JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 67, NO. 22, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.03.523

Sex Differences in Functional and CT Angiography Testing in Patients With Suspected Coronary Artery Disease

Neha J. Pagidipati, MD, MPH,[a] Kshipra Hemal,[a] Adrian Coles, PhD,[a] Daniel B. Mark, MD, MPH,[a] Rowena J. Dolor, MD, MHS,[a,b] Patricia A. Pellikka, MD,[c] Udo Hoffmann, MD,[d] Sheldon E. Litwin, MD,[e] James Udelson, MD,[f] Melissa A. Daubert, MD,[a] Svati H. Shah, MD,[a,b] Beth Martinez, BS,[a] Kerry L. Lee, PhD,[a] Pamela S. Douglas, MD[a]

ABSTRACT

BACKGROUND Although risk stratification is an important goal of cardiac noninvasive tests (NITs), few contemporary data exist on the prognostic value of different NITs according to patient sex.

OBJECTIVES The goal of this study was to compare the results and prognostic information derived from anatomic versus stress testing in stable men and women with suspected coronary artery disease.

METHODS In 8,966 patients tested at randomization (4,500 to computed tomography angiography [CTA], 52% female; 4,466 to stress testing, 53% female), we assessed the relationship between sex and NIT results and between sex and a composite of death, myocardial infarction, or unstable angina hospitalization.

RESULTS In women, a positive CTA (≥70% stenosis) was less likely than a positive stress test result (8% vs. 12%; adjusted odds ratio: 0.67). Compared with negative test results, a positive CTA was more strongly associated with subsequent clinical events than a positive stress test result (CTA-adjusted hazard ratio of 5.86 vs. stress-adjusted hazard ratio of 2.27; adjusted $p = 0.028$). Men were more likely to have a positive CTA than a positive stress test result (16% vs. 14%; adjusted odds ratio: 1.23). Compared with negative test results, a positive CTA was less strongly associated with subsequent clinical events than a positive stress test result in men, although this difference was not statistically significant (adjusted $p = 0.168$). Negative CTA and stress test results were equally likely to predict an event in both sexes. A significant interaction between sex, NIT type, and test result ($p = 0.01$) suggests that sex and NIT type jointly influence the relationship between test result and clinical events.

CONCLUSIONS The prognostic value of an NIT result varies according to test type and patient sex. Women seem to derive more prognostic information from a CTA, whereas men tend to derive similar prognostic value from both test types. (J Am Coll Cardiol 2016;67:2607–16) © 2016 by the American College of Cardiology Foundation.

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From the [a]Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina; [b]Department of Medicine, Duke University School of Medicine, Durham, North Carolina; [c]Mayo Clinic, Rochester, Minnesota; [d]Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [e]Department of Medicine, Medical University of South Carolina, Charleston, South Carolina; and the [f]Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts.
This project was supported by grants from the National Heart, Lung, and Blood Institute (R01HL098237, R01HL098236, R01HL98305, and R01HL098235). This paper does not necessarily represent the official views of the National Heart, Lung, and Blood Institute. Dr. Mark has received personal fees from Medtronic, CardioDx, and St. Jude Medical; and grant support from Eli Lilly, Bristol-Myers Squibb, Gilead Sciences, AGA Medical, Merck, Oxygen Biotherapeutics, and AstraZeneca. Dr. Hoffmann has received grant support from Siemens Healthcare and HeartFlow. Dr. Douglas has received grant support from HeartFlow; and serves on a Data and Safety Monitoring Board for GE Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 21, 2016; accepted March 24, 2016.

JACC VOL. 67, NO. 22, 2016
JUNE 7, 2016:2607–16

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CI = confidence interval

CTA = computed tomographic angiography

ECG = electrocardiography

HR = hazard ratio

MCD = microvascular coronary dysfunction

MI = myocardial infarction

NIT = noninvasive test

OR = odds ratio

Two major goals of noninvasive tests (NITs) in patients with chest pain are the diagnosis of obstructive coronary artery disease (CAD) and risk stratification because both diagnostic and prognostic information are essential to optimally guide subsequent management (1). Careful analyses of diagnostic accuracy have revealed different test performances not only by modality but also according to patient sex (2). These sex-related differences may be due to reasons as varied as baseline differences in electrocardiography (ECG) characteristics, breast attenuation, smaller coronary vessel size, and the higher prevalence of microvascular coronary dysfunction (MCD) in women, leading to a higher rate of false-positive test results in women (2-4).

SEE PAGE 2617

Given these well-established variations by sex in diagnostic test performance, it is reasonable to postulate that NITs may also provide different prognostic information in women and in men. This scenario in turn may result in differences in the relative value of anatomic versus stress testing for patients of each sex. Although older studies have compared the prognostic value of stress testing within each sex, there are few contemporary data on this issue (5-7). Furthermore, recent observational studies on the prognostic value of computed tomography angiography (CTA) do not include sex-specific analyses (8,9). A fuller understanding of the prognostic performance of these tests could aid in selecting the most effective diagnostic evaluation strategy for both women and men.

The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) randomized 10,003 outpatients with stable symptoms suggestive of CAD to a strategy of either functional or anatomic (CTA) testing (10). Over a median follow-up of 25 months, there was no difference between testing arms in clinical events overall or according to sex. However, the primary analysis did not compare the prognostic capabilities of the 2 types of tests in either women or men. Given the high percentage (53%) of women enrolled in this trial and the randomized selection of test type, it is an ideal setting in which to explore the associations between test results and clinical events in each sex. We hypothesized that the 2 types of NITs (anatomic and stress testing) would have different likelihoods of being positive in women and in men, and that the relationships between a positive test result and a clinical event, compared with those of a negative test result, would be jointly influenced by patient sex and NIT type.

METHODS

The PROMISE trial was a pragmatic comparative effectiveness trial that randomized stable symptomatic patients without known CAD requiring noninvasive testing to either an initial strategy of anatomic (CTA) or stress testing (10,11). For patients in the stress testing arm, the choice of test was left up to the clinician (exercise ECG, stress echocardiography, or stress nuclear). Randomization was stratified according to study site as well as the stress test type pre-specified by the provider.

All tests were performed and interpreted by local physicians who were responsible for all subsequent clinical decisions. A positive CTA was defined as one that showed obstructive CAD (i.e., ≥70% stenosis in at least 1 epicardial artery or ≥50% stenosis in the left main coronary artery). An exercise ECG was considered positive if there were ST-segment changes consistent with ischemia during stress or early termination (<3 min) due to reproduction of symptoms, arrhythmia, and/or hypotension. A stress echocardiography or stress nuclear test was considered positive if there was inducible ischemia in at least 1 coronary territory (anterior, inferior, or lateral) or early termination of exercise stress (<3 min) due to ST-segment changes consistent with ischemia, symptom reproduction, arrhythmia, and/or hypotension.

This secondary analysis included those patients who were tested as randomized and who had interpretable results, defined as not missing and not indeterminate. The primary endpoint was the same as that of the overall trial (a composite of death from any cause, myocardial infarction [MI], or unstable angina hospitalization), except that the major procedural complication component was omitted because it was not believed to be related to the prognostic value of the test. A composite of time to cardiovascular death or MI was a secondary outcome.

Baseline characteristics were described by using means ± SDs for continuous variables and percentages for categorical variables. Characteristics were compared between patients in each NIT arm according to sex by using chi-square testing for categorical variables and the Wilcoxon rank sum test for continuous variables.

To determine whether the likelihood of a positive test differed by type of NIT (CTA vs. stress test) in women and in men, multivariable logistic regression analyses were performed. To further determine whether these relationships were independent of risk factors, the model was adjusted according to patient age, race, baseline cardiac risk factors (history of hypertension, dyslipidemia, diabetes, tobacco use, family history of premature CAD, absence of regular exercise, CAD equivalent [defined as history of cerebrovascular disease, peripheral artery disease, and/or diabetes], and body mass index), global estimates of cardiovascular disease as derived from the Framingham risk score (12), the ASCVD (atherosclerotic cardiovascular disease) Pooled Cohort Equation risk score (13), the updated Diamond and Forrester risk score (14), typicality of chest pain, and physician's estimation of the likelihood of significant CAD. A 2-way interaction between type of NIT and sex was included to determine whether the relationship between NIT type and test positivity was modified by patient sex.

To assess the prognostic value of each type of NIT for women and for men, multivariable Cox regression models were used to examine the relationship between test result, test type, patient sex, and both the primary composite outcome and the secondary outcome of time to cardiovascular death or MI. This model included a 3-way interaction between patient sex, test type, and test result to determine whether the relationships between test result and outcomes were modified jointly by sex and NIT type. Because the comparison of interest (patients with positive test results vs. patients with negative test results) was a nonrandomized comparison, direct adjusted event curves were computed to control for possible confounders of the relationship between test result and the primary composite outcome (15). The event curves and the aforementioned Cox regression models were adjusted for the same clinical factors as in the test positivity analysis. To further investigate how negative test results affect the prognostic value of each type of NIT, Cox regression models were developed to examine the relationship between NIT type and the primary composite outcome in women and in men with a negative test result.

All statistical calculations were conducted by using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Among the 8,966 PROMISE patients who received the NIT type to which they were randomized and had interpretable results, CTA was performed in 4,500 (52% female) and stress testing in 4,466 (53% female) (Online Figure 1). Although randomization was not stratified according to sex, the characteristics of women in the 2 testing arms were relatively similar, as were those of men (**Table 1**).

EFFECT OF SEX AND TEST TYPE. There were 458 women (9.7% of 4,720 women total) who had a positive test result, with a significantly smaller proportion of positive CTAs compared with positive stress tests (8% vs. 12%; $p < 0.001$) (**Table 2**). The significance of this difference persisted after adjustment for clinical factors, with women less likely to have a positive CTA than a positive stress test (adjusted odds ratio [OR]: 0.67; 95% confidence interval [CI]: 0.55 to 0.82; $p < 0.001$) (**Table 3**). Specifically, CTA was less likely to be positive compared with exercise ECG (OR: 0.39; 95% CI: 0.25 to 0.61; $p < 0.001$) and nuclear stress testing (OR: 0.66; 95% CI: 0.53 to 0.82; $p < 0.001$) but not compared with stress echocardiography (OR: 0.90; 95% CI: 0.63 to 1.30; $p = 0.58$) (**Figure 1**).

In contrast, 640 men (15.1% of 4,246 men total) had a positive test result, with a marginally greater proportion of CTAs being positive compared with stress tests (16% vs. 14%; $p = 0.047$) (**Table 2**). After adjustment for clinical factors, men were more likely to have a positive CTA than a positive stress test (adjusted OR: 1.23; 95% CI: 1.04 to 1.47; $p = 0.019$) (**Table 3**). Specifically, in men, CTA was more likely to be positive compared with exercise ECG (OR: 1.79; 95% CI: 1.15 to 2.80; $p = 0.01$) and stress echocardiography (OR: 2.10; 95% CI: 1.45 to 3.04; $p < 0.001$) but not compared with nuclear stress testing (OR: 1.03; 95% CI: 0.85 to 1.25; $p = 0.75$) (**Figure 1**). The likelihood of a positive test result was strongly influenced by patient sex, such that the effect of test type on test result was different for women compared with men (interaction $p < 0.001$).

During the median 25 months of study follow-up, 112 women (2.4%; 57 in the CTA arm, 55 in the stress test arm) and 153 men (3.6%; 80 in the CTA arm, 73 in the stress test arm) experienced a primary endpoint event (**Table 2**). Overall, a positive NIT was strongly predictive of the composite endpoint of all-cause death/MI/hospitalization for unstable angina compared with a negative NIT (hazard ratio [HR]: 3.37; 95% CI: 2.59 to 4.38). An analysis of the interaction between sex, NIT type, and test result revealed that sex and NIT type jointly modified the association of test result (positive vs. negative) with the risk of experiencing the primary composite endpoint (adjusted interaction $p = 0.010$) (**Table 4**). Thus, the influence of test type on the relationship between test result and outcome was different for women compared with men.

In women, the association of test results (positive vs. negative) with clinical events in CTA was stronger than the association of test results with clinical events in stress tests (unadjusted HR: 6.39; 95% CI: 3.65 to 11.17 vs. 2.70; 95% CI: 1.45 to 5.03)

JACC VOL. 67, NO. 22, 2016
JUNE 7, 2016:2607–16

TABLE 1 Baseline Characteristics

	Women				Men			
	All Women (n = 4,720)	CTA (n = 2,332)	Stress Test (n = 2,388)	p Value	All Men (n = 4,246)	CTA (n = 2,168)	Stress Test (n = 2,078)	p Value
Demographics								
Age, yrs	62.4 ± 7.8	62.2 ± 7.7	62.6 ± 7.9	0.07	58.9 ± 8.3	58.6 ± 8.2	59.2 ± 8.4	0.008
Age ≥65 yrs	1,627 (34.5)	780 (33.4)	847 (35.5)	0.14	961 (22.6)	471 (21.7)	490 (23.6)	0.15
Racial or ethnic minority	1,052 (22.4)	547 (23.6)	505 (21.3)	0.06	913 (21.6)	471 (21.9)	442 (21.4)	0.70
Cardiac risk factors								
Hypertension	3,137 (66.5)	1,534 (65.8)	1,603 (67.1)	0.33	2,673 (63.0)	1,359 (62.7)	1,314 (63.2)	0.71
Diabetes	1,025 (21.7)	500 (21.4)	525 (22.0)	0.65	883 (20.8)	436 (20.1)	447 (21.5)	0.26
Metabolic syndrome	1,761 (37.3)	857 (36.7)	904 (37.9)	0.43	1,626 (38.3)	816 (37.6)	810 (39.0)	0.37
Dyslipidemia	3,258 (69.0)	1,621 (69.5)	1,637 (68.6)	0.48	2,812 (66.2)	1,408 (64.9)	1,404 (67.6)	0.07
Cerebrovascular disease	220 (4.7)	103 (4.4)	117 (4.9)	0.43	140 (3.3)	71 (3.3)	69 (3.3)	0.93
Peripheral artery disease	86 (1.8)	42 (1.8)	44 (1.8)	0.92	75 (1.8)	32 (1.5)	43 (2.1)	0.14
History of heart failure	186 (3.9)	90 (3.9)	96 (4.0)	0.77	150 (3.5)	73 (3.4)	77 (3.7)	0.55
Current or former smoker	2,162 (45.8)	1,068 (45.8)	1,094 (45.8)	0.70	2,420 (57.0)	1,224 (56.5)	1,196 (57.6)	0.02
Family history of premature CAD	1,602 (34.1)	815 (35.1)	787 (33.1)	0.15	1,237 (29.2)	645 (29.9)	592 (28.6)	0.35
History of depression	1,226 (26.0)	599 (25.7)	627 (26.3)	0.65	625 (14.7)	286 (13.2)	339 (16.3)	0.004
Participate in physical activity	2,215 (47.0)	1,101 (47.3)	1,114 (46.7)	0.70	2,393 (56.5)	1,211 (56.0)	1,182 (57.0)	0.51
BMI, kg/m^2	30.4 ± 6.5	30.4 ± 6.4	30.4 ± 6.6	0.93	30.5 ± 5.4	30.4 ± 5.4	30.5 ± 5.4	0.36
Cardiac risk scores								
Framingham	15.0 ± 9.9	14.7 ± 9.5	15.3 ± 10.2	0.17	28.7 ± 16.3	28.2 ± 16.2	29.2 ± 16.3	0.02
ASCVD Pooled Cohort Equation	12.5 ± 11.4	12.1 ± 10.9	12.9 ± 11.8	0.06	16.9 ± 11.5	16.5 ± 11.4	17.3 ± 11.5	0.01
Diamond and Forrester (2011)	28.4 ± 12.3	28.1 ± 12.1	28.6 ± 12.5	0.29	60.3 ± 17.5	60.0 ± 17.7	60.5 ± 17.2	0.13
Presenting symptoms								
Chest pain	3,455 (73.2)	1,744 (74.8)	1,711 (71.7)	0.02	3,067 (72.3)	1,578 (72.9)	1,489 (71.7)	0.40
Aching/dull	808 (23.4)	418 (24.0)	390 (22.8)	0.42	847 (27.6)	424 (26.9)	423 (28.4)	0.34
Crushing/pressure/squeezing/ tightness	1,832 (53.0)	921 (52.8)	911 (53.2)	0.80	1,413 (46.1)	754 (47.8)	659 (44.3)	0.05
Provider characterization of chest pain				0.88				0.72
Typical	526 (11.1)	261 (11.2)	265 (11.1)		501 (11.8)	260 (12.0)	241 (11.6)	
Atypical	3,671 (77.8)	1,818 (78.0)	1,853 (77.6)		3,317 (78.1)	1,683 (77.6)	1,634 (78.6)	
Physical examination								
Systolic BP, mm Hg	131.0 ± 17.1	130.8 ± 16.8	131.1 ± 17.4	0.76	131.6 ± 15.9	131.4 ± 16.1	131.8 ± 15.8	0.32
Diastolic BP, mm Hg	77.6 ± 10.2	77.4 ± 10.1	77.7 ± 10.3	0.21	80.1 ± 10.2	80.2 ± 10.2	80.1 ± 10.2	0.83

Values are mean ± SD or n (%).
ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CTA = computed tomography angiography.

(Table 4, Central Illustration). This relationship persisted after adjusting for clinical factors, with a >2-fold greater HR for the association of test results to clinical events in CTA compared with the association of test results to clinical events in stress tests (adjusted HR: 5.86; 95% CI: 3.32 to 10.35 vs. 2.27; 95% CI: 1.21 to 4.25; adjusted p = 0.028) (Table 4, Figure 2). In contrast, in men, the association of test results to clinical events in CTA was weaker than the association of test results to clinical events in stress tests (unadjusted HR: 3.69; 95% CI: 2.35 to 5.79 vs. 5.39; 95% CI: 3.39 to 8.56). This relationship persisted after adjustment for clinical factors, although the difference in adjusted HRs did not reach statistical significance (adjusted HR: 2.80; 95% CI: 1.76 to 4.45 vs. 4.42; 95% CI: 2.77 to 7.07; adjusted p = 0.168).

There was no difference in the ability of a negative CTA and a negative stress test to predict clinical events in either women or men (adjusted HR of negative CTA vs. negative stress test in women: 0.89; 95% CI: 0.57 to 1.38; adjusted HR of negative CTA vs. negative stress test in men: 1.13; 95% CI: 0.75 to 1.72; all adjusted p values = NS) (Central Illustration). In both sexes, event rates were too low to meaningfully compare prognostic value across the different modalities of stress tests. There was no interaction between patient sex, NIT type, and the relationship between a positive test result and the secondary outcome of cardiovascular death or MI (unadjusted p = 0.77).

DISCUSSION

Risk stratification is one of the primary reasons to perform noninvasive testing in patients with suspected CAD, and it provides important supplemental

TABLE 2 Test Results and Event Rates

	Women			Men		
	CTA (n = 2,332)	Stress Test (n = 2,388)	p Value	CTA (n = 2,168)	Stress Test (n = 2,078)	p Value
Positive test result	184/2,332 (7.9)	274/2,388 (11.5)	<0.001	350/2,168 (16.1)	290/2,078 (14.0)	0.046
Multivessel disease/ischemia	78/184 (42.4)	190/274 (69.3)		188/350 (53.7)	165/290 (56.9)	
Single-vessel disease/ischemia	106/184 (57.6)	84/274 (30.7)		162/350 (46.3)	125/290 (43.1)	
Negative test result	2,148/2,332 (92.1)	2,114/2,388 (88.5)	<0.001	1,818/2,168 (83.9)	1,788/2,078 (86.0)	0.046
Nonobstructive CAD/abnormal ECG with normal imaging or scar without ischemia	1,185/2,148 (55.2)	197/2,114 (9.3)		1,276/1,818 (70.2)	226/1,788 (12.6)	
Normal anatomy/no abnormalities	963/2,148 (44.8)	1917/2,114 (90.7)		542/1,818 (29.8)	1,562/1,788 (87.4)	
Revascularization within 90 d	82/2,332 (3.5)	45/2,388 (1.9)	<0.001	191/2,168 (8.8)	102/2,078 (4.9)	<0.001
Primary composite endpoint: time to death/MI/UAH	57/2,332 (2.4)	55/2,388 (2.3)	0.750	80/2,168 (3.7)	73/2,078 (3.5)	0.757
Individual components			0.007			0.778
All-cause death	28/57 (49.1)	29/55 (52.7)		34/80 (42.5)	34/73 (46.6)	
MI	5/57 (8.8)	15/55 (27.3)		19/80 (23.8)	14/73 (19.2)	
UAH	24/57 (42.1)	11/55 (20.0)		27/80 (33.8)	25/73 (34.2)	
Secondary composite endpoint: time to CV death/MI	21/2,332 (0.9)	35/2,388 (1.5)	0.073	39/2,168 (1.8)	35/2,078 (1.7)	0.775
Individual components			0.203			0.331
CV death	15/21 (71.4)	19/35 (54.3)		19/39 (48.7)	21/35 (60.0)	
MI	6/21 (28.6)	16/35 (45.7)		20/39 (51.3)	14/35 (40.0)	

Values are n/N (%).
CV = cardiovascular; ECG = electrocardiogram; MI = myocardial infarction; UAH = hospitalization for unstable angina; other abbreviations as in Table 1.

information beyond diagnosis. The current analysis suggests that women may have derived greater prognostic information from a CTA, whereas men seemed to derive similar prognostic value from a CTA and a stress test. In both sexes, a negative CTA and a negative stress test result seemed to confer a similar likelihood of a clinical event. The durability of our findings after adjustment and the significance of the interaction terms suggest that our findings are unlikely due to either clinical characteristics or chance alone.

This analysis was performed in the context of the parent PROMISE trial, which found no difference in clinical events in patients randomized to undergo CTA versus stress testing arms overall or according to sex (10). The significant interaction terms in our analyses suggest, however, that the rate of test positivity and the prognostic value of a test depend on the type of test performed and the patient's sex. Thus, although there was no difference in outcomes between the testing arms, which aggregated patients with both positive and negative test results, women with a positive CTA tended to fare worse than women with a positive stress test result. Interestingly, although men randomized to the 2 testing arms had similar outcomes in the primary trial, men with a positive stress test result had more clinical events than men with a positive CTA, although this difference did not reach statistical significance.

This apparent discrepancy between the nonsignificant role of sex and test type in the clinical outcomes of the overall trial and the highly significant role of sex and test type in the prognostic value of each type

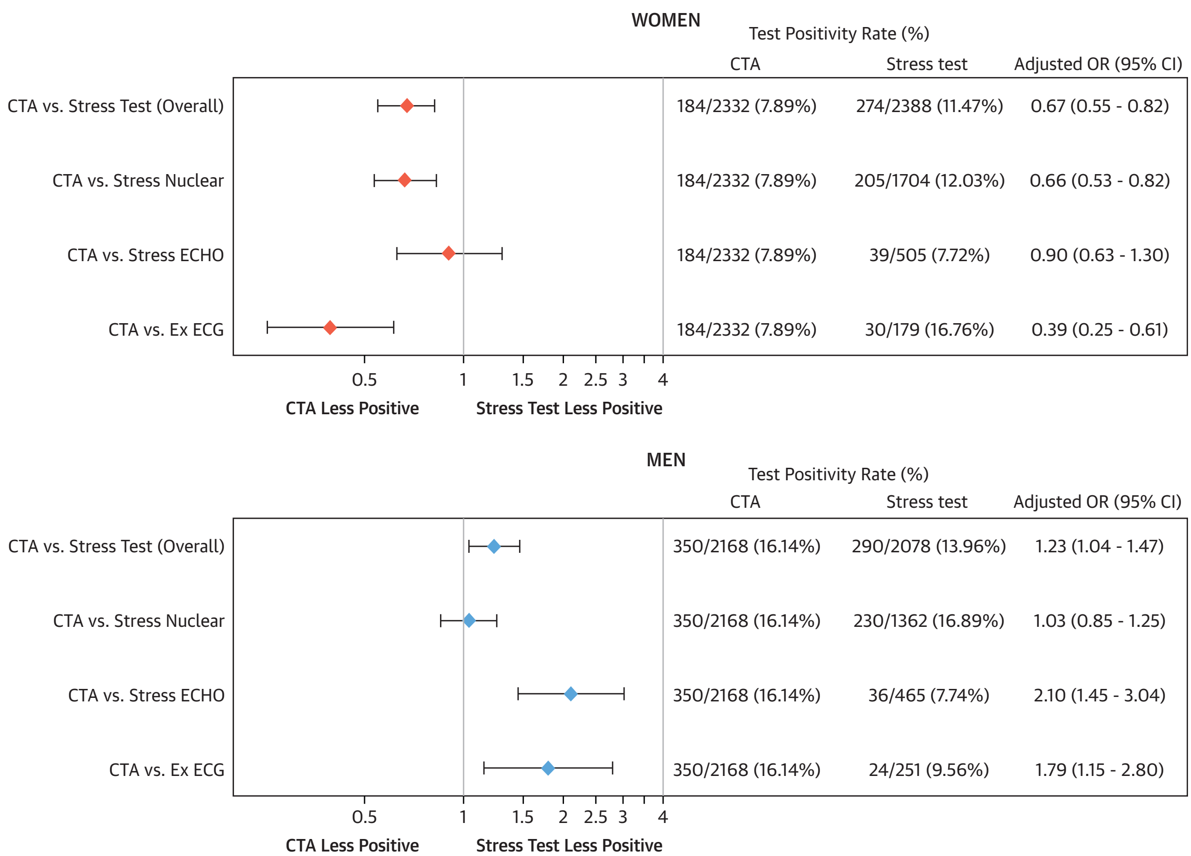
TABLE 3 Association Between NIT Type and Positive Test Results

	Positive Test Rate, No. of Positive Test Results/Sample Size (%)		CTA Versus Stress Test Unadjusted*		CTA Versus Stress Test Adjusted†	
	CTA	Stress Test	OR (95% CI)	p Value	OR (95% CI)	p Value
Interaction between randomized arm and sex			–	<0.001	–	<.001
CTA versus stress test in women	184/2,332 (7.89)	274/2,388 (11.47)	0.66 (0.54–0.80)	<0.001	0.67 (0.55–0.82)	<0.001
CTA versus stress test in men	350/2,168 (16.14)	290/2,078 (13.96)	1.19 (1.00–1.41)	0.047	1.23 (1.04–1.47)	0.019

*Unadjusted models contained sex, randomized testing arm, and interaction term. †Adjusted for age, race, BMI, CAD equivalent, Framingham risk score, ASCVD score, 2011 Diamond and Forrester score, hypertension, dyslipidemia, diabetes, family history of premature CAD, sedentary lifestyle, smoking, typicality of chest pain, and physician's estimation of likelihood of significant CAD.
CI = confidence interval; NIT = noninvasive test; OR = odds ratio; other abbreviations as in Table 1.

JACC VOL. 67, NO. 22, 2016
JUNE 7, 2016:2607–16

FIGURE 1 Adjusted Association Between Noninvasive Test Type and Result in Women and Men



In a comparison of computed tomography angiography (CTA) and various stress tests, CTA was shown to be less positive in women and stress tests were less positive for men. The associations were adjusted for age, race, body mass index, coronary artery disease (CAD) equivalent, Framingham risk score, atherosclerotic cardiovascular disease score, 2011 Diamond and Forrester score, hypertension, dyslipidemia, diabetes, family history of premature CAD, sedentary lifestyle, smoking, typicality of chest pain, and physician's estimation of likelihood of significant CAD. CI = confidence interval; ECG = electrocardiography; ECHO = echocardiography; OR = odds ratio.

of test may be approached in 3 ways. First, there are many steps in the clinical pathway of a patient between the result of their diagnostic NIT and their ultimate outcome. This pathway is especially relevant in a pragmatic, comparative effectiveness trial such as PROMISE, which did not control, for example, whether patients were referred for angiography, revascularized, prescribed appropriate pharmacological therapy, adherent to medications, or able to access follow-up care. A number of care patterns could have occurred differentially by testing arm and by sex, resulting in similar clinical events despite different capabilities of the test types to predict events in women and in men.

Second, during the trial, the providers were unaware of the possible sex-based differences in prognostic value of diagnostic testing that we have shown in this secondary analysis. Thus, they were unable to act on this information to influence future outcomes.

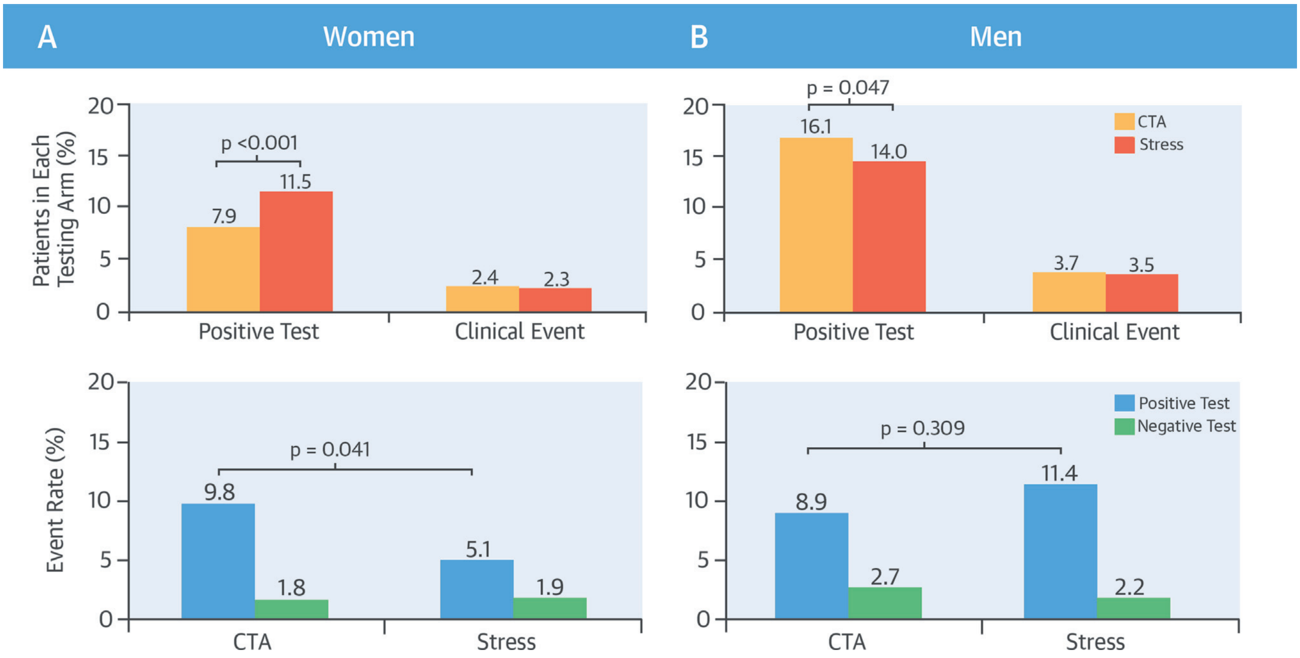
Third, it is important to note that in a setting such as PROMISE, in which event rates were similar in both testing arms in women and in men, the prognostic value of a test is at least partially determined by the number of positive test results. Thus, the observed sex-based differences in prognostic capability may be related to a higher positive rate of stress testing compared with CTA in women. In the absence of angiographic data confirming or excluding obstructive CAD in the majority of the patients, it is impossible to determine whether these "excess" positive test results represented disease that was not associated with events during trial follow-up or if they were false-positive findings.

TABLE 4 Association Between NIT Result and the Primary Composite Outcome

	Event Rate No. of Events/Sample Size (%)		Positive Versus Negative Results, Unadjusted*		Positive Versus Negative Results, Adjusted†	
	Positive Test Result	Negative Test Result	HR (95% CI)	p Value	HR (95% CI)	p Value
Interaction between test result, test type, and sex			–	0.020	–	0.010
Women						
Association of test positivity in women randomized to CTA	18/184 (9.78)	39/2,148 (1.82)	6.39 (3.65-11.17)	<0.001	5.86 (3.32-10.35)	<0.001
Association of test positivity in women randomized to stress test	14/274 (5.11)	41/2,114 (1.94)	2.70 (1.45-5.03)	0.002	2.27 (1.21-4.25)	0.011
Difference between the association in CTA and the association in stress test			–	0.043	–	0.028
Men						
Association of test positivity in men randomized to CTA	31/350 (8.86)	49/1,818 (2.70)	3.69 (2.35-5.79)	<0.001	2.80 (1.76-4.45)	<0.001
Association of test positivity in men randomized to stress test	33/290 (11.38)	40/1,788 (2.24)	5.39 (3.39-8.56)	<0.001	4.42 (2.77-7.07)	<0.001
Difference between the association in CTA and the association in stress test			–	0.249	–	0.168

*Unadjusted models contained test result, randomized testing arm, sex, and all 2- and 3-way interaction terms. †Adjusted for the same factors as in Table 3.
HR = hazard ratio; other abbreviations as in Tables 1 and 3.

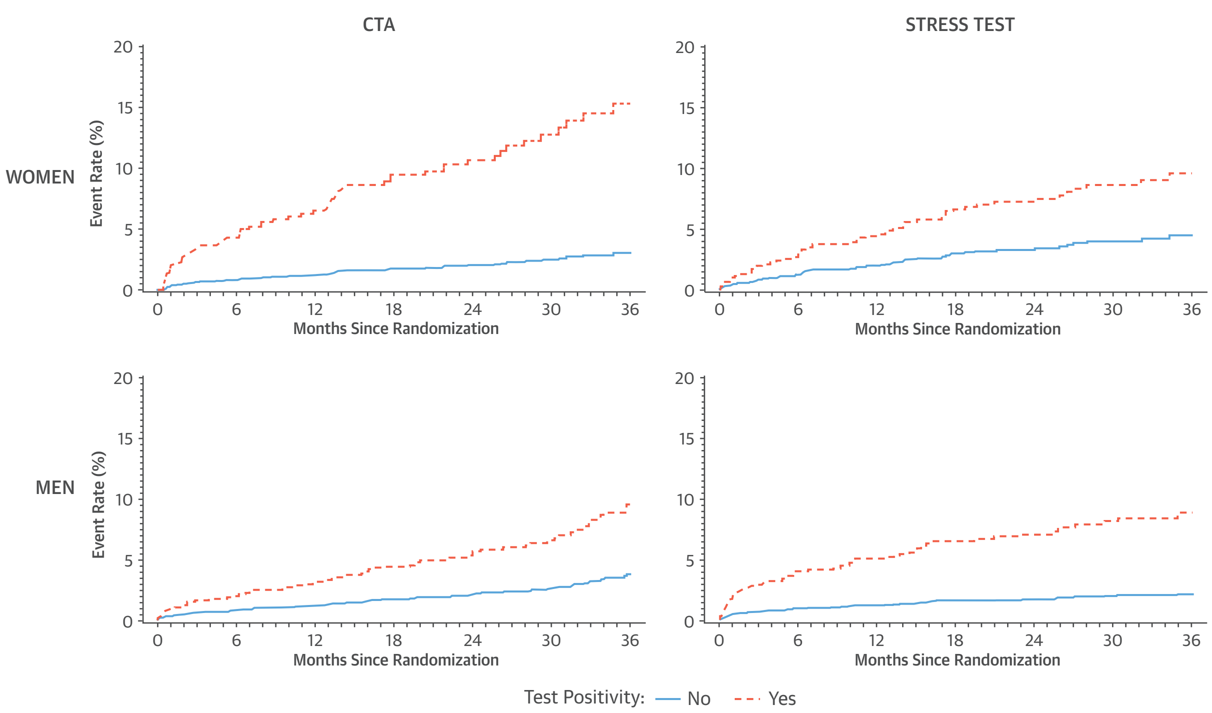
CENTRAL ILLUSTRATION Test Results and Clinical Event Rates in Women and Men



Pagidipati, N.J. et al. J Am Coll Cardiol. 2016;67(22):2607–16.

To determine whether various noninvasive tests provide different prognostic value on the basis of patient sex, results from anatomic testing via computed tomographic angiography (CTA) and stress testing were compared. Clinical event rates are the primary composite outcome consisting of all-cause death, myocardial infarction, or unstable angina hospitalization. **(A)** When comparing positive test rates and event rates according to sex in patients undergoing CTA versus stress testing, women had similar event rates in the 2 arms but higher stress test positivity rates, whereas men also had similar event rates but higher CTA positivity rates. **(B)** When assessing event rates according to positive and negative test results for each sex and according to test type, event rates for women with a negative CTA were similar to those with a negative stress test result, but the event rate with a positive CTA was significantly higher than that with a positive stress test result. Within men, the event rates were similar between the 2 testing modalities whether the test result was positive or negative.

FIGURE 2 Adjusted Event Curves of the Primary Composite Outcome Comparing Test Positivity



Event curves are shown comparing the association of positive and negative test results for each sex and according to test type with the primary composite outcome of all-cause death, myocardial infarction, or unstable angina hospitalization. Curves are adjusted for the same factors noted in Figure 1. Interaction p = 0.010. CTA = computed tomography angiography.

The known performance characteristics of the various NITs might help explain the differences in test positivity rates that we observed between women and men. Women were less likely to have a positive CTA than a positive exercise ECG or nuclear stress test result, even after adjusting for clinical factors. These findings suggest that some stress test results may be falsely positive. This outcome would be consistent with the well-documented significant false-positive rates of exercise ECG and nuclear stress testing in women (2,3). The reported high false-positive rate of approximately 28% in nuclear stress testing in women without known CAD (2) is particularly relevant to our study because the majority of patients in the functional arm received this type of test. Another reason for the higher positivity rate of stress testing in women might be the presence of ischemia in the absence of obstructive CAD, possibly due to MCD (16–18). The ability of stress tests to detect both obstructive and microvascular disease might have made them more likely to be positive than CTAs in women, and less likely to be associated with clinical events, because MCD has a lower event rate than obstructive disease (19). These results parallel data from the ROMICAT-II (Rule-Out Myocardial Ischemia/Infarction by Computer-assisted Tomography) trial, which noted greater improvement in acute chest pain care in women compared with men randomized to a CTA strategy versus usual care (20).

In contrast to the results seen in women, men in our study were less likely to have a positive stress test result than a positive CTA. Multiple factors may have contributed to this difference between the sexes, including the lower false-positive rate of stress testing and the lower prevalence of MCD in men (3,17). The lower rate of stress test positivity compared with CTA positivity in men might be related to the known discordance between obstructive CAD and ischemia, in which only a subset of obstructive lesions exhibited hemodynamic significance. In the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study, which had mostly (75%) male participants, only 35% of the lesions categorized as having 50% to 70% stenosis were functionally significant according to fractional flow reserve (21). Although the association of CTA test results with clinical events was not significantly different from that of stress test results in men, the relationship clearly trended toward a stronger association between stress test result and clinical events. Perhaps the ability of stress tests to detect only hemodynamically significant lesions allowed identification of the group of men who are most likely to have events but, with the low overall event rate, there was not enough statistical power to detect this difference.

Our study had several strengths. PROMISE was the first, large head-to-head comparative effectiveness, randomized trial of the anatomic versus stress testing strategies in stable symptomatic outpatients with adjudicated clinical events; it is, therefore, the first dataset able to rigorously address which testing strategy confers the greatest prognostic value. The trial is uniquely able to address this clinical question in women because, to our knowledge, it included the largest number of stable symptomatic women of any prospective trial of diagnostic testing to date. Our analyses harnessed these 2 strengths of PROMISE by focusing on within-sex differences between the 2 randomized testing groups, rather than on between-sex differences alone. Furthermore, our sex-specific analyses provided clinically relevant information that may help to optimize testing choice in all patients, while capitalizing on the randomization between testing strategies in PROMISE.

STUDY LIMITATIONS. Our study had several caveats that should be considered when interpreting the results. Randomization was not stratified according to patient sex; however, within each sex, the 2 testing arms were similar. Because <10% of the trial population underwent coronary angiography, we were unable to draw conclusions about the diagnostic accuracy of each testing type between sexes. Patients were followed up for a median of slightly more than 2 years, and thus there were relatively few clinical endpoint events; our ability to assess prognosis according to NIT type in each sex was limited, therefore, especially over the longer term. Finally, it is unclear whether our findings would be affected by a different mix of noninvasive testing. However, this distribution of test types reflected current community practice, as PROMISE was a pragmatic trial that left the choice of stress test type and the subsequent clinical management up to the provider.

CONCLUSIONS

The choice of NIT is a complex one and depends on many factors in addition to diagnostic test performance, such as local expertise and availability, previous testing data, body habitus, ability to exercise, radiation exposure, and suspicion for cardiac abnormalities other than, or in addition to, ischemia. Our data provide novel insights into the differences between stress testing and anatomic testing in men and women with respect to positivity rates and the prognostic information provided by each type of test, despite the presence of similar overall event rates with both tests. The prognostic value of a positive compared with a negative NIT result varied according to test type and patient sex, whereas the event rate associated with a negative test result was similar within each sex regardless of test type. Women seemed to derive more prognostic information from CTA, whereas men seemed to derive similar prognostic value from both types of tests. Further research is necessary to determine whether these findings should guide test selection and result interpretation for patients being evaluated for suspected CAD.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Neha J. Pagidipati, Duke Clinical Research Institute, Duke University School of Medicine, P.O. Box 17969, Durham, North Carolina 27715. E-mail: neha.pagidipati@dm.duke.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The prognostic value of noninvasive testing for coronary disease depends on both test and patient characteristics and varies according to sex. In a randomized trial cohort, coronary CTA and stress testing had similar prognostic value in men, whereas CTA was more predictive that functional testing among women.

TRANSLATIONAL OUTLOOK: Further research is necessary to determine whether these findings are generalizable to routine clinical practice.

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KEY WORDS coronary artery disease, imaging, noninvasive testing, prognosis, risk stratification

APPENDIX For a supplemental figure, please see the online version of this article.