complexity of epicardial coronary stenosis and a coronary severity score was calculated based on stenosis severity weighted by proximal location using previously published methods⁵³.

CRT measures were also interpreted by an expert reader (John Petersen) experienced in performance and interpretation of CRT, blinded to participant information and clinical data, using a dedicated core laboratory, in accordance with our published methods.⁵⁴

VI. Cardiac Magnetic Resonance Imaging Protocol

Same medication withdrawal and caffeine avoidance protocol as described above for CRT was used. CMRI was completed on a 1.5-Tesla MR scanner (Avanto, Siemens Healthcare, Erlangen, Germany) with ECG-gating and a phased-array cardiac-torso coil (CP Body Array Flex, Siemens Healthcare, Erlangen, Germany) using standardized protocol that includes assessment of left ventricular (LV) morphology and function, pharmacologic vasodilatory stress, rest and cold pressor stress first-pass contrast myocardial perfusion imaging using gadolinium-based contrast (Figure 3)^{37, 55, 56}

Myocardial perfusion imaging: Pharmacologic vasodilatory stress was performed using adenosine infused at a dose of 140 µg/kg/min intravenously (IV) over 2 minutes, before first-pass perfusion imaging, and continued until completion of the perfusion imaging data acquisition. For subjects with contraindication to adenosine, 400 µg intravenous bolus of regadenoson was given before first-pass perfusion imaging. First-pass contrast stress perfusion imaging was performed using 0.05 mmol/L/kg of gadolinium-diethylene triamine penta-acetic acid (Gd-DTPA, Gadodiamide, Omniscan, Amersham, Piscataway, NJ) administered (2-minutes after adenosine or 60-seconds after regadenoson) via a second IV catheter into the arm contralateral to the stress agent at a rate of 4 ml/s, followed by 30 ml saline flush at the same rate. Rest perfusion imaging was performed with the same contrast settings at least 10 minutes later to allow for contrast washout. First-pass contrast perfusion was repeated for cold pressor testing as described. Cold pressor stress utilized an ice pack wrapped around either the hand or forearm contralateral to the contrast injection, or the

forehead for 2 minutes prior to first-pass perfusion imaging and removed after completion of the first pass perfusion imaging data acquisition. For subjects where regadenoson was used as stress agent the sequence used was rest perfusion, cold pressor stress perfusion, followed by regadenoson stress perfusion.

All perfusion images were obtained in short-axis image planes grouped around the mid ventricle, to avoid partial volume effect from being too basal or too apical in slice position with the following parameters: Gradient echo-EPI hybrid sequence, TR per slice 128 ms, TE 1.07 ms, receiver bandwidth 1420 Hz/pixel, echo train length 4, readout flip angle 20°, slice thickness 8 mm, image matrix 160×79 pixels, in-plane resolution 2.7×2.2 mm², parallel imaging factor 2, imaging 3 slices every heartbeat. In the event of a peak stress heart rate of >120 bpm, 2 slices are obtained during stress first-pass imaging with exclusion of the apical LV slice position.

Delayed contrast enhancement: Immediately following the last perfusion imaging acquisition, an additional dose of 0.05 mmol/L/kg contrast was administered, bringing the total administered dose to 0.2 mmol/L/Kg. Images were obtained in 10–12 short axis slices, one horizontal long axis slice, and one vertical long axis slice in the same positions as the LV function cine images; acquired from 5–10 minutes after the last gadolinium injection to identify regional fibrosis. A single shot turbo based sequence was used with HR based TR and TE minimized at 0.98 ms. A “TI scout” image was obtained followed by single shot inversion recovery TrueFISP images.

VII. CMRI Core Laboratory Analyses

CMRI data were interpreted by computer-based analysis by an experienced reader in performance and interpretation of CMRI (Louise E. J. Thomson) masked to clinical and CRT data in a dedicated core laboratory using our published methods.^{37, 56, 57} CAAS MRV 3.4 (PIE Medical Imaging) software was used for analysis of the MPRI, LV mass and volume. The endocardial and epicardial contours were manually defined and adjusted to sample data from LV myocardium alone.

For MPRI analysis, care was taken to exclude blood pool and to exclude any linear dark rim artifact at the LV cavity/endocardial border. The LV cavity region of interest was manually adjusted to include the region of maximal signal intensity within the cavity and to exclude papillary muscle. In the case of motion, there was frame by frame adjustment of contours. Relative upslope (RU) defined as the ratio between the maximum upslope of the first-pass myocardial perfusion time-intensity curve divided by the maximum upslope of the first-pass LV cavity time-intensity curve. MPRI is calculated as stress RU divided by rest RU. An American Heart Association 16-segment model was used (true apex not imaged) where MPRI is the average of 16 segments. In the case of 2-slice image data being acquired because of high stress heart rate, data were recorded for 12-segments, and MPRI is the average of 12-segments. Subendocardial MPRI, subepicardial MPRI, whole (transmural) MPRI were calculated.

Epicardial and endocardial borders of short-axis cine images were manually traced to derive LV volumes used to generate volume-time curves and LV mass. Volume-time curve

parameters including peak ejection rate, peak ejection time, peak filling rate, and peak filling time were obtained using post-processing software. Stroke volume was calculated as end-diastolic volume minus end-systolic. Ejection fraction was calculated as stroke volume divided by end-diastolic volume.

Late gadolinium enhancement (LGE) detection quantification was performed by a single experienced operator using associated post-processing software (QMass, Medis). The extent of LGE was quantified using the full width at half-maximum method. LGE type was defined as typical scar pattern when scar was subendocardial or transmural and localized to a coronary artery distribution and atypical scar pattern when midmyocardial or epicardial.⁵⁷

VIII. Follow-Up Procedures

As mentioned above, a subgroup of 214 women completed a repeat CMRI at 1-year follow-up. A standardized protocol-directed follow-up was conducted by experienced research staff through direct, telephone and/or mail contact at 6 weeks, 1 year, and will continue to be conducted annually. The study was designed with for 4.5-year follow-up which is now extended to indefinite follow-up. Specifically, information collected on changes in demographics, risk factors, co-morbid conditions, hormonal/reproductive status, medication use, SAQ and DASI. Major cardiovascular events (death, MI, congestive heart failure (CHF), stroke), cardiovascular related hospitalization, cardiovascular procedures (noninvasive cardiac testing and diagnostic or revascularization procedures) after baseline visit are assessed through patient report at follow-ups and confirmed through review of associated medical records. For cause of death hospital record and/or death certificate are reviewed. Resource utilization and costs includes annual costs for cardiovascular hospitalizations, coronary revascularizations and angiography, outpatient testing, and outpatient visits.

IX. Laboratory Analyses

Blood serum, plasma and urine were collected at enrollment. The following markers were analyzed at core laboratories using validated methods: lipoproteins (fasting total plasma cholesterol, triglycerides (TG), and high-density lipoprotein C (HDL-C), reproductive hormones (estradiol, bioavailable estradiol, estrone, progesterone, follicle stimulating hormone (FSH), luteinizing hormone (LH)), oxidative stress (cystine and glutathione), endothelial progenitor cells (EPCs), N-terminal pro-type B-natriuretic peptide (NT-proBNP), ultra-high sensitivity cardiac troponin I (u-hs-cTnI) and urine albumin-creatinine ratio. All laboratory analyses were completed centrally at designated core laboratories. Supplemental materials contain further details on assays used.

X. Statistical Methods and Sample Size Calculations

Primary variables for all specific aims include 3 CRT measures of coronary vascular function (adenosine CFR, acetylcholine CBF and coronary diameter changes) as dichotomous variables based on cutoffs described above and as continuous variables and 7 primary CMRI measures including left ventricular morphology and function variables (LV end diastolic volume, end systolic volume, stroke volume, cardiac output, ejection fraction, myocardial wall thickness), myocardial perfusion (MPRI), and presence of LGE.

In aim 1 we evaluated the prognostic utility of CMRI measures in comparison to the CRT measures of coronary vascular dysfunction. With the proposed sample size of 200 receiving both CMRI and CRT testing using pilot data, a correlation of 0.30 was projected to be detected with 90% power, while a minimum correlation of 0.27 with 80% power. Based on pilot data we further assumed a total sample size of 200 women, and an alpha of 0.015 would permit multiple testing (primarily MPRI with 3 CRT variables). With 120 women (60%) having normal CFR and 80 (40%) having abnormal CFR, we would have moderate effect sizes of 0.47 at 80% power and 0.55 at 90% power for the MPRI.

For aim 2 to test the hypothesis that persistent CMRI abnormalities (specifically MPRI) at 1-year follow-up predict persistent symptoms of ischemia, a sample size of 200 women will achieve 80% power at a two-tailed significance level of 0.05 to detect a change in the probability of persistent symptoms from 0.50 at a mean value of the CMRI MPRI to 0.60 when the MPRI increases by one standard deviation above the mean. This change corresponds to an odds ratio of 1.49. If the R^2 for covariates is 0.20 then this odds ratio increases to 1.56. In pilot data the mean and standard deviation for the CMRI MPRI was 126 ± 51 ; thus, a difference of 51 in the CMRI MPRI would detect an absolute difference of 10% in the rate of persistent symptoms.

Aim 3 tests the hypothesis that CMRI abnormalities (specifically MPRI) predicts cardiovascular events. Primary outcomes include cardiovascular events defined as: death, death or nonfatal myocardial infarction (MI), major cardiovascular event (death, MI, CHF, or stroke), and all events (death, MI, CHF, stroke, hospitalization for angina, hospitalization for other cardiovascular event). Death was classified as cardiovascular or non-cardiovascular related, MI was classified as new pathologic Q waves;^{58, 59} or non Q-wave MI, in the setting of diagnostic elevation of cardiac enzymes.⁶⁰ Secondary outcomes: resource utilization and costs, chest pain symptoms, quality of life, functional capacity. Analysis by Doyle et al. provided data for sample size calculation for testing the prognostic value of the CMRI MPRI in women with no obstructive CAD.⁶¹ Annual event rates were calculated under two assumptions: 1) 15% of the women classified as “high risk” by MPRI; and 2) 30% of women classified as high risk. When only 15% of the cohort is diagnosed as “high risk” we will require an event rate of 6.5% in high risk women to be detected at 80% power with a two-sided alpha of 0.05, this rate drops to 5.5% when 30% of the women are diagnosed as “high risk.” These differences amount to hazard ratios of 3.33 and 2.23 and minimum detectable effect sizes of 0.32 and 0.25, respectively.

Results

As shown in Figure 1, a total of 437 women with signs and symptoms of ischemia undergoing clinically indicated coronary angiography and found to have non-obstructive CAD were enrolled at CSMC (n=242) and UF (n=195). Among the enrolled participants, 63 were excluded resulting in 374 (100% of planned enrollment) total participants completing baseline CMRI at both sites. Reasons for exclusion included: 22 self-withdrawal, 31 declined baseline CMRI, and 10 unable to perform CMRI (low GFR, contrast allergy, inability to fit into scanner.).

A subgroup of 279 (140% of planned enrollment) participants underwent clinically indicated CRT. Figure 4 demonstrates the number of women who underwent both baseline CMRI and CRT. For the women in this subgroup who completed both CRT and CMRI the average number of days between CRT and CMRI was 47 days. A second subgroup of 214 (107% of planned enrollment) participants underwent repeat CMRI at 1-year follow-up. First year prognosis follow-up was completed in 321 (75%), and yearly prognosis follow-up is ongoing at each site.

Baseline demographics and characteristics of women enrolled are shown in Table 2. Mean age was 55 ± 11 years, 87.4% had <50% CAD and 6.8% no CAD on angiogram. Three (1%) participants were re-classified as having significant (>50%) CAD by core lab after study enrollment (and were subsequently excluded from further analysis). SAQ demonstrates moderately severe angina at baseline.

Results for CRT testing and the number of participants with abnormal pathways is shown in Table 3. We also show that there is no group difference between participants that only had CRT because they were unable to complete CMRI and those that had both CRT and CMRI completed.

Among the 374 baseline CMRI exams performed, 7 (2%) were non-interpretable due to poor image quality and an additional 11 (3%) did not have complete CMRI due to pharmacologic stress or contrast delivery error, or uninterpretable left ventricular measurements. Among the 214 that completed 1-year follow-up CMRI, only 1 was non-interpretable due to poor image quality. For 40 (11%) participants, the CMRI core lab detected that half dose gadolinium defined as <0.03 mmol/L/Kg was erroneously administered at one site during the baseline CMRI. Participants who received half dose gadolinium for the baseline CMRI, also received half dose gadolinium for the 1-year follow-up CMRI for consistency, unless otherwise indicated. CMRI data analyses were conducted and MPRI was not significantly different in women who received full vs. half dose gadolinium (1.86 ± 0.49 vs. 1.82 ± 0.51 , p-value 0.62). For participants undergoing baseline CMRI with pharmacologic vasodilatory stress, adenosine was used in 252 (69%) participants and regadenoson in 112 (31%). Baseline CMRI variables are shown in Table 4. The total group mean MPRI was 1.9 ± 0.5 and 6.8% had evidence of LGE scar.

Discussion

This report summarizes the study design, methodology and baseline characteristics of the WISE-CVD study. Recruitment and study procedures are now complete, with patient follow-up ongoing. This trial successfully met its recruitment goals for all three major aims, achieving the *a priori* defined sample sizes necessary for adequate power, with low drop-out rates, despite the technical challenges associated with the invasive CRT and non-invasive CMRI study end-points. We also showed that cold pressor testing is feasible during CRT and CMRI. Additionally, our CMRI core lab detected an error in gadolinium dosing, demonstrating quality control.

INOCA in women represents a unique and difficult challenge for clinicians, due to greater symptom burden, functional disability, and greater risk for adverse outcomes compared to asymptomatic women.⁶² In our cohort of women with INOCA we found moderately severe angina at baseline. We also found that more than half the cohort had at least one abnormal CRT pathway suggesting coronary vascular dysfunction. The WISE-CVD study will address key knowledge gaps that currently exist in the diagnosis of coronary vascular function in women with INOCA including: What is the utility of CMRI for identifying coronary vascular dysfunction including CMD in women with INOCA in comparison to invasive CRT testing? What factors, including myocardial perfusion, left ventricular structure and function, myocardial LGE scar predict coronary vascular dysfunction? Can CMRI predict prognosis in terms of persistent symptoms, need for additional testing and cardiovascular outcomes?

Registry data indicates a significant gender gap, with substantially fewer women receiving evidence-based treatment following hospitalization for suspected ischemia,⁶³ likely due to the diagnostic and therapeutic uncertainty in this group. Investigation on the predictive value of noninvasive CMRI in comparison to invasive CRT to detect coronary vascular dysfunction in women with INOCA, and the prognostic value of CMRI for prediction of symptoms and cardiovascular outcomes is currently limited (Table 5).^{33–35, 61, 64–71} Our study will provide a platform for clinical trials to test therapeutic interventions in appropriately powered studies. This noninvasive imaging modality can be of great use in therapeutic trials to assess the change in myocardial perfusion in response to treatment as was done in our ranolazine trial,⁷² and could be expanded to other medical treatments being evaluated in INOCA. It would also be a useful tool to determine if response to treatment is different in those with evidence of coronary vascular dysfunction compared to those without. It would also be of great value in novel interventions, such as stem-cell therapy targeting coronary vascular dysfunction to follow change in currently after is and before challenging over time that is challenging with repeat invasive testing. Additionally, these results will provide practicing physicians with the ability to use a noninvasive assessment strategy in the clinical care of women with INOCA and potentially improve outcomes.

Our study has limitations. WISE-CVD was designed stemming from the results of the original WISE study commissioned by the NHLNBI and only included women with INOCA. Future studies should include men with INOCA and explore differences in INOCA and coronary vascular function in women compared to men as commissioned by the new NIH Sex as a Biological Variable policy. Additionally, women in the CRT subgroup were enrolled based on clinically indicated CRT and therefore this cohort is subject to referral bias.

Conclusions

The WISE-CVD study investigates the utility of noninvasive CMRI imaging to predict coronary vascular dysfunction in comparison to invasive CRT, and the prognostic value of CMRI abnormalities for persistent symptoms of ischemia and cardiovascular outcomes in women with INOCA. The WISE-CVD will provide new understanding of a non-invasive platform for future clinical trials planning for therapeutic interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Women's Ischemia Syndrome Evaluation -Coronary Vascular Dysfunction (WISE-CVD) study
- Women with ischemia with no obstructive coronary artery disease
- Utility of noninvasive CMRI to predict coronary vascular dysfunction
- Prognostic value of CMRI abnormalities for persistent symptoms of ischemia
- Prognostic value of CMRI abnormalities for cardiovascular outcomes

Figure 1. WISE-CVD Study Schematic

Study design with actual number of women enrolled and included in each subgroup. CSMC, Cedars-Sinai Medical Center; UF, University of Florida; CMRI, cardiac magnetic resonance imaging.

Nonendothelial-Dependent	Endothelial-Dependent		Nonendothelial-Dependent
Microvascular function	Microvascular function	Macrovascular function	Macrovascular function
Adenosine 18 and 36 mcg IC injections	Acetylcholine (ACH) 0.182 mcg and 18.2 mcg IC infusions and Cold Pressor Testing (CPT)		Nitroglycerin (NTG) 200 mcg IC injection
Definitions for Abnormal Coronary Reactivity Test			
Coronary Flow Reserve CFR <2.5	Δ Coronary Blood Flow Δ CBF $\leq$ 50%	Coronary Diameter Change Δ ACH $\leq$ 0% Δ CPT $\leq$ 0% (No change in diameter or constriction)	Coronary Diameter Change Δ NTG $\leq$ 20% (Less than 20% dilation)

Figure 2. Invasive Coronary Reactivity Testing Protocol and Definitions for Coronary Microvascular and Macrovascular Dysfunction

CFR, coronary flow reserve; CBF, coronary blood flow

Figure 3. Cardiac Magnetic Resonance Imaging Adenosine and Regadenoson Protocols
 LGE, late gadolinium enhancement; LVOT, left ventricular outflow tract

Figure 4. Schematic of WISE-CVD subgroups

CMRI, cardiac magnetic resonance imaging; CRT, coronary reactivity testing

Table 1.**WISE-CVD Data Collection**

Assessment	Study Time Points		
	Baseline	6-weeks	Annually
Demographics	X		X
Medical & Symptom History	X		X
Medication Log	X	X	X
Seattle Angina Questionnaire	X	X	X
Duke Activity Status Inventory	X		X
Psychosocial/Quality of Life Assessment	X		X
Physical Examination, Electrocardiogram	X		
Blood and Urine Collection	X		
Quantitative Coronary Angiography	X		
Cardiac Magnetic Resonance Imaging; n=374	X		
Follow-up events, procedures, new diagnosis		X	X
Subgroups			
Coronary Reactivity Testing; n=279	X		
1-year follow-up cardiac magnetic resonance imaging; n=214	X		1-year follow up only

Table 2.**WISE-CVD Baseline Demographic and Clinical Characteristics**

Baseline Demographics and Clinical Characteristics	Total cohort (n=429)	Baseline CMRI (n=374)	p-value
Age	55 ± 11	55 ± 11	0.1
Race			0.3
White/Not Hispanic	306 (75.9%)	281 (76.4%)	
Black/African American	31 (7.7%)	26 (7.1%)	
Hispanic/Latin	31 (7.7%)	28 (7.6%)	
Asian/Pacific Islander	14 (3.5%)	14 (3.8%)	
Other	21 (4.9%)	19 (5.1%)	
Annual Income			0.004
\$0-\$49,000	137 (35.2%)	117 (32.9%)	
\$50,000-99,000	98 (25.2%)	91 (25.6%)	
\$100,000+	154 (39.6%)	148 (41.6%)	
Highest Level of Education			<0.001
Grade and High School	16 (4%)	11 (3%)	
High School Diploma	81 (20.1%)	65 (17.7%)	
Associate Degree to Doctorate	306 (75.9%)	292 (79.4%)	
Body Mass Index (kg/m ²)	28.3 ± 7.0	28.1 ± 6.9	0.1
Hypertension	155 (41.7%)	138 (40.7%)	0.3
Dyslipidemia	61 (19.4%)	55 (18.9%)	0.4
Diabetes Mellitus	48 (12.2%)	44 (12.2%)	1.0
Cardiovascular Disease	28 (7.5%)	26 (7.6%)	1.0
Smoking Status			0.1
Former	142 (35.3%)	132 (36%)	
Current	21 (5.2%)	16 (4.4%)	
Post-menopausal	289 (71.7%)	265 (72%)	0.7
History of Pregnancy	349 (87.3%)	317 (86.9%)	0.6
Adverse Pregnancy Outcome	84 (24.4%)	76 (24.3%)	1.0
Medications			
Statins	159 (40.7%)	152 (42.5%)	0.02
ACEI	76 (19.7%)	68 (19.4%)	0.7
ARB	26 (6.9%)	24 (7%)	1.0
Beta blockers	127 (32.7%)	119 (33.6%)	0.3
Calcium Channel Blockers	87 (22.7%)	81 (23.1%)	0.7
Diuretics	57 (14.7%)	51 (14.4%)	0.6
Vasodilators	17 (4.5%)	14 (4.1%)	0.2
Nitrates	119 (30.8%)	112 (31.7%)	0.2
Hormone Replacement Therapy	188 (47.6%)	176 (48.6%)	0.2
Seattle Angina Questionnaire:			
Angina Limitation	67.6 ± 23.9	67.6 ± 23.8	0.9
Angina Frequency	63.5 ± 25.8	63.4 ± 25.9	0.8

Baseline Demographics and Clinical Characteristics	Total cohort (n=429)	Baseline CMRI (n=374)	p-value
Angina Stability	47.4 ± 26.6	47.9 ± 26.3	0.3
Angina Treatment Satisfaction	69.4 ± 24.9	69.0 ± 25.0	0.3
Angina Quality of Life	49.8 ± 24.1	49.4 ± 23.9	0.2
Seattle Angina Questionnaire-7	60.5 ± 21.4	60.3 ± 21.7	0.5
Angiographic Coronary Severity Score	9.3 ± 4.2	9.4 ± 4.3	1.0
Angiographic Findings:			0.02
No CAD (<20% stenosis)	20 (6.8%)	20 (8.2%)	
No obstructive CAD (20-50% stenosis)	256 (87.4%)	209 (85.3%)	
Obstructive CAD (>50% stenosis)	3 (1.0%)	2 (0.8%)	

N (%) or Mean ± SD

Adverse pregnancy outcomes self-report history of preeclampsia, toxemia, high blood pressure in pregnancy and/or gestational diabetes. Seattle angina questionnaire subscales scored 0-100.^{39, 73} Angiographic coronary severity score 0-100 based on stenosis severity weighted by proximal location.⁵³ CAD, coronary artery disease; ACEI, Angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 3.**WISE-CVD Invasive Coronary Reactivity Testing**

	CRT only N=276	CRT and Baseline CMRI, N=231	p-value
Invasive Measures	Mean ± SD	Mean ± SD	
LVEDP	14.4 ± 5.0	14.3 ± 5.0	0.3
CFR	2.7 ± 0.6	2.7 ± 0.7	0.4
CBF	65.9 ± 85.2	70.8 ± 89.6	0.1
ACH	− 0.35 ± 15.0	− 0.22 ± 15.1	0.8
CPT	2.7 ± 12.4	2.8 ± 12.5	0.8
NTG	14.7 ± 13.7	14.9 ± 13.8	0.6
Abnormal CRT Pathway	N (%)	N (%)	
CFR < 2.5	97 (37.5)	81 (37.5)	1.0
CBF 50%	109 (54.0)	89 (51.7)	0.1
ACH 0%	115 (48.1)	95 (47.3)	0.6
CPT 0%	97 (42.9)	82 (43.2)	0.9
NTG 20%	155 (65.4)	132 (66.0)	0.5

CRT, coronary reactivity testing; CMRI, cardiac magnetic resonance imaging. LVEDP=Left Ventricle End-Diastolic Pressure; CFR=coronary flow reserve in response to adenosine; CBF=% coronary blood flow change in response to acetylcholine; ACH=% diameter change in response to acetylcholine; CPT diameter change in response to cold pressor test; NTG=% diameter change in response to nitroglycerin.

Table 4.**WISE-CVD CMRI Variables at Baseline Visit**

Baseline CMRI Variables	Mean $\pm$ SD or N (%) N=374
Rest Heart Rate (bpm)	68.6 $\pm$ 10.7
Peak Pharmacologic Stress Heart Rate (bpm)	99.6 $\pm$ 17.0
Rest SBP (mmHg)	130.4 $\pm$ 20.1
Peak Pharmacologic Stress SBP (mmHg)	132.8 $\pm$ 24.6
Rest DBP (mmHg)	63.8 $\pm$ 13.3
Peak Pharmacologic Stress DBP (mmHg)	62.5 $\pm$ 14.6
LV Ejection Fraction (%)	67.9 $\pm$ 7.1
LV End-Diastolic Volume (mL)	122.9 $\pm$ 24.5
LV End-Diastolic Volume Index	68.0 $\pm$ 12.5
LV End-Systolic Volume (mL)	39.9 $\pm$ 13.9
LV End-Systolic Volume Index	22.1 $\pm$ 7.5
LV Stroke Volume (mL)	82.6 $\pm$ 16.6
LV Mass (g)	92.6 $\pm$ 17.2
LV Mass Index	51.1 $\pm$ 7.1
LV Mass-Volume Ratio (g/mL)	0.8 $\pm$ 0.2
Peak Filling Rate	351.8 $\pm$ 98.7
Time to Peak Filling Rate	205.3 $\pm$ 84.2
Mean Myocardial Perfusion Reserve Index	1.9 $\pm$ 0.5
Late Gadolinium Enhancement Scar	25 (6.8%)

LV, left ventricular; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 5.

Summary of studies using CMRI in INOCA

Author and Year	Sample	Population	Method	End-points/Outcomes	Follow-up
Panting et al. 2002	20 (16F, 4M) 10 controls	Cardiac syndrome X (typical angina, abnormal stress test, normal coronary angiogram)	1.5T, adenosine stress, MPRI by semi-quantitative CMRI perfusion technique	MPRI in cardiac syndrome X vs. controls	N/A
Christiansen et al. 2006	23 (15F, 8M)	Chest pain, elevated troponin, minimal angiographic CAD	1.5T, LGE	Relation between LGE and cardiac event (MI, HF, angina)	4-28 months
Assomull et al. 2007	60 (17F, 43 M)	Troponin-positive chest pain and non-obstructive CAD	1.5T, LGE, T2	Diagnostic value of CMRI	3months
Vermeltfoort et al. 2007	20 (15F, 5 M)	Cardiac Syndrome X (angina, abnormal stress test and/or reversible perfusion defect on myocardial SPECT, normal coronary angiogram)	1.5T, adenosine stress, MPRI by semi-quantitative CMRI perfusion technique	MPRI in Cardiac Syndrome X	N/A
Lanza et al. 2008	18 (11F, 7 M) 10 controls	Cardiac Syndrome X (angina, ST segment depression on exercise stress test, normal coronary arteries by angiography)	1.5T, adenosine stress, semi-quantitative CMRI perfusion technique	Relation between abnormalities in myocardial perfusion and coronary microvascular dysfunction	N/A
Doyle et al. 2010	100 women	INOCA (symptoms of myocardial ischemia, no obstructive CAD by coronary angiography)	1.5T, dipyridamole stress, MPRI by semi-quantitative CMRI perfusion technique	All-cause mortality, MI, and angina hospitalization	34 ± 16 months
Ishimori et al. 2010	20 women, 10 controls	Women with SLE, anginal chest pain, no obstructive CAD	1.5T, adenosine stress, MPRI by semi-quantitative CMRI perfusion technique	MPRI in INOCA vs. controls	N/A
Melita et al. 2011	20 women	INOCA (angina, abnormal stress testing, no obstructive CAD on angiography)	1.5T, adenosine stress, MPRI by semi-quantitative CMRI perfusion technique	Change in MPRI in ranolazine vs. placebo groups	10 weeks
Karamitsos et al. 2012	18 women, 14 controls	Cardiac Syndrome X (chest pain, abnormal exercise treadmill test, normal coronary angiogram)	3.0T, adenosine stress, absolute quantification of MBF, LGE	MBF, LGE in cardiac syndrome X vs. controls	N/A
Shufelt et al. 2013	53 women, 12 controls	INOCA (angina, abnormal stress testing, no obstructive CAD on angiography) and coronary microvascular dysfunction by invasive CRT	1.5T, adenosine stress, MPRI by semi-quantitative CMRI perfusion technique	MPRI in INOCA vs. controls	N/A
Bairey Merz et al. 2016	128 women	symptoms, abnormal coronary reactivity testing, abnormal CMRI.	1.5T, adenosine stress, MPRI by semi-quantitative CMRI perfusion technique	Change in MPRI in ranolazine vs. placebo groups	2 weeks
Zorach et al. 2018	46 (34 F, 12 M), 20 controls	INOCA (angina, no obstructive CAD on angiography)	1.5T CMRI, regadenoson stress, MPRI by quantitative CMRI perfusion, T1, LGE	Comparison MPRI, MBF, T1 in INOCA vs. controls, Relationship between MPRI and T1, LGE.	N/A

INOCA, ischemia with no obstructive coronary artery disease; CAD, coronary artery disease; CMRI, cardiac magnetic resonance imaging; MPRI, myocardial perfusion reserve index; MBF, myocardial blood flow; LGE, late gadolinium enhancement; MI, myocardial infarction; HF, heart failure; SLE, systemic lupus erythematosus.