

Sex Differences in Severity of Coronary Artery Disease, Ischemia and Symptom Burden in Patients with Moderate or Severe Ischemia:

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Background

- Many features of stable ischemic heart disease (SIHD) vary by sex.
- Differences in ischemia, coronary anatomy and symptoms by sex have not been investigated among patients with moderate or severe ischemia.
- The enrolled ISCHEMIA trial cohort that underwent coronary computed tomographic angiography (CCTA) was required to have obstructive coronary artery disease (CAD) for randomization.
- The objective of the current study was to describe sex differences in stress testing, CCTA findings and symptoms in ISCHEMIA trial participants.

Methods

- ISCHEMIA was a large multi-center randomized trial of patients with known or suspected SIHD selected for enrollment based on the finding of moderate or severe ischemia on a stress imaging test or severe ischemia on a non-imaging exercise tolerance test (ETT).
- Key exclusion criteria were acute coronary syndrome within the prior 2 months, left ventricular ejection fraction (LVEF) <35%, estimated glomerular filtration rate (eGFR) <30 mL/min, unacceptable angina severity despite maximal medical therapy, heart failure exacerbation within the last 6 months, or NYHA class III-IV heart failure.
- SIHD patients enrolled based on local reading of moderate or severe ischemia on a stress test, after which blinded CCTA was performed in most. Core laboratories reviewed stress tests and CCTAs. Participants with no obstructive CAD or with left main CAD ≥50% were excluded. Those who met eligibility criteria including CCTA (if performed) were randomized to a routine invasive or a conservative management strategy (N=5179).
- Angina was assessed using the Seattle Angina Questionnaire (SAQ).
- The primary outcome of this study was sex differences in stress test, CCTA findings and symptom severity.

Results

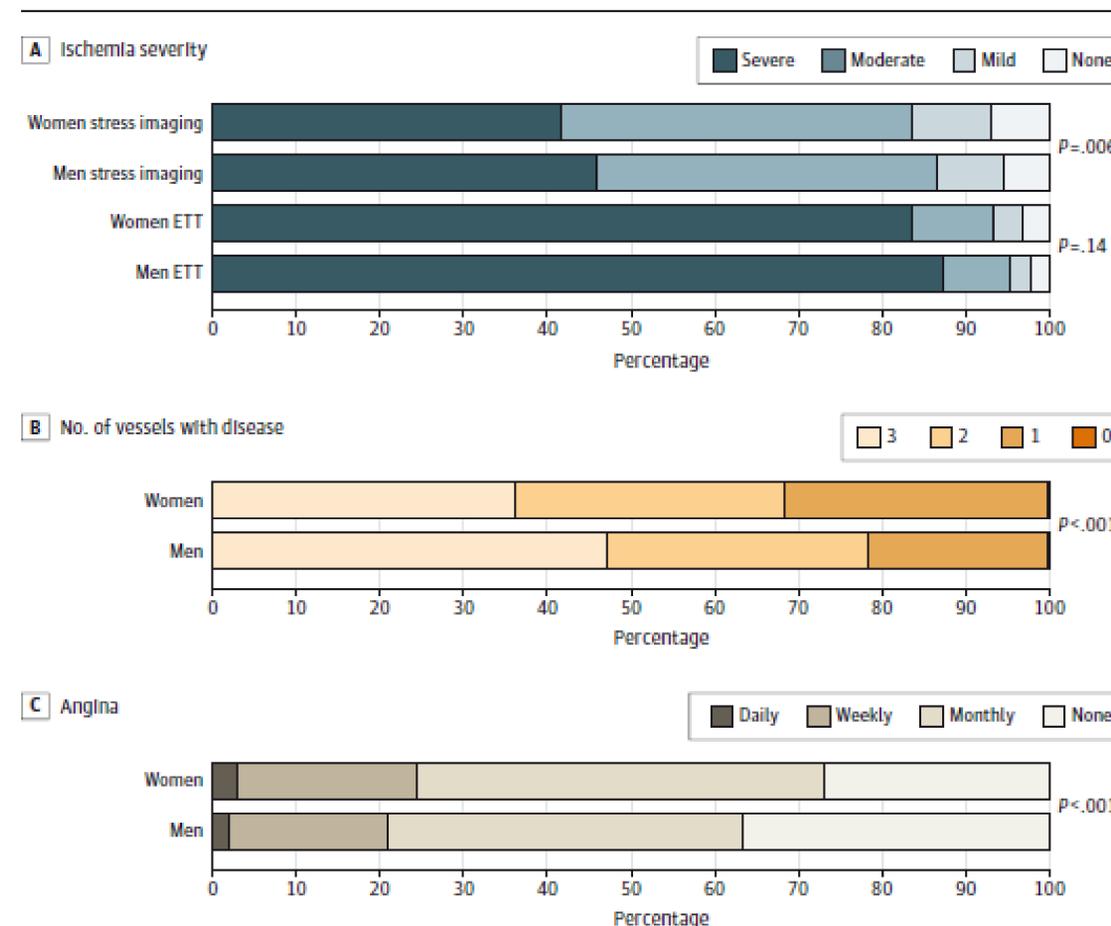
Table: Baseline Demographics of Randomized Men vs Women

Characteristic	Randomized Women (N=1,168)	Randomized Men (N=4,011)	P-value
Demographics			
Age at Randomization (yrs.), Median (IQR)	65 (59, 71)	64 (57, 70)	0.002
Race			
American Indian or Alaskan Native	3/1,154 (0.3%)	10/3,975 (0.3%)	0.002
Asian	282/1,154 (24.4%)	1,203/3,975 (30.3%)	
Native Hawaiian or Other Pacific Islander	2/1,154 (0.2%)	10/3,975 (0.3%)	
Black or African American	57/1,154 (4.9%)	147/3,975 (3.7%)	
White	808/1,154 (70.0%)	2,595/3,975 (65.3%)	
Multiple Races Reported	2/1,154 (0.2%)	10/3,975 (0.3%)	
Ethnicity			
Hispanic or Latino	188/1,091 (17.2%)	575/3,724 (15.4%)	0.15
Clinical History			
Hypertension	922/1,164 (79.2%)	2,867/3,997 (71.7%)	<.001
Diabetes	522/1,168 (44.7%)	1,642/4,011 (40.9%)	0.02
Prior Myocardial Infarction	184/1,165 (15.8%)	807/3,997 (20.2%)	<.001
Cigarette Smoking			<.001
Never Smoked	756/1,167 (64.8%)	1,453/4,007 (36.3%)	
Former Smoker	301/1,167 (25.8%)	2,025/4,007 (50.5%)	
Current Smoker	110/1,167 (9.4%)	529/4,007 (13.2%)	
Family History of Premature CAD	297/1,016 (29.2%)	873/3,474 (25.1%)	0.009
Prior MI or Prior PCI or Prior CABG	289/1,165 (24.8%)	1,281/3,997 (32.0%)	<.001
Prior Stroke	40/1,168 (3.4%)	111/4,010 (2.8%)	0.24
Prior Heart Failure	61/1,168 (5.2%)	145/4,011 (3.6%)	0.01
Ejection Fraction, Median (IQR)	N=1,053 62 (58, 68)	N=3,584 60 (55, 64)	<.001

Table 2: Stress testing and CCTA performed in Men vs Women

Characteristic	Randomized Women (N=1,168)	Randomized Men (N=4,011)	P-value
Type of Stress Test Performed			
Stress Imaging Performed	924/1,168 (79.1%)	2,985/4,011 (74.4%)	0.001
Nuclear Performed	558/1,168 (47.8%)	2,009/4,011 (50.1%)	0.16
Echo Performed	291/1,168 (24.9%)	794/4,011 (19.8%)	<.001
CMR Performed	75/1,168 (6.4%)	182/4,011 (4.5%)	0.009
Exercise Tolerance Test (ETT) Performed	244/1,168 (20.9%)	1,026/4,011 (25.6%)	0.001
CCTA Performed	816/1,168 (69.9%)	3,097/4,011 (77.2%)	<.001

Figure: Sex Differences in Ischemia Severity, Atherosclerosis and Angina among Randomized ISCHEMIA Trial Participants



* Stress imaging includes stress nuclear, stress echocardiography, and stress cardiac magnetic resonance imaging. Number of vessels diseased is shown based on the threshold of 50% stenosis. Frequency of angina is determined based on the Seattle Angina Questionnaire angina frequency scale, where 100 indicates no angina; 61 to 99, monthly angina; 31 to 60, weekly angina; and 0 to 30, daily angina. ETT indicates exercise tolerance test.

- Women were more likely to have no obstructive CAD (<50% stenosis in all vessels on CCTA), 34% versus 11%, p<0.001.
- Randomized women (23% of cohort) had more angina at baseline than randomized men (SAQ Angina Frequency score 80 vs. 90, p<0.001).
- Women had less severe ischemia on stress imaging (42% vs. 46% with severe ischemia, 42% vs. 41% moderate ischemia and 16% vs. 13% mild or no ischemia, p=0.006).
- Ischemia was similar by sex on exercise tolerance testing. Women had less extensive CAD on CCTA (36% of women vs 47% of men with three-vessel disease, 32% vs. 31% two-vessel disease and 31% vs. 22% one-vessel disease, p<0.001).
- Female sex was independently associated with greater angina frequency (OR 1.41, 95% CI 1.13-1.76).

Conclusions

- Women randomized in the ISCHEMIA trial had more frequent angina, independent of less extensive CAD and less severe ischemia than men.
- Our findings reflect inherent sex differences in the complex relationships between angina, atherosclerosis and ischemia that may have implications for testing and treatment of patients with suspected SIHD

