Evidence Assist: Coronary Computed Tomography Angiography Innovations in Noninvasive Diagnosis of Coronary Artery Disease

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Prepared by:
Evidence Synthesis Program (ESP)
Coordinating Center
VA Portland Health Care System
Portland, OR
Mark Helfand, MD, MPH, MS, Director

Authors:
Mark Helfand, MD, MPH, MS
Johanna Anderson, MPH
Kim Peterson, MS
Donald Bourne, MPH

U.S. Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

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Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

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PURPOSE AND SCOPE

The ESP Coordinating Center (ESP CC) is responding to a request from Health Services Research & Development for an evidence assist white paper. This white paper is intended to provide a conceptual overview of the capabilities, benefits and harms, and anticipated impact on resource use within the Veterans Health Administration (VHA) of coronary computed tomography angiography (CCTA) with fractional flow reserve (FFR_{CT}) technologies for the diagnosis of coronary artery disease (CAD). Findings from this white paper will be used to inform development of a Congressional Tracking Report summarizing their capabilities, cost, and implementation issues. This report is not intended to provide a formal and comprehensive assessment of the full spectrum of need and implementation facilitators and barriers necessary for VHA to consider if and whether to expand use of FFR_{CT} technologies.

CCTA TECHNOLOGIES

Patients with chest pain and low to intermediate pre-test likelihood of stable CAD are typically evaluated noninvasively. Patients who are able to exercise and have an interpretable ECG are evaluated with standard exercise ECG. For patients who cannot exercise or have an uninterpretable resting ECG, options include pharmacologic stress plus nuclear imaging with SPECT or PET scanning or with pharmacologic echocardiography.[1]

CCTA is a noninvasive heart imaging test that is positioned as a substitute for other initial noninvasive tests in patients who cannot exercise and who have an intermediate-to-high likelihood of significant coronary artery disease. It is commonly performed to determine the presence and extent of plaque buildup in the coronary arteries.[2,3] Like other noninvasive tests, CCTA can help determine the need for further evaluation with coronary angiography but, unlike stress testing, CCTA does not provide functional information.

In interpreting a CCTA, coronary calcification results in combination with overall plaque burden and presence of high-risk plaque features are used to classify cases as “high risk” (>70% stenosis in at least one vessel), “intermediate risk” (30% to 70% stenosis), “low risk” (<30% stenosis), or “inconclusive”. “High-risk” patients are referred for invasive coronary angiography (ICA), while “low-risk” patients typically have no additional testing. Patients with “intermediate-risk” lesions and those with inconclusive findings may be referred for ICA or, in some patients, for stress testing.

In the PROMISE trial, initial CCTA testing and initial stress testing had similar clinical outcomes when used to evaluate patients who have new-onset, stable chest pain.[4] CCTA generally has a high sensitivity for functionally significant coronary lesions compared to the gold standard[5] of fractional flow reserve (FFR) during ICA (range 86% to 87% in recent meta-analyses),[6,7] with few false negatives. However, the specificity is 61% to 64%,[6,7] with many false positives, often leading to the use of ICA to exclude the presence of significant CAD and assess its functional significance.

Measurement of fractional flow reserve (FFR), the ratio between maximal blood flow in a narrowed coronary artery and the normal maximal blood flow, is one approach in evaluating the functional significance of coronary lesions to identify candidates for medical management or to target lesions for coronary interventions or bypass surgery. FFR measured invasively using a

pressure wire during ICA[8,9] is widely used and considered the gold standard for detecting hemodynamically significant CAD. Novel techniques have emerged to calculate FFR noninvasively from CCTA images (FFR_{CT}) with the aim of gaining this functional information noninvasively to improve the selection of patients for invasive testing or treatment. The process of FFR_{CT} uses computational fluid dynamics, reduced order models, and/or machine learning methods to reconstruct coronary flow and pressure fields from CCTA images. This integration of functional and anatomical imaging strategies provides data on both the extent of coronary artery narrowing and the impact on blood flow.[9,10]

HEARTFLOW FFR_{CT}

HeartFlow is an FFR_{CT} technology that provides 3-dimensional FFR models using standard CCTA images. The target population are individuals who have intermediate-risk lesions on CCTA. Granted US Food and Drug Administration (FDA) 510(k) marketing clearance in December 2015 based on diagnostic accuracy findings from the HeartFlow NXT study,[11] HeartFlow is the only commercially available FFR_{CT} technology at the time of this report. Physicians or health systems can send CCTA data to HeartFlow, Inc. (Redwood City, California), which runs the analyses and provides results within 48 hours. They provide physicians with a report containing a color-coded map of the coronary arteries with estimated FFR_{CT} values, showing the physiological impact of a coronary artery narrowing on blood flow. Physicians can manipulate the model to examine each vessel and analyze the location and severity of lesions. CCTA images must be of high enough quality, without image artifacts, in order to be scanned.

Independent, locally developed machine learning and reduced order model techniques for estimating FFR from CCTA images are alternatives to HeartFlow FFR_{CT}.[6,7] Unlike HeartFlow FFR_{CT}, these technologies can be used within individual clinics or hospitals, without the need for analyses by an outside entity. However, none of these technologies are yet commercially available.

UTILIZATION, GUIDANCE, AND COVERAGE POLICIES

Many major US medical centers are using HeartFlow FFR_{CT}, including Tufts Medical Center, Loyola University Medical Center, Cedars-Sinai, and University of Kansas Health System. Recent reviews of the evidence conclude that HeartFlow FFR_{CT} has similar sensitivity, but improved specificity, compared to CCTA and thus may avoid unnecessary ICA and revascularization.[12,13] Recent guidance from the National Institute for Health and Care Excellence (NICE) in the UK recommends using HeartFlow FFR_{CT} for patients with stable recent onset chest pain and who are offered CCTA as a part of the clinical pathway.[12] Similarly, a recent Health Technology Assessment by the ECRI Institute reported that the evidence is somewhat favorable for the use of HeartFlow FFR_{CT}.[13]

The Centers for Medicare and Medicaid Services covers HeartFlow FFR_{CT} under a New Technology Ambulatory Payment Classification, which went into effect in January 2018. Hospitals enrolled in Medicare are eligible for a reimbursement rate of $1,450.50 for the addition of the HeartFlow FFR_{CT} analysis (*ie*, does not include charge for CCTA scan).[14] Additionally, several commercial payers, including Cigna and several Blue Cross Blue Shield plans, have

issued policies covering the use of HeartFlow FFR_{CT}.[15] The VHA does not currently have guidelines or coverage policies regarding the use of HeartFlow FFR_{CT} analysis.

EVIDENCE ON THE DIAGNOSTIC ACCURACY AND CLINICAL EFFECTIVENESS OF FFR_{CT} TECHNOLOGIES

METHODS

To identify literature on diagnostic accuracy and clinical effectiveness, our research librarian searched MEDLINE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials using terms for HeartFlow, fractional flow reserve, and computed tomography angiography published since 2017, the end search date of a recent systematic review (see Supplemental Materials for complete search strategies).[16] We limited the search to publications involving human subjects available in the English language. We gathered additional information by cross-checking reference lists, searching citing articles, reviewing FDA documents, searching for ongoing clinical trials, and consulting with content experts.

We focused on findings from the most recent, comprehensive, and highest-quality systematic reviews[17] examining the diagnostic accuracy (*ie*, sensitivity, specificity) or therapeutic impact (*ie*, unnecessary invasive testing, major adverse cardiac events, radiation dose exposure) of FFR_{CT} technologies. We included additional studies published since the most recent systematic review(s). One investigator first reviewed all titles, abstracts, and full-text articles, with a second investigator checking. We resolved all disagreements by consensus.

We used predefined criteria to critically appraise all included HeartFlow FFR_{CT} studies: the Cochrane ROBIS tool for systematic reviews,[18] the QUADAS-2 tool for diagnostic accuracy studies,[19] and the Cochrane ROBINS-I tool for cohort studies.[20] We abstracted data on study design, population characteristics, diagnostic accuracy, and therapeutic and clinical impact outcomes from all included studies. One reviewer first completed all data abstraction and internal validity ratings and was then checked by another. We resolved all disagreements by consensus.

We informally graded the strength of the evidence based on the Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews,[21] by considering risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. Ratings typically range from high to insufficient, reflecting our confidence that the evidence reflects the true effect. For this review, we applied the following general algorithm: evidence received a rating of low to moderate strength if it was comprised of several studies with low to moderate risk of bias and had consistent findings.

To improve our interpretation of the applicability of findings in the literature to current VHA CCTA and ICA practice patterns, we retrieved data from the VHA Corporate Data Warehouse (CDW) on the number of patients receiving CCTA tests and the number of these patients who went on to ICA within 90 days of CCTA testing. We accessed data through the VA Informatics and Computing Infrastructure.[22] We limited the data to those without acute coronary syndrome, a diagnosis of CAD, a history of previous revascularization within the year prior to CCTA, or a history of ICA, in order to best match the patients from the literature in which HeartFlow FFR_{CT} has been examined.[23] Full data on CDW codes used are available upon request.

An earlier version of this report was reviewed by peer reviewers as well as clinical leadership (see supplemental materials for disposition of peer review comments).

RESULTS

Literature Overview

Among 476 potentially relevant citations, we focused on diagnostic accuracy findings from 2 systematic reviews[6,7] (prioritized as the most recent and comprehensive) and 11 primary studies published since the most recent systematic reviews.[24-26,27-34] Additionally, we included 6 studies (in 9 publications) reporting various clinical or cost outcomes of using HeartFlow FFR_{CT}.[23,35-42] We also identified several ongoing studies examining both the diagnostic accuracy and clinical outcomes of HeartFlow FFR_{CT} and other FFR_{CT} technologies. (See Supplemental Materials for literature flowchart and full data tables)

Diagnostic Accuracy

HeartFlow FFR_{CT}

In patients with suspected coronary disease, CCTA with HeartFlow FFR_{CT} is more specific than CCTA alone when compared with the reference standard of FFR during ICA (Table 1). In 2 recent meta-analyses[6,7] the specificity of CCTA plus HeartFlow FFR_{CT} (cut-off < 0.80) was 73% to 76% HeartFlow FFR_{CT} versus 61% to 64% for CCTA alone. The sensitivities of HeartFlow FFR_{CT} and CCTA were similar (84% to 85% HeartFlow FFR_{CT} vs 86% to 87% CCTA). This indicated that the additional functional information provided by HeartFlow FFR_{CT} more accurately detects patients without functionally significant obstructive CAD. However, the precision of the specificity estimates varied between the 2 meta-analyses, with 1 meta-analysis reporting a much wider confidence interval than the other (61% to 82%[7] vs 73% to 79%).[6] We considered possible reasons for the difference in precision. For example, these meta-analyses each included 1 unique study that differed from the other. However, because their overall sample sizes were similar, this difference would not be expected to meaningfully impact precision. Also, we could not identify any clear differences in the meta-analysis techniques used between the analyses, and all included studies used an FFR cut-off value of < 0.80 to classify hemodynamically significant CAD. Therefore, the reason for the difference in precision is unclear and the upper and lower bounds may have different clinically significant implications.[43] Additionally, heterogeneity and publication bias were reported in the 2019 meta-analysis by Hamon et al.[6] Hamon et al[6] found that smaller studies reported better odds ratios, suggesting that small studies with low diagnostic performance may remain unpublished.[6]

Three studies published after the most recent systematic reviews generally reported higher sensitivity (88% to 91%) and specificity (86% to 94% in 2 studies) (Table 2) for HeartFlow FFR_{CT}, compared to what was reported in the 2 previous systematic reviews.[24-26] This may be due to improved scanner characteristics in more recent studies. The exception is that 1 study, Sand et al,[26] reported much lower specificity (55%) than the other studies. The reason for this difference is unclear but is likely due to measurement of the diagnostic accuracy per patient (vs per vessel in the other studies). Measuring diagnostic accuracy per patient may lead to lower specificity, as there are fewer observations to rule out CAD. Sand et al[26] also suggest that the lower specificity reported in their study may be explained by using a different FFR_{CT} value compared to other studies (nadir pre-vessel vs translesional value), and the use of pre-coronary

CCTA nitroglycerine tablets versus spray.[26] A strength of these findings is that they come from multiple studies that directly assessed the diagnostic accuracy of HeartFlow FFR_{CT} compared to FFR during ICA. These studies also consistently reported similar sensitivities, but higher specificities, than that of CCTA. However, our confidence in these findings is moderate, instead of high, because of some important methodological limitations: (1) Some of the studies were unclear about whether the clinicians interpreting HeartFlow FFR_{CT} or reference standard findings had knowledge of the other findings, which could potentially bias the interpretation of the results; and (2) Some studies did not include all patients in their analyses, due to unreadable CCTA scans for the HeartFlow FFR_{CT} analysis (3% to 25% with insufficient image quality)[6] or lack of invasive FFR data (*ie*, 33% without invasive FFR data),[25] and the implications of this missing data are unclear.

Table 1: Systematic Reviews on the Diagnostic Accuracy of HeartFlow

# SRs (# Primary Studies)	Patient Population	HeartFlow (7 studies)		CCTA	
		Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
2 SRs[6,7] (7 studies on HeartFlow)	Patients with stable chest pain with suspected CAD undergoing clinically indicated ICA with FFR after CCTA	84% (80 to 88) to 85% (81 to 90)	73% (61 to 82) to 76% (73 to 79)	86% (85 to 88) to 87% (84 to 91)	61% (54 to 68) to 64% (63 to 66)

Abbreviations: CAD = coronary artery disease

Table 2: New Primary Studies on the Diagnostic Accuracy of HeartFlow

Author, Year N	Patient Population (s)	Prevalence of CAD*	Sensitivity** (95% CI)	Specificity* (95% CI)
Driessen, 2019[24] 157	Suspected CAD undergoing clinically indicated ICA with FFR	45%	90% (84 to 95)	86% (82 to 89)
Pontone, 2018[25] 147	Suspected CAD undergoing clinically indicated ICA with FFR	64%	88% (82 to 94)	94% (91 to 96)
Sand, 2018[26] 143	Suspected CAD with at least 1 coronary stenosis of 40% to 90% on CCTA undergoing clinically indicated ICA with FFR	41%	Per Patient: 91% (81 to 97)	Per Patient: 55% (44 to 66)

*Functionally significant CAD classified as at least one vessel with invasive FFR $\leq$ 0.80
**Per vessel unless otherwise noted
Abbreviations: CAD = coronary artery disease; FFR = fractional flow reserve; ICA = invasive coronary angiography; CCTA = coronary computed tomography angiography

A sub-study from an observational Danish study found that, in patients with intermediate stenoses on CCTA, an FFR_{CT} score < 0.75 was more predictive of ICA results than a score in the range 0.75 to 0.80.[41] Twelve of 13 patients whose score was 0.75 or less had functionally significant coronary artery disease, but only 11/20 patients whose score was 0.76 to 0.80 did. Therefore, the potential limitations of using a cut-off value of 0.80 should be considered.

Other FFR_{CT} Technologies

Other noncommercially available FFR_{CT} technologies (*eg*, Siemens cFFR, models developed at individual institutions internationally, *etc*) have similar diagnostic accuracy to HeartFlow FFR_{CT} (Table 3). In the 2 recent meta-analyses[6,7] that included a total of 15 studies examining the diagnostic accuracy of other noncommercially available FFR_{CT} technologies, the specificity was 75% to 80%, and the sensitivity was 84% to 86%. Eight studies published after the most recent meta-analyses reported similar results but varied based on the type of technology or algorithms used (*ie*, machine learning, computational fluid dynamics, reduced order models, *etc*) (specificity range: 67% to 96%, sensitivity range: 61% to 95%) (see Supplemental Materials for complete data). This suggests that other FFR_{CT} software developed and utilized within individual

institutions may have similar impacts as HeartFlow FFR_{CT}, but the clinical impacts have not been assessed, and the diagnostic accuracy may vary depending on specific algorithms used.

Table 3: Systematic Reviews on Diagnostic Accuracy of Other FFR_{CT} Technologies

# SRs (# Primary Studies)	Patient Population	Sensitivity (95% CI)	Specificity (95% CI)
2 SRs[6,7] (15 studies on non-HeartFlow technologies)	Patients with stable chest pain with suspected or known CAD	84% (80 to 88) to 86% (81 to 89)	75% (71 to 79) to 80% (73 to 86)

Abbreviations: CAD = coronary artery disease

Adequacy of Images

In studies of HeartFlow FFR_{CT}, 10% to 13% of CCTA images were rejected for poor image quality, while 3% to 25% were rejected in studies of independent on-site FFR_{CT} technologies.[6] In real-world settings with more variation in equipment quality and physician and technician expertise, this rate may be even higher. In the cases where CCTA images are rejected due to poor image quality, CCTA would have to be repeated in order to use HeartFlow FFR_{CT}.

Diagnostic and Therapeutic Impact

The PLATFORM study[21,33,34] used a prospective, unblinded consecutive cohort design to compare the clinical outcomes of HeartFlow FFR_{CT} to usual diagnostic (noninvasive or invasive) testing in patients who had an intermediate risk of coronary disease based on the Diamond-Forrester risk model.[44] This study was not a randomized trial. In the first (control) cohort, rates of ICA and costs were measured in patients who received usual care consisting of invasive or noninvasive diagnostic evaluation followed by medical therapy or invasive procedures. Usual care testing and procedures were performed and interpreted locally at all 11 participating practices in Europe and the US, based on standard practices and physician recommendations. In the second (intervention) cohort, the same outcomes were measured in patients who received HeartFlow FFR_{CT}. For the primary analysis, patients were stratified based on the initial physician-recommended diagnostic pathway of either planned noninvasive testing or planned invasive testing.

Initial evaluation of symptomatic patients with intermediate likelihood of obstructive CAD whose physician had planned non-emergent ICA

In the PLATFORM study, use of HeartFlow FFR_{CT} reduced the 90-day rate of ICA overall from 100% to 40% in patients whose local community physicians planned ICA as the initial test to evaluate chest pain. The rate of nonobstructive ICA was 12% in the HeartFlow FFR_{CT} group versus 73% in the usual care group (risk difference -61%, 95% CI -53 to -69).[23,35,36] The rate of obstructive CAD was similar in the 2 groups. The use of FFR_{CT} did not change the proportion of patients who underwent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (28% vs 31%) or increase the rate of major adverse cardiac events (MACE) in 1 year.

The study has 2 main weaknesses. First, criteria for ordering elective ICA as the initial test to evaluate stable, intermediate-probability chest pain were not clear. On average, the patients had a pretest probability of obstructive CAD of about 50%, and about 25% of them had typical angina. The study was conducted in 2013-2015, before the ORBITA trial challenged conventional views

of the role of percutaneous coronary intervention in stable angina.[45] If the PLATFORM clinicians used overly broad criteria for using elective ICA, these results might not be relevant to current VA practice. Second, and most importantly, the study does not show that CCTA plus HeartFlow FFR_{CT} would be any more effective in reducing ICA use than another noninvasive test strategy would in this scenario. Nevertheless, the PLATFORM results are favorable, suggesting that use of FFR_{CT} in patients with new onset chest pain scheduled for elective ICA can distinguish patients who need a coronary intervention (PCI or surgery), while reducing the use of coronary angiograms in patients who do not have functionally significant coronary disease. Similar findings were reported in a sub-analysis of these patients from German sites.[36]

Initial evaluation of symptomatic patients with intermediate likelihood of obstructive CAD whose physician had planned noninvasive testing.

In the PLATFORM study, compared with usual noninvasive test strategies, use of CCTA with HeartFlow FFR_{CT} did not reduce the use of ICA in patients who did not have a definitive CCTA result. Only about 10% of patients who underwent a noninvasive workup needed ICA, whereas 12.5% of HeartFlow FFR_{CT} underwent angiography.[23] These patients had a lower pretest probability of disease (on average, 45%) and were less likely to have typical angina (13%) than the group referred directly to ICA.

A large, single-center, pre-post study conducted in a "real-world" clinical setting in Denmark describes how switching from myocardial perfusion scanning to CCTA plus selective HeartFlow FFR_{CT} as the preferred noninvasive strategy affected downstream diagnostic testing and revascularizations.[40] HeartFlow FFR_{CT} was done in patients who had intermediate (30% to 70%) stenosis on CCTA. FFR_{CT} was required in about 16% (235 of 1391) of patients who underwent CCTA. The unadjusted results of the study are summarized in Table 4. The investigators conducted a propensity score match analysis that showed a reduction in the use of ICA by -4.2 per 100 patients (95% CI -6.9 to -1.6) and a reduction in the rate of finding no obstructive disease on ICA (-12.8 per 100 ICAs, 95% CI -22.2 to -3.4). The risk difference was small and should be compared to the negative results of the PLATFORM trial in patients referred for an initially noninvasive evaluation.

Table 4. Rate of ICA with HeartFlow FFR_{CT} versus Myocardial Perfusion Scanning

Testing Strategy	Rate of ICA (unadjusted)	Rate of Negative ICA (no obstructive disease)	Rate of Coronary Revascularization	Rate of Other Noninvasive Tests (unadjusted)
Myocardial perfusion scanning	12.9%	3.9%	5.4%	20.1%
CCTA plus selective FFR_{CT}	13.7%	2.3%	7.3%	23.1%

Two prospective registry studies reported the frequency of changes in clinical management plans when HeartFlow FFR_{CT} data were added to CCTA results. These studies did not report on risk reduction of ICA or other clinical outcomes, but they give some idea of the rate of positive and negative FFR_{CT} results in practice. The primary endpoint in these studies was the reclassification

rate between CCTA alone versus CCTA and FFR_{CT}-based management plans as determined by the core laboratory.

A large, prospective international registry study (N = 5083) found that, compared with CCTA alone, CCTA plus HeartFlow FFR_{CT} changed clinical management plans for 55% to 67% of patients.[37] With CCTA alone, 53.1% of patients had intermediate stenoses or other findings that would lead to additional testing (including ICA). CCTA plus a negative HeartFlow FFR_{CT} result led to large reductions in plans to use of additional testing and increases in plans to use medical therapy. The impact of positive FFR_{CT} results would depend on clinicians' beliefs regarding appropriate indications for PCI: when the study was conducted in 2015-2017, positive HeartFlow FFR_{CT} results might have increased the use of PCI. In a small US study (N = 75)[38] in a managed health care setting, the addition of HeartFlow FFR_{CT} data was associated with reduced use for ICA (*ie*, moved straight from HeartFlow FFR_{CT} to medical therapy or coronary intervention).

The strengths of this evidence are that these studies directly evaluated outcomes of clinical relevance in actual practice. However, our confidence in these findings is generally low, as they each have important methodological weaknesses. In particular, the Danish study did not provide sufficient information about the propensity analysis to assess its validity. In the other studies, the main weakness is that it is unclear whether HeartFlow FFR_{CT} affected actual management, rather than what clinicians said their plans were. Unclear blinding of outcome measurement may have influenced changes in clinical management plans,[37] and unclear methods for measuring outcomes may have led to misclassification or potential bias in outcome measurement.[39,40]

Impact on Clinical Outcomes and Cost

The duration of follow-up to assess clinical outcomes was limited in most studies to 90 days (1 study reported outcomes up to 1 year).[35] No differences in MACE or other adverse events were reported with the use of HeartFlow FFR_{CT}, including in patients whose ICA was cancelled (see Supplemental Materials for full data tables).[23,35-39,41] A longer follow-up period would be needed to determine whether FFR_{CT} and ICA have similar rates of coronary events or if additional patients managed with FFR_{CT} undergo coronary angiography over the next 1 to 2 years. Measurement of quality of life was limited to the PLATFORM trial,[23,35,36,39] and scores were generally similar between groups, with a greater improvement in quality of life reported with HeartFlow FFR_{CT} in the planned noninvasive subgroup.

In the PLATFORM trial, mean costs at 90 days and 1 year were lower in the HeartFlow FFR_{CT} cohort compared to the usual care cohort in the subgroup of patients with planned ICA (90 days: \$7,343 HeartFlow FFR_{CT} vs \$10,734, $P < .0001$ and 1 year: \$8,127 HeartFlow FFR_{CT} vs \$12,145 usual care, $P < .0001$).[35,42] However, no differences in costs were observed between the groups in the subgroup of patients with planned noninvasive testing. Similar to the findings for impact on ICA, this indicates that the cost benefit of HeartFlow FFR_{CT} is likely limited to those initially referred for ICA.

We did not identify any studies that assessed clinical or cost outcomes of other FFR_{CT} technologies.

CONSIDERATIONS FOR THE ANTICIPATED IMPACT OF HEARTFLOW FFR_{CT}

The above-described literature suggest 3 potential clinical scenarios in which HeartFlow FFR_{CT} may be used, which include: (1) in patients who are planned to be directly referred to ICA in lieu of noninvasive evaluation, (2) as a substitute for other noninvasive testing, and (3) as a part of the clinical pathway for patients who undergo CCTA (Table 5). The impact of using HeartFlow FFR_{CT} for each scenario largely depends on their respective applicability to VHA practice patterns. Although the majority of ICAs in the VA are done for patients who have known CAD, the below described scenarios do not mention this type of FFR_{CT} utilization because it has not been studied in this population.

Table 5. Clinical Scenarios for the Use of HeartFlow FFR_{CT}*

Scenario 1: Use of HeartFlow FFR_{CT} in patients who are planned to be directly referred to ICA in lieu of noninvasive evaluation	**Scenario 2:** Use of HeartFlow FFR_{CT} for patients referred for noninvasive diagnostic testing	**Scenario 3:** Use of HeartFlow FFR_{CT} for patients undergoing CCTA who have intermediate stenosis of 1 or more vessels
Evidence: risk reduction for ICA without obstructive CAD (-61%, 95% CI -53% to -69)[23,35] NNT = 2 No difference in MACE outcomes at 1 year	Evidence: no risk reduction for ICA without obstructive CAD (6.5%, 95% CI -1.4% to 14.4%)[23,35] NNT NA No difference in MACE outcomes at 1 year	Evidence: No studies reporting risk reduction of ICA

*Estimates calculated using data from cited recent clinical studies
Abbreviations: MACE = major adverse cardiac events NNT = number needed to test; NA = not applicable; CAD = coronary artery disease; ICA = invasive coronary angiography; CCTA = coronary computed tomography angiography

Scenario 1

Among stable outpatients with suspected CAD chest pain who are referred for ICA without a noninvasive workup, the use of HeartFlow FFR_{CT} clearly reduced the use of ICA. Only 2 HeartFlow FFR_{CT} analyses were needed to prevent 1 ICA, and the impact on radiation exposure is likely to be relatively small, since CCTA scanning is substituted for angiography.

The applicability of this result to the VA is unclear. According to a study from the VA Clinical Assessment Reporting and Tracking Program, 25% of Veterans undergoing non-emergent ICA without a history of cardiac disease are directly referred to ICA without noninvasive testing,.[50] However, this study did not identify stress tests performed outside the VA that were not captured by Medicare, and so this number may be lower. Currently, clinical practice guidelines recommend direct referral only for patients who have a very high probability of disease (>90%) based on symptoms and risk factors or those who have life-threatening arrhythmia or an unexplained reduction in ejection fraction.[1] It is not known what proportion of direct referrals for ICA within the VA are consistent with these guidelines. Among candidates for a noninvasive workup who are referred directly to ICA, there is no basis for assuming that CCTA with HeartFlow FFR_{CT} would prevent more ICAs than other noninvasive tests. However, facilities

that have high rates of negative ICAs, long wait times for elective ICA, and capacity for additional CCTA might be candidates for adding HeartFlow FFR_{CT} to CCTA.

Scenario 2

Using CCTA with HeartFlow FFR_{CT} instead of a stress test as the initial noninvasive test has little impact on the use of ICA and likely increases exposure to radiation. The best evidence, from the PLATFORM study, suggests that it may increase the number of ICAs compared to usual care.[23] Evidence from other observational studies is not strong enough to change this conclusion.

Scenario 3

The third scenario, use of HeartFlow FFR_{CT} for patients who are already undergoing CCTA, is the scenario currently recommended by NICE guidelines[40,41] and promoted on the manufacturer website ("If your physician suspects coronary artery disease and orders a coronary CT, your doctor may decide that you are eligible for a HeartFlow Analysis").[46]

Little direct evidence supports the impact of this strategy, but the effect can be estimated from sensitivity and specificity estimates for CCTA versus CCTA plus FFR_{CT} in patients with intermediate stenoses (30% to 70%) on CCTA. We conducted a "what-if" analysis depicting the potential impact of adding FFR_{CT} to CCTA with the presence of an intermediate-stenosis lesion. The following general assumptions were used in the analysis (Table 6).

Table 6. Assumptions for Impact of FFR_{CT}

Variable	Estimate	Range
Prevalence of patients with intermediate-stenosis lesions on CCTA	0.55	0.35 to 0.75
Proportion of these patients who have functionally significant CAD	0.25	--
Proportion of patients with positive CCTA that undergo ICA	0.65	--
Sensitivity of CCTA alone*	0.86	(0.85 to 0.88)
Specificity of CCTA alone*	0.64	(0.63 to 0.66)
Sensitivity of FFR_{CT} *	0.84	(0.80 to 0.88)
Specificity of FFR_{CT}*	0.76	(0.73 to 0.79)

* = Hamon 2019; Abbreviations: CCTA = coronary computed tomography angiography; CAD = coronary artery disease; FFR_{CT} = fractional flow reserve computed tomography; ICA = invasive coronary angiography

Using the above assumptions, for every 1,000 patients undergoing CCTA, 34 ICAs would be prevented, or 1 for every 10 intermediate-stenosis patients. When varying these assumptions, the impact of FFR_{CT} in preventing ICAs would be lower when the probability of disease is higher, the specificity of CCTA plus FFR is lower, or the probability of intermediate stenosis is lower, while more ICAs would be prevented if more patients are referred to ICA after positive CCTA or the probability of intermediate stenosis is higher (Table 7).

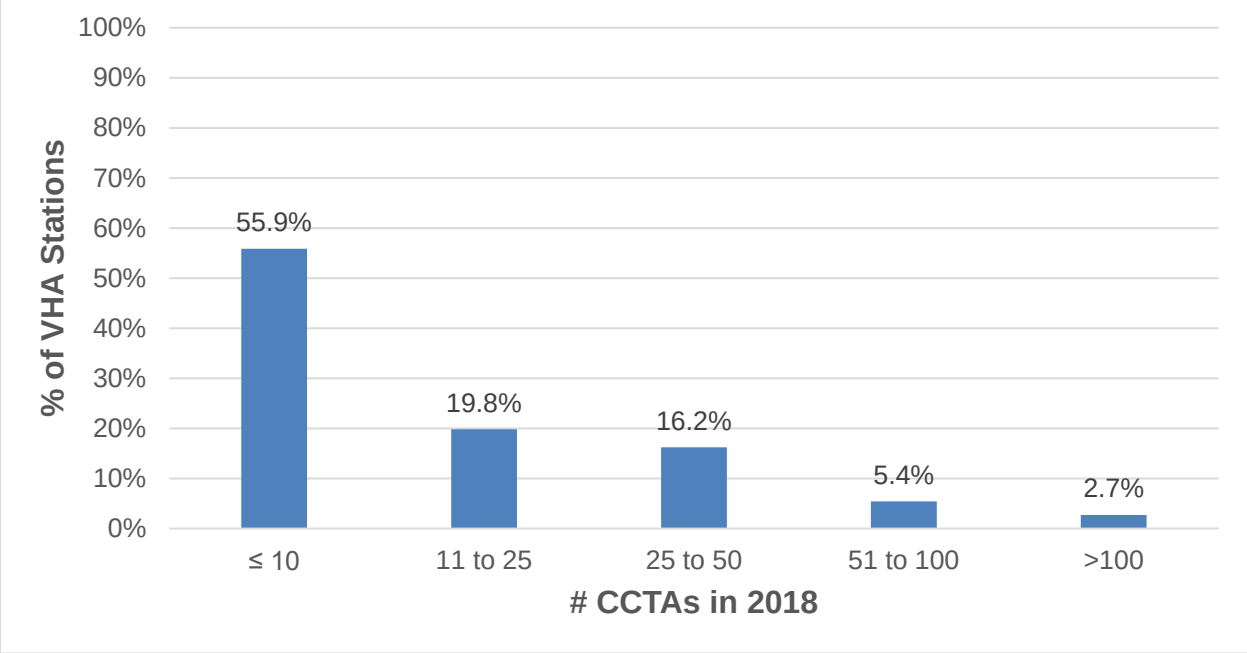
Table 7. Impact of FFR_{CT} with Varying Assumptions

Assumptions	Reduction in ICAs
Base case (Table 6)	34 per 1,000 CCTAs
Probability of CAD increased to 0.5	25 per 1,000 CCTAs

Specificity of FFR_{CT} reduced to 0.7	18 per 1,000 CCTAs
Proportion of ICA after positive CCTA increased to 0.8	42 per 1,000 CCTAs
Probability of intermediate stenosis reduced to .35	22 per 1,000 CCTAs
Probability of intermediate stenosis increased to .75	46 per 1,000 CCTAs

The applicability of these results to the VA depend on the frequency of use of CCTA within the VHA. Data from the VHA national CDW showed a total of 1,925 VHA patients without a diagnosis of CAD or prior history of revascularization or ICA undergoing CCTA testing in 2018. The majority of VHA sites (76%) reported fewer than 25 CCTAs during the calendar year (Figure 1). This low number of CCTAs reported may be influenced by access to CCTA and current American College of Cardiology Foundation/American Heart Association guidance for diagnosis of stable CAD, which recommends CCTA only for those who are unable to exercise or who have contraindications to stress testing.[47,48] Of these VHA patients undergoing CCTA, only 18.5% underwent ICA within 90 days after CCTA. This is similar to rates of ICA after CCTA in patients with suspected but unknown CAD reported in other studies (9.6[49] to 16%[50]). This indicates that most patients receiving CCTA have normal or non-obstructive results and do not end up requiring ICA. In these cases, further imaging, including FFR_{CT} analysis, is not necessary. Additionally, among Veterans who receive ICA, fewer are negative (ICA without obstructive CAD (21.4%))[51] compared with the National Cardiovascular Data Registry (39.2%).[52] The relatively low number of CCTAs performed in the VHA, along with the low rate of ICA after CCTA, and the lower rate of negative ICA, suggest that the impact of regularly utilizing HeartFlow FFR_{CT} for all patients undergoing CCTA across all VHA sites may be low.

Figure 1. Usage of CCTA Among VHA Stations



KEY FINDINGS

- Regular use of HeartFlow FFR_{CT} in place of other noninvasive tests does not appear warranted, as HeartFlow FFR_{CT} led to a higher rate of use of ICA when used as a substitute for planned noninvasive cardiovascular testing. We found no evidence to support wider use of CCTA in place of other noninvasive tests in VA.

- In patients with suspected coronary disease, CCTA with HeartFlow FFR_{CT} is more specific than CCTA alone when compared with the reference standard of FFR during ICA, and the additional functional information provided by HeartFlow FFR_{CT} more accurately detects patients without functionally significant obstructive CAD.

- We identified 3 potential clinical scenarios in which HeartFlow FFR_{CT} may be used, which include: (1) in patients who are planned to be directly referred to ICA in lieu of noninvasive evaluation, (2) as a substitute for other noninvasive testing, and (3) as a part of the clinical pathway for patients who undergo CCTA.

- HeartFlow FFR_{CT} reduces the use of coronary angiography when a high proportion of patients referred to ICA have negative results, either after direct referral to ICA with no noninvasive testing or when initial CCTA results show an intermediate-stenosis lesion.

- Key factors that could influence the impact and cost-effectiveness of HeartFlow FFR_{CT} in VA include: reasons for direct referral to ICA with no noninvasive testing, frequency of CCTA use, probability of ICA referral after positive CCTA, and prevalence of intermediate stenosis identified by CCTA and functionally significant CAD in the population. Unfortunately, we did not find data on these factors.

- The effect of FFR_{CT} on MACE outcomes is uncertain. Future research should evaluate MACE outcomes on a longer-term basis.

- As an alternative to HeartFlow FFR_{CT}, the VHA may also consider developing its own approach to FFR modeling. Although individual health care institutions have developed and utilized their own FFR_{CT} software that has shown similar diagnostic accuracy as HeartFlow FFR_{CT}, their impact on ICA or clinical outcomes is not yet known.

LIMITATIONS

Assessment of practical barriers and facilitators to HeartFlow FFR_{CT} implementation was outside the scope of this report. We did not evaluate implementation experiences within the VHA. Typically, interviews with clinical and administrative personnel can uncover gaps between expected and actual performance of a new technology.[53]

Another limitation of our study is that we were unable to incorporate data on factors that would affect the impact of HeartFlow FFR_{CT} on ICA in the VA. Specifically, we were unable to incorporate data about the reasons for direct referral to ICA with no noninvasive testing, the probability of ICA referral after positive CCTA, or the prevalence of intermediate stenosis identified by CCTA. Because the rate of negative ICAs is lower in the VA than it is in other settings, the added value of FFR_{CT} in VA may be less than that suggested by the scenarios we examined. Careful assessment of implementation experience and need is indicated prior to any decision about expanding the use of FFRCT technologies in VHA.

EVIDENCE GAPS

There are several important gaps in the evidence. First, no studies have assessed diagnostic accuracy in a VA population. As diagnostic accuracy can differ in different populations,[54] it is unclear whether the previously reported test performance characteristics from non-VA populations would be similar in VA populations and settings. The utility of FFR_{CT} depends on the characteristics of patients who undergo CCTA and on how decisions about ICA are made within a particular setting. We do not know whether VA patients who have an initial workup with CCTA are similar to those in the trials of FFR_{CT}. Second, impact of positive FFR_{CT} results in the context of current PCI practices in VA is unclear. Based on the available study conducted in 2015-2017, positive HeartFlow FFR_{CT} results might have increased the use of PCI.[37] However, we do not know how current PCI practices in VA would influence clinical decision-making based on positive FFR_{CT} results. Therefore, studies are needed to assess the diagnostic impact of FFR_{CT} technologies on the use of ICA and PCI in the VA. Third, there are few data regarding the impact of FFR_{CT} on clinical outcomes and more studies in this area are needed. Finally, we found no evidence that would justify substituting CCTA with FFR_{CT} for another noninvasive test such as nuclear MPI, especially in settings where nuclear MPI is used in accordance with current practice guidelines and is part of a well-established workflow. Additionally, we found no studies that compared FFR_{CT} to any other specific noninvasive diagnostic technologies. Direct evidence about how FFR_{CT} compares to other widely used noninvasive diagnostic tests used in the VA is a necessary precondition for considering substituting CCTA with FFR_{CT} for another noninvasive test.

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Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend content experts; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

David Atkins, MD, MPH
VA HSR&D Director

Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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