INTRODUCTION

- Myocardial perfusion imaging (MPI) with either exercise stress or pharmacologic coronary vasodilation is the subject of this guideline.

- Since MPI and stress echocardiography (SE) provide similar information, with SE performed at lower cost and without radiation, this guideline requires diversion from MPI to SE when feasible (Askew 2018; Douglas 2011; Metz 2007; Einstein 2012; Fazel 2011; Fleischmann 1998; Garber 1999; Heijenbrok-Kal 2007; Hirshfeld 2018; Marwick 2003; Pellikka 2007; Schinkel 2003; Scott-Moncrieff 2011; Sicari 2008; Sicari 2017; Yao 2003; Zhang 2014).

- However, this diversion is limited due to practical issues and physician preferences that endorse MPI without diversion in any of the following cases (see details in Scenarios that support MPI over SE in the Additional Information section) (Henzlova 2016; Askew 2018; Wolk 2013):
  - Poor quality echo images
  - Inability to exercise
  - Specific comorbidities
  - Electrocardiography (ECG)-related wall motion abnormalities
  - Elevated coronary risk

- Coronary artery disease (CAD) stenosis ≥ 50% is considered clinically significant or obstructive CAD. CAD and ischemic heart disease (IHD) mean the same thing. 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, 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, for whom we estimate the pretest probability that their chest-related symptoms are due to clinically significant (≥ 50%) CAD (below):

The 3 Types of Chest Pain or Discomfort

- **Typical Angina (Definite)** is defined as including all 3 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):

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Gender</th>
<th>Typical/Definite Angina Pectoris</th>
<th>Atypical/Probable Angina Pectoris</th>
<th>Nonanginal Chest Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=39</td>
<td>Men</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>Intermediate</td>
<td>Very low</td>
<td>Very low</td>
</tr>
<tr>
<td>40–49</td>
<td>Men</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>Intermediate</td>
<td>Low</td>
<td>Very low</td>
</tr>
<tr>
<td>50–59</td>
<td>Men</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td>&gt;=60</td>
<td>Men</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>

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

**INDICATIONS for MPI**
(Fihn 2012; Wolk 2013; Montalescot 2013; Hendel 2009)

**Suspected CAD**
(Without known history of CAD)

1. Symptomatic patients without known CAD
• Low pretest probability who are unable to exercise
• Intermediate pretest probability
• High pretest probability (SE diversion not required) (Hachamovitch 2004)
• 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 (SE diversion not required if wall motion abnormality present)
• Previously unevaluated pathologic Q waves or wall motion abnormality (evidence of prior myocardial infarction) (SE diversion not required)
• Unevaluated complete left bundle branch block (SE diversion not required)
• 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 (diversion not required for high pretest probability)
• Exercise stress ECG with intermediate Duke treadmill score
• Inconclusive/borderline coronary computed tomography angiography (CCTA) (e.g. 40-70% lesions)
• An indeterminate (equivocal, borderline, or discordant) evaluation by prior stress imaging (SE or CMR) within the past 2 years, for whom a noninvasive approach is preferable to proceeding to invasive coronary arteriography (e.g. unclear symptoms, ECG and imaging discordant, etc., but patient has severe contrast allergy, CKD, etc.)

Known Major Vessel CAD
(SE diversion not required due to increased risk in this category) (Patel 2017)

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

• Follow up MPI at 2 year intervals is approvable, if it will affect consideration of coronary revascularization (initial or additional), in patients with one of the following:
  o History of silent ischemia with severe unrevascularized CAD, and revascularization could be feasible (Deedwania 2018)
  o History of severe unrevascularized major multivessel CAD, and revascularization could be feasible
  o Ejection fraction <= 40% with severe unrevascularized CAD, 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

• Resting MPI, is appropriate for patients with reduced LVEF $\leq 50\%$ requiring myocardial viability assessment to assist with decisions regarding coronary revascularization (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 HF, 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 heart failure, especially with symptoms or signs of ischemia AND without invasive coronary angiography immediately planned (SE diversion not required) (Yancy 2013; Patel 2013; Fihn 2012)

• Newly found wall motion abnormality (SE diversion not required) (Colucci 2018)

• Ventricular arrhythmias (SE diversion not required.)
  o Sustained ventricular tachycardia (VT) $>100$ bpm, ventricular fibrillation (VF), or exercise induced VT, when invasive coronary arteriography is not the initially required test (Al-Khatib 2018, in press)
  o Nonsustained VT, multiple episodes, each $\geq 3$ beats at $\geq 100$ 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)
  o Frequent PVCs $\geq 30$/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; Al-Khatib 2017)

• Prior to Class IC antiarrhythmic drug initiation in intermediate and high global risk patients (SE diversion not required) (see global risk calculators in Additional Information section) (Kumar 2018)

• Assessment of hemodynamic significance of one of the following documented conditions (SE diversion not required) (Anagnostopoulos 2004):
  o Anomalous coronary arteries (Grani 2017)
  o Muscle bridging of coronary artery (perform with exercise stress) (Sorajja 2018)
  o Coronary aneurysms in Kawasaki’s disease (Newburger 2018)

**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 MPI, based upon cardiac risk ≥ 1%, if all 4 criteria are met:
  o Surgery is supra-inguinal vascular, intrathoracic, or intra-abdominal.

  AND

  o The patient has at least one of the additional cardiac complication risk factors:
    - Ischemic Heart Disease
    - History of stroke or TIA
    - History of congestive heart failure or ejection fraction <=35%
    - Insulin-requiring diabetes mellitus
    - Creatinine ≥ 2.0 mg/dl

  AND

  o The patient has limited functional capacity (< 4 METS), such as one of the following:
    - Cannot take care of their activities of daily living (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

  o 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 (mainly kidney or liver) transplantation is an indication for preoperative MPI, if there has not been a conclusive stress evaluation within the past year and one of the following: (SE diversion not required) (Lentine 2012).

  o The patient has limited functional capacity (< 4 METS), 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

    (Wolk 2013)

  OR

  o In a patient with ≥ 3 of the following:
    - Age > 60
    - Smoking
    - Hypertension
    - Dyslipidemia
    - Left ventricular hypertrophy
• > 1 year on dialysis (for renal transplant patients)
• Diabetes mellitus
• Prior cardiovascular disease
(Lentine 2012)

• 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, available at http://www.surgicalriskcalculator.com/miorcardiacarrest, with an application download required.

**Post Cardiac Transplantation**
(SE diversion not required, since only dobutamine SE is helpful for this group)
(Gustafsson 2016)

• During the first five years post cardiac transplantation, patients with glomerular filtration rates less than 40 mL/min/1.73 BSA, or who otherwise should not undergo annual invasive coronary arteriography

• After the first five years post cardiac transplantation:
  o Patients considered at low risk for transplant vasculopathy (i.e. with normal invasive coronary arteriography)
  o Patients with transplant coronary vasculopathy, if the risk of annual invasive coronary arteriography is not acceptable (e.g. high risk of contrast nephropathy).

**ADDITIONAL INFORMATION**
(Fihn 2012; Wolk 2013; Montalescot 2013)

**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 METS) such as one of the following:
    i. Cannot take care of their 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 small grocery bag

  • Patients who cannot walk up a single flight of stairs at even a slow pace or even 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 (COPD) 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)
• 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 PVCs
• Ventricular pre-excitation (e.g. Wolff Parkinson White)
• Complete LBBB (SE doable, but more difficult to interpret)

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

Unsuitability for MPI
(Henzlova 2016; Chareonthaitawee 2018)

• Patient cannot be adequately positioned or imaged with MPI due to comorbidity, body habitus
• Intolerance to required coronary vasodilators, pulmonary or allergic, either documented or anticipated.
• Uncontrolled hypertension, systolic > 200 or diastolic > 110
• Dipyridamole within < 48 hours
• Relative unsuitability due to:
  o Hypotension or marked bradyarrhythmia
  o Interfering medications: Theophylline/aminophylline, caffeine, or theobromine within the past 12-24 hours
  o Severe aortic stenosis
  o Seizure disorder with potential for adenosine provocation

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 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

**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)

<table>
<thead>
<tr>
<th>Risk Calculator</th>
<th>Link to Online Calculator</th>
</tr>
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<tbody>
<tr>
<td>Reynolds Risk Score</td>
<td><a href="http://www.reynoldsriskscore.org/">http://www.reynoldsriskscore.org/</a></td>
</tr>
<tr>
<td>Pooled Cohort Equation</td>
<td><a href="http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx?example">http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx?example</a></td>
</tr>
<tr>
<td>MESA Risk Calculator With addition of Coronary Artery</td>
<td><a href="https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx">https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx</a></td>
</tr>
</tbody>
</table>

**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 intravascular ultrasound (IVUS) 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 $\geq 50\%$ are considered obstructive coronary artery disease (also referred to as clinically significant), while stenoses $\leq 50\%$ 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 $\geq 70\%$ by angiography; borderline lesions are $40-70\%$ (Fihn 2012; Tobis 2007)
   ii. For a left main artery, suggested by a percentage stenosis $\geq 50\%$ or minimum lumen cross sectional area on IVUS $\leq 6$ square mm (Fihn 2012; Mintz 2016)
   iii. FFR (fractional flow reserve) $\leq 0.80$ 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 would be a coronary vessel that would typically be substantial enough for revascularization, if it were 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.

**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), 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).

**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 transient ischemic attack (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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAD</td>
<td>Antiarrhythmic drug</td>
</tr>
<tr>
<td>ADLs</td>
<td>Activities of daily living</td>
</tr>
<tr>
<td>BSA</td>
<td>Body surface area in square meters</td>
</tr>
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<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>FFR</td>
<td>Fractional flow reserve</td>
</tr>
<tr>
<td>LBBB</td>
<td>Left bundle-branch block</td>
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<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
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<td>LVH</td>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>MET</td>
<td>Estimated metabolic equivalent of exercise</td>
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<tr>
<td>MPI</td>
<td>Myocardial perfusion imaging</td>
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<tr>
<td>PFT</td>
<td>Pulmonary function test</td>
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<tr>
<td>PVCs</td>
<td>Premature ventricular contractions</td>
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<tr>
<td>SE</td>
<td>Stress echocardiography</td>
</tr>
<tr>
<td>VT</td>
<td>Ventricular tachycardia</td>
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<tr>
<td>VF</td>
<td>Ventricular fibrillation</td>
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<tr>
<td>WPW</td>
<td>Wolf Parkinson White</td>
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Reviewed / Approved by Caroline Carney, MD, Chief Medical Officer