| National Imaging Associates, Inc. | | |
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| Clinical Guidelines<br>STRESS ECHOCARDIOGRAPHY | Original Date:<br>Page 1 of 18 | February, 2010 |
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## Introduction

- Stress echocardiography (SE) refers to ultrasound imaging of the heart during exercise electrocardiography (ECG) testing, during which visualized wall motion abnormalities can provide evidence of significant coronary artery disease (CAD).

- While drug-induced stress with dobutamine can be a legitimate alternative to exercise stress testing in patients who are unable to exercise, this guideline does not require use of this modality for practical reasons with rare noted exceptions. Hence, reference in this document to SE almost always refers to exercise stress echocardiography.

- Although SE provides comparable accuracy without radiation relative to myocardial perfusion imaging (MPI), scenarios which do not permit safe and effective use of SE might be better suited for alternative stress imaging with MPI, rarely cardiovascular magnetic resonance imaging (CMR) or positron emission tomography (PET), and in some cases, non-stress imaging such as coronary computed tomography angiography (CCTA) (Askew 2018; Douglas 2011; Metz 2007; Einstein 2012; Fazel 2011; Fleischmann 1998; Heijenbrok-Kal 2007; Hirschfeld 2018; Marwick 2003; Pellikka 2007; Schinkel 2003; Scott-Moncrieff 2011; Sicari 2008; Sicari 2017; Yao 2003; Zhang 2014).

- Scenarios that support MPI over SE are detailed in the Additional Information section and include:
  (Henzlova 2016; Askew 2018; Wolk 2013)
  - Poor quality echocardiographic images
  - Inability to exercise
  - Specific comorbidities
  - ECG-related wall motion abnormalities.
  - Elevated coronary risk

- CAD stenosis $\geq$ 50% is considered clinically significant or obstructive CAD, where CAD and ischemic heart disease (IHD) are symptoms. Hemodynamically or functionally significant CAD means the degree of stenosis is severe enough to cause ischemia. This is discussed in more detail in the Additional Information section (Fihn 2012; Wolk 2013; Montalescot 2013; Gerber 2018; Tobis 2007).

- **Stable patients without known CAD** fall into 2 categories:
  (Fihn 2012; Wolk 2013; Montalescot 2013)
    - **Asymptomatic patients**, for whom Global Risk of CAD events can be determined from coronary risk factors using calculators available online. (see Part III in the Additional Information section)

    - **Symptomatic patients,** for whom we estimate the Pretest Probability that their chest-related symptoms are due to clinically significant (≥ 50%) CAD (see below):

      **The 3 Types of Chest Pain or Discomfort**

- **Typical Angina (Definite)** is defined as including all **3** of these characteristics:
  1) Substernal chest pain or discomfort with characteristic quality and duration
  2) Provoked by exertion or emotional stress
  3) Relieved by rest and/or nitroglycerine

- **Atypical Angina (Probable)** has only **2** of the above characteristics

- **Nonanginal Chest Pain/Discomfort** has only **0-1** of the above characteristics

- Once the type of chest pain has been established from the medical record, the Pretest Probability of obstructive CAD is estimated from the **Diamond Forrester Table** below, recognizing that in some cases multiple additional coronary risk factors could increase pretest probability:
  (Wolk 2013; Fihn 2012)

**Diamond Forrester Table**

| Age (Years) | Gender | Typical/Definite Angina Pectoris | Atypical/Probable Angina Pectoris | Nonanginal Chest Pain |
|---|---|---|---|---|
| <=39 | Men | Intermediate | Intermediate | Low |
| | Women | Intermediate | Very low | Very low |
| 40–49 | Men | High | Intermediate | Intermediate |
| | Women | Intermediate | Low | Very low |
| 50–59 | Men | High | Intermediate | Intermediate |
| | Women | Intermediate | Intermediate | Low |
| >=60 | Men | High | Intermediate | Intermediate |
| | Women | High | Intermediate | Intermediate |

- **Very low:** < 5% pretest probability of CAD, usually not requiring stress evaluation (Fihn 2012)
- **Low:** 5-10% pretest probability of CAD
- **Intermediate:** 10% - 90% pretest probability of CAD
- **High:** > 90% pretest probability of CAD

## INDICATIONS for STRESS ECHO

(Fihn 2012; Wolk 2013; Montalescot 2013; Pellikka 2007; Marwick 2003; Sicari 2008; Sicari 2017; Douglas 2011; Yao 2003)

### Suspected CAD

(Without known history of CAD)

**1. Symptomatic patients without known CAD**

- Low pretest probability, if ECG is uninterpretable AND patient can exercise.
- Intermediate pretest probability, if ECG is uninterpretable (Wolk, 2014).
- High pretest probability
- Repeat testing in patient with recurrent symptomatic presentation and negative result over 2 years ago
- Repeat testing in patient with new or worse symptoms and negative result at least one year ago

**2. Asymptomatic patients without known CAD:**

- Previously unevaluated ECG evidence of possible myocardial ischemia such as substantial ischemic ST segment or T wave abnormalities
- Previously unevaluated pathologic Q waves or wall motion abnormality (evidence of prior myocardial infarction)
- Unevaluated complete left bundle branch block
- Following radiation therapy to the anterior or left chest, at 5 years post inception of radiation and every 5 years thereafter (Lancellotti 2013)

**3. Incomplete or inconclusive CAD evaluation within the past 2 years, without known CAD:**

- Exercise stress ECG with low risk Duke treadmill score but patient's current symptoms indicate an intermediate or high pretest probability, which should include stress imaging
- Exercise stress ECG with intermediate Duke treadmill score
- Inconclusive/borderline CCTA (e.g. 40-70% lesions)
- An indeterminate (equivocal, borderline, or discordant) evaluation by prior stress imaging (MPI or CMR) within the past 2 years, in patients for whom a noninvasive approach is preferable to proceeding to invasive coronary arteriography (e.g. a patient presenting with unclear symptoms, ECG and imaging discordant, but with severe contrast allergy or chronic kidney disease.)

### Known Major Vessel CAD

(Patel 2017)

- Validated concern for a previous acute coronary syndrome without subsequent invasive or non-invasive coronary evaluation

- Follow up SE at 2-year intervals is approvable, if it will affect consideration of coronary revascularization (initial or additional), in patients with one of the following:
    - History of silent ischemia with severe unrevascularized CAD and revascularization could be feasible (Deedwania 2018)

- History of severe unrevascularized major multivessel CAD, without major wall motion abnormality, and revascularization could be feasible.

- Ischemia assessment following inconclusive findings of invasive coronary arteriography or CCTA, for the purpose of assessing extent of ischemia and need for additional medical, interventional, or surgical therapy

- Myocardial viability testing by low dose dobutamine stress echocardiography (myocardial perfusion imaging at rest is equally approvable) prior to coronary revascularization is reasonable in patients with left ventricular ejection fraction (LVEF) ≤ 50%, if it could significantly alter the revascularization strategy. (Patel 2013; Yancy 2013).

- New or worsening symptoms of ischemia in the absence of an acute coronary syndrome, unless the most current stress imaging study would warrant invasive coronary arteriography instead (e.g. History of high risk stress test without subsequent invasive coronary arteriography might warrant invasive coronary angiography) (Patel 2012).

- De novo heart failure (HF) patients who have known CAD, even without angina, unless the patient is not eligible for revascularization of any kind, or unless invasive coronary arteriography is immediately planned (Yancy 2013).

**Special Diagnostic Conditions, Requiring Coronary Evaluation**

- Newly diagnosed systolic or diastolic HF, when invasive coronary angiography is not immediately planned, especially when symptoms or signs of ischemia are present or suspected (SE diversion not required) (Yancy 2013, Patel 2013, Fihn 2012).
- Newly found wall motion abnormality (Colucci 2018)
- Ventricular arrhythmias:
    - Sustained ventricular tachycardia (VT) >100 bpm, ventricular fibrillation (VF), or exercise induced ventricular tachycardia (VT), when invasive coronary arteriography is not the initially required test (Al-Khatib 2018, in press)
    - Nonsustained VT, multiple episodes, each ≥ 3 beats at ≥ 100 bpm, without known cause or associated cardiac pathology, when an exercise ECG has shown an intermediate risk Duke Score or an exercise ECG could not be performed (Zimetbaum 2018)
    - Frequent premature ventricular contractions (PVCs) ≥ 30/hour, or any PVC on a 12 lead ECG, without known cause or associated cardiac pathology, when an exercise ECG has shown an intermediate risk Duke Score OR an exercise ECG is not feasible due to inability to exercise or due to an uninterpretable ECG (Cha 2012, Manolis 2018)
- Prior to Class IC antiarrhythmic drug initiation in intermediate and high global risk patients (Kumar 2018)
- Assessment of hemodynamic significance of known
    - Anomalous coronary arteries (Grani 2017),
    - Muscle bridging of a coronary artery (perform with exercise stress) (Sorajja 2018), OR
    - Coronary aneurysms in Kawasaki's disease (Newburger 2018)

## Chronic Valvular Disease
## Evaluation with Inclusion of Doppler

(Nishimura 2014; Doherty 2017; Baumgartner 2017; Steiner 2017)

- Low dose dobutamine SE for the evaluation of aortic stenosis and flow (contractile) reserve in symptomatic patients with severe aortic stenosis by calculated valve area, low flow (stroke volume ≤ 35mL/square M) /low gradient (mean < 40 mm Hg or Doppler <4 M/sec), and ejection fraction < 50% (Contractile reserve is > 20% rise in stroke volume with dobutamine).
- Exercise echo Doppler evaluation for mitral stenosis when there is a discrepancy between resting Doppler and clinical signs or symptoms.
- Exercise echo Doppler evaluation for **primary** (also known as prolapse, degenerative, unrelated to wall motion abnormality, etc.) mitral regurgitation (MR) if there is:

    - Discrepancy between exertional symptoms and severity of MR at rest
      OR
    - Need to distinguish moderate from severe MR in the asymptomatic patient

- Evaluation of **secondary** MR (also known as ischemic, related to wall motion abnormality or left ventricular dilation in cardiomyopathy, etc.), with respect to establishing an ischemic etiology

## Prior to Elective Noncardiac Surgery

(Fleischer 2014; Patel 2015)

- Patients who have no other indication for a non-invasive coronary evaluation, but are referred for preoperative cardiac evaluation, are eligible for SE, based upon cardiac risk ≥1%, if all 4 criteria are met:

    - Surgery is supra-inguinal vascular, intrathoracic, or intra-abdominal.
      AND
    - The patient has at least one of these additional cardiac complication risk factors:

        - Ischemic Heart Disease
        - History of stroke or trans ischemic attack (TIA)
        - History of congestive heart failure (CHF) or ejection fraction ≤ 35%
        - Insulin-requiring diabetes mellitus
        - Creatinine ≥ 2.0 mg/dl

      AND

    - The patient has limited functional capacity (< 4 metabolic equivalents) **such as one** of the following:
        - Cannot take care of their ADLs or ambulate
        - Cannot walk 2 blocks on level ground
        - Cannot climb 1 flight of stairs
        - Cannot vacuum, dust, do dishes, sweep, or carry small grocery bag

      AND

- There has been no non-invasive coronary testing within one year, and the result of such a test would be likely to substantially alter therapy and/or preclude proceeding with the intended surgery

- Planning for solid organ transplantation is an indication for preoperative dobutamine SE, if there has not been a conclusive stress evaluation within the past year (Lentine 2012):

  - In a patient with poor or unknown functional capacity (4 metabolic equivalents, as characterized under preoperative evaluation for noncardiac surgery section above) (Wolk 2013)

OR

  - In a patient with ≥ 3 of the following (Lentine 2012):

    - Age > 60
    - Smoking
    - Hypertension
    - Dyslipidemia
    - Left ventricular hypertrophy
    - > 1 year on dialysis (for renal transplant patients)
    - Diabetes mellitus
    - Prior cardiovascular disease

- When the above risk calculators prove inadequate, and cardiac risk could be ≥ 1%, the American College of Surgeons NSQIP Cardiac Risk Calculator can be used as a less validated alternative. It is available at http://www.surgicalriskcalculator.com/miorcardiacarrest, with an application download required.

## POST CARDIAC TRANSPLANTATION

Dobutamine SE recommended, not exercise SE
(Gustafsson 2016)

- During the first five years post cardiac transplantation, patients with glomerular filtration rates less than 40 mL/min/1.73 body surface area (BSA), or who otherwise should not undergo annual invasive coronary arteriography, are appropriate for annual SE.
- After the first five years post cardiac transplantation:

  - Patients considered at low risk for transplant vasculopathy (i.e., with normal invasive coronary arteriography) can have annual SE.

  - Patients with transplant coronary vasculopathy can have annual SE, if the risk of annual invasive coronary arteriography is not acceptable (i.e. high risk of contrast nephropathy).

## ADDITIONAL INFORMATION

(Fihn 2012; Wolk 2013; Montalescot 2013)

### I. Scenarios that support MPI over SE

(Henzlova 2016; Askew 2018)

I. Poor Quality Echo Image
- Obesity with body mass index (BMI) over 40 or poor acoustic imaging window

II. Inability to Exercise
- Physical infirmities precluding a reasonable ability to exercise for at least 3 full minutes of Bruce protocol
- The patient has limited functional capacity (< 4 metabolic equivalents) **such as one** of the following:
    i. Cannot take care of their activities of daily living (ADLs) or ambulate
    ii. Cannot walk 2 blocks on level ground
    iii. Cannot climb 1 flight of stairs
    iv. Cannot vacuum, dust, do dishes, sweep, or carry a small grocery bag

- Patients who cannot walk up a single flight of stairs at even a slow pace or perform ADLs based upon documented limitations

III. Comorbidity Related
- Prior cardiac surgery (coronary artery bypass graft or valvular), CHF with left ventricular ejection fraction ≤ 40%
- Severe chronic obstructive pulmonary disease with pulmonary function test (PFT) documentation, severe shortness of breath on minimal exertion, or requirement of home oxygen during the day
- Poorly controlled hypertension, with systolic BP > 180 or Diastolic BP > 120
- Medical instability or serious acute illness, where maximal exercise is not recommended or appropriate (e.g. acute myocarditis or pericarditis, active infective endocarditis, acute aortic dissection, etc.)
- Resting wall motion abnormalities that would make exercise SE interpretation difficult, which includes left bundle branch block
- More than moderate valvular heart disease, when coronary data, not valvular hemodynamics, are required

IV. ECG Related Uninterpretable Wall Motion
- Pacemaker or ICD
- Poorly controlled atrial fibrillation/ectopy
- Frequent ectopy, irregular rhythm
- Ventricular pre-excitation (e.g. Wolff Parkinson White)
- Complete LBBB (SE doable, but more difficult to interpret)

V. Risk Related
   a. High pretest probability in suspected CAD
   b. Intermediate or high global risk in patients requiring type IC antiarrhythmic drugs
   c. Patients with prior coronary revascularization
   d. Arrhythmia risk with exercise and provocation of arrhythmia not required for test
   e. LVEF ≤ 40%

## II. ECG Stress Test Alone versus Stress Testing with Imaging

Prominent scenarios suitable for an ECG stress test WITHOUT imaging (i.e. exercise treadmill ECG test) are inferred from the guidelines presented above, often (but not always) requiring that the patient can exercise for at least 3 minutes of Bruce protocol with achievement of near maximal heart rate AND has an interpretable ECG for ischemia during exercise (Wolk 2013):

- The (symptomatic) low or intermediate pretest probability patient who is able to exercise and has an interpretable ECG
- The (asymptomatic) high global risk patient who is able to exercise and has an interpretable ECG
- The patient who is under evaluation for exercise induced arrhythmia (or long QT interval evaluation when the resting QTc is normal), and coronary artery disease is not suspected (Al-Khatib 2017)
- The patient who requires an entrance stress test ECG for a cardiac rehab program or for an exercise prescription.

**Duke Exercise ECG Treadmill Score** calculates risk from ECG treadmill alone:

- The equation for calculating the Duke treadmill score (DTS) is: DTS = exercise time in minutes - (5 x ST deviation in mm or 0.1 mV increments) - (4 x exercise angina score), with angina score being 0 = none, 1 = non-limiting, and 2 = exercise-limiting.

- The score typically ranges from -25 to +15. These values correspond to low-risk (with a score of ≥ +5), intermediate risk (with scores ranging from - 10 to + 4), and high-risk (with a score of ≤ -11) categories.

An uninterpretable baseline ECG includes (Fihn 2012):

- Abnormalities of ST segment depression of 0.1 mV (1 mm with conventional calibration) or more
- Ischemic looking T wave inversions of at least 0.25 mV (2.5 mm with conventional calibration)
- ECG findings of probable or definite LVH, WPW, a ventricular paced rhythm, or left bundle branch block
- Digitalis use or hypokalemia
- Resting HR under 50 bpm on a beta blocker and an anticipated suboptimal workload (e.g. rate-pressure product less than 20-25K) could render inconclusive result
- Prior false positive stress ECG

## III. Global Risk of Cardiovascular Disease

**Global risk** of CAD is defined as the probability of manifesting cardiovascular disease over the next 10 years and refers to **asymptomatic** patients without known cardiovascular disease. It should be determined using one of the risk calculators below. A high risk is considered greater than a 20% risk of a cardiovascular event over the ensuing 10 years. High global risk by itself generally lacks scientific support as an indication for stress imaging (Douglas 2018). There are rare exemptions, such as patients requiring a I-C antiarrhythmic drug, who might require coronary risk stratification prior to initiation of the drug, when global risk is moderate or high.

- **CAD Risk—Low**
  10-year absolute coronary or cardiovascular risk less than 10%.
- **CAD Risk—Moderate**
  10-year absolute coronary or cardiovascular risk between 10% and 20%.
- **CAD Risk—High**
  10-year absolute coronary or cardiovascular risk of greater than 20%.

**Links to Global Cardiovascular Risk Calculators***

*Patients who have already manifested cardiovascular disease are already at high global risk and are not applicable to the calculators.

(D'Agostino 2008; Ridker 2007; McClelland 2015; Goff 2014)

| Risk Calculator | Link to Online Calculator |
|---|---|
| Framingham Cardiovascular Risk | https://reference.medscape.com/calculator/framingham-cardiovascular-disease-risk |
| Reynolds Risk Score<br>Can use if no diabetes<br>Unique for use of family history | http://www.reynoldsriskscore.org/ |
| Pooled Cohort Equation | http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx?example |
| ACC/AHA Risk Calculator | http://tools.acc.org/ASCVD-Risk-Estimator/ |
| MESA Risk Calculator<br>With addition of Coronary Artery Calcium Score, for CAD-only risk | https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx |

## IV. Definitions of Coronary Artery Disease

(Fihn 2012; Montalescot 2013; Patel 2017; Mintz 2016 Tobis 2007)

1. Percentage stenosis refers to the reduction in diameter stenosis when angiography is the method and refers to cross sectional narrowing when IVUS (intravascular ultrasound) is the method of determination.
2. Coronary artery calcification is a marker of risk, as measured by Agatston score on coronary artery calcium imaging. It is not a diagnostic tool so much as it is a **risk stratification** tool. Its incorporation into Global Risk can be achieved by using the MESA risk calculator.
3. Stenoses ≥ 50% are considered obstructive coronary artery disease (also referred to as clinically significant), while stenoses ≤ 50% are considered nonobstructive coronary artery disease (Gerber 2018).
4. Ischemia-producing disease (also called hemodynamically or functionally significant disease, for which revascularization might be appropriate) generally implies at least one of the following:
    i. Suggested by percentage diameter stenosis ≥ 70% by angiography; borderline lesions are 40-70% (Fihn 2012, Tobis 2007)
    ii. For a left main artery, suggested by a percentage stenosis ≥ 50% or minimum lumen cross sectional area on IVUS ≤ 6 square mm (Fihn 2012, Mintz 2016)
    iii. FFR (fractional flow reserve) ≤ 0.80 for a major vessel (Mintz 2016)
    iv. Demonstrable ischemic findings on stress testing (ECG or stress imaging), that are at least mild in degree
5. A major vessel is a coronary vessel that would typically be substantial enough for revascularization, if indicated. Lesser forms of coronary artery disease would be labeled as "limited" and not major (i.e. A 50% lesion in a tiny septal or modest size mid PDA would be limited obstructive coronary artery disease.)
6. Microvascular ischemic coronary artery disease, as might be described by a normal FFR (fractional flow reserve) above 0.80 with a reduced CFR (coronary flow reserve less than 2.5), has not otherwise been addressed in this manuscript, because it is very rarely an issue in compliance determinations. However, it would constitute a form of ischemic heart disease.
7. FFR (fractional flow reserve) is the distal to proximal pressure ratio across a coronary lesion during maximal hyperemia induced by either intravenous or intracoronary adenosine. Less than or equal to 0.80 is considered a significant reduction in coronary flow. Newer iterations such as iFR (instantaneous wave free ratio) might supersede basic FFR technology in the near future.
8. New technology is evolving that estimates FFR from CCTA images. This is covered under the separate NIA Guideline for FFR-CT.

## V. Anginal Equivalent

Development of an anginal equivalent (e.g. shortness of breath, fatigue, or weakness) either with or without prior coronary revascularization should be based upon the documentation of reasons to suspect that symptoms other than chest discomfort are not due to other organ systems (e.g. dyspnea due to lung disease, fatigue due to anemia, etc.), by presentation of clinical data such as respiratory rate, oximetry, lung exam, etc. (as well as d-dimer, chest CT(A), and/or PFTs, when appropriate), and then incorporated into the evaluation of coronary artery disease as would chest discomfort. Syncope per se is not an anginal equivalent (Moya 2009, Shen 2017, Fihn 2012).

## VI. Peripheral Arterial Disease/Cerebrovascular Disease

Arterial vascular disease below the renal arteries is generally referred to as peripheral arterial disease, when the ankle brachial index is < 0.9 or there is at least 50% vessel diameter narrowing on ultrasound or angiography (Hussain 2018).

Cerebrovascular disease generally refers to a history of TIA or stroke, or cerebrovascular lesions that put the patient at considerable risk for stroke (Caplan 2018).

There is no evidence to demonstrate that screening all patients with peripheral arterial disease for asymptomatic atherosclerosis in other arterial beds improves clinical outcome. Intensive treatment of risk factors through guideline directed medical therapy is the principal method for preventing adverse cardiovascular ischemic events secondary to atherosclerotic disease in other arterial beds (Gerhard-Herman 2016).

## Abbreviations

| | |
|---|---|
| AAD | antiarrhythmic drug |
| ADLs | activities of daily living |
| BSA | body surface area in square meters |
| CAD | coronary artery disease |
| ECG | electrocardiogram |
| FFR | fractional flow reserve |
| LBBB | left bundle-branch block |
| LVEF | left ventricular ejection fraction |
| LVH | left ventricular hypertrophy |
| MI | myocardial infarction |
| MET | estimated metabolic equivalent of exercise |
| MPI | myocardial perfusion imaging |
| PFT | pulmonary function test |
| PVCs | premature ventricular contractions |
| SE | stress echocardiography |
| VT | Ventricular tachycardia |
| VF | Ventricular fibrillation |
| WPW | Wolf Parkinson White |

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