

**American College of Radiology  
ACR Appropriateness Criteria®  
Chronic Chest Pain-High Probability of Coronary Artery Disease**

**Variant: 1 Chronic chest pain; high probability of coronary artery disease. No known ischemic heart disease. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
US echocardiography transthoracic stress	Usually Appropriate	○
Arteriography coronary	Usually Appropriate	☼☼☼
MRI heart function with stress without and with IV contrast	Usually Appropriate	○
MRI heart function with stress without IV contrast	Usually Appropriate	○
CTA coronary arteries with IV contrast	Usually Appropriate	☼☼☼
Rb-82 PET/CT MPI rest and stress	Usually Appropriate	☼☼☼☼
SPECT or SPECT/CT MPI rest and stress	Usually Appropriate	☼☼☼☼
US echocardiography transthoracic resting	May Be Appropriate	○
MRI heart function and morphology without and with IV contrast	May Be Appropriate	○
CT coronary calcium	May Be Appropriate	☼☼☼
US echocardiography transesophageal	Usually Not Appropriate	○
MRA coronary arteries without and with IV contrast	Usually Not Appropriate	○
MRA coronary arteries without IV contrast	Usually Not Appropriate	○
MRI heart function and morphology without IV contrast	Usually Not Appropriate	○
CTA chest with IV contrast	Usually Not Appropriate	☼☼☼
CTA triple rule out	Usually Not Appropriate	☼☼☼
Nuclear medicine ventriculography	Usually Not Appropriate	☼☼☼
CT heart function and morphology with IV contrast	Usually Not Appropriate	☼☼☼☼

**Variant: 2 Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
US echocardiography transthoracic stress	Usually Appropriate	○
Arteriography coronary	Usually Appropriate	☼☼☼
MRI heart function and morphology without and with IV contrast	Usually Appropriate	○
MRI heart function with stress without and with IV contrast	Usually Appropriate	○
MRI heart function with stress without IV contrast	Usually Appropriate	○
CTA coronary arteries with IV contrast	Usually Appropriate	☼☼☼
Rb-82 PET/CT MPI rest and stress	Usually Appropriate	☼☼☼☼
SPECT or SPECT/CT MPI rest and stress	Usually Appropriate	☼☼☼☼
US echocardiography transthoracic resting	May Be Appropriate (Disagreement)	○
MRI heart function and morphology without IV contrast	May Be Appropriate	○
CT heart function and morphology with IV contrast	May Be Appropriate	☼☼☼☼
US echocardiography transesophageal	Usually Not Appropriate	○
MRA coronary arteries without and with IV contrast	Usually Not Appropriate	○
MRA coronary arteries without IV contrast	Usually Not Appropriate	○

CT coronary calcium	Usually Not Appropriate	☢☢☢
CTA chest with IV contrast	Usually Not Appropriate	☢☢☢
CTA triple rule out	Usually Not Appropriate	☢☢☢
Nuclear medicine ventriculography	Usually Not Appropriate	☢☢☢

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## Summary of Literature Review

### Introduction/Background

Chronic chest pain of suspected cardiac origin is usually a consequence of myocardial ischemia, representing an imbalance between myocardial oxygen demand and coronary blood flow. This is usually caused by hemodynamically significant coronary stenosis due to atherosclerotic plaque formation leading to reduced myocardial perfusion. Less common coronary causes of chronic chest pain include coronary spasm, microvascular disease, congenital coronary anomalies, spontaneous coronary artery dissection (rarely), or a combination of the above entities; however, the term "coronary artery disease" (CAD) is usually reserved to imply atherosclerotic disease as a cause of stenosis. In the setting of a high probability of CAD, flow-limiting epicardial coronary artery luminal narrowing is the most likely etiology. Chest pain of myocardial ischemic origin can also occur in patients with relatively normal coronary arterial caliber but with conditions resulting in increased demand for oxygenation (eg, increased myocardial mass and workload due to systemic arterial hypertension or aortic valve stenosis). Although the symptoms of exertional angina pectoris is most commonly associated with CAD, nonischemic cardiac (eg, myocarditis, pericarditis) and extracardiac (eg, esophageal reflux or spasm) etiologies, and costochondritis should also be considered in the setting of nonexertional or atypical chest pain [1]. This document refers to evaluation of patients who present with chronic chest pain and with high clinical suspicion for CAD. This document is focused on epicardial CAD and does not discuss the microvascular disease as the cause for CAD. For evaluation of patients with acute chest pain and concern for CAD and the evaluation of patients with low to intermediate risk of CAD, please refer to the ACR Appropriateness Criteria<sup>®</sup> topics on "[Acute Nonspecific Chest Pain-Low Probability of Coronary Artery Disease](#)" [2] and "[Chronic Chest Pain-Noncardiac Etiology Unlikely: Low to Intermediate Probability of Coronary Artery Disease](#)" [3] for further guidance.

Clinical risk assessment is used to determine the pretest probability of CAD. Multiple methods are available to categorize patients as low, medium, or high risk of developing CAD. Existing methods, including the Diamond and Forrester method, Framingham risk score, coronary calcium score (CCS), and Duke Clinical Score, are based on different criteria such as age, sex, family history of CAD, type of chest pain, lipid levels, and previous cardiovascular events. One study suggests that the Diamond and Forrester method overestimates the prevalence of obstructive CAD and the Duke Clinical Score performs better in low-risk patients [4-6]. McKavanagh et al [4] suggested that stable

CAD would be more accurately risk stratified using the CCS method rather than the Diamond and Forrester method. In conclusion, risk assessment for CAD using various existing methods can lead to variable pretest probability and may stratify patients in different risk categories [6]. Pretest probability and risk of CAD is an important aspect of clinical evaluation and will be incorporated in clinical decision for low, intermediate, or high clinical probability for CAD as the cause of a patient's symptoms.

In patients with chronic chest pain with a high clinical probability of CAD or known ischemic heart disease (IHD), imaging is used to characterize known and unknown IHD. In patients with no known IHD, imaging is valuable in determining and documenting the presence, extent, and severity of obstructive coronary narrowing as well as the presence of myocardial ischemia. Imaging also allows for exclusion of nonocclusive atherosclerotic CAD and/or demonstration of abnormalities (eg, congenital or acquired coronary artery anomalies) as well as other etiologies for CAD that can produce chest pain in the absence of coronary obstructive disease.

In patients with known IHD, imaging findings are important in determining the management of patients with chronic myocardial ischemia and can serve as a decision-making tool for medical therapy, angioplasty, stenting, or surgery. Imaging can help understand long-term prognosis and expected benefit from various therapeutic options by evaluating disease location, plaque characteristics, and pre-existing myocardial infarction, as well as determining ventricular function, diastolic relaxation, and end-systolic volume [7].

### **Initial Imaging Definition**

Initial imaging is defined as imaging at the beginning of the care episode for the medical condition defined by the variant. More than one procedure can be considered usually appropriate in the initial imaging evaluation when:

- There are procedures that are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care)

OR

- There are complementary procedures (ie, more than one procedure is ordered as a set or simultaneously wherein each procedure provides unique clinical information to effectively manage the patient's care).

### **Discussion of Procedures by Variant**

**Variant 1: Chronic chest pain; high probability of coronary artery disease. No known ischemic heart disease. Initial imaging.**

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#### **A. Arteriography Coronary**

Catheter-based selective coronary angiography is historically considered the coronary imaging modality of choice with the highest spatial and temporal resolution. Although only 2-D projection images are obtained (as opposed to 3-D volumes in coronary CTA [CCTA]), selective coronary

angiography is considered to be the reference standard for depicting the anatomy and the severity of obstructive CAD and other coronary abnormalities (eg, congenital variants, coronary spasm, dissection, vasculitis) [8]. In addition to visualizing the coronary arteries, the procedure is used to guide percutaneous coronary interventions to the site of the blockage. Hemodynamic relevance of coronary stenosis identified on invasive coronary angiography (ICA) is assessed by measuring fractional flow reserve (FFR) [9,10].

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**B. CT Coronary Calcium**

Coronary artery calcification is an indicator of coronary atherosclerosis presence and can be assessed using ECG-gated noncontrast CT of the heart [11]. There are limited data on the use of CT coronary calcium in symptomatic patients at a high risk for CAD.

CCS has been shown to provide value in symptomatic individuals presenting with chest pain for risk assessment for future events [12]. A zero CCS in patients undergoing CT scanning for suspected stable angina has a high negative predictive value (NPV) for the exclusion of obstructive CAD and is associated with a good medium-term prognosis [13].

In one large multicenter study (Prospective Multicenter Imaging Study for Evaluation of Chest Pain [PROMISE] trial) that included patients with stable chest pain and no history of CAD, presence of measurable coronary artery calcification at the baseline was associated with clinical events [14]. A substudy of another larger multicenter trial (Coronary Evaluation Using Multi-Detector Spiral Computed Tomography Angiography Using 64 Detectors [CORE-64]) demonstrated that in patients with high probability of CAD and no known CAD, the absence of coronary calcification does not exclude obstructive stenosis [15]. Conversely, a prospective randomized controlled trial (Computed Tomography vs. Exercise Testing in Suspected Coronary Artery Disease [CRESCENT]) showed that in patients with stable chest pain and no known CAD, the presence of a coronary calcium and even a high total coronary artery calcification score is not clearly associated with ischemia [16].

A single-center study including patients with clinical signs and symptoms with an intermediate-to-high risk of coronary disease had a higher frequency of abnormal Rb-82 PET perfusion imaging if their CCS was  $\geq 400$  as compared with patients with a CCS of 1 to 399 (48.5% versus 21.7%,  $P < .001$ ), and a zero CCS was associated with myocardial ischemia on provocative testing in 16% in these patients [17].

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**C. CT Heart Function and Morphology**

CT heart function and morphology can provide assessment of ventricular morphology and function as well as assessment of myocardial perfusion and infarction. There are no relevant data published on the use of CT heart for assessment of heart function and regional wall motion abnormalities in patients with chronic chest pain who have a high probability for CAD.

A single-center prospective study has shown that, in patients with chronic chest pain and intermediate to high pretest probability of CAD or prior history of CAD and presence of coronary artery stenosis ( $\geq 50\%$ ), stress myocardial perfusion assessment by CT can detect myocardial

ischemia with a sensitivity, specificity, positive predictive value (PPV), and NPV of 100%, 81%, 50%, and 100%, respectively, and an area under the curve of 0.92 when compared with the reference standard single-photon emission CT (SPECT)-myocardial perfusion imaging (MPI) [18].

Several studies have validated stress CT myocardial perfusion against SPECT, stress cardiac MR (CMR), and invasive FFR in patients with suspected or known CAD (no clinical data reported on the presence or absence of chronic chest pain), and it was shown, when combined with CTA, to accurately predict perfusion abnormalities related to atherosclerotic luminal narrowing [19-23].

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**D. CTA Chest**

CTA chest has been shown to be effective in excluding noncardiac causes for chronic chest pain. It has also been shown in some studies to facilitate the diagnosis of acute coronary syndrome and the decision on emergent catheterization, when left ventricular (LV) myocardial ischemia is identified [24]. There is no relevant literature to support non-ECG-gated CTA of the chest in the evaluation of chronic chest pain for the initial evaluation of CAD in patients who are high risk and without known IHD.

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**E. CTA Triple Rule Out**

Triple rule out (TRO) is used for diagnosis of acute chest pain and simultaneous assessment of aorta, coronary arteries, and pulmonary arteries. There is no relevant literature to support the use of TRO in patients with chronic chest pain and a high probability of CAD with no known IHD.

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**F. CTA Coronary Arteries**

CTA coronary arteries can diagnose the presence of atherosclerotic plaque, the degree of coronary artery stenosis, coronary artery dissection, or congenital anomalies of coronary arteries. CCTA in symptomatic patients with chronic chest pain and both known and unknown CAD has a reported high accuracy compared with ICA and high NPV [25-28]. The CCTA ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial found 95% sensitivity, 83% specificity, 64% PPV, and 99% NPV for detection of CAD, suggesting that CCTA possesses high diagnostic accuracy for detecting coronary stenosis at thresholds of 50% [25]. A meta-analysis conducted by Haase et al [29] showed that, in patients with stable chest pain and high clinical pretest probability of obstructive CAD (67%), the PPV of CTA was 82.7% (78.3%–86.2%), and the NPV was 85.0% (80.2%–88.9%), respectively. The diagnostic performance of CCTA was not influenced by angina pectoris type [29]. The CORE-64 study reported receiver operating characteristic (ROC) area for cardiac CT of 0.93 using quantitative coronary angiography as the reference standard [30]. A meta-analysis to evaluate the diagnostic accuracy of 64-slice CCTA compared with conventional selective coronary angiography in symptomatic patients with suspected CAD included 27 studies and 1,740 patients and found that the sensitivity, specificity, PPV, and NPV were 86%, 96%, 83%, and 96.5%, respectively, by per-segment analysis and 97.5%, 91%, 93%, and 96.5%, respectively, by per-patient analysis [31].

CCTA obtained in addition to standard of care in patients with stable chest pain with a high pretest

probability of CAD has been demonstrated to result in a significantly lower rate of death from coronary heart disease or nonfatal myocardial infarction at 5 years compared with standard of care alone [32]. CCTA has been shown to change treatment among 23% of patients in the CCTA arm compared with 5% in the standard-of-care arm with increased use of preventive therapy when atherosclerosis was identified and cancellations of preventive and antianginal therapy with normal coronaries [32].

#### *CCTA and FFR-CT*

FFR-CT allows for determination of lesion-specific ischemia associated with a coronary arterial narrowing. FFR-CT is performed in conjunction with CCTA [33,34]. FFR-CT has a high diagnostic performance when compared against invasive FFR as the reference standard: 82% specificity and 74% PPV [33].

FFR-CT provides incremental improvement in accuracy over CCTA alone (84% versus 59%), mitigating the high sensitivity/low specificity tradeoff of CCTA [33]. FFR-CT correctly reclassified 68% of false-positive patients as true negatives, highlighting the potential role of FFR-CT as a gatekeeper to cardiac catheterization [35,36]. The major strength of this modality is in coupling anatomical and functional data. In a meta-analysis by Danad et al [37], FFR-CT showed high sensitivity (85%–93%) and moderate specificity (65%–75%) compared with invasive FFR, and the authors concluded that FFR-CT in combination with CCTA could significantly improve diagnostic specificity, provided the coupling of anatomic and functional measures. Another meta-analysis by Zhuang et al [38] showed a pooled sensitivity and specificity for FFR-CT at the per-patient level of 89% and 71%, respectively, whereas, on the per-vessel basis, it was 85% and 82%, respectively. No apparent difference in the sensitivity at per-patient and per-vessel level between FFR-CT and CCTA was observed (0.89 versus 0.93 at per-patient; 0.85 versus 0.88 at per-vessel). However, the specificity of FFR-CT was higher than CCTA (0.71 versus 0.32 at per-patient analysis; 0.82 versus 0.46 at per-vessel analysis) [38].

In a multicenter trial (Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Wave [ADVANCE]), 5,083 patients demonstrated the prognostic value of CTA with FFR-CT in patients with stable chest pain with a trend to lower major adverse cardiac events and lower cardiovascular death or myocardial infarction with a negative FFR-CT [39].

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#### **G. MRA Coronary Arteries Without and With IV Contrast**

Coronary MR angiography (MRA) does not assess late gadolinium enhancement or viability. MRA coronary arteries can demonstrate lumen narrowing of the proximal coronary arteries. There are limited data on the use of MRA coronary arteries without and with intravenous (IV) contrast in symptomatic patients with a high probability for CAD.

In a single-center prospective study in patients with suspected CAD, 82% sensitivity, 90% specificity, 88% PPV, and 86% NPV for detecting significant CAD were demonstrated [40].

**Variant 1: Chronic chest pain; high probability of coronary artery disease. No known ischemic heart disease. Initial imaging.**

#### **H. MRA Coronary Arteries Without IV Contrast**

There is limited data on the use of MRA coronary arteries without IV contrast in symptomatic

patients with a high probability for CAD.

A multicenter prospective trial has assessed the accuracy of MRA for detecting a  $\geq 50\%$  coronary artery stenosis in patients with [chest pain](#) and suspected newly developed or recurrent [coronary artery stenosis](#). Compared to ICA, high sensitivity (88%), moderate specificity (72%), a moderate PPV (71%), and a high NPV (88%) with an [AUC](#) of 0.87 for detecting significant [coronary artery stenosis](#) were demonstrated [41].

In symptomatic patients with an intermediate or high pretest probability for disease, noncontrast coronary MRA had a patient-based sensitivity of 96%, specificity of 68%, PPV of 79%, and NPV of 93% in the detection of functionally significant CAD as defined by a  $>90\%$  stenosis or FFR  $<0.8$  on catheter angiography. When added to a comprehensive stress-rest MRI protocol, it had a nonsignificant increase in diagnostic accuracy [42].

**Variant 1: Chronic chest pain; high probability of coronary artery disease. No known ischemic heart disease. Initial imaging.**

**I. MRI Heart Function and Morphology Without and With IV Contrast**

MRI heart function and morphology without and with IV contrast can demonstrate myocardial infarction and ischemia secondary to CAD and can provide assessment of LV wall function.

Areas of myocardial infarction detected on MRI have been shown to be a predictor of mortality and major adverse cardiac events, compared with clinical data, coronary sclerosis at angiography, or LV end-systolic volume index (ESVI) and LV ejection fraction (LVEF) in patients with suspected CAD, even when areas of infarction are small. Even a small area of infarction ( $<2\%$  of LV mass) was associated with a greater than 7-fold increase in risk for a major adverse cardiac event. Delayed-enhancement MRI in patients without known CAD is associated with lower LVEF and greater LV mass [43].

A single-center observational prospective study with 376 patients with a history suggesting stable CAD but with no history of myocardial ischemia demonstrated that evidence of myocardial infarction on CMR is an independent noninvasive marker of prognosis in stable CAD patients [44] and remains the strongest predictor of adverse events, even after adjustment for significant CAD on angiogram, LVEF, and wall motion abnormality [44,45].

**Variant 1: Chronic chest pain; high probability of coronary artery disease. No known ischemic heart disease. Initial imaging.**

**J. MRI Heart Function and Morphology Without IV Contrast**

MRI heart function and morphology without IV contrast provides assessment of ejection fraction and ventricular volumes including LVEF and ESVI with a higher sensitivity to detect prior myocardial infarct than ischemia.

There is no relevant literature to support the use of MRI heart function and morphology without IV contrast in the initial evaluation of patients with chronic chest pain and a high probability of CAD with no known IHD.

**Variant 1: Chronic chest pain; high probability of coronary artery disease. No known ischemic heart disease. Initial imaging.**

**K. MRI Heart Function with Stress Without and With IV Contrast**

MRI with function/wall motion (dobutamine stress test) and MRI with vasodilator stress perfusion (adenosine/regadenoson stress test) have been used to diagnose hemodynamically significant CAD in patients with an intermediate to high likelihood of having significant stenosis.

Investigations of MRI heart function stress for patients with known CAD indicate that patients with known (70%) or suspected (30%) CAD with inducible LV wall motion abnormalities during dobutamine CMR predict cardiac death and myocardial ischemia [46]. A single-center prospective study focusing on women with known or suspected CAD and variable clinical symptoms demonstrated that, similar to men, dobutamine CMR can identify cardiac risk in women with known or suspected IHD [47]. A single-center study of 815 consecutive patients referred for evaluation of suspected myocardial ischemia over a 10 year period has shown that stress CMR with its protocol including stress and rest myocardial perfusion, ventricular function, and late gadolinium enhancement, effectively reclassifies patient risk beyond standard clinical variables, specifically in patients at moderate to high pretest clinical risk and in patients with established CAD [48].

MRI heart function stress has a high NPV for adverse cardiac events in patients with known or suspected CAD [46,47]. A meta-analysis of 14 studies has shown that MRI heart function stress has a high NPV for adverse cardiac events, and the absence of inducible perfusion defect or wall motion abnormality shows a similar ability to identify patients with a low risk for adverse cardiac events among patients with known or suspected CAD [49]. The MR-INFORM trial investigated MRI perfusion versus combined invasive angiography with invasive FFR in patients with stable angina and an intermediate to high risk of disease. The study showed that MRI perfusion had noninferior major adverse cardiac events compared with invasive FFR with the added patient benefit of a lower incidence of revascularization [50].

A meta-analysis from pooled studies found that perfusion MRI heart function stress has a sensitivity of 89.1% and a specificity of 84.9% on a patient-based analysis using FFR as a reference, suggesting that stress perfusion MRI remains an accurate test for the detection of flow-limiting stenosis in patients with suspected or established CAD [6].

In another meta-analysis of 37 studies, including 2,191 patients with high CAD prevalence, stress CMR, using either wall motion abnormality or perfusion abnormality technique, demonstrates overall good sensitivity and specificity for the diagnosis of CAD; stress-induced wall motion abnormalities imaging demonstrated a sensitivity of 0.83 and specificity of 0.86 on a patient level (disease prevalence = 70.5%). Stress perfusion imaging demonstrated a sensitivity of 0.91 and specificity of 0.81 on a patient level (disease prevalence = 57.4%) [51].

In patients with known or suspected CAD, the presence of late gadolinium enhancement and stress perfusion defect plus abnormal wall motion are independent predictors of all hard cardiac events [52].

**Variant 1: Chronic chest pain; high probability of coronary artery disease. No known ischemic heart disease. Initial imaging.**

#### **L. MRI Heart Function with Stress Without IV Contrast**

MRI heart function stress without IV contrast can provide assessment of ventricular function/wall motion abnormalities.



A single-center prospective study of 884 patients with known (70%) or suspected (30%) CAD demonstrated that inducible LV wall motion abnormalities during dobutamine CMR predicts cardiac death and myocardial ischemia [46]. A single-center prospective study focusing on women with known or suspected CAD and variable clinical symptoms demonstrated that, similar to men, dobutamine CMR can identify cardiac risk in women with known or suspected IHD [47].

A single-center prospective study of 208 patients with suspected CAD has demonstrated a high accuracy for detecting wall motion abnormalities related to ischemia with 86.2% sensitivity and 85.7% specificity [53].

A single-center prospective study of 153 patients with suspected or known CAD, with and without chest pain, has demonstrated 83% sensitivity and 83% specificity for detecting a >50% luminal diameter narrowing based on stress-induced abnormal LV contractility [54].

**Variant 1: Chronic chest pain; high probability of coronary artery disease. No known ischemic heart disease. Initial imaging.**

**M. Nuclear Medicine Ventriculography**

Stress radionuclide ventriculography includes measurement of the ejection fraction and assessment of regional wall motion at rest and during stress. There is no relevant literature to support nuclear medicine ventriculography in the initial evaluation of patients with chronic chest pain and a high probability of CAD with no known IHD.

**Variant 1: Chronic chest pain; high probability of coronary artery disease. No known ischemic heart disease. Initial imaging.**

**N. Rb-82 PET/CT Heart**

Rb-82 PET/CT heart assesses rest myocardial perfusion and stress LVEF and quantifies rest myocardial blood flow and coronary flow reserve [55,56]. PET/CT has a reported higher accuracy over conventional nuclear techniques, MPI, and viability [55,57]. Rb-82 PET/CT has shown that myocardial perfusion, stress LVEF, and ischemic LV dysfunction are prognostically important in CAD in patients with suspected or known CAD [48]. A single-center prospective study of 510 patients with suspected CAD has shown that Rb-82 PET/CT has demonstrated sensitivity and specificity of 90% and 88% for the detection of obstructive coronary disease compared with ICA [52]. Among patients with suspected CAD, gated Rb-82 PET/CT can also identify a subset of patients with 3-vessel or left main coronary artery CAD [57].

A single-center study of 1,432 patients with known or suspected CAD has shown that the inherent ability of Rb-82 PET/CT to collect LV function data at rest and during peak stress leads to an improved detection of multivessel CAD [58]. LVEF reserve provides significant independent and incremental value to Rb-82 MPI for predicting the risk of left main/3-vessel disease [57] and future adverse events [59].

A multicenter registry study included 7,061 patients with known or suspected CAD who underwent a clinically indicated rest/stress Rb-82 PET MPI (66% of patients had chronic chest pain as the reason for the test). The extent and severity of ischemia and scarring on Rb-82 PET MPI provided powerful and incremental risk estimates of cardiac death and all-cause death compared with traditional coronary risk factors [60].

Hybrid PET scanners use CT for attenuation correction (PET/CT) following completion of the PET study. By coupling the PET perfusion examination findings to a CCTA, PET/CT permits the fusion of complementary anatomic coronary arterial and functional (perfusion) myocardial information and enhances diagnostic accuracy [60]. The results of the combined examinations can more accurately identify patients for revascularization. In a study of 110 consecutive patients with combined stress Rb-82 PET perfusion imaging and CCTA, nearly half of the significant angiographic stenoses (47%) occurred without evidence of ischemia, whereas 50% of normal PET studies were associated with some CCTA abnormality [61].

**Variant 1: Chronic chest pain; high probability of coronary artery disease. No known ischemic heart disease. Initial imaging.**

**O. SPECT or SPECT/CT MPI Rest and Stress**

Stress SPECT MPI can identify relative myocardial perfusion defects, indicating the presence of myocardial ischemia and/or infarction. The territory of the perfusion defect identifies the likely coronary artery involved and can usually distinguish between significant single-vessel and multivessel coronary arterial obstructions [62,63].

A single-center study of >900 diabetic patients demonstrated that SPECT MPI has a reported sensitivity of 87% to 89% and a specificity of 73% to 75% for detecting angiographically significant CAD [62]. Another single-center study evaluated 100 consecutive patients referred for SPECT MPI because of either chronic chest pain and no known CAD (55%) or patients with a documented history of myocardial infarction (29%) referred for risk stratification [64]. MPI and poststress and reversible regional wall motion abnormalities on exercise stress Tc-99m-gated SPECT MPI were significant predictors of angiographic disease and add incremental value to MPI for the assessment of angiographic severity [64,65].

In patients with typical angina (high pretest likelihood of disease), stress SPECT MPI is useful for estimating the extent (single vessel versus multivessel disease) and severity of coronary stenosis, which has relevance for prognosis, choice among therapeutic options, and advisability of performing coronary arteriography. A meta-analysis including 114 SPECT studies of patients with suspected or established CAD has shown the sensitivity and specificity for the detection of significant CAD and/or myocardial ischemia was 78% and 52%, respectively, with an NPV of 83% [66].

A study of 5,366 consecutive patients with suspected or established CAD who underwent stress electrocardiography-gated SPECT MPI has shown that inducible ischemia identifies which patients have a short-term benefit from revascularization, while LVEF predicts cardiac death [67]. A normal stress SPECT MPI examination in patients with an intermediate to high likelihood of CAD predicts a low rate of cardiac death or nonfatal myocardial infarction ( $\leq 1\%$  per year) [67].

*SPECT and CCTA*

Hybrid SPECT/CCTA combines the anatomical information provided by CCTA with the functional perfusion evidence of SPECT, resulting in enhanced diagnostic accuracy for detecting significant CAD compared with SPECT and CCTA alone: the sensitivity and specificity of hybrid SPECT/CCTA were 96% and 95%, respectively, compared with SPECT (93% and 79%) and CCTA (98% and 62%) alone [68]. There was 92% agreement on the necessity of revascularization in the treatment decisions based on hybrid SPECT/CCTA versus SPECT and coronary angiography alone [69].

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**P. US Echocardiography Transesophageal**

Ultrasound (US) echocardiography transesophageal provides assessment of LVEF and ESVI and structural assessment of the heart and ascending aorta. There is no relevant literature to support the use of transesophageal echocardiography in the initial evaluation of patients with chronic chest pain and a high probability of CAD with no known IHD.

**Variant 1: Chronic chest pain; high probability of coronary artery disease. No known ischemic heart disease. Initial imaging.**

**Q. US Echocardiography Transthoracic Resting**

US echocardiography transthoracic resting provides assessment of ejection fraction and ventricular volumes such as LVEF and ESVI with a higher sensitivity to detect prior myocardial infarct than ischemia. Although there is no relevant literature to support transthoracic echocardiography resting in the initial evaluation of patients with chronic chest pain and a high probability of CAD with no known IHD, this modality could be used to assess new wall motion abnormalities that might raise a concern for IHD.

**Variant 1: Chronic chest pain; high probability of coronary artery disease. No known ischemic heart disease. Initial imaging.**

**R. US Echocardiography Transthoracic Stress**

US stress 2-D echocardiography depiction of myocardial contractility during rest and stress is used for evaluation of patients with suspected regional wall motion abnormalities secondary to inducible regional ischemia. A single-center prospective study of 183 patients with suspected and known CAD has shown dobutamine-atropine stress echocardiography has a specificity of 91% in detecting significant CAD (defined as  $\geq 50\%$  coronary artery luminal diameter stenosis) [70].

In a meta-analysis of 435 patients (299 with and 136 without angiographically assessed CAD), dobutamine stress contractility echocardiography had 84% accuracy, 86% specificity, and 86% sensitivity for detecting CAD [71].

A meta-analysis of 44 studies including patients with suspected or known CAD indicated that stress echocardiography has a sensitivity of 85% and a specificity of 77% in detection of CAD (defined as  $> 50\%$  coronary artery luminal diameter stenosis) [72].

In patients with suspected or known CAD, inducible wall motion abnormality during dobutamine stress echocardiography is associated with a higher risk for subsequent cardiac events. Patients with negative dobutamine stress echocardiography exhibited a lower event rate [47].

US contrast-enhanced stress echocardiography improves endocardial visualization. A single-center prospective randomized trial that included 229 patients with suspected or know CAD has demonstrated diagnostic test rates of 100% for contrast-enhanced stress echocardiography [73].

A single-center prospective study of 101 patients with an intermediate to high probability of CAD based on clinical parameters and risk factors has demonstrated that administration of an echocardiography contrast agent (ie, microbubbles) improves endocardial visualization at rest and more so during stress, leading to a more precise interpretation with greater accuracy in evaluating CAD in patients with 2 or more nonvisualized segments and low confidence of interpretation

[71,74].

**Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

In this clinical scenario, prior definitive treatment is defined as previous coronary artery angioplasty, stent placement, or coronary arteries bypass graft.

**Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

**A. Arteriography Coronary**

Catheter-based selective coronary angiography is historically considered the coronary imaging modality of choice with the highest spatial and temporal resolution. Although only 2-D projection images are obtained (as opposed to 3-D volumes CCTA), selective coronary angiography is considered useful for depicting the anatomy and the severity of obstructive CAD and other coronary abnormalities (eg, coronary spasm, dissection, vasculitis) [8]. In addition to visualizing the coronary arteries, the procedure is used to guide percutaneous coronary interventions to the site of blockage. LV catheterization and left ventriculography are generally indicated but not always necessary to define ventricular function in patients with known angina and IHD. FFR measurement accurately estimates the functional severity of stenosis in obstructive CAD [75-77].

The ISCHEMIA trial has shown that, among patients with stable coronary disease and moderate or severe ischemia, there was no evidence that an invasive diagnostic and therapeutic strategy, compared with an initial conservative strategy, reduced the risk of ischemic cardiovascular events or death from any cause over a median of 3.2 years [78,79].

**Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

**B. CT Coronary Calcium**

There is no relevant literature to support the use of CT coronary calcium in the initial evaluation of patients with chronic chest pain and a high probability of CAD with known IHD.

**Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

**C. CT Heart Function and Morphology**

CT heart function and morphology can provide assessment of ventricular morphology and function as well as assessment of myocardial perfusion and infarction. There are no relevant data published on the use of CT heart for assessment of heart function and regional wall motion abnormalities in patients with chronic chest pain who have a high probability for CAD.

A single-center prospective study has shown that, in patients with chronic chest pain and an intermediate to high pretest probability of CAD or prior history of CAD and the presence of coronary artery stenosis ( $\geq 50\%$ ), stress myocardial perfusion assessment by CT can detect myocardial ischemia with a sensitivity, specificity, PPV, and NPV of 100%, 81%, 50%, and 100%, respectively, and an area under the curve of 0.92 when compared with the reference standard SPECT-MPI [18].

Several studies have validated stress CT myocardial perfusion against SPECT, stress CMR, and invasive FFR in patients with suspected or known CAD (no clinical data reported on presence or

absence of chronic chest pain) and was shown when combined with CTA to accurately predict perfusion abnormalities related to atherosclerotic luminal narrowing [19-23].

Patients with suspected or known CAD were evaluated with MPI using cardiac CT either in a single-phase mode for qualitative identification of ischemic myocardium [22] or in a multiphase mode for quantitative assessment of the myocardial blood flow [80].

Chronic infarction can often be differentiated from acute hypoperfusion by myocardial wall thinning or lower attenuation values (low or negative HU) as a result of fat tissue within the scar and/or calcifications [81].

### **Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

#### **D. CTA Chest**

CTA chest has been shown to be effective in excluding noncardiac causes for chronic chest pain narrowing the differential diagnosis and facilitating the appropriate triage for ICA. It has also been shown in some studies to facilitate the diagnosis of acute coronary syndrome and the decision on emergent catheterization, providing information on the ischemic myocardial area by detection of a localized decrease in LV enhancement [24].

There is no relevant literature to support the use of CTA chest in the initial evaluation of patients with chronic chest pain and a high probability of CAD with known IHD.

### **Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

#### **E. CTA Triple Rule Out**

There is no relevant literature to support the use of TRO in the initial evaluation of patients with chronic chest pain and a high probability of CAD with known IHD.

### **Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

#### **F. CTA Coronary Arteries**

CTA coronary arteries can diagnose nonobstructive and obstructive CAD and provide morphologic plaque characterization. There are no relevant data on the use of coronary CTA in patients with chronic chest pain, a high clinical suspicion of CAD, and known CAD. The largest up to date study on patients with an acute coronary syndrome and a high likelihood of CAD is VERDICT trial, assessing the diagnostic accuracy of CCTA in patients with non-ST-segment elevation acute coronary syndrome in comparison to invasive angiography. An accuracy of 89%, a sensitivity of 97%, a specificity of 72%, and a PPV of 88% was demonstrated for coronary artery stenosis detection. An NPV to rule out coronary stenoses was 91% [82]. Extrapolating from investigations of patients with a low to intermediate pretest probability for CAD, it has a high accuracy compared with ICA and a high NPV [25-28]. The CCTA ACCURACY trial found a 95% sensitivity, a 83% specificity, a 64% PPV, and a 99% NPV for the detection of CAD, suggesting that CCTA possesses high diagnostic accuracy for detecting coronary stenosis at thresholds of 50% [25]. In the CORE-64 study, the ROC area for cardiac CT was 0.93 using quantitative coronary angiography as the reference standard. CCTA also similarly predicted revascularization within 30 days as invasive angiography (ROC area 0.84 versus 0.82 for CCTA and quantitative coronary angiography, respectively) [30].

The CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) showed that patients with nonobstructive and obstructive CAD have incrementally higher rates of mortality, whereas the absence of atherosclerosis is associated with a very favorable prognosis [83]. Presence of extensive nonobstructive CAD have higher rates of adverse cardiovascular events than patients with less extensive but obstructive disease (14.5% versus 13.6%), underscoring the prognostic value of plaque burden only available with CCTA [83]. Presence of high-risk plaque features has been shown as an independent predictor of major acute coronary events in patients with nonobstructive CAD [84-87].

In patients who underwent previous coronary stenting, CCTA can identify in-stent re-stenosis. Andreini et al [88] have demonstrated specificity, PPV, NPV, and diagnostic accuracy for in-stent re-stenosis detection were 91%, 99%, 60% and 91%, respectively. In a meta-analysis conducted by Kumbhani et al [89], the overall sensitivity, specificity, PPV, and NPV for assessable stents were 91%, 91%, 68%, and 98%. No relevant data currently exists on using CCTA for initial evaluation of patients with suspected in-stent re-stenosis with chronic chest pain and a high probability of CAD with known IHD.

#### *FFR-CT*

FFR-CT allows for the determination of lesion-specific ischemia associated with a coronary arterial narrowing. FFR-CT is performed in conjunction with CCTA [33,34]. FFR-CT is available for native coronary arteries and not available in patients who underwent coronary artery bypass grafts, and it is not available for assessment of stented coronary arteries [33,34]. There is no current data on use of FFR-CT in selected groups of patients with known CAD. In patients with stable chest pain and suspected or established CAD, FFR-CT has a high diagnostic performance when compared against invasive FFR as the reference standard: 82% specificity and 74% PPV [33].

FFR-CT provides incremental improvement in the accuracy over CCTA alone (84% versus 59%), mitigating the high sensitivity/low specificity tradeoff of CCTA [33]. Another study of patients with suspected and established CAD (no data provided on clinical symptoms) has demonstrated that FFR-CT has correctly reclassified 68% of false-positive patients as true negatives, highlighting the potential role of FFR-CT as a gatekeeper to cardiac catheterization [35,36].

The major strength of this modality is in coupling anatomical and functional data. In a meta-analysis by Danad et al [37], FFR-CT showed high sensitivity (85%–93%) and moderate specificity (65%–75%) compared with invasive FFR, and the authors concluded that FFR-CT in combination with CCTA could significantly improve diagnostic specificity, provided the coupling of anatomic and functional measures. Another meta-analysis by Zhuang et al [38] showed a pooled sensitivity and specificity for FFR-CT at the per-patient level of 89% and 71%, respectively, and the per-vessel basis was 85% and 82%, respectively. No apparent difference in the sensitivity at per-patient and per-vessel level between FFR-CT and CCTA was observed (0.89 versus 0.93 at per-patient; 0.85 versus 0.88 at per-vessel). However, the specificity of FFR-CT was higher than CCTA (0.71 versus 0.32 at per-patient analysis; 0.82 versus 0.46 at per-vessel analysis) [38].

**Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

#### **G. MRA Coronary Arteries Without and With IV Contrast**

Coronary MRA does not include delayed gadolinium enhancement or viability. Coronary MRA can

demonstrate lumen narrowing of the proximal coronary arteries. There is limited data on the use of MRA coronary arteries without and with IV contrast in a symptomatic patient with a high probability for CAD.

In a single-center prospective study in patients with suspected CAD, 82% sensitivity, 90% specificity, 88% PPV, and 86% NPV for detecting significant CAD were demonstrated [40].

There are no relevant data evaluating MRA coronary arteries without and with IV contrast in symptomatic patients with a high probability for CAD.

**Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

**H. MRA Coronary Arteries Without IV Contrast**

There is limited data on the use of MRA coronary arteries without IV contrast in symptomatic patient with a high probability for CAD.

A multicenter prospective trial has assessed the accuracy of MRA for detecting a  $\geq 50\%$  coronary artery stenosis in patients with [chest pain](#) and suspected newly developed or recurrent [coronary artery stenosis](#). Compared with ICA, high sensitivity (88%), moderate specificity (72%), a moderate PPV (71%), and a high NPV (88%) with an [AUC](#) of 0.87 for detecting significant [coronary artery stenosis](#) were demonstrated [41].

In symptomatic patients with an intermediate or high pretest probability for disease, noncontrast coronary MRA had a patient-based sensitivity of 96%, a specificity of 68%, a PPV of 79%, and an NPV of 93% in the detection of functionally significant CAD as defined by a  $>90\%$  stenosis or FFR  $<0.8$  on catheter angiography. When added to a comprehensive stress-rest MRI protocol, it had a nonsignificant increase in diagnostic accuracy [42].

**Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

**I. MRI Heart Function and Morphology Without and With IV Contrast**

MRI heart function and morphology without and with IV contrast can demonstrate myocardial infarction and ischemia secondary to CAD and can provide assessment of LV wall function. Extrapolation of data on MRI heart function and morphology without and with IV contrast for patients with known CAD is provided below, with a note that no information is available regarding the presence or absence of chest pain in patients included in these studies [70,90-98].

In a multicenter study, assessment of a consecutive 1,560 patients with established or suspected CAD has shown that both LVEF and the amount of myocardial damage are independent predictors of all-cause mortality. Even in patients with near-normal LVEF, significant infarction identifies a cohort with a high risk for early mortality [70].

Demonstration of residual contractile function in dysfunctional segments in response to dobutamine stimulation at cine MRI has been shown to be better than delayed-enhancement MRI alone for prediction of recovery of segmental function 3 months after revascularization [98]. Late gadolinium enhancement MRI can demonstrate the presence, location, and transmural extent of acute and chronic myocardial infarctions [90,95], with a sensitivity of 99% for the detection of acute infarction and 94% for the detection of chronic infarction [95]. Other studies have shown that

delayed-enhancement MRI findings can be predictive of the potential for recovery of function in LV dysfunctional segments in chronic IHD [90,94]. Transmural extent of infarction can predict recovery of regional function in dysfunctional segments in patients evaluated before and several months after surgical revascularization [96].

Late gadolinium enhancement with a microvascular obstruction pattern is associated with greater infarct mass, infarction size, and extent of transmural, lower ejection fraction, more adverse cardiac events early and late, and more severe late LV remodeling [91]. Infarct size at the baseline has proved to be the strongest predictor of adverse long-term LV remodeling [92]. There is a strong linear relation between scar size, LV end-systolic and end-diastolic volumes, and LVEF. Scar size is the strongest predictor of LVEF, independent of scar location and transmural, [97]. Baseline infarct size, infarct heterogeneity, and myocardial salvage are significantly associated with 90-day LVEF [93].

**Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

**J. MRI Heart Function and Morphology Without IV Contrast**

MRI heart function and morphology without IV contrast provides assessment of ejection fraction and ventricular volumes including LVEF and ESVI with a higher sensitivity to detect prior myocardial infarct than ischemia. There is no relevant literature to support the use of MRI heart function and morphology without IV contrast in the initial evaluation of patients with chronic chest pain and a high probability of CAD with known IHD.

**Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

**K. MRI Heart Function with Stress Without and With IV Contrast**

MRI with function/wall motion (dobutamine stress test) and MRI with vasodilator stress perfusion (adenosine/regadenoson stress test) have been used to diagnose hemodynamically significant CAD in patients with an intermediate to high likelihood of having significant stenosis.

Extrapolation of data from MRI heart function and morphology without and with IV contrast for patients with known CAD is provided below with a note that there is no information available regarding the presence or absence of chest pain in patients included in those studies [46,48,49,51,52].

A single-center prospective study of 884 patients with known (70%) or suspected (30%) CAD demonstrated that inducible LV wall motion abnormalities during dobutamine CMR predicts cardiac death and myocardial ischemia [46]. A single-center prospective study focusing on women with known or suspected CAD and variable clinical symptoms demonstrated that, similar to men, dobutamine CMR can identify cardiac risk in women with known or suspected IHD [47]. A single-center study of 815 consecutive patients referred for evaluation of suspected myocardial ischemia over a 10-year period has shown that stress CMR with protocol, including stress and rest myocardial perfusion, ventricular function, and late gadolinium enhancement, effectively reclassifies patient risk beyond standard clinical variables, specifically in patients at a moderate to high pretest clinical risk and in patients with established CAD [48].

Stress CMR has a high NPV for adverse cardiac events in patients with known or suspected CAD [46,47]. A meta-analysis of 14 studies has shown that MRI heart function stress has a high NPV for



adverse cardiac events, and the absence of inducible perfusion defect or wall motion abnormality shows a similar ability to identify patients with a low risk for adverse cardiac events among patients with known or suspected CAD [49].

A meta-analysis from pooled studies found that perfusion MRI heart function stress has a sensitivity of 89.1% and a specificity of 84.9% on a patient-based analysis using FFR as a reference, suggesting that stress perfusion MRI remains an accurate test for the detection of flow-limiting stenosis in patients with suspected or established CAD [6].

Another meta-analysis of 37 studies, including 2,191 patients with high CAD prevalence, stress CMR, using either wall motion abnormality or perfusion abnormality technique, demonstrates overall good sensitivity and specificity for the diagnosis of CAD: stress-induced wall motion abnormalities imaging demonstrated a sensitivity of 0.83 and specificity of 0.86 on a patient level (disease prevalence = 70.5%). Stress perfusion imaging demonstrated a sensitivity of 0.91 and specificity of 0.81 on a patient level (disease prevalence = 57.4%) [51].

In patients with known or suspected CAD, the presence of late gadolinium enhancement and stress perfusion defect plus abnormal wall motion are independent predictors of all hard cardiac events [52].

**Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

**L. MRI Heart Function with Stress Without IV Contrast**

MRI heart function stress without IV contrast can provide assessment of ventricular function/wall motion abnormalities.

A single-center prospective study of 884 patients with known (70%) or suspected (30%) CAD demonstrated that inducible LV wall motion abnormalities during dobutamine CMR predicts cardiac death and myocardial ischemia [46]. A single-center prospective study focusing on women with known or suspected CAD and variable clinical symptoms demonstrated that, similar to men, dobutamine CMR can identify cardiac risk in women with known or suspected IHD [47].

A single-center prospective study of 208 patients with suspected CAD has demonstrated a high accuracy for detecting wall motion abnormalities related to ischemia with 86.2% sensitivity and 85.7% specificity [53].

A single-center prospective study of 153 patients with suspected or known CAD with and without chest pain has demonstrated 83% sensitivity and 83% specificity for detecting a >50% luminal diameter narrowing based on stress-induced abnormal LV contractility [54].

**Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

**M. Nuclear Medicine Ventriculography**

Stress radionuclide ventriculography includes measurement of the ejection fraction and assessment of regional wall motion at rest and during stress. There is no relevant literature to support nuclear medicine ventriculography in the initial evaluation of patients with chronic chest pain and a high probability of CAD with no known IHD.

**Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic**

## **heart disease with no prior definitive treatment. Initial imaging.**

### **N. Rb-82 PET/CT Heart**

Rb-82 PET/CT heart assesses rest myocardial perfusion and stress LVEF and quantifies rest myocardial blood flow and coronary flow reserve [55,56]. PET/CT has reported a higher accuracy over conventional nuclear techniques, MPI, and viability [55,57].

The data cited below for Rb-82 PET/CT heart are for patients with known CAD, but no information is available regarding the presence or absence of chest pain in patients included in those studies.

Gated Rb-82 PET/CT has shown that myocardial perfusion, stress LVEF, and ischemic LV dysfunction are prognostically important in CAD in patients with suspected or known CAD [48]. The inherent ability of Rb-82 PET/CT to collect LV function data at rest and during peak stress seems to result in improved detection of multivessel CAD with LVEF reserve assessment providing significant independent and incremental value to Rb-82 MPI for predicting the risk of future adverse events [59]. An increasing percentage of ischemia on PET-MPI is associated with an increase in the risk of cardiac events and all-cause death [59].

A single-center study of 1,432 patients with known or suspected CAD has shown that the inherent ability of Rb-82 PET/CT to collect LV function data at rest and during peak stress leads to an improved detection of multivessel CAD [58]. LVEF reserve provides significant independent and incremental value to Rb-82 MPI for predicting the risk of left main/3-vessel disease [57] and future adverse events [59].

A multicenter registry study included 7,061 patients with known or suspected CAD who underwent a clinically indicated rest/stress Rb-82 PET MPI (66% of patients had chronic chest pain as the reason for the test). The extent and severity of ischemia and scarring on Rb-82 PET MPI provided powerful and incremental risk estimates of cardiac death and all-cause death compared with traditional coronary risk factors [60].

### *PET and CCTA*

Hybrid PET scanners use CT for attenuation correction (PET/CT) following completion of the PET study. By coupling the PET perfusion examination findings to a CCTA, PET/CT permits the fusion of complementary anatomic coronary arterial and functional (perfusion) myocardial information and enhances diagnostic accuracy [60]. The results of the combined examinations can more accurately identify patients for revascularization. In a study of 110 consecutive patients with a combined stress Rb-82 PET perfusion imaging and CCTA, nearly half of significant angiographic stenoses (47%) occurred without evidence of ischemia, whereas 50% of normal PET studies were associated with some CCTA abnormality [61].

## **Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

### **O. SPECT or SPECT/CT MPI Rest and Stress**

Stress SPECT MPI can identify relative myocardial perfusion defects, indicating the presence of myocardial ischemia and/or infarction. By acquiring rest and stress perfusion scans, it is possible to demonstrate reversibility (ischemia) or irreversibility (infarction) of a myocardial perfusion defect. The territory of the perfusion defect identifies the likely coronary artery involved and can usually distinguish between significant single-vessel and multivessel coronary arterial obstructions. The

magnitude of the abnormality and the presence of high-risk findings also assist in clinical decision making [62,63].

The data cited below for SPECT or SPECT/CT MPI rest and stress are for patients with known CAD, but no information is available regarding the presence or absence of chest pain in patients included in these studies.

A single-center study evaluated 100 consecutive patients referred for SPECT MPI due to either chronic chest pain and no known CAD (55%) and patients with a documented history of myocardial infarction (29%) referred for risk stratification [64]. MPI and poststress and reversible regional wall motion abnormalities on exercise stress Tc-99m-gated SPECT MPI were significant predictors of angiographic disease and add incremental value to MPI for the assessment of angiographic severity [64,65].

In patients with typical angina (high pretest likelihood of disease), stress SPECT MPI is useful for estimating the extent (single vessel versus multivessel disease) and severity of coronary stenosis, which has relevance for prognosis, choice among therapeutic options, and advisability of performing coronary arteriography. A meta-analysis including 114 SPECT studies of patients with suspected or established CAD have shown sensitivity and specificity for the detection of significant CAD and/or myocardial ischemia was 78% and 52%, respectively, with an NPV of 83% [66].

A study of 5,366 consecutive patients with suspected or established CAD who underwent stress electrocardiography-gated SPECT MPI has shown that inducible ischemia identifies which patients have a short-term benefit from revascularization, whereas LVEF predicts cardiac death [67]. A normal stress SPECT MPI examination in patients with an intermediate to high likelihood of CAD predicts a low rate of cardiac death or nonfatal myocardial infarction ( $\leq 1\%$  per year) [67].

#### *SPECT and CCTA*

Hybrid SPECT/CCTA combines the anatomical information provided by CCTA with the functional perfusion evidence of SPECT, resulting in an enhanced diagnostic accuracy for detecting significant CAD compared with SPECT and CCTA alone: the sensitivity and specificity of hybrid SPECT/CCTA were 96% and 95%, respectively, compared with SPECT (93% and 79%) and CCTA (98% and 62%) alone [68]. There was 92% agreement on the necessity of revascularization in the treatment decisions based on hybrid SPECT/CCTA versus SPECT and coronary angiography alone [69].

### **Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

#### **P. US Echocardiography Transesophageal**

There is no relevant literature to support the use of transesophageal echocardiography in the initial evaluation of patients with chronic chest pain and a high probability of CAD with known IHD.

### **Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

#### **Q. US Echocardiography Transthoracic Resting**

US echocardiography transthoracic resting provides assessment of ejection fraction and ventricular volumes such as LVEF and ESVI with a higher sensitivity to detect prior myocardial infarct than ischemia. Although there is no relevant literature evaluating the use transthoracic echocardiography resting in the initial evaluation of patients with chronic chest pain and known

IHD, this modality provides information about wall motion abnormality and left ventricular function which may inform next step management of patients with IHD.

**Variant 2: Chronic chest pain; high probability of coronary artery disease. Known ischemic heart disease with no prior definitive treatment. Initial imaging.**

**R. US Echocardiography Transthoracic Stress**

US stress 2-D echocardiography depiction of myocardial contractility during rest and stress is used for the evaluation of patients with suspected regional wall motion abnormalities secondary to inducible regional ischemia.

The data cited below for US Echocardiography transthoracic stress are for patients with known CAD, but no information is available regarding the presence or absence of chest pain in patients included in those studies.

A single-center prospective study of 183 patients with suspected and known CAD has shown dobutamine-atropine stress echocardiography has a specificity of 91% in detecting significant CAD (defined as  $\geq 50\%$  coronary artery luminal diameter stenosis) [70].

In a meta-analysis of 435 patients (299 with and 136 without angiographically assessed CAD), dobutamine stress contractility echocardiography had 84% accuracy, 86% specificity, and 86% sensitivity for detecting CAD [71].

A meta-analysis of 44 studies including patients with suspected or known CAD indicated that stress echocardiography has a sensitivity of 85% and a specificity of 77% in detection of CAD (defined as  $>50\%$  coronary artery luminal diameter stenosis) [72].

In patients with suspected or known CAD, inducible wall motion abnormality during dobutamine stress echocardiography is associated with a higher risk for subsequent cardiac events. Patients with negative dobutamine stress echocardiography exhibited a lower event rate [47].

US contrast-enhanced stress echocardiography improves endocardial visualization. A single-center prospective randomized trial that included 229 patients with suspected or know CAD has demonstrated diagnostic test rates of 100% for contrast-enhanced stress echocardiography [73].

**Summary of Recommendations**

- **Variant 1:** US echocardiography transthoracic stress or arteriography coronary or CTA coronary arteries with IV contrast or MRI heart function with stress without and with IV contrast or MRI heart function with stress without IV contrast or Rb-82 PET/CT heart or SPECT or SPECT/CT MPI rest and stress is usually appropriate for the initial imaging of a patient with chronic chest pain and a high probability of CAD with no known IHD. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- **Variant 2:** US echocardiography transthoracic stress or arteriography coronary or CTA coronary arteries with IV contrast or MRI heart function and morphology without and with IV contrast or MRI heart function with stress without and with IV contrast or MRI heart function with stress without IV contrast or Rb-82 PET/CT heart or SPECT or SPECT/CT MPI rest and

stress is usually appropriate for the initial imaging of a patient with chronic chest pain and a high probability of CAD with known IHD with no prior definitive treatment. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care). The panel did not agree on recommending US echocardiography transthoracic resting for the initial imaging of a patient with chronic chest pain and a high probability of CAD with known IHD with no prior definitive treatment. There is insufficient medical literature to conclude whether or not these patients would benefit from US echocardiography transthoracic resting for this clinical scenario. US echocardiography transthoracic resting in this patient population is controversial but may be appropriate.

## Supporting Documents

The evidence table, literature search, and appendix for this topic are available at <https://acsearch.acr.org/list>. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents, please go to the ACR website at <https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria>.

## Appropriateness Category Names and Definitions
















Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

## Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been

included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared with those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#) document.

### Relative Radiation Level Designations

Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
0	0 mSv	0 mSv
	<0.1 mSv	<0.03 mSv
 	0.1-1 mSv	0.03-0.3 mSv
  	1-10 mSv	0.3-3 mSv
   	10-30 mSv	3-10 mSv
    	30-100 mSv	10-30 mSv

\*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (e.g., region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as “Varies.”

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

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