A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

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**Type of Submission – Check all that apply:**

- [ ] New Policy
- [☐] Revised Policy*
- [☒] Annual Review – No Revisions
- [ ] Statewide PDL

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

**CPB 0228 Cardiac CT, Coronary CT Angiography, Calcium Scoring and CT Fractional Flow Reserve**

Clinical content was last revised on 05/02/2019. No additional non-clinical updates were made by Corporate since the last PARP submission.

**Name of Authorized Individual (Please type or print):**

Benjamin Alouf, MD, MBA, FAAP

**Signature of Authorized Individual:**

Revised July 22, 2019
Cardiac CT, Coronary CT Angiography, Calcium Scoring and CT Fractional Flow Reserve

Number: 0228

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Aetna considers cardiac computed tomography (CT) angiography of the coronary arteries using 64-slice or greater medically necessary for the following indications:

A. Rule out obstructive coronary stenosis in symptomatic persons with a low or intermediate pre-test probability of coronary artery disease or atherosclerotic cardiovascular disease by Framingham risk scoring, Pooled Cohort Equations, or by American College of Cardiology (ACC) criteria (see Appendix),

B. Rule out obstructive coronary stenosis in persons with a low or intermediate pre-test probability of coronary artery disease or atherosclerotic cardiovascular disease by Framingham risk scoring, Pooled Cohort Equations, or by American College of Cardiology (ACC) criteria (see Appendix) with a

Policy History

Last Review
05/02/2019
Effective: 04/09/1998
Next Review: 02/27/2020

Definitions

Additional Information

Clinical Policy Bulletin
Notes
positive (i.e., greater than or equal to 1 mm ST segment depression) stress test.

C. Evaluation of asymptomatic persons at an intermediate pre-test probability of coronary heart disease or atherosclerotic cardiovascular disease by Framingham risk scoring or Pooled Cohort Equations (see Appendix) who have an equivocal or uninterpretable exercise or pharmacological stress test or have resting electrocardiogram (ECG) changes (such as left bundle branch block (LBBB), pathologic q-waves, or right bundle branch block (RBBB) with left anterior fascicular block (LAFB) in which coronary artery disease (CAD) is a possible etiology. Note: Current guidelines from the American Heart Association recommend against routine stress testing for screening asymptomatic adults.

D. Pre-operative assessment of persons scheduled to undergo 'high-risk' non-cardiac surgery, where an imaging stress test or invasive coronary angiography is being deferred unless absolutely necessary. The ACC defines high-risk surgery as emergent operations, especially in the elderly, aortic and other major vascular surgeries, peripheral vascular surgeries, and anticipated prolonged surgical procedures with large fluid shifts and/or blood loss involving the abdomen and thorax.

E. Pre-operative assessment for planned non-coronary cardiac surgeries including valvular heart disease, congenital heart disease, and pericardial disease, in lieu of cardiac catheterization as the initial imaging study, in persons with low or intermediate pretest risk of obstructive CAD.

F. Detection and delineation of suspected coronary anomalies in young persons (less than 30 years of age) with suggestive symptoms (e.g., angina, syncope, arrhythmia, and exertional dyspnea without other known etiology of these symptoms in
children and adults; dyspnea, tachypnea, wheezing, periods of pallor, irritability (episodic crying), diaphoresis, poor feeding and failure to thrive in infants).

G. Calculation of fractional flow reserve (HeartFlow FFR\textsubscript{CT}) for persons who have a coronary CTA that has shown coronary artery disease of uncertain functional significance, or is non-diagnostic.

II. Aetna considers CT angiography of cardiac morphology for pulmonary vein mapping medically necessary for the following indications:

A. Evaluation of persons needing biventricular pacemakers to accurately identify the coronary veins for lead placement.
B. Evaluation of the pulmonary veins in persons undergoing pulmonary vein isolation procedures for atrial fibrillation (pre- and post-ablation procedure).

III. Aetna considers CT angiography medically necessary for preoperative assessment of the aortic valve annulus prior to anticipated transcatheter aortic valve replacement (TAVR).

IV. Aetna considers cardiac computed tomography (CT) angiography medically necessary for evaluation of aortic erosion in symptomatic members (e.g., chest pain) who have been treated for atrial septal defect with an occlusive device.

V. Aetna considers cardiac CT for evaluating cardiac structure and morphology medically necessary for the following indications:

A. Anomalous pulmonary venous drainage;
B. Evaluation of other complex congenital heart diseases;
C. Evaluation of sinus venosum atrial-septal defect;
D. Kawasaki's disease;
E. Person scheduled or being evaluated for surgical repair of tetralogy of Fallot or other congenital heart diseases;
F. Pulmonary outflow tract obstruction;
G. Suspected or known Marfan's syndrome;
H. Evaluation of suspected native or prosthetic cardiac valve dysfunction when echocardiographic imaging is inconclusive or there is suspicion for paravalvular abscess formation.

VI. Aetna considers cardiac CT angiography experimental and investigational for persons with any of the following contraindications to the procedure because its effectiveness for indications other than the ones listed above has not been established:

A. Body mass index (BMI) greater than 40 (except when 3rd generation Dual-Source CT (DSCT) 120-kv tube voltage is utilized).
B. Inability to image at desired heart rate (under 80 beats/min), despite beta blocker administration.
C. Person with allergy or intolerance to iodinated contrast material.
D. Persons in atrial fibrillation (except when rate-controlled and 3rd generation Dual-Source CT (DSCT) 120-kv tube voltage is utilized), or with other significant arrhythmia.
E. Persons with extensive coronary calcification by plain film or with prior Agatston score greater than 1000.

Aetna considers cardiac CT angiography using less than 64-slice scanners experimental and investigational because the effectiveness of this approach has not been established.
VII. Aetna considers coronary CT angiography experimental and investigational for screening of asymptomatic persons, evaluation of atherosclerotic burden, evaluation of persons at high pre-test probability of coronary artery disease, evaluation of stent occlusion or in-stent restenosis, evaluation of persons with an equivocal PET rubidium study, identification of vulnerable plaques, monitoring of atheroma burden, and for all other indications (e.g., atrial angiosarcoma) because its effectiveness for these indications has not been established. Note: The selection of CT angiography should be made within the context of other testing modalities such as stress myocardial perfusion images or cardiac ultrasound results so that the resulting information facilitates the management decision and does not merely add a new layer of testing.

VIII. Aetna considers a single calcium scoring by means of low-dose multi-slice CT angiography, ultrafast [electron-beam] CT, or spiral [helical] CT medically necessary for screening the following: (i) asymptomatic persons age 40 years and older with diabetes; or (ii) asymptomatic persons with an intermediate (10 % to 20 %) 10-year risk of cardiac events based on Framingham Risk Scoring or Pooled Cohort Equations (see Appendix). Repeat calcium scoring is considered medically necessary only if the following criteria are met: (i) member’s most recent coronary artery calcium (CAC) scan result was zero, (ii) member’s most recent CAC scan was at least 5 years ago, and (iii) discovery of coronary calcium would change management. Otherwise, serial or repeat calcium scoring is considered experimental and investigational.
Aetna considers calcium scoring by means of low-dose CT angiography medically necessary for persons who meet criteria for diagnostic cardiac CT angiography to assess whether an adequate image of the coronary arteries can be obtained.

Aetna considers calcium scoring of the aortic valve medically necessary in the setting of persons with suspected paradoxical low-flow, low-gradient symptomatic severe aortic stenosis when transthoracic echocardiography is inconclusive.

IX. Aetna considers coronary CT angiography experimental and investigational for assessment of coronary atherosclerosis in asymptomatic diabetics who do not otherwise meet the above criteria for CT coronary angiography because of insufficient evidence.

X. Aetna considers calcium scoring (e.g., with ultrafast [electron-beam] CT, spiral [helical] CT, and multi-slice CT) experimental and investigational for all other indications because of insufficient evidence in the peer-reviewed published medical literature.

Background

Cardiac CT Angiography

Coronary computed tomography angiography (CCTA) is a noninvasive imaging modality designed to be an alternative to invasive cardiac angiography (cardiac catheterization) for diagnosing CAD by visualizing the blood flow in arterial and venous vessels. The gold standard for diagnosing coronary artery stenosis is cardiac catheterization.

Contrast-enhanced cardiac CT angiography (CTA) involves the use of multi-slice CT and intravenously administered contrast material to obtain detailed images of the blood
vessels of the heart. Beta-blockers and sublingual nitrates may be administered prior to the scan in order to lower the heart rate, avoid arrhythmia and dilate the coronary arteries. In order to allow for an improved image quality and contrast media dose reduction, the CCTA is usually ECG-triggered to adapt the scan sequence to the person's heartbeat (Bell et al., 2018).

In addition to being a non-invasive alternative to conventional invasive coronary angiography for evaluating coronary artery disease, CCTA has emerged as the gold-standard for the detection of coronary artery anomalies Ramjattan and Makaryus, 2018).

The performance of cardiac CTA has been improved by increasing the number of slices that can be acquired simultaneously by increasing the number of detector rows (AHTA, 2006). As the number of slices that can be acquired simultaneously increases, the scan time is shortened, spatial resolution is increased, and reconstruction artifacts are significantly reduced. Initial cardiac CT imaging was conducted with 4-slice detector CT. Scanning times were reduced from 40 seconds down to 20 seconds with 16-slice detector CT. With the advent of 64-slice detector CT, scanning times were reduced to a 10 second breath-hold. Current generation scanners can perform full volumetric acquisition requiring only 1 cardiac cycle (1 R-R interval) and/or can be performed without breath holding (Abbara et al., 2016).

Cardiac CTA using 64-slices has been shown in studies to have a high negative predictive value (93 to 100 %), using conventional coronary angiography as the reference standard. Given its high negative predictive value, cardiac CTA has been shown to be most useful for evaluating persons at low to intermediate risk of coronary artery disease. This would include evaluation of asymptomatic low- to intermediate-risk persons with an equivocal exercise or pharmacologic stress test, and evaluation of low- to intermediate-risk persons with chest pain. Cardiac CTA is also a useful alternative to invasive
coronary angiography for pre-operative evaluation of persons undergoing non-coronary cardiac surgery or high-risk non-cardiac surgery, where invasive coronary angiography would otherwise be indicated.

Einstein and colleagues (2007) ascertained the lifetime attributable risk (LAR) of cancer incidence associated with radiation exposure from a 64-slice computed tomography coronary angiography (CTCA) study and evaluated the influence of age, sex, and scan protocol on cancer risk. Organ doses from 64-slice CTCA to standardized phantom (computational model) male and female patients were estimated using Monte Carlo simulation methods, using standard spiral CT protocols. Age- and sex-specific LARs of individual cancers were estimated using the approach of BEIR VII and summed to obtain whole-body LARs. Main outcome measures were whole-body and organ LARs of cancer incidence. Organ doses ranged from 42 to 91 mSv for the lungs and 50 to 80 mSv for the female breast. Lifetime cancer risk estimates for standard cardiac scans varied from 1 in 143 for a 20-year-old woman to 1 in 3,261 for an 80-year-old man. Use of simulated electrocardiographically controlled tube current modulation (ECTCM) decreased these risk estimates to 1 in 219 and 1 in 5,017, respectively. Estimated cancer risks using ECTCM for a 60-year-old woman and a 60-year-old man were 1 in 715 and 1 in 1911, respectively. A combined scan of the heart and aorta had higher LARs, up to 1 in 114 for a 20-year-old woman. The highest organ LARs were for lung cancer and, in younger women, breast cancer. The authors concluded that these estimates derived from simulation models suggested that use of 64-slice CTCA is associated with a non-negligible LAR of cancer. This risk varies markedly and is considerably greater for women, younger patients, and for combined cardiac and aortic scans.

Arbab-Zadeh et al (2012) evaluated the impact of patient population characteristics on accuracy by CTA to detect obstructive CAD. For the CORE-64 (Coronary Artery
Evaluation Using 64-Row Multidetector Computed Tomography Angiography (CTA) study, a total of 371 patients underwent CTA and cardiac catheterization for the detection of obstructive CAD, defined as greater than or equal to 50% luminal stenosis by quantitative coronary angiography (QCA). This analysis includes 80 initially excluded patients with a calcium score greater than or equal to 600. Area under the receiver-operating characteristic curve (AUC) was used to evaluate CTA diagnostic accuracy compared to QCA in patients according to calcium score and pre-test probability of CAD. Analysis of patient-based quantitative CTA accuracy revealed an AUC of 0.93 (95% CI: 0.90 to 0.95). The AUC remained 0.93 (95% CI: 0.90 to 0.96) after excluding patients with known CAD but decreased to 0.81 (95% CI: 0.71 to 0.89) in patients with calcium score greater than or equal to 600 (p = 0.077). While AUCs were similar (0.93, 0.92, and 0.93, respectively) for patients with intermediate, high pre-test probability for CAD, and known CAD, negative predictive values were different: 0.90, 0.83, and 0.50, respectively. Negative predictive values decreased from 0.93 to 0.75 for patients with calcium score less than 100 or greater than or equal to 100, respectively (p = 0.053). The authors concluded that both pre-test probability for CAD and coronary calcium scoring should be considered before using CTA for excluding obstructive CAD. For that purpose, CTA is less effective in patients with calcium score greater than or equal to 600 and in patients with a high pre-test probability for obstructive CAD. (CTA is most useful as a rule-out test in patients with low-intermediate pre-test probability of disease and mild coronary calcification or those with a calcium score of zero).

The use of 64-slice CCTA scanners was associated with a non-negligible effective radiation dose and thus, may increase the lifetime attributable risk of cancer. However, second-generation CCTA scanners may be used which can decrease the amount of radiation exposure. A study by Chen and colleagues (2013) reported on 107 participants who received CCTA with a second-generation 320-detector row machine.
and compared the radiation exposure to 100 participants who had previous imaging with a first-generation scanner. For the second-generation scanner the median radiation dose was 0.93 mSv and 2.76 mSv with the first-generation scanner. This radiation dose places CT scans at an intermediate (1–10 mSv) level of risk under international guidelines, a risk level for which the corresponding benefit should be "moderate" to "substantial." Einstein and colleagues (2007) reported that the use of a 64-slice CCTA is associated with a non-negligible LAR (lifetime attributable risk) of cancer and that the risk is "Considerably greater for women, younger patients and for combined cardiac and aortic scans." CCTA requires the use of intravenous iodinated contrast and, in most cases, beta-blocker or calcium channel blocker medications to slow the heart rate prior to image acquisition. In patients with a GFR > 60, the risks for nephrotoxicity are very low (<1%). Beta-blocker and calcium channel blocker administration, particularly given the short duration of use, are associated with a very low risk (<1%) for adverse reactions. Additionally, CCTA may offer an option in obese patients as data suggests no significant reduction in sensitivity and specificity when compared to non-obese patients. Particularly on newer CT scanner platforms, diagnostic quality images are expected even in patients with modest HR control prior to acquisition, though more thorough pre-scan HR control does allow for better radiation dose reduction. Limitations to utilization of CCTA include patients with irregular heart rhythms, known high levels of coronary calcification (CAC scores > 400), borderline tachycardia (HR>80 despite pre-treatment), baseline renal impairment, and known IV contrast allergy.

A number of controlled clinical trials and registry evidence have addressed the diagnostic accuracy and clinical effectiveness of CCTA in the evaluation of symptomatic patients. Registry data can be broadly subdivided into those that address the use of CCTA to evaluate individuals with symptoms suggestive of CAD, to risk stratify individuals at risk for coronary artery disease, and those that use CCTA after
equivocal results of other cardiac imaging procedures, such as myocardial perfusion imaging (MPI) or echocardiography. In part these proposed uses result from the observation that a negative CCTA has high negative predictive value for the presence of CAD (Bluemke, 2008).

There is a large body of evidence evaluating the diagnostic characteristics of CCTA for identifying coronary lesions. The best estimate of the diagnostic characteristics of CCTA can be obtained from recent meta-analyses and systematic reviews. Sensitivities for functional stress testing tended to range between 70% and 90%, depending on the test and study, and specificities ranged between 70% and 90%. For CCTA, estimates of sensitivity from various systematic reviews are considerably higher. The guideline statement from Fihn cited studies reporting sensitivities between 93% and 97%. A meta-analysis by Ollendorf et al. of 42 studies showed a summary sensitivity estimate of 98% and a specificity of 85%. A meta-analysis of 8 studies conducted by the Ontario Health Ministry showed a summary sensitivity estimate of 97.7% and a specificity of 79%. In the meta-analysis by Nielsen et al., sensitivity of CCTA varied between 98% and 99% (depending on the analysis group). The biggest criticism of historical trials investigating the diagnostic characteristics of any non-invasive testing modality is referral bias: only patients with abnormal tests were referred for invasive coronary angiography (ICA). The recently published PICTURE trial is a prospective, multicenter investigation enrolling 230 patients with chest pain referred for MPI who were subsequently randomized to CCTA or MPI. All patients were then referred for ICA regardless of noninvasive test findings. In this trial, the sensitivity of CCTA to predict a stenosis >50% on ICA was far superior to MPI utilizing both a CCTA stenosis ≥50% (92.0% vs 54.5%, p<0.001) or ≥70% (92.6% vs 59.3%, p<0.001). The odds ratio for CAD on ICA was 12.73 (95%CI 2.43-66.55, p<0.001) for a summed stress score by MPI ≥5% (utilizing a 17-segment
model). In contrast, the odds ratio for CAD on ICA was 51.75 (95% CI 8.50-314.94, p<0.001) for CCTA utilizing a stenosis ≥50% (Ollendorf et al, 2011).

The extent and severity of CAD by CCTA has significant prognostic implications. Long term follow-up data from the CONFIRM registry observed that the absence of CAD on CCTA is associated with very favorable prognosis with major adverse cardiac event rates (MACE) of < 1% out to 7 years. This "warranty period" affords the ability to avoid future unnecessary ischemic testing and provide reassurance to patients. Lin et al found 2.09% mortality rate at 3 years of follow-up in over 2,500 symptomatic patients with nonobstructive CAD (HR 1.98 (1.06-3.69), p=0.03). Up to 25% of nonobstructive CAD (<50%) patients and 50% of obstructive CAD (≥50%) patients will not have detectable perfusion defects by single-photon emission computed tomography (SPECT), thus a significant cohort of these patients at significant risk for mortality and cardiovascular events would be underdiagnosed and incorrectly risk stratified. CCTA provided incremental prognostic information after adjusting for traditional risk factors with hazard ratios of 2.20 and 2.91 in the 2-vessel and 3-vessel groups, respectively (p=0.013 and 0.001) (Lin et al, 2011).

In addition to very robust diagnostic and prognostic performance when compared to invasive coronary angiography, there is now considerable prospective randomized data demonstrating that CCTA meaningfully guides provider decision making, resulting in improved patient outcomes. SCOT-HEART is a randomized, prospective trial of more than 4,000 patients being evaluated for stable chest pain. Following initial clinical evaluation and, in 85% of patients, an exercise stress electrocardiogram, patients were assigned to undergo CCTA or continue with their previously determined plan of care. A diagnosis of coronary heart disease was made in 47% of participants and 36% of patients were labeled as having angina due to coronary heart disease
following initial clinical evaluation. At 6 weeks, CCTA reclassified 558 (27%) patients to a diagnosis of CHD and 481 (23%) patients to a diagnosis of angina due to CHD (standard care 22 [1%] and 23 [1%]; p<0.0001). CCTA increased the provider diagnostic certainty, as well as the frequency of the diagnosis of CHD (RR 2.56, 95% CI 2.33–2.79; p<0.0001 and RR 1.09, 95% CI 1.02–1.17; p=0.0172, respectively). Furthermore, CCTA also increased provider certainty in the diagnosis of angina due to CHD (RR 1.79, 95% CI 1.62–1.96; p<0.0001). This reclassification and increase in diagnostic certainty resulted in an increased rate of change in planned investigation (15% vs 1%; p<0.0001) and in medical treatments (23% vs 5%; p<0.0001) following CCTA. While there was no significant difference in outcomes reported at 1.7 years of follow-up in the initial publication, 3-year follow-up data showed a significant reduction in both fatal and non-fatal myocardial infarction. A similar reduction in non-fatal MI was observed in the prospective, multicenter PROMISE trial, which randomized over 10,000 intermediate pre-test risk patients with stable chest pain symptoms to a strategy of functional testing or CCTA as the initial diagnostic evaluation. While PROMISE was a neutral trial with no difference in the primary endpoint between the CCTA arm (3.3%) and the functional-testing arm (3.0%, adjusted HR 1.04; 95% CI 0.83-1.29, p=0.75), death and non-fatal MI was less frequent in the CCTA arm at 12 months of follow-up (HR 0.66, p=0.049). Additionally, a recently published investigation of the PROMISE data demonstrated superior prognostic and discriminatory ability with CCTA compared with functional testing, in addition to an improvement in appropriate initiation of primary prevention medications, such as aspirin (11.8% vs 7.8%), statins (12.7% vs 6.2%), and beta blockers (8.1% vs 5.3%, p<0.0001 for all) in patients in the CCTA arm when compared to functional testing. The prevalence of healthy eating (p=0.002) and lower rates of obesity (p=0.040) were also observed following CCTA when compared to functional testing (SCOT-HEART investigators, 2015).
A recent meta-analysis combining data from PROMISE and SCOT-HEART, in addition to a 3rd prospective randomized stable chest pain trial (CAPP), concluded that CCTA was associated with a 31% reduction in non-fatal myocardial infarction (HR 0.69, 95% CI 0.49-0.98, p=0.038). While not included in this meta-analysis, recently published data from the nationwide Danish registry demonstrated that evaluation of stable chest pain with CCTA was associated with greater use of statins and aspirin, likely explaining the observed reduction in non-fatal MI in this cohort. CCTA was, however, associated with higher rates of ICA and functional testing costs (Williams et al, 2017).

This observed improvement in hard cardiovascular outcomes following CCTA is likely explained by the unique ability of CCTA to not only detect significant epicardial coronary vessel stenosis, but also to diagnose non-obstructive coronary atherosclerosis. This early detection of CAD allows for early, aggressive implementation of primary prevention medications and positively impacts patient adoption and adherence to lifestyle modifications regarding diet, exercise, smoking cessation, and weight loss. Data in 2,800 consecutive symptomatic patients undergoing CCTA at tertiary hospital centers suggested that CAD burden, even in the absence of a severe stenosis by CCTA, resulted in intensification of primary prevention medical therapy by providers. Additionally, in patients with nonobstructive CAD, those treated with statin therapy had a mortality reduction compared to those without atherosclerotic plaque on CCTA. CCTA also identified a high risk cohort of patients with extensive nonobstructive CAD in whom statin therapy was associated with a significant reduction in cardiovascular death and non-fatal MI (HR=0.18, p=0.011) (Hulten et al, 2014).

Data from the National Cardiovascular Data Registry’s (NCDR) CathPCI Registry demonstrated that, despite a multitude of noninvasive testing modalities available to providers nationwide, 58.4% of patients were found to have no or
nonobstructive CAD at the time of elective ICA. In contrast, only 30% of patients referred for ICA after CCTA were found to have nonobstructive CAD. Revascularization based on findings of high-risk CAD on CCTA was associated with a significant reduction in all-cause mortality with revascularization when compared to medical therapy alone (2.3% vs 5.3%, p=0.008) in the CONFIRM registry. Additionally, the opposite effect was observed in patients without high-risk CAD referred for revascularization compared with medical therapy (2.3% vs 1.0%, p=0.0138). The CCTA allows for more precise risk stratification beyond simple epicardial stenosis for appropriately selecting patients who benefit from revascularization. In prospective trials, CCTA was associated with increased rates of revascularization. A meta-analysis by Hulten et al looking at CCTA in the ED for acute chest pain patients demonstrated a cost savings in 3 of the 4 large randomized control trials (RCTs) and shorter hospital lengths of stay in all 4 studies. An increased referral rate for ICA (OR 1.36, 95% CI 1.03-1.80, p=0.030) and subsequent revascularization (OR 1.81, 95% CI 1.20-2.72, p=0.004) was also observed with a number needed to scan to increase ICA and revascularization over usual care by 1 of 48 and 50, respectively. The strategy of CCTA as a “gatekeeper” to the catheterization lab was recently presented in soon to be published data from the CONSERVE trial. This multicenter, prospective trial enrolled stable chest pain patients without known CAD who were referred for ICA. Patients were randomized to undergo CCTA followed by selective catheterization based on CCTA results (and at the discretion of the provider) or direct catheterization in patients with elective indications for diagnostic coronary angiography. Pre-test risk, rates of abnormal non-invasive stress testing, and symptoms were similar between the groups. CCTA followed by selective catheterization was associated with a 78% reduction (p<0.001) in per-patient testing, which included the index evaluation plus downstream costs, when compared with direct catheterization. Revascularization rates were 41% lower (p<0.001) in the selective catheterization arm, as well. This
resulted in a 50% cardiovascular cost savings ($3,338 vs $6,740, p<0.001) utilizing CCTA as a gatekeeper. Importantly, MACE outcomes were the same between the two strategies over study follow-up. In summary, CCTA can appropriately identify patients who would most benefit from referral for ICA and revascularization and result in lower rates of normal or minimally abnormal findings on ICA making CCTA an effective gatekeeper to the catheterization laboratory. The use of CCTA does seem to increase the rates of revascularization when compared to functional testing, both in the stable chest pain and ED population (Hulten, 2017).

The addition of CCTA early in the evaluation of patients presenting acutely to the emergency department with chest pain has been extensively studied in prospective, multicenter trials. A 2012 randomized trial by Hoffman and colleagues (ROMICAT II) compared the effectiveness of CCTA with that of standard evaluation in individuals suggestive of acute coronary syndrome in the emergency room. A total of 501 individuals had CCTA, 499 individuals had a standard evaluation in the emergency room. Individuals were excluded if they had known CAD. The primary endpoint of length of hospital stay was significantly reduced in the CCTA cohort. Additionally, the a priori secondary effectiveness endpoint of time to diagnosis was also decreased with CCTA. Of note, there was more downstream testing and radiation exposure was higher in the CCTA cohort. In another randomized trial, Litt et al (2012) compared individuals at low-to-intermediate risk with possible acute coronary syndromes who presented to the emergency room. Individuals were randomly assigned in a 2:1 ratio to undergo CCTA or receive traditional care. The primary outcome was safety (measured by the rate of cardiac events within 30 days). None of the participants with a negative CCTA had myocardial infarction or died within 30 days. There were no cardiac deaths in the traditional group. And while the CCTA group had a higher rate of discharge from the emergency room and decreased overall length of stay, there were no differences between the groups in the use of invasive
angiography or rate of revascularization. The CT-STAT trial (Goldstein et al) compared CCTA with MPI in the early evaluation of nearly 700 patients with acute chest pain and found a 54% reduction in time to diagnosis (p<0.0001), a 38% reduction in cost of care (p<0.0001), and no difference in MACE rates. A subsequent meta-analysis by Hulten et al concluded that ED CCTA was associated with decreased cost and reduced length of stay, but increased ICA and revascularization rates. In summary, the high negative predictive value (NPV) of CCTA in patients presenting to the ED with chest pain permits ruling out coronary disease with high accuracy. The efficiency of the workup is improved, because patients are safely and quickly discharged from the ED with no adverse outcomes among patients with negative CCTA examinations. Finally, CCTA was associated with improved clinical outcomes when instituted in the immediate post-discharge evaluation of patients with acute chest pain discharged from the ED as reported in the CATCH trial. CCTA demonstrated lower rates of a composite of cardiac death, MI, unstable angina, late symptom-driven revascularization, and chest pain readmission when compared to standard care utilizing bicycle exercise ECG or MPI (11% vs 16%, p=0.04; HR 0.62, 95% CI 0.40-0.98). Additionally, when looking only at major adverse cardiovascular events (MACE), a CCTA-guided strategy was also superior (2% vs 5%, p=0.04), predominantly driven by higher rates of myocardial infarction in the standard care cohort. CCTA was also compared to high-sensitivity troponin assays (hs-troponins) in the evaluation and disposition of acute chest pain patients presenting to the ED. In a prospective, multicenter trial of 500 patients randomized to hs-troponin based evaluation and disposition to CCTA, there was no difference in the primary endpoint of patients identified with significant CAD requiring revascularization. Additionally, ED discharge rates, ED length of stay, and incidence of undetected ACS were similar. CCTA lowered direct medical costs by 34% (p<0.01) when compared to hs-troponins and there was less downstream testing following the index ED visit (4% vs 10%, p<0.01).
An assessment by the Blue Cross Blue Shield Association Technology Evaluation Center's Evidence Street (revised June 2017) concluded that CCTA in individuals with stable chest pain and intermediate risk for CAD, the evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome for patients.

Additionally, prior assessment found that CCTA was equally powerful in patients with acute chest pain presenting to the emergency room with no known history of coronary artery disease, and found not to have evidence of acute coronary syndromes. The TEC assessment stated that evidence obtained in the emergency setting, similar to more extensive results among ambulatory patients, indicates a normal CCTA appears to provide a prognosis as good as other noninvasive tests (BCBSA, 2011).

Cardiac CT angiography often produces non-cardiac incidental findings. To evaluate the incidence, clinical importance, and costs of these incidental findings, MacHaalany, et al (2009) studied 966 consecutive patients who underwent CTA. Incidental findings were noted in 401 patients (41.5%); of these, 12 were deemed to be clinically significant (e.g., 5 thrombi, 1 aortic dissection that was not clinically suspected, 1 ruptured breast implant), and 68 were deemed to be indeterminate (e.g., 34 non-calcified pulmonary nodules less than 1 cm, 11 larger lung nodules, 9 liver nodules/cysts). After a mean 18-month follow-up, no indeterminate finding became clinically significant, although 3 malignancies were diagnosed after subsequent diagnostic tests. Non-cardiac and cancer death rates were not significantly different between patients with and without incidental findings. In all, 164 additional diagnostic tests and procedures were performed in the 80 patients with indeterminate or clinically significant incidental findings, including 1 patient who suffered empyema and abdominal abscesses as a complication of transthoracic biopsy.
In an observational study, Kim and colleagues (2013) evaluated the prevalence and characteristics of coronary atherosclerosis in asymptomatic subjects classified as low-risk by National Cholesterol Education Program (NCEP) guideline using CCTA. A total of 2,133 (49.2%) subjects, who were classified as low-risk by the NCEP guideline, of 4,339 consecutive middle-aged asymptomatic subjects who underwent CCTA with 64-slice scanners as part of a general health evaluation were included in this study. Main outcome measures were the incidence of atherosclerosis plaques and significant stenosis. In the subjects at low-risk, 11.4% (243 of 2,133) of subjects had atherosclerosis plaques, 1.3% (28 of 2,133) of subjects had significant stenosis, and 0.8% (18 of 2,133) of subjects had significant stenosis caused by non-calcified plaque (NCP). Especially, 75.0% (21 of 28) of subjects with significant stenosis and 94.4% (17 of 18) of subjects with significant stenosis caused by NCP were young adults. Mid-term follow-up (29.3 ± 14.9 months) revealed 4 subjects with cardiac events: 3 subjects with unstable angina requiring hospital stay and 1 subject with percutaneous coronary intervention. The authors concluded that although an asymptomatic population classified as low-risk by the NCEP guideline has been regarded as a minimal risk group, the prevalence of atherosclerosis plaques and significant stenosis were not negligible. However, considering very low event rate for those patients, CCTA should not be performed in low-risk asymptomatic subjects, although CCTA might have the potential for identification of high-risk groups in the selected subjects regarded as a minimal-risk group by NCEP guideline.

Dorr and associates (2013) stated that clinical studies have consistently shown that there is only a very weak correlation between the angiographically determined severity of CAD and disturbance of regional coronary perfusion. On the other hand, the results of randomized trials with a fractional flow reserve (FFR)-guided coronary intervention (DEFER, FAME I, FAME II) showed that it is not the angiographically determined morphological severity of CAD but the functional severity
determined by FFR that is critical for prognosis and the indications for re-vascularization. A non-invasive method combining the morphological image of the coronary anatomy with functional imaging of myocardial ischemia is therefore particularly desirable. An obvious solution is the combination of CCTA with a functional procedure, such as perfusion positron emission tomography (PET), perfusion single photon emission computed tomography (SPECT) or perfusion magnetic resonance imaging (MRI). This can be performed with fusion imaging or with hybrid imaging using PET-CT or SPECT-CT. First trial results with PET-CCTA and SPECT-CCTA carried out as cardiac hybrid imaging on a 64-slice CT showed a major effect to be a decrease in the number of false-positive results, significantly increasing the specificity of CCTA and SPECT. The authors concluded that although the results are promising, due to the previously high costs, low availability and the additional radiation exposure, current data are not yet sufficient to give clear recommendations for the use of hybrid imaging in patients with a low-to-intermediate risk of CAD. Moreover, they stated that ongoing prospective studies such as the SPARC or EVINCI trials will bring further clarification.

In a retrospective study, Kang et al (2014) evaluated coronary arterial lesions and assessed their correlation with clinical findings in patients with Takayasu arteritis (TA) by using coronary CT angiography. A total of 111 consecutive patients with TA (97 females, 14 males; mean age of 44 years ± 13.8 [standard deviation]; age range of 14 to 74 years) underwent CT angiography of the coronary arteries and aorta with 128-section dual-source CT. Computed tomography angiographic, clinical, and laboratory findings of each patient were retrospectively reviewed. Statistical differences between coronary CT angiographic findings and clinical parameters were examined with uni-variate analysis. Of 111 patients, 32 (28.8 %) had cardiac symptoms and the remaining 79 (71.2 %) had no cardiac symptoms; 59 patients (53.2 %) had coronary arterial lesions at coronary CT angiography. Three main
radiologic features were detected: (i) coronary ostial stenosis (n = 31, 28.0 %), (ii) non-ostial coronary arterial stenosis (n = 41, 36.9 %), and (iii) coronary aneurysm (n = 9, 8.1 %). Coronary artery ostial or luminal stenosis of 50 % or more or coronary aneurysms were observed in 26 (23.4 %) patients with TA. Patients with coronary arterial abnormalities at coronary CT angiography had higher incidences of hypertension (p = 0.02), were older at the time of CT (p = 0.01), and had longer duration of TA (p = 0.02) than those without coronary artery abnormalities. The presence of cardiac symptoms, disease activity, and other co-morbidities was not associated with differences in coronary artery involvement. The authors concluded that in patients with TA, there is a high prevalence of coronary arterial abnormalities at coronary CT angiography, regardless of disease activity or symptoms. Thus, these researchers noted that coronary CT angiography may add information on coronary artery lesions in patients with TA.

Marwick et al. (2015) discussed the potential of CCTA to serve as an effective gatekeeper to invasive coronary angiography. The authors note that functional testing prior to ICA is not widespread. Possibly as a consequence, 40% of angiograms in the National Cardiovascular Database Registry detect normal coronary arteries. The authors reviewed the PROMISE trial outcomes and noted that although the findings are insufficient to conclude the possibility of either harm or benefit from the use of CCTA, a particularly salient feature was that although catheterization was performed in more CCTA patients in the 90 days following noninvasive testing, the likelihood of nonsignificant CAD was significantly lower in the CCTA group (3.4% vs. 4.3%; p = 0.02). The authors state that CCTA is a promising noninvasive method for identification and exclusion of CAD, which may provide a diagnostic paradigm to curb unnecessary invasive testing. CCTA has the potential to serve as an effective gatekeeper to curb unnecessary ICA. However, there is no definitive evidence to favor either a
CCTA-guided or a stress testing–guided approach for evaluation of acute CP. The authors believe the PROMISE trial results are equivocal and concluded that results from future prospective multicenter studies will be needed to justify CCTA’s contribution to patients with suspected CAD for ICA.

Williams et al. (2016) conducted a prospective, randomized, controlled, multicenter trial to evaluate the consequences of CCTA-assisted diagnosis on invasive coronary angiography (ICA), preventive treatments, and clinical outcomes. A little over 4,000 patients were randomized to receive standard care or standard care plus coronary computed tomography angiography (CCTA). The investigators found that despite similar overall rates (409 vs. 401; p = 0.451), ICA was less likely to demonstrate normal coronary arteries (p < 0.001) but more likely to show obstructive CAD (p = 0.005) in those allocated to CCTA. More preventive therapies (p < 0.001) were initiated after CCTA, with each drug commencing at a median of 48 to 52 days after clinic attendance. From the median time for preventive therapy initiation (50 days), fatal and nonfatal myocardial infarction was halved in patients allocated to CCTA compared with those assigned to standard care (p = 0.020). Cumulative 6-month costs were slightly higher with CCTA: difference $462 (95% CI: $303 to $621). The investigators concluded that their findings show that CCTA allows more appropriate and effective selection of ICA related to CAD.

CCTA is generally contraindicated for decompensated heart failure; however, may be considered on a case-by-case basis (Abbara et al, 2016).

Jorgensen et al. (2017) conducted an observational, non-randomized study to compare functional testing to CCTA in patients with stable coronary artery disease. The investigators studied patients enrolled in a Danish registry who underwent initial noninvasive cardiac testing with either a CCTA or functional testing (exercise electrocardiography or nuclear stress testing) from 2009 to 2015. They further evaluated the
use of noninvasive testing, invasive procedures, medications, and medical costs within 120 days. Out of 86,705 patients, 53,744 underwent functional testing and 32,961 underwent CCTA. Compared with functional testing, there was significantly higher use of statins (15.9% vs. 9.1%), aspirin (12.7% vs. 8.5%), invasive coronary angiography (14.7% vs. 10.1%), and percutaneous coronary intervention (3.8% vs. 2.1%); all \( p < 0.001 \) after CCTA. The mean costs of subsequent testing, invasive procedures, and medications were higher after CCTA (\( p < 0.001 \)). Unadjusted rates of mortality (2.1% vs. 4.0%) and MI hospitalization (0.8% vs. 1.5%) were lower after CCTA than functional testing (both \( p < 0.001 \)). After adjustment, CCTA was associated with a comparable all-cause mortality (HR: 0.96; 95% CI: 0.88 to 1.05), and a lower risk of MI (HR: 0.71; 95% CI: 0.61 to 0.82). The investigators concluded that CCTA was associated with greater use of statins, aspirin, invasive procedures, and higher costs than functional testing in stable patients who were evaluated for suspected CAD. The investigators also concluded that although CCTA was associated with a lower risk of MI, it had a similar risk of all-cause mortality.

The Prospective Multicenter Imaging Study for Evaluation of chest pain (PROMISE) trial was a pragmatic trial that recruited a large cohort from USA and Canadian centres to determine whether an initial assessment of suspected stable CAD using CTCA reduces major adverse cardiovascular events (Douglas, et al., 2015). There was no improvement in death, myocardial infarction or major procedural complication after a median of 2-years of follow-up when compared with a functional-guided strategy.

Hoffman et al. (2017) discussed insights from the prospective, randomized, multicenter PROMISE trial which evaluated the prognostic value of noninvasive cardiovascular testing in patients with stable chest pain. The authors note that there are limited data from randomized trials comparing anatomic with functional testing for determining optimal management of
patients with stable chest pain. In the PROMISE trial, patients with stable chest pain and intermediate pretest probability for obstructive CAD were randomly assigned to functional testing (exercise electrocardiography, nuclear stress, or stress echocardiography) or CCTA. The primary end point was death, myocardial infarction, or unstable angina hospitalizations over a median follow-up of 26.1 months. Both the prevalence of normal test results and incidence rate of events in these patients were significantly lower among 4500 patients randomly assigned to CTA in comparison with 4602 patients randomly assigned to functional testing (both P<0.001). In CTA, 54.0% of events (n=74/137) occurred in patients with non-obstructive CAD (1%-69% stenosis). Prevalence of obstructive CAD and myocardial ischemia was low (11.9% versus 12.7%, respectively), with both findings having similar prognostic value (95% CI, 2.60-5.39; and 3.47; 95% CI, 2.42-4.99). When test findings were stratified as mildly, moderately, or severely abnormal, hazard ratios for events in comparison with normal tests increased proportionally for CTA (2.94, 7.67, 10.13; all p<0.001) but not for corresponding functional testing categories (0.94 [p=0.87], 2.65 [p=0.001], 3.88 [p<0.001]). They found that anatomic assessment with CCTA provided significantly better prognostic information compared to function testing (p=0.04). They noted that adding the Framingham Risk Score to functional test results significantly improved the prognostic value of functional testing. If 2714 patients with at least an intermediate Framingham Risk Score (>10%) who had a normal functional test were reclassified as being mildly abnormal, the discriminatory capacity improved to 0.69 (95% CI, 0.64-0.74).

The authors stated that contemporary stable chest pain populations present with a low prevalence of myocardial ischemia and obstructive CAD, and that in that particular population, CCTA provides better prognostic information than functional testing. The authors concluded that in this population, the detection of non-obstructive CAD identifies additional at-risk patients while consideration of the Framingham Risk Score is important for proper risk
stratification of patients with normal stress testing. These results may contribute to a better understanding of how to use this information to guide management of these patients.

Newer generation CT scanners have emerged which allows for faster, higher-quality images. Dual-Source CT (DSCT) scanners allow for a "gapless acquisition with a pitch of up to 3.4 which cannot be achieved with conventional single-source CT scanners. A high-pitch spiral acquisition can be performed in less than one second and thus information from a single heartbeat can be generated. In combination with iterative reconstruction techniques, high-pitch spiral acquisition allows for cardiac CT with sub-millSiervert doses". Contraindications include acute MI, screening asymptomatic patients with low-to-intermediate risk of CAD, evaluation of coronary artery stents less than 3 mm, and evaluation of asymptomatic patients post CABG less than 5 years old and post sent placement less than 2 years old (Bell et al., 2018).

CCTA with slower temporal resolution scanners, such as the 64-slice single-source CT scanner, is not recommended in persons with significant arrhythmia or atrial fibrillation (AF). Arrhythmias have presented a challenge due to motion artifact resulting from irregular rhythm; however, studies are now showing that newer generation CT scanners are capable of providing quality images for patients with AF. CCTA with dual-source CT scanner technology and algorithms have been developed to perform CCTA in persons with atrial fibrillation who cannot be effectively imaged with single-source CT. These newer generation CT scanners allow faster temporal resolution and are capable of producing motion-free images (Soman et al, 2017).

Yang et al. (2015) evaluated 85 patients with persistent atrial fibrillation (AF) who underwent prospective ECG-triggered sequential second-generation dual-source CCTA. Their aim was to evaluate the effects of mean heart rate (HR) and heart rate variation (HRV) on image quality and analyze the
diagnostic accuracy. Tube current and voltage were adjusted according to BMI (range 17.3-36.3 kg/m²) and iterative reconstruction was used. Image quality of coronary segments (four-point scale) and presence of significant stenosis (>50%) were evaluated. Diagnostic accuracy was analyzed in 30 of the 85 patients who underwent additional invasive coronary angiography (ICA). All subjects had AF longer than 1 year. The results showed that 8 of 1102 (0.7%) segments demonstrated poor image quality. No significant impact on image quality was found for mean HR (p=0.663) or HRV (p=0.895). On per-segment analysis, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 89.7% (26/29), 99.4% (355/357), 92.9% (26/28), and 99.2% (355/358), respectively, with excellent correlation (kappa=0.91) with ICA. Mean effective dose was 3.3±1.0 mSv. The authors concluded that "prospectively ECG-triggered sequential dual-source CCTA provides diagnostic image quality and good diagnostic accuracy for detection of coronary artery stenosis in AF patients without significant influence by HR or HRV."

The Society of Cardiovascular Computed Tomography (SCCT) guidelines committee produced an update in 2016 which states that "the development of dual-source CT and wide-detector scanners may allow imaging of selected patients with higher and irregular heart rates such as atrial fibrillation with diagnostic imaging quality. It should be acknowledged, however that coronary CTA in high or irregular heart rates typically is associated with a higher radiation dose. Moreover, in the event of irregular heart rates or atrial fibrillation it is essential that other determinants of image quality such as coronary calcification, body weight and patient cooperation are taken into consideration before deciding whether to proceed with the scan. The presence of frequent premature complexes prior to scanning therefore should trigger consideration of aborting the examination." (Abbara et al, 2016).
Prazeres et al. (2018) compared image quality and radiation dose of coronary computed tomography (CT) angiography performed with dual-source CT scanner using 2 different protocols in patients with atrial fibrillation (AF). The study included 732 subjects with AF who underwent 2 different acquisition protocols: double high-pitch (DHP) spiral acquisition and retrospective spiral acquisition. The image quality was ranked according to a qualitative score by 2 experts: 1, no evident motion; 2, minimal motion not influencing coronary artery luminal evaluation; and 3, motion with impaired luminal evaluation. A third expert was included to resolve any disagreement. The results reflected that the DHP group (24 patients, 374 segments) showed more segments classified as score 1 than the retrospective spiral acquisition group (71.3% vs 37.4%). Image quality evaluation agreement was high between observers (κ = 0.8). There was significantly lower radiation exposure for the DHP group (3.65 [1.29] vs 23.57 [10.32] mSv). The authors concluded that their comparison showed that a double high-pitch spiral protocol for CCTA acquisition resulted in lower radiation exposure and superior image quality in patients with AF compared with conventional spiral retrospective acquisition.

With the advent of the 3rd generation dual-source CT, persons with BMI greater than or equal to 40 may now be able to undergo a CCTA. Mangold et al. (2016) conducted a retrospective study to evaluate the quality of 3rd generation dual-source CT (CCTA) in obese patients. The study included 102 obese patients who had undergone CCTA performed with (3rd) generation dual-source CT, prospectively ECG-triggered acquisition at 120 kV, and automated tube current modulation. Patients were divided into three BMI groups: (i) 25-29.9 kg/m (2); (ii) 30-39.9 kg/m (2); and (iii) ≥ 40 kg/m (2). Vascular attenuation in the coronary arteries was measured. Contrast-to-noise ratio (CNR) was calculated. Image quality was subjectively evaluated using five-point scales. Image quality was considered diagnostic in 97.6 % of examinations. CNR
was consistently adequate in all groups but decreased for
groups 2 and 3 in comparison to group 1 as well as for group 3
compared to group 2 (p = 0.001, respectively). Subjective
image quality was significantly higher in group 1 compared to
group 3 (p < 0.001). The mean effective dose was 9.5 ± 3.9
mSv for group 1, 11.4 ± 4.7 mSv for group 2 and 14.0 ± 6.4
mSv for group 3. The authors concluded that diagnostic CCTA,
with 3(rd) generation DSCT at 120 kV, can routinely be
performed in persons with BMI greater than 40.

Chinnaiyan et al. (2009) investigated the dual-source
computed tomography (DSCT), which was novel at that time,
in morbidly obese patients. The authors state that persons with
BMI greater than or equal to 40 have an increased risk of
cardiovascular morbidity and mortality but have not been able
to obtain a CCTA due to reduced accuracy. The authors
conducted an observational study of 50 patients with mean
BMI 44.8. Each patient served as their own control. After a
single DSCT acquisition, standard quarter-scan image
reconstructions at a temporal resolution of 83 milliseconds
were compared with temporal resolution reconstructions at
105, 125, and 165 milliseconds. Images were evaluated for
diagnostic adequacy score and for image noise, signal-to-
noise ratio, and contrast-to-noise ratio. In each patient, the
image reconstruction with the best visual diagnostic score was
compared with the control image for quantitative measures.
The authors found that scans were of diagnostic quality in 47
(94%) patients using the "best reconstruction" compared with
38 (76%) patients using quarter-scan reconstruction.
Significant improvements were observed in noise (p < 0.0001),
contrast-to-noise ratio (p = 0.0038), and signal-to-noise ratio (p
= 0.030). The authors concluded that "CCTA with DSCT using
a modified scan protocol and adjustable temporal
reconstructions provides diagnostic image quality in >90% of
morbidly obese patients."
A 2016 guideline update produced by the Society of Cardiovascular Computed Tomography (SCCT) discussed weight considerations for CCTA. The guidelines state that "scan settings should be adjusted to the patient's body weight. Both tube voltage and tube current should be optimized to deliver the least necessary radiation for adequate image quality. In obese patients, higher tube current and tube voltage are required in order to preserve contrast to noise ratio. More importantly, tube current should be adjusted to the total volume of soft tissues within the scanned region. The specific adjustments are dependent on the scanner specifications (Abbara et al., 2016).

Non invasive Fractional Flow Reserve (HeartFlow FFRCT)

HeartFlow FFRCT (HeartFlow, Inc, Redwood City, CA) is a coronary physiologic simulation software used for the clinical qualitative and quantitative analysis of previously acquired computerized tomography Digital Imaging and Communications in Medicine (DICOM) data. The software provides a non-invasive method of estimating fractional flow reserve using standard coronary CT angiography (CCTA) image data (NICE, 2017).

FFR is the ratio between the maximum blood flow in a narrowed artery and the maximum blood flow in a normal artery. FFR is currently measured invasively using a pressure wire placed across a narrowed artery. An assessment by the BlueCross BlueShield Association Technology Evaluation Center (BCBSA, 2011) concluded that invasive fractional flow reserve guided percutaneous coronary intervention (PCI) results in better outcomes than an angiography alone guided strategy for persons who are undergoing revascularization. The assessment concluded that "The evidence is consistent with prior physiologic data and long-held beliefs that identifying stenoses is insufficient to determine when revascularization is likely to have benefit. If revascularization is anticipated in
patients with angina, evidence supports a conclusion that
FFR-guided PCI results in better outcomes than an
angiography alone-guided strategy."

A medical consultation technology document from the National
Institute for Health and Care Excellence (NICE, 2016) found
that "[t]he case for adopting HeartFlow FFRCT for estimating
fractional flow reserve from coronary CT (CCT) angiography is
supported by the evidence. The technology is non-invasive
and safe, and has a high level of diagnostic accuracy." The
consultation stated that HeartFlow FFRCT should be
considered as an option for patients with stable, recent onset
chest pain of suspected cardiac origin and a clinically
determined intermediate (10% to 90%) risk of coronary artery
disease. The consultation technology document found that,
using HeartFlow FFRCT may avoid the need for invasive
coronary angiography and revascularisation. For correct use,
HeartFlow FFRCT requires access to 64-slice (or above)
coronary CT angiography facilities.

NICE guidance (2017) states that "[t]he case for adopting
HeartFlow FFRCT for estimating fractional flow reserve from
coronary CT angiography (CCTA) is supported by the
evidence........ HeartFlow FFRCT should be considered as an
option for patients with stable, recent onset chest pain who are
offered CCTA as part of the NICE pathway on chest pain.
Using HeartFlow FFRCT may avoid the need for invasive
coronary angiography and revascularisation." The guidance
notes that, for correct use, HeartFlow FFRCT requires access
to 64-slice (or above) CCTA facilities. Because the safety and
effectiveness of FFRCT analysis has not been evaluated in
other patient subgroups, HeartFlow FFRCT is not
recommended in patients who have an acute coronary
syndrome or have had a coronary stent, coronary bypass
surgery or myocardial infarction in the past month.
The American College of Cardiology CathPCI Registry (Messenger, et al., 2017) has announced that they will allow FFRCT as an acceptable noninvasive method of documenting ischemia around the time of revascularization. Documentation of ischemia around the time of revascularization is important to the appropriate use criteria (AUC) for percutaneous coronary interventions (PCI).

Calcium Scoring

Coronary artery calcium (CAC) scoring is a noninvasive test that has been reported to detect the presence of subclinical coronary artery disease (CAD) by measuring the location and extent of calcium in the coronary arteries. Purportedly, the presence of (CAC) has been shown to be strongly correlated with the extent of atherosclerotic plaque as well as the severity of CAD. Tests to determine CAC scoring include multi-slice computed tomography, and electron beam computed tomography (EBCT), also known as ultrafast computed tomography (UFCT).

Ultrafast computed tomography (also known as electron-beam computed tomography [EBCT]) has been shown to be able to quantify the amount of calcium in the coronary arteries, and thus has been primarily investigated as a tool to predict risk of CAD. In ultrafast CT, an electron-beam is magnetically steered along stationary tungsten rings to produce a rotating X-ray beam.

Research has indicated that EBCT is highly sensitive in detecting coronary artery calcification in comparison to other types of CT. Moreover, various studies have shown a strong correlation between EBCT calcium scores and quantities of atherosclerotic plaque. However, there is skepticism about the relationship between EBCT calcium scores and the likelihood of coronary events because of the following factors:
• Calcium does not collect exclusively at sites with severe stenosis
• EBCT calcium scores do not identify the location of specific vulnerable lesions
• Substantial non-calcified plaque is frequently present in the absence of coronary artery calcification
• There are no proven relationships between coronary artery calcification and the probability of plaque rupture.

Some advocates have argued that EBCT scores could be an effective substitute for standard risk factors in predicting the risk of coronary artery disease. However, citing evidence that shows that only a small proportion of asymptomatic individuals with calcified coronary arteries ultimately develop symptomatic coronary artery disease, a 1996 American Heart Association (AHA) scientific statement on coronary artery calcification concludes that the presence of coronary artery calcium is a poor predictor of coronary artery disease risk, and that there is no role for ultrafast CT as a general screening tool to detect atherosclerosis in people who have no symptoms of the disease and no risk factors. More importantly, although a negative scan may mean a low probability of significant artery blockage in asymptomatic people with or without a previous cardiac event (e.g., myocardial infarction, bypass surgery, angioplasty, etc.), an unstable or vulnerable plaque may go undetected by ultrafast CT, and may rupture and cause thrombosis and obstruction of the coronary artery. Detrano (1999) demonstrated that the addition of EBCT data provided no added value to the risk of coronary artery disease risk determined by the Framingham and National Cholesterol Education Program risk models.

Several investigators have examined the potential role of ultrafast CT measurements of coronary artery calcium in ruling out coronary artery disease in patients with atypical anginal symptoms. The AHA report estimates that the negative
predictive value of an ultrafast CT scan in these patients ranges from 90 to 95%, and suggests that a negative study may be useful in determining the need for further work-up with exercise stress testing and/or angiography. It must be realized, however, that ultrafast CT provides only anatomic and not physiologic information. Although ultrafast CT can be used to determine whether calcium is present in the coronary arteries, it cannot replace stress testing and angiography in determining whether lesions result in significant coronary artery obstruction and ischemia. Ultrafast CT is being investigated for this proposed use.

The AHA does not recommend ultrafast CT as a replacement for stress testing and/or angiography in patients with conventional risk factors and in patients with typical anginal chest pain. The increased predictive value of ultrafast CT of the coronary arteries relative to traditional risk factor assessment is not yet defined. Although a greater amount of calcium may indicate a greater likelihood of obstructive disease, studies have shown that site-specificity and exact 1:1 correlations are not well predicted, that is, ultrafast CT can not define the location or amount of obstruction with sufficient accuracy to be of use in predicting risk of coronary artery disease, in diagnosing coronary artery disease, or in planning surgical treatment.

Several studies have shown a variability in repeated measures of coronary calcium by ultrafast CT; therefore, use of serial ultrafast CT scans in individual patients to track the progression or regression of calcium is problematic. Although there is emerging evidence that ultrafast CT may help in identifying the presence of early coronary artery disease in people with known heart disease risk factors, there is no definitive evidence that ultrafast CT can substitute for coronary angiography because the absence of calcific deposits on an ultrafast CT scan does not imply the absence of atherosclerosis. Conversely, the presence of calcium does not secure a diagnosis of significant angiographic narrowing.
There is still a need for further clarification regarding the relationship between calcification, atherosclerosis, and risk of plaque rupture.

The critical issue that defines the utility (or lack thereof) of ultrafast CT is its prognostic value. The evidence in the peer-reviewed medical literature linking detectable coronary calcium to event outcomes such as future coronary bypass surgery, angioplasty, myocardial infarction, and coronary death is limited. Large-scale prospective studies are still needed to define a role for ultrafast CT.

In a review on coronary artery calcium scoring by means of EBCT, Thomson and Hachamovitch (2002) stated that studies have indicated that the very early detection of a coronary artery burden is possible with EBCT. However, both the Prevention Conference V and the ACC/AHA Expert Consensus Document on EBCT have recommended against the routine use of EBCT for screening for CAD in asymptomatic individuals. Moreover, there is no evidence so far to support using the results of EBCT in an asymptomatic patient to select a therapy or to guide referral to invasive investigations. The clinical role of EBCT is yet to be established in terms of screening for disease or risk assessment. Electron beam computed tomography is highly sensitive, but its specificity is low. In fact, when referral to angiography is based on the results of EBCT, referrals will be made for very few patients with normal results while many referrals will be made for those with abnormal results. The outcome will be that, in clinical practice, the observed sensitivity of EBCT will be increased, and the observed specificity will be reduced. To date, there are no well-conducted studies that clearly demonstrate the incremental value of calcium scoring over traditional assessments of risk factors, and the clinical role of EBCT is yet to be established in terms of screening for disease or risk assessment. The authors' view is shared by Redberg and Shaw (2002) who stated that widespread use of EBCT is not recommended.
More research is needed to establish the effectiveness of EBCT in the role of risk factor reduction and prevention of cardiovascular disease. Furthermore, Greenland (2003) stated that "To date, most research on EBT [electron-beam computed tomography] has been observational in nature, based entirely on self-referred patients" and that the "role of EBT remains uncertain" and that "additional randomized trials to define specific roles for EBT in risk prediction" are needed.

These conclusions are consistent with those of the U.S. Preventive Services Task Force (2004), which stated that there is "insufficient evidence to recommend for or against routine screening with ... EBCT [electron beam CT] scanning for coronary calcium for either the presence of severe [coronary artery stenosis] or the prediction of [coronary heart disease] events in adults at increased risk for coronary heart disease." The USPSTF reaffirmed their position in 2009, stating that the evidence is insufficient to assess the balance of benefits and harms of using coronary artery calcification (CAC) score on electron-beam computed tomography (EBCT) to screen asymptomatic men and women with no history of CHD to prevent CHD events.

Guidelines from the American College of Cardiology and the American Heart Association on assessment of cardiovascular risk (Goff et al, 2014) concluded that CAC score may be considered to inform decision making if, after quantitative risk assessment, a risk-based treatment decision is uncertain. This was a grade E recommendation (expert opinion), meaning that "[t]here is insufficient evidence or evidence is unclear or conflicting, but this is what the Work Group recommends." The guidelines state that, on the basis of current evidence, it is the Work Group's opinion that assessments of CAC "show some promise for clinical utility among the novel risk markers, based on limited data." The Work Group noted that a review by Peters et al. (2012) provides evidence to support the contention that assessing CAC is likely to be the most useful of
the current approaches to improving risk assessment among individuals found to be at intermediate risk after formal risk assessment. Further research is recommended in this area.

American College of Cardiology/American Heart Association guidelines (Greenland et al, 2010) have two Class IIa recommendations for screening with calcium scoring, where Class IIa recommendations are defined as those for which “[t]he weight of evidence or opinion is in favor of the procedure or treatment.” Class IIa recommendations for calcium scoring are for asymptomatic patients with an intermediate (10% to 20%) 10-year risk of cardiac events based on the Framingham risk score (FRS) or other global risk algorithm, and for asymptomatic patients 40 years and older with diabetes mellitus. The guidelines state that there are no data demonstrating that serial CAC testing leads to improved outcomes or changes in therapeutic decision making.

Multi-slice (or multi-row detector) CT and spiral (or helical) CT has also been used to quantify calcium in the coronary arteries. Spiral or helical CT differs from conventional CT in that the patient is continuously rotated as he is moved. Multi-slice CT is a technical advance over spiral CT, and uses multiple rows of detector arrays to rapidly obtain multiple slices with one pass. Multi-slice CT differs from ultrafast CT in that the latter has no moving parts, and ultrafast CT scans are faster than with multi-slice CT. One study examined the accuracy of spiral CT in evaluating coronary calcification, using ultrafast CT as the gold standard for comparison, in 33 asymptomatic individuals who were referred for calcium scans. Spiral CT was reported to have a sensitivity of 74 % and a specificity of 70 % compared to ultrafast CT. An assessment of spiral CT and multi-slice CT in screening persons with coronary artery disease by the Canadian Coordinating Office for Health Technology Assessment (2003) found no adequate long-term studies on clinical outcomes of people screened with multi-slice CT or spiral CT. In addition, the assessment failed to identify studies that compared spiral
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CT and multi-slice CT with established screening modalities like risk factor algorithms. The authors noted that the low specificity of spiral CT and multi-slice CT gives rise to concern over false-positive results, and that false-positives may cause harm and expense due to inappropriate and invasive follow-up. The assessment concluded that “[t]here is insufficient evidence at this time to suggest that asymptomatic people derive clinical benefit from undergoing coronary calcification screening using MSCT [multislice CT] or spiral CT scanning.”

In an editorial accompanying a meta-analysis of electron-beam CT for CAD by Pletcher et al (2004), Ewy (2004) explained that “the clinical utility of fast computed tomography (CT) scanners (i.e., the electron beam [EB] and double helical CT scanner) is still limited. Electron beam CT is not ready for prime time.”

An assessment of the literature on calcium scoring by the German Agency for Health Technology Assessment (DAHTA, 2006) concluded that measuring coronary calcium is a "promising" tool for risk stratification, but that many questions remain unanswered about the targeted use in medical practice, including which patient groups should be screened, which calcium score threshold should be applied, and which scoring method should be used.

An assessment prepared for the National Coordinating Centre for Health Technology Assessment (Waugh et al, 2006) found: "CT examination of the coronary arteries can detect calcification indicative of arterial disease in asymptomatic people, many of whom would be at low risk when assessed by traditional risk factors. The higher the CAC score, the higher the risk. Treatment with statins can reduce that risk. However, CT screening would miss many of the most dangerous patches of arterial disease, because they are not yet calcified, and so there would be false-negative results: normal CT followed by a heart attack. There would also be false-positive results in that many calcified arteries will have
normal blood flow and will not be affected by clinically apparent thrombosis: abnormal CT not followed by a heart attack." The NCCHTA assessment concluded: "For CT screening to be cost-effective, it has to add value over risk factor scoring, by producing sufficient extra information to change treatment and hence cardiac outcomes, at an affordable cost per quality-adjusted life-year. There was insufficient evidence to support this. Most of the NSC [National Screening Committee] criteria were either not met or only partially met."

An assessment by the Institute for Clinical Effectiveness and Health Policy (Bardach, 2005) concluded: "Most consensus consider EBCT, SCT and MSCT still at their investigational stage for the following: (i) Detection of coronary artery calcifications as a screening method for asymptomatic subjects with coronary disease; (ii) Detection of coronary artery calcifications in symptomatic patients; and (iii) Assessment of coronary graft viability. No study reported that calcification measuring (plaque characterization) reduces the incidence of coronary events or death."

Detrano and associates (2008) noted that in white populations, computed tomographic measurements of coronary artery calcium (CAC) predict coronary heart disease (CHD) independently of traditional coronary risk factors. However, it is unclear if CAC predicts coronary heart disease in other racial or ethnic groups. These researchers collected data on risk factors and performed scanning for CAC in a population-based sample of 6,722 men and women, of whom 38.6% were white, 27.6% were black, 21.9% were Hispanic, and 11.9% were Chinese. The study subjects had no clinical cardiovascular disease at entry and were followed for a median of 3.8 years. There were 162 coronary events, of which 89 were major events (myocardial infarction or death from coronary heart disease). In comparison with participants with no CAC, the adjusted risk of a coronary event was
increased by a factor of 7.73 among participants with coronary calcium scores between 101 and 300 and by a factor of 9.67 among participants with scores above 300 (p < 0.001 for both comparisons). Among the 4 racial and ethnic groups, a doubling of the calcium score increased the risk of a major coronary event by 15 to 35% and the risk of any coronary event by 18 to 39%. The AUCs for the prediction of both major coronary events and any coronary event were higher when the calcium score was added to the standard risk factors. The authors concluded that the coronary calcium score is a strong predictor of incident coronary heart disease and provides predictive information beyond that provided by standard risk factors in 4 major racial and ethnic groups in the United States. No major differences among racial and ethnic groups in the predictive value of calcium scores were detected. While there were some interesting differences in the prevalence of CAC among the 4 racial and ethnic groups, what remains unclear is how this test should best be employed, or if it should be used at all, to attain better health outcomes for patients.

Calcium scoring may be useful when performed with an otherwise indicated multi-slice cardiac CTA to assess the calcium burden of the coronary arteries to determine whether an adequate scan can be obtained. The calcium score may be estimated with a scout scan, and the injection of contrast withheld if it appears that the patient has a prohibitively high calcium score. This allows one to avoid exposing the patient to unnecessary radiation from contrast if it is clear that the patient's calcium score is so high that an adequate image of the coronary vessels can not be obtained. In such cases, the patient may need invasive angiography to adequately assess the coronary vessels.

Baig and colleagues (2009) stated that CAD is present in 38% to 40% of patients starting dialysis. Both traditional and chronic kidney disease-related cardiovascular risk factors contribute to this high prevalence rate. In patients with end-
Stage renal disease, CAD, especially acute myocardial infarction, is under-diagnosed. Dobutamine stress echocardiography and, to a lesser extent, stress myocardial perfusion imaging have proved useful in screening for CAD in such patients. Coronary artery calcium scoring is less useful. Acute myocardial infarction is associated with high short- and long-term mortality in dialysis patients. Cardiac troponin I appears to be more specific than cardiac troponin T or creatine kinase MB subunits in the diagnosis of acute myocardial infarction.

Ma and colleagues (2010) examined the relationship between coronary calcium score (CCS) and angiographic stenosis on a patient-based or vessel-based analysis. A total of 91 consecutive patients underwent both low-dose 64-slice CT calcium scoring scan as well as conventional angiography of the heart. The total CCS of abnormal coronary angiogram (n = 45) was 297.38 +/- 416.93, whereas that of normal coronary angiogram (n = 46) was 5.37 +/- 9.35 (p < 0.001). The CCS and degree of stenosis were moderately correlated on patient-based or vessel-based analysis (r = 0.517, 0.521, respectively; both p < 0.001). The authors concluded that CCS could reflect the degree of vessel stenosis to some extent, but CCS of zero could not rule out CAD.

Cademartiri et al (2010) compared the coronary artery calcium score (CACS) and CTCA for the assessment of non-obstructive/obstructive CAD in high-risk asymptomatic subjects. A total of 213 consecutive asymptomatic subjects (113 males; mean age of 53.6 +/- 12.4 years) with more than 1 risk factor and an inconclusive or unfeasible non-invasive stress test result underwent CACS and CTCA in an out-patient setting. All patients underwent conventional coronary angiography (CAG). Data from CACS (threshold for positive image: Agatston score 1/100/1,000) and CTCA were compared with CAG regarding the degree of CAD (non-obstructive/obstructive; less than/greater than or = 50 % lumen reduction). The mean calcium score was 151 +/- 403 and the
prevalence of obstructive CAD was 17 % (8 % 1-vessel and 10 % 2-vessel disease). Per-patient sensitivity, specificity, positive and negative predictive values of CACS were: 97 %, 75 %, 45 %, and 100 %, respectively (Agatston greater than or equal to 1); 73 %, 90 %, 60 %, and 94 %, respectively (Agatston greater than or equal to 100); 30 %, 98 %, 79 %, and 87 %, respectively (Agatston greater than or equal to 1,000). Per-patient values for CTCA were 100 %, 98 %, 97 %, and 100 %, respectively (p < 0.05). Computed tomography coronary angiography detected 65 % prevalence of all CAD (48 % non-obstructive), while CACS detected 37 % prevalence of all CAD (21 % non-obstructive) (p < 0.05). The authors concluded that CACS proved inadequate for the detection of obstructive and non-obstructive CAD compared with CTCA. Computed tomography coronary angiography has a high diagnostic accuracy for the detection of non-obstructive and obstructive CAD in high-risk asymptomatic patients with inconclusive or unfeasible stress test results.

Hadamitzky et al (2011) compared CCTA with calcium scoring and clinical risk scores for the ability to predict cardiac events. Patients (n = 2,223) with suspected CAD undergoing CCTA were followed-up for a median of 28 months. The end point was the occurrence of cardiac events (cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalization, and coronary re-vascularization later than 90 days after CCTA). Patients with obstructive CAD had a significantly higher event rate (2.9 % per year; 95 % CI: 2.1 to 4.0) than those without obstructive CAD, having an event rate 0.3 % per year (95 % CI: 0.1 to 0.5; hazard ratio, 13.5; 95 % CI: 6.7 to 27.2; p < 0.001). Coronary computed tomography angiography had significant incremental predictive value when compared with calcium scoring, both with scores assessing the degree of stenosis (p < 0.001) and with scores assessing the number of diseased coronary segments (p = 0.027). The authors concluded that in patients with suspected CAD, CCTA
not only detects coronary stenosis but also improves prediction of cardiac events over and above conventional risk scores and calcium scoring.

In a prospective population-based study, Kavousi et al (2012) evaluated if newer risk markers for CHD risk prediction and stratification improve Framingham risk score (FRS) predictions. A total of 5,933 asymptomatic, community-dwelling participants (mean age of 69.1 years [SD, 8.5]) were included in this analysis. Traditional CHD risk factors used in the FRS (age, sex, systolic blood pressure, treatment of hypertension, total and high-density lipoprotein cholesterol levels, smoking, and diabetes) and newer CHD risk factors (N-terminal fragment of prohormone B-type natriuretic peptide levels, von Willebrand factor antigen levels, fibrinogen levels, chronic kidney disease, leukocyte count, C-reactive protein levels, homocysteine levels, uric acid levels, CACS, carotid intima-media thickness, peripheral arterial disease, and pulse wave velocity). Adding CACS to the FRS improved the accuracy of risk predictions (c-statistic increase, 0.05 [95 % CI: 0.02 to 0.06]; net re-classification index, 19.3 % overall [39.3 % in those at intermediate-risk, by FRS]). Levels of N-terminal fragment of prohormone B-type natriuretic peptide also improved risk predictions but to a lesser extent (c-statistic increase, 0.02 [CI: 0.01 to 0.04]; net re-classification index, 7.6 % overall [33.0 % in those at intermediate-risk, by FRS]). Improvements in predictions with other newer markers were marginal. The authors concluded that among 12 CHD risk markers, improvements in FRS predictions were most statistically and clinically significant with the addition of CACS. Moreover, they stated that further investigation is needed to assess whether risk refinements using CACS lead to a meaningful change in clinical outcome.

Cho and colleagues (2012) stated that the predictive value of CCTA in subjects without chest pain syndrome (CPS) has not been established. These researchers investigated the prognostic value of CAD detection by CCTA and determined
the incremental risk stratification benefit of CCTA findings compared with clinical risk factor scoring and CACS for individuals without CPS. An open-label, 12-center, 6-country observational registry of 27,125 consecutive patients undergoing CCTA and CACS was queried, and 7,590 individuals without CPS or history of CAD met the inclusion criteria. All-cause mortality and the composite of all-cause mortality and non-fatal myocardial infarction were measured. During a median follow-up of 24 months (interquartile range, 18 to 35 months), all-cause mortality occurred in 136 individuals. After risk adjustment, compared with individuals without evidence of CAD by CCTA, individuals with obstructive 2- and 3-vessel disease or left main coronary artery disease experienced higher rates of death and composite outcome (p < 0.05 for both). Both CACS and CCTA significantly improved the performance of standard risk factor prediction models for all-cause mortality and the composite outcome (likelihood ratio p < 0.05 for all), but the incremental discriminatory value associated with their inclusion was more pronounced for the composite outcome and for CACS (C statistic for model with risk factors only was 0.71; for risk factors plus CACS, 0.75; for risk factors plus CACS plus CCTA, 0.77). The net re-classification improvement resulting from the addition of CCTA to a model based on standard risk factors and CACS was negligible. The authors concluded that although the prognosis for individuals without CPS is stratified by CCTA, the additional risk-predictive advantage by CCTA is not clinically meaningful compared with a risk model based on CACS. Therefore, at present, the application of CCTA for risk assessment of individuals without CPS should not be justified.

The American College of Radiology Expert Panel on Cardiac Imaging’s clinical guideline on “Chronic chest pain - low to intermediate probability of coronary artery disease” (Woodard et al, 2012) rendered a “3” rating for CT coronary calcium (a “3” rating denotes the procedure is usually not appropriate).
Dedic et al (2016) noted that it is uncertain whether a diagnostic strategy supplemented by early CCTA is superior to contemporary standard optimal care (SOC) encompassing high-sensitivity troponin assays (hs-troponins) for patients suspected of acute coronary syndrome (ACS) in the emergency department (ED). In a prospective, open-label, multi-center, randomized trial, these researchers examined if a diagnostic strategy supplemented by early CCTA improves clinical effectiveness compared with contemporary SOC. They enrolled patients presenting with symptoms suggestive of an ACS at the ED of 5 community and 2 university hospitals in the Netherlands. Exclusion criteria included the need for urgent cardiac catheterization and history of ACS or coronary revascularization. The primary end-point was the number of patients identified with significant CAD requiring revascularization within 30 days. The study population consisted of 500 patients, of whom 236 (47%) were women (mean age of 54 ± 10 years). There was no difference in the primary end-point (22 [9%] patients underwent coronary revascularization within 30 days in the CCTA group and 17 [7%] in the SOC group [p = 0.40]). Discharge from the ED was not more frequent after CCTA (65% versus 59%, p = 0.16), and length of stay was similar (6.3 hours in both groups; p = 0.80). The CCTA group had lower direct medical costs (€337 versus €511, p < 0.01) and less outpatient testing after the index ED visit (10 [4%] versus 26 [10%], p < 0.01). There was no difference in incidence of undetected ACS. The authors concluded that CCTA, applied early in the work-up of suspected ACS, is safe and associated with less out-patient testing and lower costs. However, they stated that in the era of hs-troponins, CCTA did not identify more patients with significant CAD requiring coronary re-vascularization, shorten hospital stay, or allow for more direct discharge from the ED.

Calcium scores greater than 1000 have been taken as a relative contraindication for CCTA (Maurya et al, 2016).

A calcium score of 1000 is often used as the cutoff value.
above which a CCTA will not be diagnostic (Lin, 2017).

Coronary CT Angiography for Assessment of Coronary Atherosclerosis in Asymptomatic Diabetics

Muhlestein and Moreno (2016) noted that it is well-known that there is a very high risk of cardiovascular complications among diabetic patients. In spite of all efforts at aggressive control of diabetes and its complications, the incidence of cardiovascular morbidity and mortality remains high, including in patients with no prior symptoms, underscoring a possible advantage for appropriate screening of asymptomatic patients for the presence of obstructive CAD. These investigators reviewed the results of studies designed to evaluate a possible role of CCTA in the screening of asymptomatic diabetic patients for possible obstructive CAD. The review of current literature indicated that there is still no method of CAD screening identified that has been shown to reduce the cardiovascular risk of asymptomatic diabetic patients. Thus, the use and value of screening for CAD in asymptomatic diabetic patients remains controversial. CCTA screening has shown promise and has been demonstrated to predict future risk, but as yet has not demonstrated improvement in the outcomes of these high-risk patients. At the present state of knowledge, aggressive risk factor reduction appeared to be the most important primary prevention strategy for all asymptomatic high-risk diabetic patients. However, there remains a great need for better and more sensitive and specific screening methods, as well as more effective treatments that may allow clinicians to more accurately target diabetic patients who really are at high risk. The authors concluded that further large randomized and well-controlled clinical trials are needed to examine if screening for CAD could reduce cardiovascular event rates in patients with diabetes.

Guaricci and colleagues (2018) stated that the prognostic impact of diabetes mellitus (DM) on cardiovascular outcomes is well known. As a consequence of previous studies showing
the high incidence of CAD in diabetic patients and the relatively poor outcome compared to non-diabetic populations, DM is considered as CAD equivalent, which means that diabetic patients are labeled as asymptomatic individuals at high cardiovascular risk. Lessons learned from the analysis of prognostic studies over the past decade have challenged this dogma and now support the idea that diabetic population is not uniformly distributed in the highest risk box. Detecting CAD in asymptomatic high risk individuals is controversial and, what is more, in patients with diabetes is challenging, and that is why the reliability of traditional cardiac stress tests for detecting myocardial ischemia is limited. The authors stated that CCTA represents an emerging non-invasive technique able to explore the atherosclerotic involvement of the coronary arteries and, thus, to distinguish different risk categories tailoring this evaluation on each patient.

Lee and associates (2018) noted that it is well-known that diabetic patients have a high risk of cardiovascular events, and although there has been a tremendous effort to reduce these cardiovascular risks, the incidence of cardiovascular morbidity and mortality in diabetic patients remains high. Thus, the early detection of CAD is necessary in those diabetic patients who are at risk of cardiovascular events. Significant medical and radiological advancements, including CCTA, mean that it is now possible to examine the characteristics of plaques, instead of solely evaluating the calcium level of the coronary artery. Recently, several studies reported that the prevalence of subclinical coronary atherosclerosis (SCA) is higher than expected, and this could impact on CAD progression in asymptomatic diabetic patients. In addition, several reports suggested the potential benefit of using CCTA for screening for SCA in asymptomatic diabetic patients, which might dramatically decrease the incidence of cardiovascular events. For these reasons, the medical interest in SCA in diabetic patients is increasing. The authors concluded that the prevalence of SCA in diabetic patients is high, and the progression of coronary atherosclerosis leads to the onset of
future CV events and is associated with a poor prognosis. Moreover, they stated that although CCTA screening has not yet been demonstrated as improving the outcomes of asymptomatic diabetic patients, it has been shown to be beneficial in predicting future risk, and is promising for screening with an additional technique.

Furthermore, an UpToDate review on “Screening for coronary heart disease in patients with diabetes mellitus” (Bax et al, 2018) states that “In the 2018 Standards of Medical Care in Diabetes, the American Diabetes Association does not recommend routine screening for CHD in asymptomatic patients with diabetes, as outcomes are not improved as long as cardiovascular risk factors are treated. However, in the 2013 ESC/EASD Guidelines on diabetes, pre-diabetes, and cardiovascular disease (CVD), the writing group concludes that in asymptomatic patients routine screening is controversial and still under debate. In addition, the guidelines highlight the need for better definition of the characteristics of the patients who should be screened for CHD, stating that screening for silent myocardial ischemia may be considered in selected high-risk patients with diabetes, such as patients with peripheral artery disease or high coronary artery calcium (CAC) score or with proteinuria”.

**Appendix**

Table 1 can be used to assess if a person has a low or very low pre-test probability of CAD. Alternatively, pre-test probability of CAD can be assessed using the Framingham Risk Scoring Tool available at the following website, with low risk defined as a 10-year risk of less than 10%: Framingham Risk Scoring Tool (http://hp2010.nhlbihin.net/atpiii/calculator.asp?useretype=prof). (For details on Framingham Risk Scoring, see appendix to CPB 0381 - Cardiac Disease Risk Tests)

Table 1: ACC Criteria for Pre-test Probability of CAD by Age, Gender and Symptoms

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Typical / Definite Angina Pectoris</th>
<th>Atypical / Probable Angina Pectoris</th>
<th>Nonanginal Chest Pain</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 39</td>
<td>Men</td>
<td>Intermediate</td>
<td>Intermediate Low</td>
<td>Very Low</td>
<td></td>
</tr>
<tr>
<td>Less than 39</td>
<td>Women</td>
<td>Intermediate</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Very Low</td>
</tr>
<tr>
<td>40-49</td>
<td>Men</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate Low</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>Women</td>
<td>Intermediate Low</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Very Low</td>
</tr>
<tr>
<td>50-59</td>
<td>Men</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate Low</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>Women</td>
<td>Intermediate Low</td>
<td>Very Low</td>
<td>Very Low</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Men</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate Low</td>
<td></td>
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<td>-------</td>
<td>-----------</td>
<td>------</td>
<td>--------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>Women</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate Low</td>
<td></td>
</tr>
</tbody>
</table>

**Key:**

- **High:** greater than 90% pre-test probability
- **Intermediate:** between 10% and 90% pre-test probability
- **Low:** between 5% and 10% pre-test probability
- **Very low:** less than 5% pre-test probability

† No data exist for patients less than 30 years or greater than 69 years, but it can be assumed that prevalence of CAD increases with age. In a few cases, patients with ages at the extremes of the decades listed may have probabilities slightly outside the high or low range.

**Source:** Adapted from Taylor et al., 2010

**List 1: Clinical Classification of Chest Pain**

**Typical angina (definite):**

(i) Substernal chest discomfort with a characteristic quality and duration; and (ii) Provoked by exertion or emotional stress; and (iii) Relieved by rest or nitroglycerin

**Atypical angina (probable):**

Meets 2 of the above criteria.
Non-cardiac chest pain:

Meets 1 or none of the above criteria.


List 2: Contraindications to Exercise Stress Testing

The following contraindications to exercise stress testing are from the AHA/ACC guidelines:

- Acute aortic dissection
- Acute myocardial infarction (within 2 days)
- Acute myocarditis or pericarditis
- Acute pulmonary embolus or pulmonary infarction
- Symptomatic severe aortic stenosis
- Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
- Uncontrolled symptomatic heart failure
- Unstable angina not previously stabilized by medical therapy.

In addition, exercise stress testing is not useful in persons who are unable to exercise, persons on digoxin, persons who have a cardiac conduction abnormality that prevents achievement of an adequate heart rate response, persons on a medication (e.g., beta blockers, other negative chronotropic agents) that cannot be stopped which prevent achievement of an adequate heart rate response, and persons with an uninterpretable electrocardiogram. The American College of Cardiology defines an uninterpretable electrocardiogram as a ventricular paced rhythm, complete left bundle branch block, ventricular preexcitation arrhythmia (Wolfe Parkinson White syndrome), or greater than 1 mm ST segment depression at rest.

List 3: Contraindications to Pharmacological Stress
Testing

The following are contraindications to adenosine or dipyridamole (Persantine) stress testing:

- Active bronchospasm or reactive airway disease;
- Patients taking Persantine (contraindication to adenosine stress testing);
- Patients using methylxanthines (e.g., caffeine and aminophylline) (In general, patients should refrain from ingesting caffeine for at least 24 hours prior to adenosine or dipyridamole administration);
- Severe bradycardia (heart rate less than 40 beats/min);
- Sick sinus syndrome or greater than first-degree heart block (in persons without a ventricular-demand pacemaker);
- Systolic blood pressure less than 90 mm Hg.

The following are contraindications to dobutamine stress testing:

- Atrial tachyarrhythmias with uncontrolled ventricular response;
- History of ventricular tachycardia;
- Left bundle branch block;
- Recent (within the past week) myocardial infarction;
- Significant aortic stenosis or obstructive cardiomyopathy;
- Thoracic aortic aneurysm;
- Uncontrolled hypertension;
- Unstable angina.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+".
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Cardiac computed tomography (CT) angiography:</strong></td>
</tr>
<tr>
<td></td>
<td>CPT codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>0501T</td>
<td>Noninvasive estimated coronary fractional flow reserve (FFR) derived from coronary computed tomography angiography data using computation fluid dynamics physiologic simulation software analysis of functional data to assess the severity of coronary artery disease</td>
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<td>0504T</td>
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<tr>
<td>75571</td>
<td>Computed tomography, heart, without contrast material, with quantitative evaluation of coronary calcium [not covered for serial or repeat calcium scoring]</td>
</tr>
<tr>
<td>75572</td>
<td>Computed tomography, heart, with contrast material, for evaluation of cardiac structure and morphology (including 3D image postprocessing, assessment of cardiac function, and evaluation of venous structure, if performed)</td>
</tr>
<tr>
<td>75573</td>
<td>Computed tomography, heart, with contrast material, for evaluation of cardiac structure and morphology in the setting of congenital heart disease (including 3D image postprocessing, assessment of LV cardiac function, RV structure and function and evaluation of venous structures, if performed)</td>
</tr>
<tr>
<td>75574</td>
<td>Computed tomographic angiography, heart, coronary arteries and bypass grafts (when present), with contrast material, including 3D image postprocessing (including evaluation of cardiac structure and morphology, assessment of cardiac function, and evaluation of venous structures, if performed)</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>Other CPT codes related to the CPB:</td>
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<td>33250 - 33266</td>
<td>Cardiac tissue ablation procedures</td>
</tr>
<tr>
<td>33361 - 33369</td>
<td>Transcatheter aortic valve replacement with prosthetic valve (TAVR/TAVI)</td>
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<tr>
<td>93015 - 93024</td>
<td>Cardiovascular stress testing and ergonovine provocation test</td>
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<td>93650 - 93657</td>
<td>Intracardiac catheter ablation procedures</td>
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<td>ICD-10 codes covered if selection criteria is met (not all-inclusive):</td>
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<td>Drug or chemical induced diabetes mellitus with other circulatory complications [coronary atherosclerosis in symptomatic diabetics]</td>
</tr>
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<td>Type 1 diabetes mellitus with other circulatory complications [coronary atherosclerosis in symptomatic diabetics]</td>
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<td>E11.59</td>
<td>Type 2 diabetes mellitus with other circulatory complications [coronary atherosclerosis in symptomatic diabetics]</td>
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<tr>
<td>E13.59</td>
<td>Other specified diabetes mellitus with other circulatory complications [coronary atherosclerosis in symptomatic diabetics]</td>
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<td>Code</td>
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<tr>
<td>I06.0,</td>
<td>Rheumatic aortic stenosis and rheumatic aortic stenosis with insufficiency [in the setting of persons with suspected paradoxical low-flow, low-gradient symptomatic severe aortic stenosis when transthoracic echocardiography is inconclusive]</td>
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<td>I06.2</td>
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<tr>
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<td>Rheumatic disorders of both mitral and aortic valves, rheumatic disorders of both aortic and tricuspid valves, &amp; combined rheumatic disorders of mitral, aortic and tricuspid valves [in the setting of persons with suspected paradoxical low-flow, low-gradient symptomatic severe aortic stenosis when transthoracic echocardiography is inconclusive]</td>
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<td>I44.7</td>
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<tr>
<td>I45.10 - I45.19</td>
<td>Other and unspecified right bundle-branch block</td>
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<td>Paroxysmal atrial fibrillation, persistent atrial fibrillation, and unspecified atrial fibrillation info [when rate-controlled and 3rd generation Dual-Source CT (DSCT) 120-kv tube voltage is utilized]</td>
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<td>Atria septal defect [aortic erosion in symptomatic members (e.g., chest pain) who have been treated for atrial septal defect with an occlusive device]</td>
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<td>Q21.3</td>
<td>Tetrology of Fallot</td>
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<tr>
<td>Q23.0</td>
<td>Congenital stenosis of aortic valve [in the setting of persons with suspected paradoxical low-flow, low-gradient symptomatic severe aortic stenosis when transthoracic echocardiography is inconclusive]</td>
</tr>
<tr>
<td>Q26.0 - Q26.9</td>
<td>Congenital malformations of great veins</td>
</tr>
<tr>
<td>Q87.40 - Q87.43</td>
<td>Marfan syndrome</td>
</tr>
<tr>
<td>R07.1 - R07.9</td>
<td>Chest pain</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>R94.39</td>
<td>Abnormal result of other cardiovascular function study [covered for evaluation of asymptomatic persons at an intermediate pre-test probability of coronary heart disease by Framingham risk scoring (see Appendix) who have an equivocal or uninterpretable exercise or pharmacological stress test]</td>
</tr>
<tr>
<td>T82.01A - T82.9xxS</td>
<td>Complications of cardiac and vascular prosthetic devices, implants and grafts [when echocardiographic imaging is inconclusive or there is suspicion for paravalvular abscess formation]</td>
</tr>
<tr>
<td>Z01.810</td>
<td>Encounter for preprocedural cardiovascular examination [pre-operative assessment for planned non-coronary cardiac surgeries]</td>
</tr>
<tr>
<td>Z68.41 - Z68.45</td>
<td>Body mass index (BMI) 40.0 or greater [when 3rd generation DSCT 120-kv tube voltage is utilized]</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C38.0</td>
<td>Malignant neoplasm of heart [atrial angiosarcoma]</td>
</tr>
</tbody>
</table>

ICD-10 codes contraindicated for this CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I46.2 - I46.9</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>I47.0 - I47.9</td>
<td>Paroxysmal supraventricular tachycardia, paroxysmal ventricular tachycardia, paroxysmal tachycardia, unspecified</td>
</tr>
<tr>
<td>I49.2 - I49.3</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------------------</td>
</tr>
<tr>
<td>I48.1, I48.3 - I48.4, I48.92</td>
<td>Atrial flutter</td>
</tr>
<tr>
<td>Z68.41 - Z68.45</td>
<td>Body mass index 40 and over, adult</td>
</tr>
<tr>
<td>Z91.041</td>
<td>Radiographic dye allergy status [iodinated contrast material]</td>
</tr>
</tbody>
</table>

**Calcium Scoring:**

**HCPCS codes covered for indications listed in the CPB:**

- **S8092**  
  Electron beam computed tomography (also known as ultrafast CT, cine CT)

**ICD-10 codes covered if selection criteria is met (not all-inclusive):**

- **E08.00 - E09.9**  
  Diabetes mellitus due to underlying condition [asymptomatic persons age 40 years and older]

- **E10.10 - E13.9**  
  Diabetes mellitus [asymptomatic persons age 40 years and older]

- **Z13.6**  
  Encounter for screening for cardiovascular disorders

The above policy is based on the following references:


Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation. 2006;114:1761-1791.

66. German Agency of Health Technology Assessment (DAHTA) at German Institute for Medical Documentation and Information (DIMDI). Computed tomography for the measurement of coronary calcification in asymptomatic risk patients [summary]. Technology Assessment. Cologne, Germany; DIMDI; 2006.


86. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Coronary computed tomographic angiography in the evaluation of patients with acute chest pain. TEC Assessment Program. Chicago, IL: BCBSA; November 2011;26(9).


126. Chen MY, Shanbhag SM, Arai AE. Submillisievert median radiation dose for coronary angiography with a second-generation 320-detector row CT scanner in...


143. Ollendorf DA, Kuba M, Pearson SD. The diagnostic performance of multi-slice coronary computed


150. Soman P, Truong QA, Udelson JE. Noninvasive testing and imaging for diagnosis in patients at low to intermediate risk for acute coronary syndrome. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed July 2017.


Amendment to
Aetna Clinical Policy Bulletin Number: 0228 Cardiac CT,
Coronary CT Angiography, Calcium Scoring and CT
Fractional Flow Reserve

There are no amendments for Medicaid.