



Research paper

Effects of obesity on noninvasive test results in patients with suspected cardiac ischemia: Insights from the PROMISE trial

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ARTICLE INFO

Keywords:

Obesity
Chest pain
Angina
Coronary computed tomography angiography
Single photon emission computed tomography

ABSTRACT

Background: Obesity is a risk factor for coronary artery disease (CAD), but adiposity may mimic symptoms of CAD and reduce the accuracy of diagnostic testing.

Methods: Patients from the PROMISE trial (n = 8889) were classified according to body mass index (BMI). We assessed relationships between BMI, physician's preference of functional test, test positivity, and results of invasive coronary angiography (Cath) using logistic regression models.

Results: Nearly half (48%) of the patients had BMI ≥ 30 kg/m², and 20% had BMI ≥ 35 . Providers were more likely to prefer nuclear myocardial perfusion imaging (MPI) over other functional tests as BMI increased. The rate of test positivity with coronary computed tomographic angiography (CTA) was not different (10% vs. 12%) in patients with BMI ≥ 35 vs. < 35 . The same was true for stress echocardiogram and stress electrocardiogram (positivity 8–13%, $P > 0.8$ for both). In contrast, MPI was significantly more likely to be positive in those with BMI ≥ 35 vs. < 35 (18% vs. 13%; $P = 0.001$). The likelihood of obstructive CAD at Cath did not differ with BMI ≥ 35 vs. < 35 in patients having CTA (52% vs. 59%, $P = 0.22$), but among MPI patients, Cath positivity was only 29% with BMI ≥ 35 vs. 48% with BMI < 35 ($P = 0.005$). Radiation exposure increased with higher BMI in both MPI and CTA groups.

Conclusions: Increasing levels of obesity adversely affect the diagnostic yield of MPI more than CTA. The degree of obesity should be considered when choosing evaluation strategies for patients with chest pain.

Clinical Trial Registration: PROMISE [ClinicalTrials.gov](https://clinicaltrials.gov) number, NCT01174550

1. Introduction

The prevalence of obesity has increased dramatically over the past few decades and continues to rise in some demographic groups.¹ The most recent National Health and Nutrition Examination Survey data from 2013 to 2014 show an overall age-adjusted obesity prevalence of 37.7% in the U.S. with 5.5% of men and 9.9% of women having class 3 obesity (body mass index [BMI] ≥ 40 kg/m²).¹ Obesity is a risk factor

for the development of coronary artery disease (CAD) and also has been associated with accelerated progression of atherosclerosis.^{2–7} The proatherogenic effects of adiposity are likely both direct (e.g., mediated by adipocytokines) and indirect (e.g., mediated by comorbidities such as diabetes, hypertension and dyslipidemia).⁸ Although the true risk of CAD may be increased in patients with obesity, they commonly have symptoms that are suspicious for cardiac ischemia but are actually due to noncardiac conditions such as deconditioning, obstructive sleep

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CTA, computed tomographic angiography; D-F, Diamond-Forrester; MPI, myocardial perfusion imaging

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<https://doi.org/10.1016/j.jcct.2019.03.010>

Received 1 November 2018; Received in revised form 21 February 2019; Accepted 25 March 2019

Available online 27 March 2019

1934-5925/© 2019 Published by Elsevier Inc. on behalf of Society of Cardiovascular Computed Tomography

apnea, and musculoskeletal problems. Thus, the evaluation of an obese patient presenting with symptoms of chest discomfort or shortness of breath can be quite challenging.

Expediently arriving at a correct ascertainment of cardiac vs. noncardiac causes of chest pain is hampered by the fact that the accuracy of noninvasive testing may be reduced in obese subjects. Low exercise capacity, equipment limitations (e.g., weight limits on tables, limited bore sizes on scanners), inability of patients to lay flat or perform breath holds, and impaired image quality can all contribute to both false positive and false negative test results. Although individual imaging modalities have been studied,^{9–13} there are few if any published data directly comparing the effectiveness of different evaluation strategies in obese patients with possible cardiac ischemia. Further, current guidelines for evaluation of stable ischemic heart disease do not address the additional complexities surrounding the evaluation of patients with obesity.¹⁴ The purpose of this study was to assess the impact of increasing levels of obesity on the choice of imaging strategy by the treating physician and the subsequent diagnostic yield in terms of true positive findings defined by invasive coronary angiography (Cath).

2. Methods

2.1. Study cohort and design

The PROMISE trial was a pragmatic, comparative effectiveness trial that randomized stable symptomatic patients with suspected CAD to an initial strategy of either anatomic testing with electrocardiogram (ECG)-gated coronary computed tomographic angiography (CTA) or stress testing.^{15,16} Local or central institutional review boards approved the trial, and all patients provided written informed consent. For patients in the stress-testing arm, the choice of test was left up to the treating clinician who prespecified the noninvasive test they would prefer (exercise ECG, stress echocardiography or myocardial perfusion imaging [MPI]) for each patient if randomized to that arm. Randomization was stratified by study site and by the stress test type prespecified by the provider. All tests were performed and interpreted by local physicians according to national guideline standards.¹⁵ Site physicians were responsible for all subsequent clinical decisions including the use of Cath. The main study results have been reported previously¹⁶ and showed equivalence of clinical outcomes in the two randomized arms. The current post hoc analysis includes those patients with height and weight recorded who were tested as randomized and who had site-reported interpretable results, defined as not missing and not indeterminate (Fig. 1).

The pretest probability of obstructive CAD was estimated using the Diamond-Forrester (D-F) model that was updated in 2011.¹⁷ Patients were categorized as being at low risk (< 30%), moderate risk (30–70%), or high risk (> 70%) of having obstructive CAD. A positive CTA was defined as $\geq 70\%$ stenosis of an epicardial artery or $\geq 50\%$ left main stenosis as determined by the site investigators. 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. Stress echocardiography or MPI were considered positive if there was inducible ischemia in at least one coronary territory (anterior, inferior, or lateral), or early termination of exercise stress (< 3 min) due to ST changes consistent with ischemia, symptom reproduction, arrhythmia, and/or hypotension. A positive Cath was defined as $\geq 50\%$ stenosis in the left main or $\geq 70\%$ stenosis in at least one epicardial artery or side branch of at least 2 mm diameter.

2.2. Statistical analyses

Patients' weight status was classified according to World Health Organization categories defined by BMI. Baseline patient characteristics are reported as mean (SD) for continuous variables, and numbers and

percentages for categorical variables. Characteristics were compared across BMI categories using Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables. For purposes of comparison using a clinically relevant dichotomous classification scheme, patients with BMI ≥ 35 kg/m² (World Health Organization class 2 and 3 obesity) were compared to those with BMI < 35.

To determine whether the likelihood of a positive test differed by category of obesity, we performed multivariable logistic regression analyses with adjustment for patient age; sex; chest pain vs. other as primary symptoms; chest pain characteristics (typical, atypical, non-cardiac); 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. Similar models were fit to assess the association between BMI (as a continuous variable) and test positivity. We tested for a two-way interaction between the category of obesity and the type of non-invasive test that was used to determine whether the test modality itself modified the relationship between the category of obesity and test positivity.

Generalized linear mixed models with a logit link function were used to assess the association between BMI and prespecified choice of functional test (imaging vs. non-imaging). In addition to adjusting for the variables listed above, these models included random intercepts for sites. The nonlinear relationship between BMI and test selection was modeled using piecewise linear splines with a single knot at BMI = 25. Similar models were fit to assess the association between BMI and the likelihood of the provider selecting MPI instead of stress echocardiography.

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

3. Results

3.1. Primary trial outcomes

In the PROMISE trial, a total of 10,003 patients were enrolled between 2010 and 2013. Over a median follow-up period of 25 months, there was no significant difference in the composite endpoint of death, myocardial infarction, unstable angina hospitalization, or major procedural complication between patients in the CTA vs. the functional testing group overall or in any of the prespecified subgroup analyses.¹⁶ Of the 10,003 patients enrolled in the trial, 8889 underwent testing as randomized, had interpretable test results, and had height and weight recorded at baseline (Fig. 1). Data from these patients form the balance of this report. Of these patients, 83% were categorized as overweight (BMI ≥ 25.0) or obese (BMI ≥ 30), and 28%, 13%, and 7% had class 1 (BMI 30.0–34.9), class 2 (BMI 35.0–39.9), or class 3 obesity (BMI ≥ 40), respectively (Table 1). With increasing levels of adiposity, there were fewer white patients and more black patients (Table 1). More obese patients tended to be younger. The presence of several major cardiovascular risk factors (hypertension, diabetes, and sedentary lifestyle) increased with higher levels of obesity. In contrast, smoking was inversely related to the degree of adiposity. The highest BMI categories had higher percentages of women.

Increasingly obese patients were less likely to have chest pain and more likely to have dyspnea as their presenting symptom (Table 2). Among those with chest pain, typicality of the pain, as assessed by the treating physician, was not different across obesity categories. There were significant differences in use of cardiac medications based on BMI category, with the higher categories more likely to take an angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker and beta-adrenergic blocking agents (Table 2). There were similar demographics and risk factors based on randomization to anatomic (CTA) or functional testing within both the high BMI (≥ 35) and low BMI (< 35) categories (Table 3).

Physicians strongly favored imaging tests, particularly MPI, with

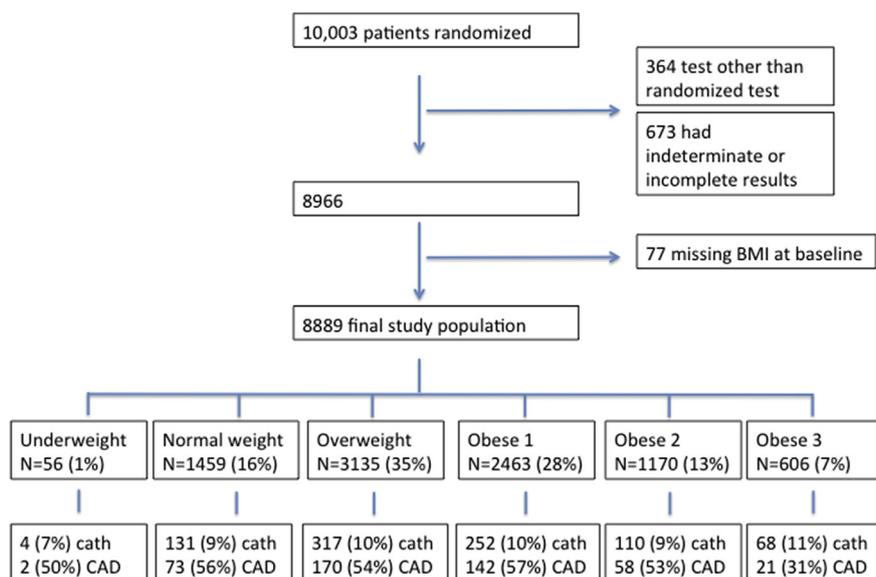


Fig. 1. Patient flow through the study. Bottom row shows the number and percentage of patients in each body mass index (BMI) category who underwent invasive coronary angiography (Cath) and who were found to have obstructive coronary artery disease (CAD) at Cath.

higher BMI. For each unit increase in BMI above 25 kg/m^2 , providers were more likely to choose MPI over stress echocardiography (adjusted odds ratio 1.06 per unit increase in BMI [95% CI 1.04–1.07]; $p < 0.001$).

We found that the predicted prevalence of obstructive CAD based on D-F risk category was different based on BMI $\geq 35 \text{ kg/m}^2$ vs. $< 35 \text{ kg/m}^2$ (Fig. 2). Specifically, compared to those with BMI $< 35 \text{ kg/m}^2$, the D-F classification more commonly categorized patients with BMI $\geq 35 \text{ kg/m}^2$ as low risk ($< 30\%$ probability of obstructive CAD), less often classified as medium risk (30–70% probability of obstructive CAD), and similarly classified as high-risk ($> 70\%$ probability of obstructive CAD; Fig. 2).

The overall frequency of positive noninvasive test results was 13.1% in patients with BMI ≥ 35 vs. 12.1% in patients with BMI < 35 (adjusted OR 1.16 [95% CI 0.98–1.37], $p = 0.081$). However, the likelihood of having a positive test result increased as BMI increased (adjusted OR 1.02 for every 1.0 unit increase in BMI [95% CI 1.00–1.03], $p < 0.007$). The likelihood of a positive test result in the patients with BMI ≥ 35 compared to those with BMI < 35 varied by testing modality (interaction $p = 0.003$; Fig. 3). The rate of positivity with CTA was slightly, but not significantly higher (10% vs. 12%, $p = \text{NS}$) in patients with BMI ≥ 35 vs. < 35 . The same appeared to be true for stress echo and stress ECG (positivity rate of 8–13%, $p > 0.8$ for both), although these latter comparisons were underpowered due to low numbers of patients undergoing these tests. In contrast, MPI was significantly more likely to be positive in those with BMI ≥ 35 vs. < 35 (18% vs. 13%; $p = 0.001$; adjusted odds ratio 1.61 [95% CI: 1.27–2.05]).

Subsequent to noninvasive testing, approximately 10% of patients in the overall study underwent Cath (Table 1, Figs. 1, Figure 4). The overall frequency of Cath was not different in those with BMI ≥ 35 vs. < 35 (10.0% vs. 9.9%). A smaller percentage of patients with positive MPI studies (defined as inducible perfusion defect in at least one coronary territory) underwent subsequent Cath compared to those with positive CTA (47% vs. 66%, $p < 0.001$). The “yield” of Cath was defined as the number of Caths showing obstructive CAD/number of Caths performed. In the overall population, the yield was 50–55% in all BMI strata except for class 3 obesity in which the yield was 29% (Table 1). The yield for patients undergoing CTA as the initial test did not differ based on a BMI cutoff of 35; specifically, the yield was 51.7% in those with BMI ≥ 35 vs. 58.8% for those with BMI below this value ($p = 0.22$). In contrast, the yields in patients undergoing MPI were

quite different: 29.5% vs. 47.8% for those with BMI ≥ 35 and < 35 , respectively ($p = 0.005$). The numbers of patients with class 2 and 3 obesity undergoing exercise electrocardiography without imaging or stress echocardiography were small (Fig. 4), and the subsets of these patients who had Cath were too few to confidently assess differences in yield between BMI groups. Nonetheless, the trends suggest that yields were similar for both exercise electrocardiography and stress echocardiography in patients with BMI ≥ 35 and < 35 . Importantly, since randomization was stratified by the prespecified test, the assignment to either MPI or CTA cohort was randomized and not a post hoc grouping, making the comparisons more valid.

Cumulative radiation exposure (90-day) increased with BMI in both CTA and MPI subgroups with mean radiation exposure being comparable in the highest BMI group (15.1 and 16.5 mSv, respectively; Table 4). As expected, those undergoing stress echo had much lower radiation exposure.

4. Discussion

In the PROMISE study population of stable symptomatic outpatients being evaluated for suspected CAD, obesity was present in approximately half of the patients, and increasing levels of obesity were associated with different patient demographics, risk factors, and stronger physician preference for MPI over other noninvasive functional tests. In patients undergoing MPI, higher levels of obesity (i.e., BMI $\geq 35 \text{ kg/m}^2$) were associated with a higher rate of positive results, and a lower yield for obstructive CAD in those referred to Cath. In contrast, in patients receiving CTA as their initial test, neither test positivity rates nor Cath yield varied by BMI.

Obesity is endemic in the United States, and the prevalence has shown continued increases in recent years.¹ Similar situations exist in most developed and developing countries around the world. Evaluation of obese patients with chest pain can be extremely challenging because adiposity simultaneously increases the risk of developing ischemic heart disease, mimics the symptoms of CAD even in its absence, and may reduce the reliability of commonly used tests to noninvasively diagnose CAD. Despite the strong need for guidance on how to evaluate and manage such patients, current guidelines are largely silent on the topic of obesity as a confounding condition.¹⁴ This may be due to a current paucity of randomized trial data that address the issue of optimizing testing strategies in obese subjects with suspected CAD.

Table 1
Patient demographics/characteristics based on BMI category.

	Underweight BMI < 18.5 N = 56; 1%	Normal 18.5–24.9 N = 1459; 16%	Overweight 25.0–29.9 N = 3135; 35%	Obese 1 30.0–34.9 N = 2463; 28%	Obese 2 35.0–39.9 N = 1170; 13%	Obese 3 ≥ 40 N = 606; 7%	P-value
Age (years)	61.2 (8.57)	62.7 (8.94)	61.3 (8.48)	60.3 (7.86)	59.1 (7.42)	58.5 (6.84)	
Female sex	42/56 (75.0%)	899/1459 (61.6%)	1499/3135 (47.8%)	1216/2463 (49.4%)	655/1170 (56.0%)	367/606 (60.6%)	< 0.001
Race							< 0.001
Multi-Racial	1/55 (1.8%)	16/1445 (1.1%)	30/3111 (1.0%)	24/2446 (1.0%)	11/1154 (1.0%)	3/603 (0.5%)	
White	49/55 (89.1%)	1250/1445 (86.5%)	2655/3111 (85.3%)	2066/2446 (84.5%)	973/1154 (84.3%)	476/603 (78.9%)	
Black	4/55 (7.3%)	107/1445 (7.4%)	272/3111 (8.7%)	299/2446 (12.2%)	154/1154 (13.3%)	112/603 (18.6%)	
Asian	1/55 (1.8%)	65/1445 (4.5%)	118/3111 (3.8%)	29/2446 (1.2%)	5/1154 (0.4%)	2/603 (0.3%)	
Ethnicity							0.063
Hispanic or Latino	3/55 (5.5%)	82/1446 (5.7%)	253/3118 (8.1%)	196/2448 (8.0%)	85/1163 (7.3%)	41/605 (6.8%)	
Not Hispanic or Latino	52/55 (94.5%)	1364/1446 (94.3%)	2865/3118 (91.9%)	2252/2448 (92.0%)	1078/1163 (92.7%)	564/605 (93.2%)	
Cardiac Risk Factors							
Hypertension	31/56 (55.4%)	698/1459 (47.8%)	1855/3135 (59.2%)	1754/2463 (71.2%)	915/1170 (78.2%)	506/606 (83.5%)	< 0.001
Diabetes	6/56 (10.7%)	153/1459 (10.5%)	417/3135 (13.3%)	645/2463 (26.2%)	382/1170 (32.6%)	281/606 (46.4%)	< 0.001
Dyslipidemia	27/56 (48.2%)	894/1459 (61.3%)	2160/3135 (68.9%)	1744/2463 (70.8%)	801/1170 (68.5%)	391/606 (64.5%)	< 0.001
Smoker (ever/never)	35/56 (62.5%)	798/1459 (54.7%)	1581/3134 (50.4%)	1282/2463 (52.1%)	565/1170 (48.3%)	282/606 (46.5%)	< 0.001
Family history of premature CAD	19/55 (34.5%)	458/1451 (31.6%)	981/3129 (31.4%)	765/2455 (31.2%)	396/1167 (33.9%)	197/605 (32.6%)	0.610
Sedentary lifestyle	23/56 (41.1%)	570/1456 (39.1%)	1348/3130 (43.1%)	1247/2459 (50.7%)	699/1170 (59.7%)	414/606 (68.3%)	< 0.001
CAD prevalence among those referred to Cath	2/4 (50.0%)	73/131 (55.7%)	168/318 (52.8%)	141/254 (55.5%)	5/110 (51.8%)	20/68 (29.4%)	0.006

Data are shown as mean (SD) or n/N (%). BMI = body mass index; CAD = coronary artery disease. Cath = invasive coronary angiography.

Table 2
Symptoms and medications by BMI category.

	Underweight BMI < 18.5 N = 56; 1%	Normal 18.5–24.9 N = 1459; 16%	Overweight 25.0–29.9 N = 3135; 35%	Obese 1 30.0–34.9 N = 2463; 28%	Obese 2 35.0–39.9 N = 1170; 13%	Obese 3 ≥ 40 N = 606; 7%	P-value
Primary Presenting Symptom							
Arm or shoulder pain	0/56 (0.0%)	32/1458 (2.2%)	79/3134 (2.5%)	58/2461 (2.4%)	33/1168 (2.8%)	18/606 (3.0%)	0.658
Back pain	1/56 (1.8%)	15/1458 (1.0%)	24/3134 (0.8%)	18/2461 (0.7%)	10/1168 (0.9%)	4/606 (0.7%)	0.850
Chest pain	47/56 (83.9%)	1087/1458 (74.6%)	2292/3134 (73.1%)	1801/2461 (73.2%)	815/1168 (69.8%)	421/606 (69.5%)	0.011
Fatigue or Weakness	0/56 (0.0%)	37/1458 (2.5%)	87/3134 (2.8%)	68/2461 (2.8%)	27/1168 (2.3%)	17/606 (2.8%)	0.780
Dyspnea	6/56 (10.7%)	188/1458 (12.9%)	441/3134 (14.1%)	383/2461 (15.6%)	203/1168 (17.4%)	117/606 (19.3%)	< 0.001
Physician Characterization of Chest Pain							
Typical	8/56 (14.3%)	145/1459 (9.9%)	358/3135 (11.4%)	279/2463 (11.3%)	148/1170 (12.6%)	80/606 (13.2%)	0.289
Atypical	42/56 (75.0%)	1152/1459 (79.0%)	2428/3135 (77.4%)	1919/2463 (77.9%)	918/1170 (78.5%)	468/606 (77.2%)	
Non-cardiac	6/56 (10.7%)	162/1459 (11.1%)	349/3135 (11.1%)	265/2463 (10.8%)	104/1170 (8.9%)	58/606 (9.6%)	
Medication Use							
Aspirin	15/55 (27.3%)	582/1366 (42.6%)	1302/2981 (43.7%)	1108/2381 (46.5%)	526/1135 (46.3%)	277/589 (47.0%)	0.006
Statin	15/55 (27.3%)	546/1366 (40.0%)	1382/2981 (46.4%)	1160/2381 (48.7%)	524/1135 (46.2%)	275/589 (46.7%)	< 0.001
Beta-blocker	17/55 (30.9%)	284/1366 (20.8%)	658/2981 (22.1%)	645/2381 (27.1%)	319/1135 (28.1%)	188/589 (31.9%)	< 0.001
ACEI or ARB	16/55 (29.1%)	397/1366 (29.1%)	1110/2981 (37.2%)	1183/2381 (49.7%)	642/1135 (56.6%)	377/589 (64.0%)	< 0.001

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker.

The PROMISE trial is the largest randomized clinical trial performed to date comparing different diagnostic strategies in the evaluation of chest pain. The size of the study population, the relatively unselected nature of the patients, and the clinician-driven evaluation process make the results broadly applicable to “real-world” care. Approximately half of the patients in this study were obese based on World Health Organization criteria, and there were large numbers of patients with class 2 and 3 obesity. The randomization process produced well-balanced groups of subjects in the functional vs. anatomic arms overall and in those with BMI above or below 35 kg/m² (Table 3). While the main results of the parent trial showed no difference in clinical outcomes between the anatomic and the functional arms,¹⁶ the results of this secondary analysis suggest that the degree of obesity should be a consideration when choosing a diagnostic testing modality. For patients with BMI < 35, functional and anatomic approaches seem to have similar utility for diagnosing obstructive CAD. However, as BMI exceeds 35, as it did in 20% of our patients, nuclear MPI appears to be particularly prone to false positive results whereas CTA seems to be less sensitive to this error. This finding is notable given the strong preference of treating physicians for MPI over other functional tests as BMI increases. The number of patients undergoing stress ECG or stress echo in this study was too small to draw conclusions about the performance of these tests in different BMI groups. Given the significant increase in radiation exposure as BMI increased, and the fact that more obese subjects tended to be younger, clinicians must fully consider the potential long-term effects when choosing diagnostic strategies for patients with chest pain.

4.1. Comparison to prior studies

Several randomized trials have compared anatomic imaging to usual care, most often functional testing, in emergency department evaluation of patients with chest pain.¹⁸ None were as large as the PROMISE study, and most focused on clinical endpoints rather than diagnostic utility. Three other randomized, prospective studies compared different testing approaches for stable chest pain patients.^{19–21} Mean BMI was slightly higher in the PROMISE cohort (30.5 kg/m²) than in the SCOT-HEART (29.7 kg/m²) or CRESCENT (28 kg/m²) trials, but similar to that in the U.S. based PICTURE trial (30.1 kg/m²).^{19–21} None of those studies have reported on whether different degrees of obesity affected the utility of the noninvasive testing strategies. Most existing literature related to obesity and noninvasive cardiac testing relies on retrospective analyses of a single testing modality such as nuclear MPI. For example, in 433 severely obese patients (mean BMI 47 kg/m²) undergoing clinically indicated MPI, 10% underwent subsequent Cath and the reported sensitivity and specificity for detecting > 50% stenosis of any coronary artery at Cath were 95% and 17%, respectively.²²

4.2. Limitations

Although PROMISE was a large, prospective, randomized clinical trial with carefully collected data and defined end points, there are certain limitations to the interpretation of the findings that are inherent in the trial design. First, approximately 10% of the total PROMISE study population underwent Cath. This percentage is in keeping with that seen in other studies of patients without known CAD undergoing non-invasive testing for evaluation of chest pain.^{18,22,23} Since most patients in the PROMISE trial did not have Cath to use as standard by which to judge the accuracy of each noninvasive test, and referral rates to Cath varied by testing modality, it is not possible to assess or directly compare the diagnostic performance of each modality, or to assess each modality without referral bias. Therefore, we expressed “yield” as the percentage of patients from each initial testing group who were referred to Cath and deemed to have significant CAD based on the invasive study. The concept of yield has been developed in previous reports

Table 3
Patient Characteristics Based on Anatomic or Functional Arm and by BMI Cut Point of 35 kg/m².

	Not Severely Obese (N = 7113)			Severely Obese (N = 1776)		
	Anatomic (N = 3589)	Functional (N = 3524)	P-value	Anatomic (N = 872)	Functional (N = 904)	P-value
Age (years)	61.6 (8.52)	60.9 (8.30)	< 0.001	59.1 (7.09)	58.8 (7.38)	0.272
Female Sex	1810/3589 (50.4%)	1846/3524 (52.4%)	0.100	501/872 (57.5%)	521/904 (57.6%)	0.939
Race			0.010			0.662
Multi-Racial	45/3562 (1.3%)	26/3495 (0.7%)		10/860 (1.2%)	4/897 (0.4%)	
White	3006/3562 (84.4%)	3014/3495 (86.2%)		708/860 (82.3%)	741/897 (82.6%)	
Black	348/3562 (9.8%)	334/3495 (9.6%)		130/860 (15.1%)	136/897 (15.2%)	
Asian	126/3562 (3.5%)	87/3495 (2.5%)		3/860 (0.3%)	4/897 (0.4%)	
Cardiac Risk Factors						
Hypertension	2172/3589 (60.5%)	2166/3524 (61.5%)	0.413	694/872 (79.6%)	727/904 (80.4%)	0.661
Diabetes	601/3589 (16.7%)	620/3524 (17.6%)	0.343	320/872 (36.7%)	343/904 (37.9%)	0.588
Dyslipidemia	2430/3589 (67.7%)	2395/3524 (68.0%)	0.817	574/872 (65.8%)	618/904 (68.4%)	0.255
Smoker (ever/never)	1844/3588 (51.4%)	1852/3524 (52.6%)	0.327	423/872 (48.5%)	424/904 (46.9%)	0.498
Sedentary Lifestyle	1620/3583 (45.2%)	1568/3518 (44.6%)	0.586	540/872 (61.9%)	573/904 (63.4%)	0.525
Risk Score						
ASCVD (2013)			0.013			0.241
Mean (SD)	14.9 (11.93)	14.3 (11.34)		14.8 (11.73)	14.3 (11.58)	
Primary Presenting Symptom			0.156			0.164
Chest Pain	2671/3586 (74.5%)	2556/3523 (72.6%)		619/872 (71.0%)	617/902 (68.4%)	
Dyspnea	489/3586 (13.6%)	529/3523 (15.0%)		142/872 (16.3%)	178/902 (19.7%)	

Data are shown as mean (SD) or n/N (%).

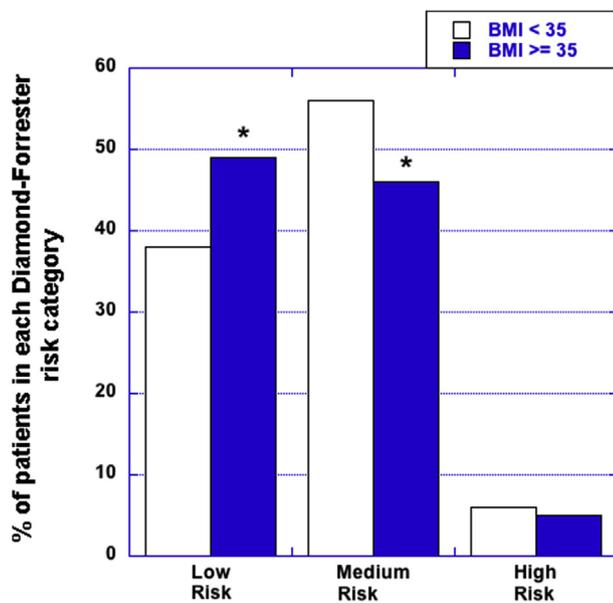


Fig. 2. Updated Diamond-Forrester risk category for likelihood of obstructive CAD in low (< 30%), medium (30–70%), and high (> 70%) risk categories based on BMI cut point of 35 kg/m². Probability of obstructive CAD (low, medium, high) based on BMI cut point of 35. The pretest probability of obstructive CAD was calculated using the updated Diamond-Forrester model. Low probability was defined as < 30%, medium probability as 30–70%, and high probability defined as > 70%. The distribution of patients with low and medium probability of obstructive CAD was different in the patients with class 2 and 3 obesity compared to those with ≤ class 1 obesity. *p < 0.05 BMI ≥ 35 vs. < 35 kg/m².

about results of diagnostic angiography^{24,25} as distinct from diagnostic test accuracy. Second, BMI is an imperfect measure of adiposity, but is readily available in most electronic health records, large population databases, and clinical trials. This parameter is easily measured, reproducible, and has been widely studied as a measure of adiposity. For

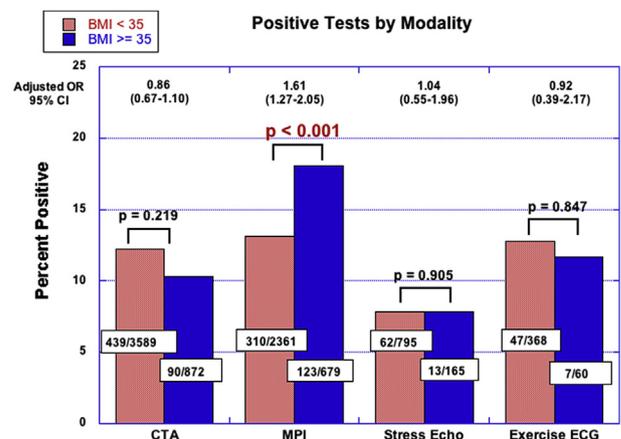


Fig. 3. Test positivity rates by testing modality with BMI cut point of 35 kg/m². Test positivity rates were similar for BMI < 35 vs. ≥ 35 for all testing modalities except myocardial perfusion imaging (MPI) where the percentage of positive tests was significantly higher in those with BMI ≥ 35. The adjusted odds ratio for a positive test in this subgroup was 1.61 vs. those with BMI < 35. The adjusted odds ratios for other testing modalities were not significant. CTA indicates coronary computed tomographic angiography; Echo, echocardiography; ECG, electrocardiogram.

example, this metric was used in a recent meta-analysis examining BMI and all-cause mortality in over 10 million subjects worldwide.²⁶ Use of BMI facilitates comparison with many other studies. While BMI misclassifies some patients in comparison to more direct measures of body fat, classification is accurate in the large majority of patients and in many large studies performs as well as waist circumference as a predictor of events or mortality.²⁷ Third, by design, all tests were performed with locally available hardware and software imaging platforms and interpreted by the site investigators. To reduce variability, each site underwent a certification and continuous quality assessment process for each testing modality and followed national recommendations for image acquisition and interpretation.¹⁵ Nonetheless, one would anticipate that variations in local equipment (e.g. use of attenuation

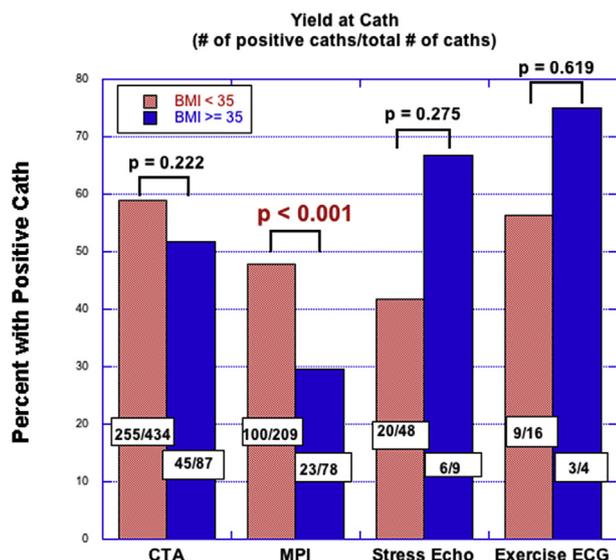


Fig. 4. Yield at invasive coronary angiography (Cath) based on testing modality and BMI cut point of 35 kg/m². The yield at invasive angiography (number of positive Caths/total number of Caths) was not different in those with BMI < 35 vs. ≥ 35 for all testing modalities except MPI, where the yield was significantly lower in those with BMI ≥ 35. The numbers for stress echocardiography and exercise ECG are low, and conclusions regarding yield in these groups are uncertain.

correction for MPI studies) and expertise could have affected the final results shown in this paper. Positron emission tomography was used infrequently in this study, but has potential advantages in assessment of obese patients. Although the strategy of local test interpretation introduces an additional source of variability, it allows for a more realistic assessment of how each test performs in a “real-world” clinical setting. Fourth, the use of fractional flow reserve measurements is considered the gold standard for assessment of lesion severity. At the time this study was done, most sites in the USA did not routinely perform fractional flow reserve measurements. Fifth, the definition(s) of test

positivity may have affected the results of the study. Sixth, there were not specific cutoffs used to define the size or severity of reversible perfusion defects, wall motion abnormalities, or ST segment changes on the electrocardiogram.¹⁶ Thus, the primary outcomes do not clearly distinguish between those with higher and lower risk features on non-invasive testing. Lastly, it is increasingly recognized that non-obstructive, milder degrees of atherosclerosis are also associated with risk of events, and this was not accounted for in the current analysis.²⁸

4.3. Conclusions

Obesity is associated with provider decision-making with regard to noninvasive test choice, probability of abnormal test results, and probability of finding obstructive disease at Cath following a positive noninvasive test. Future guidelines should incorporate information on obesity as a determinant of evaluation strategies. More research directly comparing different approaches in subjects with obesity seems warranted.

Funding and disclosures

Funded by National Heart, Lung, and Blood Institute grants R01 HL098237, R01 HL098236, R01 HL098305, and R01 HL098235. Dr. Pagidipati reports receiving research grants from Amgen, Regeneron Pharmaceuticals, Sanofi-Aventis, and Verily Life Sciences. Dr. Lee reports receiving grants from the National Institutes of Health. Dr. Mark reports receiving grants from the National Institutes of Health, as well as personal fees from CardioDx, Medtronic, Inc., and St. Jude Medical, and grants from Eli Lilly and Company, Bristol-Myers Squibb, Gilead Sciences, Inc., AGA Medical Corporation, Merck & Company, Oxygen Therapeutics, and AstraZeneca. Dr. Udelson reports receiving research grants from the NHLBI. Dr. Hoffmann reports receiving grants from American College of Radiology Imaging Network, HeartFlow Inc. and Siemens Healthcare. Dr. Douglas reports receiving grant support from HeartFlow and service on a data and safety monitoring board for GE HealthCare. The other authors report no potential conflicts of interest.

Table 4
90-Day cumulative radiation exposure by BMI category.

	Underweight BMI < 18.5 N = 56	Normal 18.5–24.9 N = 145	Overweight 25.0–29.9 N = 3135	Obese 1 30.0–34.9 N = 2463	Obese 2 35.0–39.9 N = 1170	Obese 3 ≥ 40 N = 606	P-value
Anatomical							0.000
N	26	707	1627	1229	581	291	
Median (25th, 75th)	8.0 (4.8, 10.7)	8.3 (4.4, 15.3)	9.4 (5.5, 16.9)	11.9 (7.0, 17.9)	11.5 (7.6, 18.5)	13.7 (7.9, 20.7)	
Mean (SD)	8.7 (5.7)	10.2 (7.5)	11.7 (8.1)	13.4 (8.3)	13.8 (8.8)	15.1 (8.6)	
Functional (overall)							0.000
N	30	752	1508	1234	589	315	
Median (25th, 75th)	9.2 (0.0, 11.9)	11.1 (0.0, 13.2)	11.3 (0.0, 13.2)	11.7 (0.0, 14.4)	12.2 (0.0, 15.7)	12.9 (10.3, 17.8)	
Mean (SD)	9.2 (9.2)	9.9 (9.1)	10.0 (8.8)	11.2 (8.8)	11.6 (8.9)	13.5 (8.7)	
Functional MPI							0.000
N	18	478	974	891	427	252	
Median (25th, 75th)	11.5 (10.5, 20.8)	12.5 (11.2, 15.6)	12.7 (11.3, 15.0)	12.9 (11.4, 16.7)	13.0 (11.6, 18.0)	13.8 (12.1, 9.6)	
Mean (SD)	14.8 (7.6)	14.9 (7.2)	14.9 (7.6)	15.1 (6.8)	15.6 (6.6)	16.5 (6.6)	
Functional Stress Echo							0.242
N	7	195	362	231	116	49	
Median (25th, 75th)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	
Mean (SD)	1.3 (3.5)	0.8 (3.0)	0.9 (2.9)	0.5 (2.3)	0.7 (4.0)	1.85 (5.6)	

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