Sex differences in management and outcomes of patients with stable symptoms suggestive of coronary artery disease: Insights from the PROMISE trial

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Background Although sex differences exist in the management of acute coronary syndromes, less is known about the management and outcomes of women and men with suspected coronary artery disease being evaluated with noninvasive testing (NIT).

Methods We investigated sex-based differences in NIT results and subsequent clinical management in 4,720 women and 4,246 men randomized to CT angiography versus stress testing in the PROMISE trial. Logistic regression models assessed relationships between sex and referral for catheterization, revascularization, and aspirin or statin use. Cox regression models assessed the relationship between sex and the composite of all-cause death, myocardial infarction, or unstable angina.

Results Women more often had normal NITs than men (61.0% vs 49.6%, $P < .001$) and less often had mild (29.3% vs 35.4%, $P < .001$), moderate (4.0% vs 6.8%, $P < .001$), or severe abnormalities (5.7% vs 8.3%, $P < .001$) found on NIT. Women were less likely to be referred for catheterization than men (7.6% vs 12.6%, adjusted OR 0.75 [0.62-0.90]; $P = .002$). Of those who underwent catheterization within 90 days of randomization (358 women, 534 men), fewer women than men had obstructive coronary artery disease (40.8% vs 60.9%, $P < .001$). At a 60-day visit, women were significantly less likely than men to report statin use when indicated (adjusted OR 0.81 [0.73-0.91]; $P < .001$) but were similarly likely to report aspirin use when indicated (adjusted OR 0.78 [0.56-1.08]; $P = .13$). Over a median follow-up of 25 months, women had better outcomes than men (adjusted OR 0.73 [0.57-0.94]; $P = .017$).

Conclusions Although women more frequently had normal NITs compared with men, those with abnormalities on NIT were less likely to be referred for catheterization or to receive statin therapy. The high rates of negative NIT in women, coupled with the better outcomes compared with men, strongly support the need for a sex-specific algorithm to guide NIT and chest pain management. (Am Heart J 2019;208:28-36.)

Several studies over the last 4 decades have shown differences in the diagnostic and therapeutic approaches of physicians to women and men with suspected or known ischemic heart disease.[1,2] These reports, which

assessed sex-based differences in management after functional stress testing, found disparities in referral for catheterization,[3-5] revascularization,[1,2,4] and subsequent secondary prevention medication treatment.[6] These differences were postulated to be due, at least in part, to provider awareness of the high false-positive rate of stress testing in women.[7,8] However, in the current era of medical management of coronary artery disease (CAD) and with the advent of anatomic noninvasive testing (NIT) with computed tomography angiography (CTA), which has lower false-positive rates,[8] it is unclear whether sex-based differences in the management of suspected CAD still exist. Furthermore, it is unknown whether any differences in current management translate into disparities in clinical outcomes between women and men.

We sought to address this gap in knowledge using data from the Prospective Multicenter Imaging Study for

Evaluation of Chest Pain (PROMISE).[9] PROMISE was a pragmatic comparative effectiveness trial of 10,003 outpatients with stable symptoms suggestive of CAD, randomized to a strategy of either functional or anatomic (CTA) testing. Over a median follow-up period of 25 months, there was no difference between testing arms in clinical events overall or by sex.[9] Given the high percentage (53%) of women enrolled in this trial and the fact that clinical decision making was left up to the local providers after the noninvasive test, it is an ideal setting in which to explore sex-based differences in the management and clinical outcomes of patients with stable angina who receive NIT.

Methods

Study cohort and design

PROMISE was a pragmatic randomized trial that compared initial anatomic (CTA) versus stress testing in stable symptomatic patients with suspected CAD.[9,10] The choice of stress test was left up to the clinician (exercise electrocardiogram, stress echocardiography, or stress nuclear), as were all test interpretations and all subsequent clinical decisions in both testing arms. Randomization was stratified by study site and by the stress test type that was chosen by the provider prior to randomization if the patient were to be randomized to the stress testing arm.

Categorization of CTA and stress test results into 4 tiers is outlined in Table I. A catheterization was considered positive if there was ≥70% stenosis in at least 1 epicardial artery or ≥50% stenosis in the left main artery. *Revascularization* was defined as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery. Aspirin and statin use was assessed at a 60-day postrandomization visit in individuals with the following indications: a history of stroke, transient ischemic attack, or peripheral arterial disease, or with a positive CTA or positive catheterization. In addition, individuals with a history of dyslipidemia, diabetes, or 10-year atherosclerotic cardiovascular (CV) disease risk of at least 7.5% were included in the statin analysis.[11]

The current analysis included all patients who were tested as randomized and who had *interpretable results*, defined as not missing and not indeterminate. Primary end points of the various analyses included invasive catheterization within 90 days of randomization; revascularization within 30 days of invasive catheterization; aspirin and/or statin use at 60-day visit among those with indications; and a composite of death from any cause, myocardial infarction (MI), or unstable angina hospitalization (UAH). Secondary outcomes included a composite of CV death, MI, or UAH, and a composite of CV death and MI alone.

Statistical analyses

Baseline characteristics were described using frequencies and percentages for categorical variables and mean ±

SD for continuous variables. Characteristics were compared between women and men by sex using the Wilcoxon rank sum test for continuous variables and χ^2 testing for categorical variables.

A logistic regression model was used to examine the unadjusted and adjusted association between patient sex and referral for catheterization within 90 days of randomization. The adjusted model controlled for clinically relevant covariates including NIT modality; NIT results (4-tier); body mass index (BMI) (kg/m^2); age (standardized by sex); chest pain versus other as primary symptom; chest pain typicality (typical, atypical, noncardiac); and risk factors including smoker (ever/never), diabetes mellitus, hypertension, history of peripheral artery or cerebrovascular disease, sedentary lifestyle, depression, family history of premature CAD, and dyslipidemia. In all models, linearity assumptions were assessed for continuous adjustment variables. A similar model was fit to assess whether the association between patient sex and referral for catheterization within 90 days of randomization was modified by NIT modality. In addition to the adjustment variables specified for the previous model, this model also included a 2-way interaction term between sex and NIT modality.

Among patients who underwent catheterization within 90 days of randomization, a logistic regression model was used to assess the association between sex and revascularization within 30 days of the catheterization. Time zero for this model was set as the day of the catheterization. In addition to the adjustment factors listed for the catheterization model, this model also adjusted for catheterization results (positive/negative). The relationship between sex and self-reported aspirin or statin use at 60-day follow-up was assessed with a logistic regression model among those with an indication for aspirin or statin therapy, as defined above. The adjustment covariates were the same as those in the catheterization model, with the exception of NIT results (4-tier).

Cox proportional-hazards models were used to assess the association between patient sex and the primary and secondary composite outcomes. The proportional-hazards assumption was assessed in each model. Models were fit in the overall cohort, in those who did not undergo catheterization, in those who underwent catheterization, and in those who underwent revascularization. Adjustment covariates were the same as those for the catheterization model, with the addition of catheterization referral, catheterization results, and referral for revascularization modeled as time-dependent covariates. Similar models were fit in those patients who were referred to catheterization within 90 days of randomization, with the exception that the analysis was landmarked at the time of the catheterization referral. Similar models were fit in those patients who were referred to revascularization within 30 days of catheterization referral, with the exception that those models were landmarked at the time of the referral to revascularization.

Table I. Four-tier test result definitions for CTA and stress testing

Test strata	Anatomical	Functional*		
	CTA	exercise treadmill test	Stress nuclear	Stress echo
Severely abnormal	High-risk coronary artery disease • ≥2 vessel disease (≥70%) • OR ≥50% left main stenosis • OR ≥70% proximal left anterior descending stenosis	Ischemic ECG • ST changes consistent with ischemia during stress + either severe ventricular arrhythmia OR Hypotension	Large territory inducible ischemia or mixed defect • Septal/anterior/apical territory or other single territory with transient ischemic dilatation or 2 or more coronary territories with ischemia	Large territory inducible Ischemia or mixed defect • Wall motion abnormality or mixed abnormality (infarct and ischemia) • Isolated septal/anterior/apical or other single territory + ↓EF to <35% during stress or • 2 or more coronary territories
Moderately abnormal	Obstructive coronary artery disease • ≥70% stenosis in 1 major vessel/branch	Early positive TM • Failure to reach stage 2 (<3:00 min) with ST changes OR symptoms reproduced • OR any arrhythmia or hypotension	Inducible ischemia or mixed defect • Perfusion abnormality in 1 coronary territory (lateral or inferior/posterior) OR Normal imaging but early positive TM • Failure to reach stage 2 (<3:00 min) with ST changes OR symptoms reproduced • OR any arrhythmia or hypotension	Inducible ischemia or mixed defect • Wall motion abnormality or mixed abnormality (infarct and ischemia) in 1 coronary territory (lateral or inferior/posterior) OR Normal imaging but early positive TM • Failure to reach stage 2 (<3:00 min) with ST changes OR symptoms reproduced • OR any arrhythmia or hypotension
Mildly abnormal	Nonobstructive coronary artery disease • 1%-69% stenosis in any major • vessels/branch OR <50% • left main stenosis	Late positive TM • More than stage 2 (>3:00 min) but failure to finish protocol or target heart rate achieved due to ST changes OR symptoms reproduced OR any arrhythmia or hypotension	Positive ECG • Normal perfusion or fixed perfusion defect (scar) OR Normal imaging but late positive TM • More than stage 2 (>3:00 min) but failure to finish protocol or target heart rate achieved due to ST changes OR symptoms reproduced OR any arrhythmia or hypotension	Positive ECG but normal wall motion or resting wall motion abnormality without inducible ischemia OR Normal imaging but late positive TM • More than stage 2 (>3:00 min) but failure to finish protocol or target heart rate achieved due to ST changes OR symptoms reproduced OR any arrhythmia or hypotension
Normal	Absence of coronary atherosclerosis	Normal	Normal	Normal

ECG, electrocardiogram; TM, treadmill test.
* As defined by Hoffmann et al.[22]

All statistical calculations were carried out using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics

Among the 8,966 patients in PROMISE who underwent testing as randomized and who had interpretable results, 4,500 (52% female) had CTA and 4,466 (53% female) had stress testing (Supplemental Figure 1). As previously reported,[12] in both the CTA and stress testing groups, women were older and more likely to have a history of hypertension, peripheral arterial disease or cerebrovascular disease, family history of premature CAD, depression, and a sedentary lifestyle compared with men (Table II). On the other hand, women had lower Framingham and atherosclerotic cardiovascular disease risk scores and were less likely to have a smoking history than men.

Sex differences in noninvasive test results

In both testing arms, women had more normal NITs than men (CTA: 41.3% vs 25.0%, $P < .001$; stress: 80.3% vs 75.2%, $P < .001$), and fewer mildly abnormal (CTA: 50.8% vs 58.9%, $P < .001$; stress: 8.2% vs 10.9%, $P = .003$) or moderately abnormal (CTA: 4.5% vs 7.5%,

Table II. Baseline characteristics by NIT type and sex

	CTA (n = 4500)			Stress test (n = 4466)		
Characteristic	Women (n = 2332)	Men (n = 2168)	P value	Women (n = 2388)	Men (n = 2078)	P value
Demographics						
Age, y	62.2 (7.68)	58.6 (8.25)	<.001	62.6 (7.88)	59.2 (8.42)	<.001
Racial minority	398 (17.2)	315 (14.7)	.029	358 (15.1)	285 (13.8)	<.001
Hispanic or Latino ethnicity	170/2323 (7.3%)	173/2154 (8.0%)	.370	156/2370 (6.6%)	168/2065 (8.1%)	.047
Cardiac risk factors						
Hypertension	1534/2332 (65.8%)	1359/2168 (62.7%)	.030	1603/2388 (67.1%)	1314/2078 (63.2%)	.006
Diabetes	500/2332 (21.4%)	436/2168 (20.1%)	.272	525/2388 (22.0%)	447/2078 (21.5%)	.702
Metabolic syndrome	857/2332 (36.7%)	816/2168 (37.6%)	.538	904/2388 (37.9%)	810/2078 (39.0%)	.441
Dyslipidemia	1621/2332 (69.5%)	1408/2168 (64.9%)	.001	1637/2388 (68.6%)	1404/2078 (67.6%)	.481
CAD risk equivalent	598/2332 (25.6%)	499/2168 (23.0%)	.040	635/2388 (26.6%)	522/2078 (25.1%)	.263
Peripheral arterial disease or cerebrovascular disease	134/2332 (5.7%)	94/2167 (4.3%)	.031	153/2388 (6.4%)	103/2078 (5.0%)	.038
Family history of premature CAD	815/2325 (35.1%)	645/2160 (29.9%)	<.001	787/2379 (33.1%)	592/2073 (28.6%)	.001
Depression	599/2332 (25.7%)	286/2168 (13.2%)	<.001	627/2387 (26.3%)	339/2078 (16.3%)	<.001
Smoker (ever/never)	1068/2331 (45.8%)	1224/2168 (56.5%)	<.001	1094/2388 (45.8%)	1196/2077 (57.6%)	<.001
Sedentary lifestyle	1227/2328 (52.7%)	952/2163 (44.0%)	<.001	1270/2384 (53.3%)	892/2074 (43.0%)	<.001
BMI (kg/m^2)	30.4 (6.43)	30.4 (5.38)	.769	30.4 (6.59)	30.5 (5.39)	.619
Cardiac risk scores						
Framingham risk score	14.7 (9.53)	28.2 (16.24)	.000	15.3 (10.15)	29.2 (16.32)	<.001
ASCVD pooled cohort risk equation	12.1 (10.93)	16.5 (11.40)	.000	12.9 (11.79)	17.3 (11.51)	<.001
Presenting symptoms			.290			.928
Chest pain	1744/2332 (74.8%)	1578/2165 (72.9%)		1711/2387 (71.7%)	1489/2076 (71.7%)	
Provider characterization			.647			.237
Typical	261/2332 (11.2%)	260/2168 (12.0%)		265/2388 (11.1%)	241/2078 (11.6%)	
Atypical	1818/2332 (78.0%)	1683/2168 (77.6%)		1853/2388 (77.6%)	1634/2078 (78.6%)	
Noncardiac	253/2332 (10.8%)	225/2168 (10.4%)		270/2388 (11.3%)	203/2078 (9.8%)	
Dyspnea	322/2332 (13.8%)	311/2165 (14.4%)		385/2387 (16.1%)	328/2076 (15.8%)	
Other	266/2332 (11.4%)	276/2165 (12.7%)		291/2387 (12.2%)	259/2076 (12.5%)	
Baseline medication use						
Aspirin	967/2273 (42.5%)	978/2030 (48.2%)	<.001	928/2316 (40.1%)	961/1963 (49.0%)	<.001
Statin	1028/2273 (45.2%)	945/2030 (46.6%)	.384	1026/2316 (44.3%)	938/1963 (47.8%)	.023
β-Blocker	614/2273 (27.0%)	451/2030 (22.2%)	<.001	641/2316 (27.7%)	429/1963 (21.9%)	<.001
ACEi or ARB	934/2273 (41.1%)	926/2030 (45.6%)	.003	1013/2316 (43.7%)	890/1963 (45.3%)	.294

Data reported as mean (SD) or n/N (%).
ACEi, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker.

P < .001; stress: 3.5% vs 6.0%, P < .001) test results. Although fewer women had a severe abnormality on CTA compared with men (3.3% vs 8.7%, P < .001), there was a similar proportion of women and men with a severe abnormality on stress testing (8.0% vs 7.9%, P = .98) (Table III; Figure 1).

Sex differences in processes of care after noninvasive testing

Similar proportions of women and men with severe abnormalities, mild abnormalities, or normal NITs were referred for catheterization (Table III). However, among those with a moderately abnormal NIT, fewer women than men were referred for catheterization (40.0% vs 57.5%, P < .001). After adjustment for clinical factors, including NIT type and 4-tier test result, women overall were less likely to be referred for catheterization compared with men (OR [95% CI] 0.75 [0.62-0.90], P = .002) (Table IV). This sex-based difference in referral for catheterization was not modified by type of NIT or by 4-tier NIT result (adjusted interaction P = .25).

Table III. Test results and processes of care by sex and noninvasive testing arm.

Characteristic	Overall (N = 8966)			CTA (n = 4500)			Stress test (n = 4466)		
	Women (n = 4720)	Men (n = 4246)	P value	Women (n = 2332)	Men (n = 2168)	P value	Women (n = 2388)	Men (n = 2078)	P value
Severe abnormalities	268/4720 (5.7%)	353/4246 (8.3%)	<.001	78/2332 (3.3%)	188/2168 (8.7%)	<.001	190/2388 (8.0%)	165/2078 (7.9%)	.984
Referral to ICA within 90 d of randomization	155/268 (57.8%)	221/353 (62.6%)		55/78 (70.5%)	138/188 (73.4%)		100/190 (52.6%)	83/165 (50.3%)	
ICA positive	73/155 (47.1%)	159/221 (71.9%)		40/55 (72.7%)	103/138 (74.6%)		33/100 (33.0%)	56/83 (67.5%)	
Referral for revascularization within 30 d of ICA	56/73 (76.7%)	139/159 (87.4%)		29/40 (72.5%)	91/103 (88.3%)		27/33 (81.8%)	48/56 (85.7%)	
Moderate abnormalities	190/4720 (4.0%)	287/4246 (6.8%)	<.001	106/2332 (4.5%)	162/2168 (7.5%)	<.001	84/2388 (3.5%)	125/2078 (6.0%)	<.001
Referral to ICA within 90 d of randomization	76/190 (40.0%)	165/287 (57.5%)		58/106 (54.7%)	103/162 (63.6%)		18/84 (21.4%)	62/125 (49.6%)	
ICA positive	41/76 (53.9%)	107/165 (64.8%)		32/58 (55.2%)	73/103 (70.9%)		9/18 (50.0%)	34/62 (54.8%)	
Referral for revascularization within 30 d of ICA	36/41 (87.8%)	94/107 (87.9%)		28/32 (87.5%)	64/73 (87.7%)		8/9 (88.9%)	30/34 (88.2%)	
Mild abnormalities	1382/4720 (29.3%)	1502/4246 (35.4%)	<.001	1185/2332 (50.8%)	1276/2168 (58.9%)	<.001	197/2388 (8.2%)	226/2078 (10.9%)	.003
Referral to ICA within 90 d of randomization	100/1382 (7.2%)	117/1502 (7.8%)		80/1185 (6.8%)	92/1276 (7.2%)		20/197 (10.2%)	25/226 (11.1%)	
ICA positive	28/100 (28.0%)	53/117 (45.3%)		23/80 (28.8%)	40/92 (43.5%)		5/20 (25.0%)	13/25 (52.0%)	
Referral for revascularization within 30 d of ICA	24/28 (85.7%)	39/53 (73.6%)		19/23 (82.6%)	27/40 (67.5%)		5/5 (100.0%)	12/13 (92.3%)	
Normal	2880/4720 (61.0%)	2104/4246 (49.6%)	<.001	963/2332 (41.3%)	542/2168 (25.0%)	<.001	1917/2388 (80.3%)	1562/2078 (75.2%)	<.001
Referral to ICA within 90 d of randomization	27/2880 (0.9%)	31/2104 (1.5%)		2/963 (0.2%)	1/542 (0.2%)		25/1917 (1.3%)	30/1562 (1.9%)	
ICA positive	4/27 (14.8%)	6/31 (19.4%)		0/2 (0.0%)	0/1 (0.0%)		4/25 (16.0%)	6/30 (20.0%)	
Referral for revascularization within 30 d of ICA	2/4 (50.0%)	5/6 (83.3%)		-	-		2/4 (50.0%)	5/6 (83.3%)	

Data reported as n/N (%).

Of the subjects who underwent catheterization, a significantly smaller proportion of women compared with men had obstructive CAD (40.8% vs 60.9%, P < .001), and fewer women underwent subsequent revascularization within 30 days (34.6% vs 53.6%, P < .001) (Table IV). However, after adjustment for clinical factors, including presence of obstructive CAD on catheterization, the likelihood of referral for revascularization was not significantly different in women and men (adjusted OR [95% CI] 0.73 [0.45-1.20], P = .21). This relationship was not modified by NIT modality (adjusted interaction P = .74) or catheterization results (adjusted interaction P = .62).

Of the patients with a history of dyslipidemia, stroke/transient ischemic attack (TIA), or peripheral arterial disease or with a positive CTA or catheterization showing obstructive CAD, women were less likely than men to report statin use at a 60-day visit (adjusted OR 0.81 [0.73-0.91]; P < .001). In contrast, there was no sex-based difference in likelihood of being on aspirin therapy among patients with history of stroke/TIA, with peripheral arterial disease, or with a positive CTA or catheterization (adjusted OR 0.78 [0.56-1.08]; P = .13) (Table IV).

Sex differences in outcomes after noninvasive testing

Over a median follow-up of 25 months, women had better outcomes than men both before and after adjustment for clinical factors and care, including catheterization results and revascularization (adjusted HR [95% CI] for composite outcome of death/MI/UAH: 0.74 [0.57-0.95], P = .019) (Figure 2). This also held true for the secondary outcome of CV death/MI/UAH (0.73 [0.55-0.97], P = .032) and was shy of statistical significance for CV death/MI (0.71 [0.49-1.02], P = .064).

Figure 1
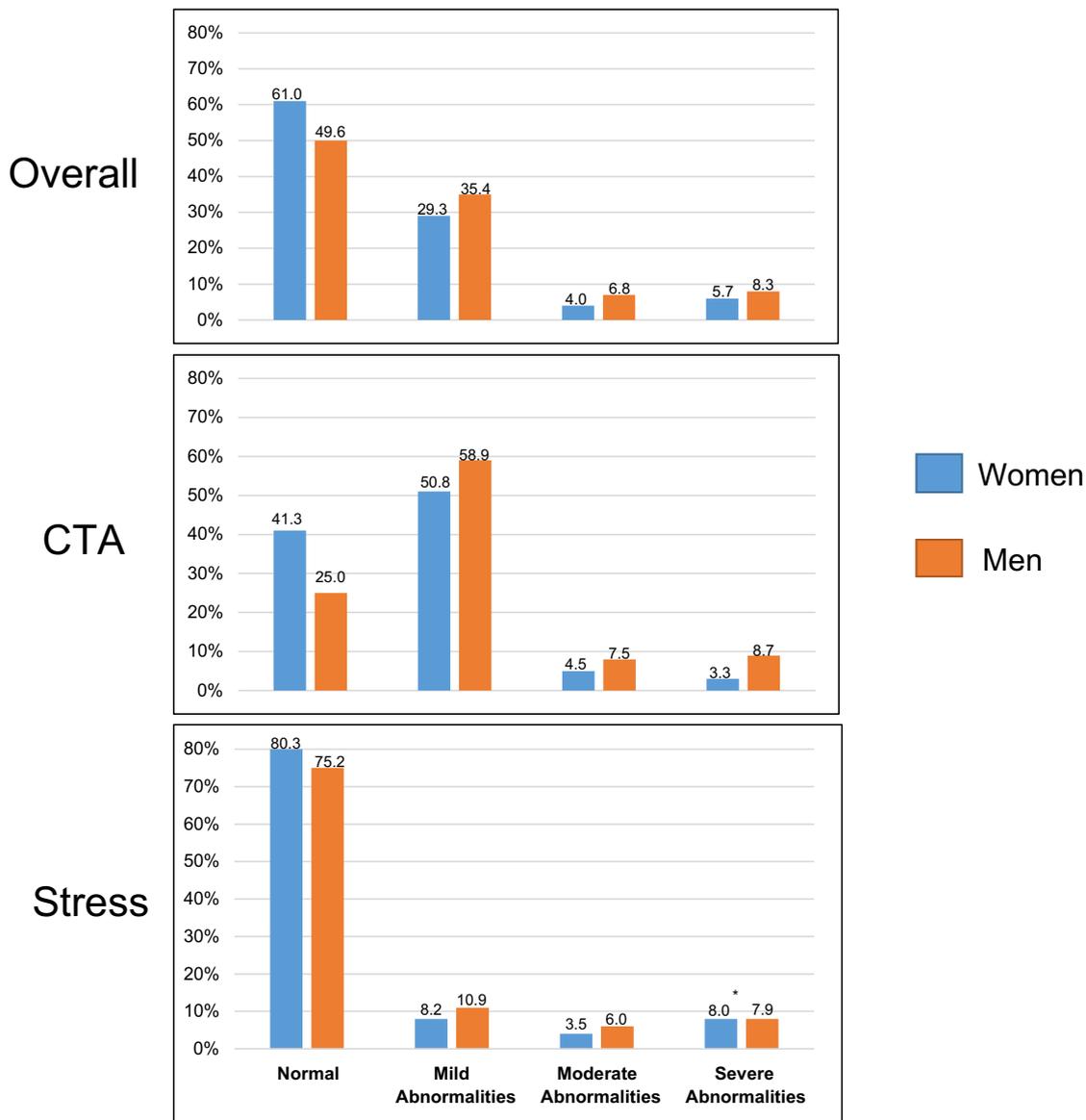
NIT test results by sex and NIT type. *This is the only nonstatistically significant comparison between women and men presented in this figure.

Compared with men, women less often experienced the primary composite end point both among those who were referred for catheterization (8.9% vs 11.1%, adjusted HR [95% CI] 0.77 [0.49-1.21], P = .26) and among those who were not (1.8% vs 2.5%, adjusted HR 0.75 [0.55-1.02], P = .07) (Figure 2). However, only when all patient groups were pooled together was a statistically significant difference in outcomes between women and men observed (0.74 [0.57-0.95], P = .019). No difference in the primary outcome was observed among women and men

who underwent revascularization (adjusted HR 1.02 [0.59-1.76], P = .94).

Discussion

Many prior studies have reported differences in management of established CAD by sex.[3,6,13] However, the increasing use of CTA as an NIT strategy may have impacted the management of women and men with suspected CAD. Our data from the PROMISE trial suggest that the large majority of patients of both sexes

Table IV. Associations between sex and processes of care measures*

Factor of interest	Frequency of event (# Events/sample size)		Unadjusted		Adjusted	
	Women	Men	OR (95% CI)	P value	OR (95% CI)	P value
Association between sex and referral for catheterization[†]						
Women vs men	358/4720 (7.58%)	534/4246 (12.58%)	0.57 (0.50-0.66)	<.001	0.75 (0.62-0.90)	.002
Association between sex and revascularization[‡]						
Women vs men	124/358 (34.64%)	286/534 (53.56%)	0.46 (0.35-0.61)	<.001	0.73 (0.45-1.20)	.214
Association between sex and medication use[§]						
Aspirin[‖]						
Women vs men	322/462 (69.70%)	480/598 (80.27%)	0.57 (0.43-0.75)	<.001	0.78 (0.56-1.08)	.131
Statin[¶]						
Women vs men	2072/3291 (62.96%)	1937/2806 (69.03%)	0.76 (0.69-0.85)	<.001	0.81 (0.73-0.91)	<.001

* For each of the models presented in the table, we tested the interaction between sex and NIT modality with the given process of care outcome measure. None of the relationships between sex and each process of care measure were modified by NIT modality (all interaction P = not significant).
† Adjusted model for catheterization referral controls for NIT modality (CTA/stress test); NIT results (4-tier); BMI (kg/m^2); age (standardized by sex); chest pain versus other as primary symptoms; chest pain typicality (typical, atypical, noncardiac); and risk factors such as smoker (ever/never), diabetes, hypertension, history of peripheral artery or cerebrovascular disease, sedentary lifestyle, depression, family history of premature CAD, and dyslipidemia.
‡ Adjusted model for revascularization controls for NIT modality (CTA/stress test); NIT results (4-tier); ICA results (positive/negative); BMI (kg/m^2); age (standardized by sex); chest pain versus other as primary symptoms; chest pain typicality (typical, atypical, noncardiac); and risk factors such as smoker (ever/never), diabetes, hypertension, history of peripheral artery or cerebrovascular disease, sedentary lifestyle, depression, family history of premature CAD, and dyslipidemia.
§ Medication use at 60-day visit. Adjusted models control for NIT modality (CTA/stress test); BMI (kg/m^2); age (standardized by sex); chest pain versus other as primary symptoms; chest pain typicality (typical, atypical, noncardiac); risk factors such as smoker (ever/never), diabetes, hypertension, history of peripheral artery or cerebrovascular disease, sedentary lifestyle, depression, family history of premature CAD, and dyslipidemia.
‖ Includes n = 1,106 patients who had a history of stroke/TIA, had peripheral arterial disease, or had a positive CTA or catheterization prior to 60-day visit.
¶ Includes n = 6,758 patients who had a history of dyslipidemia, diabetes, stroke/TIA, peripheral arterial disease, or 10-year ASCVD risk ≥7.5%, or who had a positive CTA or catheterization prior to 60-day visit.

undergoing NIT have negative results—in women more than in men and with stress testing more than with CTA. After accounting for differences in NIT results, women with stable symptoms concerning for ischemia were less likely to be referred for catheterization than men and less likely to have obstructive CAD on catheterization once referred. However, among those referred for catheterization, women and men were similarly likely to undergo revascularization. Women were less likely than men to report statin therapy use even when indicated. Despite these differences, women were less likely to experience adverse CV outcomes than their male counterparts.

Our finding that the majority of individuals who underwent stress testing had negative results, with a significantly higher rate of negative tests in women than in men, has been observed in multiple prior studies of stress testing.[14,15] We further show that, with CTA, women continue to have higher rates of negative test results than their male counterparts. A lower referral rate for catheterization in women compared with men was first shown 4 decades ago in the stable angina population[1] and has since been confirmed by many,[3-6] but not all,[16-18] subsequent studies on the matter. The reasons for this difference were postulated to be related to interpretation of stress test findings given the known sex differences in the sensitivity and specificity of stress testing.[7] Physicians may have been aware of the higher false-positive rates of exercise tolerance testing, nuclear stress testing, and echo stress testing in women[8] and may therefore have been less

likely to refer women with a positive stress test for catheterization compared with men. However, our data indicate that, even with CTA testing, which provides a visual, anatomic assessment of the amount of coronary atherosclerosis present and provides similar accuracy in both sexes,[8] women were still less frequently referred for catheterization than men after accounting for test results. This suggests that suspicion of an inaccurate noninvasive test cannot entirely explain the lower rate of catheterization referral in women. It is possible that the higher use of β-blocker therapy in women versus men could have led to fewer anginal symptoms in women and could therefore have contributed to the lower rate of referral for catheterization in women.

Nonetheless, women had better outcomes compared with men. This may be related to the higher rate of completely normal coronary anatomy seen in women compared with men. Because even mild nonobstructive disease is associated with greater CV morbidity than completely normal coronary arteries,[19] the higher prevalence of this finding in men may account, at least in part, for the higher event rate in men than in women who did not undergo catheterization. This is also likely related to the overall lower CV risk of women compared with men in this study, as evidenced by the lower Framingham and atherosclerotic cardiovascular disease (ASCVD) risk scores.

Among individuals who underwent catheterization, and specifically among those who underwent revascularization, the outcomes of women in our study were not

Figure 2
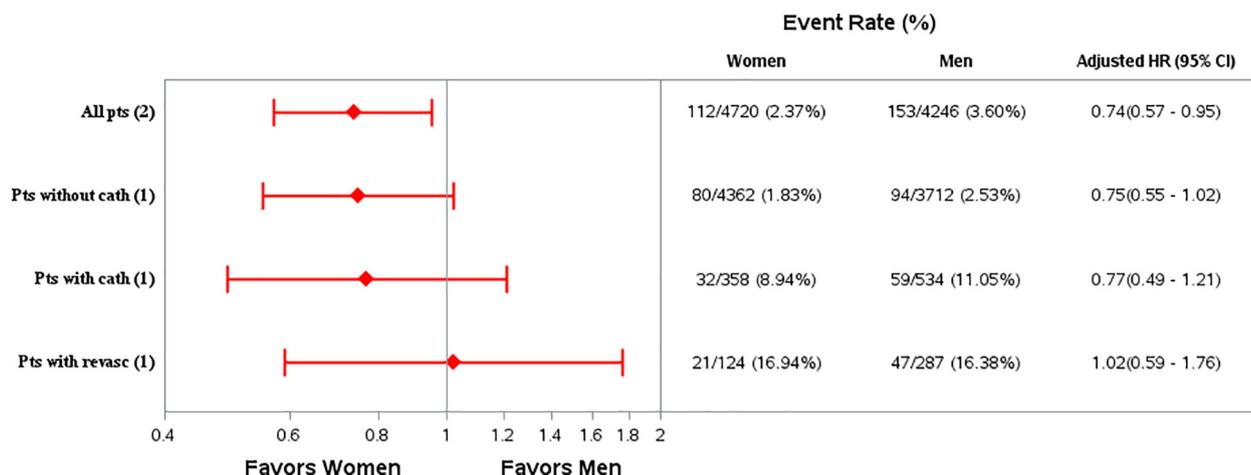
Associations between patient sex (women vs men) and the primary outcome of all-cause death, myocardial infarction, or unstable angina in different subsets of the PROMISE population. (1) Adjusted model controls for NIT modality (CTA/stress test); NIT results (4-tier); ICA referral and results (positive/negative); referral for revascularization; and factors listed in (2) below. (2) Adjusted model controls for BMI (kg/m^2); age (standardized by sex); chest pain versus other as primary symptoms; chest pain typicality (typical, atypical, noncardiac); and risk factors such as smoker (ever/never), diabetes, hypertension, history of peripheral artery or cerebrovascular disease, sedentary lifestyle, depression, family history of premature CAD, and dyslipidemia.

significantly different from those of men. Similar CV event rates in women and men with documented CAD have previously been described,[7] although a higher event rate in women in this group has also been demonstrated.[6] Our data from the PROMISE trial indicate that once women were referred for catheterization, their management with revascularization as well as their CV outcomes was similar to men who were referred for catheterization. Statin therapy, on the other hand, was lower in women, which has been shown in multiple settings in the United States.[20,21] This could be related to the lower overall ASCVD pooled cohort risk score noted in women in this study compared with men (median [25th, 75th percentile]: 8.8% [4.7%, 16.2%] vs 14.0% [8.5%, 22.5%], $P \le$ .001).

Our study has several strengths. PROMISE is the first large pragmatic comparative effectiveness trial of functional versus anatomic testing strategies in stable symptomatic outpatients, and because all decision making after NIT was left up to the providers, it provides insight into current clinical practice. Second, the trial is uniquely able to address sex-based differences in the management and outcomes of patients with suspected CAD because, to our knowledge, it includes the largest number of stable symptomatic women of any prospective trial of diagnostic testing to date.

Our study also has several caveats that should be considered when interpreting the results. Randomization was not stratified by patient sex; however, within each

sex, the 2 testing arms were similar. Physician rationale for various management decisions was not collected, so we were unable to directly evaluate the reasons behind sex-based differences in patient management. Because less than 5% of our study population underwent coronary revascularization, this study likely lacked the power to detect a difference in the adjusted likelihood of revascularization between sexes. Although patients were followed for a median of >2 years, there were relatively few clinical end point events, limiting the ability to assess differences in outcomes by sex.

Conclusion

In the PROMISE trial population, women with stable symptoms concerning for ischemia had more normal and fewer abnormal NITs than men. Women with abnormalities on NIT were less likely to be referred for catheterization than men, regardless of whether they initially underwent stress testing or anatomic imaging with CTA, and they were less likely to receive statin therapy when indicated. Nonetheless, women had better CV outcomes than their male counterparts, perhaps related to the lower overall CV risk in women in this group. Thus, discrepancies in the management of women and men with stable angina still exist, but despite these, the outcomes of women with stable angina referred for NIT were not adversely affected compared with men. Sex-specific algorithms to determine which patients need

to undergo NIT and how they should subsequently be managed are urgently needed.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.11.002.

Disclosures

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