

Medical Policy



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Title: Coronary Computed Tomography Angiography with Selective Noninvasive Fractional Flow Reserve

Related Policies:	▪ <i>Contrast-Enhanced Coronary Computed Tomography Angiography (CCTA) for Coronary Artery Evaluation</i>
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Professional / Institutional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With stable chest pain at intermediate risk of coronary artery disease being considered for invasive coronary angiography	Intervention of interest are: • Noninvasive fractional flow reserve measurement following abnormal coronary computed tomography angiography	Comparator of interest are: • Coronary computed tomography angiography without noninvasive fractional flow reserve • Invasive coronary angiography • Other noninvasive functional tests	Relevant outcomes include: • Test accuracy • Test validity • Morbid events • Quality of life • Resource utilization • Treatment-related morbidity

DESCRIPTION

Invasive coronary angiography (ICA) is clinically useful in stable ischemic heart disease when there is coronary artery obstruction that may benefit from revascularization. However, many individuals currently undergoing ICA will not benefit from revascularization. Therefore, if there are noninvasive alternatives to guide decisions about the use of ICA to spare individuals from unnecessary ICA, there is potential to improve health outcomes. Using noninvasive measurement of fractional flow reserve as part of a noninvasive imaging strategy may be beneficial to avoid the need for ICA.

OBJECTIVE

The objective of this evidence review is to evaluate whether a noninvasive imaging strategy using coronary computed tomography angiography with a noninvasive assessment of fractional flow reserve improves net health outcome when used to guide decisions about using invasive coronary angiography in patients with stable chest pain and suspected stable ischemic heart disease.

BACKGROUND

Stable Ischemic Heart Disease

Coronary artery disease (CAD) is a significant cause of morbidity and mortality. Various epidemiologic risk factors have been well studied. Evaluation of obstructive CAD involves quantifying arterial stenoses to determine whether significant narrowing is present. Lesions with stenosis more than 50% to 70% in diameter accompanied by symptoms are generally considered significant. It has been suggested that coronary computed tomography angiography (CCTA) or other noninvasive functional cardiac testing may help rule out CAD and avoid invasive coronary angiography (ICA) in patients with a low clinical likelihood of significant CAD. However, ICA is frequently unnecessary in patients with suspected stable ischemic heart disease, as evidenced by low diagnostic yields for significant obstructive CAD. Patel et al (2010) found that from a sample of over 132,000 ICAs, 48.8% of elective ICAs performed in patients with stable angina did not detect obstructive CAD (left main stenosis $\geq 50\%$ or $\geq 70\%$ in a major epicardial or branch > 2.0 mm in diameter).¹ Invasive coronary angiography is clinically useful when patients with stable angina have failed optimal medical therapy and may benefit from revascularization. A noninvasive imaging test performed before ICA as a gatekeeper, which can distinguish candidates who may benefit from early revascularization (eg, patients with unprotected left main stenosis $\geq 50\%$ or hemodynamically significant disease) from those unlikely to benefit, could avoid unnecessary invasive procedures and their potential adverse consequences. Moreover, for the large majority of patients with stable ischemic heart disease, revascularization offers no survival advantage over medical therapy; few might benefit from ICA if they have not first failed optimal medical therapy.²

Clinical Risk Prediction for Stable Ischemic Heart Disease

A 2012 collaborative medical association guideline for the diagnosis and management of patients with stable heart disease lists several class I recommendations on the use of noninvasive testing in patients with suspected stable ischemic heart disease.³ A class I recommendation indicates that a test should be performed. In general, patients with at least intermediate risk (10% to 90% risk by standard risk prediction instruments) are recommended to have some type of test, the choice depending on the interpretability of the electrocardiogram, the capacity to exercise, and the presence of comorbidity. In 2023, an updated collaborative medical association guideline for patients with chronic coronary disease was published to provide an update to and consolidate new evidence since the 2012 guideline for the diagnosis and management of patients with stable heart disease and the corresponding 2014 focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease.⁴ A class 1 recommendation states that "in patients with chronic coronary disease, it is recommended that risk stratification incorporate all available information, including noninvasive, invasive, or both cardiovascular diagnostic testing results or use validated risk scores to classify patients as low (<1%), intermediate (1%-3%), or high (>3%) yearly risk for cardiovascular death or nonfatal myocardial infarction." The text further states that noninvasive test results alone are insufficient to adequately risk stratify patients with chronic coronary disease, and the additional information improves risk prediction.

Clinical prediction scores or models have been developed to help estimate the pretest probability of CAD in individuals with stable chest pain. Diamond and Forrester (1979) developed the original version of a commonly cited clinical prediction model based on age, sex, and type of pain symptoms.^{5,6} Versteyle et al (2011) published a comparison of clinical prediction results for the Diamond and Forrester (1979) model, the Framingham risk score, the PROCAM risk score, and the SCORE risk estimation model.⁷ Min et al (2015) published another model,⁸ and in 2016 a CAD consortium developed an online calculator.^{9,10}

Gatekeepers to Invasive Coronary Angiography

Imposing an effective noninvasive gatekeeper strategy with one or more tests before planned ICA to avoid unnecessary procedures is compelling. The most important characteristic of a gatekeeper test is its ability to accurately identify and exclude clinically insignificant disease where revascularization would offer no potential benefit. From a diagnostic perspective, an optimal strategy would result in few false-negative tests while avoiding an excessive false-positive rate—it would provide a low post-test probability of significant disease. Such a test would then have a small and precise negative likelihood ratio and high negative predictive value. An effective gatekeeper would decrease the rate of ICA while increasing the diagnostic yield (defined by the presence of obstructive CAD on ICA). At the same time, there should be no increase in major adverse cardiac events (MACE). A clinically useful strategy would satisfy these diagnostic performance characteristics and impact the outcomes of interest. Various tests have been proposed as potentially appropriate for a gatekeeper function before planned ICA, including CCTA, magnetic resonance imaging, single-photon emission computed tomography, positron emission tomography, and stress echocardiography. More recently, adding noninvasive measurement of fractional flow reserve using CCTA has been suggested, combining functional and anatomic information.

Fractional Flow Reserve

Invasively measured fractional flow reserve evaluates the severity of ischemia caused by coronary artery obstructions and can predict when revascularization may be beneficial.^{11,12,13} Fractional flow reserve has not been used as a diagnostic test for ischemic heart disease, but as a test to evaluate the degree of ischemia caused by stenosis.

Invasive fractional flow reserve is rarely used in the U.S. to guide percutaneous coronary intervention (PCI). Pothineni et al (2016), using the National Inpatient Sample, reported that 201,705 PCIs were performed in 2012, but just 21,365 fractional flow reserve procedures.¹⁴ Assuming the intention of fractional flow reserve is to guide PCI, it would represent just 4.3% of PCI procedures. Whether noninvasively obtained fractional flow reserve will influence decisions concerning ICA, over and above anatomic considerations, is therefore important to establish empirically.

Randomized controlled trials and observational studies have demonstrated that fractional flow reserve-guided revascularization can improve cardiovascular outcomes, reduce revascularizations, and decrease costs.¹⁵ For example, the Fractional Flow Reserve versus Angiography for Multivessel Evaluation trial randomized 1005 patients with multivessel disease and planned PCI.^{13,16} At 1 year, compared with PCI guided by angiography alone, fractional flow reserve-guided PCI reduced the number of stents placed by approximately 30%, followed by lower rates (13.2% vs. 18.3%) of MACE (myocardial infarction, death, repeat revascularization) and at a lower cost. The clinical benefit persisted through 2 years, although by 5 years, event rates were similar between groups.¹⁷

European guidelines (2013) for stable CAD have recommended that fractional flow reserve be used "to identify hemodynamically relevant coronary lesion(s) when evidence of ischaemia is not available" (class Ia), and "[r]evascularization of stenoses with fractional flow reserve <0.80 is recommended for patients with angina symptoms or a positive stress test."¹⁸ A 2019 European guideline on chronic coronary syndromes recommends to "consider revascularization on top of medical therapy" in patients without evidence of ischaemia but with fractional flow reserve ≤ 0.80 .¹⁹ Other guidelines (2014) have recommended using "fractional flow reserve to identify haemodynamically relevant coronary lesion(s) in stable patients when evidence of ischaemia is not available" (class Ia recommendation).²⁰ The U.S. guidelines (2012) have stated that a fractional flow reserve of ≤ 0.80 provides level Ia evidence for revascularization for "significant stenoses amenable to revascularization and unacceptable angina despite guideline directed medical therapy."³ A 2023 U.S. guideline for patients with chronic coronary disease notes the following for patients with fractional flow reserve of 0.80 or less: "consideration of revascularization, antianginal therapy as per guidelines."⁴ Also, the importance of fractional flow reserve in decision making appears prominently in the 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease.²¹

Measuring fractional flow reserve during ICA can be accomplished by passing a pressure-sensing guidewire across a stenosis. Coronary hyperemia (increased blood flow) is then induced and pressure distal and proximal to the stenosis is used to calculate flow across it. Fractional flow reserve is the ratio of flow in the presence of a stenosis to flow in its absence. Fractional flow reserve levels less than 0.75 to 0.80 are considered to represent significant ischemia while those 0.94 to 1.0 are considered normal. Measurement is valid in the presence of serial stenoses, is

unaffected by collateral blood flow,²² and reproducibility is high.²³ Potential complications include adverse events related to catheter use such as vessel wall damage (dissection); the time required to obtain fractional flow reserve during a typical ICA is less than 10 minutes.

Fractional flow reserve using CCTA requires at least 64-slice CCTA and cannot be calculated when images lack sufficient quality²⁴, (11% to 13% in recent studies, eg, in obese individuals [body mass index, >35 kg/m²])^{25,26,27,28}. The presence of dense arterial calcification or an intracoronary stent can produce significant beam-hardening artifacts and may preclude satisfactory imaging. The presence of an uncontrolled rapid heart rate or arrhythmia hinders the ability to obtain diagnostically satisfactory images. Evaluation of the distal coronary arteries is generally more difficult than the visualization of the proximal and mid-segment coronary arteries due to greater cardiac motion and the smaller caliber of coronary vessels in distal locations.

Noninvasive Fractional Flow Reserve Measurement

Fractional flow reserve can be modeled noninvasively using images obtained during CCTA²⁹, (HeartFlow software termed FFR_{CT}). The process involves constructing a digital model of coronary anatomy and calculating fractional flow reserve across the entire vascular tree using computational fluid dynamics. Fractional flow reserve using CCTA can also be used for "virtual stenting" to simulate how stent placement would be predicted to improve vessel flow.³⁰

REGULATORY STATUS

In November 2014, FFR_{CT} simulation software (HeartFlow) was cleared for marketing by the FDA through the de novo 510(k) process (class II, special controls; FDA product code: PJA). In January 2016, the FFR_{CT} v2.0 device was cleared through a subsequent 510(k) process. In July 2025, HeartFlow FFR_{CT} is approved as part of Heartflow Analysis with the following indications for use.

"The Heartflow Analysis is an AI-based medical device software for the clinical quantitative and qualitative analysis of previously acquired Computed Tomography DICOM data for adult patients (ages 22 years and older) with suspected coronary artery disease. It provides anatomic data, plaque localization and characterization, as well as the calculations of FFR_{CT}, a coronary physiological simulation, computed from simulated pressure, velocity and blood flow information obtained from a 3D computer model generated from static coronary CT images. The Heartflow Analysis is intended to support the risk assessment and functional evaluation of coronary artery disease. The Heartflow Analysis is provided to support qualified clinicians to aid in the evaluation and risk assessment of coronary artery disease. The Heartflow Analysis is intended to be used by qualified clinicians in conjunction with the patient's clinical history, symptoms, and other diagnostic tests, as well as the clinician's professional judgment."

In April 2022, DeepVessel® FFR software (Keya Medical) received FDA approval through the 510(k) process.

DeepVessel FFR software is cleared:

"for the clinical quantitative and qualitative analysis of previously acquired Computed Tomography [CT] DICOM data for clinically stable symptomatic patients with coronary artery disease. It provides DVFFR (a CT-derived FFR measurement) computed from static coronary CTA images using deep learning neural networks that encode imaging, structural, and functional

characteristics of coronary arteries through learning. DEEPVESSEL FFR analysis is intended to support the functional evaluation of coronary artery disease. The results of the analysis are provided to support qualified clinicians to aid in the evaluation and assessment of coronary arteries. DEEPVESSEL FFR results are intended to be used by qualified clinicians in conjunction with the patient's clinical history, symptoms, and other diagnostic tests, as well as the clinician's professional judgment."

POLICY

- A. The use of noninvasive fractional flow reserve following a positive coronary computed tomography angiography (see Policy Guidelines) may be considered **medically necessary** to guide decisions about the use of invasive coronary angiography in individuals with stable chest pain at intermediate risk of coronary artery disease (i.e., suspected or presumed stable ischemic heart disease).
- B. The use of noninvasive fractional flow reserve not meeting the criteria outlined above is considered **experimental / investigational**.

POLICY GUIDELINES

- A. Fractional flow reserve using coronary computed tomography angiography requires at least 64-slice coronary computed tomography angiography and cannot be calculated when images lack sufficient quality (11% to 13% in recent studies; e.g., in obese individuals [body mass index, $>35 \text{ kg/m}^2$]). The presence of dense arterial calcification or an intracoronary stent can produce significant beam-hardening artifacts and may preclude satisfactory imaging. The presence of an uncontrolled rapid heart rate or arrhythmia hinders the ability to obtain diagnostically satisfactory images. Evaluation of the distal coronary arteries is generally more difficult than visualization of the proximal and mid-segment coronary arteries due to greater cardiac motion and the smaller caliber of coronary vessels in distal locations.

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RATIONALE

This evidence review was created using searches of the PubMed database. The most recent literature update was performed through April 8, 2026.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY WITH SELECTIVE NONINVASIVE FRACTIONAL FLOW RESERVE

Clinical Context and Test Purpose

The purpose of noninvasive fractional flow reserve measurement following positive coronary computed tomography angiography (CCTA) in individuals with stable chest pain at intermediate risk of coronary artery disease (CAD) being considered for invasive coronary angiography (ICA) is to select individuals who may be managed safely with observation only, instead of undergoing ICA in the short term.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with stable chest pain at intermediate risk of CAD (ie, with suspected or presumed stable ischemic heart disease) who are being considered for ICA. Individuals may have undergone prior noninvasive testing and been treated for presumed stable angina.

Interventions

The test being considered is noninvasive fractional flow reserve measurement when CCTA shows evidence of coronary artery stenosis.

Comparators

The following tests are currently being used: CCTA and conventional noninvasive imaging tests. Individuals may receive CCTA, which may be performed alone without fractional flow reserve measurement. These individuals may proceed directly to ICA. Conventional noninvasive imaging tests providing functional information, including myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT), stress echocardiography, and cardiac positron emission tomography (PET), may be used before ICA. Cardiovascular magnetic resonance imaging (MRI) is also an option.

Outcomes

The general outcomes of interest are test accuracy and validity, morbid events, quality of life, resource utilization, and treatment-related morbidity. The final outcomes of interest include ICA rates, ICA without obstructive CAD, major adverse cardiovascular events (MACE), and adverse events attributed to testing and treatment. Rates of ICA and treatment-related morbidity are typically short-term (eg, ≤ 3 months). Rates of subsequent ICA, treatment-related morbidity, MACE, quality of life, and resource utilization ascertained over a period of 1 to 3 years are also of interest.

The intermediate outcome of interest is the ability of the test to distinguish clinically significant CAD for which revascularization may provide benefit.

Study Selection Criteria

For the evaluation of clinical validity of this test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard (describe the reference standard);
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

Meta-Analyses of Per-Patient Diagnostic Accuracy

Pontone et al (2020) conducted a meta-analysis of 77 studies that evaluated the accuracy of noninvasive cardiovascular imaging modalities.³¹ Wu et al (2016) and Danad et al (2017) each had 5 studies contributing results to 2 meta-analyses^{32,33} that evaluated the diagnostic accuracy of fractional flow reserve measurement using CCTA with patients as the unit of analysis. Only the U.S. Food and Drug Administration (FDA)-cleared HeartFlow FFR_{CT} software has been evaluated prospectively across multiple sites. Three small retrospective studies have reported per-patient performance characteristics for the prototype Siemens workstation-based software.^{34,35,36} The 3 HeartFlow FFR_{CT} studies used successive software versions with reported improvement in specificity (from 54% to 79%) between versions 1.2 and 1.4.^{25,28,37} The Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT) Trial, the basis for device clearance by the FDA, was conducted at 11 sites in 8 countries (Canada, European Union, Asia).²⁸ Although not examined in the included meta-analyses, subgroup analyses suggested little variation in results by sex and age.³⁸ Effectively, the entirety of the data was obtained in patients of White or Asian descent; almost all patients were appropriate for testing according to the FDA clearance. More recent studies have evaluated machine learning (also known as deep learning) artificial intelligence algorithms for determining fractional flow reserve using CCTA, which may confound comparisons between studies that used this technology and older studies that did not.

Pontone et al (2020) performed a meta-analysis of 77 studies published through March 2017 that reported patient-level results of noninvasive imaging modalities in patients with stable CAD (either suspected or known), 7 of which were prospective studies that evaluated fractional flow reserve measurement using CCTA.³¹ No heterogeneity was found among these 7 studies ($I^2=0\%$). Per-patient and per-vessel meta-analyses were performed. Five of the 7 studies specific to fractional flow reserve measurement using CCTA reported per-patient results. The pooled per-patient results showed that fractional flow reserve measurement using CCTA had a high sensitivity and specificity (90% [$I^2=46.1\%$] and 69% [$I^2=88\%$], respectively). Among the other imaging modalities, both sensitivity and specificity were high for stress cardiac magnetic resonance (87% and 88%), PET (88% and 86%), and CCTA plus stress myocardial computed tomography perfusion (89% and 83%). Alone, CCTA had high sensitivity (93%) but poor specificity (42%). The other imaging modalities did not perform as well on a per-patient level (ie, stress echocardiogram, stress SPECT, and stress myocardial computed tomography perfusion).

Danad et al (2017) included 23 studies published between January 2002 and February 2015 evaluating the diagnostic performance of CCTA, fractional flow reserve measurement using CCTA, SPECT, stress echocardiography, MRI, or ICA compared with an invasive fractional flow reserve reference standard.³³ The 3 included fractional flow reserve measurement using CCTA studies used the HeartFlow FFR_{CT} software and had performed fractional flow reserve in at least 75% of patients. A cutoff of 0.75 defined significant stenosis in 8 (32%) studies and the remainder 0.80 (the current standard used in all fractional flow reserve measurement using CCTA studies). Per-patient and per-vessel meta-analyses were performed. Study quality was assessed using Quality

Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2)³⁹; no significant biases were identified in fractional flow reserve measurement using CCTA studies, but a high risk of biased patient selection was judged in 10 (43.4%) of the other studies. HeartFlow funded the Open Access publication; one author was a consultant to, and another was a cofounder of, the company.

On the patient level, MRI had the highest combined sensitivity (90%) and specificity (94%) for invasive fractional flow reserve, but these were estimated from only 2 studies (70 patients).³³ Fractional flow reserve measurement using CCTA had similar sensitivity, but lower specificity, and, accordingly, a lower positive likelihood ratio than MRI. The negative likelihood ratios were low (lower is better) for both fractional flow reserve measurement using CCTA and MRI; however, the confidence interval (CI) was narrower for fractional flow reserve measurement using CCTA due to a larger sample. Alone, CCTA had a slightly higher negative likelihood ratio. Results for the per-vessel area under the summary receiver operating characteristic curve were similar except for CCTA, for which per-patient results were considerably worse (eg, C statistic of 0.57 vs. 0.85). Reviewers noted heterogeneity in many estimates (eg, CCTA sensitivity, $I^2=80\%$). Finally, pooled results for some imaging tests included few studies (see Table 1 for detailed results).

Wu et al (2016) identified 7 studies (833 patients, 1377 vessels) comparing fractional flow reserve measurement using CCTA with invasively measured fractional flow reserve from searches of PubMed, Cochrane, EMBASE, Medion, and meeting abstracts through January 2016.³² Studies included patients with established or suspected stable ischemic heart disease. In addition to the 3 fractional flow reserve measurement using CCTA studies pooled by Danad et al (2017), an additional study using HeartFlow technique (44 patients; 48 vessels) and 3 additional studies (180 patients; 279 vessels) using Siemens cFFR software (not FDA approved or cleared) were identified. An invasive fractional flow reserve cutoff of 0.80 was the reference standard in all studies. Per-patient results reported in 5 studies were pooled and are reported in Table 1. All studies were rated at low risk of bias and without applicability concerns using the QUADAS-2 tool.³⁹ Appropriate bivariate meta-analyses (accounting for correlated sensitivity and specificity) were used.

As expected given study overlap, fractional flow reserve measurement using CCTA performance characteristics were similar to those reported by Danad et al (2017), but with slightly higher specificity (Table 1). The pooled per-vessel C statistic was lower (0.86) than the per-patient result (0.90). No evidence of publication bias was detected, but the number of studies was too small to assess adequately. Reviewers noted that in 2 studies fractional flow reserve measurement using CCTA results were uninterpretable in 12.0%²⁸, and 8.2%⁴⁰, of participants.

An et al (2023) conducted a meta-analysis of machine learning-based methods of determining fractional flow reserve compared to invasive methods.⁴¹ A total of 13 studies in patients with suspected or confirmed CAD were combined for the analysis. Characteristics of the studies were not provided, including the potential for bias, but the authors stated that none of the studies were "large sample size diagnostic performance studies". Machine learning fractional flow reserve had a lower sensitivity and higher specificity than invasive fractional flow determination (0.80 vs. 0.87; $p<.01$ and 0.86 vs. 0.35; $p<.01$, respectively). Heterogeneity for all assessments was high (I^2 , 57.12% to 94.52%) and the authors noted that machine learning methods differed among studies.

Table 1. Pooled Per-Patient Diagnostic Performance of Noninvasive Tests for Invasive Fractional Flow Reserve

Test	Studies	N	Sensitivity (95% CI), %	Specificity (95% CI), %	C	LR+ (95% CI)	LR- (95% CI)
Pontone et al (2020) ^{31,}							
Stress echocardiography	7	361	64 (56 to 71)	84 (78 to 89)	NR	3.51 (2.53 to 4.87)	0.45 (0.35 to 0.57)
Stress SPECT	10	682	71 (66 to 76)	79 (74 to 83)	NR	2.94 (1.96 to 4.40)	0.42 (0.28 to 0.62)
PET	4	609	88 (83 to 92)	86 (82 to 89)	NR	6.35 (4.45 to 9.07)	0.13 (0.06 to 0.28)
Stress cardiac magnetic resonance	14	1085	87 (84 to 90)	88 (85 to 90)	NR	6.65 (5.30 to 8.34)	0.15 (0.12 to 0.19)
CCTA	14	1478	93 (91 to 95)	42 (39 to 46)	NR	1.72 (1.35 to 2.18)	0.17 (0.10 to 0.30)
Stress perfusion computed tomography	6	410	79 (73 to 84)	88 (82 to 92)	NR	5.15 (2.22 to 11.92)	0.26 (0.16 to 0.42)
Fractional flow reserve using CCTA	5	664	90 (86 to 94)	69 (64 to 74)	NR	2.68 (1.66 to 4.34)	0.16 (0.11 to 0.23)
CCTA + stress perfusion computed tomography	4	248	89 (84 to 94)	83 (74 to 90)	NR	4.72 (2.60 to 8.57)	0.13 (0.08 to 0.21)
Danad et al (2017) ^{33,}							
MRI	2	70	90 (75 to 97)	94 (79 to 99)	0.94	10.3 (3.14 to 33.9)	0.12 (0.05 to 0.30)
Fractional flow reserve using CCTA	3	609	90 (85 to 93)	71 (65 to 75)	0.94	3.3 (1.78 to 6.25)	0.16 (0.11 to 0.23)
CCTA	4	694	90 (86 to 93)	39 (34 to 44)	0.57	1.5 (1.25 to 1.90)	0.22 (0.10 to 0.50)
Stress echocardiography	2	115	77 (61 to 88)	75 (63 to 85)	0.82	3.0 (1.94 to 4.65)	0.34 (0.17 to 0.66)
SPECT	3	110	70 (59 to 80)	78 (68 to 87)	0.79	3.4 (1.04 to 11.1)	0.40 (0.19 to 0.83)
ICA	2	954	69 (65 to 75)	67 (63 to 71)	0.75	2.5 (1.25 to 5.13)	0.46 (0.39 to 0.55)

Test	Studies	N	Sensitivity (95% CI), %	Specificity (95% CI), %	C	LR+ (95% CI)	LR- (95% CI)
Wu et al (2016) ³² ,							
Fractional flow reserve using CCTA	5	833	89 (85 to 93)	76 (64 to 84)	0.90	3.7 (2.41 to 5.61)	0.14 (0.09 to 0.21)
An et al (2023) ⁴¹ ,							
Fractional flow reserve using machine learning	13	NR	0.80 (0.76 to 0.83)	0.86 (0.79 to 0.91)	NR	5.8	0.22
Fractional flow reserve using invasive methods	12	NR	0.87 (0.84 to 0.90)	0.35 (0.28 to 0.43)	NR	1.3	0.36

CCTA: coronary computed tomography angiography; CI: confidence interval; ICA: invasive coronary angiography; LR: likelihood ratio; MRI: magnetic resonance imaging; NR: not reported; PET: positron emission tomography; SPECT: single-photon emission computed tomography.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Comparative Studies

Di Pietro et al (2025) conducted a meta-analysis to evaluate the clinical impact of noninvasive CCTA-derived fractional flow reserve as a first-line strategy in patients with symptomatic stable CAD.⁴² The analysis included 5 studies (3 RCTs, 2 observational) with 5282 patients (CCTA fractional flow reserve, n=2,604; control, n=2,678). Of note, a few of the included studies, including the PLATFORM, FORECAST, and TARGET studies, are described in more detail in the sections below. The control group underwent standard noninvasive cardiovascular testing, including CCTA alone, stress echocardiography, myocardial perfusion imaging (SPECT/PET), cardiac MRI, or direct referral to ICA. Compared to controls, CCTA-derived fractional flow reserve was associated with lower overall ICA rates (odds ratio [OR], 1.57; 95% CI, 1.36 to 1.81; p<.001) and significantly reduced ICA without obstructive CAD (OR, 6.63; 95% CI, 4.79 to 9.16; p<.001). However, CCTA-derived fractional flow reserve led to higher rates of coronary revascularization (OR, 0.48; 95% CI, 0.38 to 0.62; p<.001). No significant differences were observed in 1-year MACE (OR, 1.11; 95% CI, 0.86 to 1.44; p=.42), nonfatal myocardial infarction (MI) (OR, 0.73; 95% CI, 0.41 to 1.33; p=.31), all-cause mortality (OR, 1.29; 95% CI, 0.47 to 3.54; p=.63), or unplanned revascularization for angina (OR, 0.99; 95% CI, 0.65 to 1.49; p=.95).

PLATFORM Study

The Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts (PLATFORM) study compared diagnostic strategies with or without fractional flow reserve measurement using CCTA in patients with suspected stable angina but without known CAD.^{43,44} The study was conducted at 11 European Union sites. All testing was nonemergent. Patients were divided into 2 strata, according to whether the test planned before study enrollment was: (1) noninvasive or (2) ICA (the patient population of interest in this evidence review). Patients were enrolled in consecutive cohorts, with the first cohort undergoing a usual care strategy followed by a second cohort provided CCTA with fractional flow reserve measurement using CCTA performed when requested (recommended if stenoses $\geq 30\%$ were identified). Follow-up was scheduled for 90 days and 6 and 12 months after entry (99.5% of patients had 1-year follow-up data). Funding was provided by HeartFlow, and multiple authors reported receiving fees, grants, and/or support from HeartFlow. Data analyses were performed by the Duke Clinical Research Institute.

Invasive coronary angiography without obstructive disease ("no stenosis $\geq 50\%$ by core laboratory quantitative analysis or invasive fractional flow reserve < 0.80 ") at 90 days was the primary endpoint in patients with planned invasive testing. Secondary endpoints included ICA without obstructive disease following planned noninvasive testing, and (1) MACE at 1 year defined as a composite of all-cause mortality, MI, and urgent revascularization, and (2) MACE and vascular events within 14 days. Quality of life was evaluated using the Seattle Angina Questionnaire, and EuroQol-5D (5-item and 100-point visual analog scale). The CCTA studies were interpreted by site investigators; quantitative coronary angiography measurements were performed at a central laboratory, as was fractional flow reserve measurement using CCTA. Cumulative radiotherapy was also assessed. A sample size of 380 patients in the invasive strata yielded a 90% power to detect a 50% decrease in the primary endpoint given a 30% event rate (ICA without obstructive disease) with a usual care strategy and a dropout rate up to 10%.

Invasive coronary angiography was planned in 380 participants, of whom 193 (50.8%) had undergone prior noninvasive testing. The mean pretest probability in the planned ICA strata was approximately 50% (51.7% and 49.4% in the 2 groups). Fractional flow reserve measurement using CCTA was requested in 134 patients and successfully obtained in 117 (87.3%) patients. At 90 days, 73.3% of those in the usual care group had no obstructive findings on ICA compared with 12.4% in the fractional flow reserve measurement using CCTA group based on core laboratory readings (56.7% and 9.3% based on site readings). The difference was similar in a propensity-matched analysis of a subset of participants ($n=148$ from each group, or 78% of the entire sample). Prior noninvasive testing did not appear associated with nonobstructive findings. Rates of MACE were low and did not differ between strategies. Mean level of radiation exposure through 1 year was also similar in the usual care group (10.4 mSv) and the planned ICA group (10.7 mSv). No differences in quality of life were found between groups.⁴⁵

Results of the PLATFORM study supported the notion that, in patients with planned ICA, fractional flow reserve measurement using CCTA can decrease the rate of ICAs and unnecessary procedures (finding no significant obstructive disease) and that fractional flow reserve measurement using CCTA may provide clinically useful information to physicians and patients. Study limitations included a nonrandomized design; high rate of no obstructive disease with a usual care strategy (73.3%), which was higher than the 30% rate assumed in the sample size estimates; and a sample size that was small with respect to evaluating adverse cardiac events.

Although finding a large effect in patients with planned invasive testing, the nonrandomized design limits causal inferences and certainty in the magnitude of the effect. The propensity-matched analysis (in a matched subset) offers some reassurance, but the sample size was likely too small to provide robust results.

PRECISE Study

The PRECISE pragmatic RCT compared fractional flow reserve using CCTA with standard care (stress testing or catheterization) in patients with stable chest pain.⁴⁶ The trial enrolled 2103 patients from North America and Europe. The primary endpoint was a composite of clinical efficiency (invasive catheterization without obstructive CAD) and safety (death or nonfatal MI). The primary event rate was 4.2% in the fractional flow reserve using CCTA group vs 11.3% in the standard care group (hazard ratio [HR], 0.35; 95% CI, 0.25 to 0.50). Fractional flow reserve using CCTA significantly reduced invasive catheterizations without obstructive CAD (2.6% vs 10.2%; HR, 0.24; 95% CI, 0.156 to 0.36). Revascularizations were increased in the fractional flow reserve group (9.2% vs 5.2%); however, all but 1 were adjudicated to be ischemia driven. Safety components, including death and MI, showed no significant difference.

FORECAST Study

The Fractional FLOW Reserve Derived from Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain (FORECAST) study evaluated whether fractional flow reserve using CCTA improved economic and clinical outcomes as compared to standard care in 1400 patients with stable chest pain who presented to 11 rapid access chest pain clinics in the United Kingdom.⁴⁷ This open-label study randomly assigned patients to a usual care strategy based on clinical pathways (n=700) or an experimental strategy of CCTA with selective fractional flow reserve (n=700). In the usual care group, patients with a high pre-test likelihood of significant coronary disease could be referred for ICA, while those with an intermediate pre-test likelihood were referred for non-invasive evaluation, which could include stress testing and CCTA without fractional flow reserve. In the experimental group, all patients underwent CCTA as the initial test and were then selectively referred for fractional flow reserve if the CCTA demonstrated a stenosis of $\geq 40\%$ in a coronary artery segment of diameter suitable for revascularization by either a coronary stent or coronary artery bypass graft surgery.

The primary endpoint of FORECAST was cardiovascular costs over 9 months of follow-up.⁴⁷ Secondary endpoints included assessments of quality of life, angina status, and major adverse cardiac and cerebrovascular events (MACCE). In the standard care group, 439 (63%) underwent CCTA as the initial test, 187 (27%) had an initial stress test, and 47 (7%) underwent ICA. In the experimental group, 674 (96%) underwent CCTA and 254 (38%) were selected for a fractional flow reserve analysis per protocol with 5 additional patients referred for fractional flow reserve who did not meet protocol criteria. Of these 259 patients, 220 had fractional flow reserve performed; 39 patients had technical issues resulting in scans that could not be analyzed. Mean total cardiac costs at 9 months of follow-up were slightly higher in the experimental versus standard care group; however, the difference in mean costs was not significant ($p=.10$). For the major secondary endpoints, no significant differences between the groups were noted: improvement in quality of life ($p=.61$), improvement in angina severity ($p=.22$), and MACCE occurrence ($p=.80$). The experimental strategy was associated with a significant reduction in ICA (19% vs. 25%; $p=.01$). Limitations of this study include its open-label design, costs were based on UK National Health Service cost tariffs and therefore may not be generalizable to other

countries, and the precise rate of CCTA in the standard arm could not be anticipated as national guidelines were revised during the planning stage of the FORECAST study.

TARGET Study

The TARGET RCT (Effect of On-Site CT-Derived Fractional Flow Reserve on the Management of Decision Making for Patients With Stable Chest Pain) evaluated the clinical and economic effect of on-site CCTA fractional flow reserve using machine learning in patients with stable coronary artery disease and an intermediate stenosis on CCTA.⁴⁸ The study took place at 6 tertiary hospitals across China. Enrolled patients had an intermediate to high pretest probability of obstructive CAD and a CCTA demonstrating stenosis ranging from 30% to 90% in ≥ 1 major coronary artery. Patients were randomly assigned to the CCTA fractional flow reserve care group (n=608) (guideline-directed medical therapy or ICA guided by on-site CCTA fractional flow reserve) or the usual care group (n=608) (guideline-directed medical therapy or ICA guided by stress tests). The DEEPVESSEL device, which simulates fractional flow reserve values using a deep learning algorithm, was used for patients in the CCTA fractional flow reserve care group. If the CCTA fractional flow reserve was ≤ 0.80 in 1 or more major coronary arteries, the patient was referred directly for ICA; if the CCTA fractional flow reserve was > 0.80 , optimal medical therapy was recommended.

The primary outcome was the proportion of patients undergoing ICA without obstructive CAD or with obstructive CAD who did not undergo intervention (balloon dilatation, stent implantation, or coronary artery bypass surgery) within 90 days.⁴⁸ Obstructive CAD was defined as "1 or more stenoses $\geq 70\%$ on quantitative coronary analysis in a core laboratory or an invasive fractional flow reserve ≤ 0.80 , if available during the procedure." Secondary outcomes included MACE (hospitalization for unstable angina, revascularization after 90 days, nonfatal myocardial infarction, or cardiovascular death), quality of life, symptoms of angina, and overall medical expenditure during follow-up to 1 year.

Results demonstrated that 69.2% (421/608) of patients in the CCTA fractional flow reserve care group and 79.4% (483/608) of patients in the standard care group underwent ICA.⁴⁸ The use of CCTA fractional flow reserve significantly reduced the proportion of patients undergoing ICA without obstructive CAD or with obstructive CAD not undergoing intervention, when compared to usual care (28.3% [119/421] vs. 46.2% [223/483]; $p < .001$). Results were driven by a reduction in the proportion of patients undergoing ICA without obstructive CAD in the CCTA fractional flow reserve care group (20.9% [88/421]) compared with the usual care group (38.0% [184/483]). There were no statistically significant differences between treatment groups for key secondary outcomes at 1 year follow up, including MACE, quality of life and angina scores measured using the Seattle Angina Questionnaire-7, and costs. However, overall revascularization rates were increased in the CCTA fractional flow reserve care group when compared to usual care (49.7% [302/608] vs. 42.8% [260/608]; $p = .02$). Authors stated that on-site CCTA fractional flow reserve can improve the selection of patients for ICA by identifying those who are more likely to have obstructive CAD suitable for revascularization.

Prospective Cohort Studies

Jensen et al (2018) reported on a single-institution study of 774 consecutive individuals with suspicion of CAD referred for nonemergent ICA or CCTA.⁴⁹ Subjects were analyzed in 2 groups: a low-to-intermediate-risk group accounting for 76% of patients with a 31% mean pretest probability of CAD and a high-risk group accounting for 24% of patients with a 67% mean

pretest probability of CAD. Among the 745 who received CCTA, fractional flow reserve measurement using CCTA was selectively ordered in 28% of patients overall (23% in the low-to-intermediate-risk group, 41% in the high-risk group). The CCTA was considered inconclusive in 3% of subjects, and, among those with conclusive CCTA, fractional flow reserve measurement using CCTA yielded few inconclusive results, with less than 3% of cases. During a minimum 90-day follow-up, the combined testing strategy of selective fractional flow reserve measurement using CCTA resulted in avoiding ICA in 91% of low-to-intermediate risk and 75% of high-risk individuals. None of the patients who avoided ICA based on CCTA with selective fractional flow reserve measurement using CCTA were associated with serious clinical adverse events over an average of 157 days of follow-up.

Wang et al (2019) conducted a single-center prospective cohort study of the diagnostic accuracy of the DeepVessel FFR platform.⁵⁰ In 63 patients who underwent CCTA, the deep learning software was compared to wire-based (invasive) FFR. DeepVessel FFR had a higher diagnostic performance as assessed by area under the receiver-operation characteristics curve (0.928) compared to wire-based FFR (0.664). DeepVessel FFR had a sensitivity, specificity, positive predictive value, and negative predictive value of 97.14%, 75%, 82.93%, and 95.45%, respectively.

Nous et al (2020) conducted an observational study of patients with suspected CAD who were enrolled in the randomized Computed Tomography vFlins. Exercise Testing in Suspected Coronary Artery Disease (CRESCENT) I and II trials.⁵¹ The analysis included patients with evidence of $\geq 50\%$ stenosis on CCTA (N=53) who lacked contraindications to the procedure and therefore underwent machine learning fractional flow reserve measurement using CCTA (n=42). Hemodynamically significant stenosis (≤ 0.8) was identified in 27 of 53 patients (51%) using fractional flow reserve measurement using CCTA. The proportion of patients who required additional testing (37/53 with CCTA alone) would have been significantly less with fractional flow reserve measurement using CCTA (7/53; $p < .001$) and ICA would have been avoided in 13% of patients within 6 to 12 months of follow-up ($p = .016$). Fractional flow reserve measurement using CCTA would have changed the initial management strategy in 57% of patients ($p < .001$). Specifically, 17 patients would have avoided additional testing, 6 patients would have avoided revascularization, and 7 patients would have received revascularization instead of additional testing.

Qiao et al (2022) conducted a prospective, single-center, nonrandomized cohort study in patients with suspected CAD.⁵² Patients received either CCTA alone (n=567) or fractional flow reserve measurement using CCTA (n=566). The primary outcome of interest, ICA that showed nonobstructive disease at 90 days, occurred in 33.3% of the CCTA alone group and 19.8% of the fractional flow reserve group (risk difference, 13.5%; 95% CI, 8.4% to 18.6%; $p = .03$). ICA was utilized more frequently in the CCTA alone group than the fractional flow reserve group (27.5% vs. 20.3%; $p = .003$). At 1 year, MACE was more common in the CCTA alone group compared to the fractional flow reserve group (6.7% vs. 3.9%; HR, 1.73; 95% CI, 1.01 to 2.95; $p = .04$).

Retrospective Cohort Studies

Nørgaard et al (2017) reported on results from symptomatic patients referred for CCTA at a single-center in Denmark from May 2014 to April 2015.⁵³ All data were obtained from medical records and registries; the study was described as a "review" of diagnostic evaluations and was retrospectively conducted. Follow-up through 6 to 18 months was ascertained. From 1248

referred patients, 1173 underwent CCTA; 858 received medical therapy, 82 underwent ICA, 44 MPI, and 189 fractional flow reserve measurement using CCTA (185 [98%] obtained successfully). Of the 185 individuals who successfully obtained fractional flow reserve measurement using CCTA, fractional flow reserve measurement using CCTA demonstrated values of 0.80 or less in 1 or more vessels in 57 (31%) patients, and 49 (86%) went on to ICA. Whereas of the 128 with higher fractional flow reserve measurement using CCTA values, only 5 (4%) went on to ICA. Assuming ICA was planned for all patients undergoing fractional flow reserve measurement using CCTA, these results are consistent with fractional flow reserve measurement using CCTA being able to decrease the rate of ICA. However, implications are limited by the retrospective design, performance at a single-center, and lack of a comparator arm including one for CCTA alone.

Lu et al (2017) retrospectively examined a subgroup referred for ICA⁵⁴, from the completed PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial. The PROMISE trial was a pragmatic trial comparing CCTA with functional testing for the initial evaluation of patients with suspected stable ischemic heart disease.⁵⁵ Of 550 participants referred to ICA within 90 days, 279 were not considered for the analyses due to CCTA performed without nitroglycerin (n=139), CCTA not meeting slice thickness guidelines (n=90), or nondiagnostic studies (n=50). Of the remaining 271 patients, 90 scans were inadequate to obtain fractional flow reserve measurement using CCTA, leaving 181 (33%) of those referred to ICA for analysis. Compared with those excluded, patients in the analytic sample were less often obese, hypertensive, diabetic, minority, or reported a CAD equivalent symptom. The 2 groups had similar pretest probabilities of disease, revascularization rates, and MACE, but the distribution of stenoses in the analytic sample tended to be milder (p=.06). Fractional flow reserve measurement using CCTA studies were performed in a blinded manner and not available during the conduct of PROMISE for decision making.

Severe stenosis ($\geq 70\%$) or left main disease ($\geq 50\%$) were present in 110 (66%) patients by CCTA result and in 54% by ICA.⁵⁴ Over a 29-month median follow-up, MACE (death, nonfatal MI, hospitalization for unstable angina) or revascularization occurred in 51% of patients (9% MACE, 49% revascularization). A majority (72%) of the sample had at least 1 vessel with a fractional flow reserve measurement using CCTA of 0.80 or less, which was also associated with a higher risk of revascularization but with a wide CI (HR, 5.1; 95% CI, 2.6 to 11.5). If reserved for patients with a fractional flow reserve measurement using CCTA of 0.80 or less, ICAs might have been avoided in 50 patients (ie, reduced by 28%) and the rate of ICA without 50% or more stenosis from 27% (calculated 95% CI, 21% to 34%) to 15% (calculated 95% CI, 10% to 23%). If the 90 patients whose images were sent for fractional flow reserve measurement using CCTA but were unsatisfactory proceeded to ICA—as would have occurred in practice—the rate of ICA might have decreased by 18% and ICA without significant stenosis from 31% to 25%.

The authors suggested that when CCTA is used as the initial evaluation for patients with suspected stable ischemic heart disease, adding fractional flow reserve measurement using CCTA could have decreased the referral rate to ICA in PROMISE from 12.2% to 9.5%, or close to the 8.1% rate observed in the PROMISE functional testing arm.⁵⁴ The authors also noted the similarity of their findings to PLATFORM and concluded, "In this hypothesis-generating study of patients with stable chest pain referred to ICA after CCTA, we found that adding fractional flow reserve measurement using CCTA may improve the efficiency of referral to ICA, addressing a major concern of an anatomic CCTA strategy. Fractional flow reserve measurement using CCTA

has incremental value over anatomic CCTA in predicting revascularization or major adverse cardiovascular events."

This retrospective observational subgroup analysis from PROMISE would suggest that when CCTA is the initial noninvasive test for the evaluation of suspected stable ischemic heart disease, fractional flow reserve measurement using CCTA before ICA has the potential to reduce unnecessary ICAs and increase the diagnostic yield.⁵⁴ However, study limitations and potential generalizability are important to consider. First, analyses included only a third of CCTA patients referred to ICA, and some characteristics of the excluded group differed from the analytic sample. Second, conclusions assume that a fractional flow reserve measurement using CCTA greater than 0.80 will always dissuade a physician from recommending ICA and even in the presence of severe stenosis (eg, $\geq 70\%$ in any vessel or $\geq 50\%$ in the left main), or almost half (46%) of patients with a fractional flow reserve measurement using CCTA greater than 0.80. Finally, estimates including patients with either nondiagnostic CCTA studies (n=50) or studies inadequate for calculating fractional flow reserve measurement using CCTA (n=90) are more appropriate because in practice those patients would most likely proceed to ICA. Accordingly, the estimates are appropriately considered upper bounds for what might be seen in practice. It is also important to note that in the strata of the PLATFORM trial enrolling patients for initial noninvasive testing (not planned ICA), ICA was more common following CCTA and contingent fractional flow reserve measurement using CCTA than following usual care (18.3% vs. 12.0%) and ICA, with no obstructive disease more frequent in the fractional flow reserve measurement using CCTA arm (12.5% vs. 6.0%).

Qiao et al (2020) conducted a single-center retrospective study of 1121 patients who underwent CCTA followed by ICA within 90 days for evaluation of chest pain between January 2007 and December 2016.⁵⁶ Fractional flow reserve measurement using CCTA was calculated using a machine learning algorithm. Discordant fractional flow reserve findings between CCTA and ICA were found in 16.4% of patients. After the fractional flow reserve results were known, the management plan was changed in 167 patients (14.9%). Among patients who were treated with optimal medical therapy, 22.6% were reassigned to revascularization. Revascularization was avoided in 8.7% of patients. The overall rate of MACE was 10.2%. During the median follow-up of 26 months (range, 4 to 48 months), the occurrence of MACE was associated with fractional flow reserve ≤ 0.8 (HR, 6.84; 95% CI, 3.57 to 13.11; $p < .001$). Availability of fractional flow reserve using CCTA information could have reduced the rate of ICA from 100% to 45.5% and decreased the number of PCIs by 4.4%.

Yang et al (2021) conducted a single-center retrospective study between January 2006 and December 2017 in patients with suspected or known CAD.⁵⁷ All patients had received at least 2 CCTAs separated by at least 1 year with no MACE events in the interim. Machine learning fractional flow reserve measurement using CCTA datasets were available for 284 patients. Within a median follow-up of 4 years after the final CCTA, MACE (defined as acute coronary syndrome, rehospitalization, PCI, or death from cardiovascular causes), occurred in 45 patients. Both lesion-specific ($p = .02$) and vessel-specific ($p < .001$) fractional flow reserve measurement using CCTA were lower in vessels in individuals who experienced MACE than individuals who did not experience MACE. A multivariable analysis found that vessel-specific functional flow reserve measurement using CCTA ≤ 0.8 (HR, 2.4; 95% CI, 1.3 to 4.4; $p = .005$) was a predictor for MACE, along with several other parameters (ie, plaque progression, elevated coronary artery calcium,

and the presence of a high risk plaque). Fractional flow reserve measurement using CCTA ≤ 0.8 significantly increased the rate of MACE in a time to event analysis ($p < .001$).

Liu et al (2021) retrospectively studied 296 patients with CAD and $\geq 50\%$ stenosis on CCTA performed between January 2014 and December 2016.⁵⁸ All patients underwent ICA; machine learning fractional flow reserve measurement using DeepVessel FFR software was done retrospectively. After 2 years of follow-up, 72% of ICA procedures could have been avoided. Rates of MACE were similar among patients who underwent revascularization regardless of imaging modality (2.9% and 3.3%; $p = .838$).

The ADVANCE Registry Case Series

Patel et al (2020) conducted a registry study on the 1-year medical practice and clinical outcomes of fractional flow reserve measurement using CCTA for patients in the international Assessing Diagnostic Value of Non-Invasive FFR_{CT} in Coronary Care (ADVANCE) registry.⁵⁹ Patients suspected of having CAD and with atherosclerosis identified by CCTA (N=5083 from 38 international sites) were prospectively enrolled in the registry from July 15, 2015 to October 20, 2017. Investigators recorded demographics, symptoms, CCTA and fractional flow reserve measurement using CCTA findings, treatment plans, and clinical outcomes through 1 year, and these were then adjudicated by a blinded central laboratory. At 1 year, investigators had follow-up data from 4737 (93.2%) patients with fractional flow reserve measurement using CCTA. Outcomes, detailed in Table 2, were revascularization, MACE, and time to first event (all-cause death or MI, and cardiovascular death or MI). The 1-year outcomes showed low event rates in all patients; lower MACE and significantly lower cardiovascular death or MI were found in patients with a fractional flow reserve measurement using CCTA > 0.80 (negative) compared with those with positive (abnormal) fractional flow reserve measurement using CCTA. Fairbairn et al (2018) reported in another analysis of the ADVANCE registry that management plans changed in 66.9% (95% CI, 64.8 to 67.6) of patients who had fractional flow reserve measurement using CCTA.⁶⁰ Among patients originally assigned to revascularization, 22.3% were reassigned to medical therapy. The proportion of patients assigned to revascularization instead of medical therapy was small (5.4%).

Table 2. One-Year Outcomes From the ADVANCE Registry (N=4634)

	Revascularization	MACE	Time to first event	
			All-cause death or MI	Cardiovascular death or MI
Fractional flow reserve using CCTA ≤ 0.80 (n=3145, 66.39%)	n=1208 (38.40%)	n=43 (1.37%)	n=38 (1.20%)	n=25 (0.80%)
Fractional flow reserve using CCTA > 0.80 (n=1592, 33.61%)	n=89 (5.60%)	n=12 (0.75%)	n=10 (0.60%)	n=3 (0.20%)
RR	6.87	1.81	1.92	4.22
95% CI	5.59 to 8.45	0.96 to 3.43	0.96 to 3.85	1.28 to 13.95
p-value	<.001	.06	.06	.01

Source: Patel et al (2020)⁵⁹.

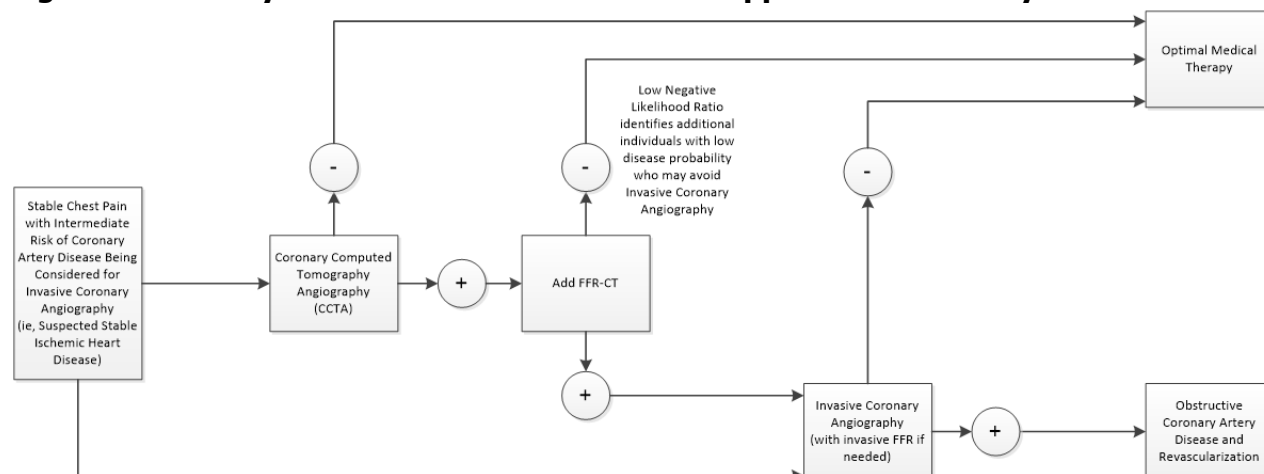
ADVANCE: Assessing Diagnostic Value of Non-Invasive FFR_{CT} in Coronary Care; CCTA: coronary computed tomography angiography; CI: confidence interval; MACE: major adverse cardiac events; MI: myocardial infarction; RR: relative risk.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Diagnostic performance can offer indirect evidence of clinical utility, assuming providers act according to a test result. As previously noted, an effective gatekeeper strategy must be able to decrease the probability of disease (rule out) sufficiently that a planned ICA would not be performed. Ruling out the disease is a function of the negative likelihood ratio that defines the degree to which a negative test decreases the posttest odds (and probability) of disease. The steps in the logic are illustrated in Figure 1.

Figure 1. Pathway for Clinical Use of FFR-CT to Support Clinical Utility



FFR-CT: fractional flow reserve using coronary computed tomography angiography.

Table 3 illustrates how a negative test would lower the probability of a hemodynamically significant obstruction from pretest probabilities of 0.25, 0.50, or 0.75 for the various tests examined in the meta-analyses. For example, according to the results of Danad et al (2017), if the pretest probability was 0.50, following a negative CCTA study the posttest probability would be 0.18.³³ In contrast, beginning with a pretest probability of 0.50, a negative fractional flow reserve measurement using CCTA would yield a posttest probability of 0.14 (Danad et al [2017]) and 0.12 (Wu et al [2016]).^{33,32} Overall, the negative likelihood ratios and posttest probability estimates for fractional flow reserve measurement using CCTA are slightly better than CCTA as well as stress echocardiography and SPECT.

Table 3. Change in Disease Probability Following a Negative Test

Study	Modality	Negative LR (95% CI)	Post-test Probability (95% CI) After Negative Test		
			Pretest Probability 0.25	Pretest Probability 0.50	Pretest Probability 0.75
Danad et al (2017) ^{33,}					
	MRI	0.12 (0.05 to 0.30)	0.04 (0.02 to 0.09)	0.11 (0.05 to 0.23)	0.26 (0.13 to 0.47)
	Fractional flow reserve using CCTA	0.16 (0.11 to 0.23)	0.05 (0.04 to 0.07)	0.14 (0.10 to 0.19)	0.32 (0.25 to 0.41)
	CCTA	0.22 (0.10 to 0.50)	0.07 (0.03 to 0.14)	0.18 (0.09 to 0.33)	0.40 (0.23 to 0.60)
	Stress echocardiography	0.34 (0.17 to 0.66)	0.10 (0.05 to 0.18)	0.25 (0.15 to 0.40)	0.50 (0.34 to 0.66)
	SPECT	0.40 (0.19 to 0.83)	0.12 (0.06 to 0.22)	0.29 (0.16 to 0.45)	0.55 (0.36 to 0.71)
	ICA	0.46 (0.39 to 0.55)	0.13 (0.12 to 0.15)	0.32 (0.28 to 0.35)	0.58 (0.54 to 0.62)
Wu et al (2016) ^{32,}					
	Fractional flow reserve using CCTA	0.14 (0.09 to 0.21)	0.04 (0.03 to 0.07)	0.12 (0.08 to 0.17)	0.30 (0.21 to 0.39)
Takx et al (2015) ^{61,}					
	MRI	0.14 (0.10 to 0.18)	0.04 (0.03 to 0.06)	0.12 (0.09 to 0.15)	0.30 (0.23 to 0.35)
	Perfusion computed tomography	0.12 (0.04 to 0.33)	0.04 (0.01 to 0.10)	0.11 (0.04 to 0.25)	0.26 (0.11 to 0.50)
	Stress echocardiography	0.42 (0.30 to 0.59)	0.12 (0.09 to 0.16)	0.30 (0.23 to 0.37)	0.56 (0.47 to 0.64)
	SPECT	0.39 (0.27 to 0.55)	0.12 (0.08 to 0.15)	0.28 (0.21 to 0.35)	0.54 (0.45 to 0.62)
	PET	0.14 (0.02 to 0.87)	0.04 (0.01 to 0.22)	0.12 (0.02 to 0.47)	0.30 (0.06 to 0.72)

CCTA: coronary computed tomography angiography; CI: confidence interval; ICA: invasive coronary angiography; LR: likelihood ratio; MRI: magnetic resonance imaging; PET: positron emission tomography; SPECT: single-photon emission computed tomography.

Curzen et al (2016) conducted a literature search that identified a single study that examined 200 consecutive individuals selected from the NXT trial population "to reproduce the methodology of

the invasive RIPCORDER study" with the elective management of stable chest pain.⁶² All subjects received CCTA including fractional flow reserve measurement using CCTA in at least 1 vessel with diameter ≥ 2 mm and diameter stenosis $\geq 30\%$ as well as ICA within 60 days of CCTA. Three experienced interventional cardiologists reviewed the CCTA results (initially without the fractional flow reserve measurement using CCTA results) and selected a management plan from the following 4 options: 1) optimal medical therapy alone; 2) PCI + optimal medical therapy; 3) coronary artery bypass graft + optimal medical therapy; or 4) more information about ischemia required. Following the initial decision, results from the fractional flow reserve measurement using CCTA were shared with the same group of interventional cardiologists who decided by consensus based on the same 4 options. A cutoff of 0.80 or less was considered significant on fractional flow reserve measurement using CCTA. A stenosis was considered significant on CCTA or ICA with 50% or more diameter narrowing. Change in management between the first decision based on CCTA only and the second decision based on CCTA plus fractional flow reserve measurement using CCTA was the primary endpoint of this study. Secondary endpoints included analysis of the vessels considered to have significant stenosis based on CCTA alone versus CCTA plus fractional flow reserve measurement using CCTA as well as vessels identified as targets for revascularization based on CCTA alone versus CCTA plus fractional flow reserve measurement using CCTA. This study was conducted by investigators in the United Kingdom and Denmark. Funding was provided by HeartFlow, and multiple authors reported receiving fees, grants, and/or support from HeartFlow.

Results for the primary endpoint (Table 4) yielded a change in management category for 72 (36%) of 200 individuals.⁶² For the 87 individuals initially assigned to PCI based on CCTA alone, the addition of the fractional flow reserve measurement using CCTA results shifted management for 26 (30%) of 87 to optimal medical therapy (ie, no ischemic lesion on fractional flow reserve measurement using CCTA) and an additional 16 (18%) individuals remained in the PCI category but fractional flow reserve measurement using CCTA identified a different target vessel for PCI. These findings provide supportive information that the improved diagnostic accuracy of fractional flow reserve measurement using CCTA in particular related to its better negative likelihood ratio compared with CCTA alone would likely lead to changes in management that would be expected to improve health outcomes.

Table 4. Summary of Overall Management Changes for Patients Using Coronary Computed Tomography Angiography Versus Coronary Computed Tomography Angiography Plus Fractional Flow Reserve using Coronary Computed Tomography Angiography

Management Category Consensus Decision	CCTA Alone, n (%)	CCTA Plus Fractional Flow Reserve using CCTA, n (%)	Strategy Change ^a (95% CI), %
More data required	38 (19.0)	0	NR
Optimal medical therapy	67 (33.5)	113 (56.5)	23 (18 to 29)
Percutaneous coronary intervention	87 (43.5)	78 (39.0)	-5 (-2 to -8)
Coronary artery bypass graft surgery	8 (4.0)	9 (4.5)	0.5 (0.1 to 3)

Source: Curzen et al (2016)⁶².

CCTA: coronary computed tomography angiography; CI: confidence interval; NR: not reported.

a $p < .001$ for between-group change, CCTA alone versus CCTA + fractional flow reserve using CCTA.

Baggiano et al (2020) conducted a retrospective analysis of patients (N=291) enrolled in the PERFusion Versus Fractional Flow Reserve CT Derived In Suspected CoroNary (PERFECTION) study, a prospective cohort study in patients with suspected CAD.⁶³ The study protocol determined the clinical management plan based on the results of the following potential assessments: CCTA, fractional flow reserve measurement using CCTA, CCTA plus stress myocardial perfusion using computed tomography, and all 3 imaging modalities combined. Clinical management included optimal medical therapy, ICA, or need for further information. Functionally significant CAD was identified in 49% of patients. Compared to CCTA alone, adding fractional flow reserve measurement using CCTA increased the proportion of patients who received optimal medical therapy (26% vs. 35%) and ICA (45% vs. 48%), and decreased the proportion of patients who needed further information (29% vs. 17%). There was a significant difference in the rate of agreement with the final management decision between CCTA and fractional flow reserve measurement using CCTA ($p = .042$), and with all 3 imaging modalities combined compared to CCTA alone ($p = .001$).

Section Summary: Coronary Computed Tomography Angiography with Selective Noninvasive Fractional Flow Reserve

Three studies including 609 patients have evaluated the diagnostic accuracy of the FDA-cleared HeartFlow FFR_{CT} software. Software used in successive studies was also revised to improve performance characteristics, particularly specificity. For example, using an earlier software version, the noninvasive fractional flow reserve derived from the computed tomography angiography for coronary lesions of intermediate stenosis severity trial reported a specificity of 54%.⁶⁴ Accordingly, pooled results from the Danad et al (2017) systematic review must be interpreted carefully. Also, there is some uncertainty in the generalizability of results obtained in these studies conducted under likely controlled conditions (eg, data from the NXT Trial²⁸, forming the basis for the FDA clearance).

There is direct evidence that compares health outcomes observed during 90-day to 2-year follow-up for strategies using CCTA particularly in combination with selective fractional flow reserve measurement using CCTA with strategies using ICA or other noninvasive imaging tests. The available evidence provides support that use of CCTA with selective fractional flow reserve measurement using CCTA is likely to reduce the use of ICA in individuals with stable chest pain who are unlikely to benefit from revascularization by demonstrating the absence of functionally significant obstructive CAD. Also, the benefits are likely to outweigh potential harms given that rates of revascularization for functionally significant obstructive CAD appear to be similar and cardiac-related adverse events do not appear to be increased following a CCTA with selective fractional flow reserve measurement using CCTA strategy. Moreover, the evidence on the diagnostic performance characteristics, particularly showing higher specificity of fractional flow reserve measurement using CCTA and better negative likelihood ratio as compared with CCTA alone, may be combined with indirect evidence that CCTA with a selective fractional flow reserve measurement using CCTA strategy would likely lead to changes in management that would be expected to improve health outcomes, particularly by limiting unnecessary ICA testing. While individual studies are noted to have specific methodologic limitations and some variation is noted in the magnitude of benefit across studies, in aggregate the evidence provides reasonable

support that the selective addition of fractional flow reserve measurement using CCTA following CCTA results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Heart Association, et al

In 2021, the American Heart Association, American College of Cardiology, American Society of Echocardiography, American College of Chest Physicians, Society for Academic Emergency Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance released a clinical practice guideline for the evaluation and diagnosis of chest pain.⁶⁵ The guideline states that for "intermediate-risk patients with acute chest pain and no known coronary artery disease (CAD), with a coronary artery stenosis of 40% to 90% in a proximal or middle coronary artery on coronary computed tomography angiography (CCTA), fractional flow reserve with computed tomography can be useful for the diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization (class of recommendation [COR]: 2a (moderate; benefit >> risk); level of evidence [LOE]: B-NR (moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies or meta-analyses of such studies)." This recommendation also applies to those intermediate-risk patients with acute chest pain and known CAD (COR: 2a; LOE: B-NR).

In 2025, the American College of Cardiology, American Heart Association, American College of Emergency Physicians, National Association of EMS Physicians, and Society for Cardiovascular Angiography & Interventions released a clinical practice guideline for the management of patients with acute coronary syndromes.⁶⁶ The guideline made the following recommendation: "In patients with non-ST-segment elevation ACS who are at intermediate or high risk of ischemic events, an invasive approach with the intent to proceed with revascularization is recommended during hospitalization to reduce major adverse cardiovascular events. In patients with non-ST-segment elevation ACS who are at low risk of ischemic events, a routine invasive or selective invasive approach with further risk stratification is recommended to help identify those who may require revascularization and to reduce major adverse cardiovascular events."

National Institute for Health and Care Excellence

In 2017, NICE endorsed fractional flow reserve using CCTA, with the following conclusions: "The committee concluded that the evidence suggests that HeartFlow FFR_{CT} is safe, has high diagnostic accuracy, and that its use may avoid the need for invasive investigations."⁶⁷ Recommendations included:

- "The case for adopting HeartFlow FFR_{CT} for estimating fractional flow reserve from CCTA is supported by the evidence. The technology is non-invasive and safe, and has a high level of diagnostic accuracy."
- "HeartFlow FFR_{CT} should be considered as an option for patients with stable, recent onset chest pain who are offered CCTA in line with the NICE guideline on chest pain. Using HeartFlow FFR_{CT} may avoid the need for invasive coronary angiography and revascularization. For correct use, HeartFlow FFR_{CT} requires access to 64-slice (or above) CCTA facilities."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT05174247	Addition of FFR _{CT} in the Diagnostic Pathway of Patients With Stable Chest Pain to Reduce Unnecessary Invasive Coronary Angiography	528	Jul 2025 (last update posted Sep 2024)
NCT04939207	Improving the Cost-effectiveness Of Coronary Artery Disease Diagnosis	825	Apr 2025 (last update posted Dec 2024)
NCT02208388	Prospective Evaluation of MyocaRdial PerFUSion ComputEd Tomography Trial: Ischemia-guided Revascularization Using Perfusion Coronary CT vs. Fractional Flow Reserve	1000	Mar 2028
<i>Unknown status</i>			
NCT03329469	The Value of Fractional Flow Reserve Derived From Coronary CT Angiography as Compared to CCTA or CCTA and Stress MPI in the Triage of Low to Intermediate Emergent Chest Pain Patients With Toshiba CT-FFR	1142	Mar 2024

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
75574	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)
75580	Noninvasive estimate of coronary fractional flow reserve from software analysis of data from a coronary computed tomography angiography.

REVISIONS	
10-15-2017	Policy added to the bcbsks.com web site on 09-15-2017 with an effective date of 10-15-2017.
01-01-2018	In Coding section: - Added CPT codes: 0501T, 0502T, 0503T, 0504T. - Removed coding bullet.
09-12-2018	Updated Description section.
	In Policy section: In Item A, added "abnormal" and removed "positive" to read, "The use of noninvasive fractional flow reserve following an abnormal coronary computed tomography angiography may be considered medically necessary to guide decisions about the use of invasive coronary angiography in patients with stable chest pain at intermediate risk of coronary artery disease (i.e., suspected or presumed stable ischemic heart disease)."
	Updated Rationale section.
	Updated References section.
08-14-2019	Updated Description section.
	In Policy section: - In Policy Guidelines, added policy language from the <i>Coronary Computed Tomography Angiography (CCTA) for Coronary Artery Evaluation</i> medical policy: - Contrast-enhanced coronary computed tomography angiography criteria include the following: - Contrast-enhanced coronary computed tomography angiography for evaluation of patients with symptoms of stable ischemic heart disease and meeting guideline criteria (see below) for a noninvasive test in the outpatient setting is considered medically necessary. The 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guidelines for the diagnosis and management of patients with stable heart disease have several class I recommendations regarding the use of noninvasive testing in patients with suspected stable ischemic heart disease. A class

REVISIONS						
	I recommendation indicates that a test should be performed. In general, patients with at least intermediate risk (10-90% risk by standard risk prediction instruments) are recommended to have some kind of test, the choice of test depending on interpretability of the ECG, capability to exercise, and presence of comorbidity.					
	Pretest Probability of CAD by age, gender, and symptoms*					
	Age (yrs)	Gender	Typical / Definite Angina Pectoris	Atypical / Probable Angina Pectoris	Nonanginal Chest Pain	Asymptomatic
	< 39	Men	Intermediate	Intermediate	Low	Very Low
		Women	Intermediate	Very Low	Very Low	Very Low
	40-49	Men	High	Intermediate	Intermediate	Low
		Women	Intermediate	Low	Very Low	Very Low
	50-59	Men	High	Intermediate	Intermediate	Low
		Women	Intermediate	Intermediate	Low	Very Low
	> 60	Men	High	Intermediate	Intermediate	Low
		Women	High	Intermediate	Intermediate	Low
	High: >90% pretest probability. Intermediate: between 10% and 90% pretest probability. Low: between 5% and 10% pretest probability. Very low: <5% pretest probability. CAD: coronary artery disease. *Modified from the ACC/AHA Exercise Testing Guidelines to reflect all age ranges. ⁶⁰					
	b. Contrast-enhanced coronary computed tomography angiography for evaluation of patients without known coronary artery disease and acute chest pain in the emergency room/emergency department setting is considered medically necessary.					
	c. Contrast-enhanced coronary computed tomography angiography for evaluation of anomalous (native) coronary arteries in patients in whom they are suspected may be considered medically necessary.					
d. Contrast-enhanced coronary computed tomography angiography for coronary artery evaluation is considered experimental / investigational for all other indications.						
Updated Rationale section.						
Updated References section.						
07-02-2021	Updated Description section.					
	Updated Rationale section.					
	Updated References section.					
07-12-2022	Updated Description Section					
	Updated Rationale Section					
	Updated References Section					
06-27-2023	Updated Description Section					
	Updated Rationale Section					
	Updated Coding Section					
	▪ Removed ICD-10 Codes					
Updated References Section						
01-01-2024	Updated Coding Section					
	▪ Removed Deleted Codes 0501T, 0502T, 0503T and 0504T (eff. 01-01-2024)					

REVISIONS	
	Added new code 75580 (eff. 01-01-2024)
06-27-2024	Updated Description Section
	Updated Rationale Section
	Updated References Section
06-24-2025	Updated Description Section
	Updated Rationale Section
	Updated Reference Section
Posted 08-11-2026 Effective 09-10-2026	Updated Description Section
	Updated Policy Section:
	Policy Statement A: changed abnormal to positive
	Updated Policy Guidelines Section:
	- Removed Policy Guidelines Statement A1, 2, 3, 4 and Pretest Probability of CAD by age, gender, and symptoms table: A. Contrast-enhanced coronary computed tomography angiography criteria include the following: - Contrast-enhanced coronary computed tomography angiography for evaluation of patients with symptoms of stable ischemic heart disease and meeting guideline criteria (see below) for a noninvasive test in the outpatient setting is considered medically necessary. The 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guidelines for the diagnosis and management of patients with stable heart disease have several class I recommendations regarding the use of noninvasive testing in patients with suspected stable ischemic heart disease. A class I recommendation indicates that a test should be performed. In general, patients with at least intermediate risk (10-90% risk by standard risk prediction instruments) are recommended to have some kind of test, the choice of test depending on interpretability of the ECG, capability to exercise, and presence of comorbidity. - Contrast-enhanced coronary computed tomography angiography for evaluation of patients without known coronary artery disease and acute chest pain in the emergency room/emergency department setting is considered medically necessary. - Contrast-enhanced coronary computed tomography angiography for evaluation of anomalous (native) coronary arteries in patients in whom they are suspected may be considered medically necessary. - Contrast-enhanced coronary computed tomography angiography for coronary artery evaluation is considered experimental / investigational for all other indications.
	Updated Rationale Section
	Updated References Section

REFERENCES

- Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med. Mar 11 2010; 362(10): 886-95. PMID 20220183
- Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. Apr 12 2007; 356(15): 1503-16. PMID 17387127
- Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. Dec 18 2012; 60(24): e44-e164. PMID 23182125

4. Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. Aug 29 2023; 148(9): e9-e119. PMID 37471501
5. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med*. Jun 14 1979; 300(24): 1350-8. PMID 440357
6. Wasfy MM, Brady TJ, Abbara S, et al. Comparison of the Diamond-Forrester method and Duke Clinical Score to predict obstructive coronary artery disease by computed tomographic angiography. *Am J Cardiol*. Apr 01 2012; 109(7): 998-1004. PMID 22236462
7. Versteysen MO, Joosen IA, Shaw LJ, et al. Comparison of Framingham, PROCAM, SCORE, and Diamond Forrester to predict coronary atherosclerosis and cardiovascular events. *J Nucl Cardiol*. Oct 2011; 18(5): 904-11. PMID 21769703
8. Min JK, Dunning A, Gransar H, et al. Medical history for prognostic risk assessment and diagnosis of stable patients with suspected coronary artery disease. *Am J Med*. Aug 2015; 128(8): 871-8. PMID 25865923
9. Genders TS, Steyerberg EW, Hunink MG, et al. Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. *BMJ*. Jun 12 2012; 344: e3485. PMID 22692650
10. CAD Consortium. Pre-test probability of CAD. 2016; https://www.qxmd.com/calculate/calculator_287/pre-test-probability-of-cad-cad-consortium. Accessed April 8, 2026.
11. De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med*. Sep 25 2014; 371(13): 1208-17. PMID 25176289
12. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. Sep 13 2012; 367(11): 991-1001. PMID 22924638
13. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. Jan 15 2009; 360(3): 213-24. PMID 19144937
14. Pothineni NV, Shah NN, Rochlani Y, et al. U.S. Trends in Inpatient Utilization of Fractional Flow Reserve and Percutaneous Coronary Intervention. *J Am Coll Cardiol*. Feb 16 2016; 67(6): 732-733. PMID 26868697
15. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). Fractional Flow Reserve and Coronary Artery Revascularization. TEC Assessment. June 2011;26:Tab 2.
16. Fearon WF, Shilane D, Pijls NH, et al. Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve. *Circulation*. Sep 17 2013; 128(12): 1335-40. PMID 23946263
17. van Nunen LX, Zimmermann FM, Tonino PA, et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. *Lancet*. Nov 07 2015; 386(10006): 1853-60. PMID 26333474
18. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. Oct 2013; 34(38): 2949-3003. PMID 23996286
19. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. Jan 14 2020; 41(3): 407-477. PMID 31504439

20. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. Oct 01 2014; 35(37): 2541-619. PMID 25173339
21. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. May 02 2017; 69(17): 2212-2241. PMID 28291663
22. Pijls NH, Van Gelder B, Van der Voort P, et al. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation*. Dec 01 1995; 92(11): 3183-93. PMID 7586302
23. de Bruyne B, Bartunek J, Sys SU, et al. Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. *Circulation*. Oct 15 1996; 94(8): 1842-9. PMID 8873658
24. HeartFlow. De Novo Classification Request for FFRct v. 1.4. 2013; https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN130045.pdf. Accessed April 8, 2026.
25. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol*. Nov 01 2011; 58(19): 1989-97. PMID 22032711
26. Min JK, Koo BK, Erglis A, et al. Effect of image quality on diagnostic accuracy of noninvasive fractional flow reserve: results from the prospective multicenter international DISCOVER-FLOW study. *J Cardiovasc Comput Tomogr*. 2012; 6(3): 191-9. PMID 22682261
27. Nakazato R, Park HB, Berman DS, et al. Noninvasive fractional flow reserve derived from computed tomography angiography for coronary lesions of intermediate stenosis severity: results from the DeFACTO study. *Circ Cardiovasc Imaging*. Nov 2013; 6(6): 881-9. PMID 24081777
28. Nørgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol*. Apr 01 2014; 63(12): 1145-1155. PMID 24486266
29. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. *J Am Coll Cardiol*. Jun 04 2013; 61(22): 2233-41. PMID 23562923
30. Kim KH, Doh JH, Koo BK, et al. A novel noninvasive technology for treatment planning using virtual coronary stenting and computed tomography-derived computed fractional flow reserve. *JACC Cardiovasc Interv*. Jan 2014; 7(1): 72-8. PMID 24332418

31. Pontone G, Guaricci AI, Palmer SC, et al. Diagnostic performance of non-invasive imaging for stable coronary artery disease: A meta-analysis. *Int J Cardiol.* Feb 01 2020; 300: 276-281. PMID 31748186
32. Wu W, Pan DR, Foin N, et al. Noninvasive fractional flow reserve derived from coronary computed tomography angiography for identification of ischemic lesions: a systematic review and meta-analysis. *Sci Rep.* Jul 05 2016; 6: 29409. PMID 27377422
33. Danad I, Szymonifka J, Twisk JWR, et al. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. *Eur Heart J.* Apr 01 2017; 38(13): 991-998. PMID 27141095
34. Renker M, Schoepf UJ, Wang R, et al. Comparison of diagnostic value of a novel noninvasive coronary computed tomography angiography method versus standard coronary angiography for assessing fractional flow reserve. *Am J Cardiol.* Nov 01 2014; 114(9): 1303-8. PMID 25205628
35. De Geer J, Sandstedt M, Björkholm A, et al. Software-based on-site estimation of fractional flow reserve using standard coronary CT angiography data. *Acta Radiol.* Oct 2016; 57(10): 1186-92. PMID 26691914
36. Wardziak Ł, Kruk M, Pleban W, et al. Coronary CTA enhanced with CTA based FFR analysis provides higher diagnostic value than invasive coronary angiography in patients with intermediate coronary stenosis. *J Cardiovasc Comput Tomogr.* 2019; 13(1): 62-67. PMID 30309764
37. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA.* Sep 26 2012; 308(12): 1237-45. PMID 22922562
38. Thompson AG, Raju R, Blanke P, et al. Diagnostic accuracy and discrimination of ischemia by fractional flow reserve CT using a clinical use rule: results from the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography study. *J Cardiovasc Comput Tomogr.* 2015; 9(2): 120-8. PMID 25819194
39. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med.* Oct 18 2011; 155(8): 529-36. PMID 22007046
40. Coenen A, Lubbers MM, Kurata A, et al. Fractional flow reserve computed from noninvasive CT angiography data: diagnostic performance of an on-site clinician-operated computational fluid dynamics algorithm. *Radiology.* Mar 2015; 274(3): 674-83. PMID 25322342
41. An Z, Tian J, Zhao X, et al. Machine Learning-Based CT Angiography-Derived Fractional Flow Reserve for Diagnosis of Functionally Significant Coronary Artery Disease. *JACC Cardiovasc Imaging.* Mar 2023; 16(3): 401-404. PMID 36889853
42. Di Pietro G, Improta R, De Filippo O, et al. Clinical impact of CCT-FFR as first-strategy in patients with symptomatic stable coronary artery disease: A systematic review and meta-analysis. *J Cardiovasc Comput Tomogr.* 2025; 19(2): 174-182. PMID 40044471
43. Douglas PS, De Bruyne B, Pontone G, et al. 1-Year Outcomes of FFRCT-Guided Care in Patients With Suspected Coronary Disease: The PLATFORM Study. *J Am Coll Cardiol.* Aug 02 2016; 68(5): 435-445. PMID 27470449
44. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. *Eur Heart J.* Dec 14 2015; 36(47): 3359-67. PMID 26330417

45. Hlatky MA, De Bruyne B, Pontone G, et al. Quality-of-Life and Economic Outcomes of Assessing Fractional Flow Reserve With Computed Tomography Angiography: PLATFORM. J Am Coll Cardiol. Dec 01 2015; 66(21): 2315-2323. PMID 26475205
46. Douglas PS, Nanna MG, Kelsey MD, et al. Comparison of an Initial Risk-Based Testing Strategy vs Usual Testing in Stable Symptomatic Patients With Suspected Coronary Artery Disease: The PRECISE Randomized Clinical Trial. JAMA Cardiol. Oct 01 2023; 8(10): 904-914. PMID 37610731
47. Curzen N, Nicholas Z, Stuart B, et al. Fractional flow reserve derived from computed tomography coronary angiography in the assessment and management of stable chest pain: the FORECAST randomized trial. Eur Heart J. Oct 01 2021; 42(37): 3844-3852. PMID 34269376
48. Yang J, Shan D, Wang X, et al. On-Site Computed Tomography-Derived Fractional Flow Reserve to Guide Management of Patients With Stable Coronary Artery Disease: The TARGET Randomized Trial. Circulation. May 02 2023; 147(18): 1369-1381. PMID 36870065
49. Jensen JM, Bøtker HE, Mathiassen ON, et al. Computed tomography derived fractional flow reserve testing in stable patients with typical angina pectoris: influence on downstream rate of invasive coronary angiography. Eur Heart J Cardiovasc Imaging. Apr 01 2018; 19(4): 405-414. PMID 28444153
50. Wang ZQ, Zhou YJ, Zhao YX, et al. Diagnostic accuracy of a deep learning approach to calculate FFR from coronary CT angiography. J Geriatr Cardiol. Jan 2019; 16(1): 42-48. PMID 30800150
51. Nous FMA, Budde RPJ, Lubbers MM, et al. Impact of machine-learning CT-derived fractional flow reserve for the diagnosis and management of coronary artery disease in the randomized CRESCENT trials. Eur Radiol. Jul 2020; 30(7): 3692-3701. PMID 32166492
52. Qiao HY, Tang CX, Schoepf UJ, et al. One-year outcomes of CCTA alone versus machine learning-based FFR CT for coronary artery disease: a single-center, prospective study. Eur Radiol. Aug 2022; 32(8): 5179-5188. PMID 35175380
53. Nørgaard BL, Hjort J, Gaur S, et al. Clinical Use of Coronary CTA-Derived FFR for Decision-Making in Stable CAD. JACC Cardiovasc Imaging. May 2017; 10(5): 541-550. PMID 27085447
54. Lu MT, Ferencik M, Roberts RS, et al. Noninvasive FFR Derived From Coronary CT Angiography: Management and Outcomes in the PROMISE Trial. JACC Cardiovasc Imaging. Nov 2017; 10(11): 1350-1358. PMID 28412436
55. Douglas PS, Hoffmann U, Lee KL, et al. PROspective Multicenter Imaging Study for Evaluation of chest pain: rationale and design of the PROMISE trial. Am Heart J. Jun 2014; 167(6): 796-803.e1. PMID 24890527
56. Qiao HY, Tang CX, Schoepf UJ, et al. Impact of machine learning-based coronary computed tomography angiography fractional flow reserve on treatment decisions and clinical outcomes in patients with suspected coronary artery disease. Eur Radiol. Nov 2020; 30(11): 5841-5851. PMID 32462444
57. Yang L, Xu PP, Schoepf UJ, et al. Serial coronary CT angiography-derived fractional flow reserve and plaque progression can predict long-term outcomes of coronary artery disease. Eur Radiol. Sep 2021; 31(9): 7110-7120. PMID 33630163
58. Liu X, Mo X, Zhang H, et al. A 2-year investigation of the impact of the computed tomography-derived fractional flow reserve calculated using a deep learning algorithm on routine decision-making for coronary artery disease management. Eur Radiol. Sep 2021; 31(9): 7039-7046. PMID 33630159

59. Patel MR, Nørgaard BL, Fairbairn TA, et al. 1-Year Impact on Medical Practice and Clinical Outcomes of FFR CT : The ADVANCE Registry. *JACC Cardiovasc Imaging*. Jan 2020; 13(1 Pt 1): 97-105. PMID 31005540
60. Fairbairn TA, Nieman K, Akasaka T, et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE Registry. *Eur Heart J*. Nov 01 2018; 39(41): 3701-3711. PMID 30165613
61. Takx RA, Blomberg BA, El Aidi H, et al. Diagnostic accuracy of stress myocardial perfusion imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis. *Circ Cardiovasc Imaging*. Jan 2015; 8(1). PMID 25596143
62. Curzen NP, Nolan J, Zaman AG, et al. Does the Routine Availability of CT-Derived FFR Influence Management of Patients With Stable Chest Pain Compared to CT Angiography Alone?: The FFR CT RIPCORDER Study. *JACC Cardiovasc Imaging*. Oct 2016; 9(10): 1188-1194. PMID 27568119
63. Baggiano A, Fusini L, Del Torto A, et al. Sequential Strategy Including FFR CT Plus Stress-CTP Impacts on Management of Patients with Stable Chest Pain: The Stress-CTP RIPCORDER Study. *J Clin Med*. Jul 08 2020; 9(7). PMID 32650379
64. Min JK, Berman DS, Budoff MJ, et al. Rationale and design of the DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) study. *J Cardiovasc Comput Tomogr*. 2011; 5(5): 301-9. PMID 21930103
65. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. Nov 30 2021; 144(22): e368-e454. PMID 34709879
66. Rao SV, O'Donoghue ML, Ruel M, et al. 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. Apr 2025; 151(13): e771-e862. PMID 40014670
67. National Institute for Health and Care Excellence. HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography [MTG32]. 2017; <https://www.nice.org.uk/guidance/mtg32>. Last updated May 19, 2021. Accessed April 8, 2026.

OTHER REFERENCES

1. Blue Cross and Blue Shield of Kansas Cardiology Liaison Committee May 2018, June 2018(CB), July 2019, January 2020.