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ORIGINAL RESEARCH

Sex Differences in Demographics, Risk Factors, Presentation, and Noninvasive Testing in Stable Outpatients With Suspected Coronary Artery Disease

Insights From the PROMISE Trial

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ABSTRACT

OBJECTIVES The aim of this study was to determine whether presentation, risk assessment, testing choices, and results differ by sex in stable symptomatic outpatients with suspected coronary artery disease (CAD).

BACKGROUND Although established CAD presentations differ by sex, little is known about stable, suspected CAD.

METHODS The characteristics of 10,003 men and women in the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial were compared using chi-square and Wilcoxon rank-sum tests. Sex differences in test selection and predictors of test positivity were examined using logistic regression.

RESULTS Women were older (62.4 years of age vs. 59.0 years of age) and were more likely to be hypertensive (66.6% vs. 63.2%), dyslipidemic (68.9% vs. 66.3%), and to have a family history of premature CAD (34.6% vs. 29.3) (all p values <0.005). Women were less likely to smoke (45.6% vs. 57.0%; $p < 0.001$), although their prevalence of diabetes was similar to that in men (21.8% vs. 21.0%; $p = 0.30$). Chest pain was the primary symptom in 73.2% of women versus 72.3% of men ($p = 0.30$), and was characterized as "crushing/pressure/squeezing/tightness" in 52.5% of women versus 46.2% of men ($p < 0.001$). Compared with men, all risk scores characterized women as being at lower risk, and providers were more likely to characterize women as having a low (<30%) pre-test probability of CAD (40.7% vs. 34.1%; $p < 0.001$). Compared with men, women were more often referred to imaging tests (adjusted odds ratio: 1.21; 95% confidence interval: 1.01 to 1.44) than nonimaging tests. Women were less likely to have a positive test (9.7% vs. 15.1%; $p < 0.001$). Although univariate predictors of test positivity were similar, in multivariable models, age, body mass index, and Framingham risk score were predictive of a positive test in women, whereas Framingham and Diamond and Forrester risk scores were predictive in men.

CONCLUSIONS Patient sex influences the entire diagnostic pathway for possible CAD, from baseline risk factors and presentation to noninvasive test outcomes. These differences highlight the need for sex-specific approaches for the evaluation of CAD. (J Am Coll Cardiol Img 2016;9:337–46) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AUC = area under the receiver-operating characteristic curve

CAD = coronary artery disease

ECG = electrocardiogram

Cardiovascular disease is the leading cause of death and disability in women in the United States, yet it remains a diagnostic challenge (1). Most studies that report sex differences in presenting symptoms and risk factor burden have examined populations with acute chest pain, acute coronary syndrome (ACS), or revascularization, but these studies do not provide guidance with regard to differences in the much more common presentation of stable chest pain (2–19). Furthermore, few studies have examined the impact of such differences on provider decisions, including assessment of the likelihood of obstructive coronary artery disease (CAD) and selection of noninvasive testing (1,5,20). Thus, a contemporary assessment of sex differences in the presentation and evaluation of stable outpatients without known heart disease is needed to better guide the management of women with suspected CAD.

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The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial, which is a recently completed randomized trial of evaluation strategies in 10,003 symptomatic nonacute patients with suspected CAD, enrolled >5,200 women, which made it an ideal setting to explore the differences in presentation and evaluation of CAD in men versus women (21,22). Accordingly, we used the PROMISE dataset to compare the demographics, risk factor profiles, clinical presentation, risk estimates, choice of functional test, and test results by sex in a contemporary population of stable symptomatic outpatients with suspected CAD. We hypothesized that demographics, symptoms, and risk factor burden would differ by sex, which would, in turn, influence provider risk estimates, subsequent diagnostic evaluation choices, and noninvasive test results.

METHODS

STUDY POPULATION. Symptomatic outpatients without a history of CAD were recruited between July 2010 and September 2013 at 193 sites in North America that participated in the PROMISE trial. The methods of the PROMISE trial have been previously described (22). In brief, after providing written informed consent, 10,003 patients (5,270 women and 4,733 men) were randomized to either functional testing (exercise electrocardiogram [ECG], stress nuclear imaging, or stress echocardiogram) or anatomical testing with ≥64-slice multidetector coronary computed tomographic angiography. Before randomization, the local clinical team specified the functional test that the patient would undergo if randomized to that arm.

DATA COLLECTION AND VARIABLES. Baseline patient data on demographics, risk factor profiles, ECG findings, symptoms, and CAD risk estimates were collected for all patients, including the patient's primary presenting symptom (chest pain, dyspnea, back pain, fatigue, and so on). If the patient had chest pain, the provider's assessment of the typicality of the chest pain symptoms was also obtained. Data on 5 risk assessment scores were calculated for the entire population: the 2008 Framingham score (23); the 2013 Atherosclerotic Cardiovascular Disease (ASCVD) score (24); the 1979 Diamond and Forrester score (25); the modified 2011 Diamond and Forrester score (26); and the 2012 combined Diamond-Forrester and CASS (Coronary Artery Surgery Study) score (27). In calculating the Framingham and ASCVD scores, the single imputation method was performed to replace missing cholesterol values (45% missing) using the observed mean cholesterol value in 5 clinically relevant subgroups. High-density lipoprotein data (45% missing) were also imputed, with separate mean high-density lipoprotein values for women and men. Test positivity was recorded for the first noninvasive test performed on patients with interpretable results. Positivity was defined as ≥70% epicardial stenosis or ≥50% left main stenosis on coronary computed tomographic angiography. An exercise ECG was considered positive if ST-segment changes consistent with ischemia during stress were detected or if the test was terminated early (<3 min) due to reproduction of symptoms, arrhythmia, and/or hypotension. Stress nuclear and stress echocardiography tests were positive if there was an inducible ischemia in at least 1 coronary territory

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(anterior, inferior, or lateral) or if an exercise stress test was terminated early (<3 min) due to reproduction of symptoms, arrhythmia, and/or hypotension. The results of tests were site-reported, in keeping with the pragmatic nature of the trial. However, in an a priori effort to standardize test report quality, every imaging report was reviewed by a cardiology faculty or senior fellow physician who underwent training before the start of the trial on the use of a prospectively designed protocol to deal with ambiguous test results. In this manner, the interpretation of ambiguous test reports was standardized for each testing modality and harmonized across imaging modalities.

STATISTICAL ANALYSIS. Demographics, risk factor profiles, ECG findings, baseline medications, clinical characteristics at presentation, pre-specified choice of functional test, and the provider's estimate of risk were compared by sex using chi-square or Fisher exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. In addition, these baseline characteristics were compared by test results within each sex.

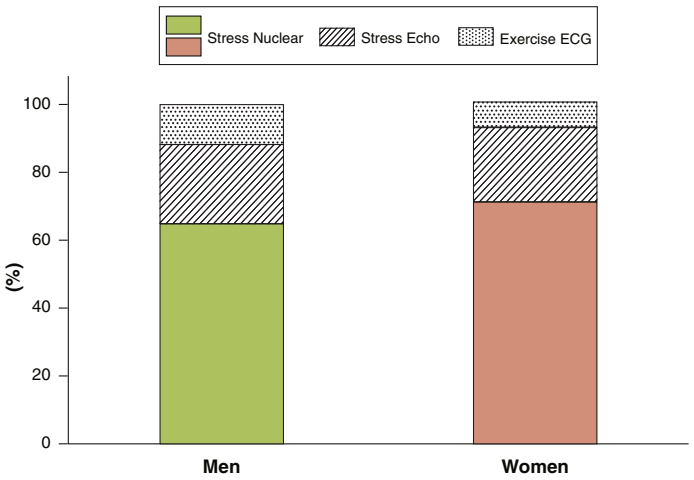
Logistic regression models were used to compare test selection in men versus women. To account for heterogeneity between women and men, multivariable models adjusted for primary symptom type, characterization of chest pain, age, body mass index (BMI), site (random effects), and risk factors (diabetes mellitus, hypertension, cerebrovascular or peripheral vascular disease, sedentary lifestyle, depression, family history of premature CAD, and dyslipidemia). Differences in the likelihood of the provider selecting imaging tests instead of nonimaging tests are expressed as adjusted odds ratios with associated 95% confidence intervals. Similar investigations were performed to assess differences in the likelihood of the provider selecting stress nuclear testing instead of stress echocardiography.

Spearman's rank correlation was used to assess the relationships between the provider estimate and the calculated likelihood of obstructive disease using the modified Diamond and Forrester score (26). Fisher's Z-transformation was used to compare the correlations between women and men.

Separate multivariable logistic regression models were constructed for men and women to determine the key predictors of diagnostic test positivity. Each model considered the following clinically relevant candidate predictors: age, race, BMI, risk factors (diabetes mellitus, hypertension, metabolic syndrome, dyslipidemia, smoking, family history of premature CAD, depression, sedentary lifestyle, cerebrovascular or peripheral vascular disease, history of heart failure, CAD equivalent), risk scores (Framingham [23], ASCVD [24], Diamond and Forrester [25], modified Diamond and Forrester [26], and combined Diamond-Forrester and CASS [27]), primary presenting symptom, and the provider's characterization of chest pain. For women and men, stepwise model selection was used to identify the subset of predictors that contained the highest amount of predictive information within the constraints of our pre-determined model entry and exit criteria (entry: $p < 0.1$; exit: $p \geq 0.2$). Age, diabetes, and the provider's characterization of chest pain were assumed to be key predictors for men and women; thus, they were forced into each model. The Hosmer-Lemeshow goodness-of-fit test was used to assess each model's calibration, and the area under the receiver-operating characteristic curve (AUC) was used to assess each model's discriminatory capacity.

All statistical analyses were conducted with SAS version 9.4 (SAS Institute, Cary, North Carolina), with $\alpha = 0.05$.

FIGURE 1 Provider's Choice of Pre-Specified Functional Test



Test	Frequency		P-value
	Men	Women	
Stress Nuclear	3055 (64.6%)	3726 (70.7%)	<0.001
Stress Echo	1096 (23.2%)	1140 (21.6%)	0.068
Exercise ECG	582 (12.3%)	404 (7.7%)	<0.001

Before randomization, providers were asked to specify the functional test they would use if the patient were to be randomized to the functional testing arm. We compared the proportion of men and women specified to each test. p Values for comparison by sex were calculated using chi-square tests. ECG = electrocardiography.

TABLE 1 Patient Characteristics and Test Positivity

	Men (n = 4,733)	Women (n = 5,270)	p Value
Demographics			
Age, yrs			
All patients	59.0 ± 8.4	62.4 ± 7.9	<0.001
Patients >50 yrs	61.0 ± 7.4	62.4 ± 7.9	<0.001
Racial or ethnic minority	1,041 (22.1)	1,207 (23.1)	0.270
Physical examinations			
BMI (kg/m^2)	30.4 ± 5.4	30.6 ± 6.7	0.223
Overweight (BMI ≥25 kg/m^2)	4,051 (86.3)	4,166 (79.9)	<0.001
Risk factors			
Hypertension	2,992 (63.2)	3,509 (66.6)	<0.001
Diabetes	993 (21.0)	1,151 (21.8)	0.298
Dyslipidemia	3,135 (66.3)	3,632 (68.9)	0.004
Cerebrovascular or peripheral vascular disease	223 (4.7)	329 (6.2)	<0.001
Family history of premature CAD	1,384 (29.3)	1,818 (34.6)	<0.001
History of depression	692 (14.6)	1,366 (25.9)	<0.001
Metabolic syndrome	1,807 (38.2)	1,965 (37.3)	0.358
Current or former smoker	2,699 (57.0)	2,405 (45.6)	<0.001
Sedentary	2,049 (43.4)	2,812 (53.5)	<0.001
Primary presenting symptoms			
Chest pain*	3,416 (72.3)	3,856 (73.2)	0.304
Chest pain characterization†			
Aching/dull	928 (27.2)	911 (23.6)	<0.001
Burning/pins and needles	351 (10.3)	319 (8.3)	0.003
Crushing/pressure/squeezing/tightness	1,577 (46.2)	2,023 (52.5)	<0.001
Other	1,063 (31.1)	1,136 (29.5)	0.125
Arm or shoulder pain	132 (2.8)	125 (2.4)	0.185
Back pain	30 (0.6)	54 (1.0)	0.033
Fatigue/weakness	164 (3.5)	113 (2.1)	<0.001
Neck or jaw pain	33 (0.7)	76 (1.4)	<0.001
Shortness of breath/dyspnea	706 (14.9)	784 (14.9)	0.937
Palpitations	94 (2.0)	142 (2.7)	0.020
Other‡	152 (3.2)	119 (2.3)	0.003
Physician characterization of typicality of chest pain			
Typical (definite angina)	576 (12.2)	590 (11.2)	0.129
Atypical (possible angina)	3,697 (78.1)	4,076 (77.3)	0.357
Nonangina	460 (9.7)	604 (11.5)	0.005
Medication use at presentation			
Beta blockers	990 (22.2)	1,409 (27.5)	<0.001
ACE inhibitor or ARB	2,022 (45.4)	2,172 (42.4)	0.003
Statin	2,097 (47.1)	2,292 (44.8)	0.021
Aspirin	2,162 (48.6)	2,118 (41.4)	<0.001
Diuretic	966 (21.7)	1,688 (33.0)	<0.001

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RESULTS

Among all trial patients, mean ages were 59 years (range 45 to 90) for men and 62 years (range 50 to 92 years) for women (Table 1). Because the inclusion criteria specified a minimum age for women of 50 years versus 45 years for men, we also examined the mean ages of only patients older than 50 years of age, and we found that, on average, women were still older. The prevalence of racial or ethnic minorities was similar between the sexes.

Women were more likely than men to have a history of hypertension, dyslipidemia, cerebrovascular or peripheral vascular disease, family history of premature CAD, depression, and a sedentary lifestyle (Table 1). Men were more likely than women to smoke and be overweight (BMI ≥25 kg/m^2). The prevalence of diabetes was similar in both men and women.

The most common primary presenting symptom in both sexes was chest pain reported by 73.2% of women versus 72.3% of men (p = 0.30) (Table 1). Men were more likely than women to characterize their chest pain as "aching/dull" and "burning/pins and needles." Women were more likely than men to characterize their pain as "crushing/pressure/squeezing/tightness." Women were more likely than men to have back pain, neck, or jaw pain, and palpitations as the primary presenting symptoms, whereas men were more likely to have fatigue and/or weakness.

The use of cardiovascular medications at baseline was common in both sexes (Table 1). Women were more likely than men to be taking beta blockers and diuretics; men were more likely than women to be taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, and aspirin. Women tended to have more abnormal ECG findings than men overall and were more likely to have ECG findings that the site physician believed could interfere with exercise stress test interpretation.

The risk of events and pre-test likelihood for coronary disease was lower for women in each of the 5 global risk scores: Framingham (23), ASCVD (24), Diamond and Forrester (25), modified Diamond and Forrester (26), and combined Diamond-Forrester and CASS (27) (Table 2). Compared with men, a higher percentage of women were characterized by their providers as having a low risk (<30%) pre-test probability for obstructive CAD, whereas a higher percentage of men were characterized as having a high risk (>70%). The correlations between provider estimation of disease and the modified Diamond and Forrester (26) score were weak and not significantly different in women and men (r = 0.313 vs. r = 0.303, respectively; p = 0.227).

TEST SELECTION. Providers were asked to prespecify a functional test for all patients before trial enrollment. A higher percentage of women were selected to undergo nuclear stress testing compared with men. Similarly, a higher percentage of men were selected to undergo exercise ECG compared with women (Figure 1). Even after adjustment for baseline age, BMI, site, risk factors, and presenting characteristics, clinicians were 21% more likely to select

imaging stress tests (stress echocardiography or stress nuclear) for women compared with men instead of nonimaging stress tests (exercise ECG) (Table 3). Among only those patients in whom an imaging stress test was selected, clinicians were 17% more likely to select stress nuclear testing for women compared with men instead of stress echocardiography (Table 4).

TEST RESULTS. Among the 8,966 patients (4,720 women, 4,246 men) who had interpretable noninvasive tests, 15.1% of men had positive test results compared with 9.7% of women (Table 1, Figure 2). In univariate analyses, age and risk factors (e.g., hypertension and diabetes) were predictive of positive tests in both men and women (Table 5). Although chest pain as a presenting characteristic was not associated with test positivity in either sex, characterization as crushing/pressure/squeezing/tightness was associated with test positivity in women, whereas burning/pins and needles was predictive in men. All risk scores were highly predictive of a positive test in both men and women.

Among the set of candidate predictors of test positivity, those that best predicted a positive test in a multivariable analysis differed in men and women (Table 6). Age, diabetes, and chest pain typicality were assumed to be key predictors of test positivity in women and men; thus, they were forced into each model. In women, only BMI and the Framingham risk score (23) provided additional predictive information within the constraints of our model's selection procedure, yielding a final model with an AUC of 0.61. In men, only the modified Diamond and Forrester score (26) and the Framingham risk score (23) provided additional predictive information, yielding a final model with an AUC of 0.65.

DISCUSSION

In this multicenter study of a large contemporary population of predominantly low- to intermediate-risk stable outpatients with symptoms suggestive of CAD, women and men differed substantially in their clinical presentation, diagnostic evaluation, and noninvasive testing results. Women had a higher prevalence of traditional cardiac risk factors, but they were more likely to be characterized as low risk by providers and existing risk scores. In addition, women were more likely to be referred for imaging stress tests compared with men, particularly nuclear stress testing, but they were less likely to have a positive test. Finally, predictors of test positivity differed between the sexes. To our knowledge, this is the largest

TABLE 1 Continued

	Men (n = 4,733)	Women (n = 5,270)	p Value
ECG findings			
ECG Q waves	195 (4.2)	259 (5.0)	0.056
ECG findings that could interfere with exercise test interpretation	235 (5.0)	351 (6.7)	<0.001
LBBB	36 (15.3)	105 (29.9)	
ST depression	45 (19.1)	80 (22.8)	
LVH with repolarization	36 (15.3)	43 (12.3)	
Other	120 (51.1)	133 (37.9)	
Test results§			
Overall test positivity	640 (15.1)	458 (9.7)	<0.001

Values are mean ± SD or n (%). *Chest pain: substernal or left anterior or chest pain: other are selected as primary symptoms. Multiple characterizations are possible. †Only applicable when chest pain: substernal or left anterior or chest pain: other are selected as primary symptoms. Multiple choices possible. ‡Includes diaphoresis and/or sweating, dizziness and/or lightheaded, epigastric and/or abdominal pain, nausea and/or vomiting, syncope, and other. §Percentages calculated from 8,966 patients (4,246 men and 4,720 women).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; ECG = electrocardiogram; LBBB = left bundle branch block; LVH = left ventricular hypertrophy.

TABLE 2 Risk Scores and Physician Assessment of CAD Likelihood

	Men (n = 4,733)	Women (n = 5,270)	p Value
Risk scores			
Framingham risk score (23)			<0.001
Mean ± SD	28.9 ± 16.4	15.0 ± 9.9	
Median (IQR)	25.0 (16.1–38.0)	12.3 (8.1–18.8)	
Min, max	2.4, 99.6	1.6, 82.9	
ASCVD pooled cohort risk prediction (24)			<0.001
Mean ± SD	17.1 ± 11.6	12.5 ± 11.5	
Median (IQR)	14.1 (8.5–22.6)	8.7 (4.7–16.2)	
Min, max	0.9, 97.8	0.6, 88.9	
Diamond and Forrester (25)			<0.001
Mean ± SD	60.6 ± 17.4	45.9 ± 19.9	
Median (IQR)	58.9 (58.9–67.1)	54.4 (32.4–54.4)	
Min, max	14.1, 94.3	8.4, 90.6	
Modified Diamond and Forrester (26)			<0.001
Mean ± SD	54.5 ± 13.6	28.3 ± 12.4	
Median (IQR)	48.9 (48.9–59.4)	27.7 (20.0–27.7)	
Min, max	24.8, 92.5	11.7, 76.3	
Combined Diamond-Forrester and CASS (27)			<0.001
Mean ± SD	64.7 ± 17.8	43.0 ± 19.0	
Median (IQR)	65.0 (65.0–72.0)	51.0 (31.0–51.0)	
Min, max	13.0, 94.0	7.0, 86.0	
Physician assessment of likelihood of epicardial stenosis, n (%)*			
Very low and low (<30%)	1,613 (34.1)	2,142 (40.7)	<0.001
Intermediate (31%–70%)	2,815 (59.6)	2,935 (55.8)	<0.001
High and very high (>70%)	299 (6.3)	182 (3.5)	<0.001

*Provider's assessment of the likelihood that subject has significant epicardial coronary stenosis or left main stenosis. Significant refers to ≥70% epicardial coronary stenosis or ≥50% left main stenosis.

ASCVD = atherosclerotic cardiovascular disease; IQR = interquartile range; other abbreviation as in Table 1.

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TABLE 3 Association Between Sex and Pre-Specified Choice of Functional Test Category (Imaging vs. Nonimaging)

Model†	Women vs. Men*	
	Odds Ratio (95% CI)	p Value
Unadjusted imaging‡	1.689 (1.478–1.930)	<0.001
Adjusted imaging§	1.205 (1.006–1.443)	0.043

*Men are the reference group. †A total of 10,003 subjects were included in the unadjusted logistic regression model. The reference test category was a nonimaging test. ‡Unadjusted model contains sex. §Adjusted model contains sex; testing site; chest pain versus other as primary symptoms; site's characterization of chest pain as typical, atypical or nonanginal; age; body mass index; and risk factors such as diabetes, hypertension, cerebrovascular or peripheral vascular disease, sedentary lifestyle, depression, family history of premature CAD, dyslipidemia.

CI = confidence interval; other abbreviation as in Table 1.

TABLE 4 Association Between Sex and Pre-Specified Choice of Functional Test for Patients in Whom an Imaging Test Was Selected (Stress Nuclear vs. Stress Echocardiography)

Model†	Women vs. Men*	
	Odds Ratio (95% CI)	p Value
Unadjusted stress nuclear‡	1.173 (1.066–1.290)	0.001
Adjusted stress nuclear§	1.168 (1.023–1.333)	0.022

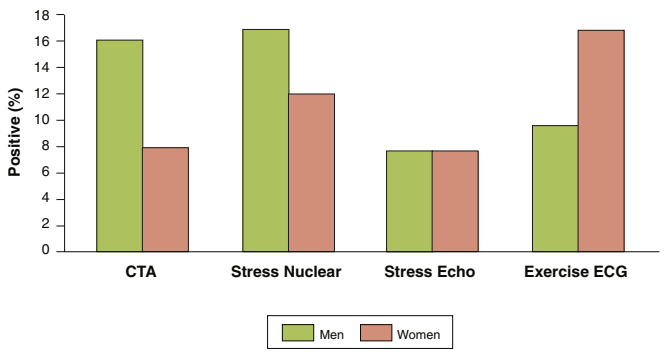
*Men are the reference group. †A total of 9,017 subjects were included in the binary logistic regression model (subjects pre-specified to exercise ECG omitted). The reference test category is stress echocardiography. ‡Unadjusted model contains sex. §Adjusted model contains sex; testing site; chest pain versus other as primary symptoms; site's characterization of chest pain as typical, atypical or nonanginal; age; body mass index; and risk factors, including diabetes, hypertension, cerebrovascular or peripheral vascular disease, sedentary lifestyle, depression, family history of premature CAD and dyslipidemia.

Abbreviations as in Tables 1 and 3.

contemporary description of sex-based differences in presentation, evaluation, and noninvasive testing results in a large, stable outpatient population evaluated for symptoms of suspected CAD.

A number of previous studies have compared differences in demographics, risk factor burden, and symptom profiles between men and women (2,4–12,28); however, most of these examined patients with an existing definite diagnosis of CAD, which was established by the diagnosis of ACS or the need for revascularization. Although such CAD populations are germane, the need for evaluation of stable chest pain or other symptoms suggestive of CAD is substantially more common, and establishing a diagnosis is arguably more difficult in this outpatient population. There have only been a few studies that examined sex differences in patients who underwent evaluation for CAD, and they are several decades old and largely from academic centers (20,28). Therefore, delineating the differences between men and women in this large contemporary population evaluated at community centers is highly relevant to informing modern clinical care.

FIGURE 2 Test Positivity Rates by Sex and Test Type



Rate of positive test results by sex and by modality for the first noninvasive test performed on patients with interpretable results. Positivity was evaluated by the criteria listed in the Methods section. CTA = computed tomography angiography; other abbreviation as in Figure 1.

Similar to previous studies that examined patients with ACS (2,3) and studies with stable chest pain populations (20,28), we found that women had a higher prevalence of all traditional risk factors, except for diabetes and smoking. In contrast to previous ACS studies, which found that women had a higher prevalence of diabetes than men, we found that the prevalence of diabetes was similar among men and women (2–4,8,10,11,13). Of note, we also found that women had a greater burden of "nontraditional" risk factors or factors that were not included in the Framingham risk score (23), such as depression, sedentary lifestyle, and family history of premature CAD (23,29).

In our study, chest pain was the most commonly exhibited symptom for both women and men, although its description differed, with women being significantly more likely to describe their pain as "crushing, pressure, squeezing, or tightness." Although previous studies have suggested that women are more likely to present with atypical symptoms than men (5,6,7,10,14), our study demonstrated that men and women were equally likely to have atypical symptoms. Women were more likely to present with back pain, neck and/or jaw pain, and palpitations in accordance with earlier studies of ACS patients, whereas men were more likely to present with fatigue and/or weakness, which is in contrast to previous investigations (15–19).

Few studies have examined sex differences in risk scores in a stable outpatient population with

suspected CAD (26,30). We found that all 5 versions of the major risk scores we examined characterized women as being at lower risk for events or obstructive CAD compared with men, although all included sex as a modifier. In the American Heart Association's 2015 update of heart disease and stroke statistics, total coronary heart disease prevalence was reported to be lower in U.S. women ages 20 years or older (5.0%) compared with men (7.6%) (31). Thus, these risk characterizations may realistically represent relative CAD rates and events in women versus men, a finding that is supported by the lower rate of test positivity in women in our population. Optimizing risk models to ensure that they adequately account for women's larger risk factor burden yet lower reported prevalence of disease is critical to optimal management of patients with suspected CAD.

In parallel with the differences in the calculated estimates of long-term risk for cardiovascular events (Framingham [23], ASCVD [24]), we found that both modified Diamond and Forrester calculated scores (26) and providers' subjective characterizations identified women as having a lower likelihood of obstructive CAD than men. These data are similar to other studies (5). The relationships between calculated CAD likelihood by Diamond and Forrester and providers' estimates were similar in men and women (data not shown), suggesting that providers' subjective assessments of risk did not differ markedly by sex. In addition, we found no sex differences in the providers' characterization of typical or atypical chest pain, although other investigators reported that providers less frequently considered chest pain to be typical in women with low to moderate risk of ACS; this finding was used to justify providers' lower estimation of risk and less frequent test referral (5).

Among our study subjects, all of whom had a requirement for noninvasive testing, clinicians more often selected imaging stress tests in women compared with men as the functional test of choice rather than nonimaging stress tests. This preference could reflect the higher likelihood in women than men to have false positive stress ECGs (1). In addition, among those selected for stress testing with imaging, women were more likely than men to be assigned to stress nuclear echocardiography more than stress echocardiography even after adjustment. Although little direct data are available to guide this choice, nuclear testing may be more sensitive for single-vessel coronary disease, which is more commonly seen in women; however, women may be more sensitive to ionizing radiation. Published meta-analyses suggest that the diagnostic accuracy of stress echocardiography does not differ by sex and prognostic value, whereas stress nuclear studies may be less accurate in women than in men (32–34).

Overall, women in our cohort were less likely to have a positive diagnostic test than men, which is consistent with the lower risk assigned to them by both risk scores and providers. A large number of characteristics were associated with a positive test, many of which were similar in men and women. However, few characteristics remained associated in the multivariable analysis, and the ability to predict a positive test was limited in both men and women with only modest AUCs. Finally, the characteristics that predicted a positive test in women differed from those in men, suggesting that different relationships between the risk factor burden and the subsequent clinical pathway may be present in women and in men.

STUDY LIMITATIONS. The PROMISE trial is one of the largest contemporary, prospectively studied cohorts of symptomatic men and women without known heart disease, and as such, it provides a unique opportunity to study sex differences in this population. The diversity of expertise and settings among 193 PROMISE sites and the broad enrollment criteria make our results highly generalizable to real-world settings. Despite these strengths, there are several issues to consider when interpreting our results. We focused on the initial presentation, evaluation, referral decision making, and test results for stable outpatients with chest pain or other symptoms suggestive of CAD, but PROMISE inclusion criteria required noninvasive testing in all patients; thus, our data did not address possible differences in referral patterns for such testing, because those patients who physicians chose not to test or to send directly to invasive catheterization were specifically excluded. However, our patient population's age, symptoms, and risk factor burden were such that all had a class I indication for noninvasive testing. Because we did not have high-sensitivity C-reactive protein data, we were unable to calculate a Reynolds risk score, which has been specifically designed for use in women (35). The selection process for the multivariable models that assessed the association of presentation characteristics with noninvasive test positivity were exploratory in nature and have not been validated for use on external datasets.

CONCLUSIONS

There are significant sex differences in the presentation and evaluation of symptomatic stable outpatients with suspected CAD. Women who present

TABLE 5 Association Between Overall Test Positivity and Presentation Characteristics in Women and Men

	Men (N = 4,246)			Women (N = 4,720)		
	Negative (n = 3,606)	Positive (n = 640)	p Value	Negative (n = 4,262)	Positive (n = 458)	p Value
Demographics						
Age, yrs						
All patients	58.4 ± 8.2*	61.8 ± 8.6*	<0.001*	62.2 ± 7.7*	64.4 ± 8.0*	<0.001*
Patients >50 yrs	2,995* (83.1)	583* (91.1)	<0.001*	4,261 (>99.9)	458 (100)	>0.999
Racial or ethnic minority	808* (22.6)	105* (16.5)	<0.001*	962 (22.7)	90 (19.8)	0.154
Physical examinations						
BMI (kg/m^2)	30.5 ± 5.4	30.4 ± 5.5	0.978	30.3 ± 6.4*	31.5 ± 7.3*	0.004*
Overweight (BMI ≥25 kg/m^2)	3,096 (86.6)	541 (85.2)	0.350	3,367 (79.7)	370 (81.1)	0.481
Risk factors						
Hypertension	2,240* (62.1)	433* (67.7)	0.008*	2,804* (65.8)	333* (72.7)	0.003*
Diabetes	717* (19.9)	166* (25.9)	<0.001*	902* (21.2)	123* (26.9)	0.005*
Dyslipidemia	2,376 (65.9)	436 (68.1)	0.271	2,927 (68.7)	331 (72.3)	0.114
Cerebrovascular or peripheral vascular disease	159 (4.4)	38 (5.9)	0.089	249* (5.8)	38* (8.3)	0.037*
Family history of premature CAD	1,052 (29.3)	185 (29.0)	0.892	1,442 (34.0)	160 (35.0)	0.650
History of depression	534 (14.8)	91 (14.2)	0.698	1,105 (25.9)	121 (26.4)	0.822
Metabolic syndrome	1,365 (37.9)	261 (40.8)	0.160	1,553* (36.4)	208* (45.4)	<0.001*
Current or former smoker	2,022* (56.1)	398* (62.2)	0.004*	1,940 (45.5)	222 (48.5)	0.230
Sedentary	1,553 (43.1)	300 (46.9)	0.070	2,243 (52.6)	262 (57.2)	0.057
Primary presenting symptoms						
Chest pain†	2,617 (72.7)	450 (70.3)	0.219	3,113 (73.1)	342 (74.7)	0.458
Chest pain characterization‡						
Aching/dull	726 (27.7)	121 (26.9)	0.709	734 (23.6)	74 (21.6)	0.421
Burning/pins and needles	261* (10.0)	61* (13.6)	0.022*	261 (8.4)	34 (9.9)	0.328
Crushing/pressure/squeezing/tightness	1,213 (46.4)	200 (44.4)	0.454	1,632* (52.4)	200* (58.5)	0.033*
Other	826 (31.6)	125 (27.8)	0.109	921 (29.6)	91 (26.6)	0.251
Shortness of breath/dyspnea	538 (14.9)	101 (15.8)	0.584	634 (14.9)	73 (15.9)	0.546
Other§	446 (12.4)	89 (13.9)	0.286	514 (12.1)	43 (9.4)	0.092
Physician characterization of typicality of chest pain						
Typical (definite angina)	381* (10.6)	120* (18.8)	<0.001*	475 (11.1)	51 (11.1)	0.995
Atypical (possible angina)	2,848* (79.0)	469* (73.3)	<0.001*	3,312 (77.7)	359 (78.4)	0.742
Nonangina	377* (10.5)	51* (8.0)	<0.001*	475 (11.1)	48 (10.5)	0.667
Assessment of risk						
Framingham risk score (23)			<0.001*			<0.001*
Mean ± SD	27.7 ± 15.8*	34.2 ± 18.0*		14.7 ± 9.6*	18.0 ± 11.2*	
Median (IQR)	24.0* (15.6-36.0)	31.1* (20.3-44.6)		12.0* (8.0-18.5)	14.7* (10.1-23.9)	
Min, max	3.8, 97.0	2.4, 99.6		1.6, 78.4	2.9, 62.6	
ASCVD pooled cohort risk prediction (24)			<0.001*			<0.001*
Mean ± SD	16.2 ± 10.9*	21.1 ± 13.3*		12.2 ± 11.2*	15.8 ± 12.6*	
Median (IQR)	13.4* (8.1-21.4)	17.8* (10.9-28.2)		8.5* (4.6-15.5)	12.3* (6.3-21.9)	
Min, max	1.2, 75.0	0.9, 97.8		0.6, 82.0	1.1, 76.5	
Diamond and Forrester (25)			<0.001*			0.003*
Mean ± SD	59.4 ± 17.3*	65.2 ± 17.7*		45.9 ± 19.8*	48.3 ± 19.3*	
Median (IQR)	58.9* (58.9-67.1)	67.1* (58.9-67.1)		54.4* (32.4-54.4)	54.4* (32.4-54.4)	
Min, max	14.1, 94.3	14.1, 94.3		8.4, 90.6	8.4, 90.6	
Modified Diamond and Forrester (26)			<0.001*			<0.001*
Mean ± SD	53.4 ± 13.2*	59.5 ± 14.1*		28.2 ± 12.2*	30.0 ± 12.8*	
Median (IQR)	48.9* (48.9-59.4)	59.4* (48.9-69.2)		27.7* (20.0-27.7)	27.7* (20.0-37.0)	
Min, max	24.8, 92.5	24.8, 92.5		11.7, 76.3	11.7, 76.3	
Combined Diamond-Forrester and CASS (27)			<0.001*			0.003*
Mean ± SD	63.6 ± 17.9*	69.0 ± 17.5*		43.0 ± 18.9*	45.2 ± 18.6*	
Median (IQR)	65.0* (65.0-72.0)	72.0* (65.0-72.0)		51.0* (31.0-51.0)	51.0* (31.0, 51.0)	
Min, max	13.0, 94.0	13.0, 94.0		7.0, 86.0	7.0, 86.0	

Continued on the next page

TABLE 5 Continued

	Men (N = 4,246)			Women (N = 4,720)		
	Negative (n = 3,606)	Positive (n = 640)	p Value	Negative (n = 4,262)	Positive (n = 458)	p Value
Physician assessment of likelihood of epicardial stenosis‖						
Very low and low (<30%)	1,303* (36.2)	168* (26.3)	<0.001*	1,763* (41.4)	163* (35.7)	0.019*
Intermediate (31%–70%)	2,122 (58.9)	385 (60.3)	0.488	2,370 (55.7)	257 (56.4)	0.783
High and very high (>70%)	179* (5.0)	85* (13.3)	<0.001*	123* (2.9)	36* (7.9)	<0.001*

Values are mean ± SD or n (%), unless indicated otherwise. *Significant results. †Chest pain: substernal or left anterior or chest pain: other are selected as primary symptoms. Multiple characterizations are possible. ‡Only applicable when chest pain: substernal or left anterior or chest pain: other are selected as primary symptoms. Multiple choices possible. §Includes diaphoresis and/or sweating, dizziness and/or lightheaded, epigastric and/or abdominal pain, nausea and/or vomiting, syncope, arm or shoulder pain, back pain, fatigue and/or weakness, neck or jaw pain, palpitations, and other. ‖Provider's assessment of the likelihood that subject has significant epicardial coronary stenosis or left main stenosis. Significant refers to ≥70% epicardial coronary stenosis or ≥50% left main stenosis.

Abbreviations as in Table 1.

with stable symptoms for CAD have a higher burden of risk factors than men and a similar prevalence of chest pain, which is more frequently characterized as "crushing/pressure/squeezing/tightness" by women. Their overall risk burden for CAD as estimated both by risk scores and providers is lower than that of men, which is consistent with the observed lower rate of test positivity. Women are more likely than men to be referred for imaging stress tests and have a different set of characteristics associated with a positive test.

TABLE 6 Multivariable Predictors of Test Positivity by Sex

	Models of Test Positivity* Odds Ratio (95% CI)	
Important Predictors	Men‡	Women†
Age	1.01 (0.98–1.04)	1.03 (1.02–1.04)
Diabetes	1.10 (0.87–1.39)	0.92 (0.70–1.22)
Chest pain characterization (reference: noncardiac)		
Atypical	0.88 (0.51–1.49)	1.07 (0.77–1.47)
Typical	0.86 (0.26–2.89)	0.95 (0.62–1.45)
Body mass index (kg/m^2)	–	1.03 (1.01–1.04)
Modified Diamond-Forrester (26)	1.02 (1.00–1.05)	–
Framingham risk score (23)	1.01 (1.00–1.02)	1.02 (1.01–1.03)
History of heart failure	0.62 (0.36–1.05)	–
Sedentary lifestyle	1.17 (0.98–1.39)	–

*Final models for women and men selected using stepwise selection (entry criterion: p value <0.1; exit criterion: p value >0.2) from the following candidate predictors: age, race, body mass index, hypertension, diabetes, metabolic syndrome, dyslipidemia, smoking (ever, never), family history of premature CAD, depression, sedentary lifestyle, cerebrovascular or peripheral vascular disease, history of heart failure, CAD equivalent, Framingham risk score (23), ASCVD risk prediction (24), Diamond-Forrester (25), Combined Diamond-Forrester and Coronary Artery Surgery Study (27), modified Diamond-Forrester (26), presenting symptom, and chest pain characterization. Age, diabetes, and chest pain characterization forced into each model. †The final model for women was well-calibrated (Hosmer-Lemeshow goodness-of-fit p value: 0.587) and had modest discriminatory capacity (AUC 0.61; 95% CI: 0.59 to 0.64). ‡The final model for men was well-calibrated (Hosmer-Lemeshow goodness-of-fit p value: 0.450) and had modest discriminatory capacity (AUC 0.65; 95% CI: 0.63 to 0.67).

AUC = area under the curve; other abbreviations as in Tables 1 to 3.

These data suggest that the known influences of sex on the pathophysiology of CAD are relevant to the entire diagnostic pathway of possible CAD and highlight the need for sex-specific approaches to CAD evaluation and testing. Continued investigation in this area is warranted to ensure optimal care for both men and women who present with stable symptoms suggestive of CAD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among stable outpatients with symptoms suspicious for CAD, women had a higher risk factor burden than men and a similar prevalence of chest pain, which was more often characterized as "crushing/pressure/squeezing/tightness" in women. Their overall risk for CAD, as estimated by providers and risk scores, was lower than that of men. Compared with men, women were more likely to be referred to imaging stress tests than nonimaging stress tests, but less likely to have a positive test. A number of characteristics predicted positive noninvasive test results, and many characteristics were similar between the sexes; however, in multivariable models, key predictors of test positivity were few and varied by sex.

TRANSLATIONAL OUTLOOK: Further studies are warranted to examine the underlying pathophysiology and implications for clinical care of the sex-based clinical differences observed along the entire diagnostic pathway of suspected CAD, including risk factor burden, presenting symptoms, and testing results.

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