HeartFlow® FFR_{CT} Analysis Clinical Dossier:

Fractional Flow Reserve (FFR) from Coronary Computed Tomography Angiography (CCTA)

From the United Kingdom's
National Institute for Health and Care Excellence (NICE)
May 2021 Guidance Document on FFR_{CT} [1]:

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

From the 2021 American Heart Association and American College of Cardiology Guideline for the Evaluation and Diagnosis of Chest Pain (November 2021) [2]:

> ***"For intermediate-risk patients with acute chest pain and no known CAD, with a coronary artery stenosis of 40% to 90% in a proximal or middle coronary artery on CCTA, FFR-CT can be useful for the diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization."***
>
> ***"For intermediate-high risk patients with stable chest pain and known coronary stenosis of 40% to 90% in a proximal or middle coronary segment on CCTA, FFR-CT can be useful for diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization."***

Table of Contents

Executive Summary

The HeartFlow® FFR_{CT} Analysis is a non-invasive, diagnostic tool used to aid clinicians in determining the physiologic impact of coronary artery disease (CAD) in patients with chest pain or other symptoms suggestive of CAD. FFR_{CT} is calculated using image data from a previously acquired coronary computed tomography angiography (CCTA). FFR_{CT} allows evaluation of each coronary stenosis for its flow limiting significance by adding a physiological dimension to the anatomical information provided by CCTA. This added information provides clinicians with meaningful insight to determine the right management option for patients with CAD. Use of FFR_{CT} is now recommended in practice guidelines and allows for a safer, more efficient diagnostic pathway, reducing dependence on invasive procedures such as invasive coronary angiography (ICA).

Background

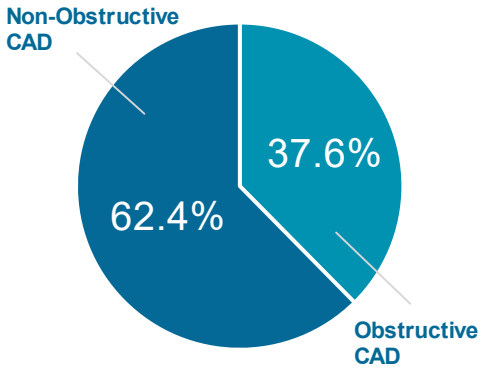
CAD is the leading cause of death worldwide, killing approximately 3.8 million men and 3.4 million women each year [3]. Stable chest pain is a common clinical presentation of CAD, with an incidence of 4% - 7% among individuals 45 to 65 years old, and 10% - 15% in those over age 65 [4], often requiring non-invasive or invasive diagnostic evaluation [5].

Current Non-invasive Tests Do a Poor Job Determining Who Has CAD

Patients with suspected CAD will typically undergo a stress test, including treadmill electrocardiogram (ECG), stress echocardiography, or nuclear myocardial perfusion imaging (i.e., SPECT), to determine whether CAD is present and the appropriate course of treatment. However, these tests have low accuracy, frequently misdiagnose, and cannot definitively answer the question of whether CAD is present.

A landmark study by Patel et al. [6] demonstrated that 62.4% of patients referred to ICA based on stress test results or symptoms had no obstructive CAD. These patients are exposed to an expensive test with procedural risk and no added clinical value. Stress testing also has a high rate of false negatives (20 – 30%) meaning that patients with a negative result are quite likely to have obstructive disease [7-10]. These patients often return with worsened or critical symptoms, and clinicians lose the opportunity for medical management shown to reduce the progression and clinical impact of CAD over time [11]. Stress tests cannot identify which patients will benefit from revascularization, as patients sent for ICA based on these tests have equivalent outcomes to those managed with medication alone [12].

Figure 1. Incidence of Obstructive CAD at time of Angiography – NCDR Cath PCI Registry



A non-invasive pathway that correctly identifies patients with CAD and determines the best treatment strategy is essential to optimize outcomes and efficiency in value-based healthcare systems.

A CCTA First Pathway Correctly Determines Who Has CAD But Can't Determine Who Will Benefit From Revascularization

While stress testing utilizes ECG signals, perfusion, or ventricular wall motion as a surrogate to identify whether a patient has obstructive CAD, CCTA directly visualizes the coronary artery walls and lumen to identify the presence of obstructive CAD. With high sensitivity, CCTA has a negative predictive value of 99%; a negative test is therefore considered a warranty against CAD for up to 8 years [13, 14]. Conversely, a positive CCTA showing severe stenosis is readily analyzed and commonly leads to referral for ICA and revascularization.

The SCOT-HEART study was a head-to-head comparison of outcomes between patients managed with stress testing alone versus those sent for CCTA. The trial showed a remarkable 41% lower rate of cardiovascular death or MI in the CCTA group after 5 years [11]. This important study, published in the New England Journal of Medicine, confirmed the benefits of CCTA in the management of patients with chest pain.

However, a limitation of CCTA as a first-line test is in characterizing whether a narrowing is impeding blood flow to the heart. In many cases, the degree of anatomic narrowing does not provide enough information to enable physicians to determine whether a patient will benefit from invasive evaluation and therapy. In these stenoses, the HeartFlow FFR_{CT} Analysis addresses the unmet need by providing physiologic information to help the physician determine whether a patient requires revascularization. FFR_{CT} delivers the specificity that CCTA lacks.

Fractional Flow Reserve (FFR) Improves Clinical Outcomes But is Rarely Used

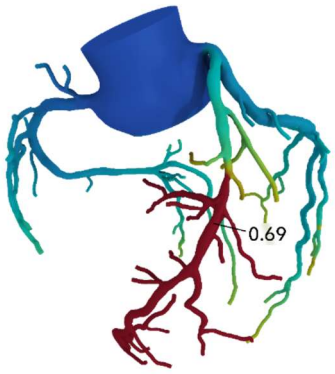
FFR is a measurement of blood flow across narrowed coronary arteries that can be performed at the time of ICA. FFR has been found to be the most accurate and reliable measure for determining the physiologic significance of a coronary lesion and predicting which patients will benefit from revascularization [15, 16]. Despite long-term data showing improved outcomes with FFR-guided decision-making, it remains significantly underutilized in practice, with FFR being used in only 6.1% of interventions for intermediate coronary lesions [17].

The HeartFlow FFR_{CT} Analysis Addresses Shortcomings in Diagnostic Pathways

The HeartFlow FFR_{CT} Analysis provides calculated FFR information from a standard CCTA, addressing two unmet needs:

- Provides functional (physiologic) information on coronary artery blood flow non-invasively.
- Helps physicians determine the physiologic significance of lesions identified by CCTA, enabling triage to the most appropriate care.

Figure 2. FFR_{CT} Coronary Artery Physiologic Map



The HeartFlow Analysis uses artificial intelligence and computational fluid dynamics to create a 3D model of the coronary arteries (Figure 2) to help the physician assess the impact blockages have on coronary blood flow. Clinicians receive the HeartFlow Analysis via a secure web interface and can comprehensively interrogate each point in the coronary anatomy to identify flow-limiting stenoses and determine the appropriate treatment strategy.

Evidence on the HeartFlow FFR_{CT} Analysis is Established and Extensive

Development, validation and adoption of the HeartFlow Analysis has been extensive and established internationally:

- The HeartFlow technology received CE Mark in 2011, FDA clearance in 2014, Canadian Medical Device Licensing in 2015, and PMDA approval in Japan in 2016.
- The CCTA and FFR_{CT} pathway is recommended in practice guidelines from physician specialty societies in the United States [2], European Union [18], and Japan [19].
- There are over 500 peer-reviewed publications specific to the FFR_{CT} Analysis which document performance, clinical utility, and long-term safety and effectiveness. Studies include large, randomized, international trials that demonstrate:

1. **Accuracy:** When using invasive FFR as the reference standard, FFR_{CT} has the highest diagnostic performance compared to other diagnostic tests including CCTA, ICA, PET, CT perfusion, and SPECT [20-24].
2. **Clinical Utility:** Use of FFR_{CT} allows physicians to choose safely the most appropriate treatment for their patients. Use of FFR_{CT} has been demonstrated to change patient management in 63% of cases and has allowed safe avoidance of ICA in > 60% of cases for patients with stable symptoms [25-42].
3. **Improved Outcomes:** The FISH&CHIPS Study demonstrated, in an univariate analysis, that the availability and use of FFR_{CT} was associated with a 14% reduction in cardiovascular mortality and an 8% reduction in all-cause mortality [43]. Long term follow-up (1 - 5 years) in almost 100,000 patients in multiple clinical trials demonstrates

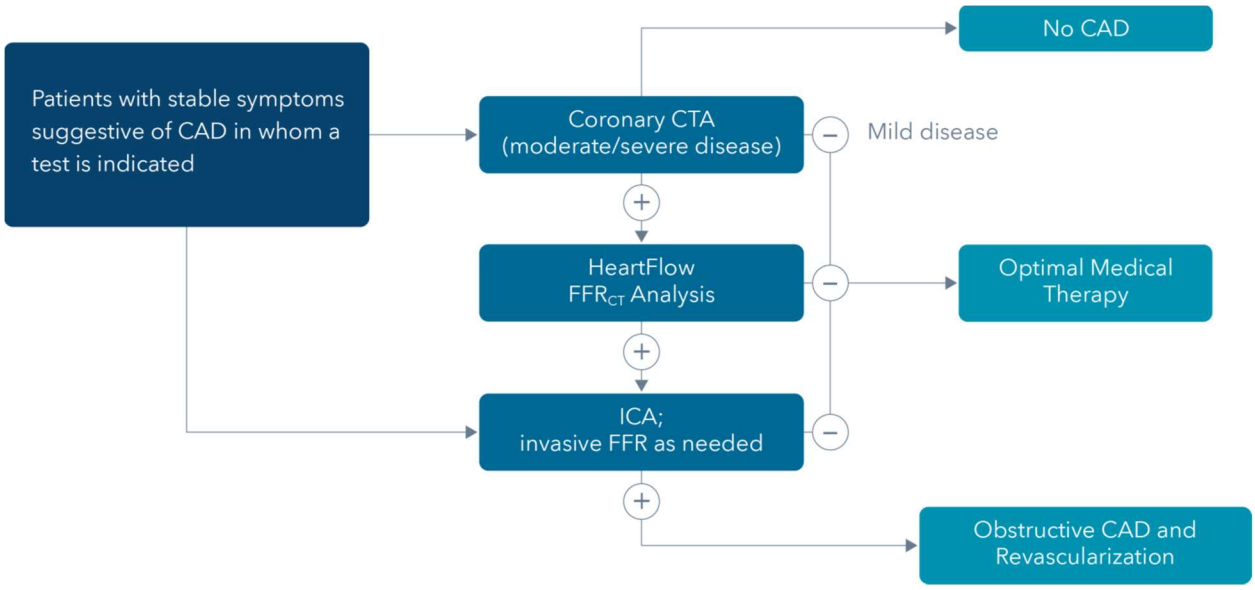
physicians can confidently determine the most appropriate treatment pathway for each patient by utilizing FFR_{CT} [27, 28, 30, 31, 33, 43-46].

4. **Cost-savings:** Clinical pathways that utilize FFR_{CT} reduce healthcare costs [25, 27, 33, 35, 37, 47-53].

- In the U.S., FFR_{CT} received a positive technology assessment by Blue Cross Blue Shield Evidence Street® [54], it is paid by Medicare through both the hospital outpatient payment system and physician fee schedule, and there are positive coverage decisions by most major health plans (United Healthcare, Aetna, Cigna, Anthem, Medicare Carriers).
- In the United Kingdom, the CCTA + FFR_{CT} pathway received a favorable recommendation from the National Institute for Health and Care Excellence (NICE), supported by NICE medical technology guidance MTG32. The national guideline (CG95) recommends CCTA as the first-line test for all stable patients with suspected CAD. Furthermore, FFR_{CT} is endorsed by UK's National Health Service and is funded nationally through the NHS Innovation and Technology Payment (ITP) program [1, 55].

A diagnostic pathway involving CCTA with FFR_{CT} (Figure 3) is rapidly becoming the preferred, less invasive, and cost-saving pathway for patients with suspected CAD.

Figure 3. Suggested Diagnostic Pathway for Patients with Suspected CAD



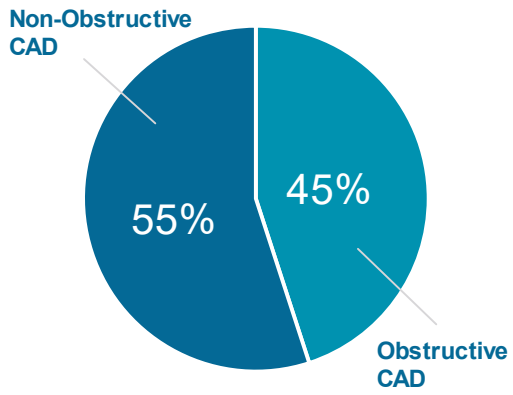
Unmet Need: A More Accurate and Non-Invasive Test to Help Establish the Presence of CAD

A frequent and critical challenge in cardiology is patients who experience chest pain yet may or may not have physiologically significant CAD. Missing the diagnosis of CAD can result in a lost opportunity for appropriate life-saving medical management or revascularization. However, sending every patient who presents with chest pain to ICA unnecessarily subjects patients to an invasive and costly procedure. Thus, non-invasive cardiac tests are often utilized to risk stratify and select patients for ICA.

Traditional non-invasive tests, including exercise treadmill electrocardiogram (ECG), stress echocardiography, and nuclear myocardial perfusion imaging (i.e., SPECT) are commonly used but do not serve this function effectively. These tests have significant limitations as follows:

- **Stress tests have known false positives** — Patients with ambiguous or positive results are commonly referred for an ICA, which has inherent risks and costs [56]. Most patients undergoing ICA are found not to have obstructive CAD. A study by Patel et al. analyzed data from almost 400,000 U.S. patients in 663 hospitals found that 62.4% of patients referred for ICA had no obstructive disease [6]. In a follow-up study in 661,063 U.S. patients who had any non-invasive test prior to ICA, 55% demonstrated nonobstructive CAD [57] (Figure 4).

Figure 4. Incidence of Obstructive CAD at time of Angiography following a noninvasive test

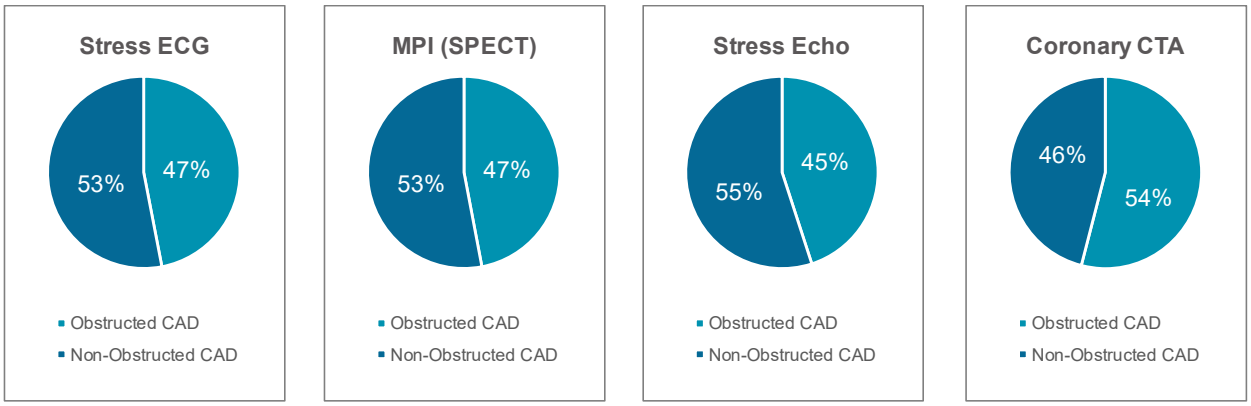


- **Stress tests have known false negatives** — In nearly 50% of patients with the most severe disease (i.e., triple vessel or left main disease) stress testing generates a negative result due to "balanced ischemia" [58, 59]. With a high rate of false negatives (20 – 30%) patients with a negative stress test are quite likely to have obstructive disease [7-9]. These patients are frequently sent home only to return with chest pain for repeat testing or have a MI resulting in urgent revascularization or death.
- **Stress tests do not effectively guide which patients will benefit from revascularization** — The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial demonstrated that patients with moderate or severe ischemia found via stress testing did not have improved outcomes with invasive therapy (ICA and revascularization) compared to medical therapy alone [12]. These results indicate that stress tests cannot effectively determine which patients will benefit from invasive therapy.
- **Stress testing does not catch early-stage disease** — Stress testing is intended to determine if a symptomatic patient has ischemia, which, despite symptoms, is often not detected at early disease stages. Early CAD may fall below the threshold for detection and

these patients lose a critical opportunity for medical management shown to reduce the progression and clinical impact of CAD over time [11].

The high rate of non-obstructive disease during elective ICA has been reported globally. A retrospective cohort study in Ontario, Canada compared rates of obstructive CAD and major adverse cardiac events (MACE) in 15,467 patients across the non-invasive modalities. There were no significant differences in obstructive CAD rates or MACE in patients undergoing initial non-invasive testing with stress ECG, MPI (SPECT), Stress Echo, or CCTA (Figure 5) [60].

Figure 5. Incidence of Nonobstructive CAD at time of Angiography – Canadian (Ontario) [60]



Of the non-invasive tests, CCTA has been shown to have a patient-based sensitivity of 99% [61], and the absence of CAD on CCTA is associated with an excellent clinical outcome for more than 8 years [13, 14]. A randomized, controlled trial from Scotland that enrolled 4,146 patients demonstrated a 41% lower rate of cardiovascular death and MI after 5 years in the group randomly assigned to undergo CCTA as compared to the standard care group managed based on stress testing [11].

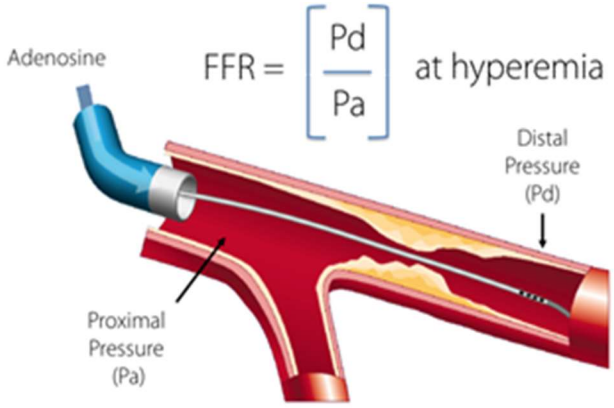
However, a key limitation of CCTA as a stand-alone first-line test lies in its inability to characterize the clinical importance of intermediate stenoses (arterial narrowings of 30-90%). CCTA as a stand-alone non-invasive test has a specificity of only 39% [62] indicating a high frequency of false positive results and thereby limiting its utility to select patients for ICA.

In intermediate stenoses, FFR_{CT} addresses the unmet need by providing physiologic information to help the physician determine whether a patient requires revascularization. FFR_{CT} delivers the specificity that CCTA lacks.

Unmet Need: An Easily Accessible Measure for Evaluating the Physiologic Significance of Stenoses

Invasive fractional flow reserve (FFR), measured during ICA, serves as the gold standard for identifying physiologically significant stenoses and is used to identify patients who may benefit from coronary revascularization. FFR is determined by placing a pressure wire across a stenosis and measuring the pressure differential (Figure 6). In a perfectly normal, non-obstructed coronary artery, the FFR "value" is 1.0. A value less than 1.0 indicates a reduction in blood flow through the coronary artery. The lower the FFR value, the greater the reduction in flow and the more significant the obstruction.

Figure 6. Fractional Flow Reserve



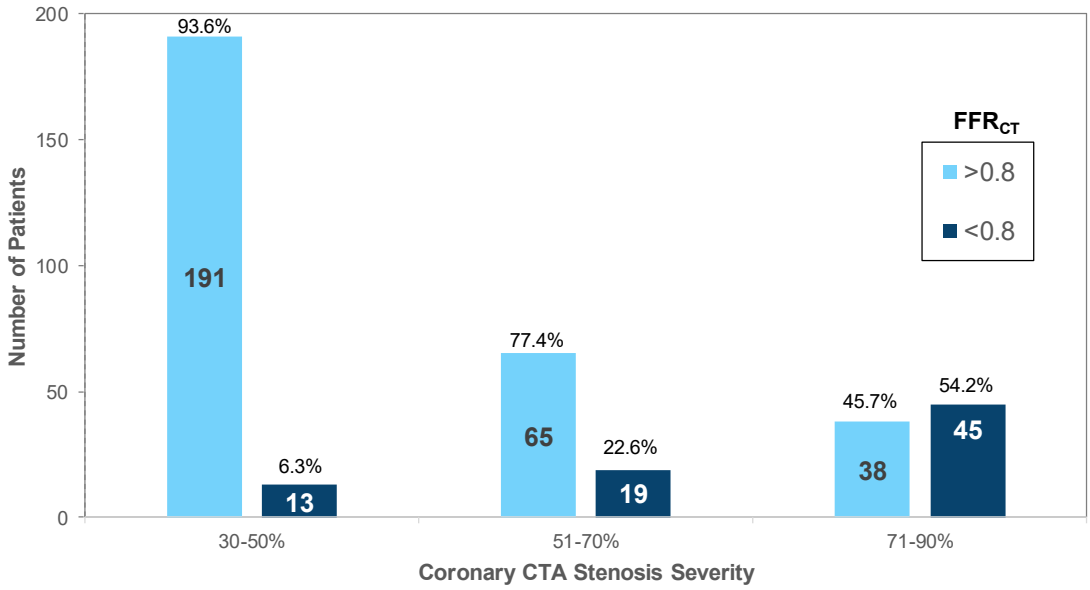
In determining the treatment plan for a patient with stable chest pain, it is important for a physician to understand both the anatomical and physiologic (also referred to as functional or hemodynamic) information for each coronary stenosis. Anatomic information alone, whether obtained by ICA or CCTA, is simply not enough. Figure 7 demonstrates how the severity of anatomical stenosis can correlate poorly with physiologic significance (FFR_{CT}) [26].

Use of FFR as a tool to guide revascularization has been shown to improve outcomes.

- The FAME study [16] randomized patients with multivessel CAD to angiography-guided Percutaneous Coronary Intervention (PCI) or FFR-guided PCI. The FFR-guided group, in which stents were placed only when a stenosis was associated with FFR ≤ 0.80, had a 28% lower rate of the composite endpoint of death, nonfatal MI, and repeat revascularization.
- In the FAME II study [15] patients in whom at least one stenosis was physiologically significant (FFR ≤ 0.80) were randomized to FFR-guided PCI or optimal medical therapy (OMT). Five-year follow-up [63] showed that patients with physiologically significant lesions (FFR ≤ 0.80) who received PCI demonstrated a 49% reduction in death, MI, and urgent revascularization compared to patients who received OMT.

- The FAME and FAME II studies proved that medically treating patients with FFR > 0.80 and performing PCI in patients with FFR ≤ 0.80 has favorable long-term outcomes including a 28% reduction in rates of cardiac death or MI [63, 64].
- Data from 9,106 patients in Canada confirms that performing PCI in ischemic lesions (FFR ≤ 0.80) improves outcomes (reduces MACE) while performing PCI in nonischemic lesions (FFR > 0.80) causes harm (increases MACE) [65].
- The ORBITA-2 trial showed that use of PCI in patients with stable chest pain and FFR ≤ 0.80 improved symptoms compared to OMT [66].

Figure 7: Distribution of Lesion Severity: CT Angiogram alone compared with FFR_{CT} (N=577)



Evidence-based professional society guidelines support the use of invasive FFR to guide PCI, with a class IA recommendation in the ESC guidelines [4, 67] and a class IIA recommendation in the American College of Cardiology (ACC) Guidelines [68].

Despite the compelling data and inclusion in guidelines, invasive FFR is infrequently used. Published data from the ACC Cath PCI registry on 61,874 ICAs documented performance of invasive FFR in only 6.1% of patients [17]. Some reasons include:

- The requirement for additional time, medication, contrast administration, radiation, and equipment during ICA.
- Current reimbursement does not provide adequate payment.

FFR is the gold standard for assessing the physiologic significance of CAD. Invasive FFR is not commonly used despite the evidence of high clinical value. FFR_{CT} provides physiologic information non-invasively, safely, and without additional procedures.

The HeartFlow FFR_{CT} Analysis

The HeartFlow FFR_{CT} Analysis utilizes deep learning algorithms, a form of artificial intelligence, and computational fluid dynamics to build a personalized, digital 3D model of each patient's coronary arteries based on previously acquired CCTA image data. The technology has been developed through decades of scientific research on image-based modeling for blood flow.

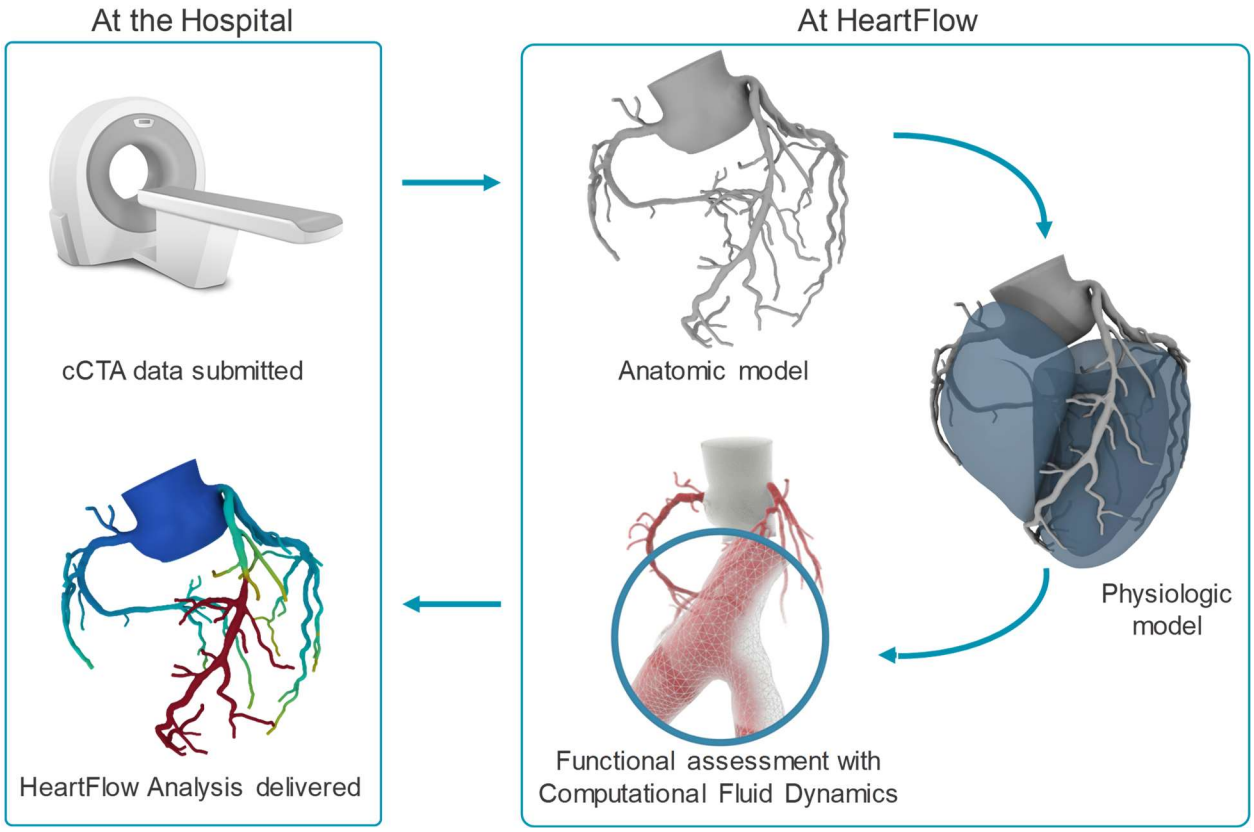
A team of highly trained analysts inspects the digital anatomic model, making any needed edits. Once this patient-specific model is completed, the HeartFlow process applies physiologic principles and computational fluid dynamics to compute blood flow and FFR_{CT} values at every point in the model. Throughout the process, rigorous and well-established protocols are followed to ensure consistent processing for every patient. The completed HeartFlow Analysis provides a color-coded, digital 3D model of the heart, reflecting the impact that blockages have on blood flow. Results are provided to the physician with an average turnaround time of less than two hours[1].

The workflow for the HeartFlow FFR_{CT} Analysis (Figure 8) is as follows:

1. Uploading of a patient's CCTA image data to HeartFlow through a secure cloud-based server;
2. Case processing involving the use of both deep learning algorithms and highly trained HeartFlow analysts;
    - Incoming CCTA data undergoes a quality inspection by analysts to ensure sufficient data quality for analysis;
    - Computerized algorithms identify and extract anatomical structures from CCTA images for segmentation and creation of a patient's personal coronary artery model;
    - Analysts inspect the model to ensure it accurately represents the CCTA data and make edits as needed;
    - A physiological model is created using the patient's anatomical model;
    - Maximal hyperemia is simulated to mimic conditions during invasive FFR evaluation;
    - Computational fluid dynamics are applied to solve millions of complex equations, resulting in a 3D coronary blood flow model;
    - The resulting model provides the calculated FFR_{CT} values throughout the modeled coronary arteries.
3. Clinicians receive the HeartFlow FFR_{CT} Analysis via a secure web portal or iOS app. They can comprehensively interrogate each point in the coronary anatomy to identify ischemic lesions and determine appropriate treatment strategies.

[1] Internal HeartFlow data on file. Commercial Turnaround Time (TAT).

Figure 8. The HeartFlow FFR_{CT} Analysis and Workflow

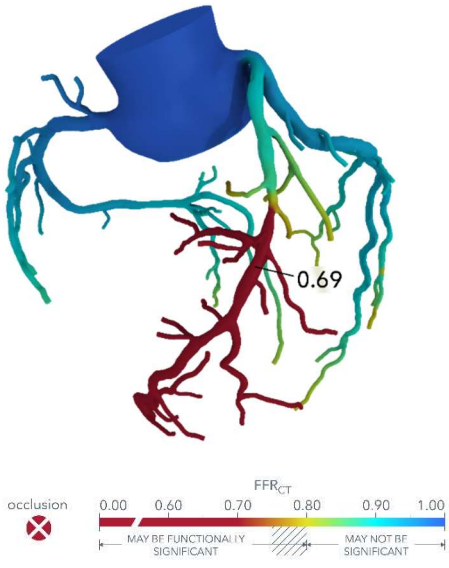


The numeric FFR_{CT} values indicate the amount of calculated coronary blood flow with 1.0 being normal (100%). $FFR_{CT} \leq 0.80$ may be considered significant and has been proven in studies to identify patients at higher risk of adverse events if managed without revascularization [33]. In Figure 9 the blue to green areas correspond to FFR_{CT} values that are greater than 0.80. Yellow to red areas indicate a significant reduction in FFR_{CT}, i.e., less than 0.80.

A sample of the HeartFlow Analysis is found in Appendix 1.

FFR_{CT} provides high diagnostic performance in patients with a wide range of coronary calcium, one of the challenges of reading accurately with CCTA. FFR_{CT} has high diagnostic accuracy in patients and vessels with low, intermediate and high levels of calcium and is superior to CCTA alone [69].

Figure 9. FFR_{CT} Coronary Artery Physiologic Map



Clinical and Analytic Validity

The HeartFlow FFR_{CT} Analysis is accurate and reliable as evidenced in multiple prospective studies. These studies have evaluated the accuracy and ability of FFR_{CT} and other non-invasive tests to diagnose ischemic disease using invasive FFR as the reference standard.

FFR_{CT} Accuracy Studies

Multicenter trials evaluated the accuracy of early developmental prototypes (**DISCOVER FLOW, DeFACTO**) or initial commercial version (NXT) of the FFR_{CT} Analysis compared with invasive FFR as the reference standard in a total of 609 patients and 1050 coronary vessels. All three studies demonstrated that the HeartFlow FFR_{CT} Analysis had higher diagnostic accuracy than CCTA alone [22-24].

The **NXT Trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps)**, the basis for De Novo FDA clearance, was a prospective accuracy study in which CCTA was performed prior to non-emergent ICA in stable patients with suspected CAD. NXT enrolled 254 patients and 484 vessels at 10 centers in Europe, Canada, Australia and the U.S.

Major Findings and Conclusions [24]

- Using invasive FFR as the reference standard:
  - FFR_{CT} had a per-patient accuracy of 81% compared with 53% for CCTA, and 77% for ICA
  - Similarly, FFR_{CT} had a per-vessel accuracy of 86% compared with 65% for CCTA, and 82% for ICA
- FFR_{CT} provided high diagnostic accuracy and discrimination for the diagnosis of physiologically significant CAD with invasive FFR as the reference standard.
- When compared to anatomic testing by CCTA, FFR_{CT} led to a marked increase in specificity.

The PACIFIC Trial and the PACIFIC FFR_{CT} Sub-Study [20]

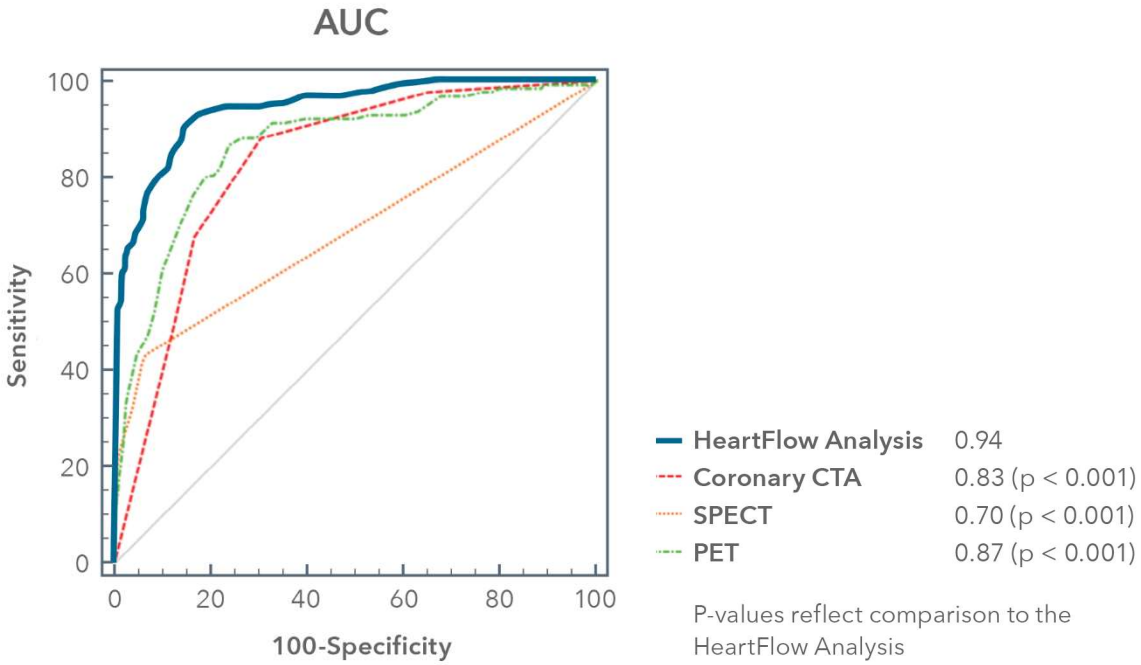
The **PACIFIC trial** was an independent, prospective, head-to-head study to evaluate the diagnostic performance of several non-invasive tests commonly used to identify physiologically significant CAD. 208 patients with suspected, stable CAD underwent CCTA, SPECT and oxygen labeled water Positron Emission Tomography (PET) and then ICA with invasive 3-vessel FFR, which served as the reference standard. The study showed that PET had better diagnostic performance than the other non-invasive modalities [70]. However, FFR_{CT} was not included in this study.

The primary objective of the **PACIFIC FFR_{CT} sub-study** was to evaluate the diagnostic performance of the HeartFlow FFR_{CT} Analysis and compare it with CCTA, SPECT, and PET. All the CCTA data acquired during the PACIFIC Trial was sent to HeartFlow to perform this sub-study.

Major Findings and Conclusions

- Of 208 PACIFIC patients, 180 had successful FFR_{CT} analysis (87%)
- Using invasive FFR as the reference standard, FFR_{CT} demonstrated the highest diagnostic performance with an AUC value of 0.94 compared with CCTA (0.83), SPECT (0.70), and PET (0.87) (all p-values < 0.001) (Figure 10)
- The investigators concluded that FFR_{CT} "showed the highest diagnostic performance for vessel-specific ischemia" and that these findings "support the use of FFR_{CT} in clinical practice for diagnosing ischemia and revascularization decision making."

Figure 10. PACIFIC Diagnostic Performance of Cardiac Imaging Methods of Coronary Artery Disease (CAD) on a Patient-Based Level



FFR_{CT} Reproducibility

Gaur et. al. [71] evaluated the reproducibility of the FFR_{CT} Analysis and of invasive FFR measurements. For FFR_{CT}, two analyses using the same CCTA data were conducted by independent analysts blinded to the other reading. For invasive FFR, a second FFR measurement was taken several minutes after the first. The authors concluded that the reproducibility of the FFR_{CT} Analysis was high and in fact equivalent to that of repeated invasive FFR measurements.

Outcomes and Clinical Utility

Many studies, including multiple randomized, controlled trials have demonstrated that use of the HeartFlow FFR_{CT} Analysis:

- Improves clinical outcomes compared to standard care.
- Allows safe deferral of many patients away from ICA.
- Provides clinicians with data to discriminate between those coronary lesions that require revascularization and those that do not.

Details regarding the design and outcomes of these studies are found in Appendix 2. The chart below provides a summary:

Study Name	Investigator	Publication	Clinical Utility Implications
The PRECISE Study	Douglas [28]	JAMA Cardiology 2023	This randomized, controlled trial found that use of the 'Precision Strategy', consisting of CCTA and FFR_{CT}, led to a 70% reduction in the composite end point of death, heart attack, or ICA without obstructive CAD at one year compared to traditional testing, which included stress testing and ICA.
The FISH&CHIPS Study	Fairbairn [43]	Eur Society of Cardiology 2023	Availability of FFR_{CT} at 25 NHS England sites led to a 14% reduction in cardiovascular mortality and an 8% reduction in all-cause mortality over 2 years compared to CCTA alone in a univariate analysis.
The FORECAST Trial	Curzen [25]	Eur Heart J 2021	This randomized, controlled trial found that use of CCTA and FFR_{CT} to evaluate patients with suspected CAD led to a 22% lower rate of ICA, a 40% reduction in additional (e.g., layered) noninvasive testing, and no difference in rates of adverse events.
The PLATFORM Study	Douglas [29] and Douglas [27]	Eur Heart J 2015 and J Am Coll Cardiol 2016	In this prospective study, 61% of planned ICAs were cancelled based on FFR_{CT} guidance without adverse clinical consequences. FFR_{CT} reduced ICAs showing no significant stenosis by 83%. At one-year, there were no adverse clinical events in the 117 patients whose ICA was cancelled based on FFR_{CT} results.
The ADVANCE Registry	Fairbairn [30], Patel [34] and Madsen [31]	Eur Heart J 2018, JACC Card Imaging 2020, and Radiology 2023	In a prospective, 38 site, 5,083 patient registry use of FFR_{CT} resulted in changes in clinical management in 2 out of 3 of patients compared to CCTA alone. Among those patients who went to ICA with a positive FFR_{CT}, 73% were revascularized. Negative FFR_{CT} (FFR_{CT} > 0.80) was associated with low rates of ICA and zero MACE at 90 days. One-year data shows that treatment decisions are durable and safe, i.e., deferral of invasive management is highly unlikely to result in later return for revascularization or an adverse event. Three-year data demonstrate that patients with normal FFR_{CT} findings (> 0.80) have lower rates (2.1%) of death or heart attack compared to patients with abnormal FFR_{CT} findings (≤ 0.80) who experienced higher rates of adverse events (6.6%)
FFR_{CT} RIPCORD	Curzen [26]	JACC Card Imaging 2016	FFR_{CT} data resulted in a change in treatment decision for 44% of patients. Of patients originally thought to require PCI, FFR_{CT}

Study Name	Investigator	Publication	Clinical Utility Implications
			findings allowed for 30% to be re-allocated to medical management and 18% to have their PCI target vessel changed.
Aarhus FFR_{CT} Experience	Jensen [32]	Eur Heart J Card Imag 2017	Use of CCTA and FFR_{CT} led to cancellation of 75% of planned ICAs in high-risk patients (use of CCTA alone would have cancelled only 46%). The same clinical strategy safely kept 91% of low-intermediate risk patients from going to ICA.
Clinical Outcomes Following FFR_{CT}	Norgaard [33]	JACC 2018	Prospective study of 3,674 consecutive patients with stable chest pain who were evaluated with CCTA and FFR_{CT} when needed. Results demonstrated that FFR_{CT} is effective for differentiating those patients with intermediate stenosis who could be managed medically versus those requiring ICA and possible stenting or CABG. Patients with intermediate stenosis by CCTA who had a negative FFR_{CT} had outcomes similar to patients who had zero-to-minimal disease by CCTA.

Long Term Clinical Outcomes

Long term follow-up (1 - 5 years) in almost 100,000 patients in multiple clinical trials demonstrates physicians can confidently determine the most appropriate treatment pathway for each patient by utilizing FFR_{CT} [27, 28, 30, 31, 33, 37, 43-46, 72, 73]. The FISH&CHIPS Study, in an univariate analysis, demonstrated that the availability and use of FFR_{CT} was associated with a 14% reduction in cardiovascular mortality and an 8% reduction in all-cause mortality in 90,000 patients over 2 years as compared to CCTA alone [43]. A meta-analysis of five studies that included 5,460 patients confirmed that a negative FFR_{CT} result (FFR_{CT} > 0.80) is associated with a low incidence of death or heart attack at 12 months compared with a positive FFR_{CT} result [46].

This data demonstrates that clinicians can safely and confidently choose medical therapy, deferring ICA, for patients with negative FFR_{CT} results. These patients have a favorable long-term prognosis with low rates of MACE. In addition, the decision to defer ICA is durable with few patients returning for later revascularization.

Conversely, patients with positive FFR_{CT} results have a significantly higher risk of experiencing MI or cardiovascular-related death, and the lower the FFR_{CT} value, the higher this risk. Clinicians are more likely to refer these patients for ICA and potential revascularization reducing their risk of an adverse event. Most patients with a positive FFR_{CT} who are sent to the cath lab undergo revascularization, indicating that physicians are able to effectively triage patients who need invasive assessment.

Clinical Diagnostic Pathway

Stable chest pain is a common clinical presentation of coronary artery disease (CAD), with an incidence of 4% - 7% among individuals 45 to 65 years old, and 10% - 15% in those over age 65 [4]. This is a large patient population for which physicians ask two fundamental questions: Does my patient have CAD? If so, what is the best management plan?

Stress testing has been the preferred pathway to determine which patients could benefit from invasive evaluation and treatment in the cath lab and those patients who would be better served by optimal medical therapy (OMT). As established in the "Unmet Need: A More Accurate and Non-Invasive Test to Help Establish the Presence of CAD" section, traditional non-invasive tests including exercise treadmill electrocardiogram (ECG), stress echocardiography, and nuclear myocardial perfusion imaging (i.e., SPECT) have significant limitations that lead to suboptimal patient outcomes and low-value care.

According to the American Heart Association, healthcare costs related to CAD in the U.S. alone exceed $318B and continue to grow at a staggering rate [74]. MedPAC, a U.S. government agency that provides Congress with analysis and policy advice on the Medicare program, stated in its 2017 annual report to Congress that stress testing in patients with stable chest pain is an especially low-value service accounting for approximately $1.2 billion annually in the U.S. Medicare system [75]. Extrapolating that amount to the remaining U.S. population covered by commercial payers easily doubles the overall low-value spend.

The ideal diagnostic pathway manages the spectrum of patients with suspected CAD by:

(1) ruling out patients who do not have disease;

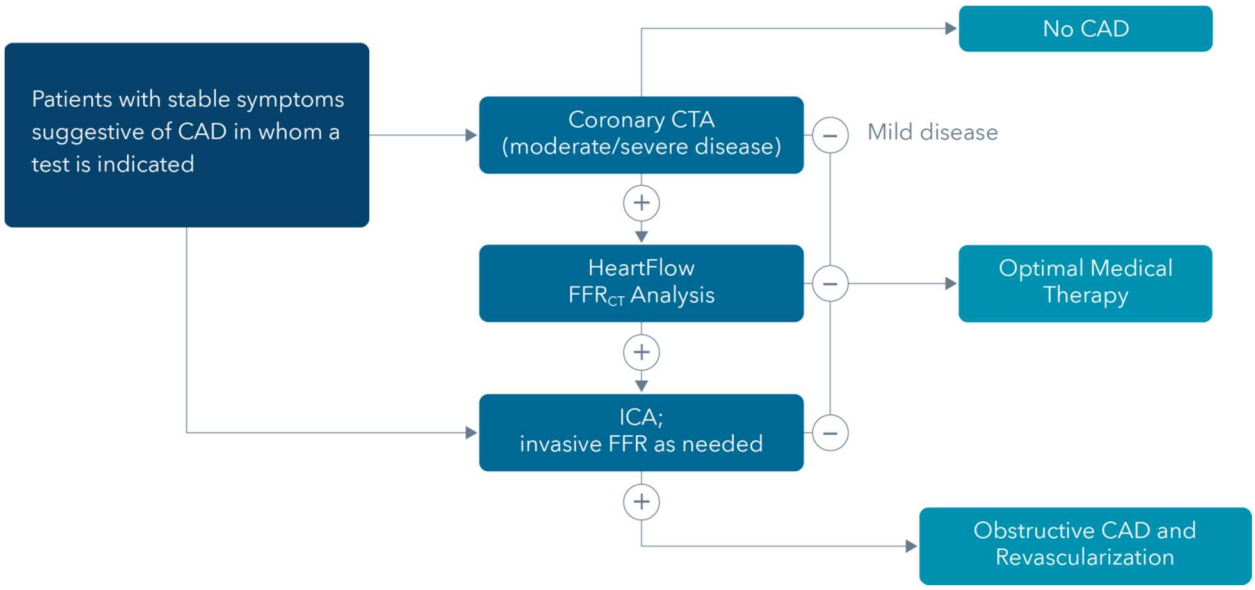
(2) identifying patients with early-stage disease who require medical management and lifestyle modification; and

(3) directing to ICA patients who are most likely to benefit from revascularization.

Significant clinical evidence demonstrates that CCTA with selective use of FFR_{CT} improves care for these patients. Practice guidelines from the United States [2], Europe [18], and Japan [19] now endorse these tests as the front-line pathway (Figure 11) to aid clinicians in diagnosing and guiding treatment decisions in patients with stable or acute chest pain with suspected or known CAD. In addition, the National Health Service (NHS) England changed their guidelines for diagnosing patients with stable chest pain to a CCTA-first with selective FFR_{CT} pathway. From 2018 to 2021, national funding to support the adoption of this pathway was provided through the NHSE Innovation and Technology Payment (ITP) program [1, 55]. Since 2021, payment for FFR_{CT} in England has been supported by the NHS MedTech Funding Mandate[2].

[2] england.nhs.uk/aac/publication/medtech-funding-mandate-policy-2021-22-guidance-for-nhs-commissioners-and-providers-of-nhs-funded-care/

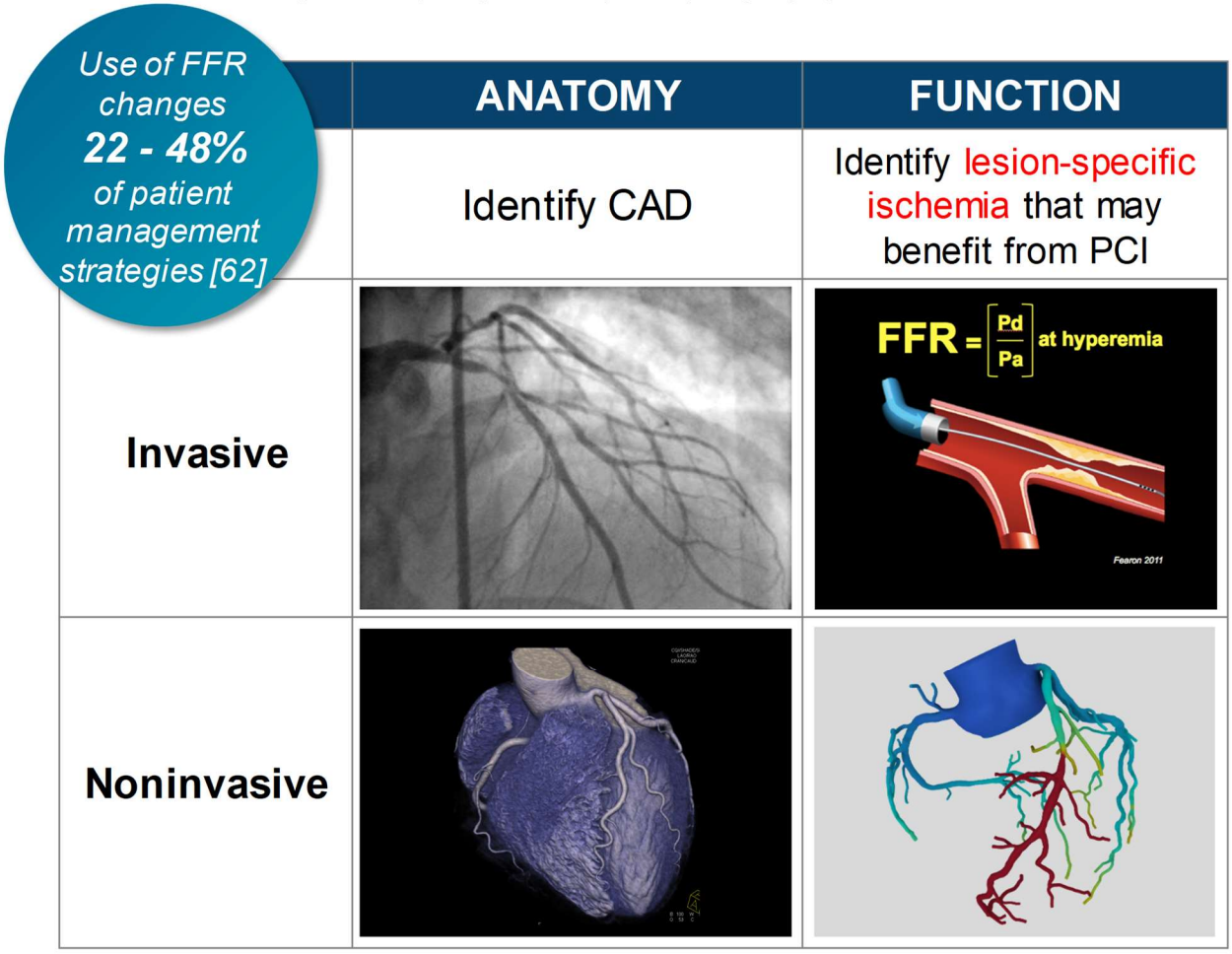
Figure 11. Suggested Diagnostic Pathway for Patients with Suspected CAD



This pathway uses CCTA as the first test for all patients with chest pain or suspected CAD. Multiple clinical trials have proven the high sensitivity of CCTA in determining the presence of CAD [61, 76]. CCTA provides anatomical images of the coronary arteries which offer the physician a clear answer to the first question of whether the patient has CAD. Additionally, when mild disease (< 30% stenosis) is present, CCTA alone provides key diagnostic data for patients who require medical management and lifestyle modification [77].

A critical limitation of CCTA is its low specificity (39% in a recent report) [62] indicating a high potential for false positive results. Even in cases where the level of stenosis is accurately determined, anatomy alone is not enough to determine the best treatment. For approximately 20% - 35% of patients who undergo CCTA [30, 33], physicians will need the physiologic data FFR_{CT} provides to assess the significance of anatomic lesions between 40 and 90% diameter stenosis in order to help determine the most appropriate treatment pathway (ICA or OMT). In a meta-analysis examining over 6,000 patients, Nagaraja et al. demonstrated that angiography-derived management strategy was changed in 22-48% of patients when FFR data (obtained invasively [FFR] or non-invasively [FFR_{CT}]) were available (Figure 12) [78].

Figure 12. Diagnosing Anatomically and Physiologically Significant CAD



Nagaraja et al, Cardiovasc Revasc Med 2017

Long term follow-up (1 - 5 years) in almost 100,000 patients in multiple clinical trials demonstrates physicians can confidently determine the most appropriate treatment pathway for patients using FFR_{CT} [27, 28, 30, 31, 33, 44-46]. The FISH&CHIPS Study, in an univariate analysis, demonstrated that the availability and use of FFR_{CT} was associated with a 14% reduction in cardiovascular mortality and an 8% reduction in all-cause mortality in 90,000 patients over 2 years as compared to CCTA alone [43]. A meta-analysis of five studies that included 5,460 patients confirmed that a negative FFR_{CT} result (FFR_{CT} > 0.80) is associated with a low incidence of death or heart attack at 12 months compared with a positive FFR_{CT} result. This data means physicians can safely defer ICA and choose OMT for patients with negative FFR_{CT} results (FFR_{CT} > 0.80) while referring patients with signs of significant CAD (FFR_{CT} ≤ 0.80) for ICA and potential revascularization.

These conclusions have been validated in two randomized, controlled trials. The Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization (PRECISE) study investigated the safety and efficacy of CCTA and FFR_{CT} compared to traditional testing, which included stress testing and ICA, in 2,103 patients at 65 sites in the US,

EU, UK, and Canada [28]. Investigators found that use of CCTA and FFR_{CT} led to a 70% reduction in the composite end point of death, heart attack, or ICA without obstructive CAD (an unnecessary catheterization) at one year. Additionally, CCTA and FFR_{CT} reduced the rate of ICA performed compared to traditional testing (12.8% vs. 16.9%) and improved efficiency in the cath lab by increasing the rate of ICA that led to revascularization (71.9% vs. 30.5%).

The fractional flow reserve derived from computed tomography coronary angiography in the assessment and management of stable chest pain (FORECAST) trial found similar conclusions by evaluating outcomes and the clinical efficacy of the CCTA and FFR_{CT} pathway in 1,400 patients at 11 sites in the UK [25]. The authors found that use of ICA was 22% lower in the CCTA and FFR_{CT} arm, the rate of ICA showing no obstructive disease (e.g., unnecessary ICAs) was 52% lower, and rates of revascularization were similar to traditional care. FORECAST reported no difference in MACE between the two groups and that these clinical benefits were delivered with no increase in costs in the UK healthcare system.

Other trials have demonstrated that use of FFR_{CT} improves clinical efficacy, primarily through reducing the need for diagnostic ICA, while identifying which patients need invasive treatment. This allows patients who do not have physiologically significant disease to avoid the procedural risk and expense of an ICA. The PLATFORM trial was a prospective, comparative effectiveness study designed to assess the impact of a clinical strategy of CCTA and FFR_{CT} for stable patients with suspected CAD who were referred for ICA [27, 29, 37]. The FFR_{CT}-guided strategy was associated with cancellation of the invasive procedure in 61% of patients. In addition, the proportion of patients who underwent ICA only to find no obstructive CAD dropped from 73% in the usual care group to 12% in the group guided by CCTA and FFR_{CT}. Importantly, there were no adverse events during 1 year of follow-up in the 117 patients whose ICA was cancelled.

ADVANCE [30, 31, 34, 79], a large prospective multicenter registry with 5,083 patients at 38 sites in North America, Europe, and Japan, provided data on real-world usage of FFR_{CT}. FFR_{CT} provided information to physicians that resulted in a change in management plan for two out of three patients (66.9%) compared to the plan after CCTA alone.

The study demonstrated that for patients with CAD by CCTA and a negative FFR_{CT} (FFR_{CT} > 0.80), medical management was safe. There were zero adverse events at 90 days for the 1,592 patients in this group. This contrasts with 19 adverse events (10 death, 4 MI, and 5 hospitalization and urgent revascularizations) in patients with positive FFR_{CT} (MACE hazard ratio 19.75, $p < 0.001$). These findings held at one and three years of follow-up as patients with a positive FFR_{CT} ($FFR_{CT} \leq 0.80$) had a significantly higher risk of cardiovascular death or MI regardless of age [80]. The investigators concluded that FFR_{CT} can safely identify patients in need of invasive assessment.

In terms of clinical utility, the investigators in ADVANCE overwhelmingly opted for a non-invasive treatment pathway when FFR_{CT} values were > 0.80. Most patients for whom OMT was the recommended treatment strategy at enrollment (n = 2,679) continued only on medical therapy at 1-year (n = 2,490, 92.9%) demonstrating that deferral of ICA is unlikely to result in a later return for revascularization. Among patients whose post-FFR_{CT} management plan was to

undergo ICA, 72.6% were revascularized demonstrating that FFR_{CT} effectively differentiated patients who needed further invasive assessment from those who could be managed with OMT.

Additional studies that report on outcomes and clinical efficacy associated with the CCTA and FFR_{CT} pathway are found in Appendix 2: Outcome and Clinical Utility Studies. Considering the significant body of evidence that supports CCTA as a superior frontline test for triaging patients and FFR_{CT} for providing physiologic data to guide appropriate revascularization, the advantages of this pathway are many, including:

- **Pathway efficiency:** For most patients, a single interaction will provide all the information required to determine whether they have CAD and if so, how to treat it. The pathway in Figure 11 illustrates how CCTA + FFR_{CT} triages the following patients:
  - Rule out CAD: CCTA alone is the best test for ruling out CAD with a negative predictive value of 99%.
  - Medical Management: FFR_{CT} can be used to support decision making for whether ICA is necessary for patients with mild to intermediate disease found on CCTA. Use of FFR_{CT} has been proven to reduce ICAs performed by more than 60%.
  - Revascularization: Patients most likely to benefit from revascularization are directed to ICA with an FFR_{CT} roadmap of the coronary arteries for more efficient treatment. Use of FFR_{CT} can increase the ratio of patients who undergo treatment in the cath lab as opposed to diagnostic testing only.
- **Safety:** Long term follow-up (1 - 5 years) in almost 100,000 patients in multiple clinical trials demonstrates physicians can confidently determine the most appropriate treatment pathway for each patient by utilizing FFR_{CT}.
- **Actionable lesion-specific information:** FFR_{CT} results provide a 3D model with a color-coded map of FFR_{CT} values to guide physicians as to which vessels may require revascularization.
- **Cost-effectiveness:** The PLATFORM trial demonstrated 26% cost-savings by safely reducing ICAs [37] while data from the PROMISE trial shows FFR_{CT} is a “dominant” strategy as it is less costly and more effective compared to stress testing [51].
- **Reduced radiation exposure:** The PROTECTION VI trial reported that improvements in CCTA technology and protocols have reduced the radiation dose by 78% in the past ten years from 23.0 mSv in 2007 to 5.1 mSv in 2017. In comparison, SPECT exposes the patient to more than twice the amount of radiation (10-12 mSv). There is no additional radiation required for the HeartFlow Analysis [81].
- **Intuitive 3D analysis for patient education:** The intuitive model helps patients understand their disease and could improve patient compliance.

The summary chart in Appendix 3 captures the numerous advantages of a CCTA with selective FFR_{CT} pathway in comparison with the various forms of stress testing and ICA.

Cost Savings

Several studies have documented that a CCTA plus selective FFR_{CT} Analysis pathway can improve care and provide cost savings.

- **PLATFORM Cost Savings:** Data from the PLATFORM clinical utility study determined the economic impact of incorporating FFR_{CT} into patient pathways. Utilizing Medicare national reimbursement rates and a $1,500 price for FFR_{CT}, PLATFORM demonstrated a 23% ($2,481/patient) reduction in costs at 90 days [82] and a 26% cost reduction ($3,109/patient) at 1 year [37]. The savings in PLATFORM came primarily from avoiding ICA based on negative FFR_{CT} results. Additional savings resulted over time due to a lower rate of hospitalizations and medical office visits when FFR_{CT} was included in the patient care pathway.
- **Resource Use and Cost Comparisons in the PRECISE Study:** The PRECISE study demonstrated that the non-invasive 'Precision Pathway', which consisted of coronary CTA and FFR_{CT}, compared to traditional testing, which included stress testing and ICA, reduced the rate of death, heart attack, or ICA without obstructive CAD by 70% at one year [28]. Using this data, Chew et al. [47] found that patients treated with the 'Precision Pathway' had similar costs to traditional testing at 45 days and a no significant cost difference at one year. The investigators also found the 'Precision Pathway' decreased diagnostic costs (mean 1-year decrease $335) while increasing therapeutic (revascularization) costs (mean 1-year increase $813), demonstrating a shift in spending from diagnostic testing to appropriate treatment of disease. This analysis also confirmed the PLATFORM results above where patients initially considered for ICA showed significant cost avoidance with CCTA and FFR_{CT}.
- **Resource Utilization in the FORECAST randomized trial:** Investigators in the FORECAST trial [25] found that use of a CCTA and FFR_{CT} pathway led to a 22% reduction in the use of ICA, a 52% lower incidence of unnecessary ICA, and no difference in rates of adverse events at nine months. These clinical benefits were delivered with no increase in overall costs within the UK NHS system.
- **Cost-effectiveness Analysis of Anatomic vs Functional Index Testing:** For this analysis, Karady et al. [51] used data from more than 10,000 patients from the PROMISE trial [56] to compare three diagnostic strategies: stress testing (nuclear stress testing, stress echocardiography, or exercise treadmill testing), CCTA alone, and CCTA coupled when appropriate with FFR_{CT}. To evaluate clinical effectiveness, the authors looked at lifetime rates of heart attack and death, as well as efficiency of patient selection for ICA and revascularization. To measure cost-effectiveness, the authors looked at quality adjusted life years (QALY) and the incremental cost-effectiveness ratio (ICER) of the three strategies. The analysis determined that the use of CCTA and FFR_{CT} was "dominant" (less costly and more effective) as compared to stress testing for assessing patients with CAD.
- **DISCOVER-FLOW Cost Effectiveness:** Using data from HeartFlow's initial validation study, DISCOVER-FLOW, Hlatky et al. [50] published a health economic analysis estimating the cost effectiveness of FFR_{CT} in 96 patients. Every patient received a CCTA, FFR_{CT}, ICA, and invasive FFR, allowing a patient-by-patient evaluation of how incorporating these tests would

influence patient diagnosis, treatment and costs. The study concluded that a strategy using FFR_{CT} would result in a 30% reduction in costs and 12% reduction in adverse events.

- **Number Needed to Treat (NNT) Analysis:** Forrest and Anderson [48] used data from PLATFORM to calculate the number of patients who would need to receive the CCTA and FFR_{CT} pathway in order to avoid a negative outcome; i.e. the number needed to treat (NNT). In this analysis a negative outcome was defined as ICA without obstructive disease. Cost assumptions included $1500 for the FFR_{CT} Analysis and $2338 for ICA (2015 OPPS Medicare National Average payment). It was determined that 1.64 patients would need the diagnostic pathway to avoid an unnecessary ICA. The average weighted cost of the CCTA + selective FFR_{CT} pathway was $1210 with a NNT of 1.64 costing $1984 to avoid the $2838 cost of the ICA.
- **PLATFORM German Cost Savings:** Colleran et al [35] conducted an analysis of 116 patients from PLATFORM sites in Germany. Compared with usual care, use of CCTA and FFR_{CT} allowed physicians to cancel ICA in 40 of 52 patients (77%). Clinical event rates were low overall in both groups with no significant difference in complications. Mean estimated medical costs were €4,217 ($4,932 U.S.) for CCTA and FFR_{CT} versus €6,894 ($8,063 U.S.) for usual care (39% reduction $p < 0.001$).
- **DYNAMIC-FFR_{CT} Study:** Fujimoto et al. [83] evaluated the clinical and economic impact of adding FFR_{CT} to decision-making in 410 patients prospectively enrolled at six sites in Japan. The investigators made an initial treatment decision (ICA, SPECT, OMT, or another test) based on CCTA alone and then a second decision when FFR_{CT} results were revealed. FFR_{CT} allowed 39.5% (92) of patients initially sent to ICA to avoid the invasive procedure. The average cost to treat patients once FFR_{CT} results were available was $999 per-patient, compared to $1,537 per-patient with CCTA alone (a 35%) reduction.
- **NXT Japan Cost Savings:** Kimura et al [52] evaluated the potential impact of a CCTA and FFR_{CT} pathway in Japan by modeling data from 254 patients in the HeartFlow NXT trial using resource costs in Japan. Four pathways were evaluated: 1) ICA-guided PCI; 2) Invasive FFR-guided PCI; 3) CCTA followed by ICA-guided PCI; 4) CCTA and FFR_{CT}-guided PCI. Pathway 1 had the highest cost ($10,360 U.S.) and highest projected death and MI rate. Use of CCTA and FFR_{CT} to select patients for PCI would result in 19% fewer cardiac events and 32% lower costs compared to ICA-guided PCI. The CCTA and FFR_{CT} pathway delivered equivalent outcomes and costs to the invasive FFR pathway without an invasive procedure.
- **UK Cost Savings:** In a retrospective analysis of consecutive patients in the United Kingdom, Rajani et al [53] estimated the potential impact of a CCTA + FFR_{CT} care pathway versus care guided by NICE guidelines. The average savings per-patient presenting with chest pain was £200 ($257 U.S.) with an annual estimated savings of £200,000 ($257,301 U.S.) for a 1000 patient cohort. Using estimated event rates from ICA and PCI according to FFR status, the study predicted use of the FFR_{CT} pathway would result in a relative reduction in event rate of 4%.

The HeartFlow FFR_{CT} Analysis in combination with a CCTA-first pathway has demonstrated cost savings to the health care system. These savings combined with the clinical and patient benefits led to the following conclusion in the NICE guidelines [1, 55]:

Based on the current evidence and assuming there is access to appropriate CCTA facilities, using HeartFlow FFR_{CT} may lead to cost savings of £391 per patient. By adopting this technology, the NHS in England may save a minimum of £9.4 million by 2022 through avoiding invasive investigation and treatment.

FFR_{CT}: A Broadly Accepted Option

Over 500 peer-reviewed publications have validated the FFR_{CT} technology and the FFR_{CT} Analysis now has widespread acceptance.

United States

- The American College of Cardiology and the American Heart Association, along with several other physician specialty societies, updated their clinical practice guideline for the evaluation and diagnosis of chest pain and now recognize the CCTA + FFR_{CT} pathway as a front-line pathway to aid clinicians in diagnosing and guiding treatment decisions in patients with stable or acute chest pain with suspected or known CAD [2]. Specifically, the guidelines gave:
    - CCTA a Level 1 recommendation (Level of Evidence A) and stated it "is effective for diagnosis of CAD, for risk stratification, and for guiding treatment decisions."
    - FFR_{CT} a Level 2a recommendation (Level of Evidence B) and stated it "can be useful for diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization" in stenoses of 40-90%.

- In June 2017, the Blue Cross Blue Shield Association's Evidence Street® conducted a technology assessment affirming that the evidence supports clinical use of the FFR_{CT} Analysis [54]. Evidence Street determined that:

    "The available evidence provides support that use of CCTA with selective FFR_{CT} is likely to reduce the use of ICA in individuals with stable chest pain who are unlikely to benefit from revascularization by demonstrating the absence of functionally significant obstructive CAD. In addition, the benefits are likely to outweigh potential harms given that rates of revascularization for functionally significant obstructive CAD appear to be similar and cardiac-related adverse events do not appear to be increased following a CCTA with selective FFR_{CT} strategy."

    "The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcome."

- In the U.S., FFR_{CT} is covered by major health plans including Medicare Carriers [Palmetto, NGS, WPS, NGS, and Noridian], Anthem, Aetna, Cigna, United Healthcare and a majority of regional BlueCross and BlueShield plans.

- Coding and Payment for FFR_{CT}
    - The American Medical Association CPT Editorial Panel has created the following Current Procedural Terminology (CPT)[3] code which describes the FFR_{CT} service:

[3] CPT Copyright 2022 American Medical Association. All rights reserved. CPT® is a registered trademark of the American Medical Association

75580 Noninvasive estimate of coronary fractional flow reserve (FFR) derived from augmentative software analysis of the data set from a coronary computed tomography angiography, with interpretation and report by a physician or other qualified health care professional

- (Use 75580 only once per coronary computed tomography angiogram)
- (When noninvasive estimate of coronary FFR derived from augmentative software analysis of the data set from a coronary computed tomography angiography with interpretation and report by a physician or other qualified health care professional is performed on the same day as the coronary computed tomography angiography, use 75580 in conjunction with 75574)

– For calendar year 2024 Hospital Outpatient Prospective Payment System (OPPS) rulemaking, the Centers for Medicare & Medicare Services (CMS) determined that FFR_{CT} should be separately payable and assigned CPT Code 75580 to Ambulatory Payment Classification (APC) 5724 (Level 4 Diagnostic Tests and Related Services) with a national average payment of $997.22.

United Kingdom

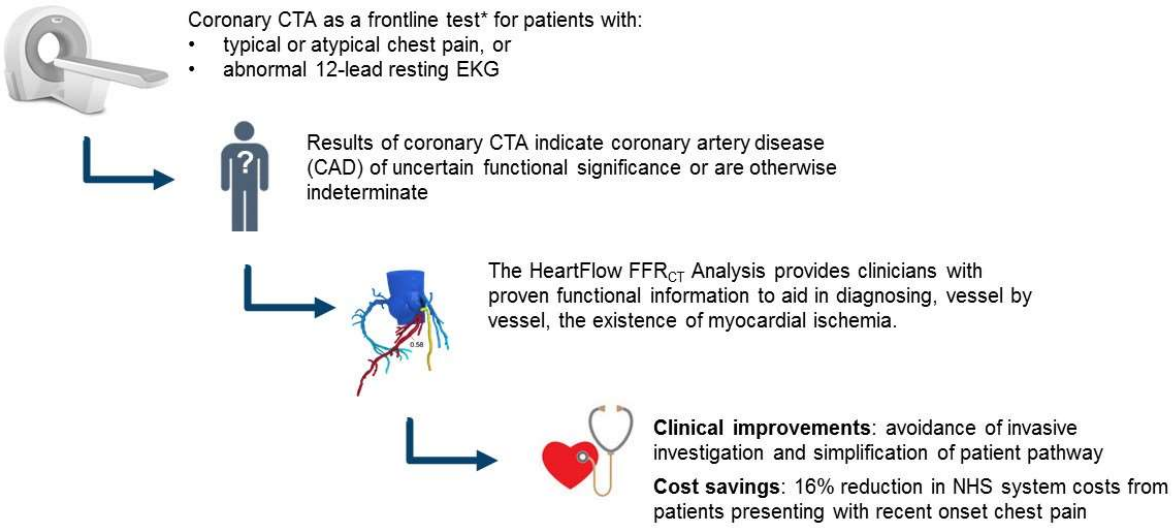
- Endorsement from the National Institute for Health and Care Excellence (NICE) is perhaps the most coveted distinction an emerging healthcare technology can earn.
  – Evidence requirements are rigorous
  – Cost effectiveness must be demonstrated
  – Endorsement has practical implications for the UK's National Health Service
- In February 2017 (and updated in May 2021) NICE issued medical technology guidance (MTG32) on HeartFlow FFR_{CT} with the following recommendations (Figure 13) [1]:

  1.1 The case for adopting HeartFlow FFR_{CT} for estimating fractional flow reserve from coronary CT angiography (CCTA) is supported by the evidence. The technology is noninvasive and safe, and has a high level of diagnostic accuracy.

  1.2 HeartFlow FFR_{CT} should be considered as an option for patients with stable, recent onset chest pain who are offered CCTA as part of the NICE pathway on chest pain. Using HeartFlow FFR_{CT} may avoid the need for invasive coronary angiography and revascularisation. For correct use, HeartFlow FFR_{CT} requires access to 64-slice (or above) CCTA facilities.

  1.3 Based on the current evidence and assuming there is access to appropriate CCTA facilities, using HeartFlow FFR_{CT} may lead to cost savings of £391 per patient. By adopting this technology, the NHS in England may save a minimum of £9.4 million by 2022 through avoiding invasive investigation and treatment.

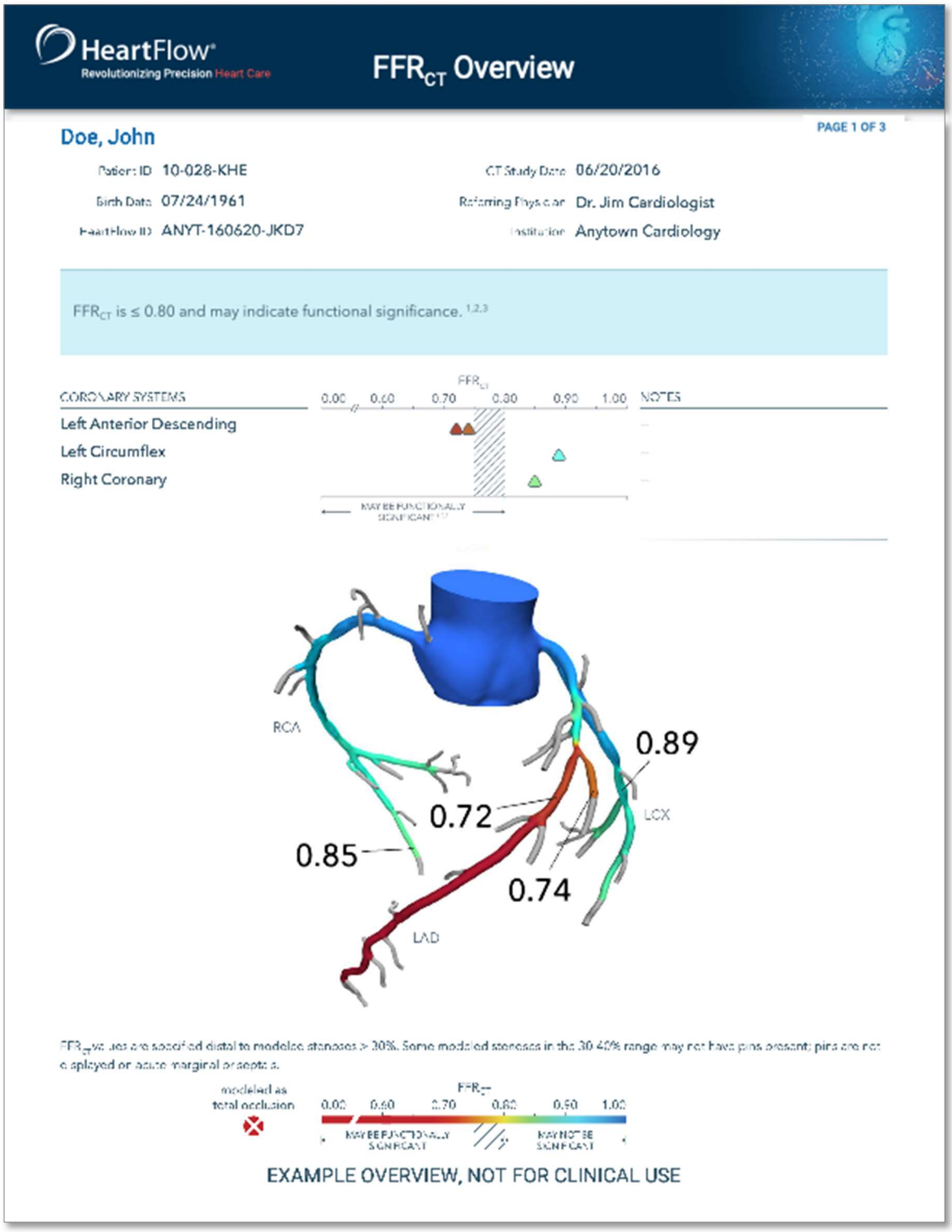
Figure 13. NICE Recommended Pathway for Patients with Recent Onset Chest Pain



Japan

- The Ministry of Health, Labour, and Welfare (MHLW) implemented national reimbursement for the HeartFlow FFR_{CT} Analysis effective January 2019.
- Practice guidelines from the Japanese Circulation Society (JCS) on the diagnosis and treatment of patients with stable CAD state that FFR_{CT} "is useful to evaluate the functional significance of intermediate stenoses on CCTA" and that its use "may aid in avoiding unnecessary invasive coronary angiography." [19]

Appendix 1: HeartFlow Analysis Example



HeartFlow®
Revolutionizing Precision Heart Care

FFR$_{CT}$ Overview

PAGE 1 OF 3

Doe, John

Patient ID 10-028-KHE
Birth Date 07/24/1961
HeartFlow ID ANYT-160620-JKD7

CT Study Date 06/20/2016
Referring Physician Dr. Jim Cardiologist
Institution Anytown Cardiology

FFR$_{CT}$ is ≤ 0.80 and may indicate functional significance. [1,2,3]

CORONARY SYSTEMS	FFR$_{CT}$ 0.00 0.60 0.70 0.80 0.90 1.00	NOTES
Left Anterior Descending		
Left Circumflex		
Right Coronary		

MAY BE FUNCTIONALLY SIGNIFICANT

RCA
0.89
LCX
0.72
0.85
0.74
LAD

FFR$_{CT}$ values are specified distal to modeled stenoses > 30%. Some modeled stenoses in the 30-40% range may not have pins present; pins are not displayed on acute marginal arteries.

modeled as total occlusion

FFR$_{CT}$ 0.00 0.60 0.70 0.80 0.90 1.00

MAY BE FUNCTIONALLY SIGNIFICANT | MAY NOT BE SIGNIFICANT

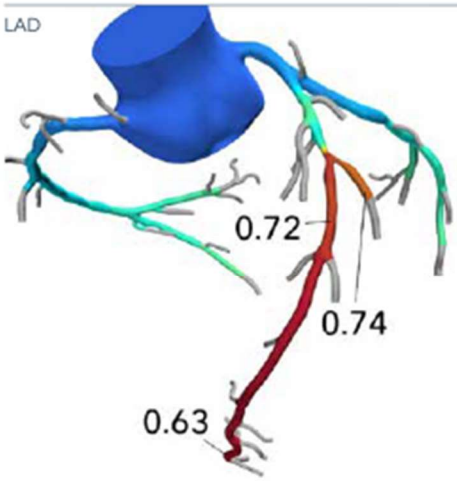
EXAMPLE OVERVIEW, NOT FOR CLINICAL USE

HEARTFLOW FFR_{CT} OVERVIEW

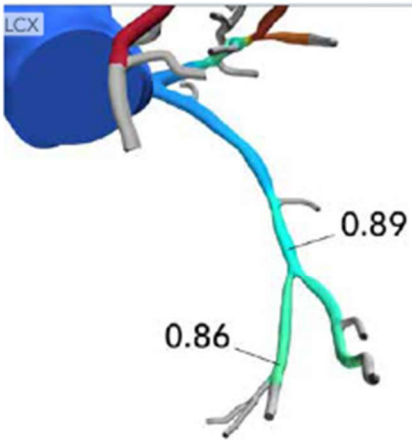
Doe, John

Patient ID	10-028-KHE	CT Study Date	06/20/2016
Birth Date	07/24/1961	Referring Physician	Dr. Jim Cardiologist
HeartFlow ID	ANYT-160620-JKD7	Institution	Anytown Cardiology

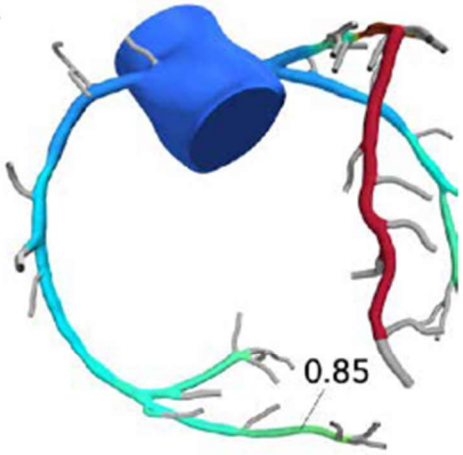
LAD



LCX



RCA



Created with FFR_{CT}_3.1.0.8 on 06/14/2021 22:19 UTC. UDI: (01)00853341006053(10)FFR_{CT}_3.1.0.8(11)2021-06-14(21)DH-210614-TSXD

EXAMPLE OVERVIEW, NOT FOR CLINICAL USE

ADDITIONAL INFORMATION

WARNINGS

- Absence of nitrate administration during coronary CTA acquisition may adversely affect the accuracy of the HeartFlow FFR_{CT} Analysis. The HeartFlow Analysis simulates maximal coronary hyperemia. Induction of coronary hyperemia commonly includes vasodilation of the epicardial coronary arteries via nitrate administration. Therefore, HeartFlow recommends following SCCT Guidelines for coronary CTA acquisition, which include the use of sublingual nitrates at the time of image acquisition.[4]
- The HeartFlow Analysis represents patient conditions at the time of CT acquisition. The duration of time and changes to patient health after CT acquisition must be assessed during interpretation. Clinical validation that supports FFR_{CT} values was limited to subjects whose CT acquisition occurred within 60 days of invasive FFR (mean 18 +/- 13 days).
- Qualitative anatomical information presented on the 3D/2D computer generated anatomical models is for orientation purposes only. Quantitative lumen diameter is representative of the geometric model, and the accuracy is dependent on the quality of the CT data provided. It does not represent artery diameter and should not be used for treatment decisions.
- Diagnostic performance of FFR_{CT} using invasive FFR as the reference standard is: 84% accurate, 82% sensitive, and 85% specific. Refer to product Instructions For Use for patient populations in which FFR_{CT} has been clinically evaluated, relevant clinical data, and product warnings.
- The performance of the HeartFlow Analysis has not been fully characterized in small vessels. Vessels with modeled lumen diameters less than 1.8 mm are grayed, and FFR_{CT} values are unavailable. When modeled lumen diameter decreases below 1.8 mm due to disease, but distally recovers to 1.8 mm or greater, FFR_{CT} values remain available. In some instances, continued distal disease and/or recovery may not be presented in the model.
- The HeartFlow Analysis has been studied in patients with prior PCI, but the FFR_{CT} values have only been validated in vessels without metallic stents.
- Because of physiologic changes in pressure and flow within regions of complex or turbulent flow (i.e. stenosis, bifurcations), pressure measurements may vary, potentially affecting measured FFR. Similarly, computed FFR_{CT} values may be affected by flow disturbances in stenoses and bifurcations.

FFR_{CT} ERROR

FFR_{CT}	COLOR	AVERAGE ERROR TO Invasive FFR † ± 1SD
≤ 0.70		-0.07 ± 0.12
0.71 - 0.75		-0.07 ± 0.12
0.76 - 0.80		-0.06 ± 0.07
0.81 - 0.85		-0.04 ± 0.05
0.86 - 0.90		-0.02 ± 0.07
0.91 - 1.0		-0.01 ± 0.04
0.0 - 1.0		-0.03 ± 0.07

† Error from the FFR_{CT} v3.0 Clinical Validation Population. Not indicative of all patient populations. Please refer to complete summary of clinical data provided in the Instructions For Use to determine the population in which the FFR_{CT} technology has been clinically validated.

REFERENCES

1. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. Tonino PA, et al. NEJM 2009; 360:213-224.
2. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. De Bruyne B, et al. NEJM 2012; 367:991-1001.
3. Diagnostic performance of non-invasive fractional flow reserve derived from coronary CT angiography in suspected coronary artery disease: The NXT Trial. Norgaard B, et al. JACC 2014; 63(12):1145-1155.
4. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography. Abbara S, et al. JCCT 2016; DOI: 10.1016/j.jcct.2016.10.002.

Created with FFR_{CT}_3.1.0.8

EXAMPLE OVERVIEW, NOT FOR CLINICAL USE

HeartFlow®

HeartFlow, Inc. | 331 E. Evelyn Avenue | Mountain View, CA 94041 | ph: +1.650.241.1221 | info@heartflow.com | heartflow.com

15991019 v7

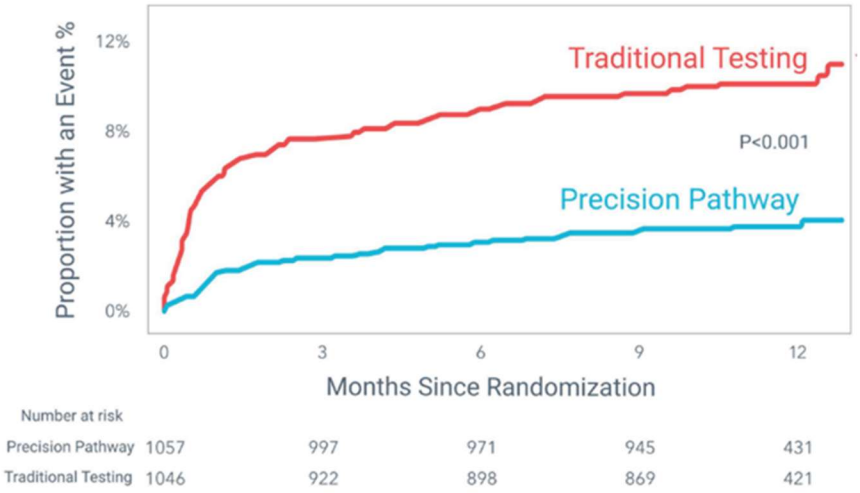
Appendix 2: Outcome and Clinical Utility Studies

The PRECISE Study [28]

The Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization (PRECISE) study was a randomized, controlled trial that investigated the safety and efficacy of the non-invasive 'Precision Pathway', which consisted of coronary CTA and FFR_{CT}, compared to traditional testing, which included stress testing and ICA. The study enrolled 2,103 patients at 65 sites in the US, EU, UK, and Canada. The primary endpoint of the study was the rate of death, heart attack, or ICA without obstructive CAD at one-year.

- Patients cared for using the 'Precision Pathway' experienced a 70% reduction in the composite end point of death, heart attack, or ICA without obstructive CAD (an unnecessary catheterization) at one year. This was due primarily to a lower rate of ICA without obstructive CAD in the 'Precision Pathway' with no statistically significant difference in the safety components of death or heart attack.
- 21% of patients identified as low risk in the 'Precision Pathway' did not undergo any testing and were safely managed with medication and no other intervention.
- The 'Precision Pathway' both reduced the rate of ICA performed compared to traditional testing (12.8% vs. 16.9%) and improved efficiency in the catheterization lab by increasing the rate of ICA that led to revascularization (71.9% vs. 30.5%).

Figure 14. Primary endpoint from the PRECISE Study

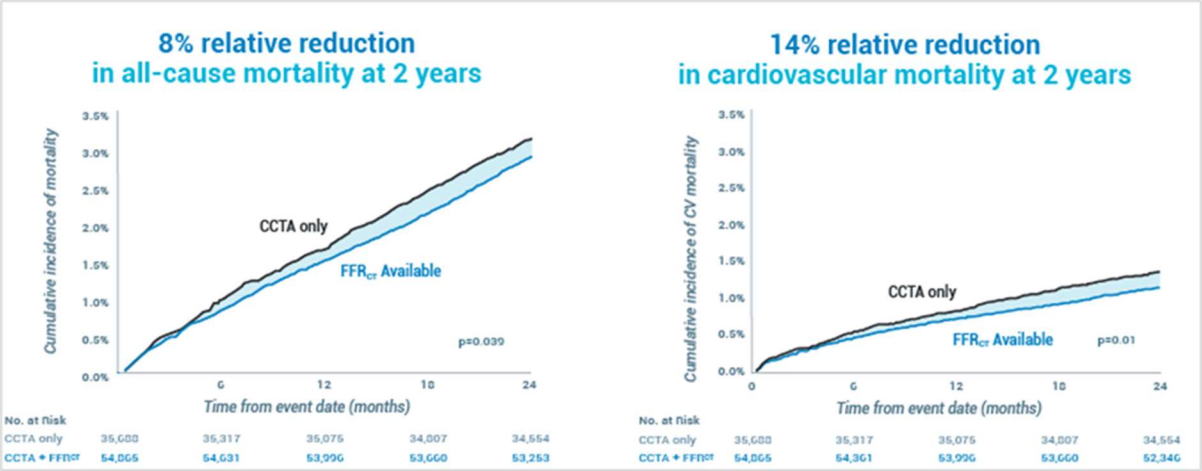


The FISH&CHIPS Study [43]

The FFR_{CT} In Stable Heart disease and Coronary Computed Tomography Angiography Helps Improve Patient Care and Societal Costs (FISH&CHIPS) study is a real world, multi-center, retrospective study including more than 90,000 patients who underwent a CCTA at one of 25 NHS England hospitals. The study assessed, at a national level, the incremental impact of adding FFR_{CT} to a CCTA-first diagnostic paradigm for evaluating and managing CAD.

FISH&CHIPS achieved its primary endpoint, in a univariate analysis, by demonstrating that the availability and use of FFR_{CT} was associated with a 14% reduction in cardiovascular mortality and an 8% reduction in all-cause mortality over 2 years, as compared to a time period when CCTA was used without any access to FFR_{CT}. In addition, use of FFR_{CT} was associated with a 14% reduction in use of non-invasive testing and a 5% reduction in the use of ICA.

Figure 15. Reduction in all-cause and cardiovascular mortality seen in the FISH&CHIPS study



The FORECAST Trial [25]

The fractional flow reserve derived from computed tomography coronary angiography in the assessment and management of stable chest pain (FORECAST) trial was the first randomized, controlled trial to evaluate clinical outcomes and resource utilization associated with the use of the CCTA and FFR_{CT} pathway compared to standard care. FORECAST enrolled 1,400 patients at 11 sites in the UK and is the first large prospective study to assess the impact of FFR_{CT} in a setting of primarily CCTA-first testing across the full range of patient risk.

Major Findings and Conclusions

- Use of ICA was 22% lower in the CCTA and FFR_{CT} arm. The rate of ICA showing no obstructive disease (e.g., unnecessary ICAs) was 52% lower in this group. Despite this, the overall rate of revascularization was similar between the two groups.
- Over nine months of follow-up, there was a 40% reduction in follow-up tests (e.g., layered testing) in the CCTA and FFR_{CT} arm.
- There was no difference in major adverse cardiovascular or cerebrovascular events (MACCE) between the two groups.
- These clinical benefits were delivered with no increase in costs in the UK healthcare system.

The PLATFORM Study [27, 29, 37, 49, 82]

The Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts (PLATFORM) study was an international, 11 center, prospective, comparative effectiveness study designed to assess the impact of a strategy using FFR_{CT} on stable patients being evaluated for suspected

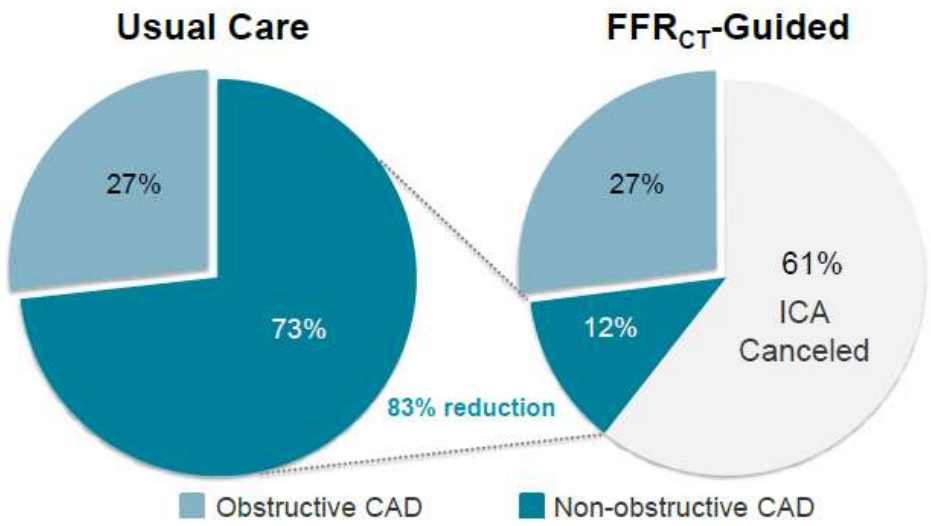
CAD and referred for ICA. The primary endpoint portion of the study included a control cohort of 187 consecutive patients referred for ICA ("usual care"). Outcomes in these patients were compared to those of an experimental cohort which consisted of 193 patients referred for ICA who instead underwent CCTA/FFR_{CT}. Results of testing and outcomes were compared between the cohorts.

PLATFORM 90-Day Outcomes [29]

The primary endpoint was the percentage of patients in whom ICA was performed and no significant CAD was found. Key study findings included (Figure 15):

- Primary endpoint: 73% of patients in the usual care group had no significant CAD found during ICA while in the FFR_{CT}-guided group that percentage dropped to 12% (an 83% reduction).
- In the FFR_{CT}-guided cohort, 61% of planned ICAs were cancelled
- No significant difference in revascularization between the two cohorts

Figure 16. 83% Reduction in nonobstructive CAD with FFR_{CT} guided PCI



Douglas, et al. EHJ 2015.

PLATFORM 1-Year Outcomes [27, 37]

- No adverse clinical events occurred in the 117 patients whose ICA was canceled because of the FFR_{CT}-guided strategy.
- There was little need for additional procedures in patients managed with FFR_{CT}-guided strategy: only four (3%) ICAs and one (<1%) PCI occurred between 90 days and one year.
- The safety and cost savings of the FFR_{CT}-guided approach were shown to be durable at one year.

Real World results in Denmark: application in low and high-risk patients [32]

This single center, all-comer consecutive cohort study examined the impact of adopting a diagnostic strategy composed of CCTA with selective FFR_{CT} for all symptomatic patients with suspected CAD (N = 774). This replaced an earlier strategy that used frontline CCTA for patients with a low-to-intermediate risk of CAD and referred patients with high risk directly to ICA. The investigators assessed the impact of the new strategy on downstream testing and treatment and adverse events.

Major Findings and Conclusions

- 181 patients (23%) had a high pre-test likelihood of CAD and would have been referred directly to ICA using the old pathway. Use of CCTA and FFR_{CT} led to cancellation of 75% of planned ICAs (115/153). Use of CCTA alone would have cancelled only 46% of planned invasive procedures.
- 593 patients (77%) had a low to intermediate pre-test likelihood of CAD and were referred to CCTA. Use of CCTA and FFR_{CT} safely kept 91% of patients (540/593) out of the catheterization lab. Use of CCTA alone would have sent an additional 100 patients (26%) for ICA.
- The overall low adverse event rate in this study is similar to that reported in recent large-scale studies [11, 37, 56, 84]. Over a mean follow-up time of 157 ± 50 days, serious adverse events occurred in four patients. None of these four patients had an ICA cancelled by FFR_{CT}.

Real World results in Denmark: Clinical Outcomes Following FFR_{CT}-Guided Management [33]

This study is a single-center observational all-comers study of consecutive symptomatic patients. The study evaluates the impact of a diagnostic pathway of CCTA with selective FFR_{CT} on clinical decision making, safety, and patient outcomes. Additionally, this study provides insights into the longer-term outcomes of utilizing the HeartFlow Analysis to guide treatment decision making.

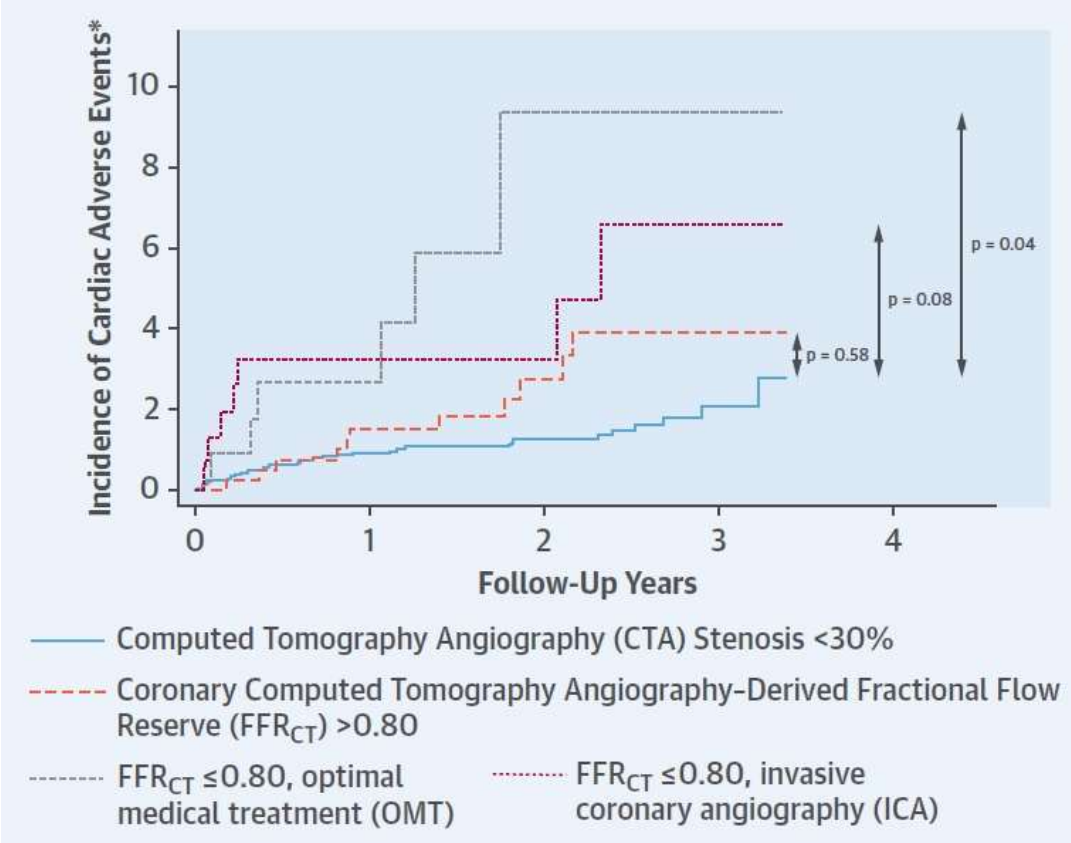
From 2014 through 2017, 3,674 consecutive patients with stable chest pain at Aarhus University Hospital in Denmark were assessed using a diagnostic pathway of CCTA plus FFR_{CT}, when appropriate. For a median of 24 (range: 8 to 41) months, a composite endpoint of death, MI, hospitalization for unstable angina, and unplanned revascularization was compared across four patient groups:

1. **Minimal disease:** CCTA with no disease or stenosis <30% sent for OMT and no additional testing (n=2,450)
2. **Non-ischemic disease:** Stenosis 30-70% and FFR_{CT} > 0.80 sent for OMT and no additional testing (n=410)
3. **Ischemic disease + OMT:** $FFR_{CT} \leq 0.80$ sent for OMT and no additional testing (n=112)
4. **Ischemic disease + ICA:** $FFR_{CT} \leq 0.80$ sent for ICA (n=155)

Major Findings and Conclusions

This real-world experience shows that FFR_{CT} allows clinicians to differentiate low-risk patients who do not need invasive diagnostic testing or intervention from high-risk patients who are likely to benefit from ICA and possible revascularization (Figure 16).

Figure 17. Clinical Outcomes



- Patients with intermediate stenosis (30-70%) by CCTA who had a negative FFR_{CT} (> 0.80) (Group 2) had long term outcomes equivalent to patients with no to minimal stenosis (0-30%) by CCTA (Group 1) (3.9% versus 2.8%, p=0.58).
- Patients with a positive FFR_{CT} (≤ 0.80) who underwent invasive assessment (Group 4) had fewer MIs than those with a positive FFR_{CT} who were managed medically (Group 3) (1.3% versus 8.0%, p<0.001).
- Only 19% of patients (697) underwent FFR_{CT} Analysis. Two-thirds of these patients had no physiologically significant disease and required no further downstream testing.
- In real world clinical practice, FFR_{CT} Analysis was effective in differentiating patients who do not require further diagnostic testing or intervention (FFR_{CT} > 0.80) from higher risk patients (FFR_{CT} ≤ 0.80) in whom further testing and possible intervention may be needed.
- 97% of scans submitted were of adequate image quality to conduct the FFR_{CT} Analysis.

The ADVANCE Registry [30, 31, 34, 79]

From 2015 through 2017, patients were enrolled in the ADVANCE Registry to assess how a diagnostic pathway of coronary CTA plus FFR_{CT} impacts clinical decision making, safety, and patient outcomes in real-world clinical practice. 5,083 patients with clinically stable CAD diagnosed by CCTA were enrolled across 38 centers in Europe, North America, and Japan. The primary endpoint was the reclassification rate of patient management strategies between solely CCTA-based plans versus FFR_{CT}-inclusive plans. Patient follow-up is planned at 90 days, 180 days, 1 year, and 3 years post-enrollment.

Major Findings and Conclusions [30]

- Availability of FFR_{CT} data resulted in revision of the clinical management plan as determined by the site investigators in 2 out of 3 of patients when compared to the initial CCTA-based treatment plan.
- FFR_{CT} led physicians to recommend ICA in only 40% of subjects despite the presence of anatomic obstructive disease in 72% of patients based on CCTA alone.
- 97% of scans submitted to HeartFlow were of adequate image quality to conduct the FFR_{CT} Analysis.
- 72.6% of patients sent to ICA based on a positive FFR_{CT} Analysis were revascularized.
- At 90 days, a negative FFR_{CT} (FFR_{CT} > 0.80) was associated with a very low rate of ICA or revascularization and with freedom from MI, death, or hospitalization for ACS requiring urgent revascularization.

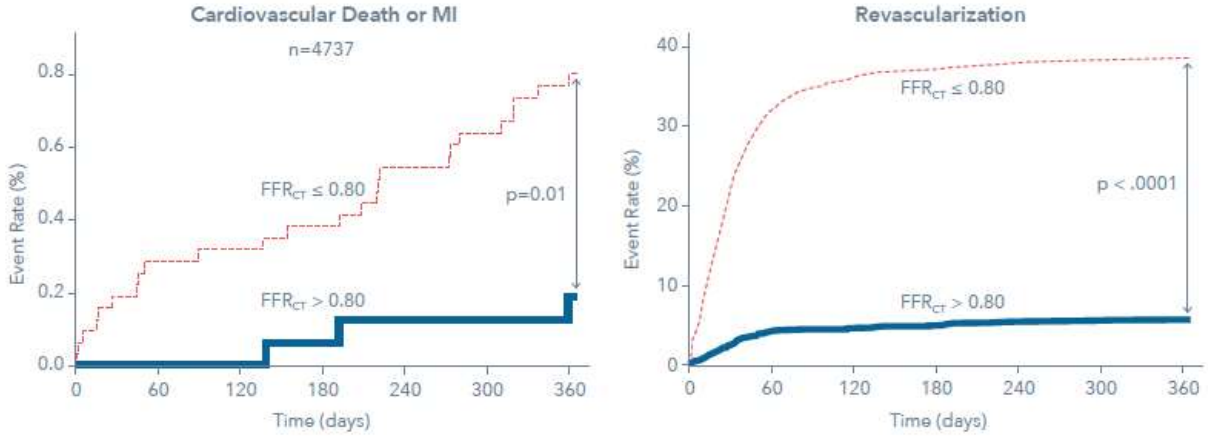
ADVANCE 1-Year Outcomes [34, 79]

- Patients with a positive FFR_{CT} (FFR_{CT} ≤ 0.80) have a significantly higher risk to experience MI or cardiovascular-related death than patients with a negative FFR_{CT} (FFR_{CT} > 0.80, p = 0.01) regardless of age [80].
- Most patients for whom medical therapy was the recommended treatment strategy at enrollment (n = 2679) continued only on medical therapy at 1-year (n = 2490, 92.9%) demonstrating that deferral of ICA is unlikely to result in a later return for revascularization.

ADVANCE DK 3-Year Outcomes [31]

The Prognostic Value of Coronary CT Angiography-derived Fractional Flow Reserve on 3-year Outcomes in Patients with Stable Angina (ADVANCE DK 3-year) study performed 3-year follow-up on 900 patients enrolled in ADVANCE at three sites in Denmark. The study found that patients with normal FFR_{CT} findings (> 0.80) had lower rates (2.1%) of the primary endpoint of death or heart attack compared to patients with abnormal FFR_{CT} findings (≤ 0.80) who experienced higher rates of adverse events (6.6%).

Figure 18. 1-year results from the ADVANCE registry



The FFR$_{CT}$ RIPCORD study [26]

The FFR$_{CT}$ RIPCORD study modeled the impact of FFR$_{CT}$ on clinical decision-making. Data from 200 consecutive cases from the NXT trial were utilized. These were patients with chest pain who had both CCTA and FFR$_{CT}$. For each case, three experienced cardiologists assessed the CCTA and recorded the location and severity of any coronary stenosis. Clinical histories were also available, and the three cardiologists reached a consensus assignment of each patient to one of four management options:

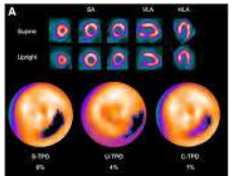
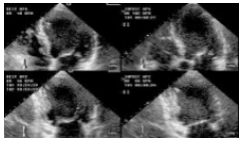
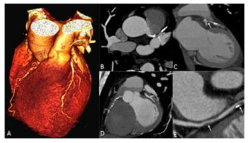
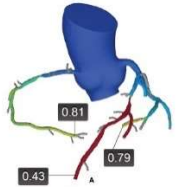
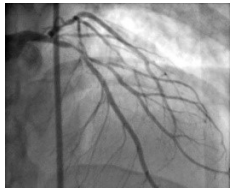
1. Optimal medical therapy (OMT) alone;
2. Percutaneous coronary intervention (PCI) + OMT;
3. Coronary artery bypass surgery (CABG) + OMT; or
4. More information about ischemia required.

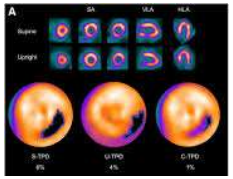
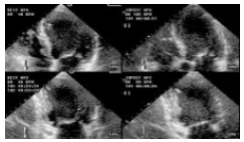
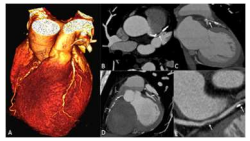
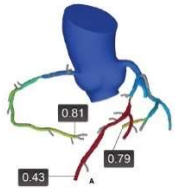
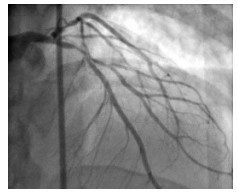
FFR$_{CT}$ data for each vessel were then revealed and the cardiologists made a second plan for each patient again reached by consensus using the same four options.

Major Findings and Conclusions

- The availability of FFR$_{CT}$ data resulted in a change in management category in 36% of patients.
- Of 87 patients originally thought to require PCI based on CCTA alone:
  - 26 (30%) were re-allocated to OMT based on no ischemic lesion found by FFR$_{CT}$
  - 16 (18%) had the target vessel for PCI changed based upon FFR$_{CT}$ findings
- FFR$_{CT}$ resulted in an overall change in the decision for treatment (combining change in management category plus change in PCI target vessel) in 44% of the study population compared to CCTA alone.

Appendix 3: Comparison of Diagnostic Tests

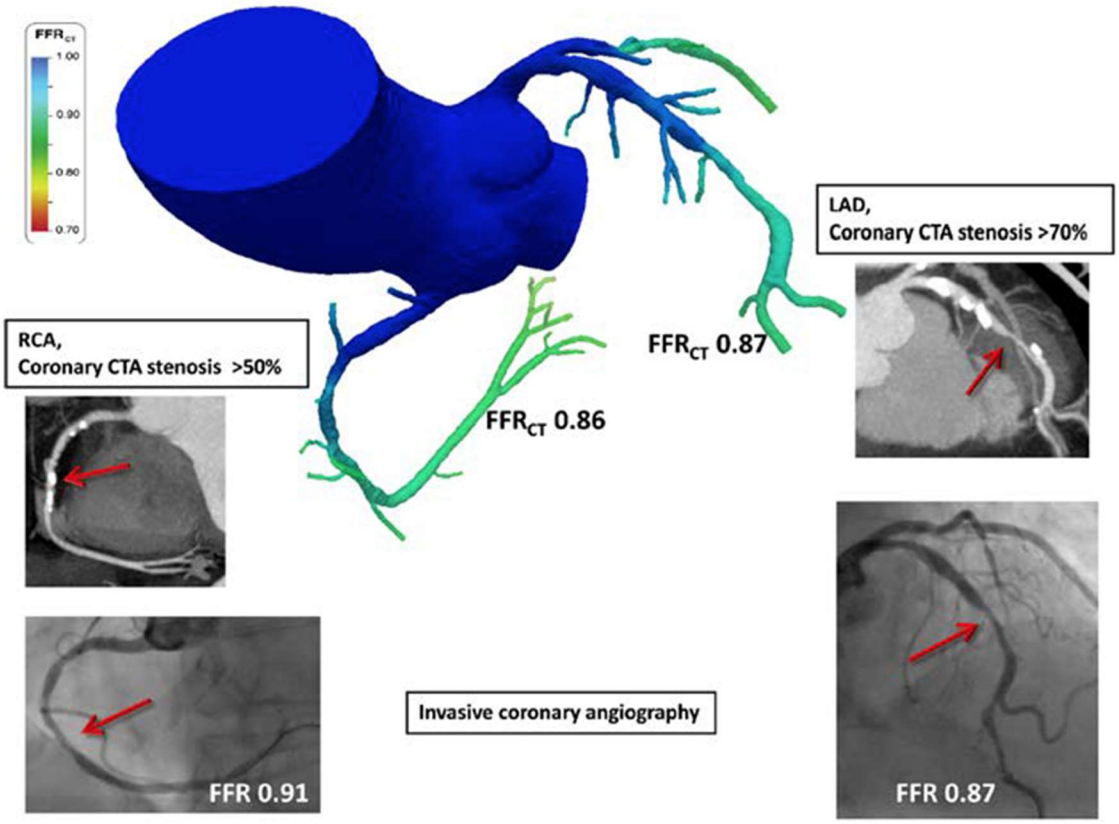
	First Line Non-invasive Tests				Invasive Tests
	Myocardial Perfusion Imaging (MPI)	**Stress Echocardiography**	**Coronary Computed Tomography Angiography (CCTA)**	**Fractional Flow Reserve Computed Tomography (FFR_{CT})**	**Invasive Coronary Angiography (ICA)**
					
Commonly Referred to as	SPECT, Nuclear Stress Test, Lexiscan	Cardiac Ultrasound, Stress Echo	Cardiac CT, CTA	FFR_{CT} Analysis, CT-FFR	Invasive Angiogram, ICA, Heart Catheterization, Diagnostic Angiogram
Description of Test	A radioisotope is delivered to the patient to visualize blood flow to the heart. Usually two rounds of imaging are performed; one at rest and one following myocardial stress induced either by exercise or drugs. Imaging of the heart under stress is used to reveal areas receiving less blood flow [85].	Ultrasound is used to view the structure and function of the heart. Usually, two rounds of imaging are performed; one at rest and one following myocardial stress induced either by exercise or drugs. The two images are compared to assess for any abnormalities in wall motion of the heart [86].	X-ray is used to visualize the structure of the heart and coronary arteries. The patient receives a dose of contrast, then the heart is scanned using a high-speed CT scanner, allowing physicians to assess the extent of occlusion in the coronary arteries [87].	Previously acquired CCTA image data is analyzed to calculate blood pressure and velocity at every point in the coronary arteries. Physicians use this pressure information, in the form of FFR_{CT} values, to identify cardiac ischemia [88].	X-ray is used to visualize the structure of the heart and coronary arteries. The physician threads a catheter into the patient's coronary arteries through an entry site in the femoral or radial artery. Contrast dye is injected to visualize the degree of coronary stenosis. In some instances, a wire is inserted into the coronary arteries to measure invasive FFR [89]
Strengths	Widely available in the U.S. although little use outside of U.S. Allows semi-quantification of % myocardium subject to ischemia.	Provides images of heart structure, left ventricular function, and valve motion which may be important in assessing heart disease.	Provides high-fidelity images of the heart structure and coronary arteries. Early stages of CAD can be identified leading to initiation of preventative therapies. Allows evaluation of plaque composition. Reduces incidence of MI and death compared to stress testing.	Provides physiologic data to accompany CCTA anatomic results so that the physician has ability to correlate the anatomical blockages from CCTA with physiologic significance from FFR_{CT}. No additional patient visit is required.	Provides anatomic assessment of coronary artery narrowing.

	First Line Non-invasive Tests				Invasive Tests
	Myocardial Perfusion Imaging (MPI)	**Stress Echocardiography**	**Coronary Computed Tomography Angiography (CCTA)**	**Fractional Flow Reserve Computed Tomography (FFR_{CT})**	**Invasive Coronary Angiography (ICA)**
					
Limitations	High radiation dose. No direct assessment of coronary artery anatomy or physiology. Does not allow assessment of early stages of CAD. Can be falsely negative with severe proximal or multivessel CAD ('balanced ischemia').	No direct assessment of coronary artery anatomy or physiology. Does not allow assessment of early stages of CAD. Can be falsely negative with severe proximal or multivessel CAD ('balanced ischemia').	May overestimate disease severity producing false positive results. Limitations include artifacts due to coronary artery calcification and high heart rates. Anatomic stenosis severity may not match physiologic severity.	Good CCTA quality required to permit completion of analysis.	Invasive procedure with clinical risks. High radiation dose. Anatomic stenosis severity may not match physiologic severity (FFR). Does not allow assessment of early stages of CAD.
Time to schedule	days - weeks	days – weeks	days - weeks	Immediate	days – weeks
Test Duration	6 - 8 hours	2-4 hours	<1 hour	median < 5 hours	1-2 hours
Additional patient visit required for test	Yes	Yes	Yes	No	Yes
Improved patient outcomes compared to other test options in stable patients	No	No	Yes	Yes	No
Radiation exposure	10 mSv [90]	None	5.1 mSv [81]	None	10 mSv [91]
Inefficiency: % of ICAs showing no obstructive disease	55% [57]	56% [57]	30% [56]	12% [29]	62% [6]

Appendix 4: Case Examples

Case #1: FFR_{CT} helped the physician identify lesions as not physiologically significant; Medical management (63-year-old woman with chest pain)

CCTA demonstrated a calcified > 50% stenosis in the mid-right coronary artery (RCA) and a non-calcified > 70% stenosis in the left anterior descending artery (LAD) (red arrows). The FFR_{CT} analysis, as interpreted by the physician, revealed that the lesions were not hemodynamically significant, with FFR_{CT} values > 0.80. In the setting of a clinical study, ICA with measurement of FFR confirmed that these stenoses do not induce ischemia, with FFR values > 0.80 in both the RCA and LAD. In clinical use, ICA would have been avoided.

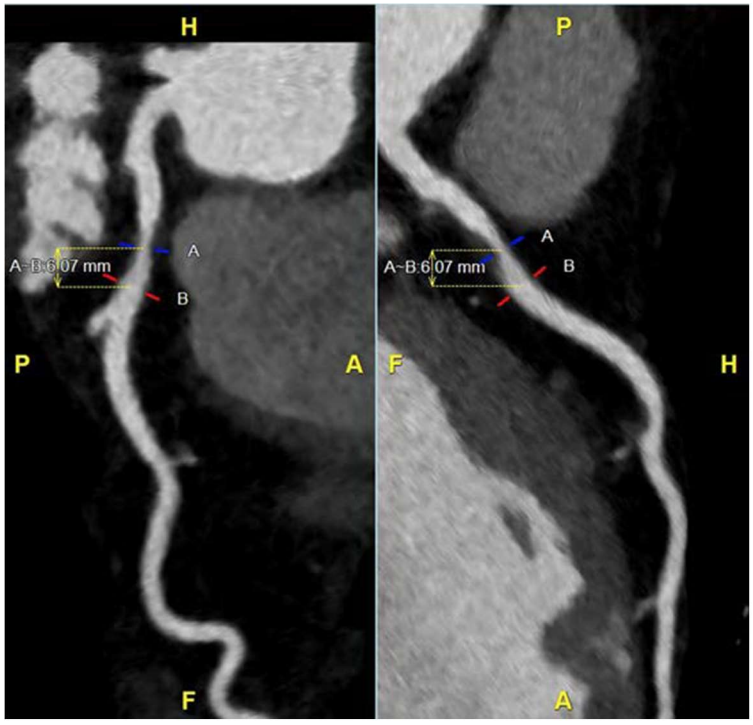


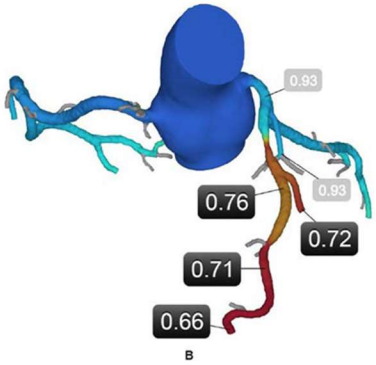
Clinical Utility

- CCTA revealed stenoses and FFR_{CT} analyzed them accurately, as verified by the FFR reference standard.
- This patient can be managed medically.
- In such cases, FFR_{CT} can follow a CCTA showing lesions of uncertain physiologic significance and eliminate the need for ICA.

Case #2: FFR_{CT} helped the physician identify obstructive CAD missed in previous non-invasive imaging (54-year-old man with negative stress test)

The patient was referred for evaluation of atypical chest pain in the inpatient setting. Non-invasive testing by stress echocardiography was negative, and CCTA revealed an area of moderate stenosis or possible imaging artifact in the proximal LAD. FFR_{CT} analysis indicated that the LAD lesion was in fact physiologically significant. This was confirmed with invasive FFR in the catheterization lab and the patient was treated with a stent in the proximal LAD.





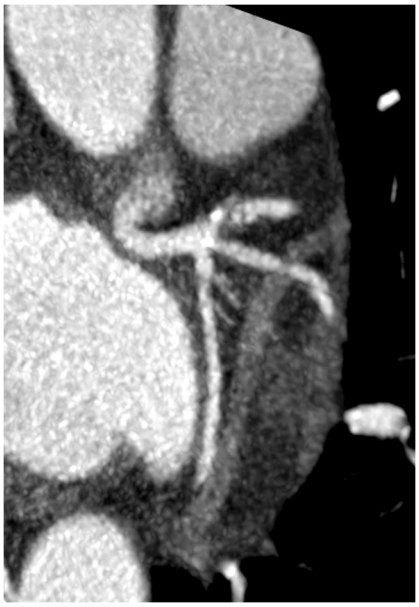
Clinical Utility

- Some non-invasive tests can miss critical CAD and lead to inadequate management plans
- FFR_{CT} helped to identify a potentially life-threatening lesion in the LAD and led to a change in treatment strategy

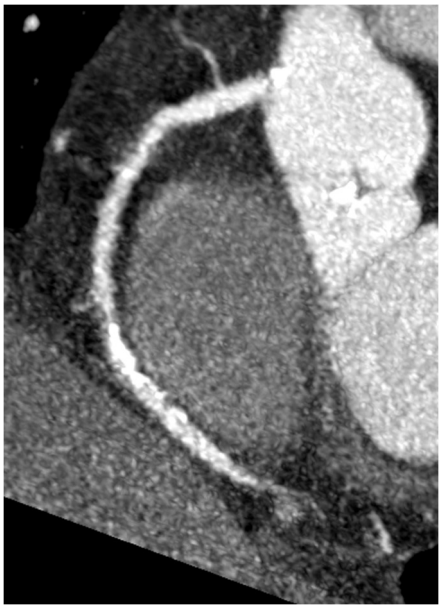
Case #3: FFR_{CT} use redefines treatment strategy (68-year-old man with planned CABG)

A 68-year-old male with multiple cardiac risk factors and shortness of breath was referred for evaluation of CAD. CCTA showed disease in all three main coronary arteries, and the patient was referred for CABG. FFR_{CT} analysis showed that lesions in both the RCA and LCX had FFR_{CT} values > 0.80, which the physician determined were not physiologically significant. The physician determined the LAD was in fact physiologically significant. The patient was rescheduled for PCI and received one stent in the proximal LAD.

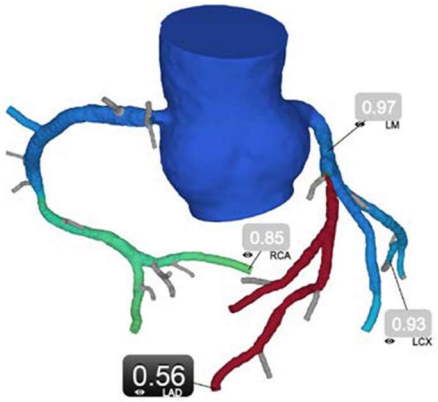
Positive CT shows significant LAD lesion



Positive CT shows moderate RCA lesion



FFR_{CT} helps differentiate between lesions that were and were not hemodynamically significant and patient referred for PCI



Clinical Utility

- Physiologic information provided by FFR_{CT} led to a change in revascularization strategy from CABG to a less invasive PCI.
- Relying on anatomy alone can lead to potential overtreatment of disease.
- Availability of FFR_{CT} data, which provides both physiologic and anatomic data, allowed this patient to avoid the cost, risk, and recovery associated with a CABG procedure.

Case #4: FFR_{CT} helped the physician identify stenosis causing chest pain missed in previous non-invasive imaging (63-year-old woman with atypical chest pain)

A 63-year-old female with multiple cardiovascular risk factors presented with atypical chest pain. Myocardial perfusion imaging (MPI, also known as SPECT) stress test was interpreted as normal. The patient's chest pain syndrome continued, and subsequently she presented to the emergency room. CCTA revealed a partially calcified left main (LM) plaque. In addition, a significant proximal LAD non-calcified plaque was also noted. The physician determined that these lesions were physiologically significant based on FFR_{CT} as evidenced by a significant drop across the LM, followed by the LAD and Left Circumflex (LCX). Stenting of the stenosis was performed with resolution of symptoms.

Clinical Utility

A CCTA/ FFR_{CT} diagnostic pathway provided an accurate depiction of this patient's CAD. Its use initially would have been safer and more economical: The delay in diagnosis in this case could have resulted in MI or death and did result in an additional emergency department evaluation.

References

1. National Institute for Health and Care Excellence. *HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography*. National Institute for Health and Care Excellence (NICE) [Medical technologies guidance] 2021 19 May 2021; Available from: https://www.nice.org.uk/guidance/mtg32.
2. Gulati, M., et al., *2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.* Circulation, 2021. **144**(22): p. e368-e454.
3. MacKay, J. and G.A. Mensah, *The Atlas of Heart Disease and Stroke.* 2010.
4. Montalescot, G., et al., *2013 ESC guidelines on the management of stable coronary artery disease.* The Task Force on the management of stable coronary artery disease of the European Society of Cardiology, 2013. **34**(38): p. 2949-3003.
5. Windecker, S., et al., *2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI).* Eur Heart J, 2014. **35**(37): p. 2541-619.
6. Patel, M.R., et al., *Low diagnostic yield of elective coronary angiography.* N Engl J Med, 2010. **362**(10): p. 886-95.
7. Arbab-Zadeh, A., *Stress testing and non-invasive coronary angiography in patients with suspected coronary artery disease: time for a new paradigm.* Heart Int, 2012. **7**(1): p. e2.
8. Nakanishi, R., et al., *Predictors of high-risk coronary artery disease in subjects with normal SPECT myocardial perfusion imaging.* J Nucl Cardiol, 2016. **23**(3): p. 530-41.
9. Yokota, S., et al., *Predictors of severe stenosis at invasive coronary angiography in patients with normal myocardial perfusion imaging.* Neth Heart J, 2018. **26**(4): p. 192-202.
10. Vavalle, J.P., et al., *Effect of the Presence and Type of Angina on Cardiovascular Events in Patients Without Known Coronary Artery Disease Referred for Elective Coronary Angiography.* JAMA Cardiol, 2016. **1**(2): p. 232-4.
11. Newby, D.E., et al., *Coronary CT Angiography and 5-Year Risk of Myocardial Infarction.* N Engl J Med, 2018. **379**(10): p. 924-933.
12. Maron, D.J., et al., *Initial Invasive or Conservative Strategy for Stable Coronary Disease.* N Engl J Med, 2020. **382**(15): p. 1395-1407.
13. Finck, T., et al., *Ten-Year Follow-Up After Coronary Computed Tomography Angiography in Patients With Suspected Coronary Artery Disease.* JACC Cardiovasc Imaging, 2018.
14. Ostrom, M.P., et al., *Mortality incidence and the severity of coronary atherosclerosis assessed by computed tomography angiography.* J Am Coll Cardiol, 2008. **52**(16): p. 1335-43.
15. De Bruyne, B., et al., *Fractional flow reserve-guided PCI for stable coronary artery disease.* N Engl J Med, 2014. **371**(13): p. 1208-17.
16. Tonino, P.A., et al., *Fractional flow reserve versus angiography for guiding percutaneous coronary intervention.* N Engl J Med, 2009. **360**(3): p. 213-24.
17. Dattilo, P.B., et al., *Contemporary patterns of fractional flow reserve and intravascular ultrasound use among patients undergoing percutaneous coronary intervention in the United States: insights from the National Cardiovascular Data Registry.* J Am Coll Cardiol, 2012. **60**(22): p. 2337-9.
18. Knuuti, J., et al., *2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.* Eur Heart J, 2020. **41**(3): p. 407-477.

19. Nakano, S., et al., *JCS 2022 Guideline Focused Update on Diagnosis and Treatment in Patients With Stable Coronary Artery Disease.* Circ J, 2022. **86**(5): p. 882-915.
20. Driessen, R.S., et al., *Comparison of Coronary Computed Angiography, Fractional Flow Reserve, and Perfusion Imaging for Ischemia Diagnosis.* J Am Coll Cardiol, 2019. **73**(2): p. 161-173.
21. Ko, B.S., 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.* Int J Cardiovasc Imaging, 2019.
22. Koo, B.K., et al., *Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study.* J Am Coll Cardiol, 2011. **58**(19): p. 1989-97.
23. Min, J.K., et al., *Diagnostic accuracy of fractional flow reserve from anatomic CT angiography.* Jama, 2012. **308**(12): p. 1237-45.
24. Norgaard, B.L., et al., *Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps).* J Am Coll Cardiol, 2014. **63**(12): p. 1145-55.
25. Curzen, N., et al., *Fractional flow reserve derived from computed tomography coronary angiography in the assessment and management of stable chest pain: the FORECAST randomized trial.* Eur Heart J, 2021. **42**(37): p. 3844-3852.
26. Curzen, N.P., et al., *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 Cardiovasc Imaging, 2016. **9**(10): p. 1188-1194.
27. Douglas, P.S., et al., *1-Year Outcomes of FFRCT-Guided Care in Patients With Suspected Coronary Disease: The PLATFORM Study.* J Am Coll Cardiol, 2016. **68**(5): p. 435-445.
28. Douglas, P.S., et al., *Comparison of an Initial Risk-Based Testing Strategy vs Usual Testing in Stable Symptomatic Patients With Suspected Coronary Artery Disease: The PRECISE Randomized Clinical Trial.* JAMA Cardiology, 2023.
29. Douglas, P.S., et al., *Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study.* Eur Heart J, 2015. **36**(47): p. 3359-67.
30. Fairbairn, T.A., et al., *Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE Registry.* Eur Heart J, 2018.
31. Madsen, K.T., et al., *Prognostic Value of Coronary CT Angiography-derived Fractional Flow Reserve on 3-year Outcomes in Patients with Stable Angina.* Radiology, 2023. **308**(3): p. e230524.
32. Moller Jensen, J., et al., *Computed tomography derived fractional flow reserve testing in stable patients with typical angina pectoris: influence on downstream rate of invasive coronary angiography.* Eur Heart J Cardiovasc Imaging, 2017.
33. Norgaard, B.L., et al., *Clinical Outcomes Using Coronary CT Angiography and FFRCT-Guided Management of Stable Chest Pain Patients.* J Am Coll Cardiol, 2018.
34. Patel, M.R., et al., *1-Year Impact on Medical Practice and Clinical Outcomes of FFR(CT): The ADVANCE Registry.* JACC Cardiovasc Imaging, 2020. **13**(1 Pt 1): p. 97-105.
35. Colleran, R., 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).
36. de Smet, K., et al., *Clinical Use of FFRct in the Evaluation of Symptomatic Patients with Intermediate (50-70%) Coronary Stenosis: Can it Improve Diagnosis and Reduce Radiation Risk and Cost?* J Cardiovasc Comput Tomogr, 2016. **10**(3).
37. Douglas, P.S., et al., *1-Year Outcomes of FFRCT-Guided Care in Patients With Suspected Coronary Disease: The PLATFORM Study.* J Am Coll Cardiol, 2016. **68**(5): p. 435-45.
38. Fares, A., *Real World Utilization of Computed Tomography Derived Fractional Flow Reserve: Single Center Initial Experience in the United States.*
39. Jang, J.J., et al., *The Impact of Fractional Flow Reserve Derived from Coronary Computed Tomography Angiography in a Managed Healthcare System -Kaiser Permanente Northern California.* J Cardiovasc Comput Tomogr, 2016. **10**(3): p. S20.
40. Lu, M.T., *Noninvasive Fractional Flow Reserve Derived From Coronary CT Angiography (FFRct): Management and Outcomes in the PROMISE Trial.* JACC Cardiovasc Imaging, 2017.
41. Cheruvu, C., et al., *Beyond Stenosis With Fractional Flow Reserve Via Computed Tomography and Advanced Plaque Analyses for the Diagnosis of Lesion-Specific Ischemia.* Can J Cardiol, 2016.
42. Rabbat, M.G., *Fractional Flow Reserve Derived From Coronary Computed Tomography Safely Defers Invasive Coronary Angiography in Patients With Stable Coronary Artery Disease.* 2016.
43. Fairbairn, T., *The FISH&CHIPS Study: FFRCT In Stable Heart disease and Coronary Computed Tomography Angiography Helps Improve Patient care and Societal costs.* European Society of Cardiology, 2023.
44. Ihdayhid, A.R., et al., *Prognostic Value and Risk Continuum of Noninvasive Fractional Flow Reserve Derived from Coronary CT Angiography.* Radiology, 2019. **292**(2): p. 343-351.
45. McNabney, C.G., et al., *Prognosis of CT-derived Fractional Flow Reserve in the Prediction of Clinical Outcomes.* Radiol Cardiothorac Imaging, 2019. **1**(2): p. e190021.
46. Nørgaard, B.L., et al., *Prognostic value of coronary computed tomography angiographic derived fractional flow reserve: a systematic review and meta-analysis.* Heart, 2022. **108**(3): p. 194-202.
47. Chew, D.S., et al., *Resource Use and Cost Comparisons of a Novel Precision Medicine Evaluation Strategy for Suspected CAD vs Usual Testing.* American Heart Association, 2023.
48. Forrest, B. and N. Anderson. *Economic Evaluation of Emerging Diagnostic Test for Coronary Artery Disease*. in *VALUE IN HEALTH*. 2017. ELSEVIER SCIENCE INC 360 PARK AVE SOUTH, NEW YORK, NY 10010-1710 USA.
49. Hlatky, M.A., et al., *Quality of Life and Economic Outcomes of Assessing Fractional Flow Reserve With Computed Tomography Angiography: The PLATFORM Study.* J Am Coll Cardiol, 2015.
50. Hlatky, M.A., et al., *Projected costs and consequences of computed tomography-determined fractional flow reserve.* Clin Cardiol, 2013. **36**(12): p. 743-8.
51. Karády, J., et al., *Cost-effectiveness Analysis of Anatomic vs Functional Index Testing in Patients With Low-Risk Stable Chest Pain.* JAMA Netw Open, 2020. **3**(12): p. e2028312.
52. Kimura, T., et al., *Cost analysis of non-invasive fractional flow reserve derived from coronary computed tomographic angiography in Japan.* Cardiovasc Interv Ther, 2015. **30**(1): p. 38-44.
53. Rajani, R., et al., *Comparative efficacy testing - fractional flow reserve by coronary computed tomography for the evaluation of patients with stable chest pain.* Int J Cardiol, 2015. **183**: p. 173-7.
54. *Coronary Computed Tomography Angiography With Selective Noninvasive Fractional Flow Reserve.* BlueCross BlueShield Association, 2017: p. 1-19.
55. *Chest pain of recent onset: assessment and diagnosis.* National Institute for Health and Care Excellence (NICE), 2016.

56. Douglas, P.S., et al., *Outcomes of anatomical versus functional testing for coronary artery disease.* N Engl J Med, 2015. **372**(14): p. 1291-300.
57. Patel, M.R., et al., *Prevalence and predictors of nonobstructive coronary artery disease identified with coronary angiography in contemporary clinical practice.* Am Heart J, 2014. **167**(6): p. 846-52.e2.
58. Berman, D.S., et al., *Comparative use of radionuclide stress testing, coronary artery calcium scanning, and noninvasive coronary angiography for diagnostic and prognostic cardiac assessment.* Semin Nucl Med, 2007. **37**(1): p. 2-16.
59. Hachamovitch, R., et al., *Incremental prognostic value of adenosine stress myocardial perfusion single-photon emission computed tomography and impact on subsequent management in patients with or suspected of having myocardial ischemia.* Am J Cardiol, 1997. **80**(4): p. 426-33.
60. Roifman, I., et al., *Comparison of Anatomic and Clinical Outcomes in Patients Undergoing Alternative Initial Noninvasive Testing Strategies for the Diagnosis of Stable Coronary Artery Disease.* J Am Heart Assoc, 2017. **6**(7).
61. Meijboom, W.B., et al., *Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study.* J Am Coll Cardiol, 2008. **52**(25): p. 2135-44.
62. Danad, I., et al., *Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis.* Eur Heart J, 2016.
63. Xaplanteris, P., et al., *Five-Year Outcomes with PCI Guided by Fractional Flow Reserve.* N Engl J Med, 2018.
64. Zimmermann, F.M., et al., *Fractional flow reserve-guided percutaneous coronary intervention vs. medical therapy for patients with stable coronary lesions: meta-analysis of individual patient data.* Eur Heart J, 2019. **40**(2): p. 180-186.
65. Sud, M., et al., *Association Between Adherence to Fractional Flow Reserve Treatment Thresholds and Major Adverse Cardiac Events in Patients With Coronary Artery Disease.* Jama, 2020. **324**(23): p. 2406-2414.
66. Rajkumar, C.A., et al., *A Placebo-Controlled Trial of Percutaneous Coronary Intervention for Stable Angina.* New England Journal of Medicine, 2023.
67. Neumann, F.J., et al., *2018 ESC/EACTS Guidelines on myocardial revascularization.* Eur Heart J, 2018.
68. Levine, G.N., et al., *2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions.* Circulation, 2011. **124**(23): p. e574-651.
69. Norgaard, B.L., et al., *Influence of Coronary Calcification on the Diagnostic Performance of CT Angiography Derived FFR in Coronary Artery Disease: A Substudy of the NXT Trial.* JACC Cardiovasc Imaging, 2015. **8**(9): p. 1045-1055.
70. Danad, I., et al., *Comparison of Coronary CT Angiography, SPECT, PET, and Hybrid Imaging for Diagnosis of Ischemic Heart Disease Determined by Fractional Flow Reserve.* JAMA Cardiol, 2017. **2**(10): p. 1100-1107.
71. Gaur, S., et al., *Fractional flow reserve derived from coronary CT angiography: variation of repeated analyses.* J Cardiovasc Comput Tomogr, 2014. **8**(4): p. 307-14.
72. Ihdayhid, A.R., et al., *Prognostic Value and Risk Continuum of Noninvasive Fractional Flow Reserve Derived from Coronary CT Angiography.* Radiology, 2019: p. 182264.
73. McNabney, C.G., et al., *Prognosis of CT-derived Fractional Flow Reserve in the Prediction of Clinical Outcomes.* Radiology: Cardiothoracic Imaging, 2019. **1**(2).

74. Benjamin, E.J., et al., *Heart disease and stroke statistics—2017 update: a report from the American Heart Association.* Circulation, 2017. **135**(10): p. e146.
75. *Medicare Payment Advisory Commision, Healthcare Spending and the Medicare Program.* June 2017.
76. Budoff, M.J., et al., *Coronary computed tomography angiography predicts subsequent cardiac outcome events: results of the Visipaque CCTA registry study.* Coron Artery Dis, 2015. **26**(4): p. 301-7.
77. Hulten, E.A., et al., *Prognostic value of cardiac computed tomography angiography: a systematic review and meta-analysis.* J Am Coll Cardiol, 2011. **57**(10): p. 1237-47.
78. Nagaraja, V., et al., *Change in angiogram-derived management strategy of patients with chest pain when some FFR data are available: How consistent is the effect?* Cardiovasc Revasc Med, 2017.
79. Patel, M.R., et al., *1-Year Impact on Medical Practice and Clinical Outcomes of FFRCT: The ADVANCE Registry.* JACC Cardiovasc Imaging, 2019.
80. Anastasius, M., et al., *The clinical utility of FFRct stratified by age.* J Cardiovasc Comput Tomogr, 2019.
81. Stocker, T.J., et al., *Reduction in radiation exposure in cardiovascular computed tomography imaging: results from the Prospective Multicenter Registry on RadiaTion Dose Estimates of Cardiac CT AngIOgraphy IN Daily Practice in 2017 (PROTECTION VI).* Eur Heart J, 2018.
82. Hlatky, M.A., et al., *Quality-of-Life and Economic Outcomes of Assessing Fractional Flow Reserve With Computed Tomography Angiography: PLATFORM.* J Am Coll Cardiol, 2015. **66**(21): p. 2315-23.
83. Fujimoto, S., et al., *Clinical impacts of CT-derived fractional flow reserve under insurance reimbursement: Results from multicenter, prospective registry.* J Cardiol, 2023.
84. *CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial.* Lancet, 2015. **385**(9985): p. 2383-91.
85. Gowd, B.M., G.V. Heller, and M.W. Parker, *Stress-only SPECT myocardial perfusion imaging: a review.* J Nucl Cardiol, 2014. **21**(6): p. 1200-12.
86. Marwick, T., *Stress Echocardiography.* Heart, 2003. **89**(1): p. 113-118.
87. Foy, A.J., et al., *Coronary Computed Tomography Angiography vs Functional Stress Testing for Patients With Suspected Coronary Artery Disease: A Systematic Review and Meta-analysis.* JAMA Intern Med, 2017. **177**(11): p. 1623-1631.
88. Taylor, C.A., T.A. Fonte, and J.K. Min, *Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis.* J Am Coll Cardiol, 2013. **61**(22): p. 2233-41.
89. Kern, M.J., *Quantitative coronary angiography: Technical issues.* Uptodate.com.
90. Einstein, A.J., et al., *Current worldwide nuclear cardiology practices and radiation exposure: results from the 65 country IAEA Nuclear Cardiology Protocols Cross-Sectional Study (INCAPS).* Eur Heart J, 2015. **36**(26): p. 1689-96.
91. Partridge, J., *Radiation in the cardiac catheter laboratory.* Heart., 2005. **91**(12): p. 1615-1620.