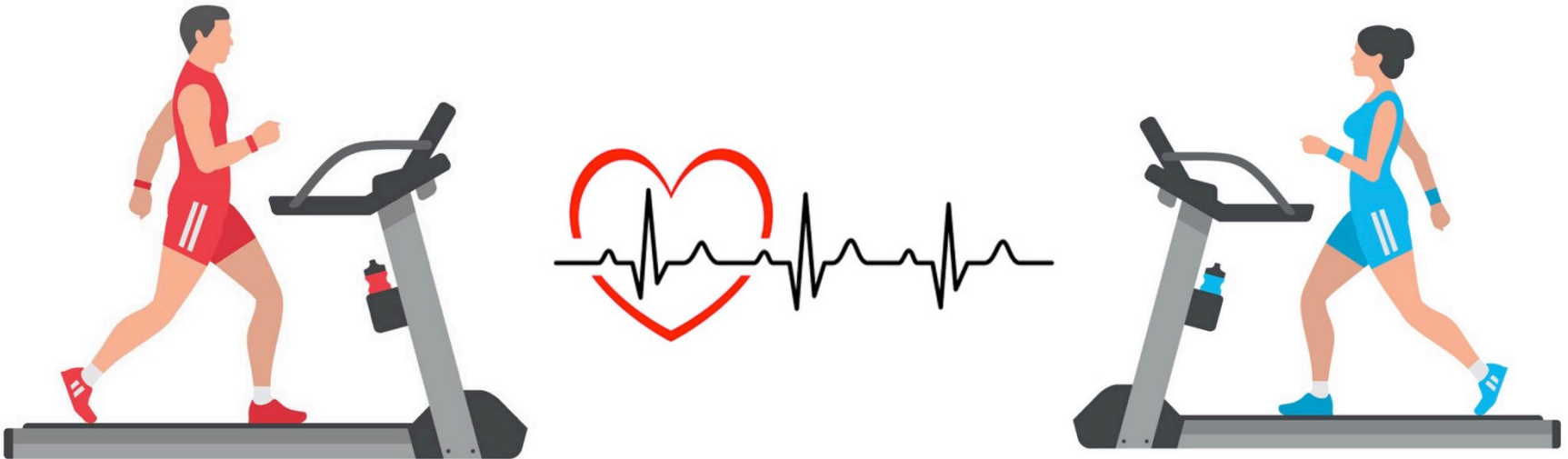# How useful is stress exercise testing in men and women?

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Faculty/Presenter Disclosure

- **Faculty:** Robinder Singh

- **Relationships with commercial interests:**
  - **Speakers Bureau/Honoraria:**
    - HLS Therapeutics
    - AstraZeneca

Objectives

- Burden of CV disease in women
  - Different symptoms?
  - Novel Risk factors?

- Exercise stress testing
  - Who should be referred?
  - How do we assess pre-test probability of CAD in females vs. males?

- Stress testing for diagnosis and prognosis in females
  - ST response
  - Non-ST variables

- Non-invasive testing algorithm for female patients
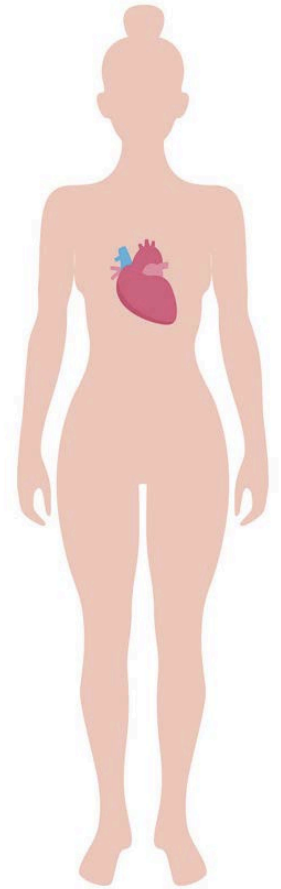
The Burden of Disease

straight to the *heart*

HEART DISEASE IS THE **#1 KILLER OF WOMEN**
IT IS MORE DEADLY THAN ALL FORMS OF CANCER COMBINED

HEART DISEASE CAUSES **1 IN 3 DEATHS** OF WOMEN EACH YEAR
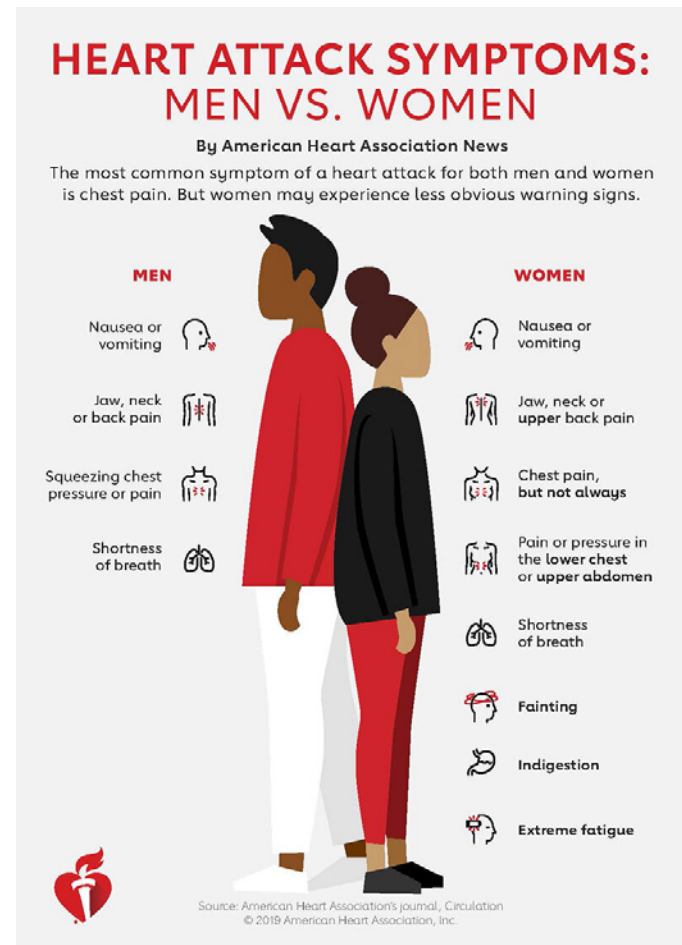
90% OF WOMEN HAVE ONE OR MORE **RISK FACTORS**

Coronary Artery Disease in Females

- Develops at a later age for females
  - Rates in younger females are increasing

- More likely to have documented ischemia with non-obstructive CAD
  - Higher incidence of microvascular disease

- Take longer to obtain medical care in the setting of ACS
  - Difference in symptoms, other psychosocial factors
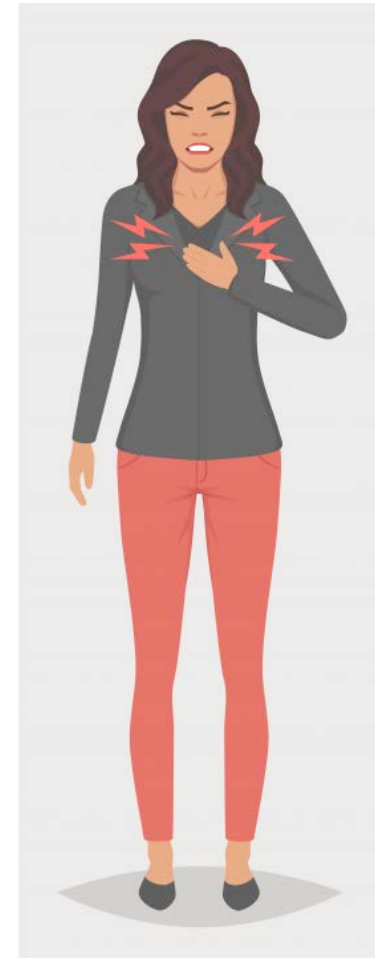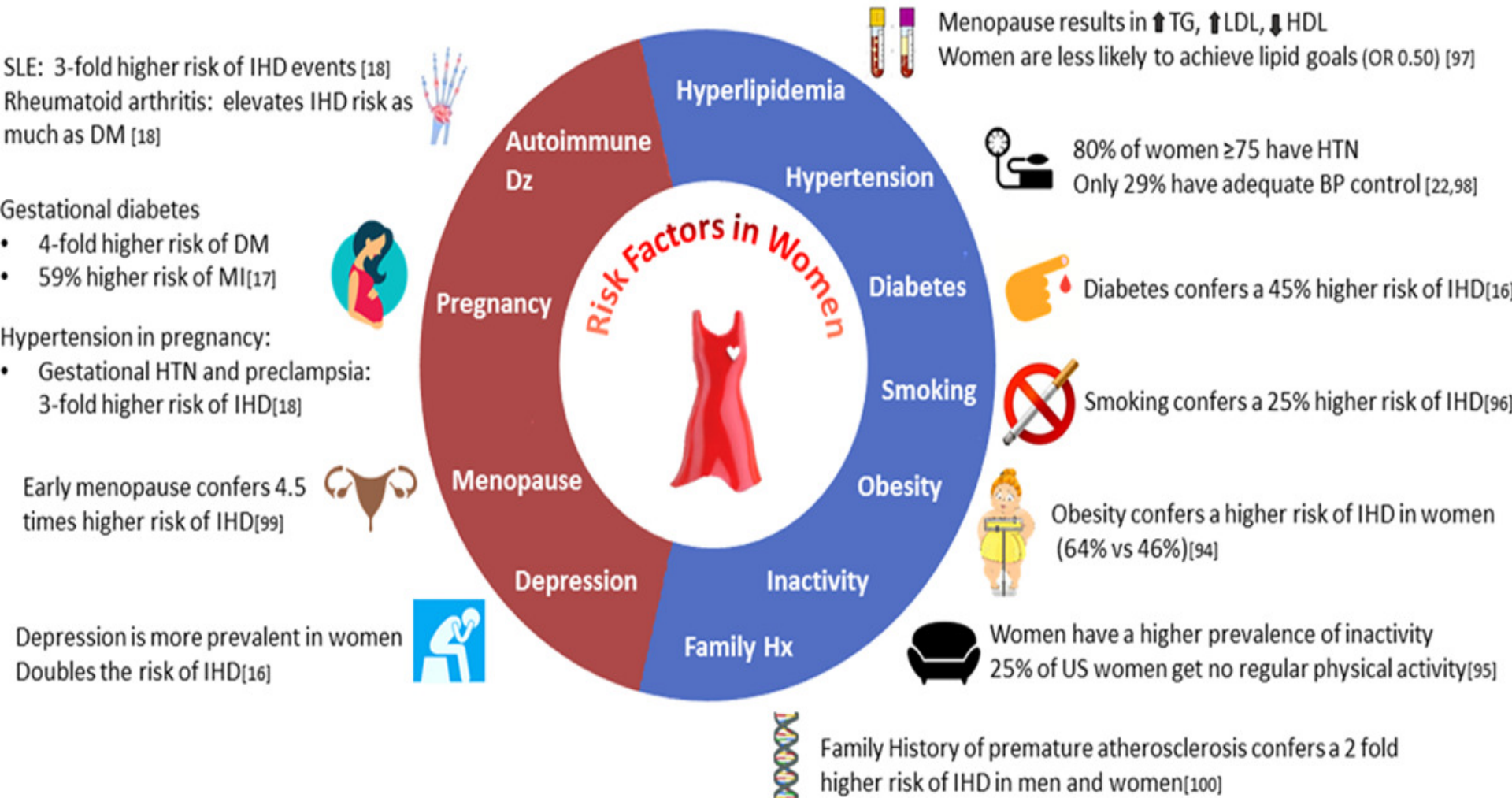
Angina in Females

- Most common presenting symptom is still chest pain/discomfort

- Different pattern and distribution of non–chest-related pain symptoms
  - More often precipitated by mental or emotional stress and less frequently by physical exertion

- More often report epigastric discomfort and associated nausea
  - Radiation of discomfort to the arms, neck, and interscapular areas
  - dyspnea and fatigue

HEART ATTACK SYMPTOMS: MEN VS. WOMEN

By American Heart Association News

The most common symptom of a heart attack for both men and women is chest pain. But women may experience less obvious warning signs.

MEN
- Nausea or vomiting
- Jaw, neck or back pain
- Squeezing chest pressure or pain
- Shortness of breath

WOMEN
- Nausea or vomiting
- Jaw, neck or upper back pain
- Chest pain, but not always
- Pain or pressure in the lower chest or upper abdomen
- Shortness of breath
- Fainting
- Indigestion
- Extreme fatigue

Source: American Heart Association's journal, Circulation
© 2019 American Heart Association, Inc.

CV Risk Factors in Females

Emerging Risk Factors

SLE: 3-fold higher risk of IHD events [18]
Rheumatoid arthritis: elevates IHD risk as much as DM [18]

Gestational diabetes
- 4-fold higher risk of DM
- 59% higher risk of MI[17]

Hypertension in pregnancy:
- Gestational HTN and preeclampsia: 3-fold higher risk of IHD[18]

Early menopause confers 4.5 times higher risk of IHD[99]

Depression is more prevalent in women Doubles the risk of IHD[16]

Traditional Risk Factors

Menopause results in ↑TG, ↑LDL, ↓HDL
Women are less likely to achieve lipid goals (OR 0.50) [97]

80% of women ≥75 have HTN
Only 29% have adequate BP control [22,98]

Diabetes confers a 45% higher risk of IHD[16]

Smoking confers a 25% higher risk of IHD[96]

Obesity confers a higher risk of IHD in women (64% vs 46%)[94]

Women have a higher prevalence of inactivity 25% of US women get no regular physical activity[95]

Family History of premature atherosclerosis confers a 2 fold higher risk of IHD in men and women[100]

Risk Factors in Women

Autoimmune Dz

Pregnancy

Menopause

Depression

Hyperlipidemia

Hypertension

Diabetes

Smoking

Obesity

Inactivity

Family Hx

Basics of Exercise Stress Testing
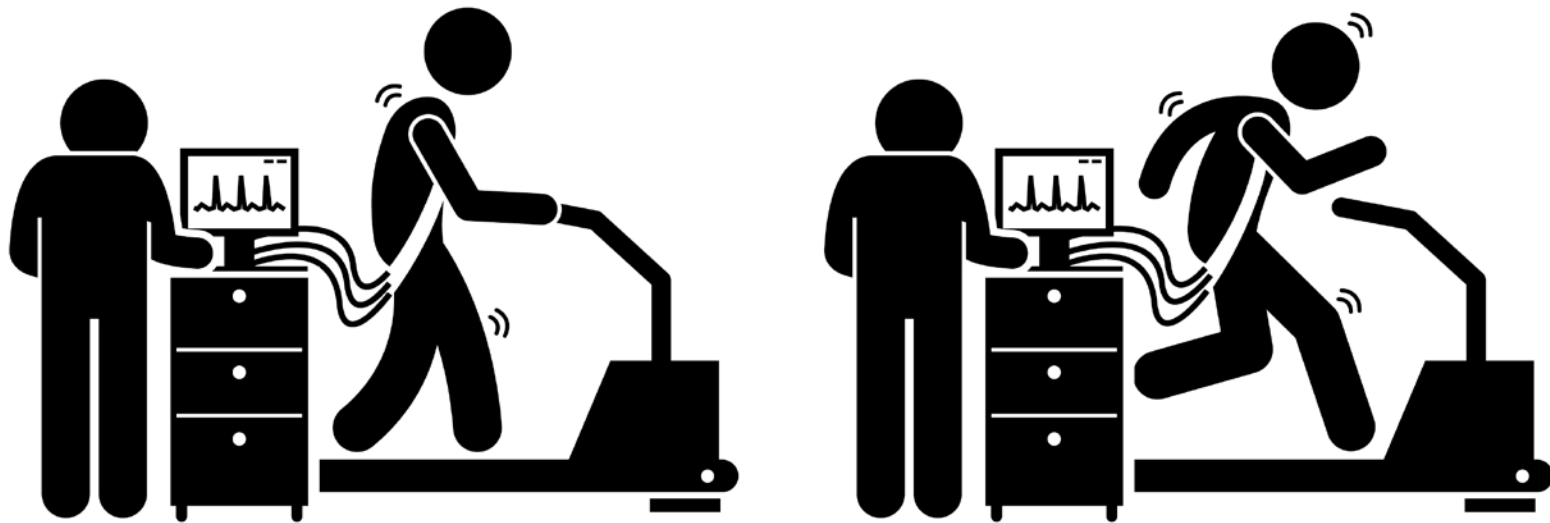
Who Should be Referred?

Class I Indication for Diagnosis of CAD

Adult patients with an **intermediate** pretest probability of CAD, based on gender, age, and **symptoms**

Assessing Pre-Test Probability

Age	Gender	Typical/Definite Angina Pectoris	Atypical/Probable Angina Pectoris	Non-Anginal Chest Pain	Asymptomatic
30-39	Males	Intermediate	Intermediate	low (<10%)	Very low (<5%)
30-39	Females	Intermediate	Very Low (<5%)	Very low	Very low
40-49	Males	High (>90%)	Intermediate	Intermediate	low
40-49	Females	Intermediate	Low	Very low	Very low
50-59	Males	High (>90%)	Intermediate	Intermediate	Low
50-59	Females	Intermediate	Intermediate	Low	Very low
60-69	Males	High	Intermediate	Intermediate	Low
60-69	Females	High	Intermediate	Intermediate	Low

High = >90% Intermediate = 10-90% Low = <10%
Very Low = <5%

Diamond and Forrester Classification:
– Able predict probability CAD based on few clinical factors
 • Age, gender, pain type most powerful

Diamond et al. NEJM 1979

Prevalence of CAD in Females

- **CONFIRM registry data**

- Pretest probability vs. CCTA prevalence of CAD
  - (n= 6329 females)
  - Symptomatic and asymptomatic patients

Predicted

Age, y	Nonanginal Chest Pain, %		Atypical Angina, %		Typical Angina, %	
	Men	Women	Men	Women	Men	Women
30−39	4	2	34	12	76	26
40−49	13	3	51	22	87	55
50−59	20	7	65	31	93	73
60−69	27	14	72	51	94	86

Observed

Gibbons et al. Circulation 2003
Cheng et al. Circulation 2011
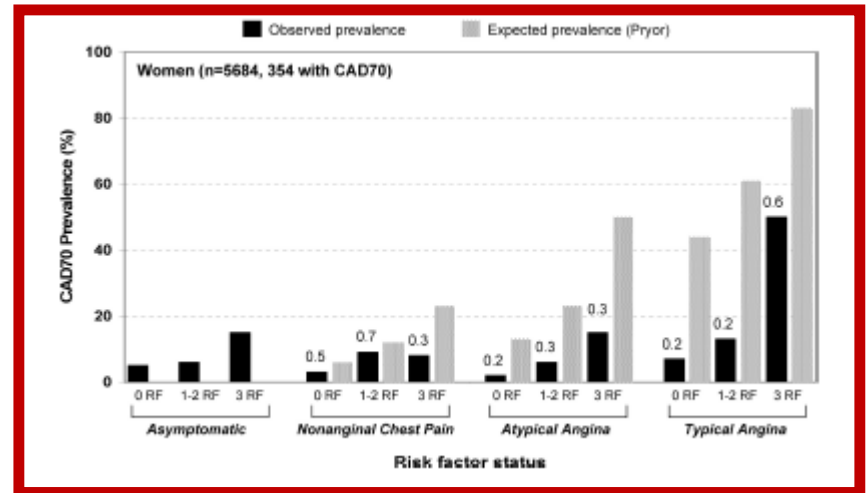
AHA Consensus Statement

Role of Noninvasive Testing in the Clinical Evaluation of Women With Suspected Ischemic Heart Disease
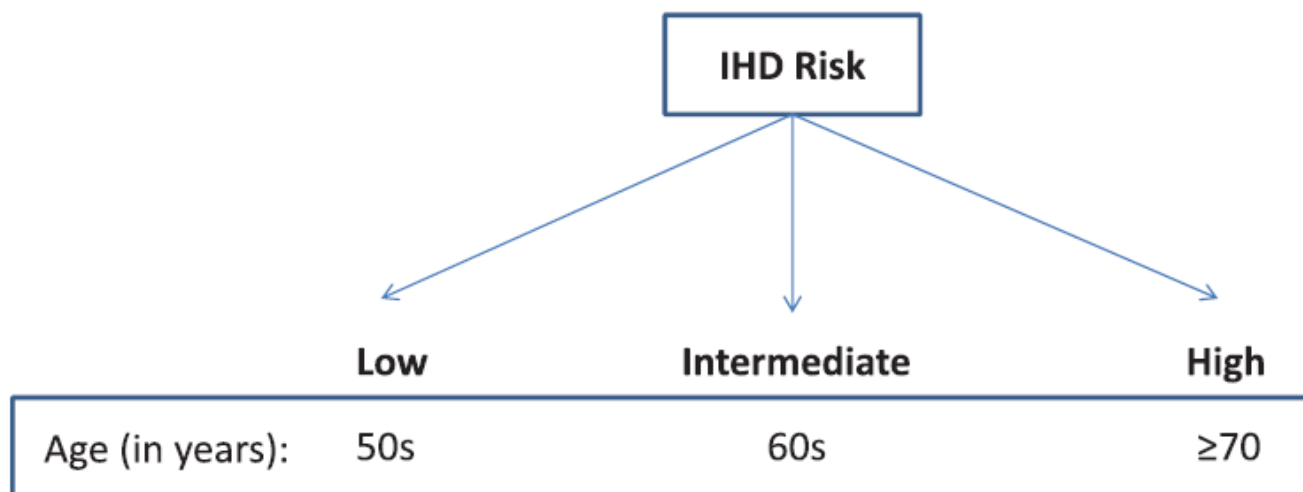## A Consensus Statement From the American Heart Association

IHD Risk

Low	Intermediate	High
Age (in years): 50s	60s	≥70

Risk Accentuation

Add 1 Risk Category

Multiple Cardiac Risk Factors
Functional Disability
Extensive Comorbidity

Table 2.   High IHD Clinical Risk Markers for Symptomatic Women

Peripheral arterial disease

Diabetes mellitus: 10-y history or poorly controlled in a woman >40 y of age

Chronic obstructive lung disease

Transient ischemic attacks or cerebrovascular accident

Chronic kidney disease

Functional disability: inability to perform activities of daily living or
    <5 estimated DASI METs

DASI METS indicates Duke Activity Status Index metabolic equivalents; and IHD, ischemic heart disease.

Mieres et al. Circulation 2014

Exercise Stress Test Interpretation

- Symptoms

- ST shift

- BP response

- HR response

- Functional Capacity

ST Depression for Diagnosis of CAD in Females

ST depression with exercise stress testing is less accurate in identifying CAD in women than in men

- Varies widely depending on study

- Women
  - Sensitivity 61% and specificity 70% [1]

- Men
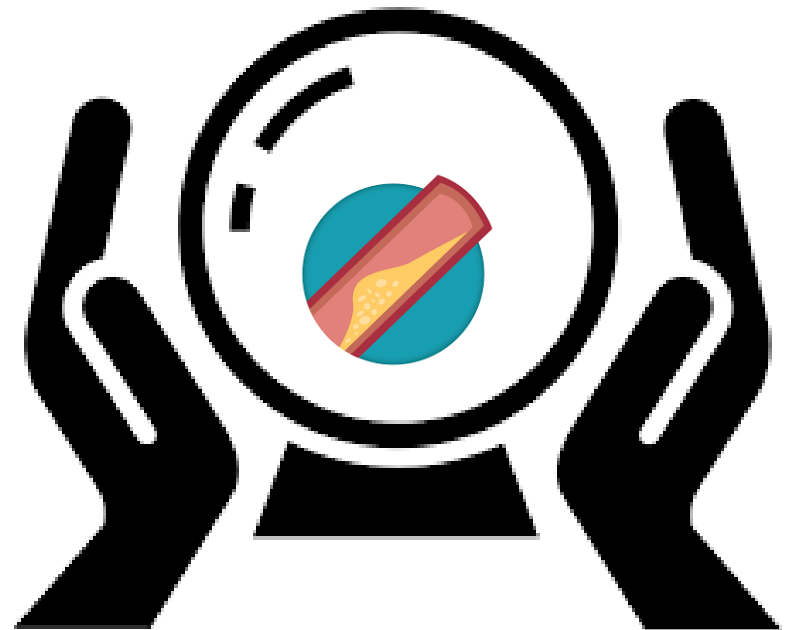 - Sensitivity 68% and specificity 77% [2]

1. Kwok et al. Am J Cardiol 1999
2. Gianrossi et al. Circulation 1989

ST Depression Between Genders

- Positive Predictive Value of ST Depression
  - Women 47%
  - Men 77%

  $P < 0.05$

- Negative Predictive Value of ST Depression
  - Women 78%
  - Men 81%

ST Shift in Females

Bottom Line:

Although females are more likely to have false positive exercise stress tests, they are still a good initial test to **RULE OUT** myocardial ischemia in symptomatic, intermediate risk females

'Ma'am...you likely do **NOT** have obstructive CAD'

Reasons for False Positive ST Shift in Females

1. More likely to have baseline ST-T changes

2. Estrogen may cause digoxin-like effect on ST segments
   - Variation of ST changes with menstrual cycle in premenopausal females [1]
   - Post menopausal females on HRT are more likely to have false positive ST depression than those not on HRT [2]

3. Women are older when presenting for stress testing, leading to decreased functional capacity and ability to induce ischemia with exercise

1. Grzybowski et al. Am Heart J 2009
2. Morise et al. Int J Cardiol 1997

ST Depression for Prognosis in Females

- ST depression has not been found to be prognostically beneficial in females
- No difference in survival between females with or without ST depression (asymptomatic individuals)
  - St. James Women Take Heart Project[1]
  - Lipid Research Clinics Project [2]
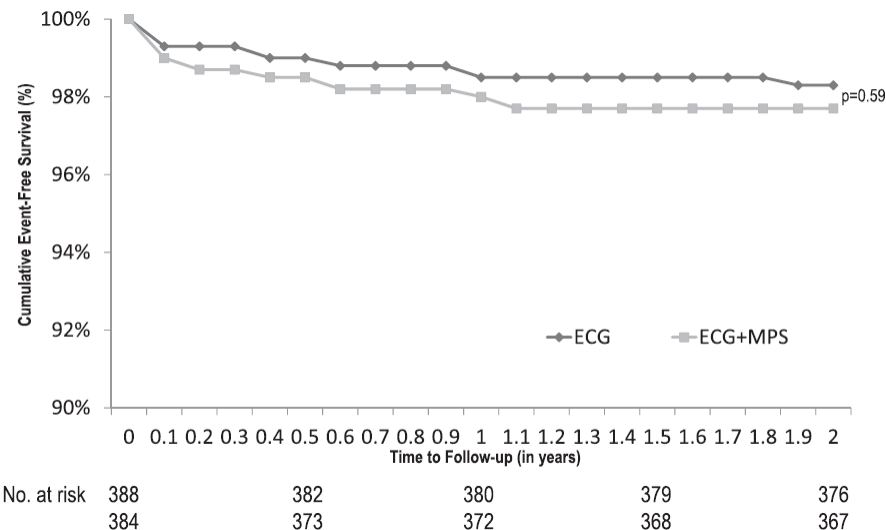
WOMEN study:
Found no difference when comparing women randomized to ETT vs. MPI at 2-years (n=824)

1. Gulatti et al. Circulation 2003
2. Mora et al. JAMA 2003
3. Shaw et al. Circulation 2011

# Exercise Stress Testing: Beyond ST Depression

Fitness/Functional Capacity

Diagnosis:

- Functional capacity has been found to be a strong predictor of CAD in asymptomatic females [1,2]

Prognosis:

- Strong prognostic predictor in both symptomatic and asymptomatic females
- Each 1 MET increase in functional capacity results in 23% fewer CV events in females [4]
- Inability to complete 5 METs associated with 3x increased risk of mortality vs. those that can complete 8 METs [4]
- Ability to complete >10METS associated with low risk of inducible ischemia on MPR [2]
  - <7METS more likely to have ischemia

Nomogram of percent normal exercise capacity for age
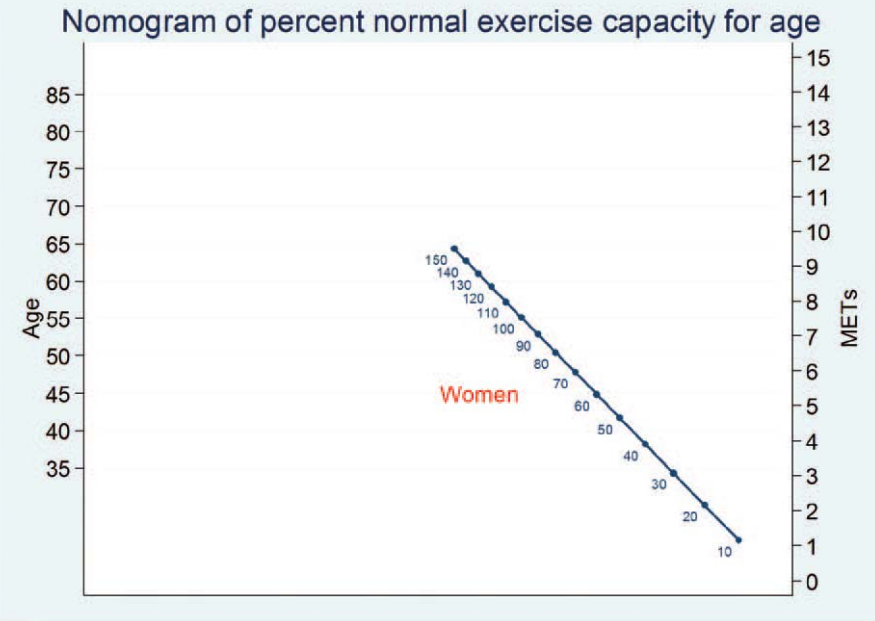
1. Robert et al. Circulation 1991
2. Bourque et al. JACC 2009
3. Roger et al. Circulation 1998
4. Gulatti et al. Circulation 1993

Duke Treadmill Score

$$\begin{matrix}\text{Duke} \\ \text{Treadmill} \\ \text{Score}\end{matrix} = \begin{matrix}\text{Exercise} \\ \text{Duration} \\ \text{(min)}\end{matrix} - 5\begin{pmatrix}\text{ST} \\ \text{Deviation} \\ \text{(mm)}\end{pmatrix} - 4\begin{pmatrix}\text{Angina} \\ \text{Index}\end{pmatrix}$$

Angina Index

0 – none, 1 – typical angina, 2 – angina causing test cessation

Score	Risk Group	Stenosis $\geq$ 75%	Multivessel Disease	1-Year Mortality
$\geq$ 5	Low	40.1%	23.7%	0.25%
-10 to 4	Intermediate	67.3%	55.0%	1.25%
$\leq$ -11	High	99.6%	93.7%	5.25%

Duke Treadmill Score in Females

Diagnosis:

- Performs equally in risk stratification

- Better at excluding significant CAD in females as compared to males

Diagnosis

Table 5. Frequency of Coronary Disease Subsets in Women and Men

Duke Treadmill Score	No Stenosis $\geq 75\%$	1 VD $\geq 75\%$	2 VD $= 75\%$	3 VD = 75% or LM
Women (n = 976)				
Low risk (33%)	80.9%	9.4%	6.2%	3.5%
Moderate risk (63%)	65.1%	14.2%	8.3%	12.4%
High risk (4%)	10.8%	18.9%	24.3%	46%
Men (n = 2246)				
Low risk (34%)	52.6%	22.4%	13.6%	11.4%
Moderate risk (54%)	17.8%	15.6%	27.9%	38.7%
High risk (12%)	1.8%	9.1%	17.5%	71.5%

LM = left main; VD = vessel disease.

Alexander et al. JACC 1998

Duke Treadmill Score for Prognosis

- Excellent prognostic tool for both sexes

- Females generally have been shown to have better survival than males for each risk category

- Women Take Heart Project:
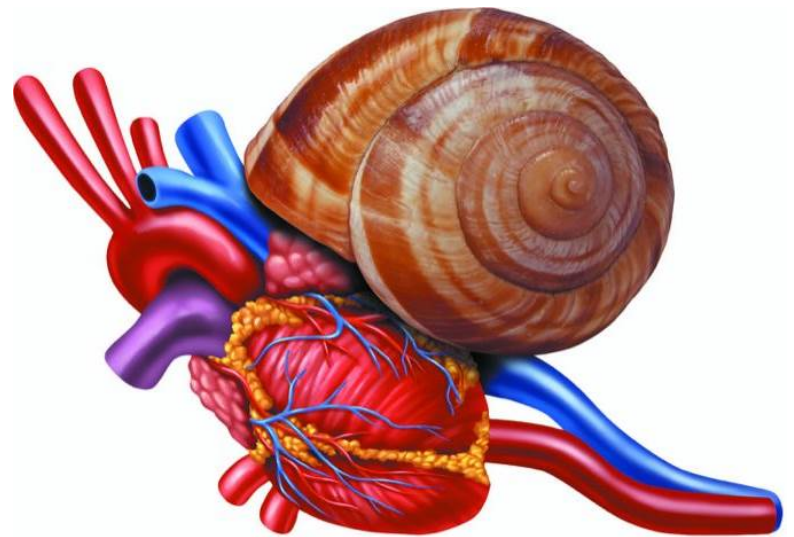 - HR all cause mortality 2.0
  - HR cardiac mortality 2.5

Gulatti et al. Am J Card. 2005
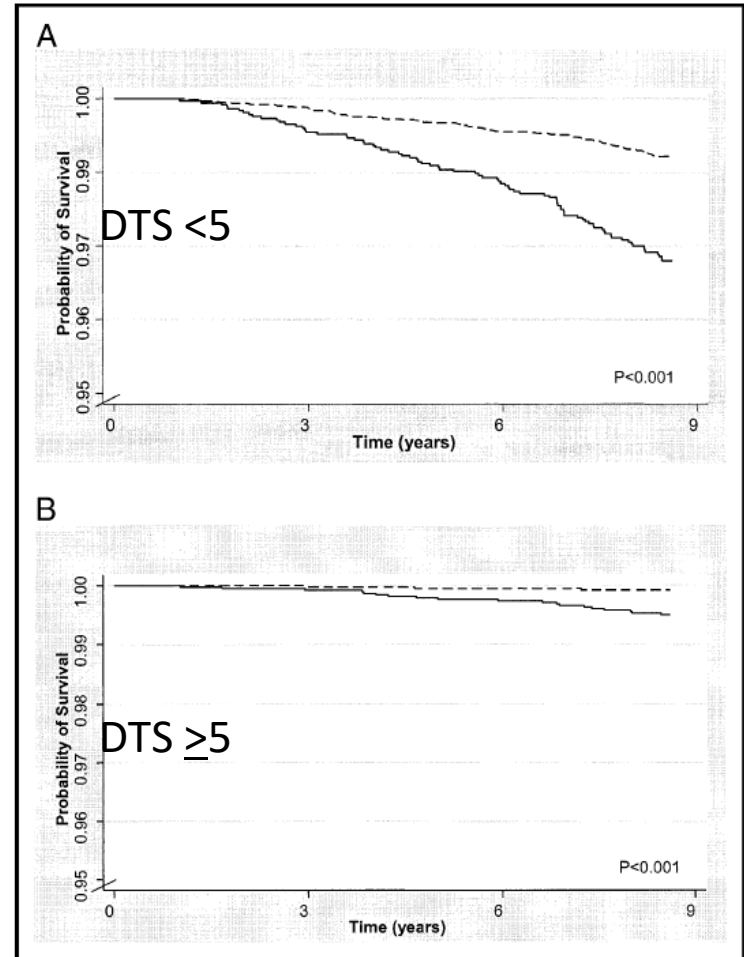
Chronotropic Response

Diagnosis

- Inability to reach 85% of maximum predicted HR is associated with an increased risk of obstructive CAD in females[1]

Prognosis

- Has been shown a predictor of poor prognosis for both males and females in numerous studies
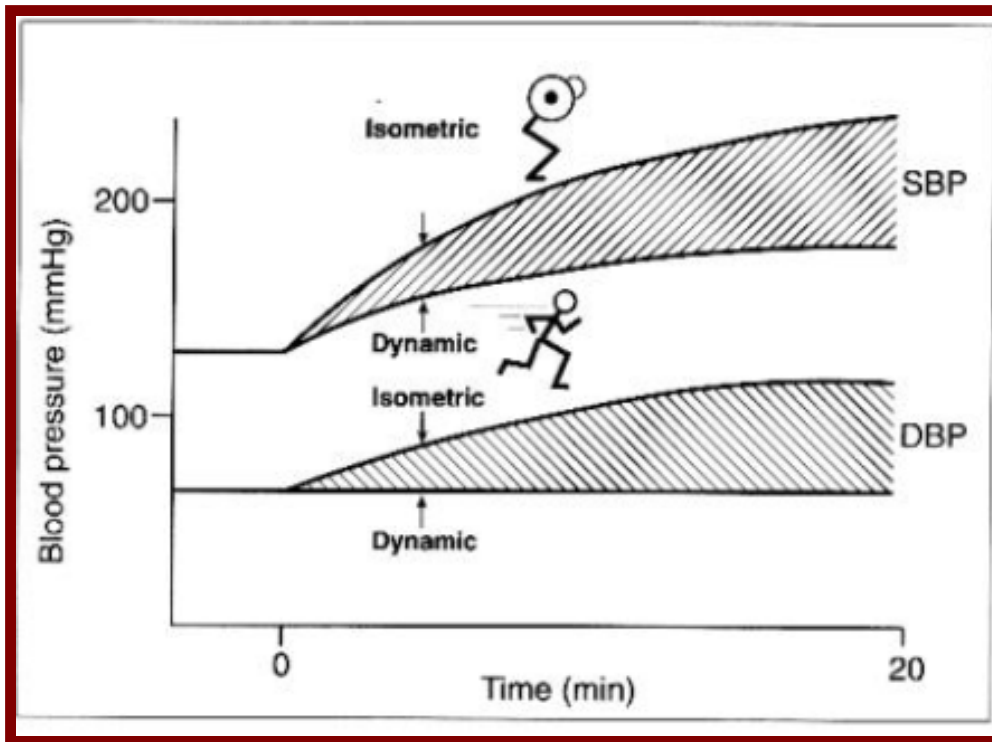
Pratt et al. Chest 1989

Abnormal Heart Rate Recovery

Definition: Inability to reduce peak HR by 12beats in 1st minute compared to peak HR

- Has substantial prognostic value for both males and females

- Independent predictor of all cause mortality in females

Vivekananthan et al. JACC 2003

Blood Pressure in Exercise

Isometric Exercise:
-SBP increases significantly more (>250mmHg)
-DBP incrases (up to 180mmHg)

Dynamic Exercise:
-Increase in SBP only (generally 150-170mmHg)

Hypotensive Response

- Fall in SBP $\geq$10mmHg during exercise
  - Sign of LV dysfunction

- In males has been shown to be a consistent predictor of left main/severe triple vessel stenosis

- Less clear in females, has been shown to be less specific
  - Occurs more commonly in females with no CAD

Hypertensive Response

- Definition
  - Females SBP >190mmHg
  - Males SBP >210mmHg

- Predictor of the development of HTN in the future for both men and women
 - HR 1.7 at 5yrs

Manolio et al. Am J Hypertens 1994

Role of Noninvasive Testing in the Clinical Evaluation of Women With Suspected Ischemic Heart Disease
A Consensus Statement From the American Heart Association

- 1. For a symptomatic woman with intermediate IHD risk who is capable of exercising at >5 METs and who has a normal rest ECG, the ETT is recommended as th initial test of choice, with imaging reserved for those women with resting ST-segment abnormalities or those unable to exercise adequately (Class I; Level of Evidence B).

- 2. As per standardized reporting, the ETT interpretation should include not only the ST-segment response and risk score measurements but also exercise capacity, chronotropic response, heart rate recovery, and the blood pressure response to exercise (Class I; Level of Evidence B).

- 3. If an ETT is indeterminate (eg, negative ECG in the setting of submaximal exercise [below age-predicted level or failure to achieve >85% predicted maximal heart rate]) or abnormal, the next step should be additional diagnostic testing with stress imaging. Individualized decision making and targeted anti-ischemic therapies after the ETT should consider the woman's ongoing symptom burden and the degree of abnormalities noted during the ETT (Class I; Level of Evidence C).

Approach to Symptomatic Women with Suspected IHD

Mieres et al. Circulation 2014
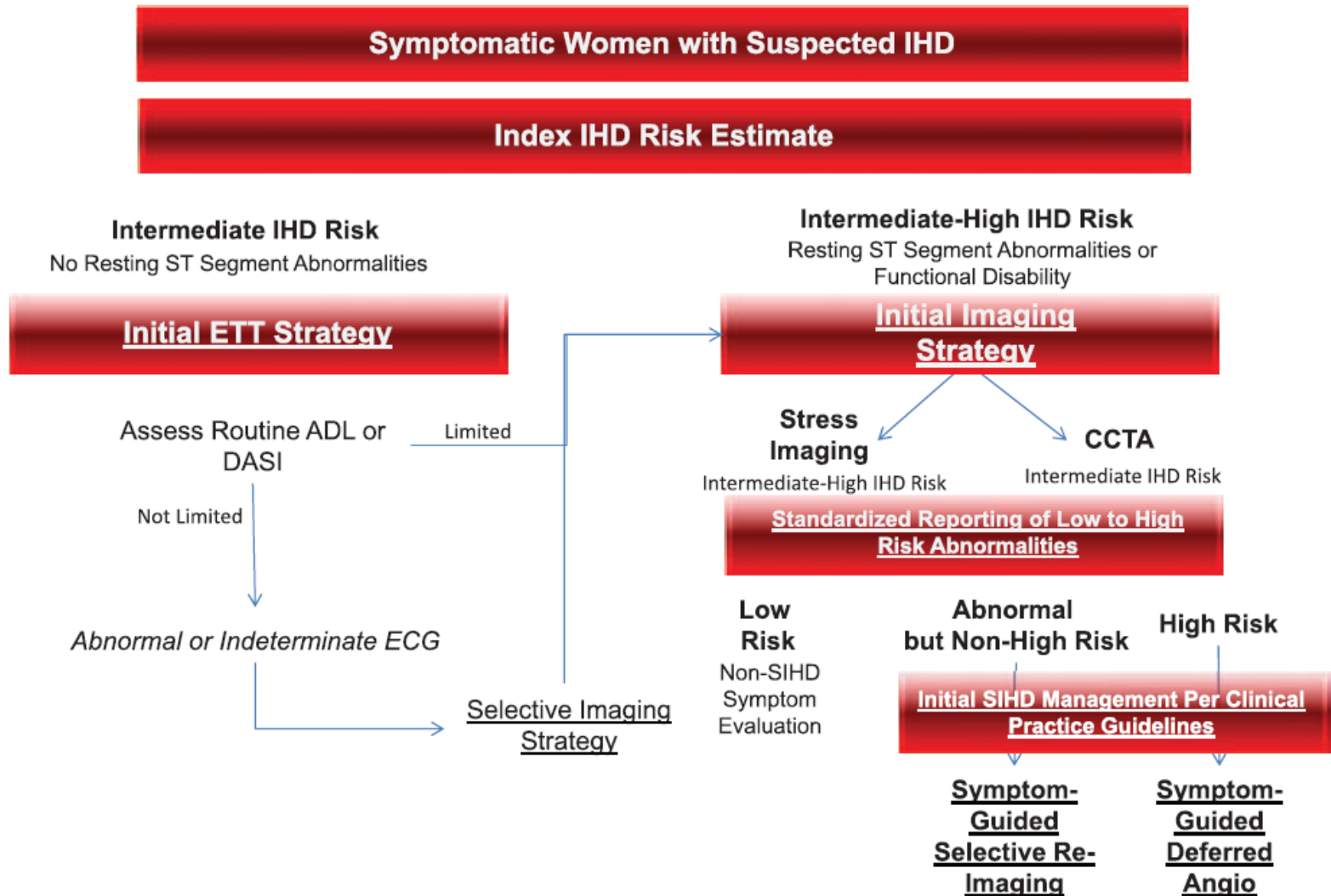
Other Non-Invasive Testing Modalities

Table 7. Summary Table for Indications to Stress Testing/ Imaging or CCTA in Women With Ischemic Symptoms

Test	Exercise Status		ECG Interpretable		Pretest Probability of IHD		
	Able	Unable	Yes	No	Low	Intermediate	High
Exercise ECG	X		X			X	
Exercise MPI	X			X		X	X
Exercise echocardiography	X			X		X	X
CCTA	X			X		X	
Pharmacological stress MPI		X	Any			X	X
Pharmacological stress echocardiography		X	Any			X	X
Pharmacological stress CMR		X	Any			X	X
CCTA		X		X		X	

Kholi et al. Circulation 2010

Accuracy of Non-Invasive Testing in Females

Table 2. Diagnostic Value of Various Stress Testing Modalities In Women

Stress Testing Modality	Sensitivity	Specificity	NPV	PPV
Exercise ECG	31–71	66–78	78	47
Exercise echocardiography	80–88	79–86	98	74
Exercise SPECT	78–88	64–91	99	87
Pharmacological echocardiography	76–90	85–94	68	94
Pharmacological SPECT	80–91	65–75	90	68

Values are percentages. PPV indicates positive predictive value.

Kholi et al. Circulation 2010
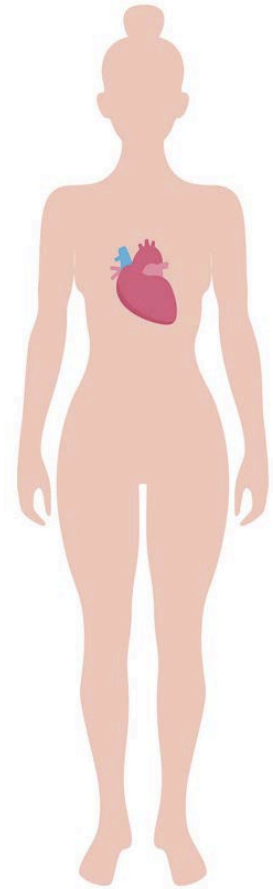
Associated Radiation Exposure

Table 3. Typical Radiation Exposure, as Measured by an Effective Dose, From Rest-Stress MPI, CCTA, and Angiography in Women

	Effective Dose, mSv
Annual background exposure	≈3
Invasive coronary angiography	≈7
Rest-stress MPI SPECT	
Technetium Tc 99m	≈11
Stress-only MPI SPECT	≈3
Dual-isotope MPI SPECT	22
Rest-stress MPI PET	
Rubidium Rb 82	≈3
Nitrogen N 13	≈2
CCTA	
Overall	≈10
With dose-reduction techniques	<2–5
Coronary artery calcium scoring	2

Kholi et al. Circulation 2010

Summary

- Heart disease is the #1 killer of women

- Angina presents differently in females vs. males

- Exercise ECG testing is less accurate in the diagnosis of CAD however has similar negative predictive value

- Aspects beyond ST shift should be assessed in when interpreting exercise stress testing

- Patient centered decision making should be used if alternative non-invasive cardiac testing is needed

Thank you

Thank you