Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015;372:1291-300. DOI: 10.1056/NEJMoa1415516

Supplementary Appendix

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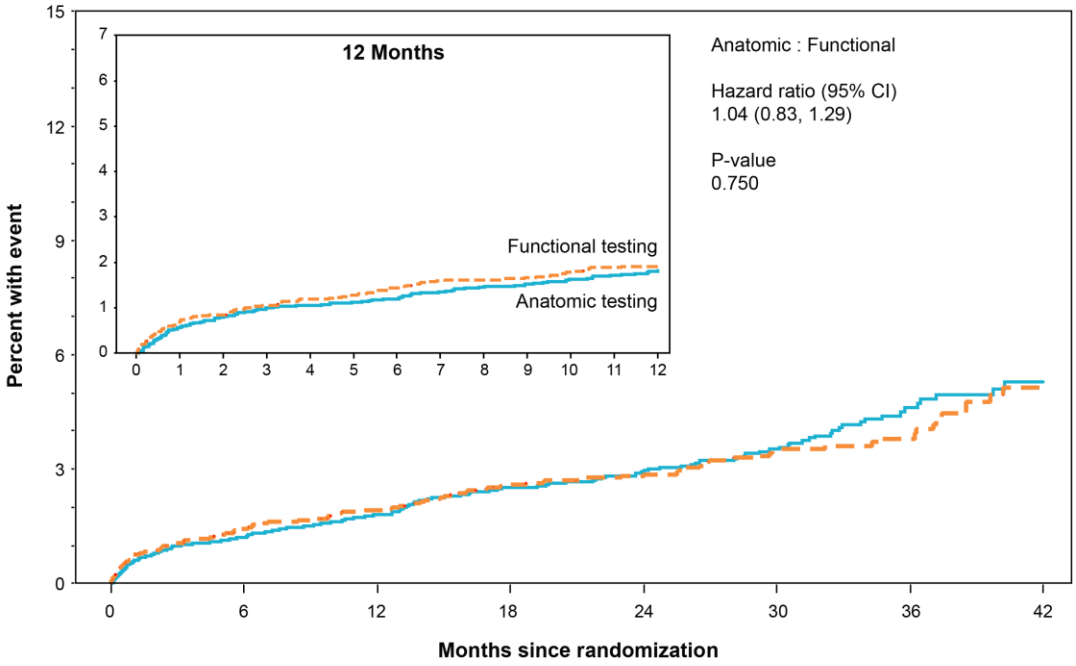
Supplemental Figure S1. Kaplan-Meier Estimates of the Composite Primary End Point and Selected Secondary End Points as a Function of Time Following Randomization

Panel A shows unadjusted Kaplan-Meier rates of the primary end point (all cause death, nonfatal myocardial infarction [MI], hospitalization for unstable angina, or major procedural complications). The adjusted hazard ratio (HR) for a CTA strategy, as compared with a usual care functional testing strategy, was 1.04 (95% CI, 0.83–1.29) (adjusted for age, sex, CAD risk equivalent [history of either diabetes, peripheral arterial disease, or cerebrovascular disease], and the pre-specification of the intended functional test if randomized to the functional testing arm). The inset graph shows the data with expanded *x* and *y* axes to highlight events occurring within 12 months of randomization; the adjusted HR based on 12-month follow-up was 0.94 (95% CI, 0.70–1.26; P=0.682).

Panel B shows unadjusted Kaplan-Meier rates of the time to primary end point plus catheterization without obstructive CAD. The adjusted HR for a CTA strategy, as compared with a usual care functional testing strategy, was 0.91; 95% CI, 0.78–1.06 (adjusted for age, sex, CAD risk equivalent [history of either diabetes, peripheral arterial disease, or cerebrovascular disease], and the pre-specification of the intended functional test if randomized to the functional testing arm). The inset graph shows the data with expanded *x* and *y* axes to highlight events occurring within 12 months of randomization; the adjusted HR based on 12-month follow-up was 0.85 (95% CI, 0.72–1.00; P=0.055).

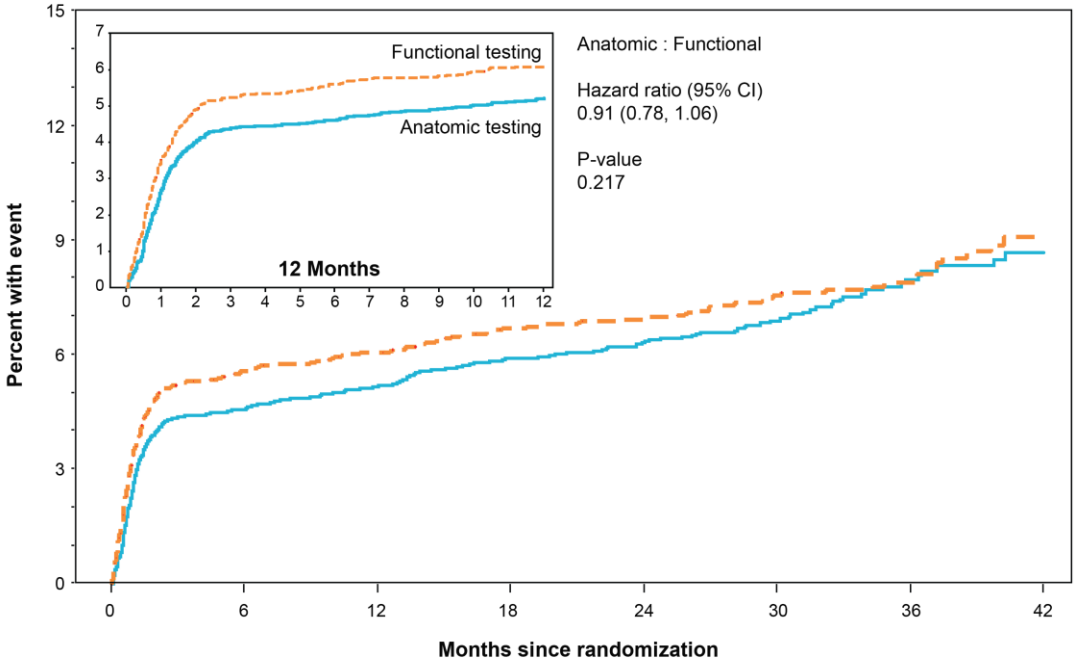
Panel C shows unadjusted Kaplan-Meier rates of the time to death or nonfatal MI. The adjusted HR for a CTA strategy, as compared with a usual care functional testing strategy, was 0.88 (95% CI, 0.67–1.15) (adjusted for age, sex, CAD risk equivalent [history of either diabetes, peripheral arterial disease, or cerebrovascular disease], and the pre-specification of the intended functional test if randomized to the functional testing arm). The inset graph shows the data with expanded *x* and *y* axes to highlight events occurring within 12 months of randomization; the adjusted HR based on 12-month follow-up was 0.66 (95% CI, 0.44–1.00; P=0.049).

A.



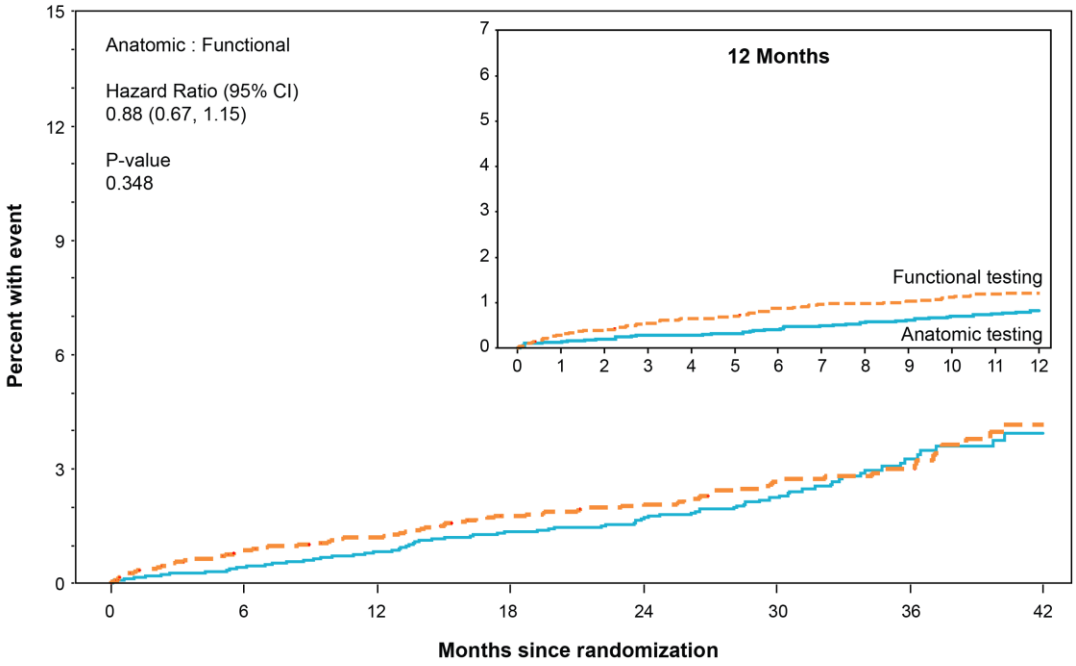
# at risk	Baseline (0)	6 Mo.	12 Mo.	18 Mo.	24 Mo.	30 Mo.	36 Mo.	42 Mo.
Anatomic testing	4996	4703	4362	3551	2652	1705	902	269
Functional testing	5007	4536	4115	3331	2388	1518	832	258

B.



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

C.



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

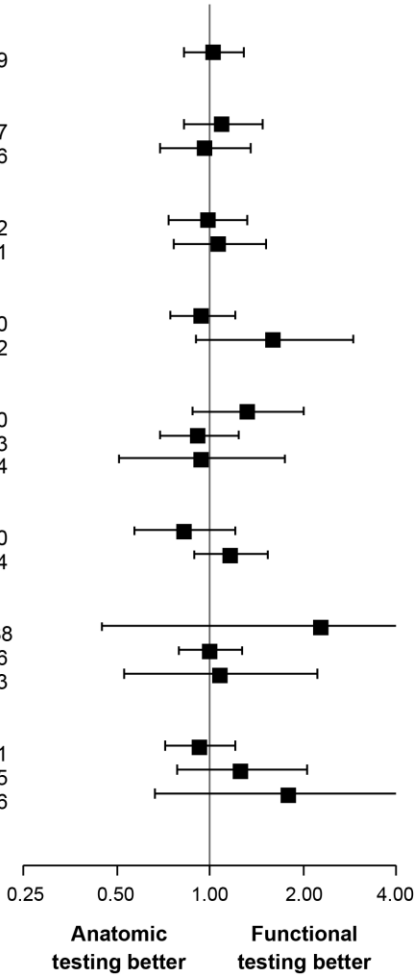
Supplemental Figure S2. Effects of a CTA Strategy on the Primary End Point, According to Baseline Characteristics

Panel A shows the effects of a CTA strategy on the primary end point, according to baseline characteristics. The primary end point was the combination of all cause death, nonfatal MI, hospitalization for unstable angina, or major procedural complications. Unadjusted HRs for the CTA strategy as compared with a usual functional testing strategy are shown; the horizontal lines indicate 95% confidence intervals.

Panel B shows the effects of a CTA strategy on the primary end point plus catheterization without obstructive CAD. Unadjusted HRs for the CTA strategy as compared with a usual functional testing strategy are shown; the horizontal lines indicate 95% confidence intervals.

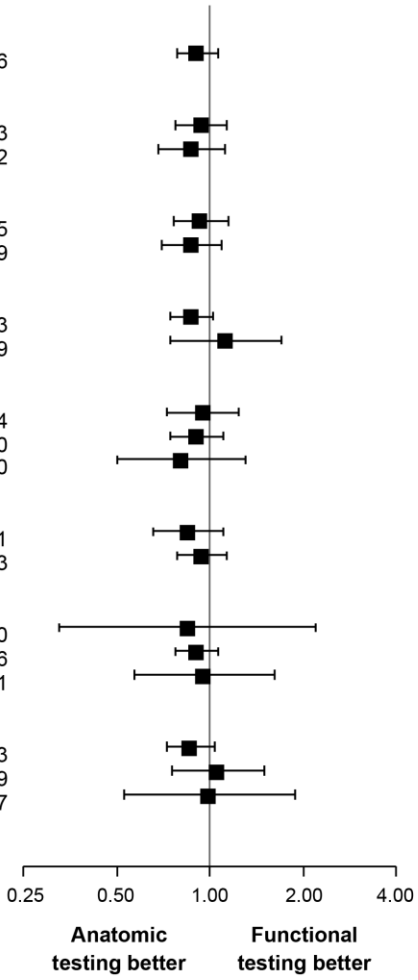
A.

Subject group	Interaction P-value	N	Hazard ratio	95% CI
All subjects		10003	1.04	0.83, 1.29
Age	0.591			
<65		7111	1.10	0.82, 1.47
≥65		2892	0.97	0.69, 1.36
Gender	0.698			
Male		4733	0.99	0.74, 1.32
Female		5270	1.08	0.76, 1.51
Race	0.100			
White		8371	0.95	0.74, 1.20
Non-white		1545	1.62	0.89, 2.92
Pre-test risk assessment	0.341			
Low risk (≤30%)		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	0.142			
Yes		2531	0.83	0.57, 1.20
No		7472	1.17	0.89, 1.54
Pretest probability of CAD	0.603			
Low risk (<10%)		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	0.293			
Stress Nuclear		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



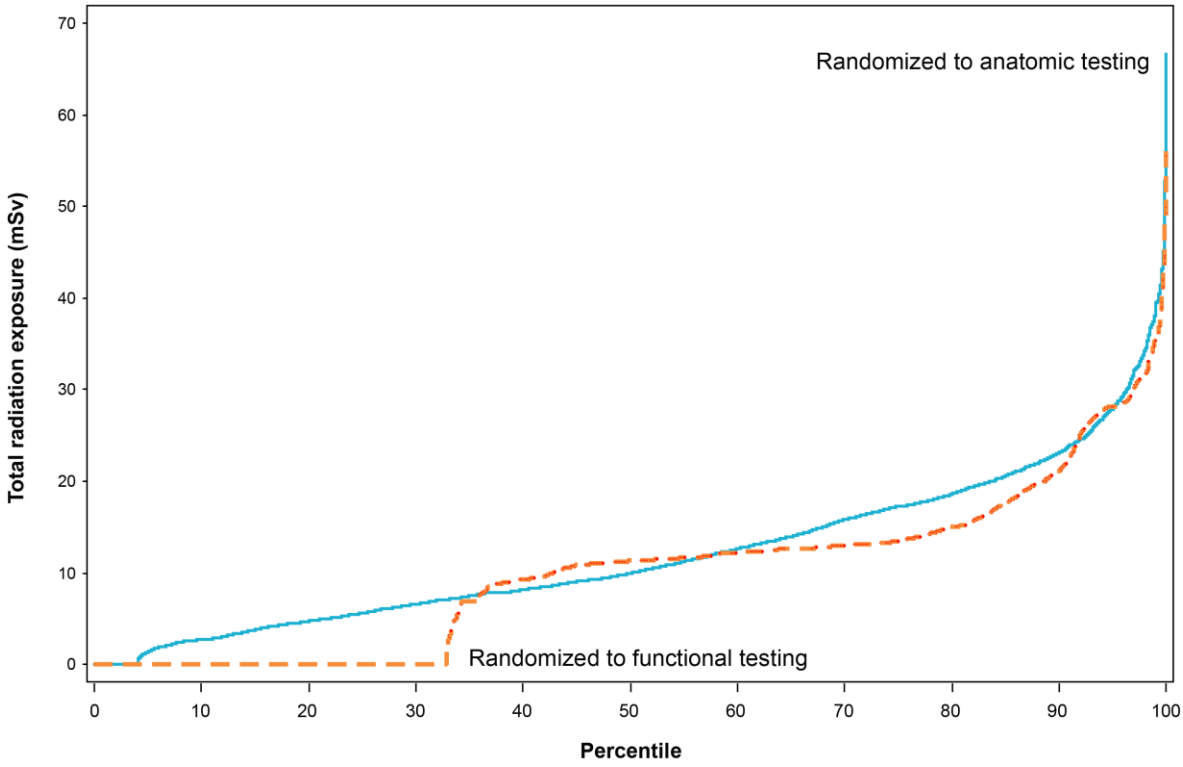
B.

Subject group	Interaction P-value	N	Hazard ratio	95% CI
All subjects		10003	0.91	0.78, 1.06
Age	0.695			
<65		7111	0.94	0.78, 1.13
≥65		2892	0.87	0.68, 1.12
Gender	0.633			
Male		4733	0.94	0.76, 1.15
Female		5270	0.87	0.70, 1.09
Race	0.260			
White		8371	0.88	0.74, 1.03
Non-white		1545	1.12	0.75, 1.69
Pre-test risk assessment	0.839			
Low risk (≤30%)		3755	0.95	0.73, 1.24
Intermediate risk (31–70%)		5750	0.90	0.74, 1.10
High risk (>70%)		481	0.81	0.50, 1.30
CAD equivalent	0.540			
Yes		2531	0.85	0.65, 1.11
No		7472	0.94	0.79, 1.13
Pretest probability of CAD	0.980			
Low risk (<10%)		250	0.85	0.33, 2.20
Intermediate risk (10–90%)		9258	0.90	0.77, 1.06
High risk (>90%)		495	0.96	0.57, 1.61
Functional test randomization stratum	0.548			
Stress Nuclear		6781	0.87	0.73, 1.03
Stress Echo		2236	1.06	0.76, 1.49
Exercise ECG		986	0.99	0.53, 1.87



Supplemental Figure S3. Cumulative Radiation Exposure at 90 Days after Randomization

The cumulative radiation exposure in patients randomized to each arm is shown as a waterfall plot, with the patients rank ordered by exposure on the *x* axis and displayed as percentiles, and exposure in mSv on the *y* axis. The flat initial line in each group represents patients who did not receive any radiation; this extends out to 32.6% in the functional testing arm.



Supplemental Table S1. Trial Inclusion and Exclusion Criteria*

Inclusion Criteria

1. New or worsening chest pain syndrome or equivalent symptoms suspicious for clinically significant CAD
2. No prior evaluation for this episode of symptoms
3. Planned non-invasive testing for diagnosis
4. Men age > 55 and women age ≥65 years
5. If age in men 45 - 54 or women 50 - 64 years, then must have increased probability of CAD due to EITHER:
   A. Diabetes Mellitus (DM) requiring medical treatment OR
   Peripheral Arterial Disease (PAD) defined as documented >50% peripheral arterial stenosis treated medically or invasively OR cerebrovascular disease (stroke, documented > 50% carotid stenosis treated medically or invasively)

OR

   B. At least one of the following cardiovascular risk factors:
   - Ongoing tobacco use
   - Hypertension
   - Abnormal ABI defined as less than <0.9
   - Dyslipidemia

6. Serum creatinine < 1.5 mg/dL within the past 90 days
7. Negative urine/serum pregnancy test for female subjects of child-bearing potential

Exclusion Criteria

1. Diagnosed or suspected ACS requiring hospitalization or urgent or emergent testing; Elevated troponin or CK-MB
2. Hemodynamically or clinically unstable condition (systolic BP < 90 mmHg, atrial or ventricular arrhythmias, or persistent resting chest pain felt to be ischemic despite adequate therapy)
3. Known CAD with prior MI, PCI, CABG or any angiographic evidence of CAD ≥50% lesion in a major epicardial vessel.
4. Any invasive coronary angiography or non-invasive anatomic or functional CV test for detection of CAD, including CTA and exercise ECG, within the previous twelve (12) months.
5. Known significant congenital, valvular (> moderate) or cardiomyopathic process (hypertrophic cardiomyopathy or reduced systolic left ventricular function (LVEF ≤ 40%)) which could explain cardiac symptoms.
6. Contraindication to undergoing a CTA, including but not limited to:
   A. Allergy to iodinated contrast agent
   B. Unable to receive beta blockers unless heart rate < 65 beats per minute
   C. Pregnancy
7. Life expectancy < 2 years
8. Unable to provide written informed consent or participate in long–term follow-up

* ABI denotes ankle-brachial index; ACS, acute coronary syndromes; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CTA, computed tomographic angiography; CV, cardiovascular; ECG, electrocardiogram; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

Supplemental Table S2. Definitions of the Components of the Primary End Point

Primary End Point:
Time to first event using the composite of the following major cardiovascular events:

- Death
- Myocardial infarction
- Major complications from cardiovascular procedures including testing (stroke, major bleeding, anaphylaxis and renal failure)
- Unstable angina hospitalization

Definitions:
All cause mortality: All cause mortality is used rather than cardiac mortality to eliminate the need for possibly difficult adjudication of causes of death, especially given the relatively low mortality expected.

Myocardial infarction**:** defined as either 1) an abnormal cardiac biomarker level > institutional ULN (either troponin or CK-MB), and either ischemic discomfort lasting > 10 minutes or ECG changes indicative of ischemia or infarction, or 2) new abnormal Q waves consistent with infarction. Additionally *peri-procedural infarctions* are defined as >3x upper limit of normal for serum CK-MB for PCI and >5x upper limit of normal for CABG.

Major complications from cardiovascular procedures and diagnostic testing which occur within 72 hours, defined as:

- Stroke is defined as an acute focal neurological deficit of sudden onset, not reversible within 24 hours, or that resolves in <24 hrs with clear evidence of a new stroke on cerebral imaging
- Bleeding is defined as major based on one or more of the following:
    - Transfusion of > 2 units heterologous packed red blood cells or whole blood
    - Decrease in hemoglobin level by ≥ 2.0 g/l
    - Need for re-operation or invasive intervention (e.g. evacuation of wound hematoma)
    - Bleeding at a critical anatomic site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome)
- Renal Failure is defined as new requirement for renal replacement therapy
- Anaphylaxis is defined as a severe contrast reaction requiring emergency respiratory and/or circulatory support

Unstable angina hospitalization: defined as 1) ischemic discomfort or equivalent symptoms requiring hospitalization within 48 hours of symptoms, 2) lasting ≥ 10 minutes at rest, or in an accelerating pattern, 3) accompanied by dynamic ST depression, ischemia on stress testing or significant epicardial coronary artery stenosis, and 4) which is considered to be myocardial ischemia upon final diagnosis.

Supplemental Table S3. Definitions of Positive Results from Diagnostic Tests

PROMISE trial
Initial Diagnostic Test Result Derivation
This table summarizes the derivation of Initial Diagnostic Test Results from the anatomic and functional tests performed in the PROMISE trial for the SAP defined 2 point (Positive vs. Negative) categories.

PROMISE Trial Primary Analysis Statistical Plan Section:
Classification of Initial Test Results (Positive vs. Negative)
Among the information that will be reported from the trial is the site interpretation based percent of patients in the PROMISE study population whose initial diagnostic test was considered ***positive***, whether randomized to CTA or to a functional test. For the purpose of this analysis, "positive" is considered as having some evidence of inducible ischemia on functional testing, or severity of stenosis on CTA likely to be associated with inducible ischemia. In this construct, evidence of prior infarct alone without ischemia is considered as "negative", as is a normal test.

For reporting this information, the following definitions will be used:

CTA will be considered positive if there is a ≥70% stenosis in either the left anterior descending (LAD), left circumflex (LCX), or right coronary artery (RCA), or a ≥50% stenosis in the left main coronary artery.

Positive Test Result. If any of these variables are true

Location	Level of stenosis
RCA (any)	Significant/severe (70-99%) Occluded (100%)
LAD (any except proximal LAD)	Significant/severe (70-99%) Occluded (100%)
Proximal LAD	Significant/severe (70-99%) Occluded (100%)
LCX (any)	Significant/severe (70-99%) Occluded (100%)
Left Main	Significant/severe (50-99%) Occluded (100%)

Negative Test Result. If no vessel is positive and at least 4 of 5 of these variables are reported and true (ie, at most one is not reported)

Location	Level of stenosis
RCA (any)	Normal (0%)
	Non-significant/mild or minor (1-49%)
	Moderate (50-69%)
LAD (any except proximal LAD)	Normal (0%)
	Non-significant/mild or minor (1-49%)
	Moderate (50-69%)
Proximal LAD	Normal (0%)
	Non-significant/mild or minor (1-49%)
	Moderate (50-69%)
LCX (any)	Normal (0%)
	Non-significant/mild or minor (1-49%)
	Moderate (50-69%)
Left Main	Normal (0%)
	Non-significant/mild or minor (1-49%)

Indeterminate Test Result. If no vessel is positive and either Left Main result is true or Proximal LAD is true or at least 2 of the 3 remaining segments are true

Location	Level of stenosis
RCA (any)	Indeterminate or Not reported
LAD (any except proximal LAD)	Indeterminate or Not reported
Proximal LAD	Indeterminate or Not reported
LCX (any)	Indeterminate or Not reported
Left Main	Indeterminate or Not reported

For CAC only CTAs the results will be classified as the following:

- **Indeterminate for any** CAC score

Cardiac Catheterization

Uses the same score system as CTA; only applies to patient who received an invasive catheterization as a first test.

Functional Testing

Stress Nuclear Imaging will be considered positive if there is a reversible perfusion defect (inducible ischemia) or mixed defect (infarct and ischemia) during stress in at least one territory.

Positive Test Result. If any of these variables are true

Territory	Myocardial Perfusion
Septal/anterior/apical	Reversible (ischemia)
	Mixed defect (infarct and Ischemia)
Lateral	Reversible (ischemia)
	Mixed defect (infarct and Ischemia)
Inferior/posterior	Reversible (ischemia)
	Mixed defect (infarct and Ischemia)

Negative Test Result. If no area is positive and 2 or more of these variables are true

Territory	Myocardial Perfusion
Septal/anterior/apical	Normal or Fixed defect (infarct)
Lateral	Normal or Fixed defect (infarct)
Inferior/posterior	Normal or Fixed defect (infarct)

Indeterminate Test Result. If no area is positive and 2 or more of these variables are true

Territory	Myocardial Perfusion
Septal/anterior/apical	Uninterpretable or Not reported
Lateral	Uninterpretable or Not reported
Inferior/posterior	Uninterpretable or Not reported

Stress Echo will be considered positive if there is a reversible wall motion abnormality or mixed abnormality during stress in at least one territory.

Positive Test Result. If any of these variables are true

Territory	Wall motion abnormality
Septal/anterior/apical	Inducible wall motion abnormality (ischemia)
	Mixed abnormality (infarct and ischemia)
Lateral	Inducible wall motion abnormality (ischemia)
	Mixed abnormality (infarct and ischemia)
Inferior/posterior	Inducible wall motion abnormality (ischemia)
	Mixed abnormality (infarct and ischemia)

Negative Test Result. If no positive results and 2 or more of these variables are true (i.e. at most one not reported)

Territory	Wall motion abnormality
Septal/anterior/apical	Normal
	Resting Wall motion abnormality without ischemia (infarct)
Lateral	Normal
	Resting Wall motion abnormality without ischemia (infarct)
Inferior/posterior	Normal
	Resting Wall motion abnormality without ischemia (infarct)

Indeterminate Test Result. If no positives and 2 or more of these variables are true

Territory	Wall motion abnormality
Septal/anterior/apical	Uninterpretable or Not reported
Lateral	Uninterpretable or Not reported
Inferior/posterior	Uninterpretable or Not reported

Exercise ECG will be considered positive if there are significant ST-segment changes consistent with ischemia.

Positive Test Result

Question	ECG result
Changes meet criteria for ischemia?	Positive

Negative Test Result

Question	ECG result
Changes meet criteria for ischemia?	Negative, no evidence of ischemia Borderline or indeterminate

Indeterminate Test Result

Question	ECG result
Changes meet criteria for ischemia?	Noninterpretable

These classifications will be based on site-reported assessments.

Supplemental Table S4. Outcomes According to Study Group at 12 Months*

	12-Month Outcomes			
	CTA strategy (N=4996)	**Functional strategy (N=5007)**	**Adjusted Hazard Ratio (95% CI)**	***P* Value**
Primary end point composite	88	91	0.94 (0.70–1.26)	0.682
All cause death	21	32		
Nonfatal MI	18	27		
Unstable angina hospitalization	49	34		
Major procedural complications	4	5		
Primary end point plus cath without obstructive CAD	256	296	0.85 (0.72–1.00)	0.055
Death or nonfatal MI	39	57	0.66 (0.44–1.00)	0.049
Death, nonfatal MI, or unstable angina hospitalization	86	88	0.95 (0.71–1.28)	0.736

* CAD denotes coronary artery disease; CTA, computed tomographic angiography; and MI, myocardial infarction.

Hazard ratios were adjusted for age, sex, CAD risk equivalent (history of either diabetes, peripheral arterial disease, or cerebrovascular disease), and the pre-specification of the intended functional test if randomized to the functional testing arm.

Supplemental Table S5. Diagnostic Test Adverse Events and Serious Adverse Events by Testing Modality

	Anatomic Testing (N=4996)	Functional Testing (N=5007)	All Patients (N=10003)
Safety events			
Number of patients with any safety event	37	21	58
Type of safety events[a]			
Exercise induced hypotension (BP fall >20 mmHg)	0	6	6
Stress induced symptoms (not resolve <20 min)	0	4	4
Rapid atrial fibrillation that does not slow or convert	0	0	0
Ventricular tachycardia	0	4	4
Hemodynamic instability (systolic BP <80 mmHg)	0	2	2
Hospital admission not in the primary end point[b]	0	5	5
Stress induced wall motion abnormality[c]	0	0	0
Any anaphylactic reaction to contrast agent[d]	0	0	0
Any events potentially related to vasodilators[e]	0	5	5
Mild contrast reaction such as rash and hives[f]	22	0	22
Extravasation of contrast into surrounding tissue[g]	12	0	12
Hemodynamic instability[h]	3	0	3
Acute bronchospasm[i]	0	0	0
Major complications			
Number of patients with any major complication	4	5	9
Type of major complications[a]			
Stroke	1	2	3
Major bleeding	3	3	6
Anaphylaxis	0	0	0
Renal failure requiring dialysis	0	0	0

[a]Multiple choices possible.

[b]Hospital admission not otherwise captured by the primary end point including that precipitated by any symptomatic event (chest pain, dyspnea, etc), persistent or worsening ischemic ECG changes, any bradycardic or tachycardic arrhythmia, or any hemodynamic changes (hyper- or hypo-tension).

[c]Stress induced wall motion abnormality that does not resolve within 20 minutes (despite treatment).

[d]Any anaphylactic reaction to contrast agent not requiring circulatory or respiratory support.

[e]Any events potentially related to the use of vasodilators such as dypridamole or adenosine, including an anaphylactic reaction to contrast agent not requiring circulatory or respiratory support.

[f]Mild contrast reaction such as rash and hives (severe reactions including anaphylaxis or death are part of the primary end point).

[g]Extravasation of contrast into the surrounding tissue of the extremity where the IV was placed and contrast administered.

[h]Hemodynamic instability, including symptomatic bradycardia or hypotension, due to the beta blockade or nitrates given for the CTA scan acquisition.

[i]Acute bronchospasm due to the beta blockade given for the CTA scan.

Patient and Provider Educational Materials

AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update (Adapted from *Circulation 2002;106;388-391*)

Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases

Smoking	
Goal	• Complete cessation. • No exposure to environmental tobacco smoke.
Interventions	• Ask about tobacco use status at every visit. • In a clear, strong, and personalized manner, advise every tobacco user to quit. • Assess the tobacco user's willingness to quit. • Assist by counseling and developing a plan for quitting. • Arrange follow-up, referral to special programs, or pharmacotherapy. • Urge avoidance of exposure to secondhand smoke at work or home.
Blood Pressure Control	
Goal	• < 140/90 mm Hg • < 130/85 mm Hg if renal insufficiency or heart failure is present • < 130/80 mm Hg if diabetes is present.
Interventions	• Promote healthy lifestyle modification. • Advocate weight reduction; reduction of sodium intake; consumption of fruits, vegetables, and low-fat dairy products; moderation of alcohol intake; and physical activity in persons with BP of ≥ 130 mm Hg systolic or 80 mm Hg diastolic. • For persons with renal insufficiency or heart failure, initiate drug therapy if BP is ≥ 130 mm Hg systolic or 85 mm Hg diastolic (≥ 80 mm Hg diastolic for patients with diabetes). • Initiate drug therapy for those with BP ≥ 140/90 mm Hg if 6 to 12 months of lifestyle modification is not effective, depending on the number of risk factors present. • Add BP medications, individualized to other patient requirements and characteristics (eg, age, race, need for drugs with specific benefits).
Dietary Intake	
Goal	• An overall healthy eating pattern.
Interventions	• Advocate consumption of a variety of fruits, vegetables, grains, low-fat or nonfat dairy products, fish, legumes, poultry, and lean meats. • Match energy intake with energy needs and make appropriate changes to achieve weight loss when indicated. • Modify food choices to reduce saturated fats (< 10% of calories), cholesterol (< 300 mg/d), and *trans*-fatty acids by substituting grains and unsaturated fatty acids from fish, vegetables, legumes, and nuts. • Limit salt intake to < 6 g/d. • Limit alcohol intake (≤ 2 drinks/d in men, ≤ 1 drink/d in women) among those who drink.

Weight Management	
Goal	• Achieve and maintain desirable weight (body mass index 18.5–24.9 kg/m^2). • When body mass index is ≥ 25 kg/m^2, waist circumference at iliac crest level ≤ 40 inches in men, ≤ 35 inches in women
Interventions	• Initiate weight-management program through caloric restriction and increased caloric expenditure as appropriate. • For overweight/obese persons, reduce body weight by 10% in first year of therapy.
Aspirin	
Goal	Low-dose aspirin in persons at higher CHD risk (especially those with 10-y risk of CHD ≥ 10%).
Interventions	• Do not recommend for patients with aspirin intolerance. • Low-dose aspirin increases risk for gastrointestinal bleeding and hemorrhagic stroke. Do not use in persons at increased risk for these diseases. • Benefits of cardiovascular risk reduction outweigh these risks in most patients at higher coronary risk. • Doses of 75–160 mg/d are as effective as higher doses. Therefore, consider 75–160 mg aspirin per day for persons at higher risk (especially those with 10-y risk of CHD of ≥ 10%).
Blood Lipid Management	
Goal	**Primary goal** • LDL-C <160 mg/dL if ≤ 1 risk factor is present; • LDL-C < 130 mg/dL if ≥ 2 risk factors are present and 10-y CHD risk is < 20%; • LDL-C < 100 mg/dL if ≥ 2 risk factors are present and 10-y CHD risk is ≥ 20% or if patient has diabetes. **Secondary goals** (if LDL-C is at goal range) If triglycerides are > 200 mg/dL, then use non-HDL-C as a secondary goal • Non-HDL-C < 190 mg/dL for ≤ 1 risk factor • Non-HDL-C < 160 mg/dL for ≥ 2 risk factors and 10-y CHD risk ≤ 20% • Non-HDL-C < 130 mg/dL for diabetics or for ≥ 2 risk factors and 10-y CHD risk >20% **Other targets for therapy** • Triglycerides > 150 mg/dL • HDL-C < 40 mg/dL in men and < 50 mg/dL in women
Interventions	• If LDL-C is above goal range, initiate additional therapeutic lifestyle changes consisting of dietary modifications to lower LDL-C: < 7% of calories from saturated fat, cholesterol < 200 mg/d, and, if further LDL-C lowering is required, dietary options (plant stanols/sterols not to exceed 2 g/d and/or increased viscous [soluble] fiber [10–25 g/d]), and additional emphasis on weight reduction and physical activity. • If LDL-C is above goal range, rule out secondary causes (liver function test, thyroid-stimulating hormone level, urinalysis). • After 12 weeks of therapeutic lifestyle change, consider LDL-lowering drug therapy if: ≥ 2 risk factors are present, 10-y risk is > 10%, and LDL-C is ≥ 130 mg/dL; ≥ 2 risk factors are present, 10-y risk is < 10%, and LDL-C is ≥ 160 mg/dL; or ≤ 1 risk factor is present and LDL-C is ≥ 190 mg/dL. • Start drugs and advance dose to bring LDL-C to goal range, usually a statin but also consider bile acid–binding resin or niacin. • If LDL-C goal not achieved, consider combination therapy (statin+resin, statin+niacin). After LDL-C goal has been reached, consider triglyceride level:

	• If 150–199 mg/dL, treat with therapeutic lifestyle changes. • If 200–499 mg/dL, treat elevated non-HDL-C with therapeutic lifestyle changes and, if necessary, consider higher doses of statin or adding niacin or fibrate. • If > 500 mg/dL, treat with fibrate or niacin to reduce risk of pancreatitis. • If HDL-C is < 40 mg/dL in men and < 50 mg/dL in women, initiate or intensify therapeutic lifestyle changes. • For higher-risk patients, consider drugs that raise HDL-C (eg, niacin, fibrates, statins).
Physical Activity	
Goal	• At least 30 min of moderate-intensity physical activity on most (and preferably all) days of the week.
Interventions	• If cardiovascular, respiratory, metabolic, orthopedic, or neurological disorders are suspected, or if patient is middle-aged or older and is sedentary, consult physician before initiating vigorous exercise program. • Moderate-intensity activities (40% to 60% of maximum capacity) are equivalent to a brisk walk (15–20 min per mile). Additional benefits are gained from vigorous-intensity activity (> 60% of maximum capacity) for 20–40 min on 3–5 d/wk. • Recommend resistance training with 8–10 different exercises, 1–2 sets per exercise, and 10–15 repetitions at moderate intensity ≥ 2 d/wk. • Flexibility training and an increase in daily lifestyle activities should complement this regimen.
Diabetes Management	
Goal	Normal fasting plasma glucose (< 110 mg/dL) and near normal HbA1c (< 7%).
Interventions	• Initiate appropriate hypoglycemic therapy to achieve near-normal fasting plasma glucose or as indicated by near-normal HbA1c. 1. First step is diet and exercise. 2. Second-step therapy is usually oral hypoglycemic drugs: sulfonylureas and/or metformin with ancillary use of acarbose and thiazolidinediones. 3. Third step therapy is insulin. • Treat other risk factors more aggressively (eg, change BP goal to < 130/80 mm Hg and LDL-C goal to < 100 mg/dL).
Chronic Atrial Fibrillation	
Goal	Normal sinus rhythm or, if chronic atrial fibrillation is present, anticoagulation with INR 2.0–3.0 (target 2.5).
Interventions	• Irregular pulse should be verified by an electrocardiogram. • Conversion of appropriate individuals to normal sinus rhythm. • For patients in chronic or intermittent atrial fibrillation, use warfarin anticoagulants to INR 2.0–3.0 (target 2.5). • Aspirin (325 mg/d) can be used as an alternative in those with certain contraindications to oral anticoagulation. • Patients < 65 y of age without high risk may be treated with aspirin.

AHA/ACC Secondary Prevention for Patients With Coronary and Other Vascular Disease: 2006 Update (Adapted from *Circulation.* 2006;113:2363-2372)

Patients covered by these guidelines include those with established coronary and other atherosclerotic vascular disease, including peripheral arterial disease, atherosclerotic aortic disease, and carotid artery disease.

Smoking	
Goal	• Complete cessation. • No exposure to environmental tobacco smoke.
Interventions	• Ask about tobacco use status at every visit. • Advise tobacco user to quit. • Assess the tobacco user's willingness to quit. • Assist by counseling and developing a plan for quitting. • Arrange follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and bupropion). • Urge avoidance of exposure to environmental tobacco smoke at work or home.
Blood Pressure Control	
Goal	• < 140/90 mm Hg • < 130/80 mm Hg if patient has diabetes or chronic kidney disease.
Interventions	**For all patients:** • Initiate or maintain lifestyle modification—weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products. **For patients with blood pressure ≥ 140/90 mm Hg (or ≥ 130/80 with chronic kidney disease or diabetes):** • As tolerated, add blood pressure medication, treating initially with beta blockers and/or ACE inhibitors, with addition of other drugs such as thiazides as needed to achieve goal blood pressure.
Lipid Management	
Goal	• LDL-C <100 mg/dL • If triglycerides are ≥ 200 mg/dL, non-HDL-C should be <130 mg/dL
Interventions	**For all patients:** • Start dietary therapy. Reduce intake of saturated fats (to < 7% of total calories), *trans*-fatty acids, and cholesterol (to < 200 mg/d). • Adding plant stanol/sterols (2 g/d) and viscous fiber (> 10 g/d) will further lower LDL-C. • Promote daily physical activity and weight management. • Encourage increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g/d) for risk reduction. For treatment of elevated triglycerides, higher doses are usually necessary for risk reduction.

Lipid Management Interventions	**For lipid management:** Assess fasting lipid profile in all patients, and within 24 hours of hospitalization for those with an acute cardiovascular or coronary event. For hospitalized patients, initiate lipid-lowering medication as recommended below before discharge according to the following schedule: • LDL-C should be < 100 mg/dL • Further reduction of LDL-C to < 70 mg/dL is reasonable. • If baseline LDL-C is ≥ 100 mg/dL, initiate LDL-lowering drug therapy. • If on-treatment LDL-C is ≥100 mg/dL, intensify LDL-lowering drug therapy (may require LDL-lowering drug combination). • If baseline LDL-C is 70 to 100 mg/dL, it is reasonable to treat to LDL-C < 70 mg/dL. • If triglycerides are 200 to 499 mg/dL, non-HDL-C should be < 130 mg/dL. • Further reduction of non-HDL-C to < 100 mg/dL is reasonable. • Therapeutic options to reduce non-HDL-C are: → More intense LDL-C–lowering therapy → Niacin (after LDL-C–lowering therapy) → Fibrate therapy (after LDL-C–lowering therapy) • If triglycerides are ≥ 500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy; and treat LDL-C to goal after triglyceride-lowering therapy. Achieve non-HDL-C < 130 mg/dL if possible.
Physical Activity	
Goal	• 30 minutes, 7 days per week (minimum 5 days per week)
Interventions	• For all patients, assess risk with a physical activity history and/or an exercise test, to guide prescription. • For all patients, encourage 30 to 60 minutes of moderate-intensity aerobic activity, such as brisk walking, on most, preferably all, days of the week, supplemented by an increase in daily lifestyle activities (eg, walking breaks at work, gardening, household work). • Encourage resistance training 2 days per week. • Advise medically supervised programs for high-risk patients (eg, recent acute coronary syndrome or revascularization, heart failure).
Weight Management	
Goal	• Body mass index 18.5–24.9 kg/m^2). • Waist circumference: men < 40 inches, women < 35 inches in women.
Interventions	• Assess body mass index and/or waist circumference on each visit and consistently encourage weight maintenance/reduction through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve a body mass index between 18.5 and 24.9 kg/m^2. • If waist circumference (measured horizontally at the iliac crest) is ≥ 35 inches in women and ; ≥ 40 inches in men, initiate lifestyle changes and consider treatment strategies for metabolic syndrome as indicated.

	• The initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline. With success, further weight loss can be attempted if indicated through further assessment.
Diabetes Management	
Goal	• HbA1c < 7%
Interventions	• Initiate lifestyle and pharmacotherapy to achieve near-normal HbA1c. • Begin vigorous modification of other risk factors (eg, physical activity, weight management, blood pressure control, and cholesterol management as recommended above). • Coordinate diabetic care with patient's primary care physician or endocrinologist.
Antiplatelet Agents/Anticoagulants	
Interventions	• Start aspirin 75 to 162 mg/d and continue indefinitely in all patients unless contraindicated. → For patients undergoing coronary artery bypass grafting, aspirin should be started within 48 hours after surgery to reduce saphenous vein graft closure. Dosing regimens ranging from 100 to 325 mg/d appear to be efficacious. Doses higher than 162 mg/d can be continued for up to 1 year. • Start and continue clopidogrel 75 mg/d in combination with aspirin for up to 12 months in patients after acute coronary syndrome or percutaneous coronary intervention with stent placement (≥ 1 month for bare metal stent, ≥ 3 months for sirolimus-eluting stent, and ≥ 6 months for paclitaxel-eluting stent). →Patients who have undergone percutaneous coronary intervention with stent placement should initially receive higher-dose aspirin at 325 mg/d for 1 month for bare metal stent, 3 months for sirolimus-eluting stent, and 6 months for paclitaxel-eluting stent. • Manage warfarin to international normalized ratio=2.0 to 3.0 for paroxysmal or chronic atrial fibrillation or flutter, and in post–myocardial infarction patients when clinically indicated (eg, atrial fibrillation, left ventricular thrombus). • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely.
Renin-Angiotensin-Aldosterone System Blockers	
Interventions	**Angiotensin converting enzyme (ACE) inhibitors:** • Start and continue indefinitely in all patients with left ventricular ejection fraction ≤ 40% and in those with hypertension, diabetes, or chronic kidney disease, unless contraindicated. • Consider for all other patients. • Among lower-risk patients with normal left ventricular ejection fraction in whom cardiovascular risk factors are well controlled and revascularization has been performed, use of ACE inhibitors may be considered optional. **Angiotensin receptor blockers (ARB):** • Use in patients who are intolerant of ACE inhibitors and have heart failure or have had a myocardial infarction with left ventricular ejection fraction ≤ 40%. • Consider in other patients who are ACE inhibitor intolerant. • Consider use in combination with ACE inhibitors in systolic-dysfunction heart failure. **Aldosterone blockade:** • Use in post–myocardial infarction patients, without significant renal dysfunction or hyperkalemia,

	who are already receiving therapeutic doses of an ACE inhibitor and f-blocker, have a left ventricular ejection fraction ≤ 40%, and have either diabetes or heart failure.
Beta Blockers	
Interventions	• Start and continue indefinitely in all patients who have had myocardial infarction, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • Consider chronic therapy for all other patients with coronary or other vascular disease or diabetes unless contraindicated.
Influenza Vaccination	
Interventions	• Patients with cardiovascular disease should have an influenza vaccination.

AHA Guideline: Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update (Adapted from *Circulation.* 2007;115:1481-1501)

These guidelines cover the primary and secondary prevention of chronic atherosclerotic vascular diseases in women ≥ 20 years of age.

Lifestyle Interventions

Cigarette Smoking

- Women should not smoke and should avoid environmental tobacco smoke.
- Provide counseling, nicotine replacement, and other pharmacotherapy as indicated in conjunction with a behavioral program or formal smoking cessation program.

Physical Activity

- Women should accumulate a minimum of 30 minutes of moderate-intensity physical activity (eg, brisk walking) on most, and preferably all, days of the week.
- Women who need to lose weight or sustain weight loss should accumulate a minimum of 60 to 90 minutes of moderate-intensity physical activity (eg, brisk walking) on most, and preferably all, days of the week.

Rehabilitation

- A comprehensive risk-reduction regimen, such as cardiovascular or stroke rehabilitation or a physician-guided home- or community-based exercise training program, should be recommended to women with a recent acute coronary syndrome or coronary intervention, new-onset or chronic angina, recent cerebrovascular event, peripheral arterial disease, or current/prior symptoms of heart failure and an LVEF < 40%

Dietary Intake

- Women should consume a diet rich in fruits and vegetables; choose whole-grain, high-fiber foods; consume fish, especially oily fish, at least twice a week; limit intake of saturated fat to < 10% of energy, and if possible to < 7%, cholesterol to < 300 mg/d, alcohol intake to no more than 1 drink per day, and sodium intake to < 2.3 g/d (approximately 1 tsp salt).
- Consumption of *trans*-fatty acids should be as low as possible (eg, <1% of energy).

Weight Maintenance/Reduction

- Women should maintain or lose weight through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve a BMI between 18.5 and 24.9 kg/m^2 and a waist circumference ≥ 35 inches.

Omega-3 Fatty Acids

- As an adjunct to diet, omega-3 fatty acids in capsule form (approximately 850 to 1000 mg of EPA and DHA) may be considered in women with CHD, and higher doses (2 to 4 g) may be used for treatment of women with high triglyceride levels.

Depression

- Consider screening women with CHD for depression and refer/treat when indicated.

Major Risk Factor Interventions

Blood Pressure—Optimal Level and Lifestyle

- Encourage an optimal blood pressure of < 120/80 mm Hg through lifestyle approaches such as weight control, increased physical activity, alcohol moderation, sodium restriction, and increased consumption of fresh fruits, vegetables, and low-fat dairy products.

Blood Pressure—Pharmacotherapy

- Pharmacotherapy is indicated when blood pressure is ≥ 140/90 mm Hg or at an even lower blood pressure in the setting of chronic kidney disease or diabetes ≥ 130/80 mm Hg).
- Thiazide diuretics should be part of the drug regimen for most patients unless contraindicated or if there are compelling indications for other agents in specific vascular diseases.
- Initial treatment of high-risk women should be with ß-blockers and/or ACE inhibitors/ARBs, with addition of other drugs such as thiazides as needed to achieve goal blood pressure.

Lipid and Lipoprotein Levels—Optimal Levels and Lifestyle

- The following levels of lipids and lipoproteins in women should be encouraged through lifestyle approaches: LDL-C < 100 mg/dL, HDL-C > 50 mg/dL, triglycerides < 150 mg/dL, and non–HDL-C (total cholesterol minus HDL cholesterol) < 130 mg/dL.
- If a woman is at high risk or has hypercholesterolemia, intake of saturated fat should be < 7% and cholesterol intake < 200 mg/d).

Lipids—Pharmacotherapy for LDL Lowering, High-risk Women

- Utilize LDL-C–lowering drug therapy simultaneously with lifestyle therapy in women with CHD to achieve an LDL-C < 100 mg/dL and similarly in women with other atherosclerotic CVD or diabetes mellitus or 10-year absolute risk > 20%.
- A reduction to < 70 mg/dL is reasonable in very-high-risk women with CHD and may require an LDL-lowering drug combination.

Lipids—Pharmacotherapy for LDL Lowering, Other At-risk Women

- Utilize LDL-C–lowering therapy if LDL-C level is ≥ 130 mg/dL with lifestyle therapy and there are multiple risk factors and 10-year absolute risk 10% to 20%.
- Utilize LDL-C–lowering therapy if LDL-C level is ≥ 160 mg/dL with lifestyle therapy and multiple risk factors even if 10-year absolute risk is <10%.
- Utilize LDL-C–lowering therapy if LDL ≥ 190 mg/dL regardless of the presence or absence of other risk factors or CVD on lifestyle therapy.

Lipid—Pharmacotherapy for Low HDL or Elevated Non-HDL, High-risk Women

- Utilize niacin or fibrate therapy when HDL-C is low or non–HDL-C is elevated in high-risk women after LDL-C goal is reached.

Lipid—Pharmacotherapy for Low HDL or Elevated Non-HDL, Other At-risk Women

- Consider niacin or fibrate therapy when HDL-C is low or non–HDL-C is elevated after LDL-C goal is reached in women with multiple risk factors and a 10-year absolute risk 10% to 20%.

Diabetes Mellitus

- Lifestyle and pharmacotherapy should be used as indicated in women with diabetes to achieve an HbA_{1C} < 7% if this can be accomplished without significant hypoglycemia.

Preventive Drug Interventions

Aspirin, High Risk

- Aspirin therapy (75 to 325 mg/d)[¶] should be used in high-risk women unless contraindicated.
- If a high-risk woman is intolerant of aspirin therapy, clopidogrel should be substituted.

Aspirin—Other At-risk or Healthy Women

- In women ≥ 65 years of age, consider aspirin therapy (81 mg daily or 100 mg every other day) if blood pressure is controlled and benefit for ischemic stroke and MI prevention is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke and in women < 65 years of age when benefit for ischemic stroke prevention is likely to outweigh adverse effects of therapy

ß-Blockers

- ß-Blockers should be used indefinitely in all women after MI, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated.

ACE inhibitors/ARBs

- ACE inhibitors should be used (unless contraindicated) in women after MI and in those with clinical evidence of heart failure or an LVEF ≤ 40% or with diabetes mellitus.
- In women after MI and in those with clinical evidence of heart failure or an LVEF ≤ 40% or with diabetes mellitus who are intolerant of ACE inhibitors, ARBs should be used instead.

Aldosterone Blockade

- Use aldosterone blockade after MI in women who do not have significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and ß-blocker, and have LVEF ≤ 40% with symptomatic heart failure.

PROspective Multicenter Imaging Study for Evaluation of Chest Pain

Physician Information Sheet

PROMISE Objective:
To determine whether an initial non-invasive anatomic imaging strategy with cardiac CT angiography (CTA) will improve clinical outcomes in subjects with symptoms concerning for coronary artery disease (CAD) relative to an initial functional testing strategy.

PROMISE Patient Population:
Patients that present with symptoms concerning for obstructive CAD who require non-urgent noninvasive diagnostic testing.

PROMISE Design:
Multicenter, randomized pragmatic comparative effectiveness trial, with anticipated enrollment of 10,000 subjects from 200-250 primary care and cardiology community practice centers in North America.

PROMISE Intervention:
Subjects will be randomized to an initial testing strategy of either:
- Cardiac computed tomographic angiography or
- Functional stress testing with exercise ECG, exercise or pharmacologic stress Echocardiography, or exercise or pharmacologic stress SPECT imaging

PROMISE End Points:
Difference in the incidence of death, myocardial infarction, major peri-procedural complications and hospitalization for unstable angina between cardiac CTA and functional stress testing strategies.

Cardiac CTA

Cardiac CTA is able to detect:
- Presence of significant coronary stenosis • Presence, extent and composition of coronary artery plaque
- Evidence of global and/or regional left ventricular (LV) functional impairment

Test Characteristics
Stenosis Detection:
• CT accurately excludes significant stenosis (> 50%) with sensitivity of 95% and a NPV of 98% as compared to invasive coronary angiography • Specificity is limited to 85% and PPV is about 80% if image evaluation is diminished by the presence of coronary artery calcification or motion • CT is considered more accurate for the detection of stenosis morphology then functional testing
Plaque Detection:
• CT is sensitive (85%) to detect non-calcified plaque larger than 1 mm • Calcified plaque detection is very accurate
• CT is the most reliable method available to detect non-obstructive CAD non-invasively *LV Function*:
• CT accuracy is comparable to MR for global and regional function

Practical Tips
• Patients with no coronary plaque on cardiac CTA have an extremely low risk for death over the next 5 years and typically do not require additional diagnostic evaluation unless there is a change in clinical status • CT may overestimate the degree of stenosis, and thus some patients with moderate stenosis may appear to have a more significant stenosis than is found on invasive angiography • Stress testing may be useful in determining the hemodynamic significance of stenoses identified on CT • More aggressive prevention strategies and risk assessment modification may be considered in patients with non-obstructive disease

Stress Echocardiography

Stress Echo is able to detect:

• Presence, extent and location of wall motion abnormality during rest and stress • Global and regional left ventricular dysfunction • High risk findings such as multivessel disease, systolic dilation • Valve disease • Other cardiac abnormalities associated with chest pain

Test Characteristics

Stenosis Detection:

• Sensitivity of exercise echo is approximately 85% and the specificity is 88% and the sensitivity of dobutamine echo is 80% and the specificity is 84% as compared to invasive coronary angiography • Stress echocardiography and nuclear perfusion imaging have similar diagnostic accuracy for the detection of coronary artery disease

Prognosis:

• A normal exercise echocardiogram is associated with an annual cardiovascular event rate of <1% and these patients typically do not require additional diagnostic evaluation unless there is a change in clinical status • Patients with extensive stress induced wall motion abnormalities in a multivessel pattern are at high risk for cardiac event including mortality

Practical Tips

• False negative stress echocardiograms are most common in those who fail to achieve an adequate stress and those with single vessel disease particularly in the left circumflex coronary artery territory • False positive stress echocardiograms can occur in any setting with mismatch of myocardial oxygen demand and myocardial perfusion (oxygen supply – i.e.: hypertension and cardiomyopathy) • Conduction abnormalities may also cause false positive interpretations due to abnormal wall motion. • Baseline LV dysfunction, failure to augment LV ejection fraction with stress, wall motion abnormality at a low workload and wall motion abnormalities in the anterior territory (or left anterior coronary artery distribution) are other high risk findings • The prognostic value of stress echocardiography in women is similar to that of men

Exercise Treadmill Test

Stress ECG is able to detect:

• Normal rest ECG • ST changes consistent with ischemia • High risk findings such as very poor exercise tolerance, severe ventricular arrhythmia/hypotension

Test Characteristics

Stenosis Detection:

• Sensitivity of 67% and a specificity of 72% for the detection of significant stenosis in patients with an intermediate pretest likelihood of CAD as compared to invasive coronary angiography

Prognosis:

•"Early positive" exercise test result (inability to complete 1st two stages of Bruce protocol, exercise induced angina and treadmill time) have been identified as independent predictors of survival • The Duke Treadmill score can identify a high risk group (score less than or equal to -11) with an average annual cardiovascular mortality greater than or equal to 5%.

Practical Tips

• ETT accuracy is slightly worse in women compared to men • Patients with LVH by ECG criteria and ST depression have a lower specificity 70% (vs 84%) with no change in sensitivity • Exercise-induced ST depression usually occurs with right bundle-branch block in the anterior chest leads (V1 through V3) and is not associated with ischemia. Lateral leads (V4 through V6) and inferior leads (II and aVF) can be used to identify ischemia • Computer processing of the exercise ECG can result in a false-positive indication of ST depression

Stress Nuclear

SPECT/PET is able to detect:
• Presence, extent and location of reversible or irreversible myocardial ischemia/scar • High-risk findings such as transient ischemic dilatation • Global and regional left ventricular dysfunction

Test Characteristics
Stenosis Detection:
• Reversible ischemia on exercise/pharmacologic SPECT or PET has been found to have sensitivities of 87% and 90%, respectively, and in contemporary protocols (Tc agents and incorporation of gated images, or PET perfusion) specificities are 85-90% for the detection of significant stenosis as compared to invasive coronary angiography

Prognosis: Annual risks for MI/death based on stress SPECT and PET findings are:

- normal: 0.3/0.5%; 0.2/0.5%
- mildly abnormal: 0.8/2.7%; 1.3/1.4%
- moderately abnormal: 2.3/2.9%; 3.6/3.0%
- severely abnormal stress: 2.9/4.2%; 6.4/5.8%

Practical Tips
• Ideally, medications should be held if possible so as to give best chance of reaching maximum stress • Pharmacologic stress can be used if patients do not reach an adequate symptomatic or heart rate end point

PROMISE Diagnostic Core

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