A Randomized Comparison of Anatomic versus Functional Diagnostic Testing Strategies in Symptomatic Patients with Suspected Coronary Artery Disease

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On behalf of the PROMISE Investigators

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Background

- New onset stable chest pain accounts for approximately 4 million stress tests annually in the United States
- Limited randomized data in stable CP pts to guide care
  - Little consensus about which test is preferable
  - Impact of testing on health-related outcomes is unexplored
- Current testing practices raise concerns regarding frequent testing of very low risk populations and high rates of finding no obstructive coronary artery disease in patients undergoing elective catheterization

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Background (cont'd)

- Coronary CT angiography (CTA) could reduce unneeded invasive testing and improve outcomes
  - Higher positive and negative predictive accuracy for CAD
  - Ability to detect a broader spectrum of CAD, including prognostically important, non-obstructive disease
  - CTA is superior to usual care in 3 RCTs of acute CP patients
- The impact of the information derived from an initial strategy of noninvasive anatomic versus functional test data on subsequent management and clinical outcomes in stable chest pain patients is unknown

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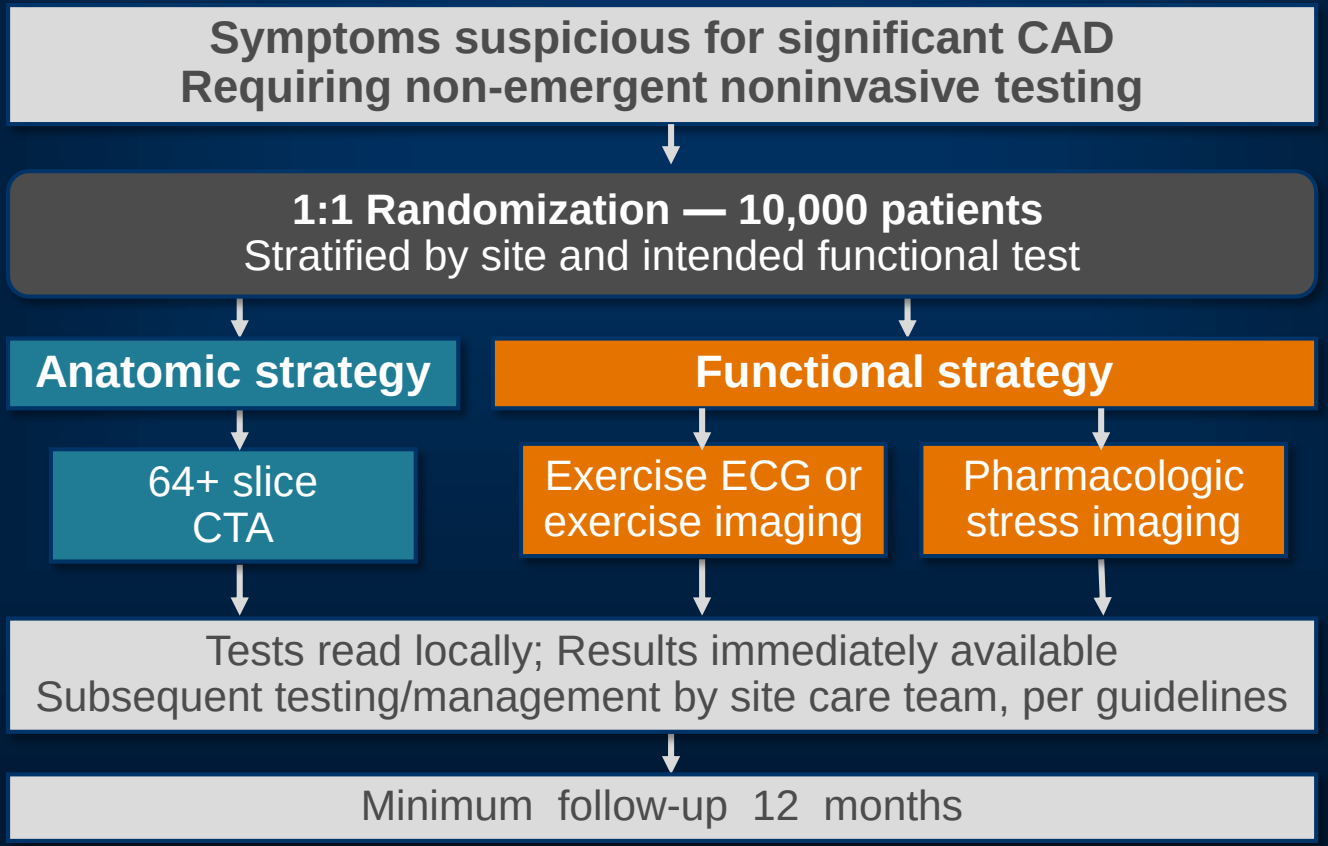
PROMISE Study Hypothesis and Design

PROspective **M**ulticenter **I**maging **S**tudy for **E**valuation of chest pain

- **Hypothesis:** As compared to functional testing, an initial strategy of anatomic testing with CTA would improve the health outcomes of patients with symptoms suspicious for CAD who require further testing

- **Design:** Multicenter, randomized, pragmatic comparative effectiveness trial comparing these two contemporary diagnostic strategies

PROMISE Trial Design



Study Population

Inclusion criteria

- Non-urgent, noninvasive CV testing clinically necessary
- No history of CAD or recent CAD evaluation
- Age ≥55 years (men) or ≥65 years (women) OR
- Age 45–54 years (men) or 50–64 years (women) with ≥1 major cardiac risk factor

Exclusion criteria

- Unstable hemodynamics or arrhythmias
- Urgent evaluation for R/O ACS
- Known significant congenital, valvular or cardiomyopathic heart disease
- Any reason the patient could not be safely randomized

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Study Procedures

- Diagnostic testing quality control for all modalities
  - Certification of sites and test readers prior to beginning enrollment
  - Ongoing quality control throughout the trial
- Tests performed and interpreted locally
  - Test information sheets outlining diagnostic and prognostic implications of findings in each modality
- Site clinical team made all subsequent care decisions; Optimal medical therapy encouraged
  - Patient and caregiver educational materials

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Effectiveness and Safety Endpoints

- Primary endpoint
  - All-cause mortality, myocardial infarction, unstable angina hospitalization, and major complications from CV procedures (stroke, bleeding, renal failure, anaphylaxis)
- Secondary endpoints
  - Primary endpoint + invasive catheterization without obstructive CAD
  - Other components of the primary endpoint
  - Invasive catheterization without obstructive CAD
  - Cumulative radiation exposure ≤90 days
  - (Resource utilization)
- All events adjudicated by blinded Clinical Events Committee

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Statistical Analysis

- Sample size was chosen to provide 90% power for detecting a 20% relative reduction in the primary endpoint with CTA
- All treatment comparisons performed as randomized (ITT)
- For clinical endpoints, time-to-event analysis was performed using the Cox model
- To account for subject heterogeneity, comparisons were adjusted for age, sex, CAD risk equivalent, and intended functional test at randomization
- All testing was two-sided and included 95% confidence intervals

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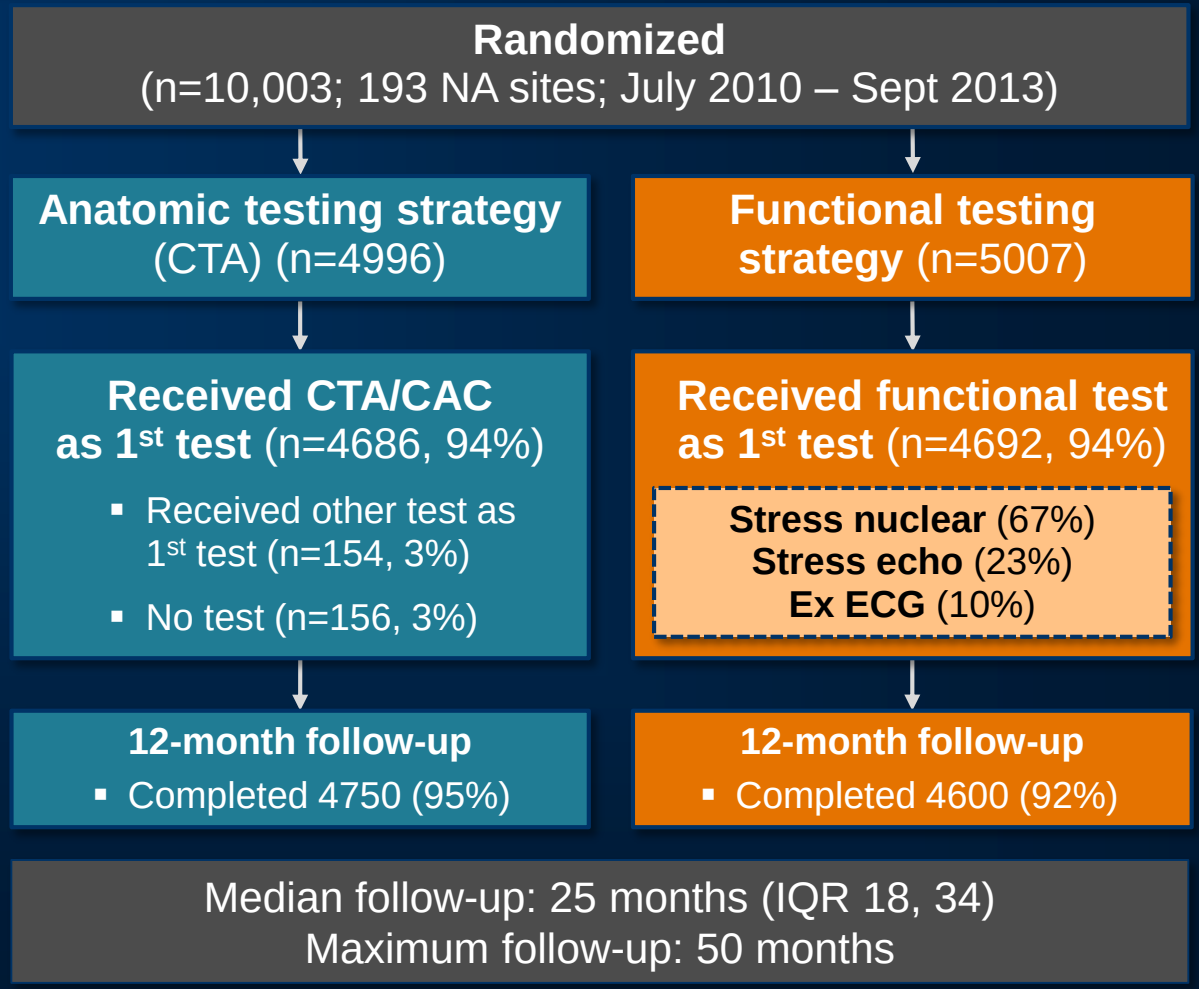
Randomization and Follow-up



Baseline Characteristics

		CTA (n=4996)	Functional (n=5007)
Demographics	Age — mean ± SD, yrs	60.7 ± 8.3	60.9 ± 8.3
	Female sex — %	52	53
	Non-white race — %	16	15
Risk factors	Hypertension — %	65	65
	Diabetes — %	21	22
	Dyslipidemia — %	67	68
	Family hx premature CAD — %	33	32
	Current or past smoking — %	51	51
1° Symptom	Chest pain or DOE — %	88	88
Anginal type	Typical or atypical — %	89	89
Pretest probability CAD	Diamond–Forrester/CASS — mean %	53.4	53.2

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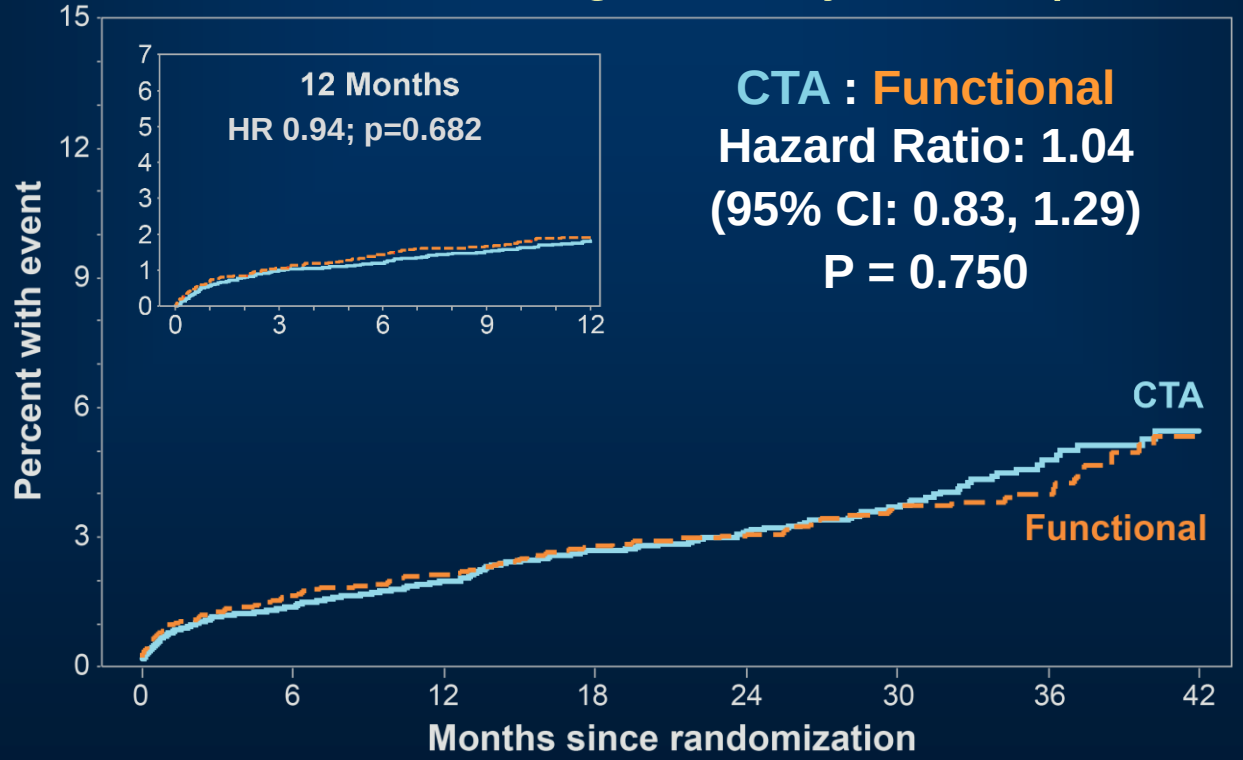
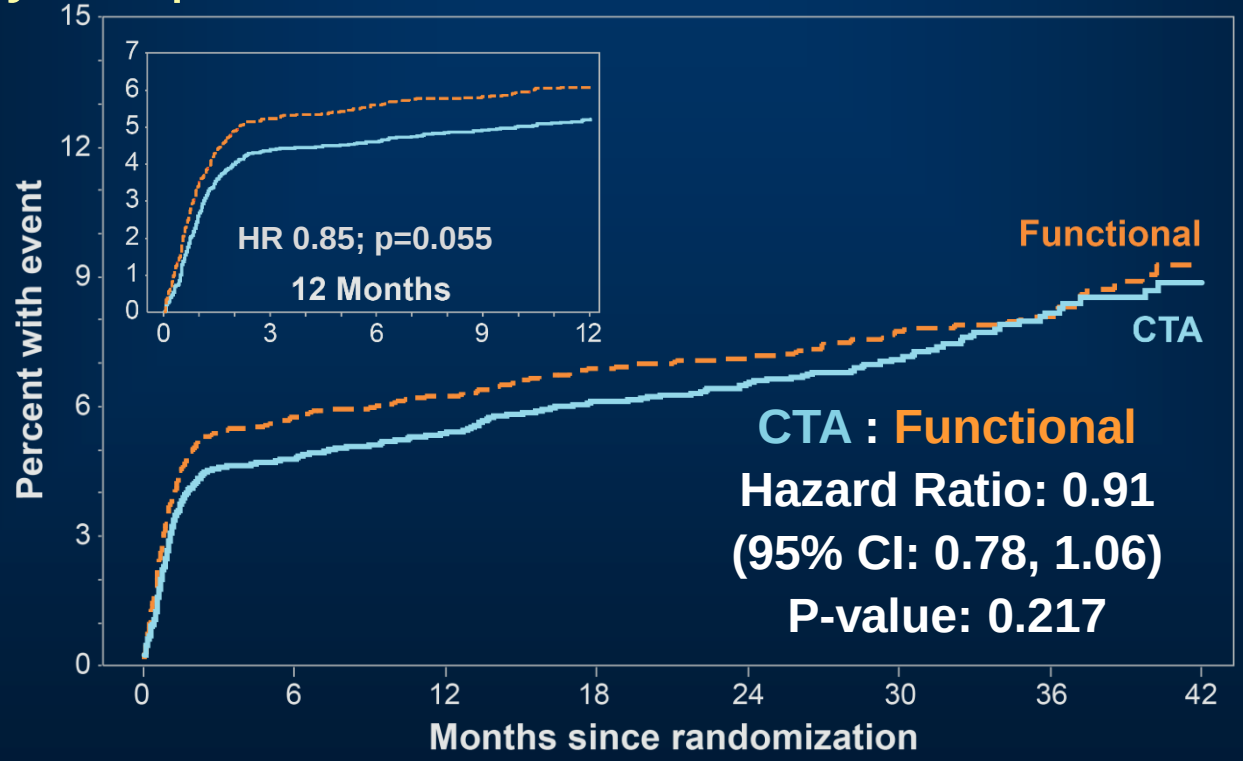
Primary Endpoint:
Death, MI, Unstable Angina, Major Complications



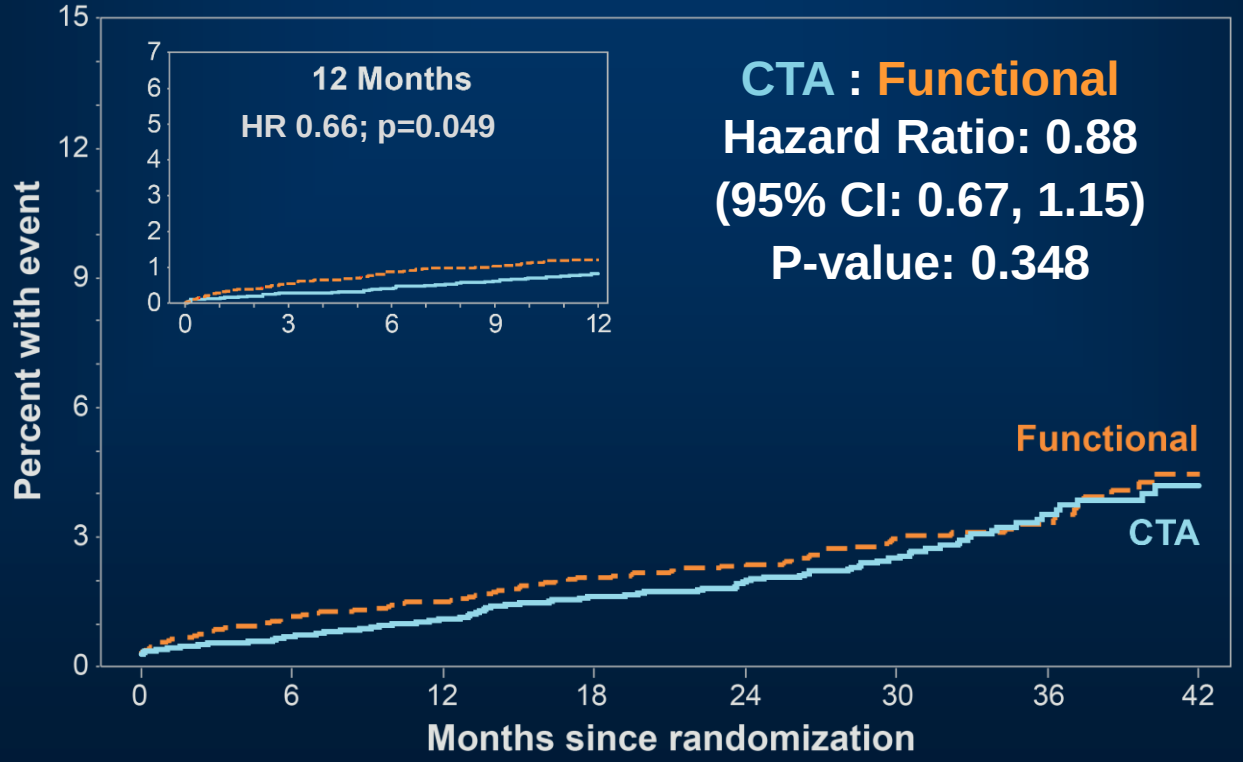
# at risk	Baseline (0)	6 Mo.	12 Mo.	18 Mo.	24 Mo.	30 Mo.	36 Mo.	42 Mo.
CTA	4996	4703	4362	3551	2652	1705	902	269
Functional	5007	4536	4115	3331	2388	1518	832	258

Secondary Endpoint:
Primary Endpoint + Catheterization w/o Obstructive CAD



# at risk	Baseline (0)	6 Mo.	12 Mo.	18 Mo.	24 Mo.	30 Mo.	36 Mo.	42 Mo.
CTA	4996	4540	4211	3430	2565	1645	868	255
Functional	5007	4341	3934	3179	2276	1438	781	244

Secondary Endpoint:
Death or Non-fatal MI



# at risk	Baseline (0)	6 Mo.	12 Mo.	18 Mo.	24 Mo.	30 Mo.	36 Mo.	42 Mo.
CTA	4996	4739	4409	3599	2686	1732	918	276
Functional	5007	4563	4148	3365	2415	1540	846	262

Clinical Endpoint Events

	CTA (n=4996)	Functional (n=5007)	Adj HR (95% CI)	P value
Primary endpoint composite	**164**	**151**	**1.04 (0.83–1.29)**	**0.750**
All-cause death	74	75		
Nonfatal MI	30	40		
Unstable angina hosp	61	41		
Major procedural complications	4	5		
Primary endpoint plus cath without obstructive CAD	**332**	**353**	**0.91 (0.78–1.06)**	**0.217**
Death or nonfatal MI	**104**	**112**	**0.88 (0.67–1.15)**	**0.348**
Death, nonfatal MI, or unstable angina hospitalization	**162**	**148**	**1.04 (0.84–1.31)**	**0.703**

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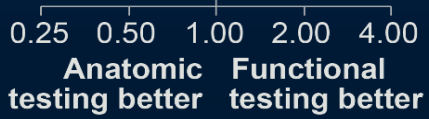
Primary Endpoint: Subgroup Analyses

Subject group		Interaction P-value	N	Hazard ratio	95% CI
All subjects			10,003	1.04	0.83, 1.29
Age	<65	0.591	7111	1.10	0.82, 1.47
	≥65		2892	0.97	0.69, 1.36
Sex	Male	0.698	4733	0.99	0.74, 1.32
	Female		5270	1.08	0.76, 1.51
Race	White	0.100	8371	0.95	0.74, 1.20
	Non-white		1545	1.62	0.89, 2.92
Pre-test risk assessment	Low risk (≤30%)	0.341	3755	1.33	0.88, 2.00
	Intermediate risk (31–70%)		5750	0.92	0.69, 1.23
	High risk (>70%)		481	0.94	0.51, 1.74
CAD equivalent	Yes	0.142	2531	0.83	0.57, 1.20
	No		7472	1.17	0.89, 1.54
Pretest probability of CAD	Low risk (<10%)	0.603	250	2.30	0.45, 11.88
	Intermediate risk (10–90%)		9258	1.00	0.79, 1.26
	High risk (>90%)		495	1.08	0.53, 2.23
Functional test randomization stratum	Stress nuclear	0.293	6781	0.93	0.72, 1.21
	Stress echo		2236	1.27	0.78, 2.05
	Exercise ECG		986	1.80	0.66, 4.86



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Secondary Endpoint:
Catheterization Without Obstructive CAD ≤90 days

	CTA (n=4996)	Functional (n=5007)	P value
Invasive catheterization without obstructive CAD — N (%)	**170 (3.4)**	**213 (4.3)**	**0.022**
Invasive catheterization	609 (12.2%)	406 (8.1%)	
With obstructive CAD (% of caths)	439 (72.1%)	193 (47.5%)	
Revascularization	311 (6.2%)	158 (3.2%)	
CABG	72	38	

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Secondary Endpoint:
Cumulative Radiation Exposure ≤90 days

Mean ± SD; mSv	CTA (n=4996)	Functional (n=5007)	P value
All patients	**12.0 ± 8.5**	**10.1 ± 9.0**	**<0.001**
No radiation exposure	4%	33%	
Intended nuclear stress test randomization stratum	12.0 ± 8.4	14.1 ± 7.6	<0.001
Intended stress echo randomization stratum	12.6 ± 9.0	1.3 ± 4.3	<0.001
Intended exercise ECG randomization stratum	10.4 ± 7.8	2.3 ± 5.4	<0.001

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Summary

- PROMISE enrolled a symptomatic, intermediate risk population for whom testing is currently recommended
- There is a low event rate in this contemporary population
- There were no significant differences in outcomes between an initial anatomic (CTA) or functional testing strategy with respect to the primary endpoint overall or in any subgroup
- An initial CTA strategy was associated with a lower rate of invasive catheterization without obstructive CAD
- Radiation exposure was higher in CTA arm overall, but lower in those patients for whom a nuclear test was specified at randomization as the intended functional test, and who were then randomized to CTA

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Conclusions

- Compared to usual care using a functional testing strategy, use of an initial anatomic testing strategy employing CTA did not improve clinical outcomes in patients with suspected CAD
- Our results suggest that CTA is a viable alternative to functional testing
- These real-world results should inform noninvasive testing choices in clinical care as well as provide guidance to future studies of diagnostic strategies in suspected heart disease

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Results Published Online Today

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ORIGINAL ARTICLE

Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease

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ABSTRACT

BACKGROUND

Many patients have symptoms suggestive of coronary artery disease (CAD) and are often evaluated with the use of diagnostic testing, although there are limited data from randomized trials to guide care.

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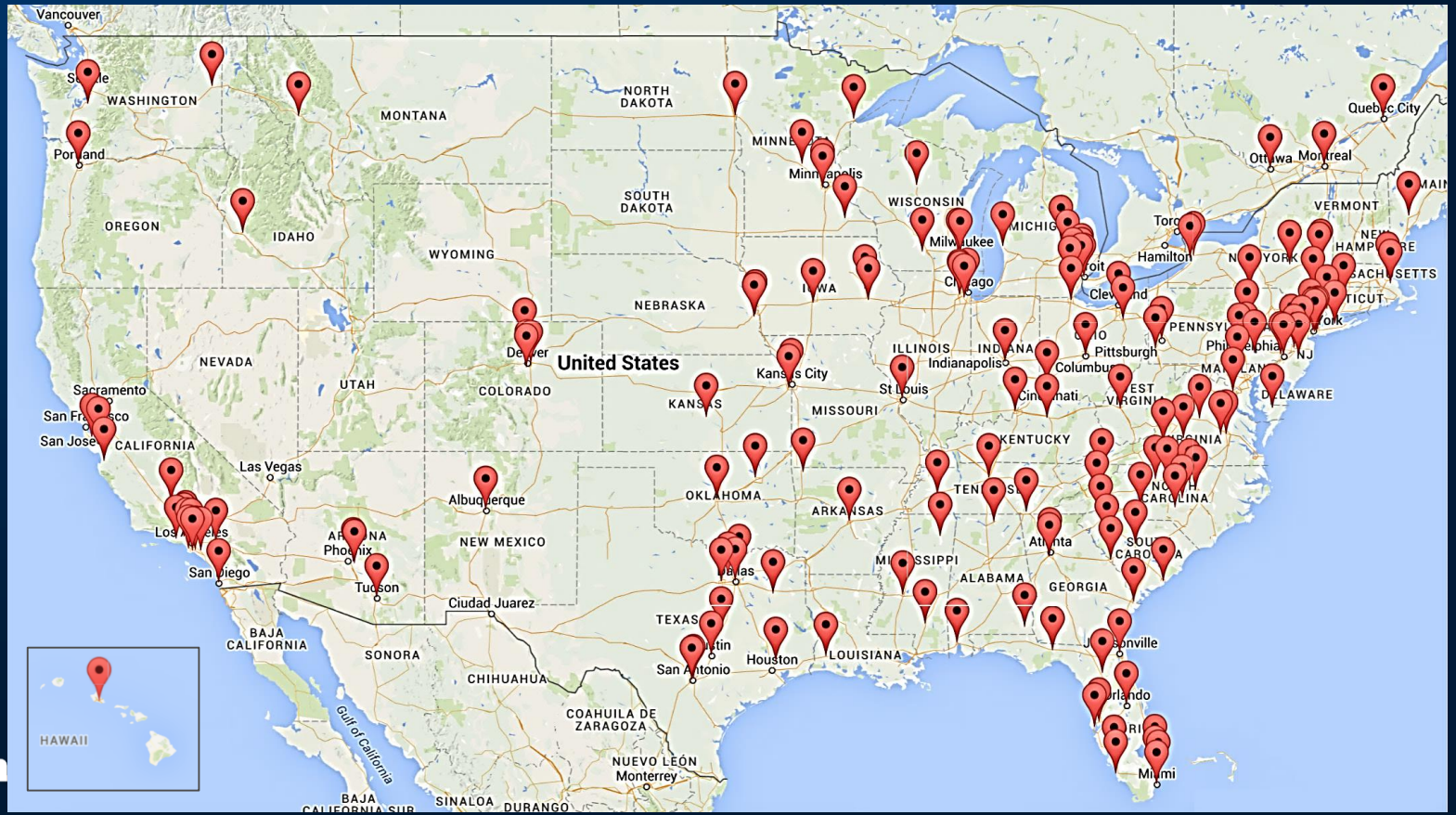
THANK YOU to PROMISE Patients and Sites…



…and to the PROMISE Team

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