20 Cardiac Computed Tomography

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Over the last 15 years, cardiac computed tomography (CT) has evolved considerably and is now an essential noninvasive tool for evaluating various forms of heart disease. The technical advances that have permitted this evolution include the development of scanner systems with improved spatial and temporal resolution, thereby allowing the acquisition of high-resolution images with virtually no motion artifacts. At the same time, improvements in scan acquisition techniques, such as axial acquisition using prospective electrocardiogram (ECG) gating, have resulted in a substantial reduction in radiation dose.[1]

Although there are currently several different types of cardiac CT, the most common clinical use is for coronary CT angiography (CCTA) where information on the amount and type of coronary plaque, as well as the severity of stenosis, is provided. The increased use of this technique is because of data demonstrating diagnostic accuracy, prognostic value, and clinical effectiveness in patients with stable or acute chest pain. Nevertheless, there have been advances in several multimodality imaging techniques, and selecting appropriate candidates for cardiac CT, and understanding which indications are most and least useful, remains fundamental for ensuring that the potential benefits of this test are fully realized. This chapter provides an overview of the various clinical applications of cardiac CT for multiple different clinical indications.

BASICS OF CARDIAC COMPUTED TOMOGRAPHY

Different Types of Cardiac Computed Tomography Exams

Cardiac CT, with or without contrast, uses x-rays to obtain high resolution three-dimensional (3D) datasets. There are various different type of cardiac CT.

- *Coronary artery calcium (CAC) scan:* Non–contrast-enhanced ECG gated study during a single cardiac phase used to identify the presence and amount of calcified coronary plaque.
- *CCTA:* Contrast-enhanced ECG gated study performed to identify the presence and amount of both calcified and noncalcified plaque, and to estimate the severity of luminal stenosis.
- *Cardiac CT to evaluate noncoronary structures:* Contrast-enhanced ECG gated images to evaluate various pathologies ranging from valvular heart disease and cardiac function to cardiac masses and pulmonary venous anatomy. Depending on the indication, certain types of cardiac CT acquire data throughout the cardiac cycle to display cine imaging. The ability to view the heart throughout the cardiac cycle can be used to determine left or right ventricular systolic function, visualize cardiac masses that are mobile, or assess for valvular heart disease.

TECHNICAL CONSIDERATIONS/IMAGE ACQUISITION

CT scanners require an x-ray source that directs photons past a collimator and through the part of the body being imaged (Fig. 20.1). As photons pass through various parts of the body they become attenuated based on the x-ray absorption characteristics of the objects through which they pass. Those that pass through the patient reach the detectors that are located on the opposite side of the patient from the x-ray source. These x-rays are recorded by the detector electronics as a string of binary numbers that can be reconstructed to two-dimensional (2D) and 3D images.

Multidetector CT scanners have multiple parallel rows of detector elements that can acquire data more rapidly and more uniformly because of improved coverage along the *z*-axis (i.e., longitudinal axis of patient). The detector width is an important determinant of spatial resolution (i.e., the ability to differentiate small structures from each other). The gantry rotation speed is an important determinant of temporal resolution, or the ability to freeze the motion of the heart. The temporal resolution is also based on whether a scanner utilizes a single x-ray source and detector array or two x-ray sources and detector arrays. With a single source system, ~180 degrees of rotation of the gantry (plus the "fan angle" related to the width of the detector array) is required to acquire an image, whereas a dual source system allows data acquisition to be reduced to an approximately 90-degree rotation. Thus if a scanner has gantry rotation speed of 280 msec and uses a single x-ray source, the temporal resolution would be approximately 140 msec, versus 70 msec with a dual source system.

During a cardiac CT, a patient is placed on the scanner bed and is connected to ECG leads. Image acquisition, with or without contrast, is then performed during predetermined "phases" of the cardiac cycle. The combination of fast image acquisition, and ECG gating (i.e., obtaining data during specific portions of the cardiac cycle) enable "freezing" of the motion of the heart. Data acquisition requires the operator to select various parameters (Table 20.1). Higher tube voltage (kilovolt

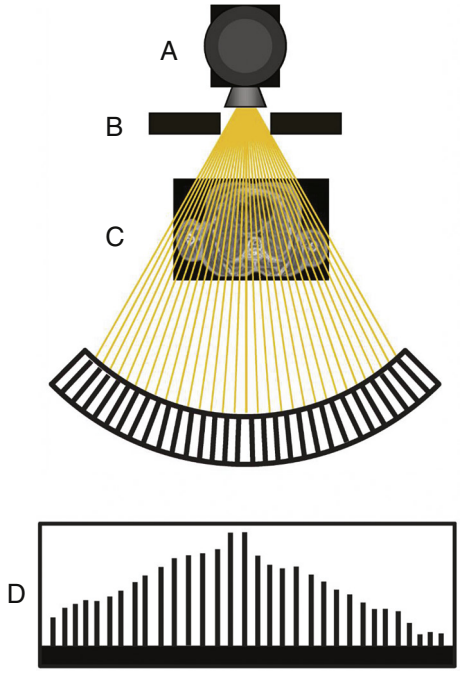


FIGURE 20.1 Computed tomography imaging requires an x-ray source *(A)* that directs photons past a collimator *(B)*. Photons are attenuated by organs in a differential pattern related to their material densities. Photons not attenuated reach multiple detectors *(C)* at which a scintillation reaction occurs. At each detector, a photon flux is generated that is a product of the number of photons emitted from the x-ray tube (milliamperes, mA), the photon energy (kilovolts, kV), and the organ tissue properties. These are calculated for every detector element *(D)*.

[kV]) allows for greater tissue penetration, but it decreases the brightness of administered intravenous (IV) contrast.

Higher tube current (milliamperes [mA]) increases the total number of photons that ultimately reach the detector elements. Both higher kV and higher mA increase the radiation dose associated with cardiac CT imaging.

RADIATION PRINCIPLES/PATIENT SAFETY

The radiation dose of cardiac CT is dependent on several parameters (see Table 20.1) determined during scan acquisition. The CT tube voltage, measured in kV, determines the energy of the emitted photons, whereas the tube current, measured in mA or milliamperes second (mAs), determine the number of photons emitted. Higher tube voltage (kV) allows for greater tissue penetration, whereas higher photon count (mA) increases the total number of photons that ultimately reach the detector elements. Both higher kV and higher mA increase the radiation dose associated with cardiac CT imaging, yet an insufficiently low setting can result in excess image noise and reduced image quality. Thus scan settings must be selected based on body habitus and the desired image quality. For instance, in obese patients, where a high degree of noise and photon attenuation is expected, higher kV is usually preferable. A higher kV may also be beneficial in cases where coronary stents or dense coronary calcifications are present. Although it is essential for imagers to understand how to select these parameters, many modern scanner systems have algorithms that may assist in selecting certain scan acquisition parameters based on the image noise that is present on the scout images.

A prospective multicenter registry study has shown that over the last decade, the estimated radiation dose associated with cardiac CT has decreased by ~78%. Specifically the median dose-length product (DLP) of CCTA decreased from 885 mGy × cm (in 2007) to 195 mGy × cm (in 2017). This DLP results in an estimated effective dose of 2.7 mSv when applying the conversion factor of k = 0.014.[1] This reduction has been

TABLE 20.1 Image Acquisition Parameters During Cardiac Computed Tomography Acquisition

		TYPICAL SETTING	EXPLANATION OF PARAMETER	IMPLICATIONS ON RADIATION DOSE OR IMAGE QUALITY	ADDITIONAL CONSIDERATIONS
Contrast	Amount of contrast	60-75 cc		Neutral	Faster scanners require less contrast; evaluation of right heart structures or a larger field of view may require more contrast
	Injection rate	5-7 cc/s	Faster injection rate increases contrast opacification of the coronary vessels	Neutral	Use of lower kV allows for improved contrast and may enable use of lower injection rate
Scan range (in *z*-axis)	Coverage	12-16 cm	Determined when setting the acquisition field of view based on localizer images	Linear association with radiation dose	Larger coverage necessary when evaluating bypass grafts or other vascular pathology
Photon energy/ amount	Tube voltage (kV)	80, 100, 120	Can be selected based on anticipated image noise versus desired radiation	Logarithmic association with radiation dose	In the presence of stents or metallic objects, higher kV may be beneficial
	Tube current (mA or mAs)	Scanner dependent (e.g., 100-400)		Linear association with radiation dose	Noncoronary studies (e.g., calcium scan) can be performed with lower mA
Acquisition mode	Axial versus helical	Axial preferred	Image acquisition during predefined portions of the cardiac cycle	Use of axial acquisition associated with ~70% lower dose (versus helical acquisition)	Axial acquisition requires regular heart rate to avoid misregistration artifacts
	ECG triggering	Prospective	When using axial acquisition, prospective ECG triggering is used		
	Phases	65%-75%	A wider phase acquisition window enables reconstruction of images from multiple portions of the cardia cycle	A wider phase acquisition window will results in higher dose	Acquisition of more phases may be beneficial when heart rate is elevated or irregular
	Tube current modulation	Turn "on" if helical acquisition performed	A technique to lower tube current across certain portions of the cardiac cycle	Used to lower radiation dose when helical acquisition is performed	The percentage reduction in tube current may be selected, depending on scanner used

ECG, Electrocardiogram; *kV,* kilovolt; *mA,* milliamperes; *mAs,* milliamperes second.

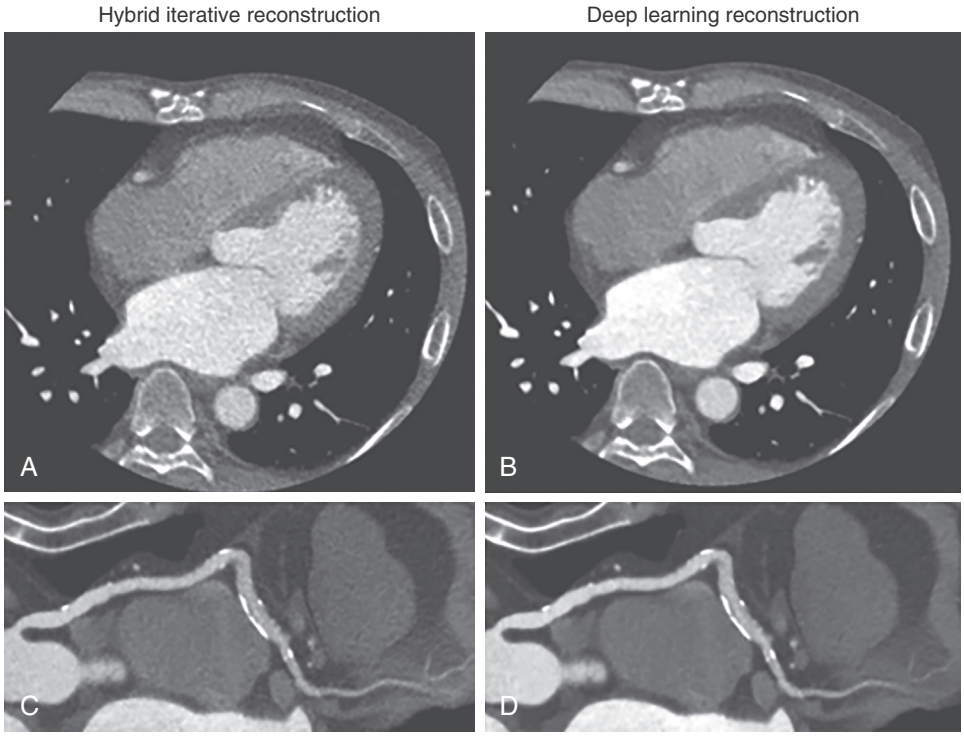


FIGURE 20.2 Reconstruction techniques for radiation reduction and coronary computed tomography angiography (CCTA) image quality. CCTA radiation dose can be reduced while maintaining high image quality by using deep learning reconstruction techniques, which provide superior image quality compared with hybrid iterative reconstruction techniques. Axial CCTA sections reconstructed by using **(A)** hybrid iterative and **(B)** deep learning techniques are shown, as is multiplanar reformatting of the right coronary artery using **(C)** hybrid iterative reconstruction and **(D)** deep learning reconstruction. (From Abdelrahman KM, et al. Coronary computed tomography angiography from clinical uses to emerging technologies. J Am Coll Cardiol 2020;76:1226-1243.)

achieved because of wider adoption of dose-saving techniques, including axial acquisition using prospective ECG triggering, low tube voltage, iterative image reconstruction (which reduces image noise, thereby allowing for image acquisition using lower kV and mA), and high-pitch helical scanning modes. Novel image reconstruction techniques using convolution neural networks and artificial intelligence are expected to further improve image quality, thus allowing for a lower radiation dose[2] (Fig. 20.2).

CORONARY ARTERY CALCIUM TESTING

Test Performance and Acquisition

CAC testing uses a noncontrast ECG gated scan to measure the amount of calcified coronary plaque. The test can be performed during a single breath-hold and does not require an IV, premedications, or any special patient preparation. When contemporary techniques are employed, the radiation dose is approximately 1 to 1.5 mSv, which is similar to the dose of a mammogram. Following image acquisition, the overall amount of calcifications can be quantified using commercially available programs, most commonly using the Agatston technique,[3] where the total calcium score is based on the amount and density of calcified plaque (Fig. 20.3).

The overall amount of coronary plaque can then be categorized as absent (CAC = 0), minimal (1 to 9), mild (10 to 99), moderate (100 to 299), severe (300 to 999), or extreme (≥1000). A CAC scan may also provide information regarding pericardial calcifications or thickness, aortic calcifications, valvular calcification, and in some cases the presence of fatty liver disease. In addition to providing information on the overall calcified plaque (i.e., total Agatston score), a CAC study should also report the CAC score of each coronary vessel, and the age-, sex-, and race-based percentiles.[4] It may also be useful to report the MESA (Multi-Ethnic Study of Atherosclerosis) coronary heart disease (CHD) score (https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx), which allows for calculation of the 10-year risk of CHD events, with and without CAC data.[5] In the near future, a MESA calculator, which will allow for the calculation of the 10-year atherosclerotic cardiovascular disease (ASCVD) risk based on the CAC test results, will allow clinicians to determine how the 10-year ASCVD risk is affected by having information on the overall amount of calcified plaque.

Clinical Data

Calcifications in the coronary arteries indicate the presence of coronary atherosclerosis, and there is a direct association between the amount of coronary calcifications and long-term risk of future cardiovascular events in both men and women, and across different races.[6] Importantly, information on CAC has been shown to provide incremental data beyond risk factors,[7-9] and results in a significant improvement in risk reclassification and discrimination.[10-12] Although the absolute CAC score is the strongest predictor of future risk, the age- and sex-based percentile is useful for determining relative risk, and it may be especially important among younger (e.g., <50) or older (e.g., >70) patients.

Although many studies have focused on the use of CAC to identify high-risk individuals, the absence of coronary calcifications (i.e., CAC score of zero) has been shown to be associated with a very low 10-year event rate, especially among individuals with a 10-year ASCVD risk that is <20%.[6,13,14] In fact, among borderline- and intermediate-risk patients, as defined by the 2018 multisociety cholesterol guideline, ~50% of individuals may have a CAC score of zero, a finding associated with a 10-year ASCVD risk that is <7.5%.[13] In such individuals it is reasonable to defer statin therapy and focus instead on lifestyle interventions, if there is a strong preference to avoid lipid-lowering therapy.

In addition to being a strong predictor of CHD events, increased CAC can also be used to predict other forms of cardiovascular disease (CVD), including atrial fibrillation, stroke, and congestive heart failure.[15-17] In addition, high CAC is associated with a higher rate of cancer and noncardiovascular death.[18,19]

Special Populations

Although CAC testing is generally only recommended for adults over the age of 40, there are studies that suggest that CAC scoring may be used selectively in adults <40 years of age. The Coronary Artery Risk Development in Young Adults (CARDIA) study included community-based participants who were 32 to 46 years old at the time of CAC testing.[20] In this unselected population, only 10% of young adults had coronary artery calcifications, yet with the use of a risk score, a subgroup of individuals with 45% prevalence of CAC could be identified.[20] The CAC Consortium is a large multicenter registry that included patients who were referred for testing and found that 34% of adults aged 30 to 49 had CAC, including 21.8% of those 30 to 39 years of age. In both of these studies, the presence of any CAC was associated with a significantly higher risk of incident CVD. Collectively, these findings

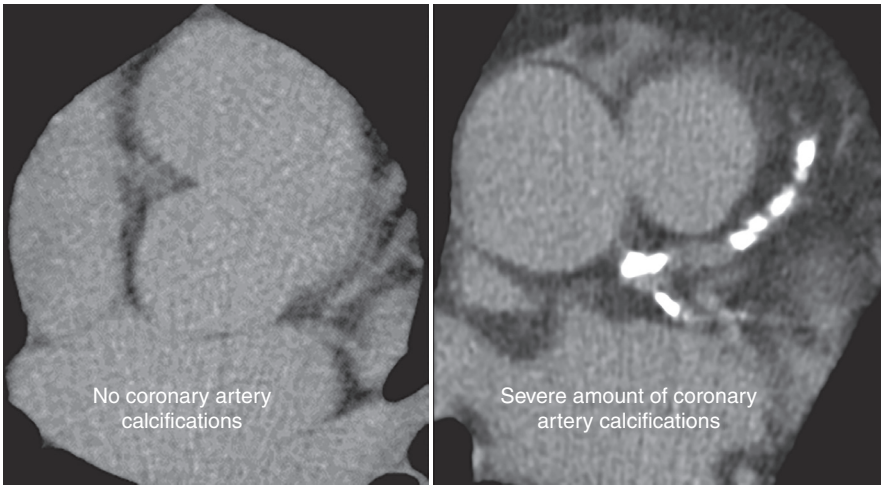


FIGURE 20.3 Examples of images from coronary artery calcium (CAC) testing. *Left:* example of patient with no evidence of calcified coronary plaque and an Agatston CAC score of zero. *Right:* example of patient with severe amount of calcified coronary plaque.

suggest that selective use of CAC in certain high-risk individuals who are 30 to 40 years of age may be reasonable, but the absence of CAC in this age group should not be reassuring and should not be used as a basis to defer any therapies. Because women, on average, develop CAC later than men, the role of CAC testing in women under the age of 40 may be even more limited.

Several studies have shown that the absence of CAC can be used to identify lower risk older adults in whom statin therapy can be deferred. Among a study evaluating 5805 BioImage participants with a mean age of 70, the presence of CAC ≤10 was found in 38% and was associated with a negative likelihood ratio of 0.2 for CHD, implying an 80% lower risk than would be expected based on traditional risk factor assssement.[21] The use of CAC as a "negative risk marker" among older adults was also established in the CAC Consortium study, in which among 2474 asymptomatic patients with a mean age of 79, those with CAC of 0 to 9 or less than the 25th percentile had a lower risk of cardiovascular and all-cause mortality.[22]

Although at any given age, women have less CAC than men, CAC has been found to predict risk in a similar manner for both men and women,[6,23] Moreover, a meta-analysis of 5 large population cohorts of women with an ASCVD risk <7.5% found that CAC was present in 36%, and that the presence of any CAC was associated with a twofold increase in incident ASCVD events.[24]

Clinical Indications and Management Recommendations

Clinical Indications

Potential uses of CAC testing in cardiovascular medicine are listed in Table 20.2. The current 2018 AHA/ACC multisociety cholesterol guideline states that in intermediate-risk or selected borderline-risk adults (i.e., 10-year ASCVD risk of 5%–20%), if the decision about statin use remains uncertain, it is reasonable to use CAC testing in the decision to withhold, postpone, or initiate statin therapy (Fig. 20.4). When CAC testing is used in this context, if the CAC score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking). The AHA/ACC guidelines indicate that if the CAC score is 1 to 99, it is reasonable to initiate statin therapy, especially in those ≥55 years of age. If the CAC score is 100 or higher or in the 75th percentile or higher, it is recommended to initiate statin therapy (Fig. 20.5). However, it is noteworthy that the finding of any CAC (i.e., CAC >0) in individuals with borderline or intermediate (5% to <20%) risk should generally favor statin therapy, as also suggested by the National Lipid Association recommendations.[13,25,26]

Management Recommendations

Because patients with elevated CAC scores have a higher risk of CVD, management recommendations focus on treatment of all underlying risk factors using lifestyle and pharmacologic therapies (see Chapters 25 and 27). The vast majority of patients with coronary artery calcifications and a baseline 10-year risk of ASCVD events >5% have a sufficiently high risk of future ASCVD events (i.e., >7.5% 10-year risk) and would benefit from lipid-lowering therapies. However, there is a linear increase with risk as the burden of calcified plaque increases. Accordingly, individuals with moderate to severe CAC should be considered for high-intensity statins.[26]

Although there are no clinical trials that have assessed the efficacy of aspirin therapy among patients with CAC, prior modeling studies from the MESA study[27,28] have suggested that individuals with a CAC score >100, and especially those with a CAC >400, may be more likely to benefit from aspirin therapy. These studies applied the estimated relative risk reduction associated with aspirin therapy to the observed event rate in individuals who have coronary artery calcifications. Accordingly, among individuals with CAC >100, the estimated number needed to treat over 5 years to reduce a cardiovascular event was lower than the number needed to harm. Based on this data, it may be reasonable to consider aspirin therapy in patients with CAC >100 who do not have bleeding-related contraindications.[29]

Individuals who have evidence of severe CAC (>300), and especially those with extreme CAC (>1000), have an annual cardiovascular event rate that is similar to the event rate observed in high-risk secondary prevention trials.[30] Accordingly, it is reasonable to consider such patients for advanced therapies that are usually reserved for secondary prevention. Although CAC measurements have not been used in prior clinical trials, several recent clinical cardiovascular outcome trials are now including the presence of underlying CAC as a potential inclusion criteria.

A common question is whether individuals with severe CAC require further testing. Because coronary revascularization has not been shown to improve outcomes among various high-risk subgroups,[31-33] individuals who are asymptomatic should be treated with aggressive preventive therapies but are unlikely to benefit from additional testing. When there is uncertainty regarding patient symptoms or exercise capacity, exercise testing may be reasonable. Even in the setting of CAC >1000, significant ischemia is only detected in ~15% of patients.[34] When further testing is considered, positron emission tomography myocardial perfusion imaging (PET MPI) may be particularly beneficial as normal myocardial blood flow reserve can be used to exclude high-risk anatomy and inform prognosis.[35,36] Invasive angiography should not be performed in asymptomatic individuals with severe CAC.

A valid concern is that CAC testing can lead to unnecessary downstream noninvasive and invasive testing. In the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) study of 2137 volunteers randomized to CAC scoring versus no CAC scoring, those receiving CAC scoring achieved lower systolic blood pressure, low-density lipoprotein (LDL) cholesterol levels, abdominal girth, and weight.[37] In this study, individuals with CAC ≥1000 had a marked increase in medical costs but constituted only 2.2% of the study population. In an economic analysis, the CAC group experienced costs and medical testing similar to those not undergoing CAC scanning.[37,38] A subsequent meta-analysis evaluating the impact of CAC testing on subsequent preventive therapies has also shown that the identification of calcified plaque is associated with increased use of lipid-lowering therapies, blood pressure–lowering therapies, use of aspirin, and dietary changes.[39]

TABLE 20.2 Potential Uses of Coronary Artery Calcium Testing

POPULATION	PURPOSE	CLINICAL INDICATIONS/DETAILS
Asymptomatic persons without established ASCVD	Screening among *select* low- and borderline-risk patients	• CAC testing may be useful for risk assessment, particularly if this will impact the use of preventive therapies • Individuals who may benefit from such testing include those with strong family history of premature CAD or systemic inflammatory disease
	Shared decision making among *selected* borderline- and intermediate-risk adults in whom the decision regarding statin use is uncertain	• In intermediate-risk or selected borderline-risk adults (i.e., 10-year ASCVD risk of 5%-20%), if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone, or initiate statin therapy (see Fig. 20.4)
	Shared decision making among *select* high-risk adults who are unable to tolerate statin therapy	• In select high-risk adults who do not have known ASCVD and are unable to tolerate statin therapy, CAC testing may be reasonable for further risk stratification if this could impact the use of additional therapies (e.g., PCSK9 inhibitors)
Symptomatic persons with no known CAD	Low-risk patients with suspected CAD	• CAC testing may be useful to identify low-risk patients who have a low likelihood of obstructive CAD versus those with CAC >0 who may benefit from additional testing
Symptomatic persons with no known CAD	As add-on to other functional testing techniques	• Among individuals who do not have known CAD, who are referred for an ischemic evaluation, add-on CAC testing may be useful to determine the presence and severity of coronary plaque (see Chapter 18 for details)

ASCVD, Atherosclerotic cardiovascular disease; *CAC,* coronary artery calcium; *CAD,* coronary artery disease.

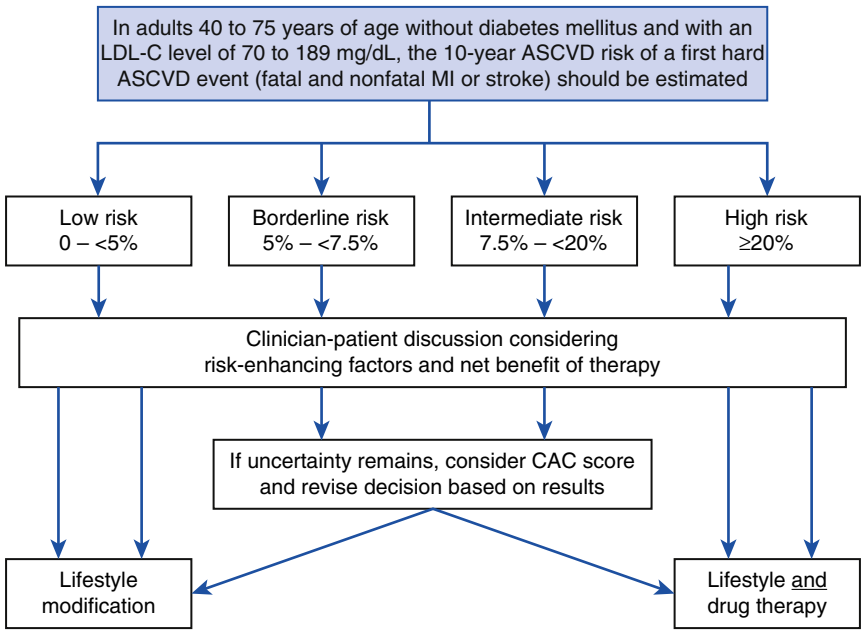


FIGURE 20.4 Overview of role of coronary artery calcium testing in deciding on therapy for the primary prevention of atherosclerotic cardiovascular disease. (From Lloyd-Jones DM, et al. RS. Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease: a special report from the American Heart Association and American College of Cardiology. J Am Coll Cardiol 2019;73:3153-3167.)

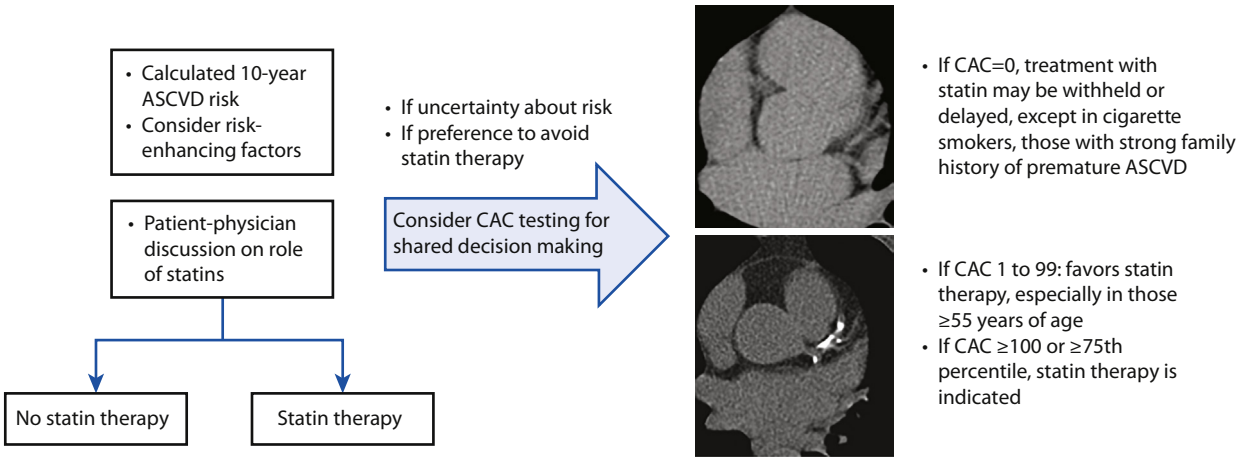


FIGURE 20.5 Overview of how to use coronary artery calcium (CAC) testing for shared decision making among borderline- and intermediate-risk individuals for whom CAC may be used to guide the decision to withhold, postpone or initiate statin therapy. (Based on Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. J Am Coll Cardiol 2019;73:e285-e350.[116])

Limitations of Coronary Artery Calcium Testing

The amount of CAC cannot be reduced with therapy, in fact, some studies have shown that statin therapy may be associated with a mild increase in CAC progression. Nevertheless, the strong association of CAC with future cardiovascular events is robust in patients who are on lipid-lowering therapies. Because the amount of CAC cannot be lowered, repeat CAC testing is not useful to assess response to therapy. Although there is substantial data on the use of CAC testing in various registries and clinical trials, there have been no large-scale clinical trials demonstrating the efficacy of CAC testing for lowering cardiovascular events.

Clinical Trials Using Coronary Artery Calcium

In the St. Francis Heart Study, 1005 patients with CAC greater than the 80th percentile were randomized to atorvastatin (20 mg) versus placebo.[40] At a 4.3-year follow-up, no differences were observed in the composite CVD endpoint (6.9% vs. 9.9%; $P = 0.08$). However, this was an underpowered study, and in a post hoc analysis, participants with a baseline CAC >400 did have a lower event rate (8.7% vs. 15.0%; $P = 0.046$) with statin therapy. Although several trials have been proposed to further investigate the potential efficacy of CAC testing, no trials have been completed to date.

Given ethical issues inherent to withholding therapy in individuals who have CAC and the increased adoption of statin therapy in primary prevention, as now promoted in various guidelines, it is unlikely that there will be a large-scale randomized trial that will randomize patients to treatment based on CAC results. A trial design only including individuals who do not currently have an indication for statin therapy will have a low event rate, thus requiring a very large sample size or a long follow-up period. As a result, such a trial would likely be prohibitively expensive.

When evaluating various future potential trial designs, it is important to recognize that the role of CAC testing has shifted form a "screening test" to a "shared decision-making test," where testing is now most commonly performed among individuals who already have an indication for statin therapy (see previous section on Clinical Indications). Recognizing these challenges, a recent National Heart Lung and Blood Institute (NHLBI) workshop proposed several possible trials using CAC testing in primary prevention. The potential opportunities identified included (1) studies evaluating the efficacy of shared decision tools using CAC, (2) studies using artificial intelligence to identify CAC on noncardiac CT and subsequently notify clinicians, (3) studies using CAC testing to enhance prevention in young adults (i.e., <45 years), and (4) studies using CAC testing in low-risk older adults to identify "healthy vascular agers" in whom treatment can be avoided.[41]

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY

How Is the Test Performed?

Image acquisition for cardiac CT was described previously (see Technical Considerations/Image Acquisition; see Table 20.1). Prior to contrast-enhanced cardiac CT exams, an 18-gauge IV is inserted to allow for rapid injection (e.g., 5 to 7 cc/s) of contrast during the scan; in some cases a 20-gauge IV may be sufficient in smaller patients. When CCTA is performed, patients are often administered nitroglycerin to dilate the coronary arteries and beta blockers (oral, or in some cases IV) to achieve a sufficiently low heart rate, in part depending on the type of scanner being used. Thus it is important to screen patients for any contraindications for these medications.

Image acquisition is performed approximately 15 to 25 seconds after starting the contrast injection to allow for maximal contrast enhancement in the coronary arteries. This can be achieved by using either a bolus tracking technique, whereby the attenuation in the ascending or descending aorta is monitored during contrast injection, or by first performing a test bolus and measuring the amount of time from injection of 10 to 15 cc of contrast until peak contrast enhancement in the ascending aorta. The scan is performed during a single breath-hold, usually lasting 5 to 10 seconds. Subsequently, the raw data obtained from the CT scanner is used to reconstruct high-resolution images that are then transferred to a dedicated workstation for interpretation.

Contraindications to CCTA include inability to tolerate contrast because of renal dysfunction (glomerular filtration rate [GFR] <30), severe contrast allergy, or uncontrolled tachycardia. Relative contraindications include the presence of atrial fibrillation, morbid obesity (e.g., body mass index [BMI] >40 kg/m^2), extensive coronary calcifications, or the presence of small stents. All of these conditions will degrade CT image quality and CT should generally be avoided unless there is a high likelihood of obtaining diagnostic image quality. For instance, some scanners have algorithms that allow for successful scanning of patients in atrial fibrillation who have controlled heart rates.[42,43] With respect to obesity, the upper weight limit for most scanners is around 450 pounds, and some scanners have certain acquisition modes that may enhance image quality in these scenarios. Although most contemporary scanners can achieve good image quality with BMI <40 kg/m^2, individuals with obesity are more likely to have reduced image quality and may have nondiagnostic scans even when maximal scanner output is used.

The presence of extensive coronary calcifications can be problematic because of calcium blooming artifacts, which may interfere with the ability to visualize the lumen and estimate the severity of stenosis. Blooming artifacts occur because of limited spatial resolution and are caused by partial volume averaging of different densities within a single voxel. As a result, the actual size of the calcium is exaggerated making the lumen smaller. Although the amount of calcium blooming has reduced considerably with new-generation scanners that have better spatial resolution, the inability to fully exclude stenosis remains an important limitation when there are dense focal calcifications. The amount of calcium "blooming" can be reduced by using higher resolution scanners,[44] reconstructing the thinnest possible slices, using a sharper reconstruction kernel, and optimizing display settings (e.g., wider grayscale window with a higher center). In addition, there are vendor-specific algorithms that are being developed to help mitigate these artifacts.[45]

Diagnostic Accuracy

The diagnostic accuracy of CCTA compared with invasive angiography has been evaluated in multiple multicenter and single-center trials. A meta-analysis[46] across 9 studies has identified a sensitivity of 97% (93 to 99) with a specificity of 78% (67 to 86) for detecting >50% stenosis. The same analysis showed that CCTA has the highest sensitivity of any noninvasive imaging technique to detect the presence of anatomic stenosis. When evaluating the diagnostic accuracy of CCTA to detect functionally significant coronary artery disease (CAD), as defined by an invasive fractional flow reserve (FFR) ≤0.80, the sensitivity of CCTA was 93% (89 to 96) with a specificity of 53% (37 to 68). The lower specificity of CTA versus invasive FFR in this meta-analysis may have been influenced by the fact that several studies excluded, by design, patients with nonobstructive CAD.

An important challenge in comparing the diagnostic accuracy of different tests is that each study is usually performed on a different group of patients. To address this challenge, two prospective studies were designed to allow for a better head-to-head comparison by having each patient undergo multiple tests.

The EVINCI (Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease) study was a multicenter prospective study designed to compare the diagnostic accuracy of noninvasive anatomic and functional imaging in identifying patients with significant CAD defined by invasive angiography.[47] Among 475 patients who each underwent multiple imaging tests including CCTA, single-photon emission computed tomography (SPECT), or PET MPI, and either cardiac magnetic resonance (CMR) or stress echocardiography, CCTA had the highest diagnostic accuracy to detect significant CAD, defined by invasive angiography as >50% stenosis of the left main stem, >70% stenosis in a major coronary vessel, or 30% to 70% stenosis with FFR ≤0.8. The sensitivity of CCTA was 91% (86 to 95), whereas the specificity was 92% (89% to 95%).

The PACIFIC trial (Prospective Comparison of Cardiac PET/CT, SPECT/CT Perfusion Imaging and CT Coronary Angiography With Invasive Coronary Angiography) provided a head-to-head comparison of different techniques against invasively measured FFR ≤0.80 as the reference standard.[48] In this study, CCTA (90%) and PET (87%) had the highest sensitivity, whereas PET and SPECT had the highest specificity. The overall diagnostic accuracy to detect lesion-specific ischemia was highest for PET.

Collectively, the available data (see side insert) support CCTA as a highly sensitive test for detecting coronary stenosis, and accordingly a high negative predictive value (NPV) to rule out CAD, especially in

populations that have a lower prevalence of disease. However, the specificity of CCTA to identify ischemia is limited, as is also the case for invasive angiography (see the section Physiologic Evaluation of Coronary Artery Disease).

Prognostic Implications

Multiple studies have evaluated the prognostic capabilities of CCTA to identify high-risk patients. The Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter Registry (CONFIRM) study evaluated a cohort of 24,775 patients without known CAD who underwent CCCTA between 2005 and 2009.[49] Over a mean follow-up of 2.3 years, nonobstructive and obstructive CAD were associated with higher risk of mortality, including a 2.6-fold increased risk of death for patients with >70% stenosis, and a 1.6-fold increased risk of death for those with <50% stenosis. Increasing risk of mortality was observed for patients with a greater number of vessels with stenosis. Importantly, incident rates of all-cause death were very low in the absence of CAD by CCTA, with an annualized rate of 0.28%.[49]

The prognostic value of CCTA has subsequently been evaluated across multiple cohorts, registries, and prospective studies, all showing an increase in events among patients who have a greater extent or severity of plaque or stenosis.[50] In the Partners registry, 3242 patients who underwent CCTA were followed over a median of 3.6 years. The presence of nonobstructive plaque was associated with a higher rate of cardiovascular death or myocardial infarction (MI). Moreover, patients who had greater than four segments with plaque (i.e., segment involvement score [SIS] >4) had the same risk of incident cardiovascular death or MI as those who had one-vessel obstructive CAD.[51] Similar increase in mortality among patients with nonobstructive plaque (SIS >4 or involving 3 vessels) was also observed in a prospective 2 center study.[52]

The prognostic value of CCTA and functional testing were compared in the PROMISE trial, where 4500 patients were randomly assigned to CCTA and 4602 were randomly assigned to functional testing.[53] The prevalence of obstructive CAD and myocardial ischemia was low (11.9% vs. 12.7%, respectively), and both finding had similar prognostic value over a median follow-up of 26.1 months. However, the overall discriminatory ability of CCTA in predicting events was significantly better than functional testing (c-index, 0.72; 95% confidence interval [CI], 0.68–0.76 vs. 0.64; 95% CI, 0.59–0.69; $P = 0.04$), a finding that was driven by the fact that CCTA identified nonobstructive CAD, a prognostically relevant finding, especially when the overall burden of ischemia and obstructive CAD are low.[53]

As suggested by the previous studies, an important aspect of CCTA is the ability to further stratify risk beyond just the presence or absence of anatomic stenosis. Indeed, emerging data have suggested that the overall amount of plaque, and various high-risk plaque (HRP) features (see the next section), may provide incremental prognostic information.

Plaque Burden and Prognosis

The Western Denmark Heart Registry[54] evaluated the prognostic value of CCTA among 23,759 symptomatic patients who underwent CCTA and were followed for the primary endpoint of major CVD (MI, stroke, and all-cause death). The overall risk of major CVD events increased in a stepwise manner with both atherosclerotic disease burden (determined by the total CAC score) and number of vessels with ≥50% stenosis. When stratified by groups of increasing CAC, patients with nonobstructive CAD had a risk of CVD events similar to those with obstructive CAD, suggesting that plaque burden, not stenosis, was the main predictor of future CVD events.[54] These findings reinforce the importance of assessing overall plaque burden, rather than just stenosis, in deciding on the role of secondary prevention therapies. As has also been shown in the PROMISE trial (see later), the vast majority (~65%) of events occurred among patients who did not have obstructive CAD.

Coronary Computed Tomography Angiography in Acute Chest Pain

To date there have been several randomized trials evaluating the safety and efficacy of using CCTA to evaluate patients with acute chest pain. Collectively, these studies have shown that the use of CCTA can reduce the time to diagnosis, hospital length of stay, and emergency department cost compared with a standard evaluation.[55] The improved efficiency of CCTA was due, in part, to the fact that this test does not require patients to be "ruled out" for MI, and can be performed after one set of negative cardiac enzymes. However, in the era of high-sensitivity troponin testing (hsTn), other testing options (including deciding on deferral of any testing) can now be pursued without a prolonged delay and patients can be more rapidly discharged from the emergency department.

Evaluating the comparative effectiveness of testing in the current era of hsTn, the Better Evaluation of Acute Chest Pain by Computed Tomography Angiography (BEACON) trial was a prospective multicenter randomized trial that compared the diagnostic strategy of early CCTA with the use of hsTn among 500 patients with suspected acute coronary syndrome (ACS).[56] In contrast to earlier trials, this study did not shorten hospital length of stay in the emergency department. In addition, there was no significant difference in the rate of revascularization within 30 days and incidence of major adverse cardiovascular events (MACE) at 30 days. However, the CCTA approach allowed for significantly reduced downstream outpatient testing and a reduction in direct medical cost.[56]

Although most studies evaluating the use of CCTA only evaluated short-term outcomes, the CATCH trial evaluated whether postdischarge CCTA-guided care in patients with normal ECG and troponin values improved long-term outcomes. The primary endpoint was a composite of cardiac death, MI, hospitalization for unstable angina, late symptom-driven revascularizations, and readmission for chest pain. Over a median follow-up of 18 months, patients randomized to CCTA-guided treatment strategy experienced fewer events compared with those evaluated using a standard of care strategy (11% vs. 16%; $P = 0.04$; hazard ratio [HR] 0.62).

With respect to long-term outcomes, one potential advantage of using CCTA is that it can detect nonobstructive CAD, and thus be used to initiate preventive therapies. Although the implementation of such therapies following CCTA have been shown to occur among patients with stable chest pain who are treated in the outpatient setting, one challenge to the use of CCTA in the acute setting is that nonurgent findings are less likely to impact future medical therapy.[57] Accordingly, better systems are needed to use information from CCTA (and other tests obtained in the emergency department) to improve long-term preventive treatments.

When considering the prospective clinical trials of CCTA for acute chest pain, it is important to recognize that most of them were performed in low-risk patients, where ultimately <10% were found to have an ACS, and of those only a small proportion represented patients with MI.

Coronary Computed Tomography Angiography in Non–ST Elevation Myocardial Infarction

Although initial trials using CCTA for the evaluation of patients with acute chest pain excluded individuals with elevated troponin levels, recent data have suggested that CCTA can be effective at excluding obstructive CAD in low- and intermediate-risk non–ST-segment elevation MI (NSTEMI) patients. A subanalysis of the Very EaRly vs Deferred Invasive evaluation using Computerized Tomography (VERDICT) trial, which included non-ST elevation ACS patients who underwent a CCTA and invasive angiography showed that the NPV of CCTA to exclude ≥50% stenosis was 91%.[58] A small randomized trial of 207 patients with elevated hsTn and inconclusive enzymes found that the use of CCTA resulted in ~33% reduction in invasive angiography while achieving similar outcomes.[59] Accordingly the 2020 European Society of Cardiology (ESC) recommends CCTA as an alternative to invasive angiography to exclude ACS when there is low-to-intermediate likelihood of CAD and when cardiac troponin and/or ECG are normal or inconclusive.[60] The selective use of CCTA to evaluate patients with elevated cardiac enzymes with potential ACS has also been used throughout the COVID-19 pandemic and has been suggested as a useful testing option by several international expert guidance documents.[61]

Age (years)	Chest pain		Dyspnea	
	Men	Women	Men	Women
30–39	≤4	≤5	0	3
40–49	≤22	≤10	12	3
50–59	≤32	≤13	20	9
60–69	≤44	≤16	27	14
70+	≤52	≤27	32	12

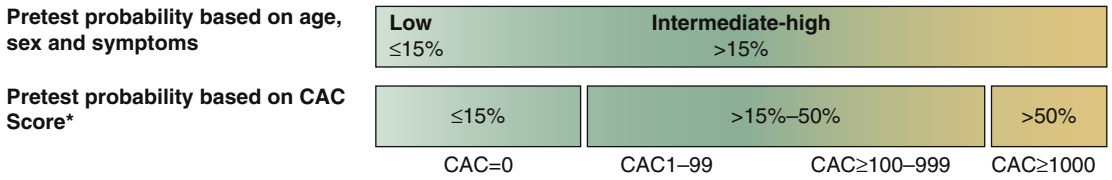


FIGURE 20.6 Pretest probability (PTP) of obstructive coronary artery disease (CAD) in symptomatic patients. The PTP shown is for patients with anginal symptoms. Patients with lower risk symptoms would be expected to have lower PTP. The *dark green shaded regions* denote the groups in which noninvasive testing is most beneficial (PTP >15%). The *light green shaded regions* denote the groups with PTP of CAD ≤15% in which the testing for diagnosis may be considered based on clinical judgment. If information on coronary artery calcium testing is available, it can also be used to further define the pretest probability estimate. The vast majority of symptomatic patients have a PTP of obstructive CAD <50%. (Data from Juarez-Orozco LE, et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. Eur Heart J Cardiovasc Imag 2019;20:1198-1207; and Winther S, et al. Incorporating coronary calcification into pre-test assessment of the likelihood of coronary artery disease. J Am Coll Cardiol 2020;76:2421-2432; Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021.)

Coronary Computed Tomography Angiography in Stable Chest Pain

The most common use of CCTA is to evaluate patients with symptoms that raise suspicion for CHD. When symptoms are chronic and associated with consistent precipitants, such as exertion or emotional stress, they are often categorized as "stable." The use of CCTA in this setting has been shown to accurately diagnose both nonobstructive and obstructive CAD, improve diagnostic certainty, and improve patient outcomes. Appropriate patient selection and management based on CCTA results is essential for maximizing the value of CCTA.

Selecting Appropriate Candidates for Coronary Computed Tomography Angiography

Although CCTA has robust capabilities to estimate the amount and severity of CAD, like other imaging tests, the accuracy and effectiveness of this test are dependent on selecting appropriate patients in whom high-quality images can be achieved. Use of contemporary scanners, which along with other advances offer improved spatial and temporal resolution, is also helpful for achieving optimal image quality. For instance, scanners that have dual source capabilities will allow imaging at higher heart rates because of improved temporal resolution. Scanners that have better spatial resolution will have less calcium blooming–related artifacts. Patients who are ideal candidates for CCTA have no known CAD, can achieve a low heart rate (e.g., <70 beats/min with medications), can hold their breath during image acquisition, and can tolerate the administration of IV contrast.

Pretest Probability of Obstructive Coronary Artery Disease

Although older guidelines have suggested that CCTA may be most effective in patients who have a low to intermediate pretest probability (PTP) of having obstructive CAD, it is noteworthy that most algorithms overestimate the likelihood of having obstructive CAD.[62-64] The latest ESC Chronic Coronary Syndrome guideline and the 2021 AHA/ACC chest pain guideline provide a useful PTP tool that was derived from 15,815 symptomatic patients according to age, sex, and type of symptoms. When evaluating this PTP tool (Fig. 20.6), the only group of patients with a PTP >50% is men over the age of 70 with chest pain, but even in this group the PTP was 52% or lower. Other recent PTPs have shown an even lower likelihood of obstructive CAD,[65] further reinforcing that risk scores alone may not be sufficient in identifying patients who truly have a high PTP of obstructive CAD.

The 2021 AHA/ACC chest pain guideline indicates that patients with stable chest pain who have a low PTP of obstructive CAD (e.g., PTP <15%) may not require further testing, whereas patients with intermediate and high PTP are most likely to benefit from further testing with either CCTA or functional testing. The severity of underlying coronary artery calcifications may be important in identifying patients with a high PTP of obstructive CAD.[65] Accordingly, when available, prior CT images should be reviewed for the presence of extensive coronary calcifications. The absence of extensive coronary calcifications may favor CCTA, whereas the presence of such findings may favor stress testing.

Patient Outcomes Following Coronary Computed Tomography Angiography

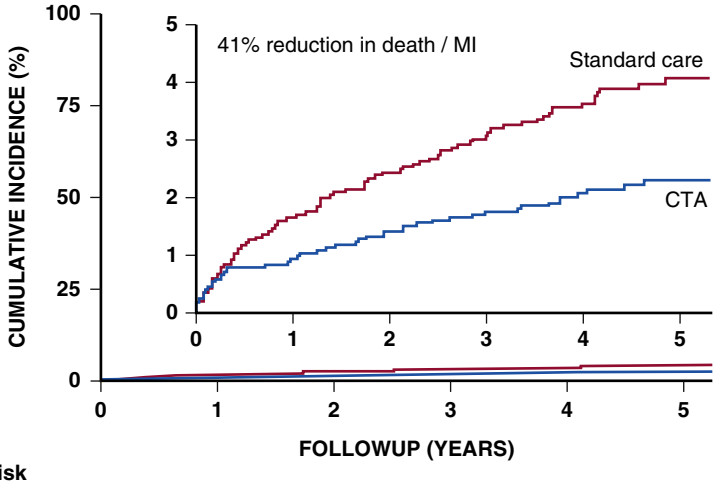
There have been several randomized controlled trials comparing CCTA with functional testing among patients with stable symptoms (these trials evaluated the impact of CCTA on diagnosis, symptoms, risk stratification, clinical management, and patient outcomes).

The SCOT-HEART (Scottish Computed Tomography of the HEART) trial was a prospective multicenter trial that randomized 4146 participants to standard care plus CCTA or standard care alone. The addition of CCTA led to a lower frequency of diagnosing angina caused by CHD, and a higher diagnostic certainty.

The CAPP (Cardiac CT for the Assessment of Patients With Pain and Plaque) and CRESCENT trials[66,67] were designed to assess the impact of CCTA on angina symptoms compared with a functional testing strategy. The use of CCTA was associated with lower levels of angina after 12 months of follow-up. Similar improvements in symptoms were seen in the SCOT-HEART trial, especially in those demonstrated to have normal coronary arteries or those with obstructive disease who underwent coronary revascularization.[50]

Hard Clinical Outcomes

The SCOT-HEART and PROMISE trials are the largest trials to date to examine the impact of CCTA on clinical outcomes. The SCOT-HEART was a prospective multicenter trial of 4146 patients with stable chest pain who were recruited across 12 centers across Scotland and



No. at risk						
Standard care	2073	2033	2008	1994	1572	856
CTA	2073	2051	2029	2015	1588	872

FIGURE 20.7 Cumulative incidence of death from coronary heart disease or nonfatal myocardial infarction in the SCOT-HEART trial. The figure shows cumulative event curves for the primary endpoint of death from coronary heart disease or nonfatal myocardial infarction among patients assigned to computed tomography angiography in addition to standard care and those assigned to standard care alone. (From Newby DE, et al. Coronary CT angiography and 5-year risk of myocardial infarction. N Engl J Med 2018;379:924-933.)

randomized to standard care plus CCTA or to standard care alone. In both groups, standard of care included the use of exercise treadmill testing in 85% of patients, while stress imaging was infrequent (9%). Over a median follow-up of 4.8 years, the addition of CCTA to standard of care resulted in a 41% reduction in the combined endpoint of CHD death or nonfatal MI (2.3% vs. 3.9%; HR 0.59; $P = 0.004$; Fig. 20.7).

The PROMISE trial compared a strategy of CCTA versus functional testing (67% nuclear stress testing, 27% stress echocardiography, 10% exercise electrocardiography). The composite primary endpoint was death, MI, hospitalization for unstable angina, or major procedural complication. Over a median follow-up of 25 months, 164 patients (3.3%) in the CCTA group and 151 (3.0%) in the functional-testing group experienced the primary outcome (HR 1.04; $P = 0.75$). Although there was no difference in this primary outcome, the use of CCTA was associated with a lower rate of death or MI at 12 months (HR 0.66; $P = 0.049$). The use of CCTA was associated with a lower incidence of invasive angiography showing no obstructive CAD during the 90 days after randomization, which was a prespecified secondary endpoint. However, more patients in the CCTA group underwent invasive angiography within 90 days of randomization (12.2% vs. 8.1%) and more patients in the CCTA group underwent coronary revascularization (6.2% vs. 3.2%). Limitations of the PROMISE study included a low event rate, as there was a total of 315 events while 800 events were anticipated to achieve 90% power to detect a 20% reduction in events. The PROMISE trial used a pragmatic design to enhance the generalizability of the results, thus patient care decisions were determined by local sites, and at a time when there was little guidance for clinicians on how to act on various CCTA findings.

A prespecified post hoc analysis from the PROMISE study was to examine cardiovascular outcomes in 2144 patients with diabetes. Patients with diabetes who underwent CCTA had a lower risk of cardiovascular death or MI compared with those who were randomized to functional stress testing (CCTA 1.1% vs. 2.6%; HR 0.39; $P = 0.01$).[68]

There are several additional nonrandomized studies suggesting that the use of CCTA may be associated with a lower event rate. A meta-analysis evaluating hard outcomes following CCTA versus usual care included the results of the PROMISE trial, the SCOT-HEART initial findings over a median follow-up of 1.7 years, and the CAPP trial. In this study, using CCTA was associated with a 30% reduction in incident MI (HR 0.69 [95% CI, 0.49–0.98]).[69] Similar reductions in MI have also been reported in a large (n = 86,705) observational Danish registry (HR 0.71 [95% CI, 0.61–0.82]).[70] The lower risk of MI was similar when comparing with patients who underwent exercise treadmill testing or those who underwent SPECT MPI.

Mechanisms Underlying Improved Patient Outcomes. A key question related to the aforementioned studies is regarding the mechanism for the reduction in event rates following CCTA. In the PROMISE and SCOT-HEART trials, and the Danish registry, when compared with functional testing approaches, the use of CCTA was associated with greater use of preventive therapies such as statins and aspirin. Further supporting these findings, other registries have also showed a stepwise increase in the use and intensity of preventive therapies when more severe stenosis is identified by CCTA.[71] The 5-year results from the SCOT-HEART trial showed that higher use of statin and antiplatelet therapies was sustained over the entire trial period. Furthermore, the observed reduction in events observed in this trial was explained by modeling, which accounted for the benefits of medical therapy.[72] Reinforcing the importance of preventive therapies, the PROMISE investigators reported that the majority of events in patients randomized the functional testing group occurred in those who did not have any abnormalities.[53] Although some have suggested that the higher use of coronary revascularization following CCTA may have contributed to a reduction in events, there are no data that such procedures are associated with improved outcomes (see the section Implications of the ISCHEMIA Trial for Coronary Computed Tomography Angiography).

Use of Invasive Angiography Following Coronary Computed Tomography Angiography

An appropriate criticism of CCTA has been that it can lead to a higher use of invasive angiography and coronary revascularization. In the PROMISE study, there was an ~50% higher use of invasive angiography and twofold increase in coronary revascularization in the CCTA arm compared with the functional testing arm. There were no significant differences in the SCOT-HEART trial, although the absolute rate of coronary revascularization was higher in the SCOT-HEART trial when compared with PROMISE (10.5% vs. 4.7%). In the SCOT-HEART trial, although the initial rates of invasive coronary angiography and coronary revascularization were higher in the CCTA group, the overall rates were similar at 5 years. In fact, when examining the utilization of such procedures beyond 12 months, the rates of invasive coronary angiography and coronary revascularization were higher in the standard-care group. These findings suggest that although CCTA may lead to a higher initial rate of invasive angiography and coronary revascularization, over longer-term follow-up these initial differences may no longer be present.

When considering the differences in revascularization following CCTA versus functional testing between SCOT-HEART and PROMISE, it is possible that geographic differences in practice patterns may play a role. In addition, in the SCOT-HEART trial CCTA was performed in addition to functional testing, most often exercise treadmill testing. It is plausible that reassuring results from functional testing may have been helpful in avoiding invasive angiography. Another factor that may account for the higher use of invasive testing following CCTA in these studies is that the PROMISE study was a pragmatic trial that started enrollment over a decade ago. Yet, this was at a time when there was a paucity of guidance to clinicians on how to manage patients based on the CCTA results (see section Patient Management Following CCTA).

Cost-Effectiveness Data

Several cost-effectiveness studies comparing CCTA with functional testing have been reported collectively showing that the costs of CCTA are similar to those that occur following stress testing. An economic analysis using hospital bills to estimate hospital-based costs in the PROMISE study showed that CCTA had costs similar to the stress testing approaches.[31] Although patients in the CCTA arm had less follow-up noninvasive testing, they had higher costs related to downstream invasive angiography

and revascularization. Similarly, results from the SCOT-HEART trial revealed slightly higher costs associated with randomization to CTA, although the cost difference of $462 was mostly attributable to the additional cost of undergoing CCTA. In the CRESCENT trial,[67] referral to exercise electrocardiography was associated with a higher rate of additional diagnostic testing and a 16% higher cost of care. Nearly half of patients in the stress testing arm had induced diagnostic testing procedures compared with only 1 in 4 in the CCTA arm ($p < 0.0001$). The cost savings achieved in the CTA arm of the CRESCENT trial were also related to the fact that 42% of this arm had a CAC score of zero and did not undergo follow-up CCTA.

A comprehensive cost analysis comparing CCTA to functional testing was also conducted by the NICE guidelines.[50] This analysis determined that CCTA has the lowest cost per correct diagnosis, and was projected to save the National Health Service approximately £16 million each year by excluding CAD with a high NPV. Based on these projections, an initial testing approach with CCTA was recommended to allow for selective use of higher cost stress testing in a smaller proportion of patients with stable chest pain.

One potential advantage of using CCTA in stable chest pain patients is the identification and treatment of nonobstructive plaque, yet the benefits of such preventive therapies are often not realized in the short term. A cost-effectiveness analysis based on patient data from the PROMISE trial that modeled the impact of preventive therapies when nonobstructive plaque was detected showed that CCTA was cost-effective, while the addition of FFRCT further lowered cost and resulted in a dominant strategy. Moreover, over a lifetime, the use of CCTA resulted in a gain of 6 months in perfect health compared with functional testing. In probabilistic sensitivity analyses, anatomic approaches were cost-effective in more than 65% of scenarios, assuming a willingness-to-pay threshold of $100,000/quality-adjusted life year (QALY). Although this study was limited by various assumptions used in the Markov model, the results suggested that anatomic strategies may present a more favorable initial diagnostic option in the evaluation of low-risk stable chest pain.[73]

Coronary Computed Tomography Angiography Plaque Characteristics

There are several CCTA-based adverse plaque characteristics (APCs) associated with a higher risk of future events (Table 20.3). An important but unknown question is whether the increased risk conferred by such plaque is caused by identification of plaque that is more likely to rupture (i.e., "vulnerable plaques"), plaque that is more likely to rapidly progress, or plaque that is more likely to result in ischemia. Regardless, it is important to recognize HRP characteristics, the presence of which could prompt intensification of preventive medical therapies, or in selected cases, referral for further testing.

High-Risk Plaque Characteristics

Low-Attenuation Plaque

Low-attenuation plaque on CCTA (Hounsfield units [HU] <30; Fig. 20.8) corresponds to lipid-rich plaque whereas noncalcified plaque with higher CT attenuation correlates with fibrous tissues. However, it is important to recognize that there is variability in CT values within plaque types that prevents the reliable subclassification of noncalcified plaques. Furthermore, CT measurements of coronary plaques can be influenced by several factors: concentration of adjacent intraluminal iodinated contrast agent, image noise, tube voltage, and the reconstruction filter.

Low-attenuation plaque is more often seen in patients with ACS,[74] and has been found to be associated with ruptured fibrous caps,[75] lesion-specific ischemia,[76] and a future risk of MI.[77] In the SCOT-HEART trial, low-attenuation plaque burden was a strong independent predictor of incident fatal or nonfatal MI (HR 1.60, 95% CI, 1.10–2.34 per doubling) beyond the CAC score or stenosis severity. Patients with low-attenuation plaque burden greater than 4% were nearly 5 times more likely to have subsequent MI[77] (eFig. 20.1).

Positive Remodeling

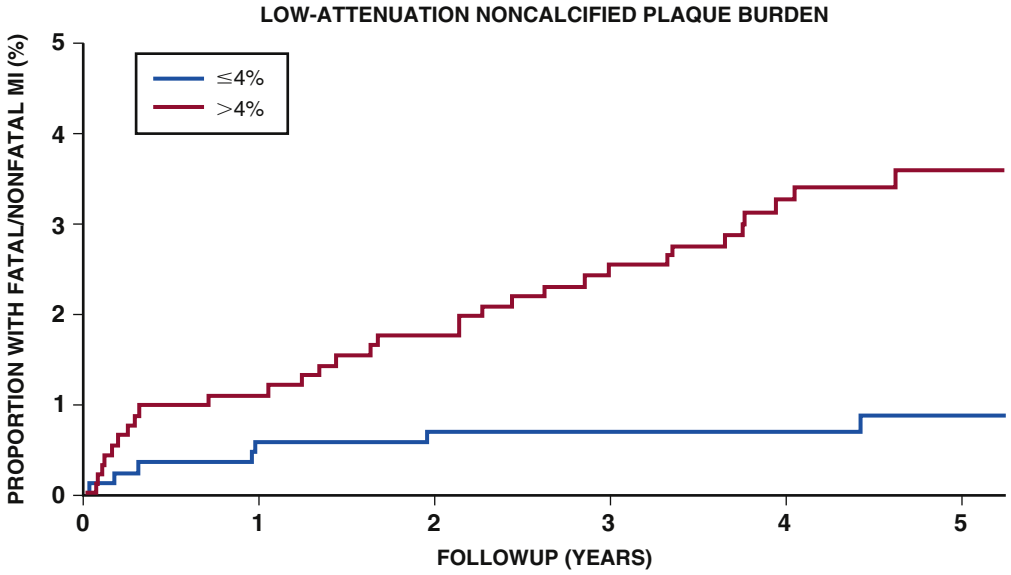
Positive remodeling describes compensatory enlargement of the vessel wall as plaque size increases outward to preserve the luminal area. This feature is associated with a larger burden of plaque, a larger necrotic core, and also higher likelihood of thin-cap fibroatheroma (TCFA) by intravascular ultrasound (IVUS).

The remodeling index is calculated as the vessel cross-sectional area at the site of maximal stenosis divided by the average of the proximal and distal reference segments' crosssectional areas. A remodeling index threshold of ≥1.1 is typically used to define positive remodeling by CCTA (Fig. 20.9).

TABLE 20.3 CCTA-Based Measurements Associated With Increased Risk

CATEGORY	MEASURE	EXPLANATION
Stenosis	Stenosis	• Luminal narrowing estimated as minimal (1%-24%), mild (25%-49%), moderate (50%-69%), severe (70%-99%), or occluded (100%)
Plaque burden	CAC scores	• Overall burden of calcified plaque, which serves as an effective surrogate for overall plaque burden, and provides strong prognostic data
	Segment involvement score	• Number of coronary segments with plaque, which can provide an estimate of the overall extent of plaque, which can provide incremental prognostic value
	Plaque volume	• Quantitative assessment of the overall amount of plaque. Higher plaque volume is associated with higher risk of adverse events and a higher likelihood of flow-limiting CAD
Adverse plaque characteristics (see Fig. 20.11)	Positive remodeling	• Compensatory enlargement of the vessel wall that occurs at the site of the atherosclerotic lesion as the plaque size increases, resulting in the preservation of luminal area
	Low-attenuation plaque	• Correspond to lipid rich plaques (HU <30)
	Spotty calcifications	• Small, dense (>130 HU) plaque component surrounded by noncalcified plaque tissue
	Napkin-ring sign	• A central area of low CT attenuation in contact with the lumen that has a ring-like higher attenuation plaque surrounding this central area
Hemodynamics	FFR_{CT}	• Measure of lesion-specific hemodynamic significance that estimates FFR by applying computational fluid dynamics to rest CCTA data (see Fig. 20.12)
	ESS	• ESS is the tangential force generated by the friction of flowing blood on the endothelial surface of the arterial wall
		• Low ESS triggers an endothelial cell gene expression resulting in reduced nitric oxide production, increased LDL uptake, and local oxidative stress and inflammation. These processes may lead to the development of high-risk lesions
Inflammation	Pericoronary fat attenuation index (FAI)	• Reflects inflammation in the perivascular adipose tissue resulting from nearby coronary inflammation (see Fig. 20.14 for details.)

CAC, Coronary artery calcium; *CAD,* coronary artery disease; *CCTA,* coronary computed tomography angiography; *ESS,* endothelial shear stress; *FFR,* fractional flow reserve; *FFRCT,* fraction flow research computed tomography; *HU,* Hounsfield units; *LDL,* low-density lipoprotein.



Low-attenuation noncalcified plaque burden						
≤4%	862 (100)	856 (99)	851 (99)	849 (98)	659 (76)	360 (42)
>4%	907 (100)	895 (99)	885 (98)	874 (96)	694 (77)	383 (42)

EFIGURE 20.1 Low-attenuation plaque burden and fatal or nonfatal myocardial infarction (MI). Cumulative incidence of fatal or nonfatal myocardial infarction in patients with and without a low-attenuation plaque burden greater than 4%. (From Williams MC, et al. Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction. Circulation 2020;141:1452-1462.)

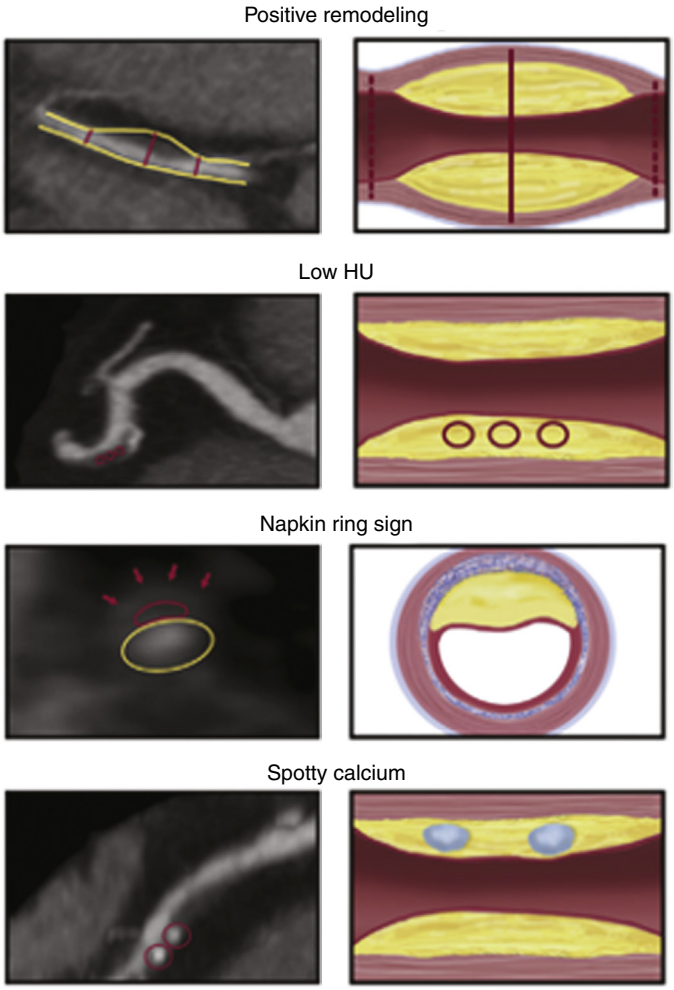


FIGURE 20.8 High-risk coronary plaque features. Positive remodeling: noncalcified plaque with positive remodeling. The two *dotted red lines* demonstrate the vessel diameters at the proximal and distal references (both 1.8 mm), and the *solid red line* demonstrates the maximal vessel diameter in the midportion of the plaque (2.7 mm). The remodeling index is 1.5. Low Hounsfield units (HU) plaque: partially calcified plaque in the mid right coronary artery with low <30 HU plaque. The *red circles* demonstrate the three regions of interest, with mean computed tomography (CT) numbers of 22, 19, and 20 HU. Napkin-ring sign: napkin-ring sign plaque in the mid left anterior descending coronary artery. Schematic cross-sectional view of the napkin-ring sign. The *red line* demonstrates the central low HU area of the plaque adjacent to the lumen (*yellow ellipse*) surrounded by a peripheral rim of the higher CT attenuation (*red arrows*). Spotty calcium: partially calcified plaque in the mid right coronary artery with spotty calcification (diameter <3 mm in all directions; *red circles*). (Adapted from Puchner SB, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II Trial. J Am Coll Cardiol 2014;64:684-692.)

Napkin-Ring Sign

Napkin-ring sign (NRS) describes plaques that on cross-section have a ring-like peripheral enhancement surrounding low CT attenuation in the center (Fig. 20.10). The central area of low attenuation represents, based on pathologic correlation, a large necrotic core, and the higher surrounding ring-like attenuation may be caused by fibrous plaque. However, the peripheral enhancement may also be caused by the vasa vasorum.[78] NRS has been shown to have a high specificity to identify TCFA on optical coherence tomography (OCT), or culprit ACS lesions, and future risk of ACS.[78] Plaques with the NRS contain large necrotic cores and, although infrequent, they have a higher association with future events than other APCs.

Spotty Calcifications

Spotty calcifications are defined as small, dense (>130 HU) plaque components surrounded by noncalcified plaque tissue. Compared with intermediate (1 to 3 mm) calcifications, small (<1 mm) spotty calcification have the strongest association with HRP features defined by virtual histology IVUS, and may represent plaques that are more likely to accelerate.[78] However, the impact of spotty calcifications on plaque stability is controversial, and this feature is a weaker marker of future risk compared with other APCs, such as low-attenuation plaque and positive remodeling.

Plaque Characteristics and Incident Risk

When interpreting CCTA results, it is useful to identify the presence of potential HRP, or APCs. However, such findings are common and have a low specificity for predicting future events. In the SCOT-HEART study, 34% of participants had at least one APC (low-attenuation plaque, positive remodeling, NRS, or spotty calcifications), including 40% of those with nonobstructive plaque and 75% of those with obstructive plaque.[79] As expected, the frequency was higher among individuals who were older or had more risk factors. Although participants who experienced CHD death or MI were 3 times as likely to have at least one APC, the positive predictive value of these findings was low (4.1% when APCs present vs. 1.4% if APCs absent). Notably, APCs were not associated with increased risk once accounting for overall plaque burden, as measured by CAC.[79] In the PROMISE study,[80] HRP characteristics (which only included positive remodeling, low CT attenuation, and NRS) occurred in 15% of patients and were associated with a higher risk of future events (HR 2.7). However, the predictive value was stronger among women, young individuals, and those with nonobstructive plaque.

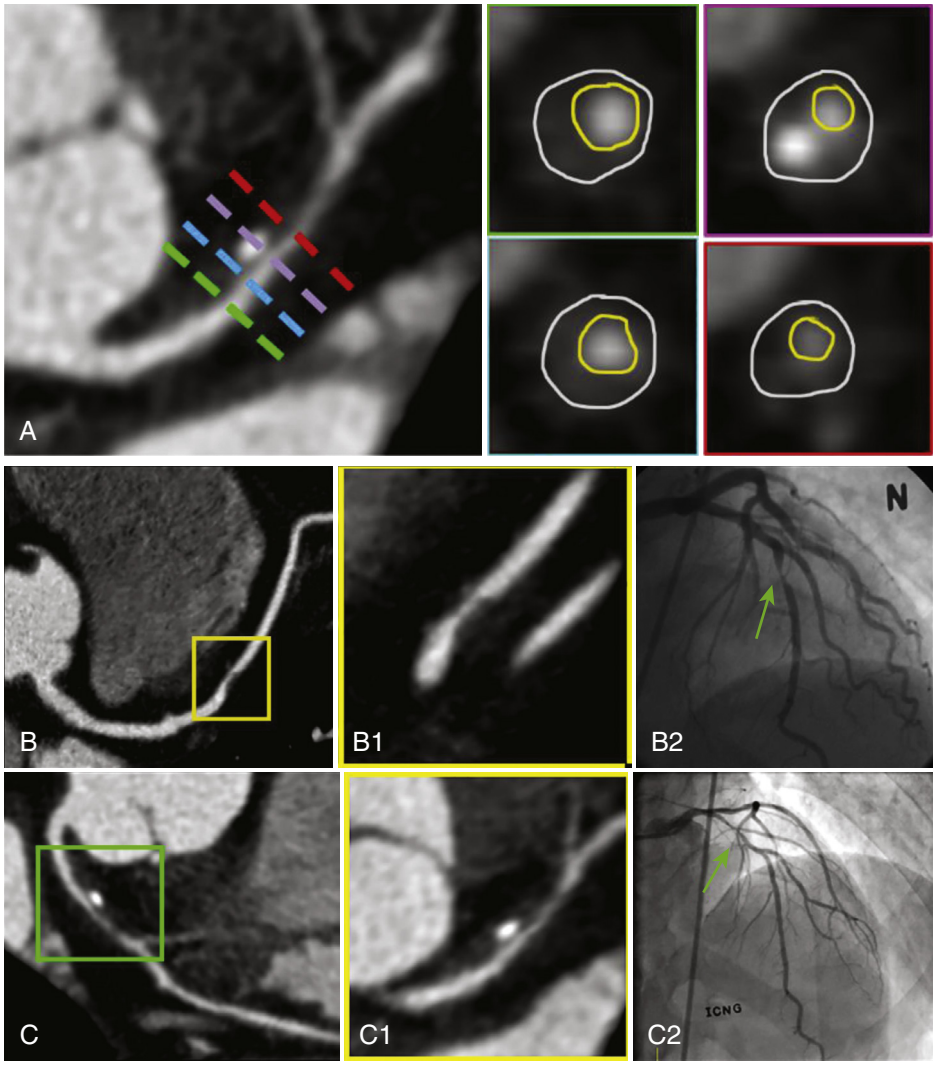
Recognizing the limited specificity of APCs for identifying high-risk patients, plaque features should not just be thought of as binary (i.e., present or absent). For instance, the larger the low-attenuation plaque volume and the more expansive the positive remodeling, the greater is the risk of plaque rupture.[50] Also plaques that have multiple APCs have higher risk. For instance, patients with plaques that have both low-attenuation and positive remodeling (so-called two-feature positive plaque) have been shown to have a higher risk of future events. When evaluating patient risk, the abovementioned factors should always be interpreted in the context of other risk factors and the overall amount of plaque and severity of coronary stenosis.[50,71]

Plaque Features and Myocardial Ischemia

Because it is well recognized that anatomic stenosis, whether by CCTA or invasive angiography, is often inadequate for identifying ischemia,[81,82] a common question is what plaque characteristics are more likely to cause myocardial ischemia. Although the aforementioned HRP features that predict a higher risk of adverse events have also been associated with lesion-specific ischemia,[50] these features have not consistently been found to add incremental data to the evaluation of stenosis.[83] Furthermore, it is unclear if the predictive value of HRP is caused by the identification of specific types of plaque, or if these features are simply markers of having larger plaque burden. A prospective multicenter study of 252 patients from 17 centers evaluated the role of APCs, including positive remodeling, low-attenuation plaque, and spotty calcifications for identification of ischemia-causing coronary artery lesions.[76] A dose-response relationship was noted for increasing numbers of APCs and ischemia, with two or more APCs associated with a 12-fold increase in the rate of ischemia. This improvement for identification of ischemia existed only for positive remodeling (odds ratio [OR] 5.3) and low-attenuation plaque (OR 2.1), with no improvement noted for spotty calcifications. Importantly, arteries exhibiting positive remodeling were useful for diagnosis of lesion-specific ischemia for stenoses of 50% or greater and 50% or less, the latter present in almost 17% of ischemic lesions.[76]

One of the most robust markers of ischemia by CCTA is the percentage aggregate plaque volume (%APV), which is the sum of the entire plaque volume within a vessel divided by the sum of the vessel volume from the artery ostium to the distal end of the coronary lesion. In a study of 58 lesions, %APV demonstrated high discriminatory capacity to identify vessel ischemia beyond traditional diameter stenosis alone (0.85 vs. 0.68)[84] (eFig. 20.2).

The CREDENCE trial provided further data that the overall amount and type of plaque is a strong determinant of ischemia. This was a multicenter trial of 612 patients designed to compare the diagnostic accuracy of comprehensive anatomic versus functional imaging measures



EFIGURE 20.2 Relationship of aggregate plaque volume and coronary artery ischemia. **A,** Aggregate plaque volume percent (%APV) can be calculated by the ratio of the plaque area over the vessel area to the length of a coronary vessel; 1-mm cross-sectional areas are traced for vessel, lumen, and plaque areas. **B,** High-grade stenoses (*yellow box*) that are associated with low %APV **(B1)** are less likely to cause ischemia **(B2). C,** In contrast, stenoses (*green box*) associated with high %APV **(C1)** are more likely to produce ischemia **(C2)**. (Modified from Nakazato R, et al. Aggregate plaque volume by coronary computed tomography angiography is superior and incremental to luminal narrowing for diagnosis of ischemic lesions of intermediate stenosis severity. J Am Coll Cardiol 2013;62:460-467.)

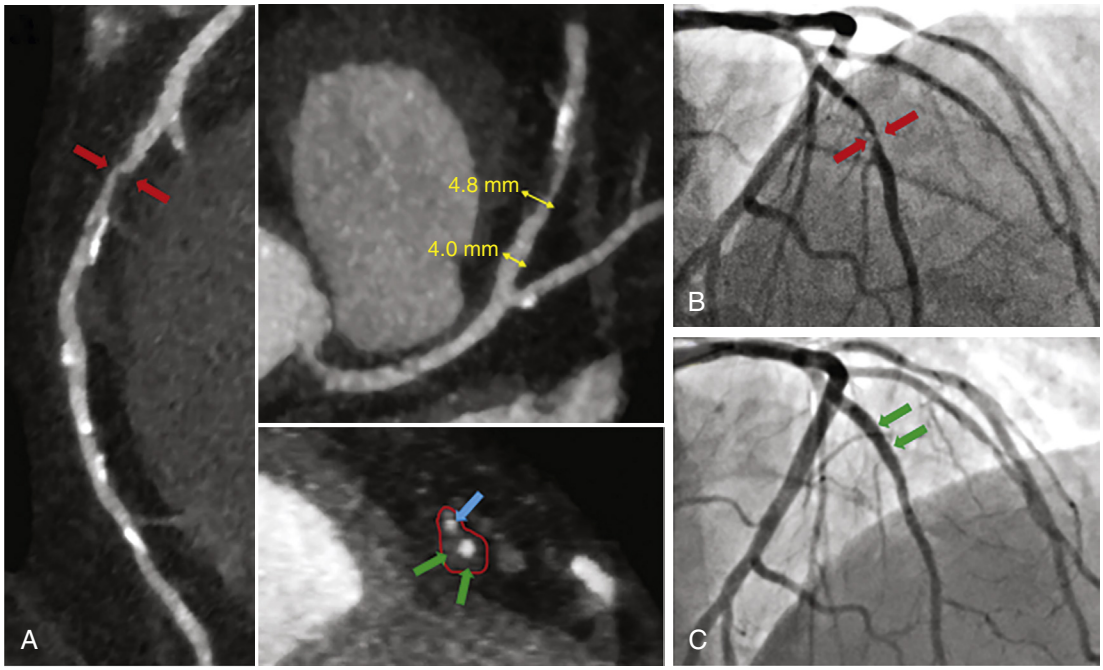


FIGURE 20.9 Example of severe stenosis associated with high-risk plaque features. A 74-year-old man with hypertension and hyperlipidemia presented with several months of intermittent chest pain. Electrocardiogram and echocardiogram were unremarkable. Coronary computed tomography angiography showed **(A)** large amount of predominantly noncalcified plaque in the mid left anterior descending (LAD) artery resulting in severe stenosis (70%–99%) (*red arrows*). High-risk plaque features included (1) positive remodeling: *two yellow double-headed arrows* demonstrate the maximal vessel diameters at the proximal (4.0 mm) and the mid portion of the plaque (4.8 mm); remodeling index is 1.2; (2) low Hounsfield units plaque (<30 HU) (*green arrows*); and (3) spotty calcification (*blue arrow*). **B,** Invasive angiography showed severe stenosis of the mid LAD (*red arrows*). **C,** Status post successful percutaneous coronary intervention of the mid LAD (*green arrows*).

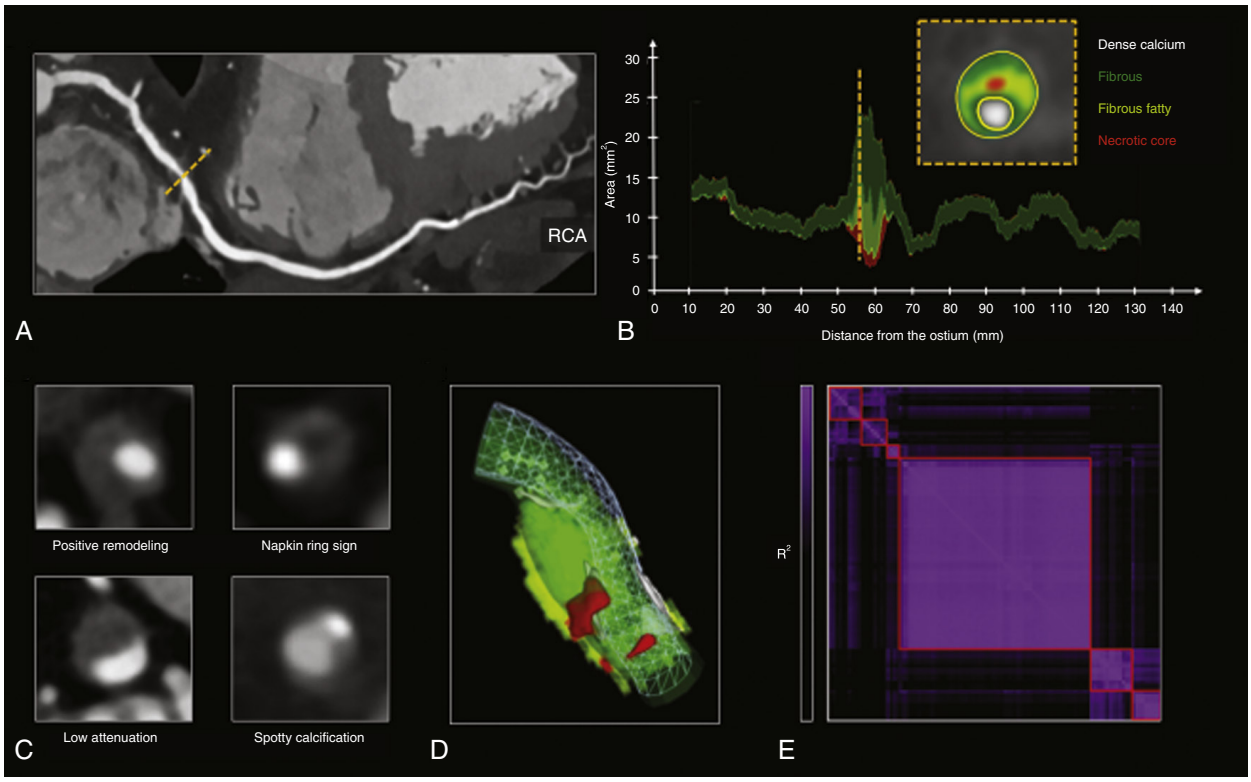


FIGURE 20.10 **Identification of high-risk plaque features using radiomics.** **A,** Curved multiplanar reconstruction of the right coronary artery with a noncalcified plaque showing positive remodeling *(dashed line)*. **B,** Volumetric plaque quantification. Contribution of different plaque components at each cross-sectional area along the vessel. A representative cross section is shown in the boxed inset. **C,** Qualitative high-risk plaque features. **D,** Volume-rendered image of the plaque in which the different plaque components are shown using different colors. **E,** Heat map showing the regression R^2 value between each pair of radiomic features. The information can be used for clustering analysis to show unique structural components. (Courtesy Drs. M. Kolossvary and P. Maurovich-Horvat, Semmelweis University, Budapest, Hungary.)

for estimating vessel-specific invasive FFR.[85] Overall, an invasive FFR ≤0.80 was present in 26.5% of 1727 vessels. The comprehensive composite of anatomic variables (stenosis severity, percentage of noncalcified atheroma volume, lumen volume, the number of lesions with HRP, and the number of lesions with stenosis greater than 30%) had superior discrimination to detect abnormal invasive FFR than MPI (area under the curve [AUC] for CCTA of 0.81 vs. 0.67 for MPI; $P < 0.001$). Of note, FFRCT was not additive to the comprehensive anatomic model, supporting the concept that plaque burden and plaque characteristics are important determinants of pressure decrement across a vessel. Although the extensive quantitative plaque characterization that was performed in this study is currently not used in clinical practice, it is likely that future software will enable greater adoption of such measures.

PLAQUE PROGRESSION AND MEDICAL THERAPY

There have been several studies evaluating the impact of various medical and lifestyle therapies on coronary plaque, as assessed by CCTA. The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) study was a multicenter registry that included 1255 patients who underwent serial CCTA. In this study, statin use was associated with slower progression of overall coronary plaque volume, with increased calcified plaque and reduction of HRP features.[86] The EVAPORATE trial (Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy) used serial CCTA to evaluate the impact of adding 4 g/day of icosapent ethyl to statin and diet therapy. The study included 80 patients and showed significant regression of low-attenuation plaque and noncalcified plaque over 18 months[87] (see eFig. 20.3 for an example of plaque regression).

Perivascular Fat Attenuation

An emerging novel marker of risk on CCTA is the perivascular fat attenuation index[88] (FAI) and perivascular fat radiomic profile[89] (FRP) (Fig. 20.11). Coronary inflammation drives phenotypic changes in perivascular adipose tissue (PVAT) that can be captured by measuring a CT-derived perivascular FAI. Persistence of vascular inflammation leads to further changes in PVAT composition, characterized by increased extracellular fibrosis and local angiogenesis. These changes may be detected by radiomic phenotyping of PVAT using the signature FRP. FAI and FRP provide incremental prognostic value for future fatal or nonfatal cardiac events.[88,89]

Physiologic Evaluation of Coronary Artery Disease

A known limitation of CCTA, and invasive angiography, is that anatomy alone is often insufficient for determining whether there is myocardial- or lesion-specific ischemia. Cardiac CT techniques that can be used to determine this include CT FFR and CT perfusion.

Computed Tomography Fractional Flow Reserve

FFR derived from CCTA (CT FFR) is a method for deriving three-vessel FFR values using typically acquired CCTA (Fig. 20.12; see Fig. 36.17). Because CT FFR is determined from the CCTA dataset, it requires no additional testing and no additional radiation. The advantage of CT FFR is that it provides lesion-specific ischemia, and thus may help inform revascularization decisions.

FFRCT calculations are based on the application of computational fluid dynamics to CCTA to determine coronary fluid pressure, velocity, and flow. To calculate FFRCT, coronary arteries and left ventricular myocardium are segmented with subvoxel resolution. Rest coronary flow for each artery is calculated as a function of the myocardial mass it subtends and a calculation of distal intramyocardial microcirculatory resistance. Hyperemia is then modeled by estimating the response of the coronary arteries to adenosine. The final step in the calculation of FFRCT is the distribution of tetrahedral meshes through each artery and its branch, then solving the fluid dynamic equations to estimate FFR values at every point along the coronary artery bed.

Diagnostic Accuracy (see Fig. 36.17)

The diagnostic performance of FFRCT has been evaluated in multiple prospective multicenter trials, with more recent trials representing improvement in FFRCT technology related to improved image segmentation and flow modeling. The Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT) was a prospective multicenter trial that included 254 patients referred for clinically indicated invasive angiography. CCTA and FFRCT were performed, with 484 vessels directly interrogated by invasive FFR. The area under the receiver operating characteristic (ROC) curve for FFRCT was 0.90 and 0.93 on a per-patient and per-vessel basis, respectively, which corresponded to an overall per-vessel diagnostic accuracy of 86%.[90]

A post hoc analysis from the PACIFIC trial[91] evaluated the diagnostic accuracy of FFRCT among the 208 patients included in this trial, with FFRCT evaluable in 505 (83%) vessels that were thus included in the primary per-vessel analysis. When evaluating this population, the AUC for FFRCT was 0.94 (95% CI, 0.92–0.96), and significantly higher than CCTA alone (0.83; 95% CI, 0.80–0.86; $P < 0.001$), SPECT (0.70; 95% CI, 0.65–0.74; $P < 0.001$), and PET (0.87; 95% CI, 0.83–0.90; $P < 0.001$) (eFig. 20.4). The sensitivity of FFRCT (90%) was higher than any of the other modalities, whereas the specificity of FFRCT (86%) was comparable to CCTA and PET. A notable limitation of this substudy was that 17% of vessels were nonevaluable by FFRCT and were excluded from the primary analysis.

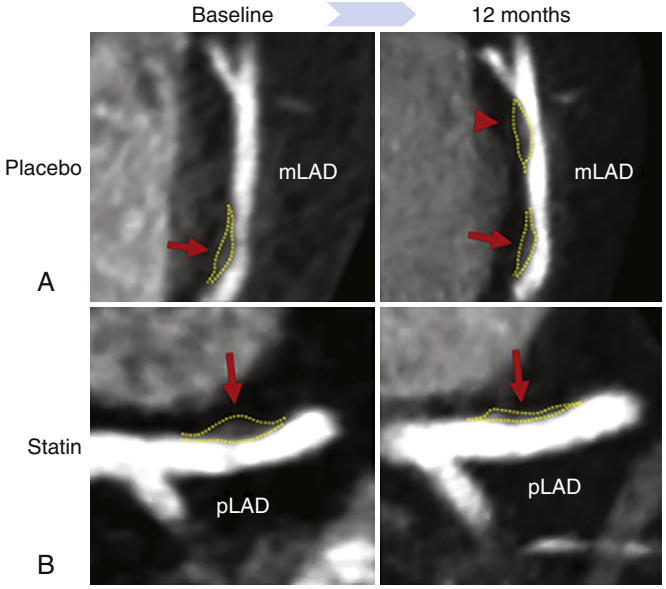
Although the specificity of FFRCT is comparable to other functional techniques, it is notable that it is a lesion-specific measure, which is fundamentally different from measuring abnormalities in myocardial flow (see Chapter 18).

Clinical Effectiveness

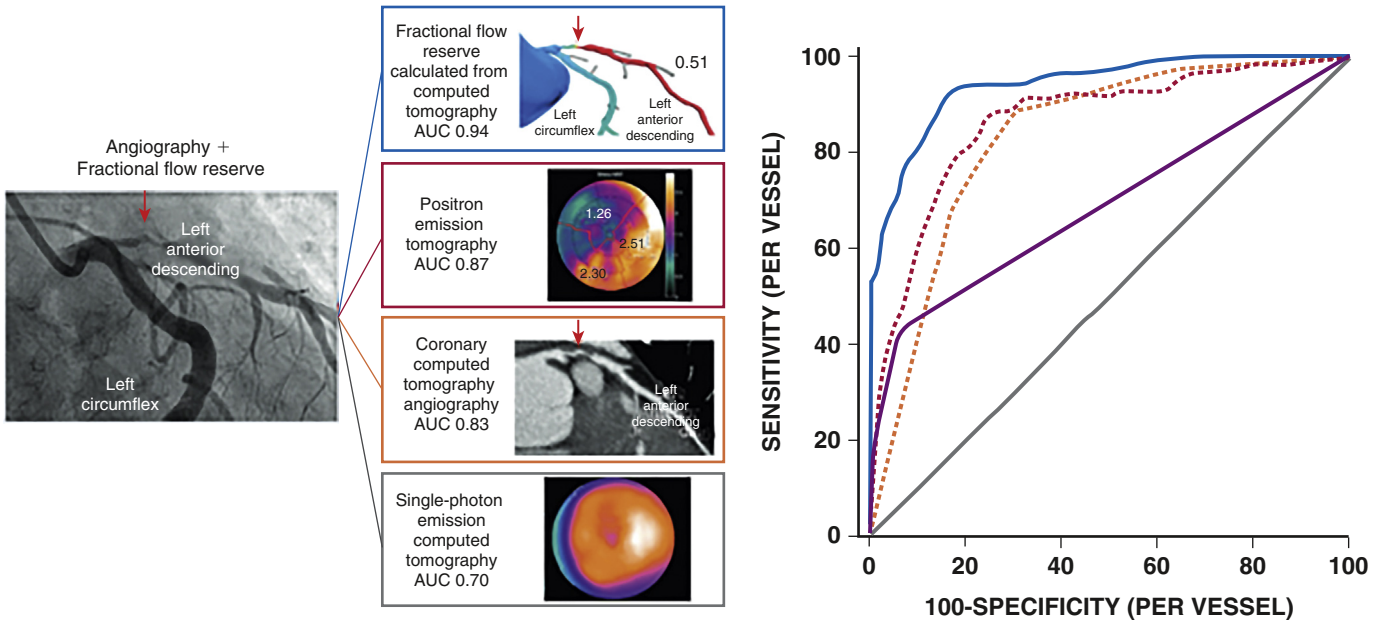
FFRCT has been assessed for its ability to alter the clinical management of patients undergoing noninvasive and invasive testing. In the crossover-design Prospective Longitudinal Trial of FFRCT Outcome and Resource Impacts (PLATFORM), 584 symptomatic patients with suspected CAD were assigned to either usual care or a CCTA-FFR_{CT}-based evaluation to determine the rates of nonobstructive CAD (<50%) at invasive coronary angiography (ICA). Two separate cohorts were studied, referred for invasive assessment and for noninvasive stress testing. Among patients intended to undergo invasive angiography, a CCTA-FFRCT approach resulted in a significantly higher rate of obstructive CAD at ICA (73% vs. 12%) and also resulted in 61% of ICAs being canceled after CCTA-FFRCT findings were known. These cancellations were associated with 32% lower costs and similar quality-of-life measures by a CCTA-FFRCT algorithm compared with usual care, a finding that extended to the 1-year follow-up. In contrast, among patients referred to noninvasive imaging, the rates of nonobstructive CAD at ICA were not statistically different (13% vs. 6%). For these patients undergoing noninvasive imaging, quality-of-life measures were higher with a CCTA-FFRCT-based strategy than with usual care, although with higher costs ($2766 vs. $2137).

The Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care (ADVANCE) registry was a prospective multicenter registry that included 5083 patients from 38 sites who were referred for CCTA with FFRCT.[92] This study found that the addition of FFRCT to CCTA results in a modification to the anticipated treatment plan in two-thirds of patients. However, the true magnitude of how often FFRCT may impact care was likely overestimated as anticipated treatment plans were made by a core lab reviewing angiographic findings alone. The ADVANCE registry also evaluated the safety of deferring revascularization when FFRCT is greater than 0.8. Over a 90-day follow-up, none of the 1952 subjects with negative FFRCT experienced death, MI, or unplanned hospitalization for ACS and urgent revascularization. In contrast, there were 19 adverse events (10 deaths, 4 MIs, and 5 hospitalizations for urgent revascularization) in patients with positive FFRCT (HR 19.75; $P < 0.001$).[92] At 1 year, there was a trend toward lower MACE ($P = 0.062$) and significantly lower cardiovascular death or MI ($P = 0.01$) in patients with a negative FFRct compared with patients with abnormal FFRCT.[93]

The utility of FFRCT following CCTA was also evaluated in a large single-center registry of 3674 consecutive patients with stable chest pain who were evaluated with CCTA followed by selective FFRCT for those with intermediate stenosis (30% to 70%).[94] FFRCT was performed for 697 patients (18% of the cohort), reflecting the fact that this test is only needed for a minority of CCTA cases, when there is stenosis of uncertain hemodynamic significance. Notably, patients



EFIGURE 20.3 Example of coronary plaque changes on serial coronary computed tomography angiography. New mLAD plaque (*arrowhead*) developed in a participant on placebo. **A,** Second, more proximal mLAD plaque was unchanged (*arrow*). **B,** Proximal LAD plaque that regressed on follow-up after treatment with statin (*arrow*). *m LAD,* Mid left anterior descending; *pLAD,* proximal left anterior descending. (From Foldyna B, et al. Individual coronary plaque changes on serial CT angiography: within-patient heterogeneity, natural history, and statin effects in HIV. J Cardiovasc Comput Tomogr 2020;14:144-148.)



EFIGURE 20.4 Discriminative ability of imaging modalities for the detection of per-vessel fractional flow reserve-defined ischemia. Significance of stable coronary artery disease, as defined by invasive FFR, was prospectively tested with several noninvasive imaging modalities. Each patient underwent FFRCT, PET, CCTA, SPECT, and ICA with FFR, regardless of imaging results as illustrated by the typical imaging findings of a severe left anterior descending artery stenosis in the *colored boxes.* Curves with corresponding colors indicate that FFRCT demonstrated the greatest area under the curve (AUC) for the detection of per-vessel ischemia. *CCTA,* Coronary computed tomography angiography; *FFR,* fractional flow reserve; *FFRCT,* fractional flow reserve calculated from computed tomography; *ICA,* invasive coronary angiography; *PET,* positron emission tomography; *SPECT,* single-photon emission computed tomography. (From Driessen RS, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. J Am Coll Cardiol 2019;73:161-173.)

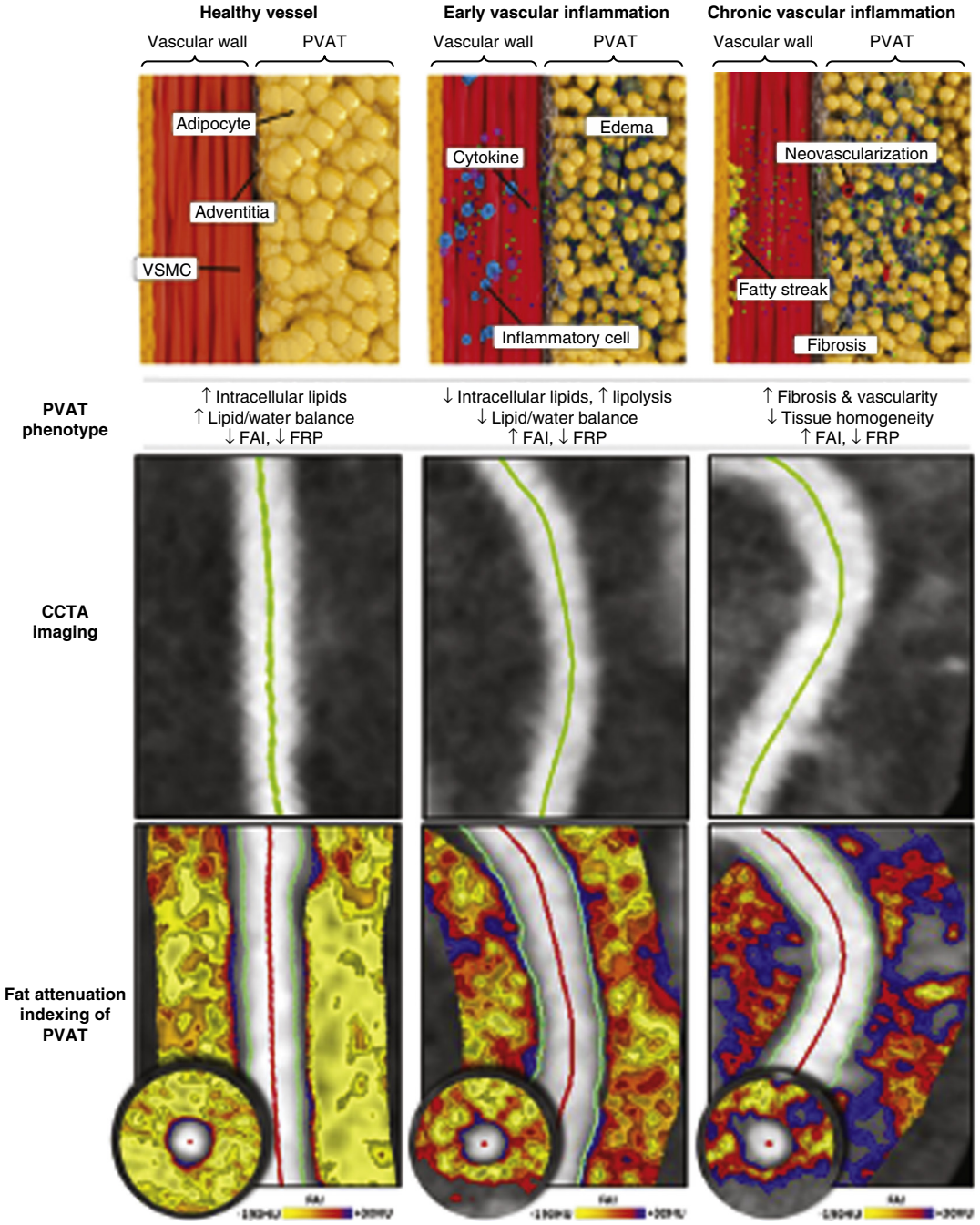


FIGURE 20.11 Schematic representation of the biology underlying fat attenuation index (FAI) and fat radiomic profile (FRP). Early coronary inflammation drives lipolysis and inhibits adipogenesis in perivascular adipocytes, shifting the composition of perivascular adipose tissue (PVAT) toward the aqueous phase, at the expense of the lipid phase (*top middle panel*). Persistent chronic vascular inflammation may lead to further changes of the perivascular space, such as fibrosis and angiogenesis (*top right panel*). These changes may not be visible on coronary computed tomography angiography, as they may precede plaque formation (*middle panels*). Perivascular fat attenuation indexing identifies arteries with low inflammation (*bottom left panel*), early vascular inflammation (*bottom middle panel*), or chronic vascular inflammation *(bottom right panel).* Early vascular inflammation is quantified by the perivascular FAI and chronic vascular inflammation by the perivascular FRP. (Courtesy Charalambos Antoniades, MD, PhD, University of Oxford.)

with intermediate stenosis who had a negative FFRCT (>0.80) had similar long-term outcomes when compared with patients with no to minimal stenosis (0% to 30%) by CCTA. On the other hand, adverse events were higher among patients with an abnormal FFRCT who were not referred for invasive angiography. Although the latter findings may be influenced by selection bias (i.e., patients who were not treated could have been higher risk), the overall findings from this trial support the safety of using CT-FFR to defer coronary revascularization in patients who have intermediate lesions that are deemed non–flow limiting.[94]

When integrating data from FFRCT into clinical management decisions, there are several important factors to consider. FFRCT may aid decision making in lesions that have intermediate stenosis (i.e., 40% to 70%) in the proximal or mid-coronary vessel (see Table 20.4 for guideline-based recommendations). Because FFRCT declines along the length of the vessel with serial focal lesions or areas of diffuse disease, it is important to correlate the pressure loss to specific lesions, which can only be established by direct comparison between the CCTA lesion location and the FFRct 3D model.[95] When doing so, FFRCT >0.80 indicates that a lesion is unlikely to be hemodynamically significant and revascularization can be safely deferred. Although most studies have used a dichotomous interpretation strategy, FFRCT values (similar to invasive FFR) have a continuous relationship, and the lower the FFRct values, the higher the likelihood of hemodynamic significance and the risk of adverse events.[95] When FFRCT is between 0.76 and 0.80, additional information may be useful for deciding on

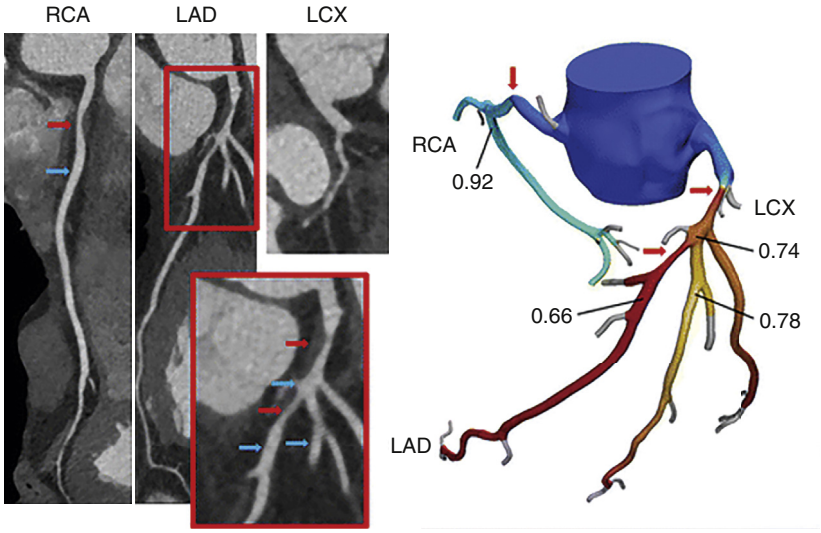


FIGURE 20.12 FFR_{CT} assessment in vessels with serial lesions in a 53-year-old man with typical angina. *Left:* Coronary computed tomography angiography curved multiplanar reconstructions demonstrate a proximal 60% right coronary artery (RCA) stenosis (*red arrow*) and two serial stenoses in the left anterior descending artery (LAD) (one lesion in the proximal segment with 70% or greater diameter stenosis, and a 50% to 69% diameter stenosis lesion distal to the takeoff of the second diagonal [*red arrows*]). *Blue arrows* indicate where the FFR_{CT} values were assessed. *Right:* in the FFR_{CT} three-dimensional model, the FFR_{CT} value 10 mm distal to the proximal LAD stenosis was 0.74 and thus had hemodynamic significance, whereas FFR_{CT} 15 mm distal to the second LAD stenosis was 0.66. FFR_{CT} 10 mm distal to the lower border of the proximal RCA stenosis was 0.92, thus this lesion had low likelihood of being hemodynamically significant. Of note, pressure recovery was observed in the proximal part of the second diagonal with a step-up in FFR_{CT} from 0.74 in the LAD to 0.78 when moving downstream the diagonal branch. LCX = left circumflex coronary artery. (From Nørgaard BL, et al. Coronary CT angiography-derived fractional flow reserve testing in patients with stable coronary artery disease: recommendations on interpretation and reporting. Radiol Cardiothorac Imaging 2019;1:e190050.)

the potential role of revascularization, including lesion location, presence of HRP features, patient symptoms, or the translesional FFRCT gradient.[95]

There are several noteworthy limitations of FFRCT. At present, this technique is performed by a single vendor and is associated with additional cost, although this has been shown to be cost-effective because of the avoidance of invasive angiography and coronary revascularization in a subgroup of patients.[73] FFRCT requires excellent CCTA image quality, and artifacts, such as motion, misalignment, low contrast, or blooming from coronary calcification, may impair the diagnostic reliability of this technique. FFRCT is not recommended in vessels with prior stents or in patients who have undergone bypass surgery.

Coronary Tomography Perfusion

CT perfusion is a technique in which the myocardium can be visualized on CT datasets to determine whether there is a stress-induced or rest myocardial perfusion defects. On rest CCTA images, a resting perfusion defect (i.e., subendocardial hypoenhancement of the myocardium) can be used to identify areas of prior infarction or high-grade stenosis. Other features of a prior infarction on CCTA include areas of fatty metaplasia, intramyocardial calcifications, wall thinning, and wall motion abnormalities, in cases where multiphase data were acquired. Several small studies have shown the incremental data of resting myocardial perfusion defects beyond CCTA alone, especially for the detection of ACSs among patients with acute chest pain.

Stress Computed Tomography Perfusion

CT stress perfusion imaging can performed when images are acquired during vasodilator stress.[96] Typically, two separate acquisitions are performed: (1) a rest CCTA, which is used for evaluation of the coronary arteries and resting MPI, and (2) a stress CT, which is used for the evaluation of stress-induced perfusion defects. The sequence of imaging depends on the clinical scenario. In patients with known CAD in which stress perfusion is desired, there are advantages to acquiring this data first, and then obtaining the CCTA dataset 15 to 20 minutes later. Another approach is to first obtain the rest CCTA dataset, especially if the absence of significant CAD may be used to avoid the stress component of the exam.

Multiple single-center studies and two multicenter studies have evaluated the diagnostic accuracy of various stress CT perfusion protocols against both invasive and noninvasive techniques, showing good accuracy for detecting anatomic stenosis or myocardial ischemia.[96] The value of stress CT perfusion is greatest when added to the CCTA data, where CT perfusion can increase the specificity of anatomic stenosis measures to detect myocardial ischemia.

Stress CT perfusion can provide simultaneous data on both CCTA and myocardial perfusion. Furthermore, it can be performed on-site, and at the same time as the CCTA exam. CT perfusion can also be performed in patients who have significant coronary calcification and stents, and it is generally less dependent on high image quality than CCTA, as it does not require high spatial resolution. However, when compared with nuclear and CMR myocardial perfusing imaging, CT has lower contrast resolution. In addition, there are certain artifacts that may impact the diagnostic accuracy of CT perfusion including beam-hardening artifacts and motion-related artifacts. CT perfusion also requires a higher amount of contrast and higher radiation dose than routine CCTA studies. Despite robust data on the diagnostic accuracy of this technique, there is currently a paucity of clinical effectiveness data, insufficient insurance coverage, and limited clinical expertise; thus this technique has not been widely adopted and remains mostly investigational.

Comparing and Integrating Different Techniques

A single-center study of 147 consecutive patients scheduled for invasive angiography with invasive FFR who underwent both FFR-CT and stress CT perfusion showed that both FFRCT and stress CT perfusion improved specificity and positive predictive values compared with CCTA alone. Although this study suggests that both techniques may be comparable for evaluating the functional significance of CAD lesions,[97] there is a paucity of data comparing these techniques, and overall significantly more data supporting the accuracy and safety of CT-FFR.

Implications of the ISCHEMIA Trial for Coronary Computed Tomography Angiography

The ISCHEMIA trial[31] found that among stable patients who had evidence of moderate to severe ischemia on stress testing, an initial invasive strategy, when compared with an initial conservative strategy, was not associated with a reduction in the primary outcome of cardiovascular death, MI, hospitalization for unstable angina, hospitalization for heart failure, or resuscitated cardiac arrest over a median follow-up of 3.3 years. Similar results were also observed for the prespecified secondary endpoint of cardiovascular death or MI, and across multiple other prespecified subgroup analyses. However, an initial invasive strategy was associated with a reduction in angina and improved quality of life, but only in those who had frequent symptoms of angina. In this trial, CCTA was useful for excluding left main disease (~5%) or nonobstructive CAD (~14%). Thus, in the presence of significant ischemia, if a decision is made to pursue medical management alone, CCTA should be considered for excluding high-risk anatomy.

The ISCHEMIA trial did not evaluate the effectiveness of any single imaging strategy; instead it reinforced the concept that contemporary medical therapy is highly effective in reducing the risk of cardiovascular outcomes. In fact, over a median follow-up of 3.3 years, the primary composite endpoint occurred in only 15.5% of patients in the conservative arm and 13.8% of patients in the invasive arm ($P = 0.34$).[31] The are several notable implications of this trial when considering the role of CCTA in evaluating patients with stable CAD.

TABLE 20.4 Select U.S. and European Guideline Recommendations

GUIDELINES	CLINICAL SCENARIO	RECOMMENDATION
U.S. Multisociety Cholesterol Guidelines[116]	CAC testing in prevention	• In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone, or initiate statin therapy (COR 2a; LOE: B-NR)
2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes[117]	Initial diagnostic management of symptomatic patients with suspected coronary artery disease	• Noninvasive functional imaging for myocardial ischemia* or CCTA is recommended as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone (Class 1, Level B) Additional guidance: "Coronary CTA is the preferred test 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" • CCTA should be considered as an alternative to invasive angiography if another noninvasive test is equivocal or nondiagnostic (Class 2a, Level C) • 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 (Class 3, Level C)
	Recommendations for investigations in patients with suspected vasospastic angina	• Invasive angiography or CCTA is recommended in patients with characteristic episodic resting angina and ST-segment changes, which resolve with nitrates and/or calcium antagonists, to determine the extent of underlying coronary disease (Class 1, Level C)
	Recommendations for valvular disease in chronic coronary syndromes	• CCTA should be considered as an alternative to coronary angiography before valve intervention in patients with severe valvular heart disease and low probability of CAD (Class 2a, Level C)
2020 ESC Guidelines for management of ACS[60]	Patients presenting without persistent ST-segment elevations	• CCTA is recommended as an alternative to invasive angiography to exclude ACS when there is a low-to-intermediate likelihood of CAD and when cardiac troponin and/or ECG are normal or inconclusive (Class 1, Level A) • In patients with no recurrence of chest pain, normal ECG findings, and normal levels of cardiac troponin (preferably high sensitivity), but still with a suspected ACS, a noninvasive stress test (preferably with imaging) for inducible ischemia or CCTA is recommended before deciding on an invasive approach (Class 1, Level B)
2021 AHA/ACC and others: Guideline for the Evaluation and Diagnosis of Chest Pain[118]	Patients with acute chest pain	• For intermediate-risk patients with acute chest pain and no known coronary artery disease eligible for diagnostic testing following a negative or inconclusive evaluation for acute coronary syndrome, CCTA is useful for exclusion of atherosclerotic plaque and obstructive coronary artery disease (Class 1, Level A)
	Patients with stable chest pain	• For intermediate–high risk patients with stable chest pain and no known coronary artery disease, CCTA is effective for diagnosis of CAD, for risk stratification, and for guiding treatment decisions. (Class 1, Level A) • For intermediate–high risk patients with stable chest pain and known coronary stenosis of 40% to 90% in a proximal or middle coronary segment on CCTA, FFRCT can be useful for diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization (Class 2a, Level B)
	Patients with prior bypass surgery	• In patients with prior CABG surgery presenting with acute chest pain who do not have ACS, performing stress imaging is effective to evaluate for myocardial ischemia or CCTA for graft stenosis or occlusion. (Class 1, Level C) • In patients who have had prior coronary artery bypass surgery presenting with stable chest pain who are suspected to have myocardial ischemia, it is reasonable to perform stress imaging or CCTA to evaluate for myocardial ischemia or graft stenosis or occlusion. (Class 2a, Level C)
	Patients with stable chest pain and known nonobstructive plaque	• For symptomatic patients with known nonobstructive CAD who have stable chest pain, CCTA is reasonable for determining atherosclerotic plaque burden and progression to obstructive CAD, and guiding therapeutic decision making (Class 2a, Level B-NR)

*Stress echocardiography, stress cardiac magnetic resonance, single-photon emission CT, or positron emission tomography
ACC, American College of Cardiology; *ACS,* acute coronary syndrome; *AHA,* American Heart Association; *CAC,* coronary artery calcium; *CAD,* coronary artery disease; *CCTA,* coronary computed tomographic angiography; *ECG,* electrocardiogram; *ESC,* European Society of Cardiology; *FFR,* fractional flow reserve.

Patient Management Considerations

Among patients who do not have known CAD, CCTA can identify the need and intensity of medical therapy (Fig. 20.13) and identify patients who may benefit from additional noninvasive or invasive testing to determine the need for coronary revascularization. Pertinent to the ISCHEMIA trial results, CCTA may be useful to rule out underlying high-risk coronary anatomy, particularly when symptoms are infrequent and conservative management is being considered. Indeed, one of the strengths of CCTA lies in its ability to identify a wide spectrum of CAD, ranging from nonobstructive plaque to extensive multivessel disease. Another advantage of using CCTA as a front-line test has to do with its diagnostic efficiency: the majority of individuals with no history of CAD who are evaluated with CCTA will have no CAD, or nonobstructive CAD, and will not need further testing. For example, in the PROMISE study only 14% of patients had ≥50% stenosis,[98] and in the CRESCENT I and II trials only 14% had ≥50% stenosis.[99] In the absence of significant CAD, CCTA can also identify various other alternative explanations for a patient's symptoms ranging from aortic or pulmonary disease to pericardial and esophageal pathologies (Fig. 20.14).

The finding that most patients with stable symptoms can be effectively treated with medical therapy has implications for how CCTA results should be used in patient management (see Fig. 20.13). Specifically, most patients only require preventive therapies following CCTA, and invasive angiography should be reserved for patients that have

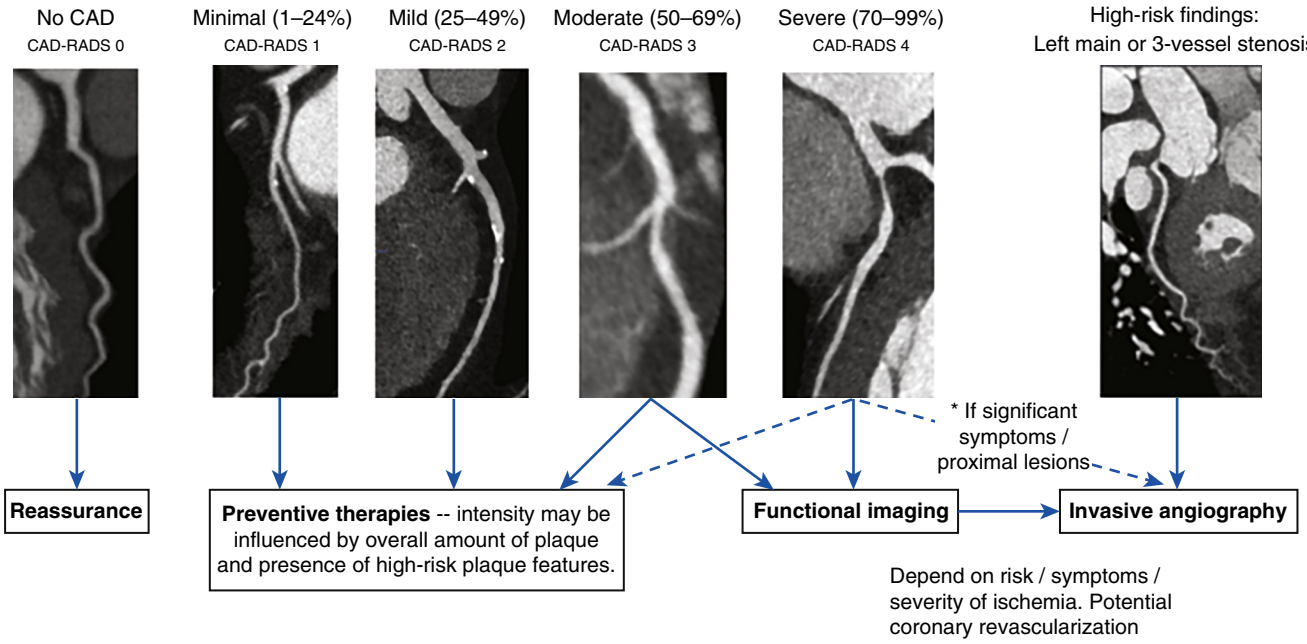


FIGURE 20.13 Patient management recommendation following coronary computed tomography angiography in stable chest pain.

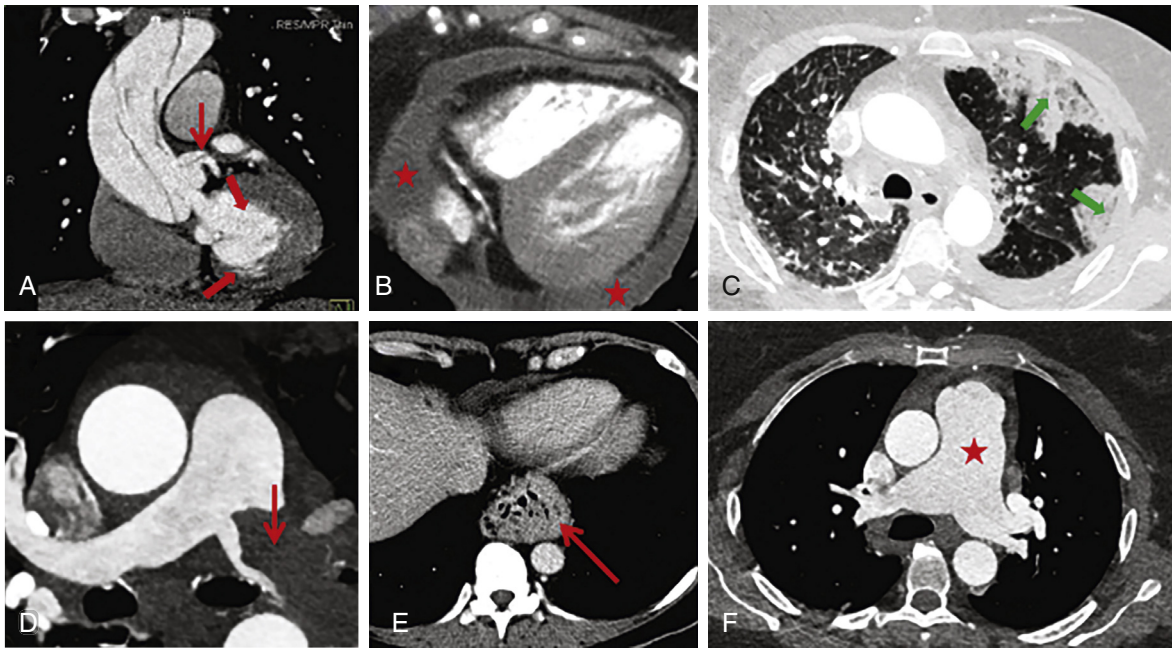


FIGURE 20.14 Examples of various etiologies of chest pain or dyspnea diagnosed on cardiac computed tomography. A, Aortic dissection extending into the left main coronary artery. **B,** Pericardial effusion. **C,** Pulmonary infarction. **D,** Pulmonary embolus. **E,** Hiatal hernia. **F,** Dilated pulmonary artery in a patient with pulmonary hypertension.

high-risk anatomy (e.g., left main stenosis or three-vessel obstructive CAD), or those with obstructive CAD with frequent or unstable symptoms. Nevertheless, in some patients it may be unclear if their symptoms are related to their underlying CAD, and in such cases functional testing, including exercise testing alone, may be helpful for establishing the potential benefit of coronary revascularization (see Chapter 15).

Patient Management Recommendations

Patient management recommendations are summarized in Fig. 20.13, and they are based on an expert consensus document (CAD-RADS),[100] recent guidelines, and implications of the ISCHEMIA trial discussed previously.

Normal CCTA (CAD-RADS 0): Patients who have no plaque or stenosis should be reassured that they have an excellent prognosis, and a nonatherosclerotic cause of symptoms should be considered. Preventive lifestyle therapies should be the main focus for reducing the risk of future events, as should be the case in all adults, and for all the following groups.

Nonobstructive plaque (CAD-RADS 1 or 2): Patients with minimal (1% to 24%) or mid (25% to 49%) stenosis should also be evaluated for potential nonatherosclerotic causes of their symptoms, as it is unlikely that their plaque is flow limiting. In select cases of mild (25% to 49%) stenosis in which there is a large amount of diffuse plaque or HRP features, a noninvasive evaluation for ischemia can be considered, if there are frequent symptoms and a high suspicion for ongoing ischemia. Patient management should focus on lifestyle and pharmacologic preventive therapies, as per prevention guidelines (see Chapter 25). However, for patients who are not on such therapies, the identification of plaque, especially if extensive, should prompt the initiation or intensification of pharmacotherapy. When

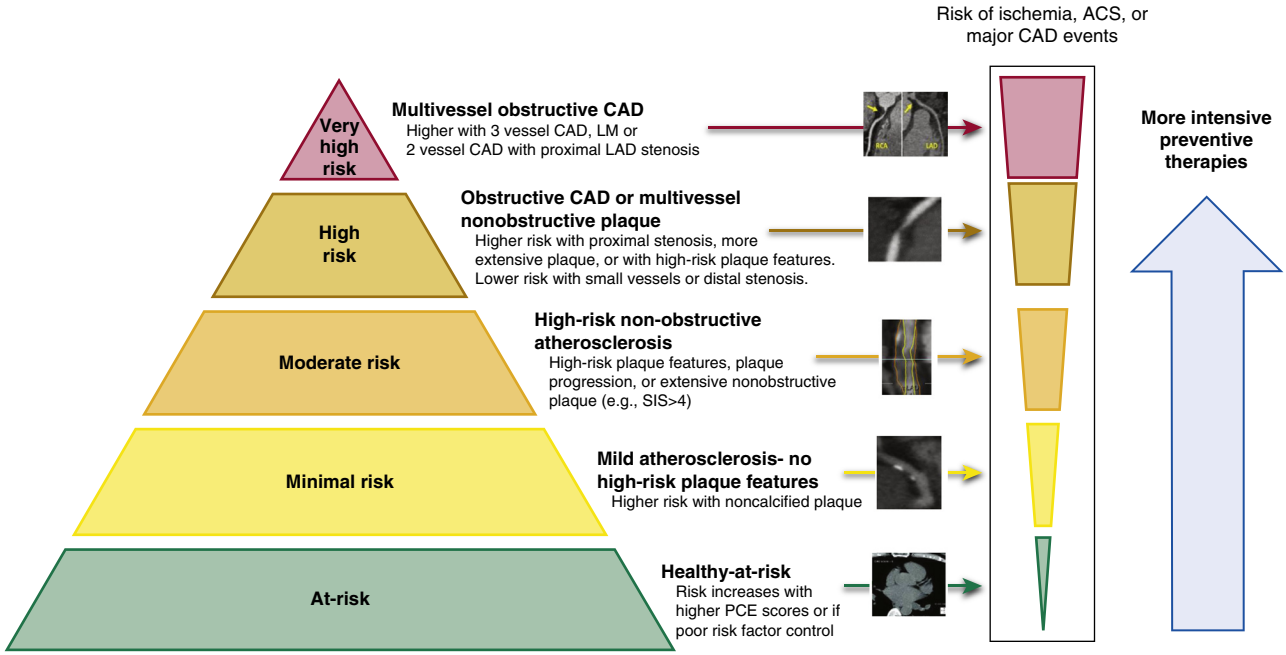


FIGURE 20.15 Stages of atherosclerosis. Patients with more extensive, multivessel coronary artery disease are at highest risk, whereas those without any plaque or stenosis comprise those at lowest risk. (From Shaw LJ, et al. Society of Cardiovascular Computed Tomography/North American Society of Cardiovascular Imaging—Expert Consensus Document on Coronary CT Imaging of Atherosclerotic Plaque. J Cardiovasc Comput Tomogr 2021;15:93-109.)

deciding on the intensity of preventive therapies, it is important to consider the level of risk by integrating data on clinical risk factors and the level of risk associated with the CCTA findings. Fig. 20.15 provides an overview of various stages of atherosclerosis detected by CCTA. Risk level can be determined based on the amount or extent of plaque (e.g., number of segments or vessels that have coronary plaque and CAC score, if available), the presence of HRP features (see section Coronary Computed Tomography Angiography Plaque Characteristics), plaque progression, lesion location, and extent of obstructive CAD. Patients who have moderate to high risk have an event rate that is similar to secondary prevention cohorts and are more likely to benefit from high-intensity lipid-lowering therapy and antiplatelet therapy, if there are no contraindications.

Moderate stenosis (50% to 69%; CAD-RADS 3). In addition to the previous recommendation regarding preventive therapies, functional assessment may be considered if there are frequent symptoms. Routine invasive angiography should be avoided unless there are frequent or unstable symptoms.

Severe stenosis (70% to 99%; CAD-RADS 3). In addition to the previous recommendation regarding preventive therapies, either functional assessment or invasive angiography may be considered if there are frequent symptoms. In the presence of left main disease or three-vessel obstructive (≥70%) CAD, invasive angiography is recommended.

Total occlusion (100%; CAD-RADS 4). In addition to the previous recommendation regarding preventive therapies, invasive angiography and/or viability assessment should be considered. In such cases it is important to consider CCTA factors that can predict the likelihood of successful revascularization, including amount of coronary calcifications and the length of the occluded segment.

Special Populations

Diabetes (see also Chapter 31)*:* While routine CCTA in asymptomatic individuals who are on baseline preventive therapies has not been shown to improve patient outcomes, subgroup analyses from both the PROMISE and SCOT-HEART studies suggested that the use of CCTA among symptomatic patients with diabetes may be associated with improved outcomes (see the previous section Hard Clinical Outcomes) when compared with functional testing approaches.[101] Given that individuals with diabetes are more likely to have diffuse plaque, have faster plaque progression, and have a higher rate of adverse cardiovascular events, it is plausible that CCTA may have unique advantages in identifying patients who may benefit from more aggressive interventions. Integration of plaque volume, HRP features, and luminal stenosis may provide the most robust long-term risk prediction.[102]

Women (see also Chapter 91)*:* Although women are less likely to have obstructive CAD than men, CCTA allows for the accurate detection of nonobstructive plaque, including overall plaque extent, and HRP features. CCTA has similar accuracy and prognostic value in men and women, although in the PROMISE study the prognostic value of HRP was stronger in women than in men.[80] In the multicenter ROMICAT II trial, women with acute chest pain had a greater reduction in length of stay than men when CCTA was compared with standard of care, a finding which likely reflects the lower prevalence and severity of CAD in women (58% of women had a normal CCTA vs. 37% of men; $P < 0.001$).[23] CCTA is also the only noninvasive test that can be used to detect spontaneous coronary artery dissection (SCAD; see Fig. 20.16, for example), although this diagnosis requires excellent CCTA image quality, and is limited in evaluating small distal vessels.[103]

Anomalous coronary arteries: CCTA is a useful noninvasive test used to evaluate patients with known or suspected anomalous origin of the coronary arteries (Fig. 20.17). When such abnormalities are identified, CCTA can describe the type of abnormality and various features that may help inform patient management (Fig. 20.18).[104,105] In general, vessels with a retroaortic or prepulmonic course are considered benign, whereas the highest risk of sudden death is attributed when there is an anomalous left main coronary artery arising from the right cusp with an interarterial course; this is an infrequent variant. Patients who have a right coronary artery arising from the left cusp with an interarterial course, or those with a subpulmonic (also known as transseptal) left main arising from the right cusp have a variable level of risk and require a careful assessment that integrates clinical and imaging findings. Among 5991 consecutive patients evaluated by CCTA in the PARTNERS registry, the prevalence of an anomalous coronary artery originating from the opposite sinus of Valsalva (ACAOS) was 1.7%, and the vast majority were benign variants. CCTA-derived features that were associated with subsequent revascularization included slit-like narrowing of the origin, interarterial course, intramural course, and narrowing of proximal anomalous vessel of >5.4 mm in length.[104] (Fig. 20.18 shows examples of various features.)

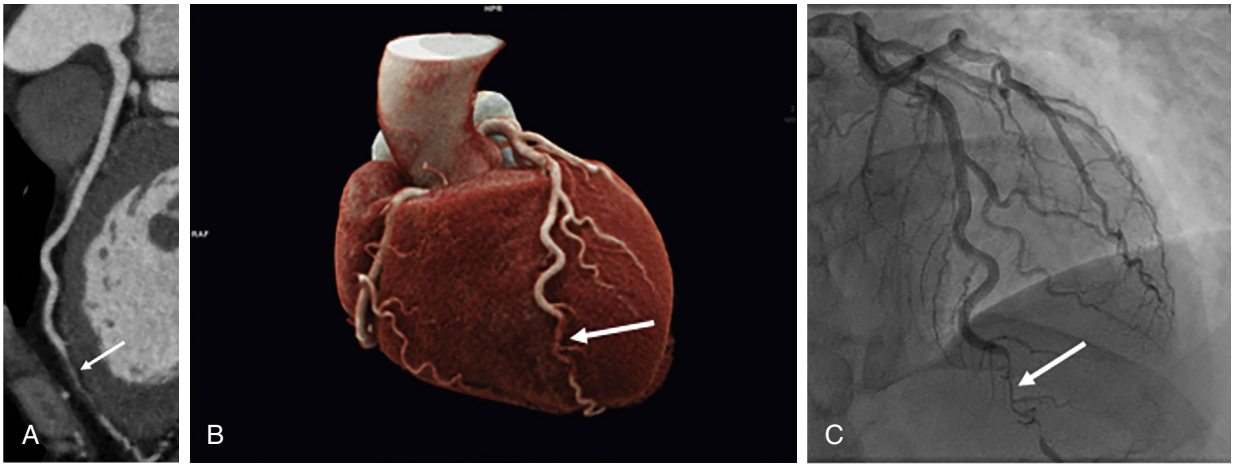


FIGURE 20.16 Example of spontaneous coronary artery dissection diagnosed by coronary computed tomography angiography. Images show dissection of distal left anterior descending artery (*white arrow*) on curved multiplanar reformatting image **(A),** three-dimensional cinematic volume-rendered image **(B),** and invasive angiography **(C).** (Courtesy of Dr. Sumit Gupta, Brigham and Women's Hospital, Boston.)

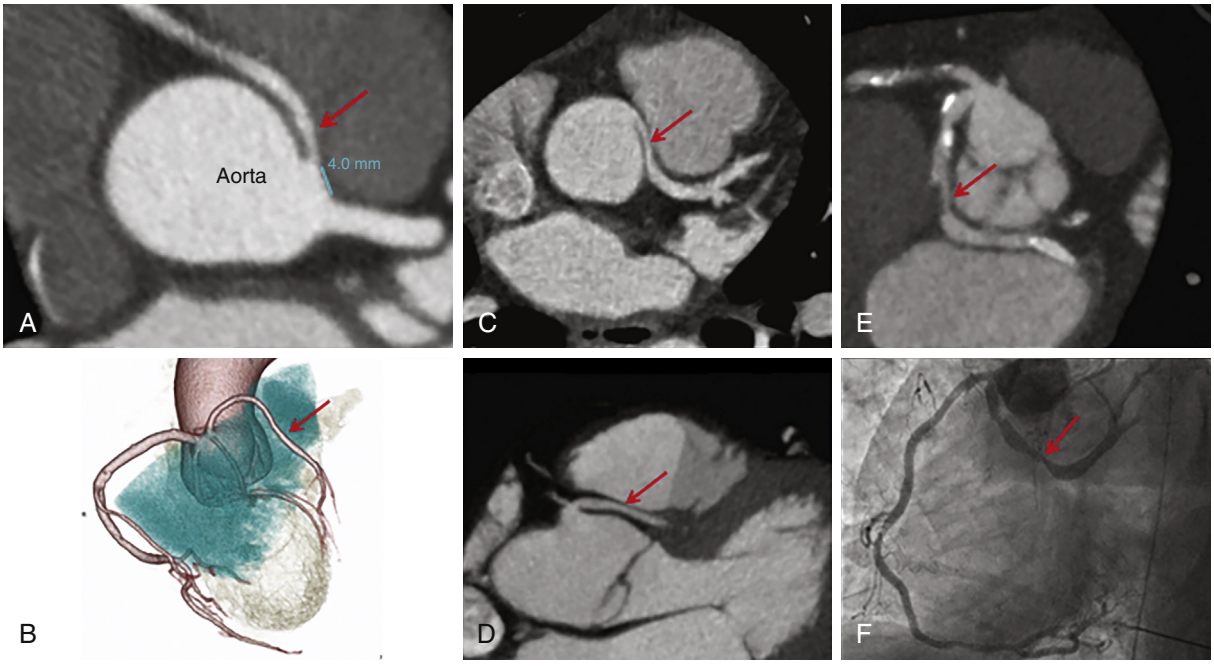


FIGURE 20.17 Examples of anomalous aortic origin of the coronary arteries from the opposite cusp. A, Right coronary artery arising from the left coronary cusp with an interarterial course between the aorta and the pulmonary artery. **B,** Three-dimensional volume-rendered image showing the left anterior descending (LAD) artery arising from the right coronary artery with a prepulmonic LAD (i.e., anterior to the pulmonary artery) The *translucent blue volume* is used to show the right ventricular outflow tract and pulmonary artery. **C,** Left main arising from the right coronary cusp with an interarterial course. **D,** Left main arising from the right coronary cusp below the pulmonic valve traveling in a transeptal course. **E,** Left circumflex (LCX) arising from the right coronary cusp and traveling in a retroaortic course posterior to the aorta. The LCX has a large amount of plaque and moderate stenosis (*red arrow*). **F,** Invasive angiography images corresponding to **(E)** illustrating the retroaortic LCX.

Coronary Artery Bypass Grafts: CCTA has been shown to be highly accurate for detecting stenosis in arterial or venous bypass grafts. However, the evaluation of native coronary arteries in patients with prior coronary artery bypass grafting can be challenging, because of the common occurrence of underlying severe coronary calcifications of the native vessels. Therefore, CCTA may be better suited if the main clinical question pertains to patency of the bypass grafts.[50]

Prior heart transplantation: CCTA has been used as a surrogate for invasive angiography to diagnose coronary allograft vasculopathy (CAV) following cardiac transplantation. The use of CCTA in this setting requires expertise, and it may be challenging in patients who have elevated heart rate. A meta-analysis of 13 studies evaluating the diagnostic performance of CCTA compared with invasive angiography found that on a per-patient basis, CCTA detected any CAV (any luminal irregularities) or significant CAV (≥50% stenosis) with a sensitivity of 97% and 94%, and specificity of 81% and 92%, respectively.[50] FFRct may further improve the identification of hemodynamically significant CAD.

Guidelines

Table 20.4 provides an overview of key CCTA recommendations from the most recent ESC and AHA/ACC guidelines. Both guidelines provide a class I recommendation for use of CCTA as an initial testing option in stable and acute chest pain. Nevertheless, there are multiple available testing options across these clinical scenarios. Although guideline-based recommendations are often lacking in this regard, clinicians are required to select the best initial testing option for each patient. This requires a careful consideration of various factors, including clinical data (e.g., the anticipated impact of the test on patient management), the results of prior tests (when available), the likelihood of having high image quality, and local availability and expertise.

The 2019 ESC guidelines stated that CCTA is the preferred test 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. The 2021 AHA/ACC guidelines stated that CCTA may be preferred among patients less than 65 years of age and those

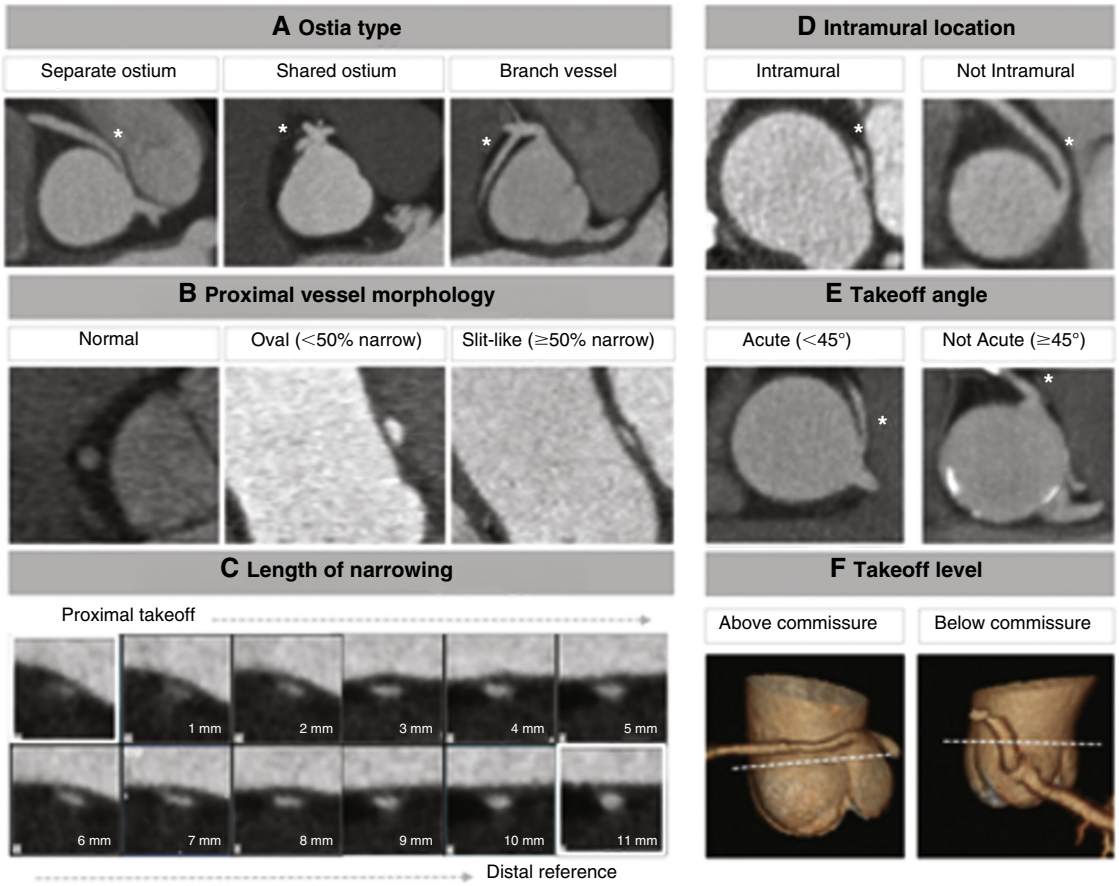


FIGURE 20.18 Coronary computed tomography (CT) angiography features for evaluating patients with anomalous aortic origin of the coronary arteries (AAOCA). A, Multiplanar axial CT reconstruction at the level of the coronary artery takeoff demonstrating AAOCA ostia types (separate ostium, shared ostium, and branch vessel). **B,** Proximal vessel morphology in double oblique view using the percentage of lumen diameter narrowing compared with normal distal reference (not shown), stratified by normal, oval shape (<50% narrowing), and slit-like narrowing (≥50% narrowing). **C,** Centerline length of vessel narrowing shown in double oblique view extending from the AAOCA vessel takeoff to the normal caliber distal reference. **D,** Multiplanar axial reformation demonstrating AAOCA vessels with and without an intramural takeoff (proximal course within the aortic wall). **E,** AAOCA takeoff angle obtained in the multiplanar axial reconstruction at the level of the AAOCA ostium. **F,** AAOCA vessel takeoff level (above/below aortic valve commissure) shown in three-dimensional reformatted images. Asterisk denotes anomalous coronary artery. (From Cheezum MK, et al. Anomalous aortic origin of a coronary artery from the inappropriate sinus of Valsalva. J Am Coll Cardiol 2017;69:1592-1608.)

not on optimal preventive therapies (see the sections Pretest Probability of Obstructive Coronary Artery Disease and Selecting Appropriate Candidates for Coronary Computed Tomography Angiography).

Table 20.5 provides a summary of the Society of Cardiovascular Computed Tomography (SCCT) CCTA expert consensus recommendations,[50] which address the use of CCTA and cardiac CT for various cardiovascular conditions.

ASSESSMENT OF CARDIOVASCULAR STRUCTURE AND FUNCTION

Beyond coronary artery stenosis and plaque, cardiac CT can be used to visualize various cardiac pathologies including pericardial, myocardial, and valvular heart disease.

Pericardial and Myocardial Disease

Pericardial thickening and calcifications visualized on cardiac CT can be useful in assessing patients with suspected pericardial constriction, and the use of multiphase imaging can also be used to identify individuals who have pericardial adhesions. Other pericardial pathologies that can be detected on cardiac CT include pericardial cysts, pericardial effusions, and pericardial masses (see Chapter 86).

There are various forms of myocardial and infiltrative heart disease that can be identified on routine cardiac CT (Fig. 20.19). Images at end diastole can be used to measure left and right ventricular wall thickness, and left and right ventricular size. When a multiphase dataset is obtained during image acquisition, a qualitative or quantitative assessment of left and right ventricular systolic function can be obtained,[106] and images can be evaluated for regional wall motion abnormalities (Video 20.1). Since the acquisition of multiphase data is associated with a higher radiation dose (because of the use of a helical acquisition, or when using either a helical or axial acquisition mode from opening of the phase acquisition window to include data throughout the cardiac cycle), most CCTA studies should be performed in diastole only. However, a multiphase acquisition may be helpful when data regarding left or right ventricular function are desired, in selected cases with congenital heart disease, when evaluating right ventricular morphology in suspected arrhythmogenic right ventricular cardiomyopathy (ARVC), or when evaluating for scar prior to ablation procedures.

Late enhancement imaging on CT refers to the acquisition of images ~8 minutes after contrast administration. Similar to late gadolinium enhancement imaging on CMR, iodinated contrast is an extracellular contrast agent that has delayed washout from areas of abnormal myocardium. In individuals who are unable to undergo CMR, late enchantment imaging on CT may be used to detect myocardial scar. Recent studies have also shown that CT can identify individuals with cardiac amyloidosis by quantifying the extracellular volume (ECV), a technique that may have a potential future role when evaluating patients prior to transcatheter aortic valve replacement (TAVR).[107]

Valvular Heart Disease (see Part VIII)

Cardiac CT has emerged as a useful test to evaluate various forms of valvular heart disease. Although all four cardiac valves can be assessed when a multiphase acquisition is performed (Fig. 20.20), imaging of the tricuspid valve is more challenging, but is now used to guide various emerging percutaneous repair options. The severity of aortic stenosis can be determined by calculating the Agatston calcium score of the

TABLE 20.5 Summary of Society of Cardiovascular Computed Tomography Coronary Computed Tomography Angiography Expert Consensus Recommendations

Evaluation of Stable CAD: CCTA in Native Vessels
• It is appropriate to perform CCTA as the first-line test for evaluating patients with no known CAD who present with stable typical or atypical chest pain, or other symptoms that are thought to represent a possible anginal equivalent (e.g., dyspnea on exertion, jaw pain)
• It is appropriate to perform CCTA as a first-line test for evaluating patients with known CAD who present with stable typical or atypical chest pain, or other symptoms that are thought to represent a possible anginal equivalent (e.g., dyspnea on exertion, jaw pain)
• It is appropriate to perform CCTA following a nonconclusive functional test to obtain more precision regarding diagnosis and prognosis, if such information will influence subsequent patient management
• It is recommended to perform CCTA as the first-line test when considering evaluation for revascularization strategies using the ISCHEMIA Trial
• It may be appropriate to perform CCTA in selected asymptomatic high-risk individuals, especially in those who have a higher likelihood of having a large amount of noncalcified plaque
• It is rarely appropriate to perform CCTA in very low-risk symptomatic patients, e.g., <40 years of age with noncardiac symptoms (chest wall pain, pleuritic chest pain)
• It is rarely appropriate to perform CCTA in low- and intermediate-risk asymptomatic patients
Evaluation of Stable CAD: CCTA Post-Revascularization
• It is appropriate to perform CCTA in symptomatic patients with intracoronary stent diameter ≥3.0 mm. Measures to improve accuracy of stent imaging should be used to include strict heart rate control (goal <60 beats/min), iterative reconstruction, sharp kernel reconstruction, and mono-energetic reconstructions (when available). Protocols to optimize stent imaging should be developed and followed
• It may be appropriate to perform CCTA in symptomatic patients with stents <3.0 mm, especially those known to have thin stent struts (<100 mm) in proximal, nonbifurcation locations
• It is appropriate to perform CCTA for evaluation of patients with prior CABG, particularly if graft patency is the primary objective
• It is appropriate to perform CCT to visualize grafts and other structures prior to re-do cardiac surgery
Evaluation of Stable CAD: CCTA with FFR or CTP
• It may be appropriate to perform CT-derived FFR and CT myocardial perfusion imaging to evaluate the functional significance of intermediate stenoses on CCTA (30%-90% diameter stenosis) particularly in the setting of multivessel disease to help guide ICA referral and revascularization treatment planning. LM stenosis ≥50% and severe triple vessel disease should undergo invasive coronary angiography
• Adding FFRCT and stress-CTP to CCTA increases specificity, positive predictive value, and diagnostic accuracy over regular CCTA
• FFRCT and stress-CTP may be largely comparable in diagnostic utility. CTP is a potentially valuable alternative particularly when CT-FFR is technically difficult (e.g., suboptimal CCTA quality, prior revascularization)
Evaluation of Stable CAD: CCTA and CCT in Other Conditions
• It is appropriate to perform CCTA for coronary artery evaluation prior to noncoronary cardiac surgery as an equivalent alternative to invasive angiography in selected patients, e.g., low-intermediate probability of CAD, younger patients with primarily nondegenerative valvular conditions
• CCTA may be considered an appropriate alternative to other noninvasive tests for evaluation of selected patients prior to noncardiac surgery
• It is appropriate to perform CCTA to exclude CAD in patients with suspected nonischemic cardiomyopathy
• It may be appropriate to perform late-enhancement CT imaging to detect infiltrative heart disease or scar in selected patients who have nonischemic or ischemic cardiomyopathy and who cannot undergo cardiac MRI. Such imaging may be performed if it has the potential to impact the diagnosis and/or treatment (e.g., planning for ablation therapy)
• It may be appropriate to perform CCTA as an alternative to invasive coronary angiography for the screening of patients for coronary allograft vasculopathy in selected clinical practice settings
• It is appropriate to perform CCTA for the evaluation of coronary anomalies
• It is appropriate to ECG gate aortic dissection and aneurysm CTA, as well as pulmonary embolus studies in men >45 years and women >55 years, and analyze and report the coronary arteries
• CCT with a limited delayed image (60 s) is an appropriate alternative to TEE when the primary aim is to exclude LA/LAA thrombus and in patients where the risks associated with TEE outweigh the benefits. In all situations, CCT and TEE should be discussed with the patient in the setting of shared decision making
• It may be appropriate to perform late enhancement CT imaging for the evaluation of myocardial viability in selected patients who cannot undergo cardiac MRI. Such imaging may be performed if it has the potential to impact the diagnosis and/or treatment (e.g., planning for revascularization)
Reporting on CCT Coronary and Noncoronary Information
• CAD-RADs reporting is recommended
• It is appropriate to report prior myocardial infarction when its features are evident on CCT
• It is appropriate to report remote myocardial infarction when fatty metaplasia or calcification within an area of infarction are present

CABG, Coronary artery bypass grafting; *CAD,* coronary artery disease; *CAD-RADs,* Coronary Artery Disease-Reporting and Data System; *CCTA,* coronary computed tomography angiography; *CTP,* computed tomography perfusion; *FFRCT,* computed tomography–derived FFR; *ICA,* invasive coronary angiography; *LA,* left atrium; *LAA,* left atrial appendage; *LM,* left main coronary; *MRI,* magnetic resonance imaging; *TEE,* transesophageal echocardiogram.
Adapted from Narula J, et al. SCCT 2021 Expert Consensus Document on Coronary Computed Tomographic Angiography: a report of the Society of Cardiovascular Computed Tomography. J Cardiovasc Comput Tomogr. 2020;S1934-5925(20)30473-1.

aortic valve (see Figs. 72.3 and 72.11), in which a measure >2065 in men and >1274 in women has been found to provide good discriminatory value for diagnosing severe aortic stenosis, and identifying patients with adverse prognosis.[108] In addition, direct planimetry at the level of the aortic valve leaflet tips can be performed to measure the aortic valve area. Similarly, the presence of aortic regurgitation can be accurately evaluated by assessing for aortic valve closure during diastole. Several studies have shown that direct planimetry of the regurgitant orifice can be used to estimate the severity of aortic regurgitation.

One particular advantage of cardiac CT is the ability to evaluate patients with mechanical valves, as such valves often have significant artifacts on echocardiography. When there is suspicion for valve dysfunction, cardiac CT can evaluate for valvular thrombosis (Video 20.2) and pannus (Fig. 20.21; see Fig. 79.5C). When endocarditis is suspected,

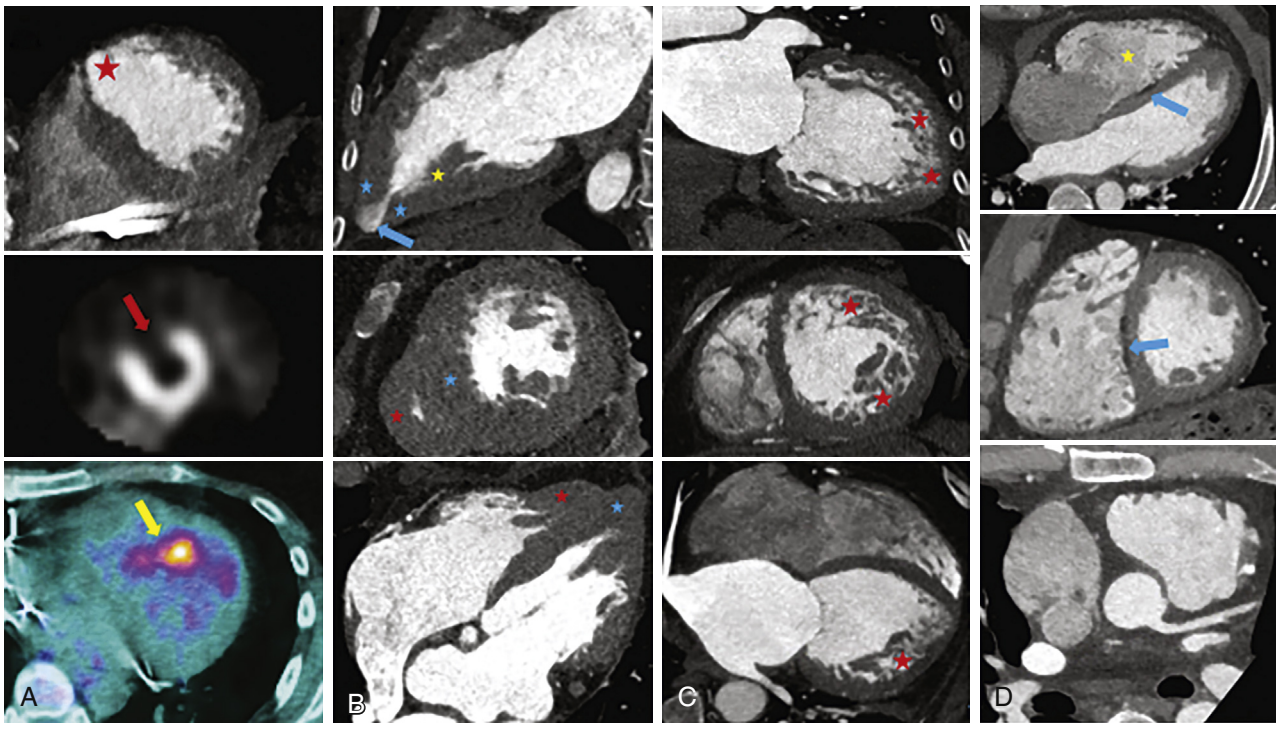


FIGURE 20.19 Examples of various cardiomyopathies on cardiac computed tomography (CT). A, Cardiac sarcoidosis. *Top panel:* Cardiac CT showing a large aneurysm of the mid anterior and anteroseptal segments associated with myocardial thinning and akinesis (*red star*). *Middle panel*: Resting technetium-99m perfusion scan showing a severe perfusion defect in the mid anterior and anteroseptal segments (*red arrow). Bottom panel*: F18-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan demonstrating a small region of intense FDG uptake in the same region (*yellow arrow*). **B,** Apical hypertrophic cardiomyopathy. Increased left ventricular (LV) apical wall thickness (*blue stars*) and apical displacement of the papillary muscle (*yellow star*). There is an LV apical aneurysm (*blue arrow*) without LV cavity thrombus. In addition, there is hypertrophy of the right ventricular apex (*red stars*). **C,** LV noncompaction cardiomyopathy. There are prominent LV trabeculations along the anterior, inferior, and lateral walls, and the LV apical segments (*red stars*). Gated CT images also showed a reduced LV ejection fraction of 20% with global hypokinesis. The end-diastolic ratio of noncompacted to compacted myocardium was 3.8 (normal <2.3). **D,** Arrhythmogenic cardiomyopathy. Cardiac CT images showing a dilated right atrium and right ventricle (*yellow star*). There is also fatty infiltration of the interventricular septum (*blue arrow*). Coronary CT angiography showed no evidence of plaque or stenosis. (Courtesy Dr. Vasvi Singh, Brigham and Women's Hospital, Boston.)

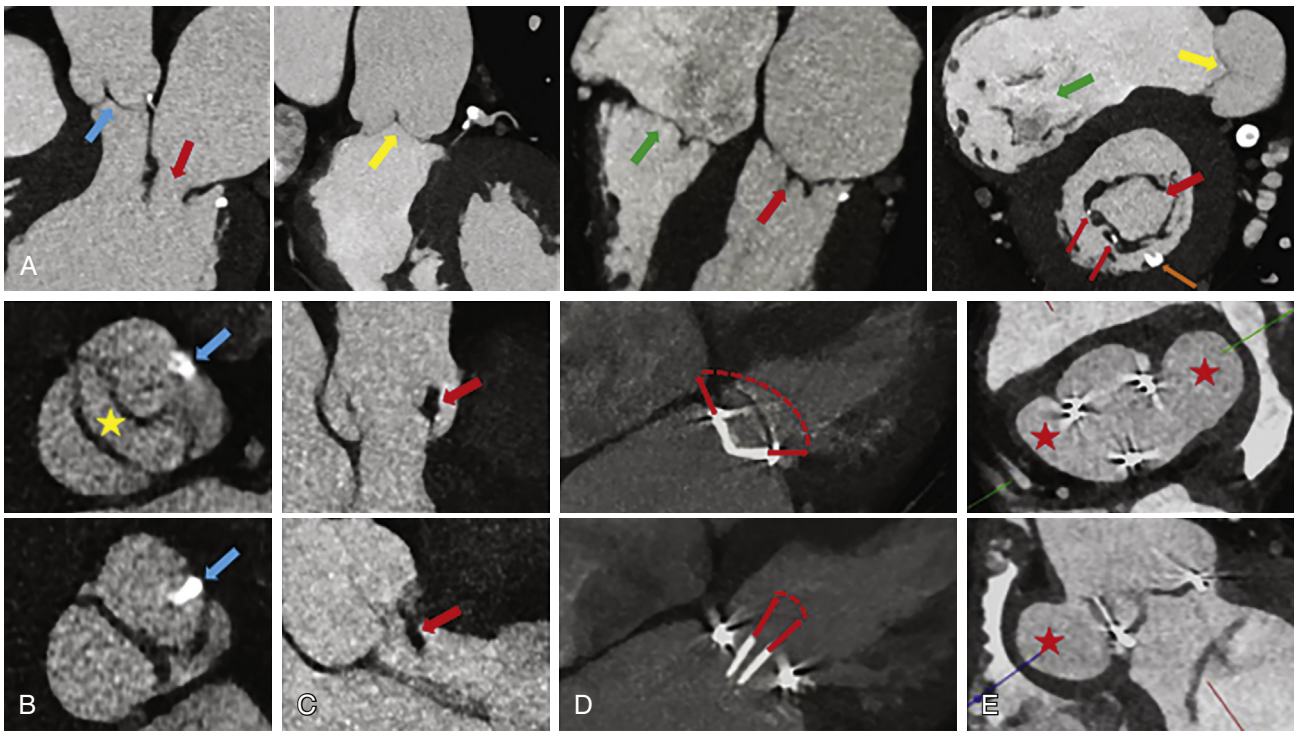


FIGURE 20.20 Examples of assessing valvular heart disease on cardiac computed tomography. A, Normal appearances of aortic valve (*blue arrow*), pulmonic valve (*yellow arrows*), and tricuspid valve (*green arrows*) in different phases of the cardiac cycle. Mitral valve (*red arrows*) in different phases of the cardiac cycle; the mitral valve leaflets are mildly thickened with calcifications (*small red arrow*), and there is mild posterior mitral annular calcification (*small orange arrow*). **B,** Bicuspid aortic valve during systole and diastole. There is fusion of the right and left coronary cusps with calcification of the fusion raphe (*blue arrows*). The bicuspid valve has an elliptical opening (*yellow star*) visualized during systole. **C,** Mobile aortic valve vegetation (*red arrows*) visualized during systole and diastole (prolapses into the left ventricular outflow tract) in a patient with gram-positive bacteremia and sepsis. **D,** Normal functioning St. Jude's mechanical bileaflet mitral valve prosthesis during ventricular systole and diastole. The prosthetic leaflets have normal closing and opening angles (*red arrows*). **E,** Pseudoaneurysms (*red stars*) developed as a complication of bioprosthetic aortic valve infective endocarditis, visualized during systole and diastole. (Courtesy Dr. Vasvi Singh, Brigham and Women's Hospital, Boston.)

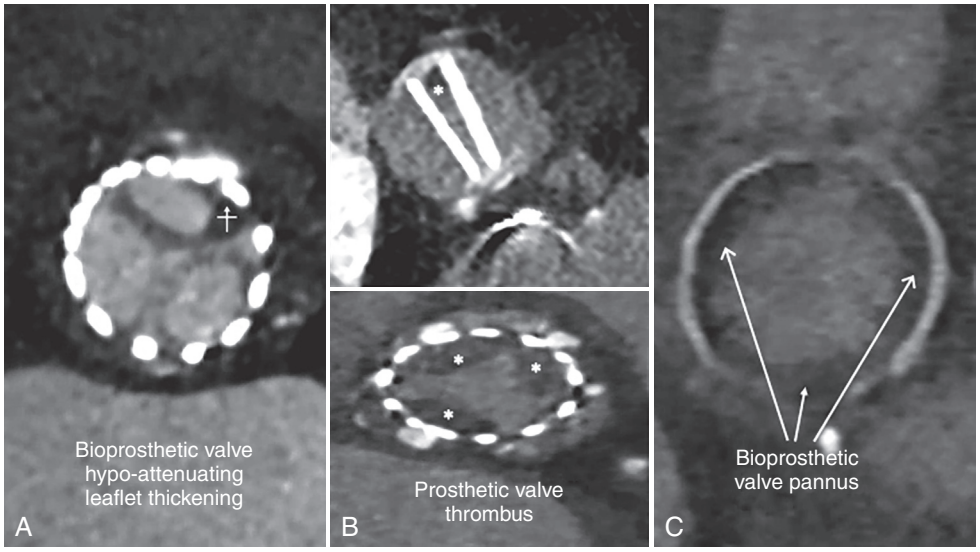


FIGURE 20.21 **Examples of valve thrombosis versus pannus. A,** Bioprosthetic valve demonstrating hypoattenuation leaflet thickening consistent with subclinical thrombosis. **B,** Mechanical (*top*) and bioprosthetic (*bottom*) valves with thrombus. **C,** Bioprosthetic valve with pannus.

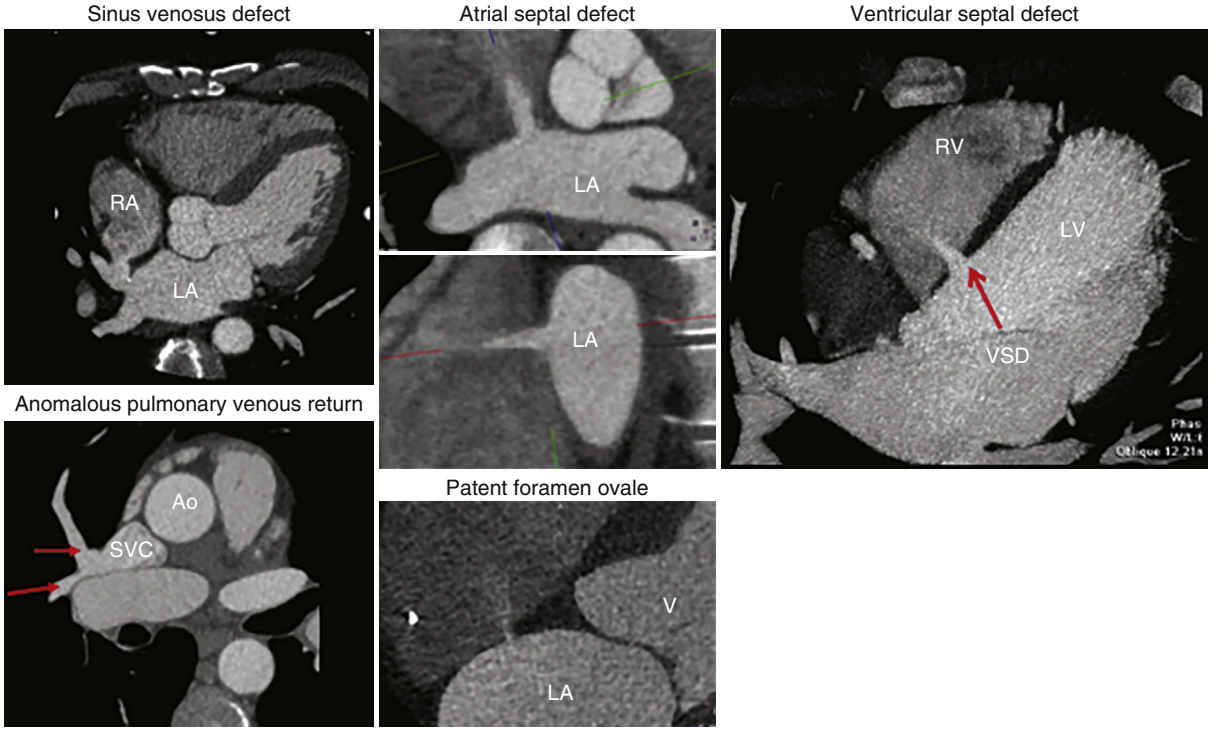


FIGURE 20.22 Examples of various intracardiac shunts on cardiac computed tomography. *Ao,* Aorta; *LA,* left atrium; *RA,* right atrium; *SVC,* superior vena cava, *VSD,* ventricular septal defect.

cardiac CT can be useful for the evaluation of both native and prosthetic valves. In native valves, cardiac CT can detect vegetations with a high diagnostic accuracy, although very small vegetations can be challenging to detect. In prosthetic valves, cardiac CT can identify paravalvular lesions, such as a pseudoaneurysm, abscess, or fistula. The 2015 ESC Guidelines for Management of Infective Endocarditis categorize paravalvular lesions by CCT as a major criteria for diagnosing endocarditis as part of the modified criteria for the diagnosis of infective endocarditis.[109]

Shunts

Cardiac CT can be useful for assessing for various intracardiac defects including atrial septal defects, ventricular septal defects, and anomalous pulmonary venous drainage (Fig. 20.22). In addition, CCT can detect patent foreman ovale, sinus venous defects, and unroofed coronary sinus. When such defects are identified, cardiac CT may be helpful in assessing the feasibility of percutaneous versus surgical closure techniques.

Use of Cardiac Computed Tomography for Structural Heart Disease Interventions

Cardiac CT has evolved to become an important imaging modality for preprocedural guidance and postprocedural follow-up for many of structural heart disease interventions. These include imaging for transcatheter heart valve replacement, left atrial appendage occlusion, and arrhythmia ablation.

Pre-Transcatheter Aortic Valve Replacement

Cardiac CT is an essential imaging test prior to TAVR, and it has been shown to improve procedural outcomes and prevent complications (Fig. 20.23).[110] CT imaging prior to TAVR generally includes two scans using a single contrast injection: (1) cardiac ECG gated dataset of the aortic root and heart followed by (2) nongated vascular CTA of the chest, abdomen, and pelvis. An alternative option is to acquire an ECG gated dataset of the entire chest and then to acquire a nongated

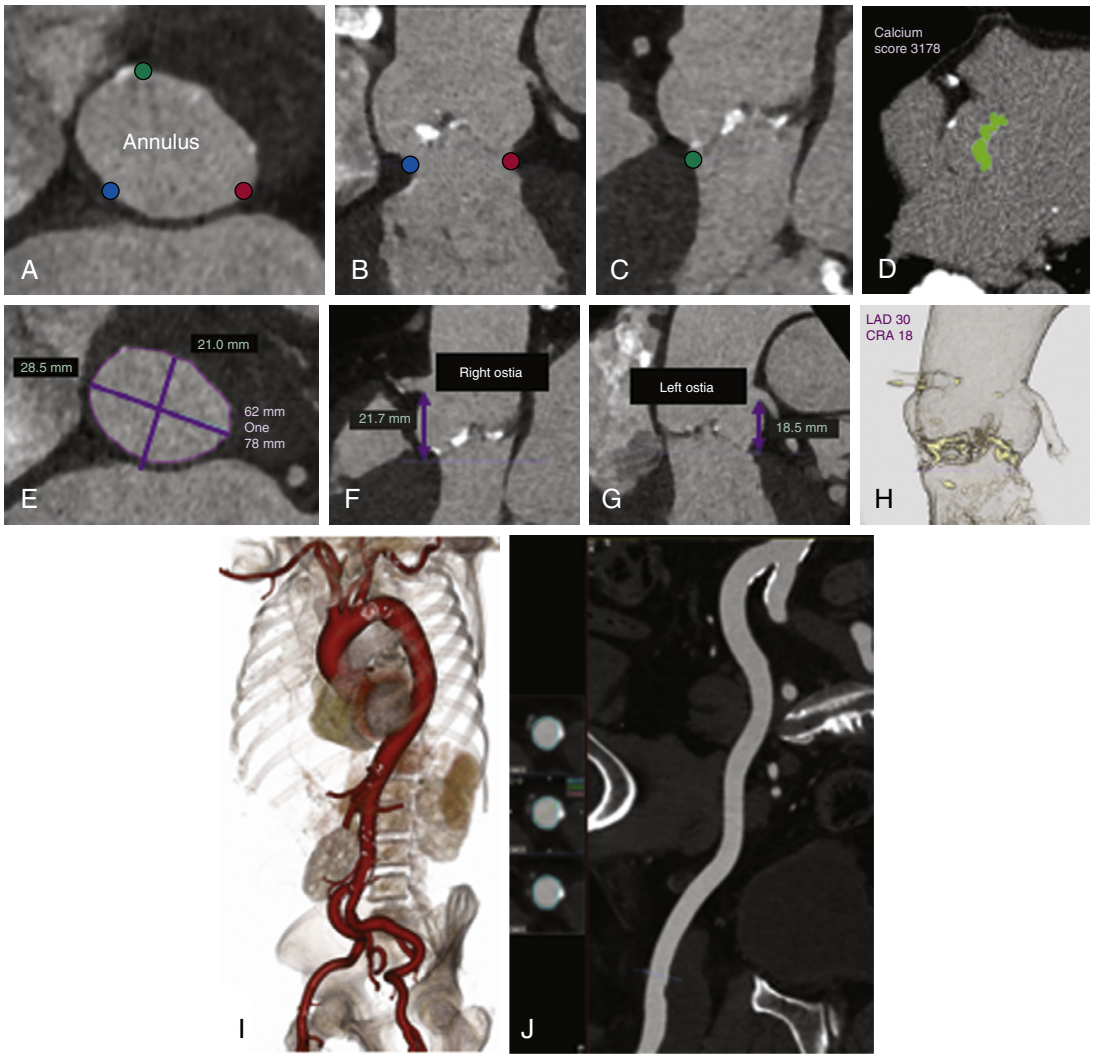


FIGURE 20.23 Cardiovascular computed tomography for preprocedural planning of transcatheter aortic valve replacement (TAVR). A, Short-axis view of the aortic annulus to mark the nadir of each cusp (*green, right cusp; red, left cusp; blue, noncoronary cusp*). **B** and **C,** Corresponding long-axis views of the aortic root showing the correct placement of the markers on the nadirs. **D,** Aortic valve calcium score for stenosis severity. **E,** Annulus view for major and minor axis diameters, area, and perimeter. **F** and **G,** Coronary ostia height measurements. **H,** Three-dimensional virtual reality (3DVR) showing the en face annular plane for TAVR deployment planning. **I,** 3DVR for access vessel tortuosity and calcification. **J,** Curved multiplanar reformat for access vessel diameters. (Courtesy Michael Steigner, Brigham and Women's Hospital, Boston, MA.)

vascular CTA of the abdomen and pelvis. Because the aortic root dimensions are usually larger in systole, systolic imaging is required (if only one portion of the cardiac cycle is acquired); however, coverage during the entire cardiac cycle may be beneficial. In addition, if there is uncertainty regarding whether severe aortic stenosis is present, a noncontrast ECG gated scan covering the aortic root may be added, as the aortic valve calcium score may be helpful in assessing aortic stenosis severity. (see section Valvular Heart Disease). The previously mentioned protocol uses a contrast volume ranging from 50 to 100 mL using a flow rate of 4 to 6 ms/s. A slower flow rate may be helpful when trying to minimize the amount of contrast, together with using lower tube voltage (e.g., 80 kV). Prospective high-pitch imaging is an alternative option that can help lower the contrast dose while maintaining a high image quality. Table 20.6 summarizes the recommendations on aortic root data that should be evaluated and reported prior to potential TAVR.[110]

Post-Transcatheter Aortic Valve Replacement (see Chapter 74)

Following TAVR, cardiac CT may be considered if there is clinical concern for valve thrombosis, infective endocarditis, or structural valve degeneration. Concern for thrombosis may exist if there is an increase in aortic valve gradients on echocardiography, especially if these also occur in the presence of any signs or symptoms of aortic stenosis. Features of leaflet thrombosis on cardiac CT include hypoattenuated leaflet thickening (HALT) (Fig. 20.24) and reduced leaflet motion, also referred to as hypoattenuation affecting motion (HAM). Leaflet thickening appears meniscal-shaped on the long axis, with greater thickness at the base than toward the center of the leaflet. Such thickening should be described based on location, extent in length, and overall thickness. Restricted motion should be reported as present or absent. Most cases of HALT with reduced leaflet motion are likely subclinical. Oral anticoagulation is associated with a lower rate of developing HALT or HAM. When such abnormalities are identified, initiation of oral anticoagulation is associated with a subsequent reduction in leaflet thickening. Nevertheless, it is unclear if treatment of subclinical leaflet thrombosis is beneficial or if it can lead to a lower rate of valve degeneration.

Evaluation Pre-Transcatheter Mitral Valve Replacement (see Chapter 78)

Cardiac CT has an essential role in selecting potential candidates for transcatheter mitral valve replacement (TMVR) by measuring the mitral valve dimensions and area and also estimating the risk of paravalvular regurgitation or left ventricular outflow track (LVOT) obstruction. The latter is achieved by using 3D visualization software to simulate the position of the implanted mitral valve and measuring the resulting "neo-LVOT" and thus the potential risk of LVOT obstruction (Fig. 20.25). Cardiac CT can also be used for 3D geometry of the mitral valve, which has a complex D-shaped structure with a saddle-shaped morphology. A single-center retrospective study has estimated that ~50% of patients evaluated for TMVR have a contraindication for the procedure based on cardiac CT such as high

TABLE 20.6 Aortic Root Assessment During Transcatheter Aortic Valve Replacement

	DETAILS TO REPORT	TIPS/RATIONALE
Aortic annulus	• Annular area, dimensions (long- and short-axis), perimeter	• Select phase with largest annular dimensions
Landing zone calcium (landing zone includes the valve cusps, annulus, and the LVOT)	• None, mild, moderate, severe • Annular and subannular calcifications should be described as crescent/flat/adherent or protruding and its relation to the aortic cusps	• Severe subannular calcification may indicate a higher risk of heart block/need for a pacemaker, especially if preexisting RBBB • Large protruding nodules of calcification, particularly below the noncoronary cusp, may increase the risk of annular rupture/paravalvular regurgitation

Valve morphology	• BAV morphology:
	  • Number of commissures
	  • Presence of absence of a raphe
	  • Presence and degree of raphe calcification (mild, moderate, severe)
		• BAV and severe raphe calcification associated with higher likelihood of paravalvular regurgitation

Coronary ostial height and sinus of Valsalva assessment	• Low coronary ostial height from the annulus • Sinus of Valsalva mean diameter	• Low coronary height (<12 mm) and sinus of Valsalva mean diameter <30 mm associated with higher risk of coronary occlusion • Coronary height and sinus of Valsalva width should be interpreted in the context of annular dimensions, overall root dimensions, and the anticipated THV size
Aortic root measurements	• STJ diameter and height • Ascending aorta dimensions	• When using balloon-expandable devices in low STJ height, STJ diameter should be compared with the anticipated THV size
Optimal fluoroscopic angles	• Reported as degrees LAO or RAO with the corresponding values for cranial or caudal angulation	• Only valid if patient positioned supine in the CT scanner

BAV, Bicuspid aortic valve; *CT,* computed tomography; *LVOT,* left ventricular outflow track; *RBB,* right bundle branch block; *STJ,* sinotubular junction; *THV,* transcatheter heart valve.

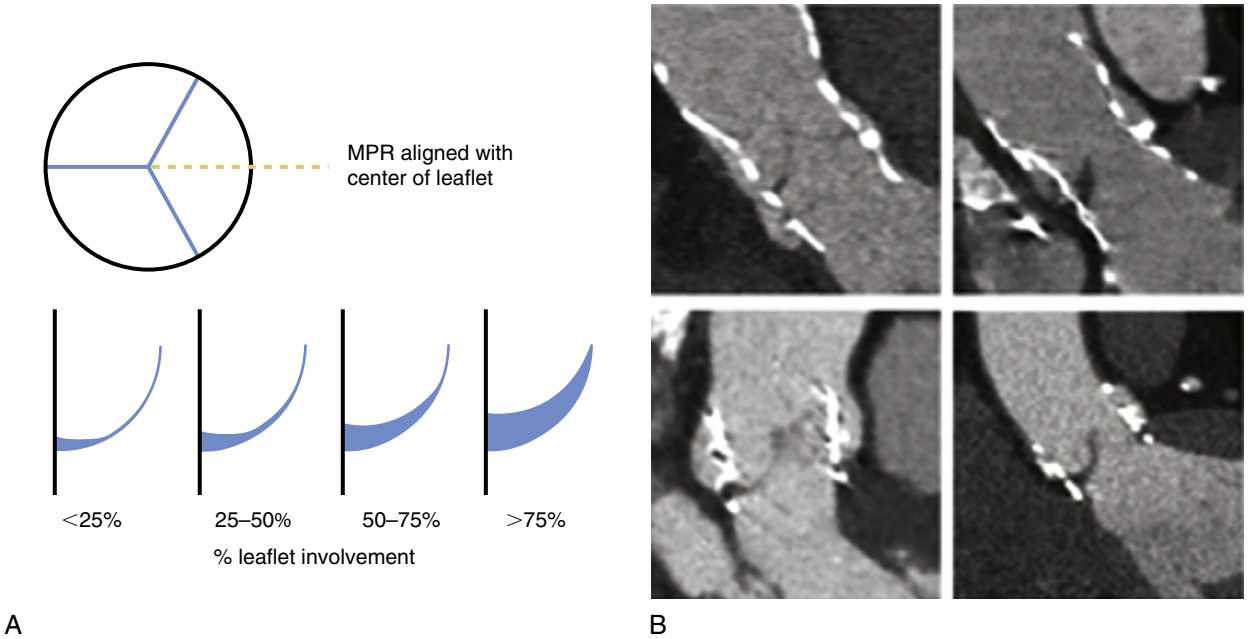


FIGURE 20.24 Post transcatheter aortic valve replacement assessment. A, How to use multiplanar (MPR) alignment for semiquantitative grading of hypoattenuated leaflet thickening. The *dashed yellow line* indicates the orientation of the long-axis views in the lower row, aligned with the center of the cusps. The extent of leaflet thickening can be graded on a subjective four-tier grading scale along the curvilinear orientation of the leaflet. Typically, hypoattenuated leaflet thickening appears meniscal shaped on long-axis reformats, with greater thickness at the base than toward the center of the leaflet. **B,** Examples of hypoattenuated leaflet thickening in both self-expandable (*upper row*) and balloon-expandable devices (*lower row*) with varying degree of thickening. Limited to base, i.e., <25% leaflet involvement (*left column*) and near complete leaflet involvement, i.e., >75% (*right column*). (From Blanke P, et al. Computed tomography imaging in the context of transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR): an expert consensus document of the Society of Cardiovascular Computed Tomography. J Cardiovasc Comput Tomogr 2019;13:1-20.)

risk of LVOT obstruction, a large annular size, or an insufficient amount of mitral annular calcifications.[110a] As future generations of transcatheter mitral valves will expand the feasibility of TMVR procedures, cardiac CT will continue to play an integral role in patient and device selection.

Evaluation of Left Atrial Appendage (for Thrombus, Pre-Left Atrial Appendage Occlusion Devices)

Cardiac CT can be used to image the left atrial appendage (LAA) morphology and size and exclude the presence of an LAA clot.[50] Notably, a filling defect in the LAA can represent slow flow, and thus postcontrast delayed imaging may be necessary to confirm the presence of a clot (Fig. 20.26). A meta-analysis that included 19 studies identified a sensitivity and specificity of cardiac CT of 96% and 92%; however, when only studies (n = 7) that included delayed imaging were evaluated, the sensitivity and specificity increased to 100% and 99%.[111] A large single-center study that used a combination of transesophageal echocardiogram (TEE) and intracardiac echocardiography as the reference standard also demonstrated a sensitivity and NPV of 100% when using cardiac CT with delayed imaging. In this study, the specificity of cardiac CT when combining positive and equivocal CCT results was 98%.[112]

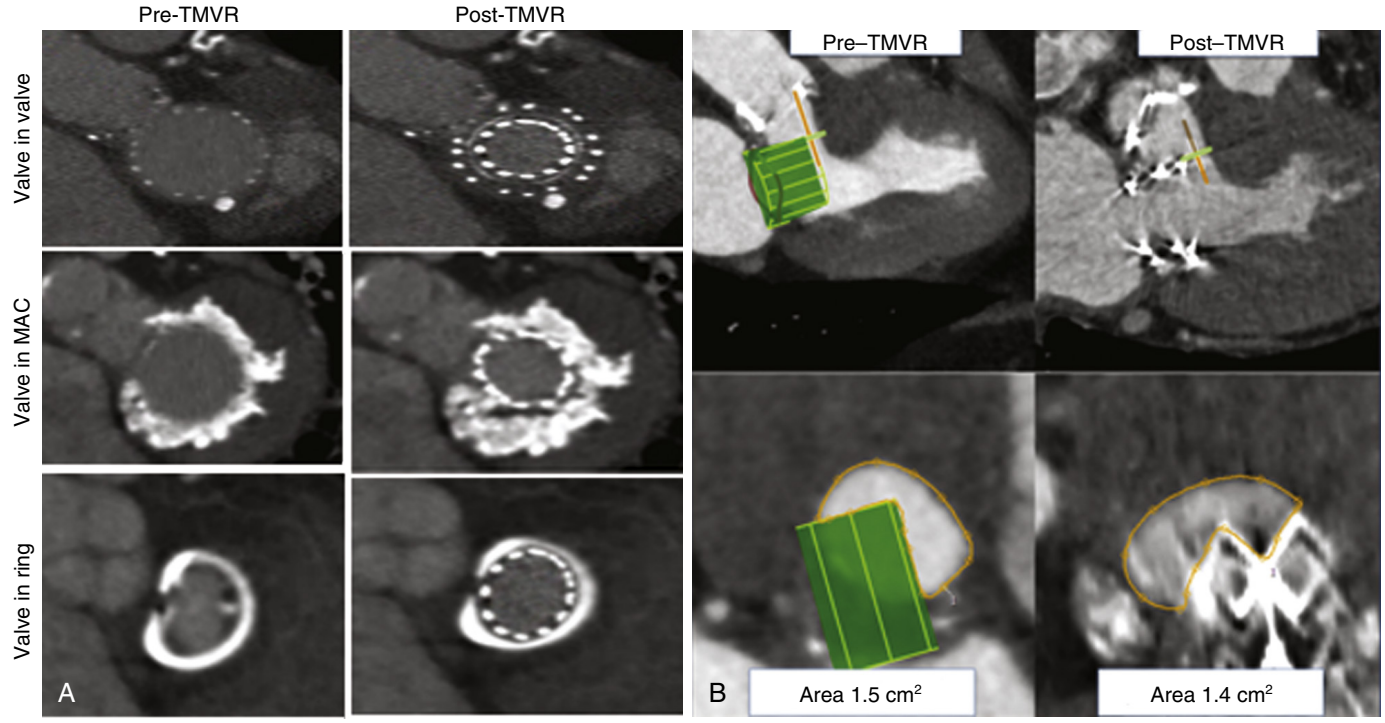


FIGURE 20.25 **A,** Pre- and post-transcatheter mitral valve replacement (TMVR) evaluation using cardiac computed tomography (CCT) for a valve-in-valve, valve-in-mitral angular calcification, and valve-in-ring scenarios. **B,** Pre-TMVR CCT in a valve-in-valve case projected a neo-left ventricular outflow tract (LVOT) area of 1.5 m^2. Post-TMVR CCT demonstrated a neo-LVOT area of 1.4 cm^2. (A, From Ge Y, et al. Role of cardiac CT in pre-procedure planning for transcatheter mitral valve replacement. JACC Cardiovasc Imaging 2021 [online ahead of print]. doi:10.1016/j.jcmg.2020.12.018)

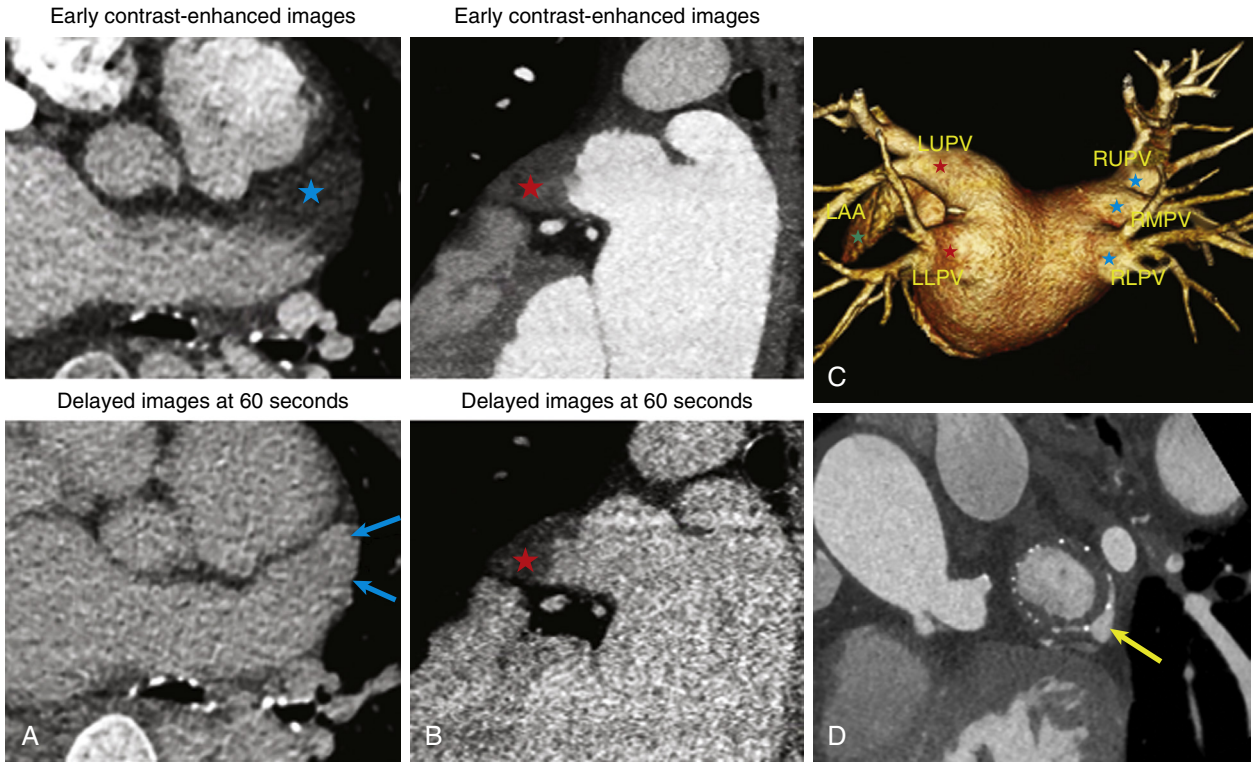


FIGURE 20.26 **Evaluation of left atrial appendage and pulmonary venous anatomy.** **A,** *Top:* Early contrast-enhanced images showing a filling defect in the left atrial appendage (LAA), which can represent low-flow state or a thrombus (*blue star*). *Bottom:* Delayed images acquired after 60 seconds demonstrates complete contrast opacification of the LAA (*blue arrows*) confirming the absence of a LAA thrombus. **B,** *Top panel:* Early contrast-enhanced images showing a filling defect in the LAA. *Bottom panel:* Delayed images acquired after 60 seconds demonstrate a persistent filling defect, thereby confirming the presence of a LAA thrombus (*red star*). **C,** Three-dimensional volume-rendered reconstruction of pulmonary vein anatomy. There are two pulmonary veins (PVs) on the left (*red stars*) (left upper [LUPV] and left lower [LLPV]), and three PVs on the right (*blue stars*) (right upper [RUPV], right middle [RMPV], and right lower [RLPV]). The LAA (*green star*) is adjacent to the LUPV. **D,** Incomplete contrast opacification following LAA occlusion device, including a gap (*yellow arrow*) at the ostium of the appendage.

Although TEE and CCT have overlapping capabilities in evaluating the LAA, selecting the best test may depend on the specific clinical situation. When it is important to also evaluate for underlying valvular disease, TEE is the preferred modality. In patients who are being evaluated for a pulmonary vein isolation (PVI) or LAA occlusion device placement, cardiac CT may be preferred if this test is already being performed for evaluating pulmonary vein or LAA anatomy.

Cardiac CT is increasingly being used to evaluate patients prior to LAA occlusion device implantation and in selected cases as follow-up to assess procedure success (see Fig. 20.26).

Evaluation of Cardiac Masses

Cardiac CT can provide useful information when evaluating patients with cardiac masses.[113] Although echocardiography and CMR are often the preferred initial testing options for such patients, cardiac CT may be helpful for masses that may involve the coronary arteries, for instance, when there is uncertainty whether a mass encases the coronary arteries, or when determining whether the coronary arteries provide blood supply to the mass. In addition, cardiac CT can be helpful for evaluating pseudoaneurysms of the heart (where high spatial resolution may be helpful in differentiating an aneurysm from a pseudoaneurysm), especially if these involve bypass grafts or the coronary arteries.[114]

FUTURE DIRECTIONS

CAC and CCTA are likely to have an increasing role in allocating preventive therapies in primary prevention.[41] With respect to CAC testing, future scan acquisition and image processing techniques will further lower the radiation dose of this exam, enhancing the prognostic value. Current ongoing research, including the SCOT-HEART 2 trial (https://clinicaltrials.gov/ct2/show/NCT03920176), will assess the potential efficacy and cost-effectiveness of CCTA in primary prevention. Ultimately, the distinction between primary and secondary prevention may lessen, as the amount of underlying plaque, and thereby risk level, may be incorporated in clinical trials and guidelines.

As CCTA becomes increasingly used in the evaluation of symptomatic patients with suspected CAD, future studies will be required to demonstrate how it is being used in clinical care, and the impact of this test on subsequent medical therapies, downstream procedures, and patient outcomes. Ultimately, findings on CCTA, including the overall amount and type of plaque, will be used to determine patient risk and guide the intensity of medical therapy. To achieve this paradigm, future clinical trials will be required to assess the efficacy of various treatments based on CCTA or CAC inclusion criteria. Because the clinical effectiveness of CCTA relies on obtaining high image quality and ensuring that the test results are used appropriately, continued technologic advances that promote high quality imaging and educational efforts to ensure the test in interpreted and used correctly remain essential.[115] Ultimately, the acquisition and interpretation of CCTA findings may be enhanced by artificial intelligence, making this technology easier to disseminate across different practice environments.

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