PROVIDER LED ENTITY

Coronary Artery Disease AUC: 2022 Update

09/27/2022

Appropriateness of advanced imaging procedures* in patients with coronary artery disease (suspected or diagnosed):

*including CT coronary artery calcium (CAC), coronary CT angiography (CCTA), stress cardiac MRI (CMR), and stress radionuclide myocardial perfusion imaging (PET or SPECT) – stress echocardiography, exercise ECG, and invasive coronary angiography also included

Abbreviation list:

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACR	American College of Radiology
AHA	American Heart Association
AUC	Appropriate Use Criteria
CABG	Coronary artery bypass grafting
CAC	Coronary artery calcium
CAD	Coronary artery disease
CCTA	Coronary CT angiography
CHD	Coronary heart disease
CI	Confidence interval
CMR	Cardiac MRI
CT	Computed tomography
CVD	Cardiovascular disease
EACI	European Association of Cardiovascular Imaging
ECG	Electrocardiography
ESC	European Society of Cardiology
FFR	Fractional flow reserve
FT	Functional testing
ICA	Invasive coronary angiogram
IHD	Ischemic heart disease
MPI	Myocardial perfusion imaging
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NPV	Negative predictive value
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PLE	Provider Led Entity
PPV	Positive predictive value
PTP	Pre-test probability
PVC	Premature ventricular contraction
RNI	Radionuclide imaging
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SPECT	Single-photon emission computed tomography

Appropriate Use Criteria: How to Use this Document

The CDI Quality Institute follows the recommendation framework defined by the Appraisal of Guidelines for Research & Evaluation (AGREE II), AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) and a modified version of the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) to evaluate the strength of recommendations concerning advanced imaging. Considerations used to determine a recommendation are listed below.

Primary recommendation (green): A strong recommendation for initial imaging for this presentation; there is confidence that the desirable effects of imaging outweigh its undesirable effects.

Alternative recommendation (yellow): A conditional recommendation for imaging; the desirable effects of imaging likely outweigh its undesirable effects, although some uncertainty may exist. The individual patient's circumstances, preferences, and values should be considered on a case-by-case basis. This may include: contraindication to the primary recommendation, specific clinical circumstances that require use of the alternative recommendation, or the primary recommendation has results that are inconclusive or incongruent with the patient's clinical diagnosis.

Recommendation against imaging (red): The undesirable effects of imaging outweigh any desirable effects. Additionally, the recommendation may be impractical or not feasible in the targeted population and/or practice setting(s).

Coronary Artery Disease AUC Summary:

In patients with suspected coronary artery disease (CAD) who are **asymptomatic**, an initial assessment of global risk is recommended. If a risk-based treatment decision is uncertain, further assessment may be considered to inform decision making. CT coronary artery calcium (CAC) is a sensitive technique to detect and quantify coronary calcium, a marker of atherosclerosis. Imaging with stress modalities or coronary CT angiography (CCTA) can also be useful for select patients, based on the clinical likelihood of CAD and other specific risk factors.

When **symptoms** are present and there is suspicion to warrant cardiac evaluation, assessment of a patient's pretest probability (PTP) of CAD is indicated using a validated risk assessment tool. Information concerning risk factors, resting ECG findings, and/or coronary calcification scores can improve risk assessment. Diagnostic testing in those with a PTP < 5% should only be performed for compelling reasons. When the PTP is 5-15%, factors such as patient preference, resource availability, and clinical judgment are important considerations for testing. Anatomic (e.g., CCTA) or functional/stress imaging is generally appropriate whenever the patient has a high risk of CAD (> 15%) or if specific conditions are present (e.g., confirmed heart failure, ventricular tachycardia, frequent PVCs). CCTA has a high negative predictive value and superior diagnostic accuracy compared to other tests. It is preferred in patients with a low-to-intermediate range of CAD probability, no previous diagnosis of CAD, and when good image quality is likely. However, recommendations generally require 64-slice CT as a minimum threshold for use, which may limit accessibility. Functional imaging can demonstrate myocardial perfusion or contraction abnormalities. It typically has better rule-in power and may be preferred for those at the higher end of the range of clinical likelihood. The choice of anatomic vs. functional testing and the choice of a specific modality may ultimately dependent on local expertise and experience, patient preferences and characteristics, and any contraindications to imaging (e.g., inability to exercise, bronchospastic disease, claustrophobia, allergies to contrast, presence of metal implants).

Follow-up or sequential testing can be useful for asymptomatic patients with an intermediate-to-high global CAD risk and when previous testing was performed > 2 years prior. It is also generally appropriate when a previous test was equivocal or abnormal, and/or if there are new or worsening symptoms. In patients with a history of **revascularization**, additional testing can be used if there are new symptoms or if it has been determined that prior revascularization was incomplete. In select cases, further testing following left main coronary stenting, or at > 5-year intervals after coronary artery bypass graft (CABG) surgery or > 2-year intervals after percutaneous coronary intervention (PCI) may be appropriate.

Definitions & assumptions:

- **"Patient unable to exercise":** Patient inability to exercise is assumed to be due to non-cardiovascular issues such as arthritis, and not cardiovascular issues that would inherently increase a patient's risk (Wolk et al [*ACCF* et al] 2014).
- **"Baseline ECG abnormalities that prevent interpretation of the ST-segment changes during stress":** This term includes ECGs with resting abnormalities, such as ST-segment depression (≥ 0.10 mV), left bundle branch block (LBBB), Wolff-Parkinson-White syndrome, digoxin use, or a ventricular paced rhythm that would make the exercise ECG difficult to interpret (Wolk et al [*ACCF* et al] 2014; Knuuti et al [*ESC*] 2020; PLE expert panel consensus opinion).
- **CT coronary artery calcium (CAC):** Cardiac CT for quantitative evaluation of coronary artery calcification using either electron beam CT or multi-detector CT.
- **Functional imaging**: Functional tests for CAD detect myocardial ischemia through ECG changes, wall motion abnormalities (stress CMR or stress echocardiography), or perfusion changes (SPECT, PET, myocardial contrast echocardiography, or contrast CMR) (Knuuti et al [*ESC*] 2020). The mode of stress testing is preferred to be exercise for those able to do so (Gulati et al [*AHA* et al] 2021). For those unable to exercise or with ECG abnormalities that prevent interpretation of the ST-segment changes during stress, it is assumed that pharmacological stress is performed (Verberne et al 2015; Henzlova et al 2016). For CMR, it is assumed that vasodilator stress perfusion is used (Wolk et al [*ACCF* et al] 2014).
    - **PET imaging**: Commonly used radiopharmaceuticals for PET imaging include ammonia (13NH3), rubidium chloride (82 RbCl) and 2-(18F) FLURO-2DEOXY-D-GLUCOSE (FDG).
    - **SPECT imaging**: Commonly used radiopharmaceuticals for SPECT imaging include Thallium-201 Chloride, Technetium-99m Sestamibi, and Technetium-99m Tetrofosmin.
- **Anatomical imaging**: Non-invasive anatomic testing for CAD directly visualizes the coronary artery lumen and wall using multidectector CT (usually 64-slice or higher) and intravenous contrast agent. It provides high accuracy for the detection of obstructive coronary stenosis similar to that of catheterization, as well as plaque analysis and morphological information (Knuuti et al [*ESC*] 2020). Intermediate levels of stenosis (50-80%) may not be functionally significant, however, and functional testing is typically recommended for further evaluation in these patients.
    - **CT derived fractional flow reserve (FFR-CT):** While not a stand-alone service, the ability to measure FFR by CT has the potential to expand the clinical application of CCTA in clinically stable symptomatic CAD patients where available (e.g., Norgaard et al 2014; Driessen et al 2019). It should not be used in those with contraindications to CCTA, including extensive coronary calcification and/or arrhythmias, or in post-CABG patients (*CMS Local Coverage Determination* 2021) Thus, recommendations throughout this document for CCTA should assume "with or without fractional flow reserve assessed by CT (FFR-CT)".

Evaluation for coronary artery disease in asymptomatic patients without known coronary artery disease

Low global CAD risk*:

- **Red – Stress ECG**
- **Red – CT coronary artery calcium**
- **Red – Stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Red – Stress echocardiography**
- **Red – Stress cardiac MRI**
- **Red – Coronary CT angiography**
- **Red – Invasive coronary angiography**

Intermediate global CAD risk:

- **Green – CT coronary artery calcium**
- **Yellow – Stress ECG**
- **Red – Stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Red – Stress echocardiography**
- **Red – Stress cardiac MRI**
- **Red – Coronary CT angiography**
- **Red – Invasive coronary angiography**

High global CAD risk:**

- **Green – Stress ECG**
- **Yellow – Coronary CT angiography**
- **Yellow – Stress echocardiography**
- **Yellow – Stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Yellow – Stress cardiac MRI**
- **Yellow – CT coronary artery calcium*****
- **Red – Invasive coronary angiography**

*Asymptomatic patients considered to be at low risk of CAD do not typically require advanced imaging (Ghoshhajra et al [*ACR*] 2021; Greenland et al [*ACCF/AHA*] 2010: class III recommendation (no benefit), level B evidence; Greenland et al [*ACCF/AHA*] 2007).

**In addition to those categorized as "high risk" on a global risk score, also includes patients with previous CAC score $\geq$ 400, diabetes, family history of premature CVD or hyperlipidemia, chronic kidney disease, and/or known atherosclerotic vascular disease (Greenland et al [*ACCF/AHA*] 2007; Wolk et al [*ACCF* et al] 2014; Knuuti et al [*ESC*] 2020; Schindler et al [*SNMMI* et al] 2020).

***If CAC score has not been previously assessed and the patient is not already a candidate for intensive risk reducing therapy.

Level of Evidence: CT coronary artery calcium: moderate; stress radionuclide myocardial perfusion imaging: moderate; stress cardiac MRI: low; coronary CT angiography: low; stress echocardiography: moderate

Notes concerning applicability and/or patient preferences: It is recommended to take account for locally available technology and expertise, the person and their preferences, and any contraindications (e.g., disabilities, frailty, limited ability to exercise, claustrophobia, metal implants, allergy to contrast) when deciding on the imaging method (*NICE* 2016). If more than one modality falls into the same appropriate use category, it is assumed that physician judgment and available local expertise are used to determine the correct test for an individual patient (Wolk et al [*ACCF* et al 2014). The patient should be engaged in a process of shared decision-making before determining the final choice of the cardiac test modality (Gulati et al [*AHA* et al] 2021).

In the recommendations, 64-slice CT is generally required as a minimum threshold for coronary CT angiography, which may limit accessibility.

Guideline and PLE expert panel consensus opinion summary:
The identification of those patients who may benefit from early intervention prior to development of symptoms has been shown to reduce mortality and morbidity (Ghoshhajra et al [*ACR*] 2021). In an effort to lower the high burden of coronary deaths in asymptomatic adults, numerous measurements of risk factors and risk markers, as well as stress tests, are often performed as screening investigations, particularly in those patients with high risk (Knuuti et al [*ESC*] 2020).

Global risk assessment
Assessment of risk is recommended in every patient being evaluated for suspected CAD (Greenland et al [*ACCF/AHA*] 2010; Knuuti et al [*ESC*] 2020). Risk assessment in asymptomatic individuals stratifies patients based on a 10-year risk of cardiovascular mortality (Wolk et al [*ACCF* et al] 2014). Several traditional risk factors are associated with higher risk for CVD events: older age, male sex, high blood pressure, current smoking, abnormal cholesterol levels, diabetes, obesity, and physical inactivity (*USPSTF* 2018a). Global risk scores (*Framingham Risk Score, Reynolds Risk Score*, *Systematic Coronary Risk Evaluation* [*SCORE*], *ASCVD risk calculator*, etc.), have used these risk factors to categorize patients in broad terms as “low risk”, “intermediate risk”, and “high risk” (Greenland et al [*ACCF/AHA*] 2010; *USPSTF* 2018a). In general, there is agreement that persons with a 10-year CVD event risk > 20% are high risk (Greenland et al [*ACCF/AHA*] 2010; Wolk et al [ACCF et al] 2014; USPSTF 2018a; Grundy et al [*AHA* et al] 2019). The threshold for dividing low- from intermediate-risk is not uniform, however, with scores proposing cutoff values anywhere from <5% to < 10% risk over 10 years (Greenland et al [*ACCF/AHA*] 2010; Wolk et al [*ACCF* et al] 2014; USPSTF 2018a; Grundy et al [*AHA* et al] 2019; Ghoshhajra et al [*ACR*] 2021). In general, these risk factors are strong markers for disease at a population level but are poor risk discriminators for CAD on an individual level (Greenland et al [*ACCF/AHA*] 2010; Ghoshhajra et al [*ACR*] 2021).

Clinical judgment can be used to modify assessments of global risk for cardiovascular disease. Diabetes, chronic kidney disease, and known atherosclerotic vascular disease (e.g., peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease, stroke, or TIA) may indicate a high risk for CAD and preclude further evaluation of risk (Greenland et al [*ACCF/AHA*] 2007; Wolk et al [*ACCF* et al] 2014; Knuuti et al [*ESC*] 2020). A family history of premature CAD (< 55 years of age in men or < 65 years of age in women) is also of significant consideration in the assessment of risk (Wolk et al [*ACCF* et al] 2014; Greenland et al [*ACCF/AHA*] 2010), and these subjects should be screened for familial hypercholesterolemia (Knuuti et al [*ESC*] 2020: class I, level B evidence). Patients with chronic inflammatory diseases and those undergoing treatment for cancer may also need additional evaluation and counseling (Knuuti et al [*ESC*] 2020).

If, after quantitative risk assessment, a risk-based treatment decision is uncertain, a resting ECG or echocardiogram may be appropriate (Greenland et al [*ACCF/AHA*] 2010: level B/C evidence; Knuuti et al [*ESC*] 2020). Assessment of CT CAC score, along with high-sensitivity C-reactive protein (hs-CRP), carotid artery ultrasound, and/or ankle-brachial index (ABI), may also be considered in select patients to further inform treatment decision making (Goff et al [*ACC/AHA*] 2014: class IIb recommendation, level B evidence; Greenland et al [*ACCF/AHA*] 2010: class IIa, level B evidence; Knuuti et al [*ESC*] 2020: class IIb, level B evidence; Grundy et al [*AHA* et al] 2019). The *US Preventive Services Task Force* notes, however, that the current evidence is insufficient to assess the balance of benefits and harms of routinely adding these nontraditional risk factors to cardiovascular disease risk assessment (*USPSTF* 2018a).

Stress ECG
In those who are able to exercise, an exercise ECG is considered appropriate for cardiovascular risk assessment in asymptomatic subjects with high global risk, and may be considered in intermediate-risk adults (Greenland et al [*ACCF* et al] 2010: class IIb, level B evidence; Wolk et al [*ACCF* et al] 2014). An exercise ECG is rarely appropriate for asymptomatic patients at low risk, and of no diagnostic value in patients with ECG abnormalities that prevent interpretation of the ST-segment changes during stress (including LBBB, paced rhythm, Wolff-Parkinson-White syndrome, ≥ 0.1 mV ST-segment depression on resting ECG, or those treated with digitalis) (Knuuti et al [*ESC*] 2020; Wolk et al [*ACCF* et al] 2014; (*USPSTF* 2018b: grade D recommendation; PLE expert panel consensus opinion).

CT coronary artery calcium (CAC)
Studies have shown that CT CAC score can predict future mortality and major cardiac events, and aids in improving risk-stratification beyond conventional risk factor-based scores alone (Ghoshhajra et al [*ACR*] 2021). Measurement of coronary artery calcium with noncontrast CT is primarily helpful for use in asymptomatic patients of intermediate global risk (Wolk et al [*ACCF* et al] 2014; Ghoshhajra et al [*ACR*] 2021; Greenland et al [*ACCF/AHA*] 2007; Greenland et al [*ACCF/AHA*] 2010: class IIa recommendation, level B evidence; PLE expert panel consensus opinion). The presence of an elevated CAC score (≥ 400) increases the likelihood of obstructive CAD and risk of events, especially in patients with multiple coronary risk factors (Schindler et al [*SNMMI* et al] 2020). CAC measurement is not always advised in asymptomatic patients with high CHD risk, as they may already be candidates for intensive risk reducing therapies (Greenland et al [*ACCF* et al] 2007). CT CAC measurement is not indicated in patients considered to be at low risk for CHD (Ghoshhajra et al [*ACR*] 2021; Greenland et al [*ACCF/AHA*] 2010: class III recommendation (no benefit), level B evidence; Greenland et al [*ACCF/AHA*] 2007). In addition, CT scanning should generally not be done in men < 40 and women < 50 due to the very low prevalence of detectable calcium in these age groups (Greenland et al [*ACCF/AHA*] 2010).

Stress radionuclide myocardial perfusion imaging (**PET or SPECT**)
In asymptomatic patients with a low or intermediate pretest global CAD risk, the use of stress-rest perfusion imaging is rarely appropriate (Knuuti et al [*ESC*] 2020: class III, level C recommendation; Schindler et al [*SNMMI* et al] 2020: score 1, score 2; Greenland et al [*ACCF/AHA*] 2010: level C evidence; Wolk et al [*ACCF* et al] 2014; Ghoshhajra et al [*ACR*] 2021). In asymptomatic patients with a higher pretest global CAD risk, available data suggest a possible role for stress perfusion imaging (Greenland et al [*ACCF/AHA*] 2010. This includes those who have an uninterpretable resting ECG or are unable to exercise or have an elevated [≥ 400] CAC (Agatston) score (Schindler et al [*SNMMI* et al] 2020: score 5; Wolk et al [*ACCF* et al] 2014; Schindler et al [*SNMMI* et al] 2020: score 6; Greenland et al [*ACCF/AHA*] 2010: level C evidence; PLE expert panel consensus opinion). It also includes patients with specific risk factors (e.g., diabetes, strong family history of CHD) (Knuuti et al [*ESC*] 2020: class IIb, level C evidence;

Greenland et al [*ACCF/AHA*] 2010: level C evidence; Schindler et al [*SNMMI* et al] 2020: score 8).

Stress echocardiography
Stress echocardiography is a test predominantly used in symptomatic patients to assist in the diagnosis of obstructive CAD (Greenland et al [*ACCF/AHA*] 2010). It is typically not recommended for asymptomatic adults with low or intermediate global risk of CAD (Ghoshhajra et al [*ACR*] 2021; Greenland et al [*ACCF/AHA*] 2010; PLE expert panel consensus opinion), but may be considered for risk assessment in those with high risk (Greenland et al [*ACCF/AHA*] 2010: class III, level B evidence; Wolk et al [*ACCF* et al] 2014).

Stress cardiac MRI (CMR)
In low-risk asymptomatic adults, functional imaging for ischemia is not indicated for further diagnostic assessment (Knuuti et al [*ESC*] 2020: class III, level C recommendation). While MRI is typically not used for testing asymptomatic persons (Greenland et al [*ACCF/AHA*] 2010), the use of stress CMR may be appropriate in the detection of CAD among those with high global risk (Wolk et al [*ACCF* et al] 2014; Kuuti et al [*ESC*] 2020: class IIb, level C recommendation).

Coronary CT angiography (CCTA)
CCTA is typically not recommended for cardiovascular risk assessment in low- or intermediate-risk asymptomatic adults (Greenland et al [*ACCF/AHA*] 2010: level C evidence; Knuuti et al [*ESC*] 2020: class III, level C recommendation; Wolk et al [*ACCF* et al] 2014). In high-risk asymptomatic adults (e.g., diabetes, strong family history of CAD) or when previous risk-assessment testing suggests a high risk of CAD, it may be considered for cardiovascular risk assessment (Knuuti et al [*ESC*] 2020: class IIb, level C recommendation; Ghoshhajra et al [*ACR*] 2021; Wolk et al [*ACCF* et al] 2014).

Invasive coronary angiography
Invasive coronary angiography is not recommended to assess risk in asymptomatic patients with no evidence of ischemia on noninvasive testing (Wolk et al [*ACCF* et al] 2014).

Clinical and imaging notes:

- Risk assessment for atherosclerotic cardiovascular disease is intended to aid in determining the appropriate lifestyle changes and pharmacological interventions to reduce a patient's risk of adverse cardiovascular outcomes (e.g., myocardial infarction, stroke, cardiovascular death) (Ghoshhajra et al [*ACR*] 2021).
- A fast CT CAC study is completed within 10 to 15 min, requiring only a few seconds of scanning time (Greenland et al [*ACCF/AHA*] 2007). A CAC score predicts atherosclerotic cardiovascular disease events in a graded fashion and is independent of other risk factors, such as age, sex, and ethnicity (Grundy et al [*AHA*] 2019).
- One purpose of CAC scoring is that it can reclassify risk identification of patients who will potentially benefit from statin therapy (Grundy et al [*AHA*] 2019; Ghoshhajra et al [*ACR*] 2021). CAC scoring is especially useful in older adults to improve specificity (Grundy et al [*AHA*] 2019).

Evidence update (2016 - Present)
Moderate Level of Evidence
Bell et al (2022), in a systematic review and meta-analysis, evaluated the incremental value of CAC scans (CACS) above and beyond traditional cardiovascular risk assessment. Eligible studies were cohort studies in primary prevention populations that used a CVD risk calculator recommended by national guidelines (e.g., Framingham Risk Score) and assessed and reported incremental discrimination with CACS for

estimating risk of a future cardiovascular event. A total of 6 eligible cohort studies were identified (total n = 1,043 CVD events in 17,961 participants). The C statistic (probability that a randomly selected patient experienced an event) for the CVD risk models without CACS ranged from 0.693 to 0.80. The pooled gain in C statistic from adding CACS was 0.036 (95%CI, 0.020-0.052). Among participants classified as being at low risk by risk score and reclassified as intermediate or high risk by CACS, 85.5% (65 of 76) to 96.4% (349 of 362) did not have a CVD event during follow-up. Among participants classified as being at high risk by risk score and reclassified as being at low risk by CACS, 91.4% (202 of 221) to 99.2% (502 of 506) did not have a CVD event during follow-up. The authors conclude that CACS appear to add some further discrimination to traditional CVD risk assessment equations, but the modest gain may be outweighed by incidental findings or radiation risks. Although CACS may have a role for refining risk assessment in selected patients, which patients would benefit remains unclear.

Low Level of Evidence

Dudum et al (2019), in a multi-center retrospective cohort study of 14,169 asymptomatic individuals, sought to assess consideration of CAC scoring in low-risk individuals (< 5%) with a family history of coronary heart disease (CHD). All CAC scans (93% using electron beam tomography with remainder utilizing MDCT) were physician referred and performed in patients without history of CHD. Individuals were followed for an average of 11.6 years. The event rate for all-cause mortality was 1.2 per 1,000 person-years, 0.3 per 1,000 person-years for CVD-specific mortality, and 0.2 per 1,000 person-years for CHD-specific mortality. In multivariable Cox proportional hazard models, those with CAC > 100 had a 2.2 (95% CI 1.5–3.3) higher risk of all-cause mortality, 4.3 (95% CI 1.9–9.5) times higher risk of CVD-specific mortality, and a 10.4 (95% CI 3.2–33.7) times higher risk of CHD-specific mortality compared to individuals with CAC=0. The authors conclude that in otherwise low risk patients with family history of CHD, CAC > 100 was associated with increased risk of all-cause/CHD mortality.

Dedic et al (2016) sought to determine whether CCTA improves risk prediction beyond CAC measurement in 665 patients from two academic hospitals without symptoms of CAD, but at high risk of developing CAD. Patients were considered high risk due to presence of a markedly elevated single cardiovascular risk factor (e.g., diabetes, family history, peripheral artery disease, severe hypertension). During a median follow-up of 3.0 (range 1.3-4.1) years, adverse events occurred in 40 subjects (6.0%). By multivariate analysis adjusted for age, gender, and CAC score, obstructive CAD on CCTA (≥ 50% luminal stenosis) was a significant predictor of adverse events (hazard ratio 5.9 [CI: 1.3-26.1]). Addition of CCTA to age, gender, plus CAC score, increased the C statistic from 0.81 to 0.84 and resulted in a total net reclassification index of 0.19 (p < 0.01). The authors conclude that CCTA has incremental prognostic value and risk reclassification benefit beyond CAC score in patients without CAD symptoms but with high risk of developing CVD.

Suspected coronary artery disease: symptomatic patient, no known coronary artery disease, initial testing

Low pretest probability; interpretable ECG and patient able to exercise:

- Green – Exercise stress ECG
- Yellow – Exercise stress echocardiography
- Yellow – Coronary CT angiography
- Red – Stress radionuclide myocardial perfusion imaging (PET or SPECT)
- Red – Stress cardiac MRI
- Red – Invasive coronary angiography
- Red – CT coronary artery calcium

Low pretest probability; patient unable to exercise and/or with baseline ECG abnormalities that prevent interpretation of the ST-segment changes during stress:

- Yellow – Pharmacological stress echocardiography
- Yellow – Pharmacological stress radionuclide myocardial perfusion imaging (PET or SPECT)
- Yellow – Pharmacological stress cardiac MRI
- Yellow – Coronary CT angiography
- Red – Invasive coronary angiography
- Red – CT coronary artery calcium

Intermediate pretest probability; interpretable ECG and patient able to exercise:

- Green – Exercise stress ECG
- Green – Exercise stress radionuclide myocardial perfusion imaging (PET or SPECT)
- Green – Exercise stress echocardiography
- Green – Coronary CT angiography
- Yellow – Exercise stress cardiac MRI
- Red – Invasive coronary angiography
- Red – CT coronary artery calcium

Intermediate pretest probability; patient unable to exercise and/or with baseline ECG abnormalities that prevent interpretation of the ST-segment changes during stress:

- Green – Pharmacological stress radionuclide myocardial perfusion imaging (PET or SPECT)
- Green – Pharmacological stress echocardiography
- Green – Pharmacological stress cardiac MRI
- Green – Coronary CT angiography
- Yellow – Invasive coronary angiography
- Red – CT coronary artery calcium

<u>High</u> pretest probability; interpretable ECG <u>and</u> patient able to exercise:

- **Green – Exercise stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Green – Exercise stress echocardiography**
- **Green – Exercise stress cardiac MRI**
- **Green – Coronary CT angiography**
- **Green – Invasive coronary angiography**
- **Yellow – Exercise stress ECG**
- **Red – CT coronary artery calcium**

<u>High</u> pretest probability; patient unable to exercise and/or with baseline ECG abnormalities that prevent interpretation of the ST-segment changes during stress:

- **Green – Pharmacological stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Green – Pharmacological stress echocardiography**
- **Green – Pharmacological stress cardiac MRI**
- **Green – Invasive coronary angiography**
- **Green – Coronary CT angiography**
- **Red – CT coronary artery calcium**

History of new-onset heart failure, ventricular tachycardia, ventricular fibrillation, or frequent PVCs with suspected underlying CAD:

- **Green – Stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Green – Stress echocardiography**
- **Green – Stress cardiac MRI**
- **Green – Invasive coronary angiography**
- **Yellow – Stress ECG**
- **Yellow - Coronary CT angiography**
- **Red – CT coronary artery calcium**

<u>Level of Evidence:</u> coronary CT angiography: high; stress radionuclide myocardial perfusion imaging: high; stress cardiac MRI: moderate; CT coronary artery calcium: low; stress echocardiography: high

<u>Notes concerning applicability and/or patient preferences:</u> The approach to the diagnostic evaluation of patients with no known CAD should be guided by the ability to achieve high-quality imaging as well as local availability and expertise (Gulati et al [*AHA* et al] 2021). It is recommended to take account for locally available technology, the person and their preferences, and any contraindications (e.g., disabilities, frailty, limited ability to exercise, claustrophobia, metal implants, allergy to contrast) when deciding on the imaging method (*NICE* 2016). If more than one modality falls into the same appropriate use category, it is assumed that physician judgment and available local expertise are used to determine the correct test for an individual patient (Wolk et al [*ACCF* et al 2014). The patient should be engaged in a process of shared decision-making before determining the final choice of the cardiac test modality (Gulati et al [*AHA* et al] 2021).

In the recommendations, 64-slice CT is generally required as a minimum threshold for coronary CT angiography, which may limit accessibility.

Guideline and PLE expert panel consensus opinion summary:

Clinical risk assessment and stratification

When symptoms are present and there is sufficient suspicion of heart disease to warrant cardiac evaluation, it is helpful to estimate a patient's pretest probability of CAD (Wolk et al [*ACCF* et al] 2014; Shah et al [*ACR*] 2018; Knuuti et al [*ESC*] 2020). A clinical risk assessment tool can help stratify patients into low, intermediate, or high pretest probability of CAD (Shah et al [*ACR*] 2018). Stratification of risk in these tools generally uses criteria such as patient age, sex, family history of CAD, type of chest pain, lipid levels, and previous cardiovascular events (Litmanovich et al [*ACR*] 2021). Risk assessment in symptomatic individuals stratifies patients based on the 1-year risk of cardiovascular mortality (Wolk et al [*ACCF* et al] 2014; Knuuti et al [*ESC*] 2020). According to the new *ESC* guidelines, low event risk is defined as a cardiac mortality rate of < 1%, moderate risk as 1-3%, and high risk as > 3% (Knuuti et al [*ESC*] 2020).

The *Diamond-Forrester* model (Diamond & Forrester, 1979) was among the first to be used for classifying pretest probabilities (PTPs), and is commonly used to this day. However, some studies note that this model may overestimate the probability of CAD (e.g., Genders et al 2011; Reeh et al 2018), and recent analyses of contemporary data have demonstrated that the pretest probability of obstructive CAD based on age, sex, and the nature of the patient's symptoms is much lower than that published in previous guidelines (Gulati et al [*AHA* et al] 2021; Knuuti et al [*ESC*] 2020; Juarez-Orozco et al 2019; Foldyna et al 2018). Application of the contemporary data PTP results in the reclassification of a number of patients.

Age (years)	**Sex**	**Typical Angina**		**Atypical Chest Pain**		**Non-anginal**	
		Diamond-Forrester*	**Contemporary Data****	**Diamond-Forrester***	**Contemporary Data****	**Diamond-Forrester***	**Contemporary Data****
30-39	**Men**	10-90%	<5%	10-90%	<5%	5-10%	<5%
30-39	**Women**	10-90%	<5%	<5%	<5%	<5%	<5%
40-49	**Men**	>90%	>15%	10-90%	5-15%	10-90%	<5%
40-49	**Women**	10-90%	5-15%	5-10%	5-15%	<5%	<5%
50-59	**Men**	>90%	>15%	10-90%	>15%	10-90%	5-15%
50-59	**Women**	10-90%	5-15%	10-90%	5-15%	5-10%	<5%
60-69	**Men**	>90%	>15%	10-90%	>15%	10-90%	>15%
60-69	**Women**	>90%	>15%	10-90%	5-15%	10-90%	5-15%
70+	**Men**	>90%	>15%	10-90%	>15%	10-90%	>15%
70+	**Women**	>90%	>15%	10-90%	>15%	10-90%	5-15%

(Diamond & Forrester 1979; Wolk et al [*ACCF* et al] 2014; Knuuti et al [*ESC*] 2020; Juarez-Orozco et al 2019; Foldyna et al 2018; Reeh et al 2018; Cheng et al 2011)

***High:** > 90% pre-test probability. **Intermediate:** between 10% and 90% pre-test probability. **Low:** between 5% and 10% pre-test probability. **Very Low:** <5% pre-test probability.

****>15%** denotes groups in which non-invasive testing is most beneficial. **5%-15%** denotes the groups in which testing for diagnosis may be considered after assessing the overall clinical likelihood based on modifiers. **<5%** denotes groups that have such a low probability of disease that diagnostic testing should be performed for only compelling reasons.

Studies have shown that outcomes for patients with a PTP of < 15% is good (annual risk of cardiovascular death < 1%), and that it is generally safe to defer routine testing in this population (Knuuti et al [*ESC*] 2020). Recent studies have also shown that when tested, the prevalence of obstructive CAD is < 5% in patients with a PTP < 15% (Knuuti et al [*ESC*] 2020). With these updated PTPs, patients with a PTP < 5% can be assumed to have such a low probability of disease that diagnostic testing should only be performed for compelling reasons. When the PTP is 5-15%, patient preference, local resources / availability of tests, clinical judgment, and appropriate patient information remain important considerations when making a decision to proceed with non-invasive diagnostic testing (Knuuti et al [*ESC*] 2020). Patients should not routinely undergo invasive testing unless data indicates a high likelihood of obstructive disease (Knuuti et al [*ESC*] 2020). Recent validation studies have shown that the new *ESC* classification is well-calibrated, may improve disease prediction, and can change the downstream diagnostic pathway in a significant proportion of cases (e.g., Winther et al 2021; Lopes et al 2020; Bittencourt et al 2016; Carli & Gupta 2019; Baskaran et al 2019).

Models that incorporate information concerning risk factors for CVD, resting ECG changes, or coronary calcification scores can further improve risk assessment, compared with age, sex, and symptoms alone (Knuuti et al [*ESC*] 2020). For example, abnormalities on resting ECG and/or presence of clinical risk factors such as diabetes, dyslipidemia, family history of early CVD, or smoking history will increase the probability of obstructive CAD (Knuuti et al [*ESC*] 2020). Together, these factors may be important in refining the likelihood obstructive CAD in patients with a PTP of 5-15% (Knuuti et al [*ESC*] 2020).

Basic first-line testing in symptomatic patients may include standard laboratory testing, a resting ECG, or ambulatory ECG monitoring (Knuuti et al [*ESC*] 2020). Chest radiography may also be indicated to evaluate for other potential cardiac, pulmonary, and thoracic causes of symptoms (Knuuti et al [*ESC*] 2020; Gulati et al [*AHA* et al] 2021: class I, level C-EO evidence). A resting ECG is recommended in patients without an obvious, noncardiac cause of chest pain, as Q-wave, ST-segment, or T-wave changes can be used to improve estimations of the PTP (Fihn et al [*ACCF* et al] 2012: class I, level B evidence; *NICE* 2016; Knuuti et al [*ESC*] 2020; Gulati et al [*AHA* et al] 2021: class I, level B-NR evidence). A resting echocardiography can be useful to assess cardiac structure and function (Fihn et al [*ACCF* et al] 2012: class I, level B evidence; Knuuti et al [*ESC*] 2020). After clinical assessment and initial workup, many individuals diagnosed with non-anginal chest pain may not require further diagnostic imaging, except in certain circumstances, such as resting ECG ST-T changes or Q waves (*NICE* 2016).

If, after quantitative risk assessment and first-line testing, a risk-based treatment decision is still uncertain, assessment of CT CAC score, family history, high-sensitivity C-reactive protein (hs-CRP), and/or ankle-brachial index (ABI) may also be considered to inform treatment decision making (Goff et al [*ACC/AHA*] 2014: class IIb recommendation, level B evidence). Detection of significant coronary artery calcification on CT CAC can be used to improve estimations of the pretest probability (PTP) of obstructive CAD (Knuuti et al [*ESC*] 2020; Litmanovich et al [*ACR*] 2021; Gulati et al [*AHA* et al] 2021). In patients presenting with stable angina, a positive CT CAC score is more accurate than clinical risk stratification tools for determining which patients have CAD, and is also predictive of which patients may have significant stenosis or those in need of additional diagnostic testing (Gulati et al [*AHA* et al] 2021; Shah et al [*ACR*] 2018). A CT CAC score of “zero” does not always exclude significant coronary plaque burden, however, and additional testing may still be necessary (Shah et al [*ACR*] 2018; Knuuti et al [*ESC*] 2020).

Exercise ECG

Exercise ECG has inferior diagnostic performance compared with diagnostic imaging tests, and has limited power to rule-in or rule-out obstructive CAD (Knuuti et al [*ESC*] 2020; Gulati et al [*AHA* et al] 2021). In patients with a low pretest probability of obstructive CAD, exercise ECG testing has a reported negative predictive value (NPV) of 98%-99% and is reasonable as a first-line test for excluding myocardial ischemia and determining functional capacity (Fihn et al [*ACCF* et al] 2012: class IIa, level C evidence; Gulati et al [*AHA* et al] 2021: class IIa, level B-NR evidence). However, its positive predictive value (PPV) in these patients is limited, and therefore exercise ECG alone should not be used in this population (*NICE* 2016; Knuuti et al [*ESC*] 2020). Stress ECG may also be considered as an alternative test to rule-in/rule-out CAD when non-invasive imaging is not available (Knuuti et al [*ESC*] 2020: class IIb, level B evidence). Exercise ECG testing is recommended for patients with an intermediate pretest probability of CAD, and may be reasonable for those with a high pretest probability of CAD (Fihn et al [*ACCF* et al] 2012: class I, level A evidence; Gulati et al [*AHA* et al] 2021: class 2a, level B-R evidence), unless the patient is incapable of at least moderate physical functioning (Fihn et al [*ACCF* et al] 2012: class III, level C evidence).

Coronary CT angiography (CCTA)
CCTA has been shown to be of value in CAD imaging because of its high NPV (Shah et al [*ACR*] 2018; Litmanovich et al [*ACR*] 2021). It is recommended as an initial test for diagnosing symptomatic patients when obstructive CAD cannot be excluded by clinical assessment alone (Knuuti et al [*ESC*] 2020: class I, level B recommendation). CCTA has superior diagnostic accuracy compared to other examinations, provides coronary artery stenosis evaluation similar to that of catheterization, and may allow for more appropriate selection of patients for downstream testing (Knuuti et al [*ESC*] 2020; Shah et al [*ACR*] 2018; Litmanovich et al [*ACR*] 2021).

In general, CCTA is preferred in patients with a lower range of clinical likelihood of CAD, no previous diagnosis of CAD, and characteristics associated with a high likelihood of good image quality (Knuuti et al [*ESC*] 2020; Shah et al [*ACR*] 2018).

For patients with intermediate or high pretest probability of CAD, CCTA is also reasonable (Fihn et al [*ACCF* et al] 2012; class IIa/IIb, level B/level C evidence; Wolk et al [*ACCF* et al] 2014; Litmanovich et al [*ACR*] 2021; Gulati et al [*AHA* et al] 2021: class I, level A evidence), because "real" higher risk may be much lower than previously expected based on newer PTP models proposed by the *ESC* (Knuuti et al [*ESC*] 2020; PLE expert panel consensus opinion). CCTA can also be offered if clinical assessment indicates non-anginal chest pain but resting ECG indicates ST-T changes or Q waves (*NICE* 2016). The use of CCTA may be appropriate for detection of CAD when any of the following conditions are present and good image quality is still likely: newly diagnosed heart failure, ventricular tachycardia, ventricular fibrillation, or frequent premature ventricular contractions (PVCs) (Wolk et al [*ACCF* et al] 2014; Knuuti et al [*ESC*] 2020; White et al [*ACR*] 2018).

CCTA is not recommended when extensive coronary calcification, irregular heart rate, significant obesity, inability to cooperate with breath-hold commands, or any other conditions make obtaining good image quality unlikely (Knuuti et al [*ESC*] 2020: class III, level C evidence).

Stress radionuclide myocardial perfusion imaging (**PET or SPECT**)
Non-invasive functional (stress) imaging is a core component of the diagnostic pathway and is recommended for many symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone (Knuuti et al [*ESC*] 2020: class I, level B recommendation; Shah et al [*ACR*] 2018). Stress imaging can be useful in low risk patients when there is an inability to exercise or an uninterpretable ECG (Wolk et al [*ACCF*] 2014). The use of stress imaging is also appropriate in the detection of CAD for symptomatic patients with intermediate or high pre-test probability of CAD, regardless of ability to exercise or if ECG is interpretable (Gulati et al [*AHA* et al] 2021: class I, level B-R evidence; Litmanovich et al [*ACR*] 2021; Fihn et al [*ACCF* et al 2012: class I/class IIa, level B evidence;

Wolk et al [*ACCF* et al] 2014; Schindler et al [*SNMMI* et al] 2020: score 7, score 8, score 9). Among such patients, PET may be preferred to SPECT, if available, to improve diagnostic accuracy and decrease the rate of nondiagnostic test results (Gulati et al [*AHA* et al] 2021: class 2a, level B-R evidence). Stress imaging is also generally appropriate for detection of CAD for patients with any of the following conditions: newly diagnosed heart failure, ventricular tachycardia (VT), ventricular fibrillation, or frequent premature ventricular contractions (PVCs) (Wolk et al [*ACCF* et al] 2014; White et al [*ACR*] 2018; Schindler et al [*SNMMI*] 2020; Fihn et al [*ACCF* et al] 2012: class IIb, level C evidence).

Stress cardiac MRI (CMR)
Functional (stress) CMR provides high sensitivity and specificity for ischemia by the induction of wall motion abnormality (Shah et al [*ACR*] 2018). In general, the use of stress CMR is appropriate for patients with intermediate to high pre-test probability of CAD (Gulati et al [*AHA* et al] 2021: class I, level B-R evidence; Litmanovich et al [*ACR*] 2021; Wolk et al [*ACCF* et al] 2014; Fihn et al [*ACCF* et al] 2012: class IIa, level B evidence). The use of stress CMR is also generally appropriate for detection of suspected CAD in patients with any of the following conditions: newly diagnosed heart failure, ventricular tachycardia, ventricular fibrillation, or frequent premature ventricular contractions (PVCs) (Wolk et al [*ACCF* et al] 2014; White et al [*ACR*] 2018). It can also be useful whenever echocardiographic examination is nondiagnostic (Shah et al [*ACR*] 2018). Stress CMR is typically not recommended for patients with a low pre-test probability (Fihn et al [*ACCF* et al] 2012: class III (no benefit), level C evidence; PLE expert panel consensus opinion) unless patient has uninterpretable ECG and/or is unable to exercise (Wolk et al [*ACCF*] 2014).

Stress echocardiography
The prognostic value of stress echocardiography has been demonstrated in large observational series with low rates of CAD events for patients with normal test results, particularly those with good exercise tolerance (Gulati et al [*AHA* et al] 2021). It is primarily useful to evaluate for wall motion abnormalities, and can provide data regarding flow reserve, which can aid in patient risk stratification (Shah et al [*ACR*] 2018). For patients with a low pretest probability of obstructive IHD, standard stress echocardiography might be reasonable (Fihn et al [*ACCF* et al] 2012: class IIa/IIb, level C evidence; Wolk et al [*ACCF* et al] 2014; Shah et al [*ACR*] 2018). For patients with intermediate to high pretest probability, stress imaging with echocardiography is recommended (Gulati et al [*AHA* et al] 2021: class I, level B-R evidence; Litmanovich et al [*ACR*] 2021; Fihn et al [*ACCF* et al] 2012: class I/class IIa, level B evidence; Wolk et al [*ACCF* et al] 2014; Shah et al [*ACR*] 2018). In any situation where a SPECT MPI study cannot be performed, stress echocardiogram may be substituted (Shah et al [*ACR*] 2018). The use of stress echocardiography is also generally appropriate for detection of CAD in patients with newly diagnosed heart failure, ventricular tachycardia, ventricular fibrillation, or frequent premature ventricular contractions (PVCs) (Wolk et al [*ACCF* et al] 2014; White et al [*ACR*] 2018).

Invasive coronary angiography:
Invasive coronary angiography is not recommended to assess low risk patients who have not undergone noninvasive risk testing (Fihn et al [*ACCF* et al] 2012: class III, level C evidence). It can be offered as a third-line investigation when the results of non-invasive anatomical and functional imaging are inconclusive (*NICE* 2016; Knuuti et al [*ESC*] 2020: class IIa, level B evidence). In patients with a high clinical likelihood of CAD, severe symptoms refractory to medical therapy, or typical angina at a low level of exercise, proceeding directly to coronary angiography is a reasonable option for depicting the anatomy and severity of obstructive CAD and other coronary abnormalities (Knuuti et al [*ESC*] 2020: class I, level B evidence; Maron et al 2020; Litmanovich et al [*ACR*] 2021). However, contemporary randomized trials support that candidates for elective coronary angiography may be safely triaged using

CCTA or noninvasive stress testing (Gulati et al [*AHA* et al] 2021). The use of invasive coronary angiography is also generally appropriate for detection of CAD in patients with newly diagnosed heart failure, ventricular tachycardia, ventricular fibrillation, or frequent premature ventricular contractions (PVCs) (Wolk et al [*ACCF* et al] 2014; White et al [*ACR*] 2018).

<u>Clinical notes:</u>

- Symptomatic patients may present with any constellation of clinical findings consistent with CAD. Examples may include chest pain or tightness, epigastric pain, shoulder pain, or jaw pain. Non-chest pain symptoms (e.g., dyspnea) or signs (e.g., new electrocardiographic abnormalities) that are thought to be consistent with CAD may also be an ischemic equivalent (Wolk et al [*ACCF* et al] 2014).
- Chest radiography can rapidly demonstrate many noncardiac causes of chronic chest pain, including a variety of diseases of the mediastinum, pleura, or lung (Shah et al [*ACR*] 2018).
- Echocardiography is an important clinical tool for the exclusion of alternative causes of chest pain and can aid in diagnosing concurrent cardiac disease, such as valvular heart diseases, heart failure, and most cardiomyopathies; however, these diseases often coexist with obstructive CAD (Knuuti et al [*ESC*] 2020).
- For revascularization decisions, information on both anatomy and ischemia is needed (Knuuti et al [*ESC*] 2020).
- In all cases, the imaging physician must select the appropriate combination of imaging parameters to acquire a diagnostic examination at a radiation dose that is as low as reasonably achievable (Shah et al [*ACR*] 2018).

<u>Evidence update (2016-present):</u>

High Level of Evidence

The DISCHARGE Trial Group (Maurovich-Horvat et al 2022), in a multicenter randomized trial, compared CTA with invasive coronary angiography (ICA) in guideline-directed management of stable chest pain. All patients were referred for ICA at one of 26 European centers and had intermediate pretest probability of obstructive CAD. The primary outcome was major adverse cardiovascular event over 3.5 years, with secondary outcome of procedure-related complications. A total of 3,561 patients were enrolled, with complete follow-up available for 3,523 (98.9%). Major adverse cardiovascular events occurred in 38 of 1,808 patients (2.1%) in the CTA group and 52 of 1,753 (3.0%) in the ICA group (hazard ratio, 0.70; 95% CI: 0.46-1.07; P = 0.10). Major procedure-related complications occurred in 9 patients (0.5%) in the CTA group and 33 (1.9%) in the ICA group (hazard ratio, 0.26; 95% CI: 0.13-0.55). Frequency of coronary revascularization procedures was lower in the CTA group than in the ICA group (256 patients [14.2%] vs. 315 patients [18.0%]; hazard ratio, 0.76; 95% CI: 0.65-0.90). Quality-of-life outcomes assessed at follow-up were also similar in the two groups, and medical therapy did not differ substantially between groups at follow-up. The authors conclude that a strategy of initial CTA resulted in no significant difference in the incidence of major adverse cardiovascular events as compared with ICA but was associated with a lower risk of major procedure-related complications and revascularization procedures.

Haase et al (2019), in a meta-analysis, examined whether CCTA should be performed in patients with any clinical probability of CAD. A total of 65 prospective diagnostic accuracy studies (n = 5,332) that examined CCTA with reference standard of coronary angiography, using ≥ 50% diameter reduction cutoff value for obstructive CAD, were included. All patients had a clinical indication for coronary angiography due to suspected CAD, and both tests were performed in all patients. Primary outcomes were positive (PPV) and negative (NPV) predictive values of CCTA as a function of clinical pretest probability of obstructive CAD. For a pretest probability range of 7-67%, the treat threshold of > 50%

and the no-treat threshold of < 15% post-test probability were obtained using CCTA. At a pretest probability of 7%, the PPV of CCTA was 50.9% (95% CI, 43.3%-57.7%) and the NPV of CCTA was 97.8% (96.4%-98.7%); corresponding values at a pretest probability of 67% were 82.7% (78.3%-86.2%) and 85.0% (80.2%-88.9%), respectively. The overall sensitivity of CCTA was 95.2% (92.6%-96.9%), specificity was 79.2% (74.9%-82.9%), and area under the curve was 0.897 (0.889-0.906). The authors conclude that the diagnosis of obstructive CAD using CCTA in patients with stable chest pain was most accurate when the clinical pretest probability was between 7%-67%.

The SCOT-HEART Investigators (2018), in an open-label, multi-center, parallel-group trial, randomly assigned patients with stable chest pain to standard care + CCTA (n = 2,073) or standard care alone (2,073) to determine the effect of CCTA on 5-year clinical outcomes. The primary end point was death from CHD or nonfatal myocardial infarction at 5 years. The 5-year rate of the primary end point was lower in the CCTA group than in the standard-care group (2.3% vs. 3.9%; hazard ratio, 0.59; 95% CI, 0.41 to 0.84; P = 0.004). Although rates of invasive coronary angiography and coronary revascularization were higher for CCTA group than standard-care group in the first few months of follow-up, overall rates were similar at 5 years. More preventive therapies were initiated in patients in the CCTA group (OR, 1.40; 95% CI, 1.19 to 1.65), as were more antianginal therapies (OR, 1.27; 95% CI, 1.05 to 1.54). There were no significant between-group differences in the rates of cardiovascular or noncardiovascular deaths or deaths from any cause. The authors conclude that the use of CCTA in addition to standard care in patients with stable chest pain resulted in a significantly lower rate of death from coronary heart disease or nonfatal myocardial infarction at 5 years than standard care alone, without resulting in a significantly higher rate of coronary angiography or coronary revascularization.

Moderate Level of Evidence

Chow et al (2021), in a prospective cohort study, sought to confirm the incremental prognostic value of CCTA measured over a prolonged follow-up duration. Over a total of 99 months, 8,667 consecutive CCTA patients without history of myocardial infarction, revascularization, or congenital heart disease (mean age = 57.1) were prospectively enrolled and followed for a mean duration of 7 years. At follow-up, there were a total of 723 major adverse events (MAE), 278 major adverse cardiac events (MACE), 547 all-cause deaths, 110 cardiac deaths, and 104 non-fatal myocardial infarctions. Patients without coronary atherosclerosis at time of CCTA had very low annual event rate for both MAE and MACE (0.45%/year and 0.19%/year, respectively). Both MAE and MACE increased with increasing total plaque score and severity of CAD. Patients with high-risk CAD had annual MAE and MACE rates of 3.52%/year and 2.58%/year, respectively. The authors conclude that CCTA has independent and incremental prognostic value that is durable over time, and that the absence of coronary atherosclerosis portends an excellent prognosis.

Curzen et al (2021) tested whether an evaluation strategy based on fractional flow reserve using CCTA (FFR_{CT}) would improve clinical outcomes compared with standard care. A total of 1,400 patients with stable chest pain in 11 centers were randomized to initial testing with CCTA with selective FFR_{CT} (experimental group) or standard clinical care pathways (standard group). Most patients had an initial CCTA: 439 (63%) in the standard group vs. 674 (96%) in the experimental group, 254 of whom (38%) underwent FFR_{CT}. Major adverse cardiac and cerebrovascular events did not differ significantly (10.2% in the experimental group vs. 10.6% in the standard group) and angina and quality of life improved to a similar degree over follow-up in both randomized groups. Invasive angiography was reduced significantly in the experimental group (19% vs. 25%, P = 0.01). The authors conclude that a strategy of CCTA with selective FFR_{CT} in patients with stable angina did not differ significantly from standard clinical care pathways in clinical outcomes, but did reduce the use of invasive coronary angiography.

Yang et al (2019), in a meta-analysis, compared the diagnostic accuracy of stress myocardial perfusion imaging between CMR and nuclear medical imaging (SPECT or PET) for the diagnosis of hemodynamically significant CAD, with FFR as the reference standard. A total of 28 articles (n = 2,665) met the inclusion criteria and were included in the meta-analysis: 14 CMR, 13 SPECT, and 5 PET articles. The results demonstrated a pooled sensitivity of 0.88 (95% confidence interval [CI]: 0.80–0.93), 0.69 (95% CI: 0.56–0.79), and 0.83 (95% CI: 0.70–0.91), and a pooled specificity of 0.89 (95% CI: 0.85–0.93), 0.85 (95% CI, 0.80–0.89), and 0.89 (95% CI, 0.86–0.91) for CMR, SPECT, and PET, respectively. The area under the curve (AUC) of CMR, PET, and SPECT was 0.94 (95% CI, 0.92–0.96), 0.92 (95% CI, 0.89–0.94), and 0.87 (95% CI, 0.83–0.89), respectively. The authors conclude that CMR and PET both have high accuracy and SPECT has moderate accuracy to detect hemodynamically significant CAD.

Knuuti et al (2018), in a meta-analysis, aimed to determine the ranges of pre-test probability (PTP) of coronary artery disease (CAD) in which stress ECG, stress echocardiography, CCTA, SPECT, PET, and CMR can reclassify patients into a post-test probability that defines (> 85%) or excludes (< 15%) anatomically and functionally (defined by a fractional flow reserve [FFR] < 0.8) significant CAD. Studies with > 100 patients with stable CAD that utilized these techniques with either ICA or ICA + FFR as reference were included. A total of 28,664 patients from 132 studies that used ICA as reference, and 4,131 from 23 studies using FFR, were analyzed. Stress ECG was found to rule-in and rule-out anatomically significant CAD only when PTP was ≥ 80% (76–83%) and ≤ 19% (15–25%), respectively. CCTA was able to rule-in anatomic CAD at a PTP ≥ 58% (45–70%) and rule-out at a PTP ≤ 80% (65–94%). The corresponding PTP values for functionally significant CAD were ≥ 75% (67–83%) and ≤ 57% (40–72%) for CCTA, and ≥ 71% (59–81%) and ≤ 27% (24–31%) for ICA, demonstrating poorer performance of anatomic imaging against FFR. In contrast, functional imaging (PET, stress CMR, SPECT) was able to rule-in functionally significant CAD when PTP was ≥ 46–59% and rule-out when PTP was ≤ 34–57%. The authors conclude that selection of a diagnostic technique for any given patient to rule-in or rule-out CAD should be based on the optimal PTP range for each test and on the assumed reference standard.

Buckert et al (2018), in a prospective RCT, evaluated a CMR-based management approach for 200 patients with stable CAD. Patients with symptomatic CAD were randomized to diagnostic coronary angiography (group 1) or adenosine stress CMR (group 2). Primary endpoint was composite of cardiac death and nonfatal myocardial infarction. In group 1, 45 revascularizations (45.9%) were performed. In group 2, 27 patients (28.1%) were referred to revascularization because of ischemia on CMR. At 12-month follow-up, 7 primary events occurred: 3 in group 1 (event rate 3.1%) and 4 in group 2 (event rate 4.2%), with no statistically significant difference (p = 0.72). Over the next 2 years, 6 additional events were observed, giving a total of 4 events in group 1 and 9 events in group 2 (event rate 4.1% vs. 9.4%; p = 0.25). Group 2 showed significant quality-of-life improvement after 1 year in comparison to group 1. The authors conclude that a CMR-based strategy for stable CAD patients was safe, reduced revascularization procedure, and resulted in better quality of life at 12-mo follow-up, though noninferiority could not be proved.

Low Level of Evidence

Houssany-Pissot et al (2020) conducted a multicenter retrospective study of 4,952 patients to evaluate the rate of strictly normal invasive coronary angiogram (ICA) following a positive non-invasive test (functional testing (FT): n = 3,272 or CCTA: n = 1,676). Patients were categorized into five subgroups according to pre-test probability (PTP) of CAD. Results of ICA were defined as normal ICA, non-obstructive CAD (non-oCAD) and obstructive CAD (oCAD). Results found normal ICA in 819 patients, (16.5%), non-oCAD in 1,193 patients (24.1%), and oCAD in 2,940 patients (59.4%). Without considering

PTP, CCTA compared to FT showed less frequently normal ICA (7% vs. 16.5%), and more frequent CAD (non-oCAD: 27.9% vs. 22.2%; oCAD: 65.1% vs. 56.4%) (all p<0.0001). When differences in PTP were considered, CCTA always showed lower rates of normal ICA than FT. In low and lower-intermediate risk patients, CCTA detected more frequent oCAD than FT (p<0.001). The authors conclude that CCTA is a better alternative than FT to limit unnecessary ICA, regardless of PTP value, without missing abnormal ICA.

Rudzinski et al (2018), in a prospective randomized trial, evaluated whether the use of CCTA as a first-line anatomical test in 120 patients with suspected CAD may reduce the number of invasive coronary angiographies (ICA). Patients with indications to ICA were randomized 1:1 to undergo CCTA vs. direct ICA. The number of invasively examined patients was reduced by 64.4% in the CCTA group compared to the ICA group (21 vs. 59, p < 0.0001). The number of patients with ICAs not followed by coronary intervention was reduced by 88.1% with CCTA (5 vs. 42, p < 0.0001). There were no significant differences regarding the median volume of contrast (CCTA 80.3 ml [65.0–165.0] vs ICA 90.0 ml [55.0–100.0], p=0.099), with a non-significant trend towards higher radiation dose in the CCTA group (9.9 mSv [7.0–22.1] vs 9.4 mSv [5.2–14.0], p=0.05). There were no acute cardiovascular events. The authors conclude that CCTA may hypothetically act as an effective 'gatekeeper' to the cath lab in the diagnosis of stable patients with current indications for ICA.

Lee et al (2018), in a retrospective study, suggested a risk stratification strategy using CCTA in 798 consecutive patients with anatomic CAD but without myocardial ischemia on SPECT imaging. The primary outcome was occurrence of adverse cardiac events, including cardiac death, nonfatal myocardial infarction, unstable angina, and late revascularization. Of the enrolled patients, 542 (68%) showed no perfusion defect (PD) on SPECT. During follow-up (median, 22.6 mo), adverse cardiac events occurred in 23 patients without PD (4.6%). Presence of plaque in ≥ 4 coronary segments, plaque in left main or proximal left anterior descending coronary artery, and partially calcified plaque presence were independent predictors of adverse events. When CCTA score was defined based on these 3 predictors (0–3 points), annualized event rates increased with increasing CCTA scores. Patients with a CCTA score of 3 were associated with a 23-fold risk increase (adjusted HR 23.18; p = 0.003) and showed unfavorable event-free survival, comparable to those with PD on SPECT (p = 0.191). The authors conclude that CCTA allows further risk stratification in patients with negative SPECT.

Danand et al (2017), in a prospective study, sought to establish the diagnostic accuracy of CCTA, SPECT, and PET, and also to explore the incremental value of hybrid imaging compared with fractional flow reserve (FFR) in 208 patients with suspected CAD. Patients underwent CCTA, PET, and SPECT, followed by invasive coronary angiography (ICA) and FFR measurements of all coronary arteries within 2 weeks. Main outcome was hemodynamically significant stenosis in ≥ 1 coronary artery as indicated by FFR of ≤ 0.80 and relative diagnostic accuracy of SPECT, PET, and CCTA in detecting hemodynamically significant CAD. Sensitivity was 90% (95%CI, 82%-95%) for CCTA, 57% (95%CI, 46%-67%) for SPECT, and 87% (95%CI, 78%-93%) for PET, whereas specificity was 60% (95%CI, 51%-69%) for CCTA, 94% (95%CI, 88%-98%) for SPECT, and 84% (95%CI, 75%-89%) for PET. Diagnostic accuracy was highest for PET (85%; 95%CI, 80%-90%) compared with that of CCTA (74%; 95%CI, 67%-79%; P = .003) and SPECT (77%; 95%CI, 71%-83%; P = .02). Diagnostic accuracy was not enhanced by either hybrid SPECT and CCTA (76%; 95%CI, 70%-82%; P = .75) or by PET and CCTA (84%; 95%CI, 79%-89%; P = .82), but resulted in an increase in specificity (P = .004) at the cost of a decrease in sensitivity (P = .001). The authors conclude that PET exhibited the highest accuracy for diagnosis of myocardial ischemia.

Follow-up/sequential testing for coronary artery disease: no previous revascularization, no symptoms or stable symptoms

Abnormal or equivocal noninvasive test* for CAD performed in prior 90 days:

- **Green – Stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Green – Stress echocardiography**
- **Green – Stress cardiac MRI**
- **Green – Coronary CT angiography**
- **Yellow – Stress ECG**
- **Yellow – Invasive coronary angiography**
- **Red – CT coronary artery calcium**

Abnormal coronary artery calcium (Agatston) score performed in prior 90 days:**

- **Green – Stress ECG**
- **Yellow – Stress echocardiography**
- **Yellow – Stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Yellow – Stress cardiac MRI**
- **Yellow – Coronary CT angiography**
- **Red – Invasive coronary angiography**
- **Red – CT coronary artery calcium**

Low global CAD risk or last test performed > 90 days and < 2 years ago:

- **Red – Stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Red – Stress echocardiography**
- **Red – Stress cardiac MRI**
- **Red – Coronary CT angiography**
- **Red – Stress ECG**
- **Red – Invasive coronary angiography**
- **Red – CT coronary artery calcium**

Intermediate-to-high global CAD risk and last test performed ≥ 2 years ago:

- **Yellow – Stress ECG**
- **Yellow – Stress echocardiography**
- **Yellow – Stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Yellow – Stress cardiac MRI**
- **Red – Coronary CT angiography**
- **Red – Invasive coronary angiography**
- **Red – CT coronary artery calcium**

*Includes ECG, stress testing, or CCTA; assumes not repeat of the previously used testing modality.

**Such as ≥ 400 in asymptomatic patients (Greenland et al [*ACCF/AHA*] 2010; Schindler et al [*SNMMI* et al] 2020) or > 100 in patients with stable symptoms (Wolk et al [*ACCF* et al] 2014).

Level of Evidence: coronary CT angiography: moderate; stress radionuclide myocardial perfusion imaging: moderate; stress cardiac MRI: moderate; stress echocardiography: moderate

Notes concerning applicability and/or patient preferences: It is recommended to take account for locally available technology and expertise, the person and their preferences, and any contraindications (e.g., disabilities, frailty, limited ability to exercise, claustrophobia, metal implants, allergy to contrast) when deciding on the imaging method (*NICE* 2016). If more than one modality falls into the same appropriate use category, it is assumed that physician judgment and available local expertise are used to determine the correct test for an individual patient (Wolk et al [*ACCF* et al 2014). The patient should be engaged in a process of shared decision-making before determining the final choice of the cardiac test modality (Gulati et al [*AHA* et al] 2021).

In the recommendations, 64-slice CT is generally required as a minimum threshold for coronary CT angiography, which may limit accessibility.

Guideline and PLE expert panel consensus opinion summary:

Stress ECG

In patients who have no new or worsening symptoms, no prior evidence of silent ischemia, and are not at high risk for a recurrent cardiac event, the usefulness of annual surveillance exercise ECG testing is not well established (Fihn et al [*ACCF* et al] 2012). Standard exercise ECG testing might be considered for follow-up assessment in patients who have had prior evidence of silent ischemia or are at high risk for a recurrent cardiac event, are able to exercise to an adequate workload, and have an interpretable ECG (Fihn et al [*ACCF* et al]: class IIa, level C evidence). It can also be useful when prior CCTA or coronary angiography are abnormal or uncertain, or when prior CT CAC score is abnormal (Agatston score > 100) (Wolk et al [*ACCF* et al] 2014).

Stress echocardiography

Stress echocardiography can be useful for follow-up assessment at 2-year or longer intervals in patients with CAD with prior evidence of silent ischemia, or who are at high risk for a recurrent cardiac event (Fihn et al [*ACCF* et al] 2012: class IIa, level C evidence). It is also generally recommended in those with stable symptoms and any of the following (Wolk et al [*ACCF* et al] 2014):

- Normal prior exercise ECG test ≥ 2 years ago with intermediate to high global CAD risk
- Normal prior stress imaging study ≥ 2 years ago with intermediate to high global CAD risk
- Nonobstructive CAD on angiogram > 2 years ago with intermediate to high global CAD risk.
- Abnormal prior exercise ECG test ≥ 2 years ago
- Abnormal prior stress imaging study ≥ 2 years ago
- Obstructive CAD on prior coronary angiography ≥ 2 years ago
- Results ≥ 100 on prior coronary calcium Agatston score

Stress echocardiography is also appropriate for risk assessment of CAD in patients with equivocal, borderline, or discordant testing in the past 90 days (Wolk et al [*ACCF* et al] 2014). This includes abnormal results on exercise ECG, CCTA, or [non-echo] stress imaging (Wolk et al [*ACCF* et al] 2014; Knuuti et al [*ESC*] 2020: class IIb, level B recommendation; Gulati et al [*AHA* et al] 2021: class 2a, level B-NR evidence). After an initial stress ECG, data support an improved diagnostic accuracy and improved risk stratification with further stress imaging (Gulati et al [*AHA* et al] 2021).

Stress radionuclide myocardial perfusion imaging (**PET or SPECT**)

Stress nuclear myocardial perfusion imaging can be useful for follow-up assessment at 2-year or longer intervals in patients with CAD with prior evidence of silent ischemia, or who are at high risk for a recurrent cardiac event (Fihn et al [*ACCF* et al] 2012: class IIa, level C evidence). It is also generally recommended in those with stable symptoms and any of the following (Wolk et al [*ACCF* et al] 2014):

- Normal prior exercise ECG test ≥ 2 years ago with intermediate to high global CAD risk
- Normal prior stress imaging study ≥ 2 years ago with intermediate to high global CAD risk
- Nonobstructive CAD on angiogram > 2 years ago with intermediate to high global CAD risk
- Abnormal prior exercise ECG test ≥ 2 years ago
- Abnormal prior stress imaging study ≥ 2 years ago
- Obstructive CAD on prior coronary angiography ≥ 2 years ago
- Results ≥ 100 on prior coronary calcium (Agatston) score

In general, functional imaging for myocardial ischemia is recommended if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic (Gulati et al [*AHA* et al] 2021: class 2a, level B-NR evidence; Knuuti et al [*ESC*] 2020: class IIb, level B recommendation; *NICE* 2016; Wolk et al [*ACCF* et al] 2014). Cardiac radionuclide imaging (RNI) is appropriate for risk assessment of CAD in patients with equivocal, borderline, discordant, or abnormal stress testing within the past 90 days, including exercise ECG or [non-RNI] stress imaging (Wolk et al [*ACCF* et al] 2014). After an initial stress ECG, data support an improved diagnostic accuracy and improved risk stratification with further stress imaging (Gulati et al [*AHA* et al] 2021).

Stress cardiac MRI (CMR)

Stress CMR can be useful for follow-up assessment at 2-year or longer intervals in patients with CAD with prior evidence of silent ischemia, or who are at high risk for a recurrent cardiac event (Fihn et al [*ACCF* et al] 2012: class IIa, level C evidence). It is also generally recommended in those with stable symptoms and any of the following (Wolk et al [*ACCF* et al] 2014):

- Normal prior exercise ECG test ≥ 2 years ago with intermediate to high global CAD risk
- Normal prior stress imaging study ≥ 2 years ago with intermediate to high global CAD risk
- Nonobstructive CAD on angiogram > 2 years ago with intermediate to high global CAD risk
- Abnormal prior stress imaging study ≥ 2 years ago
- Obstructive CAD on prior coronary angiography ≥ 2 years ago
- Results 100-40 on prior coronary calcium (Agatston) score with high global CAD risk, or Agatston score > 400

In general, functional imaging for myocardial ischemia is recommended if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic (Gulati et al [*AHA* et al] 2021: class 2a, level B-NR evidence; Knuuti et al [*ESC*] 2020: class IIb, level B recommendation; Wolk et al [*ACCF* et al] 2014). In patients with recent abnormal/uncertain exercise ECG test in the past 90 days (and without intervening revascularization), stress CMR may be appropriate (Wolk et al [*ACCF* et al] 2014). It may also be appropriate to further evaluate for obstructive CAD after [non-CMR] stress imaging study (Wolk et al [*ACCF* et al] 2014). After an initial stress ECG, data support an improved diagnostic accuracy and improved risk stratification with further stress imaging (Gulati et al [*AHA* et al] 2021).

Coronary CT angiography

Coronary CTA is not recommended as a routine follow-up test for patients with established CAD (Knuuti et al [*ESC*] 2020: class III, level C recommendation). Its use is rarely appropriate for follow-up testing in patients who are asymptomatic or with stable symptoms, including those at high global risk or when last test was performed ≥ 2 years ago (Wolk et al [*ACCF* et al] 2014). CCTA is appropriate, however, whenever there is discordance between prior ECG exercise testing and imaging results, or whenever prior stress imaging results are equivocal (Gulati et al [*AHA* et al] 2021: class 2a, level B-NR evidence; Wolk et al [*ACCF* et al] 2014; Fihn et al [*ACCF* et al] 2012: class IIa, level C evidence). For intermediate-high risk patients with stable chest pain after a negative stress test but with high clinical suspicion of CAD, CCTA may be reasonable (Gulati et al [*AHA* et al] 2021: class 2a, level C-EO evidence). CCTA is also appropriate when CT CAC (e.g., Agatston score > 100), exercise ECG, or stress imaging results within the past 90 days are abnormal and intervening revascularization is not pursued (Wolk et al [*ACCF* et al] 2014).

Invasive coronary angiography
Invasive coronary angiography is not recommended to further assess risk in patients who have preserved LV function and lower-risk criteria on noninvasive testing (Fihn et al [*ACCF* et al] 2012: class III, level B evidence). Its use is also not recommended in patients with CT CAC (Agatston score) > 100 (Wolk et al [*ACCF* et al] 2014), but can be considered in patients with an abnormal prior exercise ECG or stress imaging study, or when obstructive CAD is found on prior CCTA (Wolk et al [*ACCF* et al] 2014). For intermediate-high risk patients with stable chest pain after a negative stress test but with high clinical suspicion of CAD, invasive coronary angiography may be reasonable (Gulati et al [*AHA* et al] 2021: class 2a, level C-EO evidence).

<u>Clinical notes:</u>

- Patients with stable CAD should receive periodic follow-up, at least annually, to include all of the following: assessment of symptoms and clinical function; surveillance for complications; monitoring of cardiac risk factors; and assessment of the adequacy of and adherence to recommended lifestyle changes and medical therapy (Fihn et al [*ACCF* et al] 2012).

<u>Evidence update (2016-present):</u>
Low Level of Evidence
Pezel et al (2021) assessed the long-term prognostic value of vasodilator stress perfusion CMR in asymptomatic patients with obstructive CAD. Consecutive patients referred for CMR were followed for the occurrence of major adverse cardiovascular events (MACE), defined as cardiovascular mortality or recurrent non-fatal myocardial infarction (MI). Known obstructive CAD was defined by history of PCI, CABG, or myocardial infarction. A total of 1,529 patients were enrolled, with 1,342 patients (87.8%; mean age 67,7 years) completing the follow-up (median 8.3 years). A total of 195 had MACE (14.5%). Patients without stress-induced myocardial ischemia had a low annualized rate of MACE (2.4%), whereas the annualized rate of MACE was higher for those with mild (7.3%), moderate (16.8%) or severe ischemia (42.2%); P < 0.001). In multivariable stepwise Cox regression, myocardial ischemia and late gadolinium enhancement (LGE) were independent predictors of MACE (HR 2.80; 95% CI: 2.10-3.73, p < 0.001 and HR 1.51; 95% CI: 1.01-2.27; p = 0.045). The authors conclude that vasodilator stress CMR-induced myocardial ischemia and LGE are good long-term predictors for the incidence of MACE in asymptomatic patients with obstructive CAD.

Follow-up/sequential testing for coronary artery disease: no previous revascularization, new or worsening symptoms

- **Green – Stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Green – Stress echocardiography**
- **Green – Stress cardiac MRI**
- **Green – Invasive coronary angiography**
- **Yellow – Coronary CT angiography**
- **Yellow – Stress ECG**
- **Red – CT coronary artery calcium**

Level of Evidence: coronary CT angiography: moderate; stress radionuclide myocardial perfusion imaging: moderate; stress cardiac MRI: moderate; stress echocardiography: moderate

Notes concerning applicability and/or patient preferences: It is recommended to take account for locally available technology and expertise, the person and their preferences, and any contraindications (e.g., disabilities, frailty, limited ability to exercise, claustrophobia, metal implants, allergy to contrast) when deciding on the imaging method (*NICE* 2016). If more than one modality falls into the same appropriate use category, it is assumed that physician judgment and available local expertise are used to determine the correct test for an individual patient (Wolk et al [*ACCF* et al 2014). The patient should be engaged in a process of shared decision-making before determining the final choice of the cardiac test modality (Gulati et al [*AHA* et al] 2021).

In the recommendations, 64-slice CT is generally required as a minimum threshold for coronary CT angiography, which may limit accessibility.

Guideline and PLE expert panel consensus opinion summary:

Stress ECG

Standard exercise ECG testing can be useful follow-up testing in those with new or worsening symptoms (Fihn et al [*ACCF*] 2012: class I, level B evidence; Wolk et al [*ACCF* et al] 2014). It is particularly recommended when obstructive CAD is present on prior invasive coronary angiography, or CT CAC score is abnormal (Agatston score > 100) (Wolk et al [*ACCF*] 2014. Its use is not recommended in patients who a) are incapable of at least moderate physical functioning or have disabling comorbidity (Fihn et al [*ACCF* et al] 2012: class III, level C evidence), or b) have an abnormal prior stress study (Wolk et al [*ACCF*] 2014).

Coronary CT angiography

The use of CCTA is appropriate for follow-up testing in patients with new or worsening symptoms following an ECG test, or when a prior stress imaging study is abnormal. CCTA may be useful in patients with new/worsening symptoms who have an abnormal calcium score (Agatston score > 100) (Wolk et al [*ACCF* et al] 2014), unless there is known moderate or severe calcification (Fihn et al [*ACCF* et al] 2012: class IIb, level B evidence).

CCTA is not indicated for follow-up testing in patients with new or worsening symptoms and any of the following (Wolk et al [*ACCF* et al] 2014):

- Nonobstructive CAD on coronary angiography

- Normal prior stress imaging study
- Obstructive CAD on prior CCTA study
- Obstructive CAD on prior invasive coronary angiography

Coronary CTA is also not recommended when conditions make good image quality unlikely, including: extensive coronary calcification, irregular heart rate, significant obesity, inability to cooperate with breath-hold commands (Knuuti et al [*ESC*] 2020: class III, level C recommendation; Fihn et al [*ACCF* et al] 2012: class III (no benefit), level B evidence).

Stress imaging: radionuclide myocardial perfusion imaging (PET or SPECT), cardiac MRI (CMR), or echocardiography

For confirmed CAD, non-invasive functional testing can be offered whenever there is uncertainty about whether the chest pain is being caused by myocardial ischemia (*NICE* 2016). Exercise with nuclear MPI, CMR, or echocardiography is reasonable in patients with known stable CAD who have new or worsening symptoms who have - a) at least moderate physical functioning and no disabling comorbidity, or b) previously required imaging with exercise stress, or c) known multivessel disease or high risk for multivessel disease (Fihn et al [*ACCF* et al] 2012: class I/IIa, level B evidence; Wolk et al [*ACCF* et al] 2014).

Non-invasive functional testing is indicated in patients with known CAD and new, recurrent or worsening symptoms and any of the following criteria (Wolk et al [*ACCF* et al] 2014):

- Normal prior exercise ECG test or stress imaging test
- Abnormal prior exercise ECG
- Abnormal prior stress imaging test
- CAD on invasive or noninvasive coronary angiography
- Abnormal CCTA calcium (Agatston score > 100)

Non-invasive functional imaging for myocardial ischemia can be offered if CT coronary angiography has shown CAD of uncertain functional significance or is non-diagnostic (*NICE* 2016). CMR may be considered in patients with suspected CAD when an echocardiogram (having used contrast) is inconclusive (Knuuti et al [*ESC*] 2020: class IIb, level C recommendation). In these patients, CMR can provide useful information on cardiac anatomy and systolic cardiac function (Knuuti et al [*ESC*] 2020: Class IIb, Level C recommendation). The use of stress imaging may also be appropriate for risk assessment in patients with stable CAD who are being considered for revascularization of known coronary stenosis of unclear physiological significance (Fihn et al [*ACCF* et al] 2012: class I, level B evidence).

Invasive coronary angiography:

Invasive coronary angiography is recommended for patients whose clinical characteristics and results of noninvasive testing indicate a high likelihood of severe ischemic heart disease and the benefits are deemed to exceed risk (Fihn et al [*ACCF* et al] 2012: class I, level C evidence; Wolk et al [*ACCF* et al] 2014). It is also reasonable to further assess risk in those with depressed LV function and moderate risk criteria on noninvasive testing with demonstrable ischemia (Fihn et al [*ACCF* et al] 2012: class IIa, level C evidence), and in patients with inconclusive prognostic information after noninvasive testing (or when noninvasive testing is contraindicated or inadequate) (Fihn et al [*ACCF* et al] 2012: class IIa, level C evidence). In patients with a long-standing diagnosis of chronic coronary syndrome, its use is recommended for risk stratification in patients with severe CAD, particularly if the symptoms are refractory to medical treatment or if they have a high-risk clinical profile (Knuuti et al [*ESC*] 2020: class I, level C evidence). Its use is also reasonable for patients with who have unsatisfactory quality of life due to angina, have preserved LV function, and have intermediate risk criteria on noninvasive testing (Fihn et al [*ACCF* et al] 2012: class IIa, level C evidence).

Clinical notes:

- Patients with long-standing diagnosis of chronic coronary syndrome should undergo periodic visits to assess potential changes in risk status, adherence to treatment targets, and the development of comorbidities (Knuuti et al [*ESC*] 2020).
- For revascularization decisions, information on both anatomy and ischemia is needed (Knuuti et al [*ESC*] 2020).

Evidence update (2016-present):

There were no new articles that significantly affected the recommendations or conclusions found in the guidelines referenced above.

Follow-up/sequential testing for coronary artery disease: history of previous revascularization (PCI or CABG)

Symptomatic patient:

- **Green – Stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Green – Stress echocardiography**
- **Green – Stress cardiac MRI**
- **Green – Coronary CT angiography**
- **Green – Invasive coronary angiography**
- **Yellow – Stress ECG**
- **Red – CT coronary artery calcium**

Asymptomatic patient with incomplete previous revascularization; additional revascularization feasible:

- **Green – Stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Green – Stress echocardiography**
- **Green – Stress cardiac MRI**
- **Yellow – Stress ECG**
- **Red – Coronary CT angiography**
- **Red – Invasive coronary angiography**
- **Red – CT coronary artery calcium**

Asymptomatic patient with prior left main coronary stent (≥ 2-year interval):

- **Yellow – Stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Yellow – Stress echocardiography**
- **Yellow – Stress cardiac MRI**
- **Yellow – Stress ECG**
- **Yellow – Coronary CT angiography**
- **Yellow – Invasive coronary angiography**
- **Red – CT coronary artery calcium**

Asymptomatic patient with ≥ 5-year interval after CABG or ≥ 2-year interval after PCI*:

- **Yellow – Stress radionuclide myocardial perfusion imaging (PET or SPECT)**
- **Yellow – Stress echocardiography**
- **Yellow – Stress cardiac MRI**
- **Yellow – Stress ECG**
- **Red – Coronary CT angiography**
- **Red – Invasive coronary angiography**
- **Red – CT coronary artery calcium**

*Advanced imaging is generally not appropriate for asymptomatic patients if performed more frequently than at a) 5-year intervals after CABG or b) 2-year intervals after PCI (Fihn et al [*ACCF* et al] 2012, class III: no benefit, level of evidence: C; Wolk et al [*ACCF* et al] 2014).

Level of Evidence: stress radionuclide myocardial perfusion imaging: high; coronary CT angiography: moderate; stress cardiac MRI: moderate; stress echocardiography: moderate

Notes concerning applicability and/or patient preferences: It is recommended to take account for locally available technology and expertise, the person and their preferences, and any contraindications (e.g., disabilities, frailty, limited ability to exercise, claustrophobia, metal implants, allergy to contrast) when deciding on the imaging method (*NICE* 2016). If more than one modality falls into the same appropriate use category, it is assumed that physician judgment and available local expertise are used to determine the correct test for an individual patient (Wolk et al [*ACCF* et al 2014). The patient should be engaged in a process of shared decision-making before determining the final choice of the cardiac test modality (Gulati et al [*AHA* et al] 2021).

In the recommendations, 64-slice CT is generally required as a minimum threshold for coronary CT angiography, which may limit accessibility.

Guideline and PLE expert panel consensus opinion summary:

Stress ECG

In symptomatic post-revascularization patients, exercise ECG may be appropriate (Wolk et al [*ACCF* et al] 2014). It may also be appropriate for asymptomatic patients with incomplete revascularization, prior left main coronary stent, or > 5 years after CABG or > 2 years after PCI (Wolk et al [*ACCF* et al] 2014).

Coronary CT angiography

CCTA is useful for the imaging of symptomatic post-revascularization (PCI or CABG) patients (Wolk et al [*ACCF* et al] 2014), with an extremely high rate of graft disease accuracy (PLE expert panel consensus opinion). For patients who have stable chest pain with previous coronary revascularization, CCTA is reasonable to evaluate bypass graft or stent patency (for stents ≥ 3 mm) (Gulati et al [*AHA* et al] 2021: class 2a, level B-NR evidence). In those who have had prior CABG surgery who are suspected to have myocardial ischemia, CCTA is reasonable to evaluate for myocardial ischemia or graft stenosis or occlusion (Gulati et al [*AHA* et al] 2021: class 2a, level C-LD evidence). CCTA may also be useful to assess patency of prior left main coronary stents, and can identify in-stent re-stenosis (Fihn et al [*ACCF* et al] 2012: class IIb, level B evidence; Wolk et al [*ACCF* et al] 2014; Litmanonvich et al [*ACR*] 2021).

CCTA should not be performed for assessment of native coronary arteries with moderate or severe calcification or with coronary stents < 3 mm (Fihn et al [*ACCF* et al] 2012: class III (no benefit), level B evidence; PLE expert panel consensus opinion). It is also not generally recommended for routine follow-up assessment after CABG or PCI in patients with stable symptoms or patients who are asymptomatic if performed more frequently than 5 year intervals following CABG or 2 year intervals following PCA (Fihn et al [*ACCF* et al] 2012: class III (no benefit), level C evidence; Wolk et al [*ACCF* et al] 2014; PLE expert panel consensus opinion).

Stress imaging: radionuclide myocardial perfusion imaging (PET or SPECT), cardiac MRI (CMR), or echocardiography

The use of stress imaging is appropriate for symptomatic post-revascularization (PCI or CABG) patients (Wolk et al [*ACCF* et al] 2014), including whenever there is uncertainty about whether chest pain is caused by myocardial ischemia (*NICE* 2016). In patients who have had prior CABG surgery presenting with stable chest pain who are suspected to have myocardial ischemia, it is reasonable to perform stress imaging to evaluate for myocardial ischemia or graft stenosis or occlusion (Gulati et al [*AHA* et al] 2021: class 2a, level C-LD evidence). It may be appropriate to evaluate asymptomatic patients with the following scenarios (Wolk et al [*ACCF* et al] 2014; Fihn et al [*ACCF* et al] 2012: class IIa, level C evidence; Schidler et al [*SNMMI* et al] 2020: score 6):

- Incomplete revascularization and additional revascularization is feasible,
- Prior left main coronary stent,
- > 5 years after CABG, or
- > 2 years after PCI

Stress imaging is not recommended in asymptomatic patients with history of CABG of < 5 years or PCI < 2 years (Schindler et al [*SNMMI* et al] 2020: score 2; Fihn et al [*ACCF* et al] 2012: class III (no benefit), level C evidence; Wolk et al [*ACCF* et al] 2014).

Invasive coronary angiography
In symptomatic post-revascularization patients (PCI or CABG), invasive coronary angiography is appropriate (Wolk et al [*ACCF*] et al 2014). In patients who have had prior CABG surgery presenting with stable chest pain whose noninvasive stress test results show moderate-to-severe ischemia, or in those suspected to have myocardial ischemia with indeterminate/nondiagnostic stress test, invasive coronary angiography is recommended for guiding therapeutic decision-making (Gulati et al [*AHA* et al] 2021: class I, level C-LD evidence). It may also be appropriate for asymptomatic patients with prior left main coronary stent (Wolk et al [*ACCF*] et al 2014). Its use is not appropriate for asymptomatic patients with previous history of CABG or PCI (Wolk et al [*ACCF* et al 2014).

<u>Clinical notes:</u>

- After revascularization, patients should be monitored vigilantly, because they are at greater risk for complications (Knuuti et al [*ESC*] 2020).
- To assess a patient's risk > 1 year after revascularization, an annual evaluation by a cardiovascular practitioner is warranted, even if the patient is asymptomatic (Knuuti et al [*ESC*] 2020).

<u>Evidence update (2016-present):</u>
Low Level of Evidence
Pezel et al (2021) assessed the long-term prognostic value of vasodilator stress perfusion CMR in asymptomatic patients with obstructive CAD. Consecutive patients referred for CMR were followed for the occurrence of major adverse cardiovascular events (MACE), defined as cardiovascular mortality or recurrent non-fatal myocardial infarction (MI). Known obstructive CAD was defined by history of PCI, CABG, or myocardial infarction. A total of 1,529 patients were enrolled, with 1,342 patients (87.8%; mean age 67,7 years) completing the follow-up (median 8.3 years). A total of 195 had MACE (14.5%). Patients without stress-induced myocardial ischemia had a low annualized rate of MACE (2.4%), whereas the annualized rate of MACE was higher for those with mild (7.3%), moderate (16.8%) or severe ischemia (42.2%); P < 0.001). In multivariable stepwise Cox regression, myocardial ischemia and late gadolinium enhancement (LGE) were independent predictors of MACE (HR 2.80; 95% CI: 2.10-3.73, p < 0.001 and HR 1.51; 95% CI: 1.01-2.27; p = 0.045). The authors conclude that vasodilator stress CMR-induced myocardial ischemia and LGE are good long-term predictors for the incidence of MACE in asymptomatic patients with obstructive CAD.

Pontone et al (2016), in a prospective study, compared an anatomic (CCTA) versus a functional (stress-CMR) strategy in 600 symptomatic patients with previous myocardial revascularization procedures. Patients were divided evenly into the groups (n = 300) and followed-up for subsequent noninvasive tests, invasive coronary angiography, revascularization procedures, cumulative effective radiation dose, and major adverse cardiac events. The mean follow-up for CCTA and stress-CMR groups was similar (773.6 ± 345 versus 752.8 ± 291 days; P=0.21). Compared with stress-CMR, CCTA was associated with a higher rate of subsequent noninvasive tests (28% vs 17%; P=0.0009), invasive coronary angiography (31% vs 20%; P=0.0009), and revascularization procedures (24% vs 16%; P=0.007). Stress-CMR strategy was associated with a significant reduction of radiation exposure (59%; P<0.001). Patients undergoing stress-CMR also showed a lower rate of major adverse cardiac events (5% vs 10%; P<0.010).

Guideline exclusions:

- Patients who have features consistent with emergent conditions or who are treated acutely
- Evaluation of perioperative risk in patients undergoing non-coronary cardiac surgery
- Transesophageal echocardiogram (TEE)
- Vasospastic angina
- Primary diagnosis of syncope without ischemic equivalent
- Pregnant patients
- Pediatric patients
- AI applications

AUC Revision History:

Revision Date:	New AUC Clinical Scenario(s):	Approved By:
05/11/2021	n/a	CDI Quality Institute's Multidisciplinary Committee
09/27/2022	n/a	RAYUS Quality Institute's Multidisciplinary Committee

Information on our evidence development process, including our conflicts of interest policy is available on our website at **https://rayusradiology.com/ple**

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Appropriateness of Advanced Imaging in Patients with Coronary Artery Disease (suspected or diagnosed): Bibliography

09/27/2022

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