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ORIGINAL RESEARCH

# Temporal Trends in Angina, Myocardial Perfusion, and Left Ventricular Remodeling in Women With No Obstructive Coronary Artery Disease Over 1-Year Follow-Up: Results From WISE-CVD

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**BACKGROUND:** Women with ischemia and no obstructive coronary artery disease are increasingly recognized and found to be at risk for major adverse cardiovascular events.

**METHODS AND RESULTS:** In 214 women with suspected ischemia and no obstructive coronary artery disease who completed baseline and 1-year follow-up vasodilatory stress cardiac magnetic resonance imaging, we investigated temporal trends in angina (Seattle Angina Questionnaire [SAQ]), myocardial perfusion reserve index, blood pressure, and left ventricular (LV) remodeling and function from baseline to 1-year follow-up and explored associations between these different parameters. We observed concordant positive trends in 4/5 SAQ domains, SAQ-7, myocardial perfusion reserve index, blood pressure, LV mass, and LV mass-to-volume ratio. There was no association between SAQ-7 improvement and myocardial perfusion reserve index improvement over 1-year follow-up ($P$=0.1). Higher indexed LV end-diastolic volume and time to peak filling rate at baseline were associated with increased odds of clinically relevant SAQ-7 improvement (odds ratio [OR], 1.05; 95% CI, 1.0–1.1; and OR, 2.40; 95% CI, 1.1–5.0, respectively). Hypertension was associated with decreased odds of SAQ-7 improvement (OR, 0.41; 95% CI, 0.19–0.91).

**CONCLUSIONS:** In women with ischemia and no obstructive coronary artery disease clinically treated with cardiac medications over 1 year, we observed concurrent temporal trends toward improvement in SAQ, myocardial perfusion reserve index, blood pressure, LV mass, and LV mass-to volume ratio. We showed that abnormalities in LV morphology and diastolic function at baseline were predictive of clinically significant improvement in angina at follow-up, whereas history of hypertension was associated with lower odds. Future studies are needed to assess the mechanisms and treatments responsible for the improvements we observed.

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**Key Words:** angina ■ cardiovascular magnetic resonance imaging ■ ischemic heart disease ■ left ventricular remodeling ■ quality of life

Individuals presenting with signs and symptoms of myocardial ischemia and found to have no obstructive coronary artery disease on invasive coronary angiography, referred to as INOCA, are increasingly recognized.[1–4] INOCA is more common in women, with close to two thirds of women undergoing coronary

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## CLINICAL PERSPECTIVE

### What Is New?

- Women with ischemia and no obstructive coronary artery disease clinically treated with cardiac medications over 1 year have concurrent temporal trends toward improvement in angina, myocardial perfusion, and cardiac morphology and diastolic function.
- Abnormalities in left ventricular morphology and diastolic function at baseline were predictive of clinically significant improvement in angina at follow-up.
- History of hypertension was associated with lower odds of clinically significant improvement in angina at follow-up.

### What Are the Clinical Implications?

- Our findings suggest that in women with ischemia and no obstructive coronary artery disease, symptoms may be a good surrogate for those with more severe disease.
- Our findings support the use of noninvasive advanced cardiovascular imaging to follow changes in myocardial perfusion and cardiac remodeling in future ischemia and no obstructive coronary artery disease trials.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **CMRI** | cardiac magnetic resonance imaging |
| **INOCA** | ischemia and no obstructive coronary artery disease |
| **LV** | left ventricular |
| **MPRI** | myocardial perfusion reserve index |
| **SAQ** | Seattle Angina Questionnaire |
| **WISE** | Women's Ischemia Syndrome Evaluation |
| **WISE-CVD** | Women's Ischemia Syndrome Evaluation–Coronary Vascular Dysfunction |

angiography for suspected ischemic heart disease found to have no obstructive coronary artery disease.[5,6] Despite the absence of obstructive coronary artery disease, INOCA is associated with increased risk of major adverse cardiac events.[7–9] In the WISE (Women's Ischemic Syndrome Evaluation) study, women with INOCA had elevated rates of repeat angiography triggered by symptom burden and were 4 times more likely than men to be readmitted within 180 days with acute coronary syndrome/angina.[7,8]

Studies have evaluated progression of angina in women with INOCA and showed that persistence of chest pain at 1-year follow-up is associated with increased risk of major adverse cardiovascular events.[10–12] However, the progression of myocardial perfusion and left ventricular (LV) morphology and function over time in women with INOCA is not well described. Similarly, how changes in anginal symptoms, myocardial perfusion, and LV morphology and function are related over time in women with INOCA is poorly understood.

In the WISE-CVD (Women's Ischemia Syndrome Evaluation–Coronary Vascular Dysfunction) prospective study, we investigated temporal trends from baseline to 1-year follow-up in angina, myocardial perfusion, and LV remodeling and function in women with signs and symptoms suggestive of INOCA and the relationship between these changes.

## METHODS

### Study Design

Women were enrolled in the National Heart, Lung, and Blood Institute–sponsored WISE-CVD study (NCT00832702) after invasive coronary angiography ordered by the treating physician for signs and/or symptoms of ischemia demonstrated no obstructive coronary artery disease (defined as <50% diameter stenosis in epicardial arteries) as previously described.[13] Exclusion criteria included acute myocardial infarction within 30 days, planned percutaneous intervention or coronary bypass surgery, primary valvular disease, cardiogenic shock or intra-aortic balloon pump, New York Heart Association Class III or IV heart failure, ejection fraction <40%, hypertrophic cardiomyopathy, severe renal or liver disease, pregnancy, life expectancy <6 months, and contraindications to angiography (hypersensitivity to contrast, active bleeding, bleeding diathesis, renal dysfunction). Institutional review boards at Cedars-Sinai Medical Center, Los Angeles and University of Florida, Gainesville approved the project, and all participants provided written informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

A total of 374 women completed baseline cardiac magnetic resonance imaging (CMRI) and a prespecified subgroup of 214 completed both baseline and 1-year follow-up CMRI (Figure 1). A Seattle Angina Questionnaire (SAQ) was collected at baseline intake and follow-up visit. The SAQ and short form SAQ-7 are validated tools for assessment of angina in women and

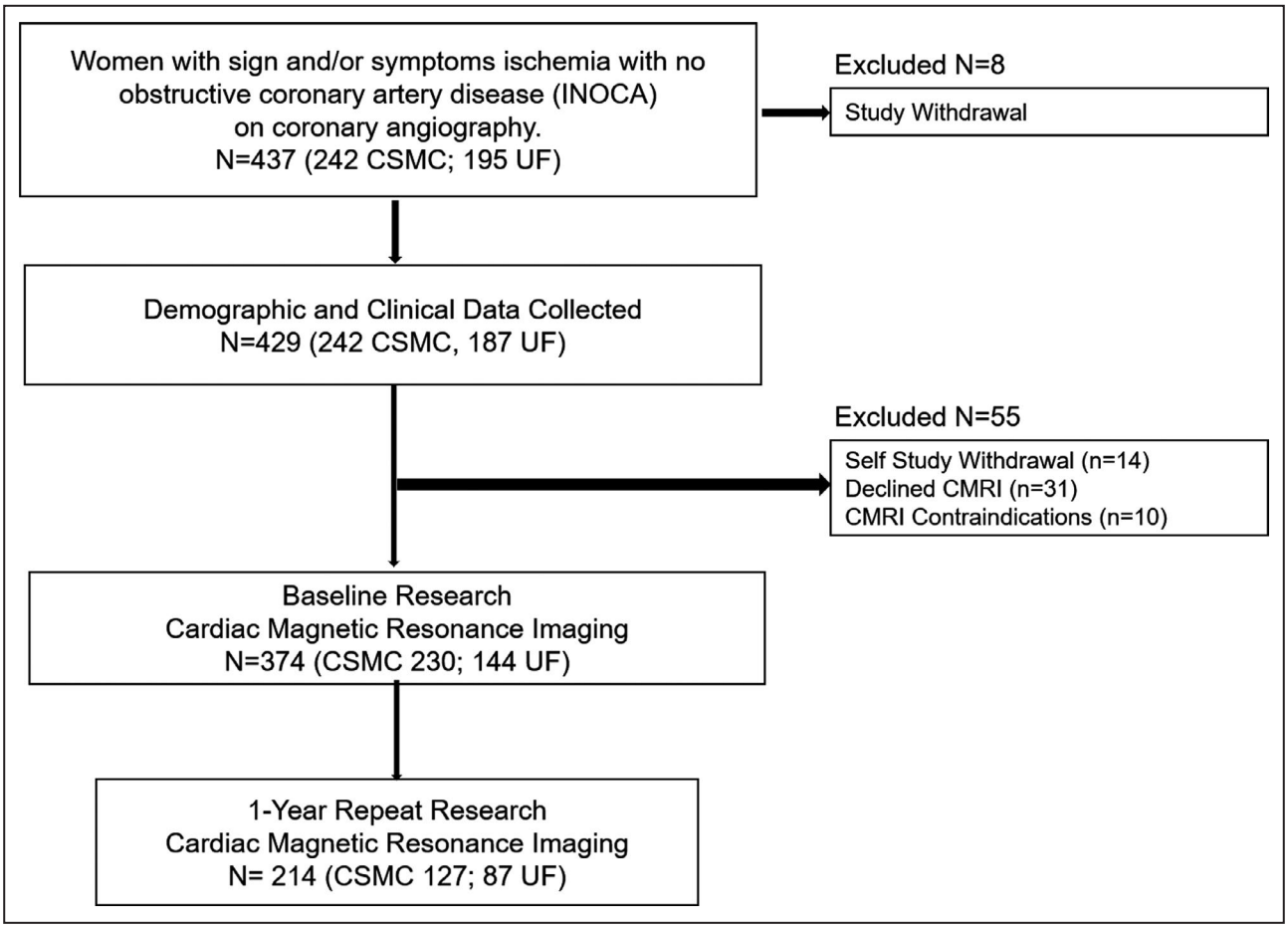


**Figure 1. WISE-CVD flowchart.**
CMRI indicates cardiac magnetic resonance imaging; CSMC, Cedars-Sinai Medical Center; UF, University of Florida; and WISE-CVD, Women's Ischemia Syndrome Evaluation–Coronary Vascular Dysfunction.

men.[14–16] The SAQ summary score, 5 SAQ subscales (physical limitation, angina stability, angina frequency, treatment satisfaction, disease perception) and SAQ-7 (physical limitation, angina frequency, disease perception) are scored from 0 to 100, where a higher score indicates better quality of life, and a change of 10 points is considered clinically relevant.[15] Optimal medical therapy and therapeutic lifestyle changes were deployed by treating physicians.

## CMRI and CMRI Analysis

Women underwent CMRI at baseline and 1-year follow-up. CMRI was performed in the supine position on a 1.5 T CMRI (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany) with ECG gating at baseline and 1-year follow-up. A highly standardized protocol was used for the assessment of LV morphology and function, pharmacologic stress first-pass myocardial perfusion imaging, and delayed contrast enhancement, as previously described.[13,17,18] Rest and pharmacologic stress first-pass myocardial perfusion imaging was performed with adenosine or regadenoson as stress agent and gadolinium-based contrast. First-pass perfusion images were obtained in basal, mid, and distal short-axis image planes.

CMRI analysis was performed using commercially available software (CAAS MRV 3.3, Pie Medical Imaging B.V., The Netherlands) to assess myocardial perfusion reserve index (MPRI), LV mass, LV volumes, LV early peak filling rate, and time to peak filling rate by manually tracing the epicardial and endocardial borders of the short-axis cine images as previously described.[13,17,18]

## Statistical Analysis

Continuous variables were summarized using means and standard deviations and percentages for categorical variables. Change in SAQ subscales, SAQ-7, rest and pharmacologic stress hemodynamic parameters, and CMRI variables (including MPRI and LV morphology and function parameters) from baseline to 1-year follow-up were tested using paired t tests. In women with nonmissing data for SAQ-7 and MPRI at both baseline and follow-up (n=181), the chi-squared test was used

to assess the association between clinically significant SAQ-7 improvement (defined as ≥10-point improvement in SAQ-7) and MPRI improvement (defined as >0 improvement in MPRI) over 1-year follow-up. To examine the relationship between baseline, 1-year follow-up and change in SAQ subscales and SAQ-7 in subjects with persistently low MPRI (defined as MPRI <1.84 at both baseline and follow-up CMRI) compared with those without, Wilcoxon rank-sum tests were used because SAQ subscales were not normally distributed.

Logistic models were used to determine the factors associated with 2 outcomes: clinically significant improvement in SAQ-7 and improvement in MPRI. Variable selection in the logistic models was done using a combination of stepwise variable selection procedures and best subset selection on the basis of the score statistic using a significance level of 0.05 for inclusion into the final model. The model for clinically significant SAQ-7 improvement included 170 subjects with nonmissing data for baseline SAQ-7 score, history of hypertension, indexed LV end-diastolic volume and time to peak filling rate. The model for MPRI improvement included 199 subjects and only baseline MPRI as an explanatory factor. A significance level of 0.05 was used for all tests. Analyses were ran using SAS version 9.4 (SAS Institute, Cary, NC).

# RESULTS

## Temporal Trends in Angina, Myocardial Perfusion, Hemodynamics, and LV Remodeling and Function From Baseline to 1-Year

Table 1 shows demographics and baseline clinical characteristics of the 214 women with suspected INOCA included in the analysis. At 1-year follow-up we observed angina improvement in 4 of 5 SAQ subscales, with greatest improvement in the SAQ quality of life, and SAQ-7 (Table 2). We found that 89 (46%) women had clinically significant improvement in SAQ-7 over 1-year follow-up. We also observed improvement in rest and stress hemodynamics, MPRI, and measures of LV remodeling over a 1-year period (Table 3). Key findings are shown in Figure 2.

## Relations Between Angina, Myocardial Perfusion, and LV Remodeling and Function

We did not find an association between clinically significant SAQ-7 improvement and MPRI improvement over 1-year follow-up ($P$=0.1). We found that 56 (28%) women had persistently low MPRI at follow-up. Baseline SAQ quality of life and SAQ-7 scores were lower in women with persistently low MPRI compared with women without (Table 4). One-year follow-up SAQ domains or SAQ-7 scores were not different in women with persistently low MPRI compared with women without. Change in SAQ disease perception over 1 year was higher in women with persistently low MPRI compared with those without (19.1±19.9 versus 10.4±24.4; $P$=0.01; results not present in table).

In the logistic model, we found lower odds of clinically significant SAQ-7 improvement associated with hypertension history and higher SAQ-7 at baseline (odds ratio [OR], 0.4; 95% CI, 0.2–0.9; and OR, 0.95; 95% CI,

**Table 1. Demographics and Baseline Clinical Characteristics (N=214)**

| Demographics and Clinical Characteristics | N (%), Mean±SD |
|---|---|
| Age, y | 54.6±10.4 |
| Race/Ethnicity | |
| White/Non-Hispanic | 157 (73.4) |
| Black | 14 (6.5) |
| Hispanic/Latin | 20 (9.4) |
| Asian/Pacific Islander | 10 (4.7) |
| Other | 13 (6.1) |
| Hypertension | 78 (39.4) |
| Dyslipidemia | 32 (19.4) |
| Diabetes mellitus | 22 (10.6) |
| Ever smoker | 89 (41.8) |
| Current smoker | 9 (4.2) |
| Postmenopausal | 155 (72.4) |
| Family history of coronary disease | 93 (47.5) |
| Body mass index, kg/m$^2$ | 28.6±7.1 |
| DASI score | 8.69±5.66 |
| Lipids | |
| Total cholesterol | 182.18±37.38 |
| Triglycerides | 120.09±81.75 |
| HDL cholesterol | 60.10±17.35 |
| LDL cholesterol | 98.16±32.79 |
| Glucose | 94.79±20.29 |
| Creatinine | 0.76±0.14 |
| Angiographic findings | |
| No CAD (<20% stenosis) | 15 (8.9) |
| No obstructive CAD (20%–50% stenosis) | 140 (83.3) |
| Medications | |
| ACEI or ARB | 49 (26) |
| Statins | 86 (45) |
| β-Blockers | 65 (35) |
| Calcium channel blockers | 31 (17) |
| Nitrates | 55 (29) |
| Ranolazine | 12 (7) |

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; DASI, Duke Activity Status Index; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

**Table 2. Seattle Angina Questionnaire at Baseline and 1-Year Follow-Up (N=214)**

| SAQ | Baseline SAQ Scores | 1-y Follow-Up SAQ Scores | Change SAQ Baseline to 1-y Follow-Up | *P* Value for Change* |
|---|---|---|---|---|
| SAQ subscales | | | | |
| Angina limitation | 67.4±24.6 | 71.6±23.3 | 5.6±22.6 | <0.001† |
| Angina stability | 48.8±27.3 | 52.9±22.0 | 3.4±35.4 | 0.2 |
| Angina frequency | 62.6±26.6 | 70.5±23.8 | 8.0±24.7 | <0.001† |
| Treatment satisfaction | 71.3±24.7 | 77.4±21.0 | 6.0±25.1 | 0.001† |
| Disease perception | 50.1±23.9 | 63.1±24.4 | 13.2±24.0 | <0.001† |
| SAQ summary score | 59.9±17.9 | 67.1±16.3 | 7.2±16.8 | <0.001† |
| SAQ-7 | 60.4±22.3 | 69.1±20.8 | 9.2±18.7 | <0.001† |

SAQ indicates Seattle Angina Questionnaire.
*Paired t tests.
†Significant *P* value change from baseline to 1 year.

0.93–0.96, respectively). Increased odds of clinically relevant SAQ-7 improvement was associated with higher indexed LV end-diastolic volume and time to peak filling rate at baseline (OR, 1.1; 95% CI, 1.0–1.1; and OR, 2.4; 95% CI, 1.1–5.0, respectively). The only variable associated with MPRI improvement was baseline MPRI (OR, 12.6; 95% CI, 5.3–29.9).

## DISCUSSION

To our knowledge, this is the first prospective cohort of women with INOCA with repeated advanced cardiac imaging demonstrating concordant trends in angina, myocardial perfusion, and LV remodeling and function over 1-year follow-up. Although we did not find a

**Table 3. Stress Cardiac Magnetic Resonance Imaging Hemodynamics, Myocardial Perfusion, and Cardiac Morphology and Function Variables at Baseline and 1-Year Follow-Up (N=214)**

| CMRI Variables | Baseline | 1-y Follow-Up | Change Baseline to 1-y Follow-Up | *P* Value for Change* |
|---|---|---|---|---|
| Rest and pharmacologic stress hemodynamics | | | | |
| Rest heart rate, bpm | 68.3±10.4 | 67.9±11.1 | −0.5±10.9 | 0.5 |
| Peak stress heart rate, bpm | 98.2±17.2 | 97.9±15.2 | −0.3±14.4 | 0.8 |
| Rest SBP, mm Hg | 130.3±20.4 | 128.1±17.6 | −2.2±20.4 | 0.1 |
| Peak stress SBP, mm Hg | 133.3±24.5 | 128.3±20.5 | −5.1±22.7 | 0.002† |
| Rest DBP, mm Hg | 64.9±13.4 | 61.8±11.7 | −3.3±14.9 | 0.002† |
| Peak stress DBP, mm Hg | 62.4±14.2 | 61.3±15.1 | −1.5±16.4 | 0.2 |
| MPRI | | | | |
| Mean MPRI | 1.8±0.5 | 2.0±0.5 | 0.2±0.6 | <0.001† |
| Mean MPRI/rest pressure product | 1.6±0.5 | 1.7±0.6 | 0.1±0.7 | 0.005† |
| Subendocardial MPRI | 1.6±0.4 | 1.8±0.5 | 0.2±0.5 | <0.001† |
| Subepicardial MPRI | 1.9±0.5 | 2.1±0.6 | 0.2±0.7 | 0.002† |
| LV morphology and function | | | | |
| LV ejection fraction, % | 67.4±7.5 | 67.8±6.5 | 0.3±5.7 | 0.5 |
| LV end-diastolic volume, mL | 122.7±24.9 | 122.5±23.6 | 0.8±15.1 | 0.5 |
| LV end-systolic volume, mL | 40.5±14.3 | 39.6±12.8 | −0.5±8.9 | 0.5 |
| LV stroke volume, mL | 81.9±16.8 | 82.6±15.9 | 1.3±13.3 | 0.2 |
| PFR, mL/s | 355.5±98.7 | 347.4±88.2 | −5.0±79.0 | 0.4 |
| PFR/LV end-diastolic volume, s | 2.9±0.6 | 2.9±0.6 | −0.1±0.6 | 0.3 |
| Time to peak filling rate, ms | 197.7±63.9 | 190.4±71.0 | −7.4±87.4 | 0.3 |
| LV mass, g | 92.7±16.4 | 91.1±16.7 | −1.5±6.6 | 0.003† |
| LV mass index | 50.7±6.4 | 49.9±6.7 | −0.8±3.6 | 0.002† |
| LV mass-volume ratio, g/mL | 0.8±0.2 | 0.8±0.2 | −0.02±0.1 | 0.018† |

DBP indicates diastolic blood pressure; LV, left ventricular; MPRI, myocardial perfusion reserve index; PFR, peak filling rate; and SBP, systolic blood pressure.
*Paired t tests.
†Significant *P* value change from baseline to 1 year.

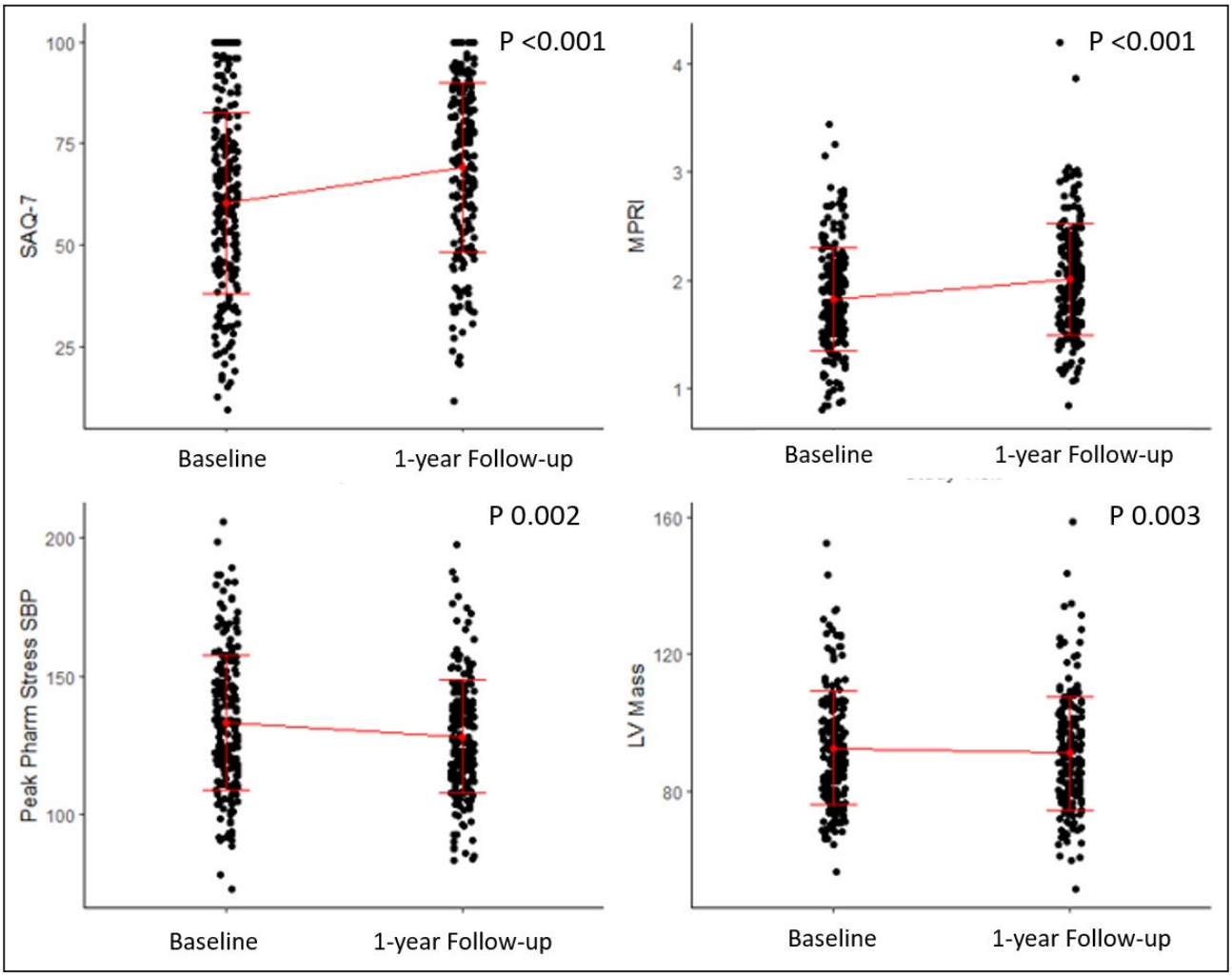


**Figure 2. Change in angina, myocardial perfusion, stress hemodynamics, and LV morphology over 1 year (N=214).**
LV indicates left ventricular; MPRI, myocardial perfusion reserve index; SAQ, Seattle Angina Questionnaire; and SBP, systolic blood pressure.

relationship between angina and myocardial perfusion improvement, we found that women with persistently low myocardial perfusion had worse physical limitation, angina frequency, and quality of life at baseline. We also showed that abnormalities in LV morphology and diastolic function at baseline were predictive of clinically significant improvement in angina at follow-up, whereas history of hypertension was associated with lower odds.

We expected improvements in myocardial perfusion to lead to improvements in angina as reported in prior pharmacologic PROBE (Prospective Randomized Open Blinded End-Point) trials[19–22]; however, in our study we did not find a direct correlation between improvement in myocardial perfusion and angina. Angina in women with INOCA can result from multiple coronary abnormalities, including coronary microvascular dysfunction, endothelial dysfunction, macrovascular dysfunction, myocardial bridging, and spasm.[17,23,24] In a prior trial, the correlation between angina improvement and CMRI myocardial perfusion reserve was reported in the subset of women with coronary microvascular dysfunction diagnosed invasively through low coronary flow reserve.[21,22] We hypothesize that in our cohort of women with INOCA, angina improvement was multifactorial and not driven only by improvement in myocardial perfusion. Furthermore, we observed that women with persistently low myocardial perfusion had worse physical limitation, angina frequency, and quality of life assessed through SAQ-7 at baseline. These results suggest that in women with INOCA, symptoms at time of diagnosis may be a good surrogate for those with more severe disease.

We also found that abnormalities in LV morphology and diastolic function at baseline, higher LV end-diastolic volume and time to peak filling rate, were predictive of clinically significant improvement in angina at follow-up. These findings support the interrelationship between angina and LV morphology and function in women with INOCA. In women with INOCA,

**Table 4. Baseline SAQ Scores in Women With and Without Persistent Low Myocardial Perfusion at Baseline and 1-Year Follow-Up**

| Baseline SAQ Scores | Persistently Low Myocardial Perfusion* | | *P* Value† |
|---|---|---|---|
| | Yes (N=56) | No (N=142) | |
| SAQ subscales | | | |
| Angina limitation | 63.3±23.8 | 69.2±24.8 | 0.1 |
| Angina stability | 45.5±28.5 | 51.2±26.5 | 0.2 |
| Angina frequency | 57.8±28.1 | 65.7±26.1 | 0.07 |
| Treatment satisfaction | 78.1±18.4 | 69.7±26.4 | 0.07 |
| Quality of life | 45.3±20.2 | 52.8±24.7 | 0.04‡ |
| SAQ summary score | 57.8±17.6 | 61.6±17.8 | 0.1 |
| SAQ-7 | 55.3±22.0 | 63.3±22.4 | 0.02‡ |

SAQ indicates Seattle Angina Questionnaire.
*Persistently low myocardial perfusion reserved index defined as <1.84 at baseline and 1-year follow-up.
†Wilcoxon rank-sum tests.
‡Significant *P* value change from baseline to 1 year.

impaired myocardial blood flow can result in myocardial ischemia that over time leads to LV dysfunction and increase in LV diastolic pressure.[18,25,26] Cannon et al[27] showed that patients with angina and abnormal vasodilator reserve have abnormalities in LV function. In addition, our study shows that history of hypertension was associated with lower odds of angina improvement. Hypertension is associated with remodeling of coronary arteries and leads to arteriolar constriction and reduced coronary flow reserve, which develops over time and may not be reversed in 1 year's time.[28,29]

Studies on the natural history of INOCA are lacking.[30] We observe concordant trends in angina, myocardial perfusion, LV morphology, and blood pressure improvement in women with signs and symptoms of INOCA clinically treated with cardiac medications over 1 year. Our findings are consistent with prior pharmacologic PROBE trials, which showed improvement in angina and myocardial perfusion over shorter follow-up.[19–22] Although our lack of randomized placebo-controlled clinical trial design limited our ability to determine the role of cardiac medications, we hypothesize that the improvement observed may be in part attributable to changes in cardiac medications by the treating physicians over a 1-year period. These changes require further exploration in future studies as prognostic indicators for long-term outcomes as we have seen with persistent angina in prior studies.[10–12]

Our study has strengths and limitations. Strengths include a large sample size of nearly 200 women and use of validated measures and core laboratories. Because of the observational nature of our study and the absence of control subjects, our findings of concordant improvement in angina, myocardial perfusion, and LV remodeling may be attributable to regression to the mean, although our blinded core laboratory readings somewhat moderate this. Improvement in myocardial perfusion may also be related to scan variability, as we previously demonstrated there is a 20% coefficient of variation for MPRI between scans.[31] We were unable to assess the relationship between cardiac medications, angina, and myocardial perfusion because of treatment bias, relatively small sample size for each cardiac medication drug class, simultaneous use of multiple cardiac medications, collection of data on medication use at only 2 time points, and the lack of randomized placebo-control design.

## CONCLUSIONS

Women with INOCA represent a diagnostic and therapeutic challenge. In women with INOCA clinically treated with cardiac medication over 1 year, we observed concurrent temporal trends toward improvement in angina, myocardial perfusion, LV morphology and function, and blood pressure. Although we did not find a relationship between angina and myocardial perfusion improvement, our findings suggest that in women with INOCA, symptoms may be a good surrogate for those with more severe disease. Our study supports the use of noninvasive advanced cardiovascular imaging to follow changes in myocardial perfusion and LV remodeling in future INOCA trials. We showed that abnormalities in LV morphology and diastolic function at baseline were predictive of clinically significant improvement in angina at follow-up, whereas history of hypertension was associated with lower odds. Future studies are needed to assess the mechanisms and treatments responsible for the improvements we observed.

## ARTICLE INFORMATION

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## REFERENCES

1. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med*. 2015;372:1291–1300.
2. Jespersen L, Hvelplund A, Abildstrom SZ, Pedersen F, Galatius S, Madsen JK, Jorgensen E, Kelbaek H, Prescott E. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J*. 2012;33:734–744.
3. Maddox TM, Stanislawski MA, Grunwald GK, Bradley SM, Ho PM, Tsai TT, Patel MR, Sandhu A, Valle J, Magid DJ, et al. Nonobstructive coronary artery disease and risk of myocardial infarction. *JAMA*. 2014;312:1754–1763.
4. Pepine CJ, Ferdinand KC, Shaw LJ, Light-McGroary KA, Shah RU, Gulati M, Duvernoy C, Walsh MN, Bairey Merz CN. Emergence of nonobstructive coronary artery disease: a woman's problem and need for change in definition on angiography. *J Am Coll Cardiol*. 2015;66:1918–1933.
5. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, Johnson BD, Pepine CJ, Mankad S, Sharaf BL, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (wise) study: part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol*. 2006;47:S21–S29.
6. Shaw LJ, Bairey Merz CN, Pepine CJ, Reis SE, Bittner V, Kelsey SF, Olson M, Johnson BD, Mankad S, Sharaf BL, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) study: part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. *J Am Coll Cardiol*. 2006;47:S4–S20.
7. Gulati M, Cooper-DeHoff RM, McClure C, Johnson BD, Shaw LJ, Handberg EM, Zineh I, Kelsey SF, Arnsdorf MF, Black HR, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med*. 2009;169:843–850.
8. Kothawade K, Bairey Merz CN. Microvascular coronary dysfunction in women: pathophysiology, diagnosis, and management. *Curr Probl Cardiol*. 2011;36:291–318.
9. Sharaf B, Wood T, Shaw L, Johnson BD, Kelsey S, Anderson RD, Pepine CJ, Bairey Merz CN. Adverse outcomes among women presenting with signs and symptoms of ischemia and no obstructive coronary artery disease: findings from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE) angiographic core laboratory. *Am Heart J*. 2013;166:134–141.
10. AlBadri A, Bairey Merz CN, Johnson BD, Wei J, Mehta PK, Cook-Wiens G, Reis SE, Kelsey SF, Bittner V, Sopko G, et al. Impact of abnormal coronary reactivity on long-term clinical outcomes in women. *J Am Coll Cardiol*. 2019;73:684–693.
11. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, Dorbala S, Blankstein R, Rimoldi O, Camici PG, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation*. 2014;129:2518–2527.
12. Taqueti VR, Shaw LJ, Cook NR, Murthy VL, Shah NR, Foster CR, Hainer J, Blankstein R, Dorbala S, Di Carli MF. Excess cardiovascular risk in women relative to men referred for coronary angiography is associated with severely impaired coronary flow reserve, not obstructive disease. *Circulation*. 2017;135:566–577.
13. Quesada O, AlBadri A, Wei J, Shufelt C, Mehta PK, Maughan J, Suppogu N, Aldiwani H, Cook-Wiens G, Nelson MD, et al. Design, methodology and baseline characteristics of the Women's Ischemia Syndrome Evaluation–Coronary Vascular Dysfunction (WISE-CVD). *Am Heart J*. 2020;220:224–236.
14. Kimble LP, Dunbar SB, Weintraub WS, McGuire DB, Fazio S, De AK, Strickland O. The Seattle Angina Questionnaire: reliability and validity in women with chronic stable angina. *Heart Dis*. 2002;4:206–211.
15. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M, Fihn SD. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol*. 1995;25:333–341.
16. Chan PS, Jones PG, Arnold SA, Spertus JA. Development and validation of a short version of the Seattle Angina Questionnaire. *Circ Cardiovasc Qual Outcomes*. 2014;7:640–647.
17. Thomson LE, Wei J, Agarwal M, Haft-Baradaran A, Shufelt C, Mehta PK, Gill EB, Johnson BD, Kenkre T, Handberg EM, et al. Cardiac magnetic resonance myocardial perfusion reserve index is reduced in women with coronary microvascular dysfunction. A National Heart, Lung, and Blood Institute–sponsored study from the Women's Ischemia Syndrome Evaluation. *Circ Cardiovasc Imaging*. 2015;8:e002481.
18. Nelson MD, Szczepaniak LS, Wei J, Haftabaradaren A, Bharadwaj M, Sharif B, Mehta P, Zhang X, Thomson LE, Berman DS, et al. Diastolic dysfunction in women with signs and symptoms of ischemia in the absence of obstructive coronary artery disease: a hypothesis-generating study. *Circ Cardiovasc Imaging*. 2014;7:510–516.
19. Pauly DF, Johnson BD, Anderson RD, Handberg EM, Smith KM, Cooper-DeHoff RM, Sopko G, Sharaf BM, Kelsey SF, Merz CN, et al. In women with symptoms of cardiac ischemia, nonobstructive coronary arteries, and microvascular dysfunction, angiotensin-converting enzyme inhibition is associated with improved microvascular function: a double-blind randomized study from the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE). *Am Heart J*. 2011;162:678–684.
20. Mehta PK, Goykhman P, Thomson LE, Shufelt C, Wei J, Yang Y, Gill E, Minissian M, Shaw LJ, Slomka PJ, et al. Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease. *JACC Cardiovasc Imaging*. 2011;4:514–522.
21. Bairey Merz CN, Handberg EM, Shufelt CL, Mehta PK, Minissian MB, Wei J, Thomson LE, Berman DS, Shaw LJ, Petersen JW, et al. A randomized, placebo-controlled trial of late Na current inhibition (ranolazine) in coronary microvascular dysfunction (CMD): impact on angina and myocardial perfusion reserve. *Eur Heart J*. 2016;37:1504–1513.

22. Rambarat CA, Elgendy IY, Handberg EM, Bairey Merz CN, Wei J, Minissian MB, Nelson MD, Thomson LEJ, Berman DS, Shaw LJ, et al. Late sodium channel blockade improves angina and myocardial perfusion in patients with severe coronary microvascular dysfunction: Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction ancillary study. *Int J Cardiol*. 2019;276:8–13.
23. Lee BK, Lim HS, Fearon WF, Yong AS, Yamada R, Tanaka S, Lee DP, Yeung AC, Tremmel JA. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. *Circulation*. 2015;131:1054–1060.
24. Reis SE, Holubkov R, Conrad Smith AJ, Kelsey SF, Sharaf BL, Reichek N, Rogers WJ, Merz CN, Sopko G, Pepine CJ, et al. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. *Am Heart J*. 2001;141:735–741.
25. Maseri A, Crea F, Kaski JC, Crake T. Mechanisms of angina pectoris in syndrome X. *J Am Coll Cardiol*. 1991;17:499–506.
26. Nelson MD, Sharif B, Shaw JL, Cook-Wiens G, Wei J, Shufelt C, Mehta PK, Thomson LEJ, Berman DS, Thompson RB, et al. Myocardial tissue deformation is reduced in subjects with coronary microvascular dysfunction but not rescued by treatment with ranolazine. *Clin Cardiol*. 2017;40:300–306.
27. Cannon RO III, Bonow RO, Bacharach SL, Green MV, Rosing DR, Leon MB, Watson RM, Epstein SE. Left ventricular dysfunction in patients with angina pectoris, normal epicardial coronary arteries, and abnormal vasodilator reserve. *Circulation*. 1985;71:218–226.
28. Rizzoni D, Palombo C, Porteri E, Muiesan ML, Kozakova M, La Canna G, Nardi M, Guelfi D, Salvetti M, Morizzo C, et al. Relationships between coronary flow vasodilator capacity and small artery remodelling in hypertensive patients. *J Hypertens*. 2003;21:625–631.
29. Palombo C, Kozakova M, Magagna A, Bigalli G, Morizzo C, Ghiadoni L, Virdis A, Emdin M, Taddei S, L'Abbate A, et al. Early impairment of coronary flow reserve and increase in minimum coronary resistance in borderline hypertensive patients. *J Hypertens*. 2000;18:453–459.
30. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research agenda for the next decade. *Circulation*. 2017;135:1075–1092.
31. Al-Badri A, Wei J, Landes S, Motwani M, Cook-Wiens G, Nelson MD, Mehta PK, Shufelt C, Sharif B, Li D, et al. Inter-scan reproducibility of cardiovascular magnetic resonance imaging-derived myocardial perfusion reserve index in women with no obstructive coronary artery disease. *Curr Trends Clin Med Imaging*. 2018;2:555587.