Evidence Brief: Coronary Computed Tomography Angiography with Fractional Flow Reserve in Noninvasive Diagnosis of Coronary Artery Disease

June 2021

Prepared for:

Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service
Washington, DC 20420

Prepared by:

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

Authors:

Johanna Anderson, MPH
Sarah Young, MPH
Mark Helfand, MD, MPH, MS

VA | 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.

The program is composed of three ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

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

Recommended citation: Anderson J, Young S, Helfand M. Evidence Brief: Coronary Computed Tomography Angiography with Fractional Flow Reserve in Noninvasive Diagnosis of Coronary Artery Disease. Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #09-199; 2021. Available at: https://www.hsrd.research.va.gov/publications/esp/reports.cfm.

This report is based on research conducted by the Evidence Synthesis Program (ESP) Center located at the **Portland VA Health Care System, Portland, OR,** funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

TABLE OF CONTENTS

FIGURES AND TABLES

EXECUTIVE SUMMARY

Key Findings

- **Diagnostic accuracy**
  Previous findings: Compared to coronary computed tomography angiography (CCTA) alone, HeartFlow FFR_{CT} analysis (HeartFlow) likely has good diagnostic accuracy, and a higher specificity and similar sensitivity for identifying obstructive coronary disease when using a reference standard of invasive fractional flow reserve.
  New evidence: Several new studies agree with these findings.
- **Patients referred directly for invasive coronary angiography (ICA)**
  Previous findings: HeartFlow reduced ICA use in community settings, but the applicability to VA settings is low.
  New evidence: None
- **Patients with suspected coronary disease referred for noninvasive testing**
  Previous findings: In community settings, HeartFlow increased ICA use compared to other noninvasive strategies.
  New evidence: None
- **Patients with suspected coronary disease referred for CCTA**
  Previous findings: None
  New evidence: A single new study examined ICA use in patients with suspected coronary disease undergoing CCTA, but findings are limited by major methodological concerns.
- **Effect on cardiac events**
  Previous findings: In the short term (90 days to 1 year), rates of cardiac events were similar in those receiving HeartFlow and those receiving other diagnostic strategies, and in patients whose clinical management plans changed after use of HeartFlow compared to those whose clinical management plans did not change with use of HeartFlow.
  New evidence: Several new studies agree with these findings.
- **Future research**
  Research in VA settings and comparing HeartFlow to specific noninvasive strategies is needed to determine the potential impact of HeartFlow within the VA.

Background

The Evidence Synthesis Program is responding to a request from the VA Health Services Research and Development Service (HSR&D) for an updated evidence brief on the diagnostic, therapeutic, and clinical impact of CCTA with FFR_{CT} technologies for the diagnosis of CAD. Findings from this review will be used to inform use of FFR_{CT} technologies in the VHA.

Methods

To identify studies, we searched MEDLINE®, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and other sources up to February 2021. We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence. See our PROSPERO protocol for our full methods.

Noninvasive diagnostic strategies for evaluation of patients with stable chest pain include functional imaging (single-photon emission CT, positron emission tomography scanning, pharmacologic echocardiography, *etc*), and anatomic imaging with coronary computed tomography angiography (CCTA). CCTA generally has good diagnostic accuracy, but it lacks the ability to assess the functional significance of coronary artery disease (CAD). Fractional flow reserve (FFR) measured invasively during coronary angiography is considered the gold standard for detecting hemodynamically significant CAD. Noninvasive techniques have been developed to estimate FFR from CCTA images (FFR_{CT}) with the aim of gaining both functional and anatomical information on the extent of coronary artery narrowing and the impact on blood flow.

HeartFlow, currently the only commercially available and FDA-cleared FFR_{CT} technology, uses computer modeling and CCTA images to produce color-coded maps showing functionally significant coronary artery narrowing.

In 2019, the Evidence Synthesis Program (ESP) prepared a white paper report synthesizing the evidence on the diagnostic accuracy and therapeutic and clinical impact of FFR_{CT} technologies for the diagnosis of CAD. Three clinical scenarios for the potential use of HeartFlow were identified from the literature, and, for each scenario, important gaps in the evidence were described (Table ES-1). Briefly, we found that in community settings, HeartFlow FFR_{CT} analysis reduced the use of ICA among patients referred directly to ICA. This evidence was not applicable to the VA, where practices regarding direct referral to ICA and use of CCTA differ from those in community settings. We did not find compelling evidence that using CCTA plus HeartFlow would reduce ICA use in patients who undergo other types of noninvasive testing for suspected coronary disease.

Table ES-1. Evidence Gaps Identified in 2019 ESP Report on FFR_{CT} Technologies

Outcome		Evidence Gaps Identified in 2019 ESP Report
Diagnostic Accuracy		No evidence in VA.
ICA Use	Clinical Scenario 1: HeartFlow use in patients directly referred to ICA	Evidence has low applicability to VA settings because of differences in ICA referral practices and use of CCTA.
	Clinical Scenario 2: HeartFlow use as a substitute for other noninvasive testing	No direct comparison to other noninvasive strategies. Evidence has low applicability to VA settings because of differences in ICA referral practices and use of CCTA.
	Clinical Scenario 3: HeartFlow use in patients referred for CCTA	No evidence.
Clinical Outcomes		No evidence on long-term clinical outcomes. No evidence in VA settings.

Abbreviations: ESP=Evidence Synthesis Program, ICA=Invasive coronary angiography, VA=Veterans Administration.

The goal of the present report was to provide an updated synthesis of the evidence on the use of HeartFlow for noninvasive diagnosis of CAD, focusing on evidence that is most relevant to the VA and most applicable to evidence gaps identified in the 2019 ESP review. Based on our updated summary of findings (Table ES-2), we found that new evidence has not resolved the evidence gaps identified in the 2019 ESP report:

- **Diagnostic accuracy:** New evidence on the diagnostic accuracy of HeartFlow agreed with findings from the 2019 ESP report, confirming that HeartFlow likely has good diagnostic accuracy and a higher specificity and similar sensitivity for identifying obstructive coronary disease to that of CCTA alone. No studies were in VA settings.
- **ICA Use:** *Clinical Scenario 1:* No new evidence examined HeartFlow use in patients planned to be directly referred to ICA.

  Clinical Scenario 2: No new evidence examined HeartFlow use as a substitute for other noninvasive testing.

Clinical Scenario 3: A single new study compared HeartFlow use in patients undergoing CCTA alone or HeartFlow. However, this study had severe methodological limitations. Although the specificity of HeartFlow is improved over CCTA alone, the impact on downstream utilization of ICA needs to be verified.

- **Clinical Outcomes:** New evidence supports previous findings that short-term (90 days to 1 year) rates of cardiac events are similar in those receiving HeartFlow and those receiving other diagnostic strategies, and in patients whose clinical management plans changed after use of HeartFlow compared to those whose clinical management plans did not change with use of HeartFlow. A single new study on longer-term (~5 years) clinical outcomes reported rates of major adverse cardiac events but did not compare clinical events between those receiving HeartFlow and other diagnostic strategies.

Table ES-2. Updated Summary of Findings

Outcome	Evidence	Summary of Findings
Diagnostic Accuracy	3 SRs[1-3] *(1 new)* 7 primary studies[4-10] *(5 new)*	Several systematic reviews with few study limitations and precise estimates consistently reported good diagnostic accuracy for HeartFlow (AUC range 0.87 to 0.89). Several primary studies published since the systematic reviews with moderate study limitations generally supported these findings but had a broader range of estimates (AUC range 0.82 to 0.94). **Moderate SOE**
ICA Use	1 cohort[11] *(0 new)*	*Scenario 1: Compared to direct referral to ICA* HeartFlow reduced ICA use compared to planned ICA in a single cohort directly comparing HeartFlow to planned ICA. **Low SOE** (moderate study limitations and imprecise estimates)
	2 cohorts[11,12] *(0 new)*	*Scenario 2: Compared to other noninvasive strategies* HeartFlow may increase ICA use compared to other noninvasive testing strategies. Two cohorts reported conflicting findings. **Low SOE** (moderate study limitations, imprecise estimates, inconsistent results, and limited comparisons to specific noninvasive testing strategies)
	1 cohort[13] *(1 new)*	*Scenario 3: Compared to CCTA alone* It is unclear whether HeartFlow reduces ICA use compared to CCTA alone. A single cohort with severe study limitations and unknown precision directly compared HeartFlow to CCTA alone. **Insufficient SOE**
Change in Clinical Management	3 cohorts[14-16] *(1 new)* 6 case series[17-23] *(3 new)*	*Scenario 3: Compared to CCTA alone* HeartFlow changed treatment plans in 28% to 67% of patients compared to CCTA alone (48% to 91% had ICA cancellation) in several cohorts and case series with moderate study limitations and mostly precise estimates reporting a wide range of estimates of changes in treatment plans. **Moderate SOE**
Adverse Clinical Events	3 cohorts[11,15,16,24] *(0 new)* 4 case series[19,21,22,25-28] *(2 new)*	MACE events were low (<2%) at 90 days to 1 year in patients receiving HeartFlow and were similar in patients receiving HeartFlow or other diagnostic strategies in several cohorts and case series with generally consistent findings. **Low SOE** (moderate study limitations, unknown precision, and sparse data)

Abbreviations. AUC=area under the curve, CCTA=coronary computed tomography angiography, CI=confidence interval, ICA=invasive coronary angiography, MACE=major adverse cardiac events, SOE=strength of evidence, SR=systematic review.

Data from the VA Corporate Data Warehouse show that use of CCTA within the VA remains relatively low (~2000 performed each year from 2018 to 2020), suggesting that regular use of HeartFlow for all patients referred for CCTA within the VA may have a low impact on ICA use. However, targeted use of HeartFlow in facilities with a high volume of CCTA use in specific clinical scenarios may have the potential to reduce unnecessary use of coronary angiography. CCTA use, a prerequisite for using FFR_{CT} analysis, is unlikely to change in the VA unless clinicians are persuaded by direct evidence that a CCTA-based strategy is preferable to other noninvasive strategies. Challenges in integrating HeartFlow into current clinical pathways and the need for access to and training for CCTA remain barriers for the use of HeartFlow within the VA. Population (demographics, cardiac risk factors, *etc*) and clinical (types of noninvasive strategies used, access to CCTA and/or ICA, *etc*) characteristics may differ between the VA and those in trials of HeartFlow, and research in VA settings is needed to determine the potential impact of HeartFlow within the VA. Controlled studies of ICA rates in patients with suspected coronary disease receiving CCTA or other noninvasive strategies and comparing HeartFlow to specific noninvasive strategies are needed.

EVIDENCE BRIEF

PURPOSE

The ESP Coordinating Center (ESP CC) is responding to a request from the VA Health Services Research and Development Service (HSR&D) for an updated evidence brief on the diagnostic, therapeutic, and clinical impact of coronary computed tomography angiography (CCTA) with fractional flow reserve (FFR_{CT}) technologies for the diagnosis of coronary artery disease (CAD). Findings from this review will be used to inform use of HeartFlow FFR_{CT} analysis in the Veterans Health Administration (VHA).

BACKGROUND

A more detailed background is provided in the 2019 ESP report on FFR_{CT} technologies.[29]

CCTA TECHNOLOGIES

Patients with chest pain and low to intermediate pre-test probability of stable CAD are typically evaluated noninvasively, commonly with standard exercise electrocardiogram (ECG) for patients who are able to exercise. For patients who cannot exercise or have an uninterpretable resting ECG, noninvasive functional imaging options include pharmacologic stress plus nuclear imaging (single-photon emission CT (SPECT) or positron emission tomography (PET) scanning) or pharmacologic echocardiography.[30] Noninvasive anatomical imaging with CCTA is another option for patients who cannot exercise and who have intermediate to high probability of significant coronary artery disease.[31,32]

CCTA generally has a high sensitivity for functionally significant coronary lesions (range 86% to 95% in recent meta-analyses[2,3,33]), with few false negatives. However, the specificity is 61% to 79%,[2,3,33] and the potential for false positives often leads to the use of invasive coronary angiography (ICA) to exclude the presence of significant CAD and assess its functional significance. The gold standard for detecting hemodynamically significant CAD is fractional flow reserve (FFR), or the fraction of maximum blood flow in a restricted artery.[34] Measurement of FFR requires an invasive procedure to place a pressure wire to calculate pressure and blood flow information,[35,36] and novel techniques have emerged to calculate FFR noninvasively from CCTA images (FFR_{CT}). The aim of FFR_{CT} is to gain both functional and anatomical information on the extent of coronary artery narrowing and the impact on blood flow.[36,37]

HeartFlow FFR_{CT} Analysis

HeartFlow uses computer modeling and CCTA images to produce noninvasive 3-dimensional FFR models, and is the only commercially available and FDA-cleared FFR_{CT} technology.[38,39] Physicians or health systems can send high-quality (*ie*, artifact-free) CCTA images to HeartFlow, Inc. (Redwood City, California), where the images are used to produce a color-coded map of the coronary arteries with estimated FFR values. The map shows the physiological impact of coronary artery narrowing on blood flow, and physicians can manipulate the model to examine each vessel and analyze the location and severity of lesions. HeartFlow also offers an interactive tool ("HeartFlow Planner"), which can model various clinical scenarios and treatment plans based on the patient-specific HeartFlow model.[40]

A recent Health Technology Assessment by the ECRI Institute reported that evidence on the diagnostic accuracy and therapeutic and clinical impact is somewhat favorable for the use of HeartFlow for guiding treatment in patients with suspected CAD.[41] Recent narrative reviews generally agree that HeartFlow offers advantages in noninvasive diagnosis of CAD with improved diagnostic accuracy and reductions in ICA use in specific clinical situations.[42,43] Additionally, guidance from the National Institute for Health and Care Excellence (NICE) in the UK recommends using HeartFlow for patients with stable recent onset chest pain who are offered CCTA as a part of the clinical pathway.[44] In the US, many major medical centers use HeartFlow, and the Centers for Medicare and Medicaid Services (CMS) and several commercial payers cover the use of HeartFlow in specific clinical situations.[45,46] The VA does not currently have guidelines or coverage policies regarding the use of HeartFlow FFR_{CT} analysis.

Other FFR_{CT} Technologies

Numerous other FFR_{CT} algorithms exist, including Siemens Healthcare cFFR, Canon Medical Systems CT-FFR, and independent, locally developed machine learning and reduced order modeling techniques.[2,3,38] Unlike HeartFlow, these technologies can be used within individual clinics, hospitals, or research environments without the need for analyses by an outside entity. However, none are commercially available or FDA cleared at the time of this report.

2019 ESP CC REPORT ON FFR_{CT} TECHNOLOGIES

In 2019, the ESP prepared a white paper report synthesizing the evidence on the diagnostic accuracy and therapeutic and clinical impact of FFR_{CT} technologies for the diagnosis of CAD.[29] Key findings and evidence gaps from this report are summarized in Table 1. For diagnostic accuracy outcomes, 2 meta-analyses and several subsequent primary studies generally agreed that HeartFlow is more specific than CCTA alone, using a reference standard of invasive FFR. Studies examining reductions in ICA use fell into 3 clinical scenarios for the potential use of HeartFlow: (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 referred for CCTA. The PLATFORM trial[11] reported that HeartFlow reduced the use of coronary angiography in patients planned to be directly referred to ICA (scenario 1), but led to a higher rate of coronary angiography in patients planned for noninvasive testing (scenario 2). No studies reported on ICA use as a part of the clinical pathway for patients referred for CCTA (scenario 3). Evidence on the impact of the use of HeartFlow on clinical outcomes was limited to short-term (90-day to 1-year) findings.

As no trials were conducted in VA settings – and because the utility of HeartFlow depends on clinical practices and frequency of use of CCTA, the characteristics of patients who undergo CCTA, and on how decisions about ICA are made within a particular setting – the previous report concluded that additional trials were necessary to understand the potential impact of HeartFlow use within the VA. Additionally, further data on the long-term impact of HeartFlow on clinical outcomes were needed. Finally, existing evidence did not justify substituting CCTA with FFR_{CT} for other noninvasive tests, and direct evidence was needed about how HeartFlow compares to other noninvasive diagnostic tests, specifically those widely used in the VA.

Table 1. Summary of Findings and Evidence Gaps in 2019 ESP Report

2019 ESP Report Summary of Select Key Findings	**Diagnostic accuracy:** In patients with suspected coronary disease, CCTA with HeartFlow is more specific than CCTA alone using the reference standard of invasive FFR. The additional functional information provided by HeartFlow more accurately detects patients without functionally significant obstructive CAD.
	Reduction in ICA use: • *Clinical Scenario 1: In patients planned to be directly referred to ICA:* HeartFlow led to a lower rate of coronary angiography in patients planned to be directly referred to ICA. • *Clinical Scenario 2: As a substitute for other noninvasive testing:* HeartFlow led to a higher rate of ICA use when used as a substitute for planned noninvasive cardiovascular testing. • *Clinical Scenario 3: In patients referred for CCTA:* No evidence on the impact on ICA use.
	Clinical outcomes: Rates of MACE outcomes were low and were similar between patients using HeartFlow and other diagnostic strategies. The effect on longer-term MACE outcomes is uncertain.
Evidence Gaps for VA	**Reduction in ICA use:** Evidence is needed in a VA setting demonstrating a reduction in ICA with HeartFlow compared to current VA diagnostic strategies.
	Clinical outcomes: Evidence is needed demonstrating the impact of HeartFlow compared to current VA diagnostic strategies on longer-term clinical and MACE outcomes.

Abbreviations: CCTA=coronary computed tomography angiography, FFR=fractional flow reserve, ICA=invasive coronary angiography, MACE=major adverse cardiovascular events.

The goal of the present report was to provide an updated synthesis of the evidence on the use of HeartFlow for noninvasive diagnosis of CAD, focusing on evidence that is most relevant to the VA and most applicable to evidence gaps identified in the 2019 ESP review.

METHODS

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; CRD42021243717).

KEY QUESTIONS

Key Question 1: What is the diagnostic accuracy of HeartFlow FFR_{CT} analysis for diagnosing CAD?

Key Question 2: What is the diagnostic and therapeutic impact of HeartFlow FFR_{CT} analysis in guiding the diagnosis and treatment of CAD?

Key Question 3: What is the impact of the use of HeartFlow FFR_{CT} analysis on clinical outcomes and cost in the diagnosis and treatment of CAD?

ELIGIBILITY CRITERIA

The ESP included studies that met the following criteria:

- **P**opulation: Adult candidates for non-invasive evaluation for coronary disease or invasive coronary angiography
- **I**ntervention: HeartFlow FFR_{CT} analysis
- **C**omparator: Any other diagnostic strategy for CAD (coronary computed tomography angiography [CCTA], exercise electrocardiogram [ECG], exercise or pharmacologic stress echocardiography, exercise or pharmacologic cardiac nuclear imaging with single-photon emission computed tomography [SPECT], positron emission tomography [PET], cardiovascular magnetic resonance [CMR], *etc*)
- **O**utcomes: Diagnostic accuracy (sensitivity, specificity, *etc*), use of invasive coronary angiography, changes in clinical or therapeutic management of patients, cost, major adverse cardiac events (MACE), other adverse clinical events (mortality, myocardial infarction, *etc*)
- **T**iming: Any
- **S**etting: Any
- **S**tudy design: Any, but we may prioritize articles using a best evidence approach to accommodate the timeline.

DATA SOURCES AND SEARCHES

To identify recent literature on diagnostic accuracy and clinical effectiveness, we 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 2019, the end search date of our recent evidence review[29] (see

Appendix A in supplemental materials for complete search strategies). The search was limited to publications involving human subjects available in the English language. Additional information was gathered by cross-checking reference lists, searching citing articles, reviewing FDA documents, searching for ongoing clinical trials, and consulting with content experts. One investigator first reviewed all titles, abstracts, and full-text articles, with a second investigator checking. All disagreements were resolved by consensus or discussion with a third reviewer.

DATA ABSTRACTION AND ASSESSMENT

We abstracted data on study design, population characteristics, diagnostic accuracy, and therapeutic and clinical impact outcomes from all included studies. All data abstraction was first completed by 1 reviewer then checked by another reviewer. We used predefined criteria to critically appraise all included studies, including the Cochrane ROBIS tool for systematic reviews,[47] the QUADAS-2 tool for diagnostic accuracy studies,[48] the Cochrane ROBINS-I tool for cohort studies,[49] and the tool developed by Murad et al[50] for case series. For noncomparative studies assessing changes in clinical management plans and real-world implications of utilizing HeartFlow, we used ROBINS-I to identify strengths and deficiencies of the studies. All included studies were appraised independently by 2 reviewers. Disagreements were resolved by consensus or discussion with a third reviewer.

We graded the strength of the evidence based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.[51] This approach provides a rating of confidence in reported findings based on study methodology (design, quality, and risk of bias), consistency (whether effects are in the same direction and have a consistent magnitude), directness (whether assessed outcomes are clinically important to patients and providers), and precision (narrowness of the range of confidence intervals). For this review, we applied the following general algorithm: *high strength* evidence consisted of multiple studies with low study limitations, direct outcomes, narrow confidence intervals, and consistent findings; *moderate strength* evidence consisted of multiple studies with low to moderate study limitations, direct outcomes, and consistent findings; *low strength* evidence consisted of single or multiple studies with moderate study limitations and wide confidence intervals and/or inconsistent findings; and *insufficient* evidence consisted of a single study with moderate or high study limitations, or no available trials. Strength of evidence ratings were applied to primary outcomes for all included studies.

SYNTHESIS

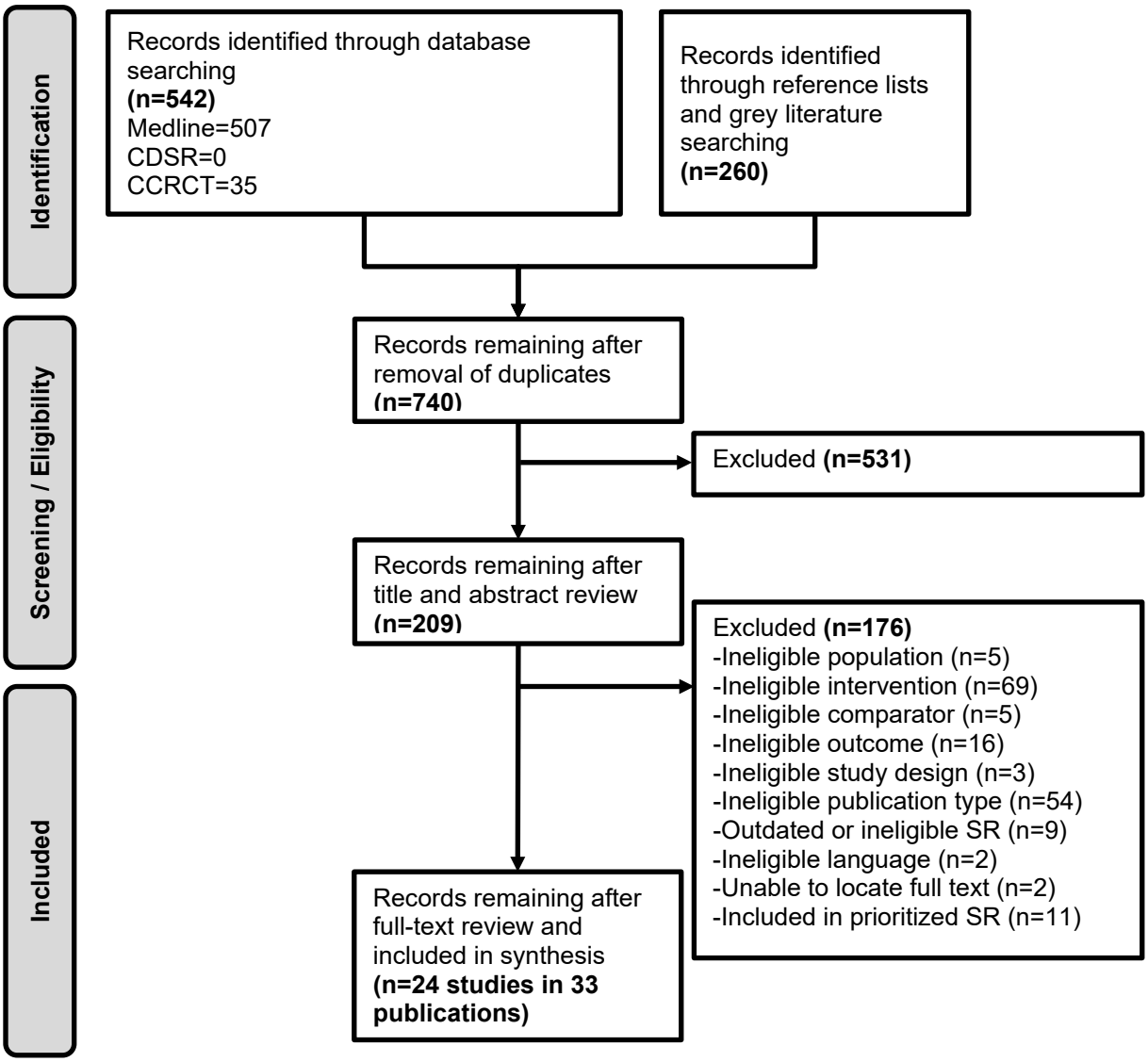
We synthesized available evidence narratively by outcome and clinical scenario. To improve our interpretation of the applicability of findings to current VA practice patterns, we retrieved data from the VA Corporate Data Warehouse (CDW) on the number of patients receiving CCTA tests and the number of these patients who went on to ICA within 90 days of CCTA testing. We accessed data through the VA Informatics and Computing Infrastructure.[52] To better match VA patients with participants in trials of HeartFlow, we limited the data to patients without acute coronary syndrome, a diagnosis of CAD, a history of previous revascularization within the year prior to CCTA, or a history of ICA.[11] CDW codes used are available upon request. Finally, a technical expert panel (TEP) provided input on the clinical relevance of evidence and important considerations for use of HeartFlow within the VA.

RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 1) summarizes the results of the study selection process (see Appendix B in supplemental materials for full list of excluded studies).

Figure 1. Literature Flow Chart



Abbreviations. CCRCT=Cochrane Central Register of Controlled Trials, CDSR=Cochrane Database of Systematic Reviews, SR=Systematic Review.

LITERATURE OVERVIEW

Among 740 potentially relevant citations, we included 3 systematic reviews[1-3] (1 new since 2019 ESP report) and 7 primary studies[4-10] (5 new since 2019 ESP report) on diagnostic accuracy, and 14 studies (in 23 publications)[11-28,53-57] reporting diagnostic or therapeutic impact or clinical or cost outcomes (7 new since 2019 ESP report) (Table 2, see Appendix C in supplemental materials for full study details). We also identified 6 ongoing studies examining the use of HeartFlow. Most of these studies examine diagnostic accuracy, but a few examine clinical outcomes, including 1 ongoing trial comparing clinical and cost outcomes of using CCTA with selected FFR_{CT} or usual care (see Appendix D in supplemental materials for list of ongoing studies).

Diagnostic Accuracy

One meta-analysis[1] and 5 primary studies[4,5,7,9,10] published since the 2019 ESP report examined the diagnostic accuracy of HeartFlow. The new meta-analysis included 1 primary study not included in either of the previously included meta-analyses. Diagnostic accuracy of HeartFlow was assessed in patients with suspected CAD undergoing CCTA, often along with other noninvasive testing (*ie*, SPECT, PET), compared to the reference standard of ICA with invasive FFR measurement. All studies used a cut-off value of FFR ≤ 0.80 to identify functionally significant CAD. Sample sizes of included studies ranged from 51 to 208 patients, with the exception of 1 study that included nearly 1500 patients[5] (although it is unclear how many patients in this study were included in the diagnostic accuracy analysis). The applicability of this evidence to patients with low to intermediate pre-test risk of CAD is unclear as several studies excluded patients with low to intermediate risk of CAD[8,9] or limited analyses to those with known CAD[10] or at least 30% stenosis on ICA.[4] Findings of several studies may have been impacted by unclear blinding of HeartFlow and/or invasive FFR values, and by exclusion of patients from analyses due to unreadable CCTA scans or lack of invasive FFR data.

Therapeutic and Clinical Outcomes

Seven studies published since the 2019 ESP report examined therapeutic or clinical outcomes of HeartFlow.[13,14,17,20,23,26,28] Most were noncomparative studies, reporting on real-world clinical experiences and changes in clinical management plans in patients with an intermediate risk of CAD undergoing CCTA; none were RCTs (Table 2). Several new sub-analyses of the Assessing Diagnostic Value of Noninvasive FFR_{CT} in Coronary Care (ADVANCE) registry, an international registry of over 5,000 patients with suspected CAD (> 30% stenosis on CCTA) undergoing HeartFlow FFR_{CT} analysis from 2015 to 2017, examined outcomes by various demographic factors (age, gender, *etc*).[19,22,25,27,53-55] All but 2 studies included at least 200 patients (range: 75 to 5,083). Studies frequently had important methodological limitations, including lack of concurrent control groups, unclear methods for selecting patients into the study, baseline differences between comparison groups, lack of or unclear methods for statistical adjustment, and exclusion of patients with missing FFR_{CT} data.

Table 2. Characteristics of HeartFlow Studies with Therapeutic and/or Clinical Outcomes

Author, Year Study Type	Sample Size Follow-Up	Population	Patient Demographics	Cardiac Risk Factors Pre-test Probability[a]	Comparator	Outcomes Assessed
ADVANCE Registry						
Anastasius, 2020[25] Intl registry	N=4553 1 year	Clinically stable symptomatic patients diagnosed with CAD by CCTA with FFRCT result	Age: 66.1 Male: 66.5% Race: NR	Diabetes: 22.1% Hypertension: 60.1% Hyperlipidemia: 58.5% Risk score: 51.6%	None	ICA use, MACE
Fairbairn, 2020[53] Patel, 2020[27] Intl registry	N=4737 90 days 1 year	Clinically stable symptomatic patients diagnosed with CAD by CCTA with FFRCT result	Age: 66.1 Male: 66.2% Race NR	Diabetes: 21.9% Hypertension: 59.8% Hyperlipidemia: 58.1% Risk score: 51.6%	None	ICA use, MACE
Fairbairn, 2018[19] Nous, 2021[54] Intl registry	N=5083 90 days 1 year	Clinically stable symptomatic patients diagnosed with CAD by CCTA	Age: 66 Male: 65.9% Race NR	Diabetes: 22.3% Hypertension: 59.9% Hyperlipidemia: 58.2% Risk score: 51.3%	None	ICA use, change in treatment plan, MACE
Pontone, 2019[55] Intl registry	N=2778 NR	Clinically stable symptomatic patients diagnosed with CAD by CCTA with FFRCT result	Age: 66 Male: 66% Race NR	Diabetes: 22% History of smoking: 61% Hyperlipidemia: 61% Risk score: NR	None	FFRCT rejection rate
Shiono, 2019[22] Intl registry	N=1829 90 days	Clinically stable symptomatic patients diagnosed with CAD by CCTA in Japan	Age: 69.4 Male: 65.4% Race: NR	Diabetes: 32.5% Hypertension: 60.2% Hyperlipidemia: 60.2% Risk score: 55%	None	ICA use, change in treatment plan, MACE
PLATFORM						
Colleran, 2017[56] Prospective cohort	N=116 1 year	Symptomatic adult patients with intermediate likelihood of obstructive CAD, without known CAD in Germany	Age: 59.9 Male: 57.7% 1.7% racial/ethnic minority	Diabetes: 13.0% Hypertension: 62.8% Dyslipidemia: 21.5% Risk score: 50.1%	Originally planned testing: ICA	ICA use, cost, quality of life

Douglas, 2015[11] Douglas, 2016[24] Hlatky, 2015[57] Prospective cohort	N=584 90 days 1 year	Symptomatic adult patients with intermediate likelihood of obstructive CAD, without known CAD	Age: 60.9 Male: 60.4% 1.5% racial/ethnic minority	Diabetes: 13.7% Hypertension: 54.3% Dyslipidemia: 34.8% Risk score: 49%	Originally planned testing ("usual care"): non-invasive testing ICA	ICA use, MACE, cost, quality of life scores
Other Studies						
Andreini, 2019[14] Prospective cohort	**N=223 NR**	**Patients with CAD diagnosed with ICA or CCTA and candidates for PCI or CABG**	**Age: 67.6 Male: 84.3% Race: NR**	**Diabetes: 37.7% Hypertension: 74.9% Hyperlipidemia: 70% Risk score: NR**	**CCTA or ICA**	**Treatment decision change between PCI and CABG**
Baggiano, 2020[17] Retrospective analysis[b]	**N=291 NR**	**Symptomatic patients scheduled for ICA + invasive FFR**	**Age: 65 Male: 76% Race: NR**	**Diabetes: 19% Hypertension: 74% Risk score: 65%**	**None**	**Reclassification rate, clinical plan agreement with actual patient management**
Curzen, 2016[18] Retrospective analysis[c]	N=200 NR	Patients with suspected stable CAD and at least one stenosis (30–90%) on CCTA undergoing nonemergent ICA	NR	NR	None	Change in clinical management plan,
Fares, 2019[20] Case series	**N=207 NR**	**Patients with suspected CAD referred for FFRCT**	**Age: 69.5 Male: 46.4% Race: 28.5% African American, 66.4% White**	**Diabetes: 21.5% Hypertension: 67.7% Dyslipidemia: 66.7% Risk score: NR**	**None**	**Change in clinical recommendation**
Ihdayhid, 2019[26] Case series	**N=206 4.7 yrs (median)**	**Patients with suspected stable CAD and at least 1 stenosis (30–90%) on CCTA undergoing nonemergent ICA with FFRCT**	**Age: 64 Male: 64.1% Race: 68.4% White, 31.6% Asian**	**Diabetes: 22.8% Hypertension: 65.5% Hypercholesterolemia: 81.1% Risk score: 54.2%**	**None**	**MACE, composite outcome (death, MI and any revascularization)**
Jang, 2016[21] Case series	N=75 NR	Patients undergoing CCTA and referred for ICA	Age: 60 Male: 75% Race NR	NR	None	Clinical management plan changed, MACE

Jensen, 2018[15] Prospective cohort	N=774 90 days	Symptomatic patients referred to non-emergent ICA or CCTA on suspicion of stable CAD	Age: 59 Male: 52% Race: NR	Diabetes: 9% Hypertension: 37% Hyperlipidemia: 32% Risk score: 40%	CCTA alone (planned ICA or planned CCTA)	ICA cancellation, MACE
Norgaard, 2020[28] **Case series**	**N=975** **2.2 yrs (median)**	**Patients with suspected chronic coronary syndrome and stenosis (30–70%) on CCTA**	**Age: 61.9** **Male: 59.1%** **Race NR**	**Diabetes: 12.0%** **Hypertension: 45.4%** **Hyperlipidemia: 37.7%** **Risk score: 44.8%**	**None**	**Composite outcome (death, MI, hospitalization, revascularization)**
Norgaard, 2017[16] (Clinical use) Retrospective cohort	N=1248 6 to 8 months	Symptomatic patients with suspected CAD undergoing CCTA	Age: 57 Male: 47% Race: NR	Diabetes: 10% Hypertension: 34% Hyperlipidemia: 29% Risk score: 34%	CCTA alone	ICA cancellation, MACE
Norgaard, 2017[12] (Myocardial perfusion) Retrospective cohort	N=3523 3 months	Symptomatic patients with suspected CAD undergoing CCTA	Age: 56.5 Male: 47.0% Race: NR	Diabetes: 7.9% Hypertension: 35.4% Hyperlipidemia: 30.5% Risk score: 33.2%	MPI (Period 1) FFRCT (Period 2-3)	ICA use
Rabbat, 2020[13] **Prospective cohort**	**N=431** **NR**	**Patients with suspected CAD referred for CCTA**	**Age: 58.9** **Male: 48.4%** **Race: NR**	**Diabetes: 16.7%** **Hypertension: 59.5%** **Hyperlipidemia: 63%** **Intermediate risk: 89.2%**	**CCTA alone**	**ICA use**
Van Belle, 2021[23] **Case series**	**N=101** **NR**	**Patients with at least 1 stenosis ≥ 40% with FFRCT and undergoing ICA**	**NR**	**NR**	**ICA**	**PCI strategy change**

Notes. Boldface indicates new evidence since 2019 ESP report. [a] Diamond-Forrester risk score, [b] Analysis of PERFECTION diagnostic accuracy study, [c] Analysis of NXT diagnostic accuracy study.
Abbreviations. CABG=coronary artery bypass graft, CAD=coronary artery disease, CCTA=coronary computed tomography angiography, FFRCT=fractional flow reserve using computed tomography, ICA=invasive coronary angiography, Intl=international, MACE=major adverse cardiovascular event, MI=myocardial infarction, MPI=myocardial perfusion imaging, PCI=percutaneous coronary intervention.

KEY QUESTION 1: DIAGNOSTIC ACCURACY OF HEARTFLOW

One new systematic review[1] agreed with previous findings, reporting good diagnostic accuracy of HeartFlow, and higher specificity for identifying obstructive coronary disease than CCTA alone in patients with suspected coronary disease using a reference standard of FFR during ICA (specificity range = 73% to 76% HeartFlow vs 61% to 64% CCTA alone) (Table 3).[1-3] The accuracy of HeartFlow was higher than that of CCTA (AUC range = 0.87 to 0.89 HeartFlow vs 0.82 CCTA alone), while sensitivities were similar (84% to 85% HeartFlow vs 86% to 88% CCTA).

Table 3. Diagnostic Accuracy of HeartFlow from Included Systematic Reviews

Systematic Review[a]		Celeng, 2018[3]	Hamon, 2019[2]	**Pontone, 2020[1]**
Patient Population		Patients with stable chest pain with suspected CAD undergoing clinically indicated ICA with FFR after CCTA		
Heart-Flow	**Sensitivity[b] [95% CI]**	85% [81, 90]	84% [80, 88]	**85% [81, 88]**
	Specificity[b] [95% CI]	73% [61, 82]	76%[73, 79]	**75% [72, 78]**
	AUC [95% CI]	0.87 [NR]	0.89 [NR]	**0.89 [NR]**
CCTA	**Sensitivity[b] [95% CI]**	87% [84, 91]	86% [85, 88]	**88% [85, 90]**
	Specificity[b] [95% CI]	61% [54, 68]	64% [63, 66]	**64% [61, 66]**
	AUC [95% CI]	NR	0.82 [NR]	**0.82 [NR]**

Notes. Boldface indicates new evidence since 2019 ESP report. [a] Each SR included a subset of 9 studies on HeartFlow. [b] Per-vessel.
Abbreviations. CAD=coronary artery disease, CCTA=coronary computed tomography angiography, FFR=fractional flow reserve, ICA=invasive coronary angiography.

Seven studies (5 new since 2019 ESP report) published after the most recent systematic reviews generally agreed with the findings of those reviews. Sensitivity (range = 81% to 92%), specificity (range = 68% to 94%), and accuracy (AUC range = 0.82 to 0.94) estimates for HeartFlow varied, but generally showed similar sensitivity and higher specificity and diagnostic accuracy than CCTA alone (Table 4).[4-10] The variation in estimates among studies may be due to differences in study populations, CCTA procedures (*ie*, imaging technique), or study methods (*eg*, whether clinicians interpreting HeartFlow had knowledge of reference standard findings). Multiple studies directly assessing the diagnostic accuracy of HeartFlow compared to FFR during ICA reported similar sensitivities, but higher specificities, than that of CCTA, strengthening our confidence in these findings. However, no studies have assessed diagnostic accuracy in a VA population.

All included studies used a FFR_{CT} cut-off value of ≤ 0.80. An evaluation of the diagnostic performance of HeartFlow according to different FFR_{CT} cut-off values in patients with suspected CAD undergoing invasive FFR found that specificity values were higher with a cut-off of $FFR_{CT} \leq 0.75$ compared to $FFR_{CT} \leq 0.80$ (75% and 59%, respectively), with acceptable sensitivity (95% for $FFR_{CT} = 0.80$ and 86% for $FFR_{CT} = 0.75$).[58]Additionally, 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.[16]

Table 4: Primary Studies on the Diagnostic Accuracy of HeartFlow[a]

Author, Year (N)	Patient Population	CAD[b]	Sensitivity[c] [95% CI]	Specificity[c] [95% CI]	AUC [95% CI]
Bom, 2021[4] (132)	**Suspected CAD and ≥ 30% stenosis on ICA**	**NR**	**90% [83, 96]**	**68% [58, 77]**	**0.89 [0.83 to 0.93]**
Cami, 2020[5] (1,484)	**Evaluated for myocardial ischemia**	**NR**	**Distal: 92% [NR] Terminal: 92% [NR]**	**Distal: 86% [NR] Terminal: 50% [NR]**	**Distal: 0.91 [NR] Terminal: 0.83 [NR]**
Driessen, 2019[6] (157)	Suspected CAD and clinically indicated ICA with FFR	45%	90% [84, 95]	86% [82, 89]	0.94 [0.92 to 0.96]
Ko, 2019[7] (51)	**Suspected CAD and clinically indicated ICA with FFR**	**49%**	**81% [63, 93]**	**85% [73, 93]**	**0.90 [0.82 to 0.98]**
Pontone, 2019a[8] (147)	Suspected CAD and clinically indicated ICA with FFR	45%	88% [82, 94]	94% [91, 96]	0.93 [0.91 to 0.96]
Pontone, 2019b[9] (85)	**Suspected CAD and clinically indicated ICA with FFR**	**57%**	**86% [78, 94]**	**75% [68, 82]**	**0.88 [0.83 to 0.92]**
Tanigaki, 2019[10] (152)	**Stable CAD identified by CCTA**	**46%**	**82% [76, 88]**	**70% [64, 74]**	**0.82 [0.76 to 0.87]**

Notes. Boldface indicates new evidence since 2019 ESP report. [a] Not included in previous meta-analyses. [b] Prevalence of functionally significant CAD classified as at least one vessel with invasive FFR ≤ 0.80. [c] Per-vessel.
Abbreviations. CAD=coronary artery disease, CCTA=coronary computed tomography angiography, FFR=fractional flow reserve, ICA=invasive coronary angiography.

KEY QUESTION 2: DIAGNOSTIC AND THERAPEUTIC IMPACT OF HEARTFLOW

Use of Invasive Coronary Angiography

Several clinical scenarios were previously identified for the potential impact of HeartFlow on use of ICA. No new evidence examined the impact of HeartFlow on ICA use in patients directly referred to ICA (scenario 1), or as a substitute for other noninvasive strategies (scenario 2). A single new study examined reduction in ICA with use of HeartFlow in patients referred for CCTA (scenario 3).

Scenario 1: Use of HeartFlow in patients who are planned to be directly referred to ICA in lieu of noninvasive evaluation

No new studies examined impact of HeartFlow on the use of ICA in patients planned to be directly referred to ICA. As previously described, the PLATFORM study[11] compared consecutive cohorts of patients receiving usual care (invasive or noninvasive diagnostic evaluation followed by medical therapy or invasive procedures) or HeartFlow. Findings from this study suggest that use of HeartFlow in patients with new onset chest pain scheduled for elective ICA can reduce the use of coronary angiograms in patients who do not have functionally

significant coronary disease. In this trial, use of HeartFlow 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 group versus 73% in the usual care group (risk difference = -61%, 95% CI [-53, -69]). The rate of obstructive CAD was similar in the 2 groups. Similar findings were reported in a sub-analysis of these patients from German sites.[56] Our confidence in these findings is limited because the criteria for ordering elective ICA were unclear and may differ across clinical settings, including between VA and non-VA settings. Additionally, these findings are from a single study and it is unknown if further studies would have consistent findings.

Scenario 2: Use of HeartFlow as a substitute for other noninvasive testing

No new studies examined impact of HeartFlow on the use of ICA in patients planned for other noninvasive testing. The PLATFORM study showed that HeartFlow did not reduce the use of ICA in patients who were planned for noninvasive testing. Only about 10% of patients who underwent a noninvasive workup needed ICA, whereas 12.5% of HeartFlow patients underwent angiography.[11] A previously described single-center, pre-post study in Denmark[12] reported findings that conflicted with the PLATFORM trial, with a reduction in the use of ICA (-4.2 per 100 patients, 95% CI [-6.9, -1.6]) and a reduction in the rate of finding no obstructive disease on ICA (-12.8 per 100 ICAs, 95% CI [-22.2, -3.4]) after switching the preferred noninvasive strategy from myocardial perfusion imaging to CCTA plus selective HeartFlow (in patients with intermediate stenosis on CCTA). However, the risk difference was small and should be considered alongside the negative results of the PLATFORM trial in patients referred for an initially noninvasive evaluation. Our confidence in these findings is limited by inconsistent findings and lack of direct comparison to specific noninvasive strategies, including those routinely used in the VA.

Scenario 3: Use of HeartFlow as a part of the clinical pathway for patients who undergo CCTA

One new single-center study[13] in the US described the impact of implementing HeartFlow in patients without known CAD referred for CCTA. ICA utilization was compared among consecutive patients receiving HeartFlow during a specific time period and a historical control group receiving CCTA alone. This study has major methodological limitations, including use of a historical control group with unclear methods for selection of patients. There were important baseline differences between patients receiving HeartFlow and the historical control group (anginal typicality, prior stress testing, *etc*), and it is likely that these differences impacted downstream use of ICA. Additionally, introduction of HeartFlow into the clinic may have influenced ICA referral patterns among clinicians. Although ICA use was similar overall (17% [65/387] HeartFlow vs 18% [8/44] historical control), among patients with at least 1 vessel with ≥ 50% diameter stenosis, ICA use was reduced with HeartFlow (45% [55/121] HeartFlow vs 80% [8/10] historical control). Our confidence in these findings is very low, as they are from a single study with severe methodological limitations. In the previously described ADVANCE registry,[54] overall 90-day ICA use was 43.9%, and several subgroup analyses[22,25,53] of the registry reported similar findings (the registry did not have a comparison to patients not receiving HeartFlow).

Change in Clinical Management

Several new registry- or hospital system-based studies reported changes in clinical management plans or rates of ICA cancellation based on HeartFlow or CCTA alone[14-22] (Table 5). Most studies compared clinical management plans within a single group of patients, with clinicians making clinical decisions based on CCTA images or HeartFlow FFR_{CT} analyses of the same patients. Rates of changes in clinical management plans among the new studies varied (range = 24% to 55.8%)[17,20,22] but were generally lower than those previously reported (range = 36% to 66.9%).[18,19,21] Rates of ICA cancellation ranged from 48% to 91%.[15,16,21] The variability in these findings likely arises from differences in patient populations (*ie*, patients with suspected CAD vs those with known CAD or documented stenosis), local variation in clinical management and physician practices, and availability of ICA. One new study[14] compared management plans between 2 heart teams, randomized to make a treatment decision between percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) based on coronary angiography or on CCTA. Each heart team then had to make a second treatment decision based on results from HeartFlow. Compared to CCTA or ICA, 7% and 6.6% of patients had a treatment decision change between PCI and CABG with the additional HeartFlow information, respectively.

Table 5. Changes in Clinical Management with HeartFlow

Author, Year (N)	Population	Change in Clinical Management
Andreini, 2019[14] (223)	**Patients with CAD diagnosed with ICA or CCTA and candidates for PCI or CABG**	**Change btwn CABG and PCI: 7% (95% CI 3.4, 10.6)[a] vs CCTA 6.6% (95% CI [3.1, 10.1])[a] vs ICA**
Baggiano, 2020[17] (291)	**Symptomatic patients scheduled for ICA + invasive FFR**	**28% (95% CI [22.8, 31.2])[a]**
Curzen, 2016[18] (200)	Patients with suspected CAD with at least one stenosis (30–90%) on CCTA undergoing nonemergent ICA	36% (95% CI [29.3, 42.7])[a]
Fairbairn, 2018[19] (5,083)	Patients with suspected CAD with documented atherosclerosis (>30%) on CCTA	66.9% (95% CI [64.8, 67.6])
Fares, 2019[20] (207)	**Patients with suspected CAD referred for FFRCT**	**24% (95% CI [17.4, 30.6])[a]**
Jang, 2016[21] (75)	Patients with suspected CAD undergoing CCTA and referred for ICA.	55% ICA cancellation: 48%
Jensen, 2018[15] (774)	Patients with suspected CAD referred to non-emergent ICA or CCTA	ICA cancellation: 75% (high risk), 91% (low-intermediate risk)
Norgaard, 2017 (clinical use)[16] (1,248)	Patients with suspected CAD undergoing CCTA	ICA cancellation: 66% (95% CI [59, 73])[a]
Shiono, 2019[22] (1,829)	**Japanese patients with suspected CAD with documented atherosclerosis (>30%) on CCTA**	**55.8% (95% CI [53.5, 58.1])[a]**

Notes. Boldface indicates new evidence since 2019 ESP report. [a] ESP Calculated.
Abbreviations. CABG=coronary artery bypass graft, CAD=coronary artery diseases, CCTA=coronary computed angiography tomography, FFR=fractional flow reserve, ICA=invasive coronary angiography, PCI=percutaneous coronary intervention.

Studies directly evaluated outcomes of clinical relevance in actual practice. However, our confidence in these findings is limited by important methodological weaknesses, including lack of control groups (all patients received HeartFlow in most studies) and unclear blinding of imaging results (*ie*, the same clinicians made clinical recommendations based on CCTA alone or HeartFlow) in several studies, which may have influenced changes in clinical management plans. Additionally, most studies did not assess whether HeartFlow affected actual clinical management of patients (treatment received) but focused on changes in the initial clinician management plan.

KEY QUESTION 3: IMPACT OF HEARTFLOW ON CLINICAL OUTCOMES AND COST

Rates of cardiovascular and other adverse events were low and were similar in those receiving HeartFlow or other diagnostic strategies, and in those whose clinical management plans were changed with HeartFlow (including in those who had ICA cancelled based on HeartFlow results) and those whose clinical management plans were not changed (Table 6).[11,15,16,19,21,24,26,54] One new sub-analysis of the NXT trial (designed to examine the diagnostic accuracy of HeartFlow)[59] reported a longer-term rate of major adverse cardiac events (MACE; 9.7% at a median of 4.7 years) among patients receiving HeartFlow, but did not compare MACE rates to those in patients utilizing other diagnostic strategies.[26] Although MACE and other clinical event rates were consistently low, only the PLATFORM trial compared event rates in patients receiving HeartFlow to other diagnostic strategies, and only a single study included follow-up longer than 1 year.

Table 6. Cardiac and Clinical Events

Author, Year	Follow-up	MACE or Other Adverse Cardiac Events
Douglas, 2015[11]/ 2016[24]	90 days 1 year	*90 days: 2* (0.7%) HeartFlow vs 0 usual care MACE *1 year:* 2 (0.7%) HeartFlow vs 2 (1.0%) usual care MACE (0 in patients whose ICA was canceled based on HeartFlow results)
Fairbairn, 2018[19] **Nous, 2021[54]**	90 days **1 year**	*90 days:* 19 (0.4%) MACE ***1 year:* 59 (1.2%) MACE**
Ihdayhid, 2019[26]	**4.7 years (median)**	**20 MACE (9.7%)**
Jang, 2016[21]	1 year	No significant difference in cardiovascular events between patients with changed vs unchanged management with HeartFlow (data NR)
Jensen, 2018[15]	90 days	14 (1.8%) clinical adverse events (0 in patients whose ICA was canceled based on HeartFlow results)
Norgaard, 2017[16] (clinical)	90 days	0 serious adverse cardiac events (including in patients whose ICA was canceled based on HeartFlow results)

Notes. Boldface indicates new evidence since 2019 ESP report.
Abbreviations. ICA=invasive coronary angiography, MACE=major adverse cardiovascular event.

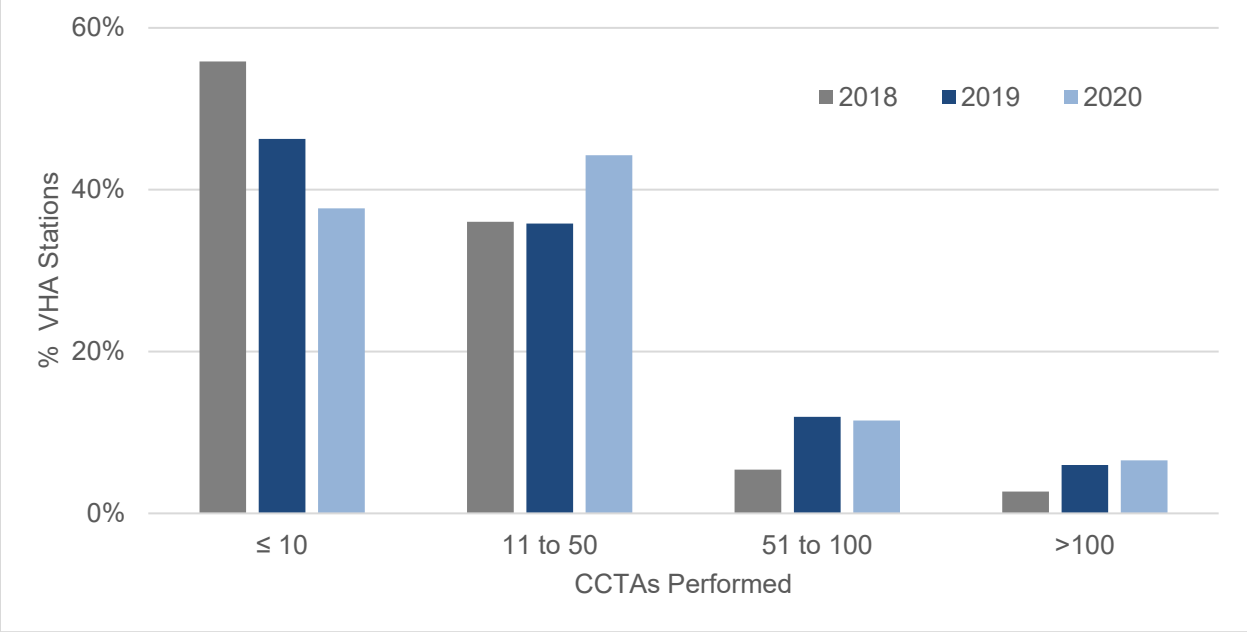
No new studies examined cost or quality of life outcomes. As previously described, quality of life scores in the PLATFORM trial[24,57] were generally similar between groups, with a greater improvement in quality of life reported with HeartFlow in the planned noninvasive subgroup. Mean costs at 90 days and 1 year were lower in the HeartFlow cohort compared to the usual care

cohort in the subgroup of patients planned to receive ICA, but no differences in costs were observed between the groups in patients planned to receive noninvasive testing.[24,57]

CONSIDERATIONS FOR THE USE OF HEARTFLOW IN VA

The potential impact of HeartFlow depends on the use of CCTA because CCTA images are needed for the HeartFlow FFR_{CT} analysis. The VA currently employs the 2012 American College of Cardiology Foundation and American Heart Association guidance for diagnosis of CAD, which recommends CCTA only for those who are unable to exercise or who have contraindications to stress testing.[60,61] Data from the VA national CDW shows that around 2,000 VA patients without a diagnosis of CAD or prior history of revascularization or ICA underwent CCTA testing each year from 2018 to 2020 (1,925 patients in 2018, 2,007 patients in 2019 and 1,828 patients in 2020). Among facilities performing at least 1 CCTA, more than 80% of VA sites reported fewer than 50 CCTAs during the calendar years 2018 to 2020 (Figure 2), with around 40% to 60% of VA sites performing 10 CCTAs or fewer. Only 3 to 4 VA sites reported doing 100 CCTAs or more per year from 2018 to 2020.

Figure 2. Usage of Coronary Computed Tomography Angiography (CCTA) Among VA Stations Performing at Least 1 CCTA Each Calendar Year



Among VA patients undergoing CCTA, only 18.5% underwent ICA within 90 days after CCTA, indicating that most patients receiving CCTA have normal or non-obstructive results and do not end up requiring ICA or have extensive coronary artery disease not amenable to ICA intervention. In these cases, further imaging, including HeartFlow FFR_{CT} analysis, is usually not necessary. Similar rates of ICA after CCTA in patients with suspected but unknown CAD have been reported in other studies (9.6% to 16%).[62-65]

CCTA is generally used less often in the US compared to Europe due to differences in guidance recommendations, reimbursement structures, and clinical practices and training.[66] Guidance from the European Society of Cardiology[67] and the National Institute for Health and Care Excellence[68]

in the UK recommend use of CCTA as a first-line diagnostic strategy for patients with stable chest pain or chronic coronary syndrome. In an analysis of CCTA use among the Medicare population from 2006 to 2016, CCTA use in the US peaked in 2007 (210.3 per 100,000), and then declined until 2014, after which CCTA usage began to rise again, reaching 131.0 per 100,000 in 2016.[69] A recent American College of Cardiology State-of-the-Art Review outlined supportive evidence for expanded use of CCTA in the US.[66] However, barriers to increasing the use of CCTA in the US remain, including limited access to equipment, limited availability and support of technical training for clinicians, and lack of updated guidance for use of CCTA.

The potential impact of targeted HeartFlow use in patients referred for CCTA in the VA was estimated in the previous ESP report from data on the sensitivity and specificity of HeartFlow and CCTA alone. Using assumptions for the prevalence of patients with intermediate-stenosis lesions on CCTA, the proportion of these patients who have functionally significant CAD, and the proportion of patients with positive CCTA that undergo ICA, an estimated 34 ICAs could be prevented for every 1,000 patients undergoing CCTA.[29]

ADEQUACY OF CCTA IMAGES FOR HEARTFLOW FFR_{CT}

HeartFlow FFR_{CT} analysis requires adequate-quality CCTA images to estimate FFR data. In studies on the therapeutic and clinical impact of HeartFlow reporting rates of acceptance of CCTA images, 79% to 98.6% of images were adequate for HeartFlow FFR_{CT} analysis. Variation in equipment quality and physician and CT technologist expertise may influence the adequacy of CCTA images and are important considerations for potential implementation of HeartFlow. When CCTA images are rejected due to poor image quality, CCTA must be repeated to use HeartFlow.

SUMMARY AND DISCUSSION

New evidence did not resolve the evidence gaps identified in the 2019 ESP report. New evidence on the diagnostic accuracy of HeartFlow agreed with findings from the 2019 ESP report, confirming that HeartFlow has good diagnostic accuracy and is more specific than CCTA alone when compared with the reference standard of invasive FFR. No new studies assessed reduction in ICA use with HeartFlow use in patients directly referred to ICA or as a substitute for other noninvasive tests. In the PLATFORM trial,[11] use of HeartFlow reduced the use of coronary angiography in patients directly referred to ICA. However, use of HeartFlow as a substitute for other noninvasive tests led to a higher rate of ICA use in this trial.[11] New evidence showed no difference in ICA use overall with the use of HeartFlow in patients referred for CCTA, but a reduction in ICA use among patients with at least 1 vessel with ≥ 50% diameter stenosis.[13] However, severe methodological limitations of this study limit our confidence in these findings. HeartFlow likely changes treatment plans compared to decisions made based on CCTA alone, but the impact on actual treatment received is less clear. Although the specificity of HeartFlow is improved over CCTA alone, the impact on downstream utilization of ICA needs to be verified.

New evidence supported previous findings of low short-term (90 days to 1 year) rates of cardiac events with similar rates in those receiving HeartFlow and other diagnostic strategies, and in those whose clinical management plans changed because of HeartFlow and those whose management plans were unchanged. New evidence on longer-term clinical outcomes showed that MACE rates at around 5 years increased to almost 10% (compared to <2% at 90 days to 1 year) among those receiving HeartFlow. However, comparison of clinical outcomes in patients receiving HeartFlow to other diagnostic strategies are lacking. The findings of generally low clinical event rates align with those reported in the PROMISE trial, which examined outcomes of stable symptomatic outpatients without known CAD randomly assigned to receive CCTA or functional testing (all-cause death/myocardial infarction/unstable angina: 3.1% CCTA vs 3.0% functional testing, median follow-up of 26.1 months).[70] These findings question the overall impact of diagnostic testing strategy on clinical outcomes, including the potential of HeartFlow to impact downstream clinical outcomes. Given the apparently limited impact of diagnostic testing strategy on clinical outcomes, studies of HeartFlow have emphasized the potential for a reduction in the unnecessary use of invasive procedures. However, clinical practice patterns, including routine use of ICA, may vary across different clinical settings. It is important to consider whether reduction in ICA use is appropriate as the key outcome for determining the impact of HeartFlow in all settings, specifically in settings where ICA is not routinely used.

Key considerations for the use of HeartFlow in the VA are the availability and frequency of use of CCTA, technical training for clinicians, and potential challenges of integrating HeartFlow into the clinical workflow. The relatively low number of CCTAs performed in the VA, along with the low rate of ICA after CCTA, suggest that regular use of HeartFlow among all patients referred CCTA may have a low impact on ICA use in the VA. However, if utilization of CCTA within the VA increases in light of updated guidance from the European Society of Cardiology[67] and a review of the evidence by the American College of Cardiology[69] supporting use of CCTA as a first-line diagnostic strategy, HeartFlow has the potential to reduce ICA use in certain clinical scenarios, including as a targeted add-on for patients with CCTA findings that are borderline for obstructive disease. Although few VA sites performed more than 100 CCTAs per year, assessment of the impact of HeartFlow in these high-volume centers could identify the potential

clinical implications of use of HeartFlow within the VA. Another important consideration is the low volume of CCTAs within the VA may impact image quality for HeartFlow analysis. VA sites with less technical expertise in conducting CCTAs may experience a higher rate of rejection of images for HeartFlow FFR_{CT} analysis, and it may be necessary for sites to perform a minimum number of CCTAs per year to stay adequately trained and experienced in CCTA techniques.

Other FFR_{CT} algorithms, including Siemens Healthcare cFFR, Canon Medical Systems CT-FFR and independent, locally developed machine learning and reduced order modeling techniques are alternatives to HeartFlow.[2,3,38] Although none of these technologies are yet commercially available or FDA cleared, they can be used within individual clinics, hospitals, or research environments without the need for analyses by an outside entity. The VA may consider developing its own approach to noninvasive FFR modeling, but evidence on the diagnostic and clinical impact of these alternatives is minimal and was outside the scope of this review.

LIMITATIONS

There are several important limitations of the evidence base. No randomized controlled trials investigated the impact of HeartFlow on diagnostic or clinical outcomes. Cohort studies comparing HeartFlow to other noninvasive strategies (including CCTA alone) or ICA were often limited by unbalanced baseline patient characteristics (*eg*, type of chest pain, cardiac risk factors, demographics, *etc*). These differences may influence outcomes (*ie*, one group may be more likely to be referred to ICA due to type of chest pain or cardiac risk factors). Statistical adjustment for baseline differences between groups was inadequate, or unable to be fully assessed due to lack of information on adjustment methods. Without balanced comparison groups, differences in outcomes could have been due to patient characteristics linked to ICA referrals rather than use of HeartFlow. To determine the impact of HeartFlow compared to other diagnostic strategies, an ideal trial would enroll patients at a distinct point in their diagnostic workup (*ie*, at symptom onset) and randomize them to receive either HeartFlow or another invasive or noninvasive strategy for diagnosis of CAD, equalizing patient characteristics across groups. Adequate sample size, blinding of patients and outcome assessors, and standardized assessment of outcomes over a specific period of time are also important.

Limitations of our review methods include use of a second reviewer check during study selection and data abstraction rather than dual independent review. Additionally, only FDA-cleared FFR_{CT} technologies were eligible for this review, limiting our assessment to studies of HeartFlow FFR_{CT} analysis. No studies examined HeartFlow compared to other noninvasive FFR_{CT} technologies (locally developed algorithms, *etc*) and the clinical impact of these alternatives compared to HeartFlow is unknown.

EVIDENCE GAPS AND FUTURE RESEARCH

Substantial gaps in the evidence remain. Most importantly, no studies have assessed HeartFlow in a VA setting. The utility of HeartFlow depends on the characteristics of patients who undergo diagnostic testing and on how clinical decisions are made within a particular setting. Patient characteristics and clinical pathways may differ between non-VA and VA populations and settings, and the impact of HeartFlow within the VA remains unknown. Only 2 studies examined the impact of HeartFlow on the use of ICA in patients referred for noninvasive testing, and

comparison of HeartFlow to specific noninvasive strategies is lacking. Clinical decisions and diagnostic pathways likely differ within the VA compared to those in community settings in studies of HeartFlow and direct evidence about how HeartFlow compares to diagnostic tests widely used in the VA is needed. Additionally, only a single study (with serious methodological limitations) examined the impact on ICA use of adding HeartFlow to the clinical pathway for patients referred for CCTA, which is the clinical scenario promoted on the manufacturer website.[40] Controlled studies of ICA rates in patients with suspected coronary disease receiving CCTA or other noninvasive strategies and comparing HeartFlow to specific noninvasive strategies are needed.

CONCLUSIONS

New evidence did not sufficiently address the evidence gaps identified in the 2019 ESP report. The impact of regularly utilizing HeartFlow for all patients referred for CCTA within the VA is likely low, given the relatively low number of CCTAs performed in the VA and the unclear impact of HeartFlow compared to noninvasive strategies currently used within the VA. However, use of HeartFlow in facilities with a high volume of CCTAs in specific clinical scenarios may have the potential to reduce unnecessary use of coronary angiography. Short-term rates of adverse cardiac events are likely low and do not differ in those receiving HeartFlow or other diagnostic strategies, but additional research is needed on longer-term clinical outcomes comparing rates of adverse cardiac events between HeartFlow and other diagnostic strategies. Research in VA settings and comparing HeartFlow to specific noninvasive strategies is needed to determine the potential impact of HeartFlow within the VA.

ACKNOWLEDGMENTS

This topic was developed in response to a request from the VA Health Services Research and Development Service for an updated evidence review on the diagnostic, therapeutic, and clinical impact of FFR_{CT} technologies in the noninvasive diagnosis of CAD. The scope was further developed with input from Operational Partners (below) and the ESP Coordinating Center review team.

The authors gratefully acknowledge Kathryn Vela for literature searching and Rachel Ward for editorial and citation management support, and the following individuals for their contributions to this project:

Operational Partners

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

David Atkins, MD, MPH
VA HSR&D Director

Technical Expert Panel (TEP)

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

Paul Hess, MD
University of Colorado School of Medicine

Jeffrey Chenoweth, MD
Acting Director, VHA National Radiology Program

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.

REFERENCES

1. 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.* 2020;300:276-281.
2. Hamon M, Geindreau D, Guittet L, Bauters C, Hamon M. Additional diagnostic value of new ct imaging techniques for the functional assessment of coronary artery disease: A meta-analysis. *European Radiology.* 2019;29(6):3044-3061.
3. Celeng C, Leiner T, Maurovich-Horvat P, et al. Anatomical and functional computed tomography for diagnosing hemodynamically significant coronary artery disease: A meta-analysis. *JACC: Cardiovascular Imaging.* 2018:S1936-1878X(1918)30681-30688.
4. Bom MJ, Driessen RS, Kurata A, et al. Diagnostic value of comprehensive on-site and off-site coronary ct angiography for identifying hemodynamically obstructive coronary artery disease. *Journal of Cardiovascular Computed Tomography.* 2021;15(1):37-45.
5. Cami E, Tagami T, Raff G, et al. Importance of measurement site on assessment of lesion-specific ischemia and diagnostic performance by coronary computed tomography angiography-derived fractional flow reserve. *Journal of Cardiovascular Computed Tomography.* 2020;29:29.
6. Driessen RS, Danad I, Stuijfzand WJ, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. *Journal of the American College of Cardiology.* 2019;73(2):161-173.
7. Ko BS, Linde JJ, Ihdayhid AR, et al. Non-invasive ct-derived fractional flow reserve and static rest and stress ct myocardial perfusion imaging for detection of haemodynamically significant coronary stenosis. *The International Journal of Cardiovascular Imaging.* 2019;35(11):2103-2112.
8. Pontone G, Baggiano A, Andreini D, et al. Stress computed tomography perfusion versus fractional flow reserve ct derived in suspected coronary artery disease: The PERFECTION study. *JACC: Cardiovascular Imaging.* 2019;12(8 Pt 1):1487-1497.
9. Pontone G, Baggiano A, Andreini D, et al. Dynamic stress computed tomography perfusion with a whole-heart coverage scanner in addition to coronary computed tomography angiography and fractional flow reserve computed tomography derived. *JACC: Cardiovascular Imaging.* 2019;12(12):2460-2471.
10. Tanigaki T, Emori H, Kawase Y, et al. Qfr versus FFR derived from computed tomography for functional assessment of coronary artery stenosis. *JACC: Cardiovascular Interventions.* 2019;12(20):2050-2059.
11. 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. *European Heart Journal.* 2015;36(47):3359-3367.
12. Norgaard BL, Gormsen LC, Botker HE, et al. Myocardial perfusion imaging versus computed tomography angiography-derived fractional flow reserve testing in stable patients with intermediate-range coronary lesions: Influence on downstream diagnostic workflows and invasive angiography findings. *Journal of the American Heart Association.* 2017;6(8):22.

13. Rabbat M, Leipsic J, Bax J, et al. Fractional flow reserve derived from coronary computed tomography angiography safely defers invasive coronary angiography in patients with stable coronary artery disease. *Journal of Clinical Medicine.* 2020;9(2):24.
14. Andreini D, Modolo R, Katagiri Y, et al. Impact of fractional flow reserve derived from coronary computed tomography angiography on heart team treatment decision-making in patients with multivessel coronary artery disease: Insights from the syntax iii revolution trial. *Circulation: Cardiovascular Interventions.* 2019;12(12):e007607.
15. 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. *European Heart Journal Cardiovascular Imaging.* 2018;19(4):405-414.
16. Norgaard BL, Hjort J, Gaur S, et al. Clinical use of coronary cta-derived FFR for decision-making in stable cad. *JACC: Cardiovascular Imaging.* 2017;10(5):541-550.
17. 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 ripcord study. *Journal of Clinical Medicine.* 2020;9(7):08.
18. Curzen NP, Nolan J, Zaman AG, Norgaard BL, Rajani R. Does the routine availability of ct-derived FFR influence management of patients with stable chest pain compared to ct angiography alone?: The FFRCT ripcord study. *JACC Cardiovascular Imaging.* 2016;9(10):1188-1194.
19. 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. *European Heart Journal.* 2018;39(41):3701-3711.
20. Fares A, Alaiti MA, Alkhalil A, et al. Real world utilization of computed tomography derived fractional flow reserve: Single center experience in the united states. *Cardiovascular Revascularization Medicine.* 2019;20(12):1043-1047.
21. Jang J, Krishnaswami A, Rogers C, Hung Y, Sengupta S. The impact of fractional flow reserve derived from coronary computed tomography angiography in a managed healthcare system – kaiser permanente northern california [abstract #50]. *Journal of Cardiovascular Computed Tomography.* 2016;10(3):S1-S96.
22. Shiono Y, Matsuo H, Kawasaki T, et al. Clinical impact of coronary computed tomography angiography-derived fractional flow reserve on japanese population in the advance registry. *Circulation Journal.* 2019;83(6):1293-1301.
23. Van Belle E, Raposo L, Bravo Baptista S, et al. Impact of an interactive ct/FFR_{ct} interventional planner on coronary artery disease management decision making. *JACC: Cardiovascular Imaging.* 2021;04:04.
24. 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. *Journal of the American College of Cardiology.* 2016;68(5):435-445.
25. Anastasius M, Maggiore P, Huang A, et al. The clinical utility of FFRCT stratified by age. *Journal of Cardiovascular Computed Tomography.* 2020;23:23.
26. Ihdayhid AR, Norgaard BL, Gaur S, et al. Prognostic value and risk continuum of noninvasive fractional flow reserve derived from coronary ct angiography. *Radiology.* 2019;292(2):343-351.

27. Patel MR, Norgaard BL, Fairbairn TA, et al. 1-year impact on medical practice and clinical outcomes of FFR_{ct}: The advance registry. *JACC: Cardiovascular Imaging.* 2020;13(1 Pt 1):97-105.
28. Norgaard BL, Mortensen MB, Parner E, et al. Clinical outcomes following real-world computed tomography angiography-derived fractional flow reserve testing in chronic coronary syndrome patients with calcification. *European Heart Journal Cardiovascular Imaging.* 2020;13:13.
29. Helfand M, Anderson J, Peterson K, D B. *Evidence assist: Coronary computed tomography angiography innovations in noninvasive diagnosis of coronary artery disease.* Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #09-199; 2019. Available at: https://www.hsrd.research.va.gov/publications/esp/reports.cfm;2019.
30. Katz D, Gavin M. In the clinic: Stable ischemic heart disease. *Annals of Internal Medicine.* 2019.
31. Lan W-C, Chen Y-H, Liu S-H. Non-invasive imaging modalities for the diagnosis of coronary artery disease: The present and the future. *Tzu Chi Medical Journal.* 2013;25(4):206-212.
32. Siontis GC, Mavridis D, Greenwood JP, et al. Outcomes of non-invasive diagnostic modalities for the detection of coronary artery disease: Network meta-analysis of diagnostic randomised controlled trials. *BMJ.* 2018;360:k504.
33. Haase R SP, Gueret P, et al. . Diagnosis of obstructive coronary artery disease using computed tomography angiography in patients with stable chest pain depending on clinical probability and in clinically important subgroups: Meta-analysis of individual patient data. *BMJ (Clinical Research Ed).* 2019;365(l1945).
34. Hecht HS, Narula J, Fearon WF. Fractional flow reserve and coronary computed tomographic angiography: A review and critical analysis. *Circulation Research.* 2016;119(2):300-316.
35. Leber WA. Is FFR-ct a “game changer” in the diagnostic management of stable coronary artery disease? *Herz.* 2016;41(5):398-404.
36. Xie X, Zheng M, Wen D, Li Y, Xie S. A new cfd based non-invasive method for functional diagnosis of coronary stenosis. *Biomedical Engineering Online.* 2018;17(1):36.
37. Ball C, Pontone G, Rabbat M. Fractional flow reserve derived from coronary computed tomography angiography datasets: The next frontier in noninvasive assessment of coronary artery disease. *Biomedical Research International.* 2018;2018:2680430.
38. Khav N IA, Ko B Ct-derived fractional flow reserve (ct-FFR) in the evaluation of coronary artery disease. *Heart, Lung & Circulation.* 2020;29:1621-1632.
39. HeartFlow. HeartFlow. 2018; https://www.heartflow.com/. Accessed April 30, 2019.
40. HeartFlow Inc. Non-invasive cardiac test. https://www.heartflow.com/patients/overview/. Accessed April, 2021.
41. ECRI Institute. Ffrct software (HeartFlow, inc.) for evaluating coronary artery diease. 2020.
42. Huang A MP, Brown RA, et al. . Ct-derived fractional flow reserve (ffrct): From gatekeeping to roadmapping. *Canadian Association of Radiologists Journal.* 2020;71(2):201-207.

43. Chen J WL, Pope KL, Meek LJ, Rosamond T, Walker CM. Ffrct: Current status. *AJR Am J Roentgenol.* 2020;216(3):640-648.
44. NICE. Qangio xa 3d/qfr imaging software for assessing coronary obstructions - medtech innovation briefing (mib146). 2018.
45. Ernst CB. HeartFlow announces decision by centers for medicare & medicaid services to assign a new technology payment classification to HeartFlow® ffrct analysis. 2017; https://www.businesswire.com/news/home/20171106005472/en/HeartFlow-Announces-Decision-Centers-Medicare-Medicaid-Services. Accessed March 19, 2019.
46. New policy decisions give millions access to HeartFlow ffrct analysis. 2018; https://www.dicardiology.com/content/new-policy-decisions-give-millions-access-heartflow-ffrct-analysis. Accessed March 19, 2019.
47. Whiting P, Savović J, Higgins JP, et al. Robis: A new tool to assess risk of bias in systematic reviews was developed. *Journal of Clinical Epidemiology.* 2016;69:225-234.
48. Whiting P, Rutjes AW, Westwood ME, et al. Quadas-2: A revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine.* 2011;155:529-536.
49. Sterne JA, Hernán MA, Reeves BC, et al. Robins-i: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016;355:i4919.
50. Murad MH SS, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evidence-Based Medicine.* 2018;23(2):60-63.
51. Berkman ND, Lohr KN, Ansari M, et al. *Grading the strength of a body of evidence when assessing health care interventions for the effective health care program of the agency for healthcare research and quality: An update methods guide for effectiveness and comparative effectiveness reviews.* Rockville, MD: Agency for Healthcare Research and Quality;2013.
52. US Department of Veterans Affairs. VA informatics and computing infrastructure (vinci). https://www.hsrd.research.va.gov/for_researchers/vinci/. Accessed April 23, 2019.
53. Fairbairn TA, Dobson R, Hurwitz-Koweek L, et al. Sex differences in coronary computed tomography angiography-derived fractional flow reserve: Lessons from advance. *JACC: Cardiovascular Imaging.* 2020;13(12):2576-2587.
54. Nous F, Budde RPJ, Fairbairn TA, et al. Temporal changes in FFR_{ct}-guided management of coronary artery disease - lessons from the advance registry. *Journal of Cardiovascular Computed Tomography.* 2021;15(1):48-55.
55. Pontone G, Weir-McCall JR, Baggiano A, et al. Determinants of rejection rate for coronary ct angiography fractional flow reserve analysis. *Radiology.* 2019;292(3):597-605.
56. Colleran R, Douglas PS, Hadamitzky M, et al. An FFRCT diagnostic strategy versus usual care in patients with suspected coronary artery disease planned for invasive coronary angiography at german sites: One-year results of a subgroup analysis of the platform (prospective longitudinal trial of FFRCT: Outcome and resource impacts) study. *Open Heart.* 2017;4(1).
57. 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. *Journal of the American College of Cardiology.* 2015;66(21):2315-2323.
58. Matsumura-Nakano Y, Kawaji T, Shiomi H, et al. Optimal cutoff value of fractional flow reserve derived from coronary computed tomography angiography for predicting

hemodynamically significant coronary artery disease. *Circulation Cardiovascular imaging.* 2019;12(8):e008905.
59. Norgaard 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). *Journal of the American College of Cardiology.* 2014;63(12):1145-1155.
60. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 acc/aha/aats/pcna/scai/sts focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease. *Circulation.* 2014;130(19):1749-1767.
61. 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: Executive summary: 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. *Circulation.* 2012;126(25):3097-3137.
62. Jorgensen ME, Andersson C, Norgaard BL, et al. Functional testing or coronary computed tomography angiography in patients with stable coronary artery diease. *Journal of the American College of Cardiology.* 2017;69(14):1761-1770.
63. Hachamovitch R, Nutter B, Hlatky MA, et al. Patient management after noninvasive cardiac imaging results from sparc (study of myocardial perfusion and coronary anatomy imaging roles in coronary artery disease). *Journal of the American College of Cardiology.* 2012;59(5):462-474.
64. Zorlak A, Zorlak A, Thomassen A, et al. Patients with suspected coronary artery disease referred for examinations in the era of coronary computed tomography angiography. *American Journal of Cardiology.* 2015;116(3):344-349.
65. Bittencourt MS, Hulten EA, Murthy VL, et al. Clinical outcomes after evaluation of stable chest pain by coronary computed tomographic angiography versus usual care: A meta-analysis. *Circulation: Cardiovascular Imaging.* 2016;9(4).
66. Abdelrahman KM, Chen MY, Dey AK, et al. Coronary computed tomography angiography from clinical uses to emerging technologies. *Journal of the American College of Cardiology.* 2020;76(10):1126-1243.
67. Knuuti J, Wijns W, Saraste A, et al. 2019 esc guidelines for the diagnosis and management of chronic coronary syndromes. *European Heart Journal.* 2020;41:407-477.
68. NICE. *HeartFlow FFRCT for estimating fractional flow reserve from coronary ct angiography.* 2017.
69. Levin DC, Parker L, Halpern EJ, Rao VM. Coronary ct angiography: Reversal of earlier utilization trends. *American College of Radiology.* 2018;16:147-155.
70. Hoffmann U, Ferencik M, Udelson JE, et al. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: Insights from the promise trial (prospective multicenter imaging study for evaluation of chest pain). *Circulation.* 2017;135(24):2320-2332.