Noninvasive Fractional Flow Reserve Derived From Coronary CT Angiography

Clinical Data and Scientific Principles

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ABSTRACT

Fractional flow reserve derived from coronary computed tomography angiography enables noninvasive assessment of the hemodynamic significance of coronary artery lesions and coupling of the anatomic severity of a coronary stenosis with its physiological effects. Since its initial demonstration of feasibility of use in humans in 2011, a significant body of clinical evidence has developed to evaluate the diagnostic performance of coronary computed tomography angiography-derived fractional flow reserve compared with an invasive fractional flow reserve reference standard. The purpose of this paper was to describe the scientific principles and to review the clinical data of this technology recently approved by the U.S. Food and Drug Administration. (J Am Coll Cardiol Img 2015;8:1209–22) © 2015 by the American College of Cardiology Foundation.

STRENGTHS AND LIMITATIONS OF CURRENT METHODS OF NONINVASIVE CORONARY ARTERY DISEASE IMAGING

For several decades, stress testing has served as the cornerstone for assessment of symptomatic individuals with suspected or known coronary artery disease (CAD) (1). When stress testing is performed in conjunction with noninvasive imaging, an array of methods are used, including stress echocardiography and myocardial perfusion imaging (MPI) by single-photon emission computed tomography (SPECT), positron emission tomography, and cardiac magnetic resonance. These tests identify stress-induced regional wall motion abnormalities or reductions in coronary flow reserve (CFR) as a surrogate marker for flow-limiting epicardial coronary artery stenosis (2,3). Among these methods, MPI by SPECT remains the most commonly used technique for noninvasive CAD evaluation in the United States, and it accounts for approximately three-fourths of the 10 million stress imaging tests performed in the United States annually.

The rationale for the use of CFR for diagnosing CAD stems from the pioneering research of Gould and Lipscomb (4), who demonstrated compromise of flow with progressive narrowing of the coronary luminal diameter. Importantly, this reduced CFR is used simply as a surrogate for myocardial ischemia.
(an inadequacy of myocardial oxygen for a given metabolic state) and has never been validated in a human model. Although reductions in CFR manifest generally predictable reductions at hyperemic flow states for coronary stenosis ≥70%, the relationship between coronary stenosis and myocardial ischemia is nevertheless complex. Approximately 1 in 5 high-grade lesions with ≥70% stenosis do not cause ischemia, and diminution of coronary flow can begin as early as 40% diameter stenosis or in the context of diffuse or serial “nonobstructive” stenosis (5). Furthermore, CFR accounts for abnormalities across the entirety of the coronary vascular bed, which includes not only the epicardial coronary arteries but also the intramyocardial pre-arteriolar, arteriolar, and capillary circulations (6). Precise localization of CFR abnormalities to the epicardial versus nonepicardial vessels is vital, given that effective treatments exist for the former (including both medical therapy and revascularization), but no known effective treatments exist for the latter.

Recent clinical data have assessed the diagnostic specificity of MPI for patients undergoing invasive coronary angiography (ICA). In the nuclear substudy of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, only 32% of patients with ≥70% stenosis exhibited severe ischemia and 40% manifested no or mild ischemia according to MPI (7). Similarly, among >650,000 patients undergoing nonemergent ICA recorded in the National Cardiovascular Data Registry, noninvasive stress test findings offered minimal discriminatory value for identifying and excluding anatomically “obstructive” coronary stenosis (C index 0.75 vs. 0.74 for clinical evaluation vs. noninvasive testing) (8). Similar findings were observed in a 47-center study in Michigan: among 6,198 patients, stress imaging test results were not predictive of high-grade coronary lesions at the time of ICA (odds ratio: 0.79; 95% confidence interval: 0.56 to 1.11; p = 0.17) (9). Collectively, nearly two-thirds of patients undergoing nonemergent ICA do not have anatomically obstructive CAD.

Recently, coronary computed tomography angiography (CTA) has been offered as an anatomic alternative to stress imaging testing (1). Based on several prospective multicenter studies, coronary CTA exhibits high diagnostic performance for the identification and exclusion of anatomically obstructive coronary stenosis compared with an ICA reference standard. Coronary CTA findings are prognostically important and serve as effective guides toward medical and invasive management. However, similar to limitations of CFR that manifest a generally weak association with ischemia, and further emphasizing the complex relationship between stenosis and flow, coronary CTA has exhibited low specificity for identification of ischemia-causing coronary stenosis (10). Indeed, >50% of lesions considered anatomically obstructive according to coronary CTA do not cause ischemia. These findings are not singular to coronary CTA but are observed uniformly for all anatomic methods of coronary imaging, including ICA and intravascular ultrasound.

**INVASIVE FRACTIONAL FLOW RESERVE**

Fractional flow reserve (FFR) performed at the time of ICA for combined anatomic-physiological evaluation represents the current gold standard for determining whether a coronary artery stenosis causes ischemia (11). FFR is defined as the ratio of maximal hyperemic flow to part of the myocardium in the presence of a stenosis in the supplying epicardial artery to the maximum hyperemic flow in the same myocardial territory in the hypothetical case in which the supplying artery is normal. An FFR ≤0.80 (i.e., when the distal coronary pressure is 80% of the aortic pressure under conditions of maximal hyperemia) is commonly accepted as the threshold below which a lesion is considered ischemia causing. Deferral of percutaneous coronary intervention (PCI) for vessels with an FFR >0.80 is associated with improved clinical outcomes and reduced costs compared with an ICA alone-guided intervention (12). Conversely, coronary revascularization in vessels with a measured FFR ≤0.80 is associated with reduced risk of death, myocardial infarction, or urgent revascularization compared with an ICA alone-guided revascularization or optimal medical therapy (OMT) alone (13,14). Based on these and other data, current guidelines regarding myocardial revascularization assign a Class IA recommendation to FFR for the assessment of coronary artery stenoses with a diameter reduction ranging from 50% to 90% unless there is noninvasive proof of ischemia (15).

**CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY-DERIVED FRACTIONAL FLOW RESERVE**

Coronary computed tomography angiography-derived fractional flow reserve (FFRCT) is a novel noninvasive approach for precise localization of ischemia-causing coronary stenoses (Central Illustration). It applies
computational fluid dynamics (CFD) to calculate “3-vessel” FFR from typically acquired coronary CTA images with no need for additional imaging or vasodilators (16). The present review considers the scientific principles and summarizes the prior and ongoing clinical data informing the appropriate use of FFRCT in daily practice.

**Steps to Calculate FFRCT.** The application of CFD to calculate fluid pressure, velocity, and flow is ubiquitous in engineering, including for the design of automobiles and aircrafts (17). In these examples, the fluid dynamic to be evaluated is air, whereas in the case of FFRCT, the fluid dynamic to be evaluated is blood. Any mathematical model of flow, whether air or blood, requires 3 elements: 1) description of the anatomic region of interest; 2) “boundary conditions” to define physiological relationships between variables at the boundaries of the region; and 3) understanding the physical laws of fluid flow within the region. Although the anatomic region of interest and the boundary conditions are unique to each patient and vessel, the governing equations describing the physical laws of blood flow, velocity, and pressure are universal. Calculation of FFRCT requires 5 basic steps: 1) creation of patient-specific anatomic models from coronary CTA; 2) quantification of the total and vessel-specific baseline coronary artery flow in the hypothetical case in which the supplying vessels are normal; 3) determination of the baseline myocardial microcirculatory resistance; 4) quantification of the changes in coronary resistance with hyperemia;
and 5) application of CFD methods for calculation of coronary flow, pressure, and velocity at rest and hyperemia. The step-by-step methods for calculating FFR_{CT} are illustrated in Figure 1.

**Step 1. Creating Patient-Specific Anatomic Models From Coronary CTA.** Pressure losses along the coronary artery are not just determined by the stenotic segments but by the totality of coronary artery anatomy and blood flow from the ostia to the distal measurement point (Figure 1A) (18). Lesion length, serial lesions, and diffuse disease affect coronary flow and pressure. In addition, the perfusion territory downstream of a coronary lesion affects the flow through that lesion and thus the pressure loss. Creation of patient-specific anatomic models of the coronary arteries for FFR_{CT} analysis therefore requires a faithful representation of lumen dimensions for the primary coronary arteries as well as the secondary

![FIGURE 1 Step-by-Step Method for Calculation of FFR_{CT}](image-url)
and tertiary branches that define the perfusion territory downstream of a stenosis. These representations are now reliably achieved with image acquisition from ≥64-detector row coronary CTA (19).

Importantly, the advantages of the FFR<sub>CT</sub> technique compared with workstation-based algorithms include: 1) improved spatial resolution; and 2) automated segmentation algorithms for whole-heart CFD calculations (Figure 1B). Pertaining to the first factor, because the resistance of a coronary artery segment can be approximated by using Poiseuille’s solution as inversely related to vessel diameter to the fourth power, limits in spatial resolution of coronary CTA may introduce large errors in stenosis diameter and pressure drop, and calculated FFR<sub>CT</sub>. Reconstruction of image data with the smallest field of view will achieve an isotropic spatial resolution to ~0.5 mm; thus, even 1-voxel differences in a 2-mm vessel can result in a 25% difference in diameter stenosis severity. To address this outcome, FFR<sub>CT</sub> is facilitated through advanced automated image segmentation methods that use subvoxel resolution techniques (Figure 1C). Image segmentation is the process of labeling voxels within a computed tomography (CT) image to create a 3-dimensional reconstruction of the heart and coronary arteries, whereas subvoxel resolution techniques increase the spatial resolution of the CT image (generally ~0.5 to 0.8 mm) by subdivision of voxels into different intensities based on intensities in neighboring subvoxels. By these methods, image information from a complete vessel cross-section and neighboring cross-sections can be used to estimate the diameter (or more generally, the lumen boundary) of the vessel. Prior evidence, both theoretical and empirical, has demonstrated improved resolution by using subvoxel techniques applied to CTA to ~0.25 mm (20). Second, CFD calculations of FFR<sub>CT</sub> necessitate discretization of a finite set of 3-dimensional volumes within the coronary artery image data (Figure 1D). Millions of tetrahedral “elements” are generated within the coronary artery image data, with increasing density at the lateral boundaries of the coronary lumen, at which the governing equations of blood flow are solved. To solve for these equations requires not only automated generation of mesh elements but also successful 3-dimensional representation of mesh elements at all points in the coronary tree (including bifurcations and trifurcations); this feature is not available with commercially available workstations.

**Step 2. Quantify Total and Vessel-Specific Coronary Artery Flow.** Allometric scaling laws serve as the foundation for step 2 (quantification of total and vessel-specific coronary artery flow) and step 3 (determination of myocardial microcirculatory resistance). Allometric scaling laws refer to the relationships of an object size to its anatomy or physiology, which can describe relationship of deviation of an object from congruent organization or isometry. Universally, allometric scaling laws relating biologic variables to organism size have the form $Y = Y_0M^b$, in which $M$ is mass, $b$ is the scaling exponent, and $Y_0$ is a normalization constant.

For step 2, the allometric scaling law used is the core scientific principle that baseline coronary artery flow is proportional to left ventricular myocardial mass: $Q_{cor} \propto M_{myo}^{0.75}$ (Figure 1E). This principle is used with a patient’s blood pressure to compute total baseline coronary artery resistance. Intuitively, this method makes sense: increases in muscle mass occur as a function of greater flow. This premise underscores the general approach to quantification of myocardial blood flow per unit myocardial mass according to positron emission tomography (e.g., millimeters per minute per gram), which denotes a reliance of organ size to organ flow. Experimentally, this relationship was substantiated by Choy et al. (21), who investigated scaling of myocardial flow and mass in a porcine model using microspheres to quantify total coronary flow. In this study, the investigators observed a scaling exponent of 0.74 ± 0.04, with an $r^2$ value of 0.97. These data were confirmed in several different animal models, with scaling exponents ranging between 0.74 and 0.776.

**Step 3. Determine Myocardial Microcirculatory Resistance.** In this step, the core scientific principle used in the FFR<sub>CT</sub> physiological model is that the microvascular resistance is inversely proportional to vessel area, a finding that is associated with increasing value as blood traverses from the conduit epicardial vessels into the intramyocardial pre-arterioles, arterioles, and capillary beds. Assuming that epicardial coronary stenoses are not flow-limiting under resting conditions (i.e., in the absence of rest angina), this principle implies that flow through each branch of the epicardial model created from coronary CTA data is related to its area. These findings are based on a continuous as well as a longitudinal adaptation of coronary vessel caliber to flow (22,23). Such adaptive mechanisms occur during the progression of atherosclerotic disease through compensatory outward remodeling of arteries to maintain coronary luminal integrity. As disease progresses beyond a threshold at which the artery can no longer outwardly remodel, constrictive remodeling occurs and vessel lumen size decreases, which also reduces flow. Examples of the principle relating flow to arterial caliber can be
observed in the dilated coronary artery size of patients with hypertrophic and dilated cardiomyopathies (who have increased coronary flow demand from increased left ventricular myocardial mass) or in peripheral arteriovenous fistulas used for hemodialysis, which may increase in size over time due to increased flow (24). Both of these illustrations are examples of “form-function” relationships, wherein the form (anatomy) of an object precisely informs its function (physiology).

As shown in Figure 1F, the form-function relationship between flow and vessel size enables determination of baseline flow and resistance in a coronary artery based on the size of the artery and the perfusion territory downstream. The ability to isolate specific coronary vessels in relation to their downstream microcirculatory resistance also enables determination of “myocardium at risk.” This is analogous to the methods used by Gould et al. (6), who used similar form-function principles to determine the fraction of left ventricular mass at risk distal to a stenosis from anatomic measurements of vessel sizes obtained from arteriograms. In these studies, radiolabeled microspheres quantifying flow were related to vessel lengths and diameters, with a curvilinear relationship observed between coronary artery caliber and dependent myocardial mass.

Step 4. Quantify Changes in Coronary Resistance at Hyperemia. No vasodilator (e.g., adenosine, regadenoson) is used in this step to quantify hyperemia; rather, the hyperemic response is calculated computationally. In this step, the core scientific principle of FFRCT is that microcirculatory resistance decreases predictably at maximal hyperemia. This principle is based on the data of Wilson et al. (25), who evaluated the effects of increasing concentrations of adenosine on total coronary resistance index. A maximum reduction in the coronary resistance index (to 0.24 ± 0.01) was observed at an intravenous adenosine dose of 140 μg/kg/min, beyond which no further reduction could be observed. These findings have informed the dose of adenosine needed to induce hyperemia during stress testing and invasive FFR, and they form the basis for the resistance calculations in FFRCT.

Importantly, in the study by Wilson et al. (25), the coefficient of variation in patients with normal CFR was ~4%, which suggests a reliability and precision of hyperemia across a population of patients. These data from “normal subjects” inform the FFRCT model for computing the resistance to flow of the microvasculature downstream of each epicardial coronary artery (Figure 1G). Notably, given the predictability of reductions in resistance, dose-dependent titration of resistance can be calculated for any given FFRCT value. This method allows calculation of FFRCT values across a physiologically realistic range (e.g., increasing levels of exercise); this may allow not only for determination of which coronary stenoses cause ischemia but also at precisely what level of increased coronary flow the ischemia is encountered.

Step 5. Apply CFD Methods for Calculation of Coronary Flow, Pressure, and Velocity at Rest and Hyperemia. Fundamental to the laws governing fluid dynamics are the Navier-Stokes equations, which serve as the foundation for mathematical analyses of coronary circulation behaviors. These equations are conceptually simple, a statement of the conservation of mass and a generalization of Newton’s second law (F = ma) to a fluid but are a mathematically complex system of nonlinear partial differential equations (Figure 1H). This complexity of the Navier-Stokes equations of fluid dynamics precluded their direct solution until the advent of the digital computer and numerical methods. Furthermore, while general-purpose solvers of CFD are available in the aerospace, automotive, and other industries, solving for the equations of human blood flow in arteries poses unique challenges due to the time- and spatially-varying properties of coronary arteries and because flow in coronary arteries is intrinsically coupled to the heart on one end and the microcirculation on the other.

Several methods exist to solve for the Navier-Stokes equations for FFRCT, including lumped-parameter models, 1-dimensional wave models, and 3-dimensional models. In the lumped-parameter method, spatially varying properties of arteries are lumped into large discrete components (26). For example, the fluid resistance along the length of a vessel is represented as a single resistive element with parameter values derived by using an idealized solution assuming steady, axisymmetric, unidirectional flow in a circular cylindrical model of a blood vessel. Although the simplicity of lumped-parameter models enables whole body models of the circulation with general computational ease, it is invalid in diseased segments in which blood flow is not steady, axisymmetric, or unidirectional and the vessel segments are not circular cylinders. FFRCT has been explored in investigational software programs by using 1-dimensional wave models, which are derived by averaging the Navier-Stokes equations over a vessel cross-section assuming the axial velocity profile is the same at all locations along the vessel and in all vessels and that pressure is constant over the vessel cross-section (27). Although the assumptions made for
the 1-dimensional models are reasonable for computing flow and pressure in large, straight, and generally healthy segments, they are invalid in segments that are small, near side branches or bifurcations, or with complex nonuniform luminal compromise, as often occur from coronary atheroma. Thus, $\text{FFR}_{\text{CT}}$ is calculated by using 3-dimensional models of blood flow, which offer the advantage of direct representation of the true geometry of the circulation, the full complexity of 3-dimensional pulsatile or unsteady flow (including turbulence), and inclusion of complex material models for blood or blood vessels (Figure 11).

Overall, the calculation of $\text{FFR}_{\text{CT}}$ can take up to 8 h, but most calculations can be done within a few hours. Future iterations incorporating automated segmentation methods and machine-learning techniques offer hope that $\text{FFR}_{\text{CT}}$ can be calculated within minutes.

**CLINICAL DATA FOR FFR$_{\text{CT}}$**

In a landmark paper, Fryback and Thornbury (28) contextualized technology evaluation for diagnostic imaging, describing a hierarchical model of efficacy. This model describes the ideal evidence base necessary for proof of the value of a diagnostic imaging test and addresses factors related to diagnostic accuracy and technical quality, diagnostic and therapeutic impact, and patient and societal outcomes. Since its initial demonstration of feasibility of use in humans in 2011, a significant body of clinical evidence for $\text{FFR}_{\text{CT}}$ has developed to evaluate its diagnostic performance with an invasive FFR reference standard. At present, 11 multicenter clinical trials of $\text{FFR}_{\text{CT}}$ have been completed ($n = 5$), are ongoing ($n = 4$), or are being actively designed ($n = 2$) (Tables 1 to 3). We herein describe the available and ongoing clinical data for $\text{FFR}_{\text{CT}}$ that address these issues, constraining our discussion to results derived from or informing the design of prospective multicenter trials of $\text{FFR}_{\text{CT}}$.

**DIAGNOSTIC ACCURACY AND REPRODUCIBILITY OF FFR$_{\text{CT}}$.** The diagnostic performance of $\text{FFR}_{\text{CT}}$ has been evaluated in 3 prospective, multicenter clinical trials using measured FFR as the reference standard and blinded core laboratory controls: DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve), DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography), and NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). These 3 studies comprise a total of 609 patients and 1,050 vessels.

The first clinical trial to evaluate $\text{FFR}_{\text{CT}}$ technology was the DISCOVER-FLOW trial, which included 103 patients and 159 vessels from 4 sites in the United States, Europe, and Asia (29). $\text{FFR}_{\text{CT}}$ improved diagnostic accuracy by 42% compared with coronary CTA (84% vs. 59%), which occurred as a result of a 2-fold improvement in specificity (84% vs. 40%) with no changes in sensitivity (87% vs. 91%). $\text{FFR}_{\text{CT}}$ exhibited significant improvement in discrimination of ischemia with an increase in the area under the receiver-operating characteristic curve (AUC) compared with coronary CTA (0.90 vs. 0.75; $p < 0.001$). The DISCOVER-FLOW trial was conducted with the first generation (version 1.0) of $\text{FFR}_{\text{CT}}$ algorithms (16), and the quality of the image data was ensured by excluding coronary CTA scans that were deemed nonevaluable by the $\text{FFR}_{\text{CT}}$ core laboratory.

The DeFACTO study comprised 252 patients at 17 centers with 407 vessels directly interrogated by using FFR (30). Parallel to the DISCOVER-FLOW findings, the diagnostic accuracy of $\text{FFR}_{\text{CT}}$ was higher than CT stenosis (73% vs. 64%), which occurred as a function of improved specificity (54% vs. 42%) and comparable sensitivity (90% vs. 84%) to coronary CTA. $\text{FFR}_{\text{CT}}$ demonstrated superior per-patient and per-vessel discrimination of ischemia compared with coronary CTA, with AUCs of 0.81 versus 0.68 ($p < 0.001$) and 0.81 versus 0.75 ($p < 0.001$), respectively. The DeFACTO trial was conducted with second-generation (version 1.2) $\text{FFR}_{\text{CT}}$ algorithms, and CT image quality for inclusion in the study was determined by an external CT core laboratory.

The most recently performed NXT trial investigated the diagnostic performance of $\text{FFR}_{\text{CT}}$ in 254 patients and 484 vessels (31). The per-vessel accuracy and specificity to identify arteries that caused myocardial ischemia were significantly higher for $\text{FFR}_{\text{CT}}$ (86% and 86%) than for coronary CTA (65% and 60%) ($p < 0.001$). Sensitivity was unchanged at 83% for coronary CTA and 84% for $\text{FFR}_{\text{CT}}$. $\text{FFR}_{\text{CT}}$ also demonstrated superior per-patient and per-vessel

| TABLE 1 | Patient-Based Diagnostic Performance of Noninvasive Imaging Versus Fractional Flow Reserve (40) |
| --- | --- | --- |
|  | Sensitivity, PLR | Specificity, NLR |
| N |  |  |
| SPECT | 533 | 74%, 3.13 | 79%, 0.39 |
| Echo | 177 | 69%, 3.68 | 84%, 0.42 |
| CMR | 798 | 89%, 6.29 | 87%, 0.14 |
| PET | 224 | 84%, 6.53 | 87%, 0.14 |
| CT | 316 | 88%, 3.79 | 80%, 0.12 |

CT = computed tomography; CMR = cardiac magnetic resonance; NLR = negative likelihood ratio; PET = positron emission tomography; PLR = positive likelihood ratio; SPECT = single-photon emission computed tomography.
it incorporated refinements in image-processing methods and physiological modeling, using information derived from study patients of earlier trials.

The reproducibility of FFR and FFR<sub>CT</sub> were evaluated in 28 patients (58 vessels) in a substudy of NXT (31). FFR<sub>CT</sub> was then performed twice for each patient by 2 independent blinded analysts at different time points. The coefficient of variation of FFR<sub>CT</sub> was 3.4% (95% confidence interval: 1.4 to 4.6) versus 2.7% (95% confidence interval: 1.8 to 3.3) for FFR. As with any noninvasive test compared with invasive FFR, there were differences. The average errors associated with FFR<sub>CT</sub> versus FFR differed by FFR<sub>CT</sub> value and were highest to FFR<sub>CT</sub> value, they were: 0.0013; 0.76 to 0.80, 0.05; 0.86 to 0.90, 0.03; 0.71 to 0.75, 0.03; 0.13; 0.76 to 0.80, 0.03; 0.08; 0.81 to 0.85, 0.05; 0.07; 0.86 to 0.90, 0.03; 0.06; and 0.91 to 1.00, 0.01; ± 0.05 (29–31).

The continually improving diagnostic performance of FFR<sub>CT</sub> is a “moving target.” Even among the 3 trials performed to date (29–31), newer generation iterations were sequentially evaluated. Currently, machine learning (a form of artificial intelligence) is being applied to FFR<sub>CT</sub> to train automated image

### TABLE 2 Completed Multicenter Trials or Registries of FFR<sub>CT</sub>

<table>
<thead>
<tr>
<th>Study Name (Ref. #)</th>
<th>NCT</th>
<th>n</th>
<th>Study Findings</th>
<th>Per-Vessel</th>
<th>Per-Patient</th>
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<td></td>
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<td></td>
<td></td>
<td>Sensitivity, PPV</td>
<td>Specificity, NPV</td>
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<td>DISCOVER-FLOW (29)</td>
<td>NL</td>
<td>103</td>
<td>Diagnostic performance trial evaluating first version of FFR&lt;sub&gt;CT&lt;/sub&gt; (version 1.0)</td>
<td>88%, 74%</td>
<td>82%, 92%</td>
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<tr>
<td>DeFACTO (30)</td>
<td>NCT01233518</td>
<td>252</td>
<td>Diagnostic performance trial evaluating older version of FFR&lt;sub&gt;CT&lt;/sub&gt; (version 1.2)</td>
<td>83%, NR</td>
<td>78%, NR</td>
</tr>
<tr>
<td>NXT (31)</td>
<td>NCT01757678</td>
<td>254</td>
<td>Diagnostic performance trial evaluating latest generation version of FFR&lt;sub&gt;CT&lt;/sub&gt; (version 1.4)</td>
<td>84%, 61%</td>
<td>86%, 95%</td>
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<td>RIPCORD-FFRCT (35)</td>
<td>NL</td>
<td>200</td>
<td>Evaluation of the diagnostic impact of FFR&lt;sub&gt;CT&lt;/sub&gt; to guide medical versus invasive therapies</td>
<td>36% change in management based on FFR&lt;sub&gt;CT&lt;/sub&gt;</td>
<td>23% increase in DMT alone</td>
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<tr>
<td>PLATFORM (41)</td>
<td>NCT01943903</td>
<td>580</td>
<td>Sequential longitudinal cohort study demonstrating 61% reduction in CATH normalcy for FFR&lt;sub&gt;CT&lt;/sub&gt;-guided vs. coronary CTA-guided care</td>
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CABG — coronary artery bypass graft; DeFACTO — Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography; DISCOVER-FLOW — Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve; FFR<sub>CT</sub> — coronary computed tomography angiography-derived fractional flow reserve; NCT — National Clinical Trial; NL — not listed; NPV — negative predictive value; NR — not reported; NXT — Analysis of Coronary Blood Flow Using CT Angiography; Next Steps; DMT — optimal medical therapy; PCI — percutaneous coronary intervention; PLATFORM — Prospective Longitudinal Trial of FFR<sub>CT</sub>: Outcome and Resource Impacts; OMT — Optimized Medical Therapies; PET — positron emission tomography; PPV — positive predictive value.

### TABLE 3 Prospective Multicenter Trials or Registries of FFR<sub>CT</sub>

<table>
<thead>
<tr>
<th>Study Name</th>
<th>NCT</th>
<th>n</th>
<th>Study Findings/Objectives</th>
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<tr>
<td>Trial Ongoing</td>
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<tr>
<td>CREDENCE</td>
<td>NCT02173275</td>
<td>618</td>
<td>Direct head-to-head comparison of coronary CTA plus FFR&lt;sub&gt;CT&lt;/sub&gt; versus myocardial perfusion imaging by SPECT or PET</td>
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<td>PERFECTION</td>
<td>NYL</td>
<td>NYL</td>
<td>Comparison of FFR&lt;sub&gt;CT&lt;/sub&gt; versus single-energy CT rest/stress perfusion imaging</td>
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<td>DECIDE-Gold</td>
<td>NCT02178904</td>
<td>156</td>
<td>Comparison of FFR&lt;sub&gt;CT&lt;/sub&gt; versus dual-energy CT rest/stress perfusion imaging</td>
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<td>CONSERVE</td>
<td>NCT01810198</td>
<td>1500</td>
<td>Evaluation of FFR&lt;sub&gt;CT&lt;/sub&gt; as a &quot;gatekeeper&quot; to invasive coronary angiography</td>
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<td>ADVANCE</td>
<td>NCT02499679</td>
<td>ND</td>
<td>Prospective longitudinal registry to evaluate prognostic implications of FFR&lt;sub&gt;CT&lt;/sub&gt;</td>
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<tr>
<td>Being discussed</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FAME-FFRCT</td>
<td>NYL</td>
<td>ND</td>
<td>Randomized controlled trial evaluating FFR&lt;sub&gt;CT&lt;/sub&gt;-guided strategies versus standard of care</td>
</tr>
</tbody>
</table>

ADVANCE = Assessing Diagnostic Value of Non-invasive FFR<sub>CT</sub> in Coronary Care; CONSERVE = Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization; CREDENCE = Computed Tomographic Evaluation of Atherosclerotic Diseases of Myocardial Ischemia; CTA = computed tomography angiography; DECIDE-Gold = Dual Energy CT for Ischemia Determination Compared to "Gold Standard" Non-Invasive and Invasive Techniques; NYL = not yet listed; other abbreviations as in Tables 1 and 2.
analysis algorithms to robustly extract anatomic models accurately from coronary CTA data. These methods can also be used to refine the ability of FFR\textsubscript{CT} to more precisely localize ischemia-causing coronary lesions by identifying image-based relationships that cannot be determined with the use of traditional regression methods. By their nature, these machine-learning methods will continually iterate data-driven predictions and improve FFR\textsubscript{CT} algorithms over time with less need for human input. In addition, machine-learning methods can be used to compute the sensitivity of FFR\textsubscript{CT} computations to geometric uncertainty arising from variations in image quality or physiological variability, which can be used to compute confidence intervals to aid clinical decision making (33).

**SELECT SUBPOPULATIONS AND FFR\textsubscript{CT} DIAGNOSTIC PERFORMANCE.** FFR\textsubscript{CT} was evaluated for patients with intermediate stenosis severity (30% to 70%) in the DeFACTO study, in which a >2-fold increase in sensitivity was observed for FFR\textsubscript{CT} over coronary CTA stenosis alone (82% vs. 37%), with no compromise in specificity (Figure 2C) (34). In the NXT study, improved specificity of FFR\textsubscript{CT} compared with coronary CTA was observed (79% vs. 32%; \(p < 0.0001\)), with no differences in specificity (85% vs. 93%).

The diagnostic accuracy of FFR\textsubscript{CT} and coronary CTA was compared for ischemia evaluation in patients with severely elevated coronary artery calcium scores \(>400\) (Figure 2A). In the NXT trial, per-patient accuracy and specificity were higher for FFR\textsubscript{CT} than for coronary CTA (75% vs. 44% and 69% vs. 23% [both \(p < 0.0001\)], with no sacrifice in sensitivity. These findings were in accordance with those observed in the DeFACTO trial.

To date, no FFR\textsubscript{CT} study has been reported that examines its diagnostic performance in a myriad of patient cohorts, which may display important differences in microvascular resistance and, hence, differing accuracies of FFR\textsubscript{CT}. These cohorts include those with left ventricular hypertrophy, diabetic patients (with increased fibrosis), or patients with prior myocardial infarction or post-revascularization.

**IMAGE ACQUISITION PROTOCOLS, CORONARY CTA IMAGING ARTIFACTS, AND FFR\textsubscript{CT} PERFORMANCE.** Consistent among the DISCOVER-FLOW, DeFACTO, and NXT trials was an observed improvement in overall diagnostic accuracy that stemmed from a significant reduction in “false-positive” coronary CTA studies, wherein a stenosis was considered high-grade, but lesion-specific ischemia was not present. However, there were also numerous findings related to image acquisition protocols, image quality, and imaging artifacts. Although no special imaging protocols are required for FFR\textsubscript{CT}, adherence to Society of Cardiovascular Computed Tomography guidelines is recommended to maintain high image quality for accurate results. These protocols include the recommended use of pre-coronary CTA nitrates and beta-blockers for maximal visualization of the coronary artery lumen and minimization of motion artifact.

Noncompliance with the Society of Cardiovascular Computed Tomography recommendations regarding coronary CTA imaging protocols is associated with impaired diagnostic performance of FFR\textsubscript{CT}. In the DeFACTO trial, administration of a beta-blocker and nitroglycerin increased FFR\textsubscript{CT} specificity (66.0% vs. 51.0% [\(p = 0.03\)] and 75.0% vs. 54.0% [\(p = 0.013\)], with a lower systematic bias observed after beta-blocker administration (\(-0.084\) vs. \(-0.048\); \(p = 0.008\)). The per-vessel specificity improved from 54% for patients who received sublingual nitrates \(>30\) min before the acquisition of coronary CTA data to 75% for patients administered sublingual nitrates \(\leq30\) min before the coronary CTA acquisition.

In the DeFACTO and NXT clinical trials, 11% and 13% of studies, respectively, were rejected because of low image quality. Low image quality can occur from common coronary CTA artifacts, including misregistration, coronary motion, or poor opacification of the coronary arteries. In the DeFACTO study, coronary CTA misalignment artifacts resulted in impaired sensitivity of FFR\textsubscript{CT} compared with images without misalignment artifacts (43.0% vs. 86.0%; \(p = 0.001\)), with resultant reductions in overall accuracy (56.0% vs. 71.0%; \(p = 0.03\)). In both the DeFACTO and NXT studies, FFR\textsubscript{CT} accuracy was unaffected by motion or increasing coronary calcium score.

To date, FFR\textsubscript{CT} studies have evaluated its diagnostic power for ischemia by using an invasive FFR standard compared with coronary CTA alone or other coronary CTA-based approaches (e.g., transluminal attenuation gradient or plaque characterization), without comparative evaluation versus stress imaging tests. Three ongoing clinical trials are testing FFR\textsubscript{CT} against other methods for MPI. The CREDENCE (Computed Tomographic Evaluation of Atherosclerotic DeTermiNants of Myocardial IsChEmia) trial is a 20-site study of 618 patients undergoing coronary CTA plus FFR\textsubscript{CT}, MPI SPECT, positron emission tomography or cardiac magnetic resonance, and ICA with FFR (NCT02173275). In the first 309 patients, coronary CTA and MPI scores will be developed that account for the totality of information imparted by coronary CTA and stress testing. These will include: severity, location, extent, and distribution of
coronary stenoses; atherosclerotic plaque volume and characteristics; and FFRCT. For stress imaging testing, these data will include not only the presence of perfusion defects but also their location, extent, severity, and reversibility; also included were ancillary imaging (e.g., transient ischemic dilation), exercise treadmill, and electrocardiographic findings. The scores will be subsequently validated and compared with each other in the next 309 patients. These data should definitively determine which noninvasive diagnostic tests are optimal for diagnosis of lesion-specific ischemia with a robust derivation/validation design. Two additional multicenter trials (PERFECTION and DECIDE-Gold [Dual Energy CT

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for Ischemia Determination Compared to “Gold Standard” Non-Invasive and Invasive Techniques [NCT02178904]) will compare the diagnostic performance of FFR<sub>CT</sub> against single-energy and dual-energy CT perfusion stress testing, respectively, using FFR as a reference standard.

**DIAGNOSTIC AND THERAPEUTIC IMPACT**

An emerging body of evidence suggests that the use of FFR<sub>CT</sub> may affect patient-specific diagnostic approaches as well as therapeutic options. In the RIPCORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain?) study, Curzen et al. (35) evaluated 200 consecutive patients from the NXT trial to determine whether the addition of noninvasive FFR<sub>CT</sub> to coronary CTA in patients with stable chest pain would lead to: 1) changes in the interpretation of lesion-specific “significance”; or 2) changes in the management plan (36). In this study, 3 cardiologists reviewed the coronary CTA images and their site-recorded interpretations, and by consensus decided on a management plan consisting of OMT alone, PCI plus OMT, coronary artery bypass graft (CABG) plus OMT, or deferred decision until after invasive FFR was performed. The interventionalists were then provided the FFR<sub>CT</sub> data and reported whether their management plan would remain the same or change. Notably, 77% (65 of 84) and 46% (38 of 83) of lesions with 51% to 70% and 71% to 90% stenosis, respectively, were found not to cause ischemia according to FFR<sub>CT</sub>. These findings were associated with an overall change in management in 36% of patients (n = 72), with a 23% increase in planned use of OMT alone, a 5% decrease in planned PCI, and a 0.5% increase in planned CABG. Among patients assigned to PCI, 18% (16 of 87) saw a change in target vessels based on the FFR<sub>CT</sub> result.

**PATIENT AND SOCIETAL OUTCOMES**

To evaluate the cost efficiency (or minimization of health care costs with equivalent or improved clinical outcomes) of FFR<sub>CT</sub>-based strategies, Hlatky et al. (37) constructed a decision analysis comparing 5 clinical
strategies: 1) ICA with stenosis-based PCI; 2) ICA with FFR-guided PCI; 3) coronary CTA followed by ICA and stenosis-based PCI; 4) coronary CTA followed by ICA and FFR-guided PCI; and 5) coronary CTA–FFR\textsubscript{CT} followed by FFR\textsubscript{CT}-guided PCI (37). The projected initial management costs were highest for ICA with stenosis-based PCI and lowest for the coronary CTA–FFR\textsubscript{CT} followed by FFR\textsubscript{CT}-guided PCI ($10,702 vs. $7,674, respectively), an economic benefit associated with a 12% reduction in adverse cardiovascular events at 1 year.

Such findings informed the design of the multicenter, pragmatic, comparative effectiveness PLATFORM (Prospective Longitudinal\textsuperscript{A}l Trial of FFR\textsubscript{CT}: Outcome and Resource \textsuperscript{I}mpacts) trial, a 584-patient, prospective, controlled utility trial evaluating patients with an intermediate likelihood of CAD (updated Diamond-Forrester risk scores 20% to 80%) who are being referred for noninvasive evaluation (first cohort) or ICA (second cohort) (NCT01943903) (36). Longitudinally, sites evaluated patients by using standard of care approaches (first phase) and then an approach based on coronary CTA–FFR\textsubscript{CT} (second phase). The primary endpoint of PLATFORM was the rates of ICA without anatomically “obstructive” CAD, with important secondary endpoints related to costs, resource utilization, quality of life, and radiation exposure. Results are anticipated shortly.

Each of the aforementioned trials evaluates radiation exposure as a secondary endpoint, given concerns regarding the safety of the different diagnostic testing approaches. This principle of safety is well described and an important goal to any diagnostic test but is largely irrelevant to the discussion of FFR\textsubscript{CT}. FFR\textsubscript{CT} requires no additional imaging and hence no additional radiation or intervention beyond what is already acquired through coronary CTA.

**FUTURE LARGE-SCALE FFR\textsubscript{CT} CLINICAL STUDIES**

Given the recent introduction of FFR\textsubscript{CT}, its long-term prognostic utility and its incremental value for risk stratification beyond coronary CTA findings are unknown. ADVANCE (Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care) is a multicenter registry that will evaluate the clinical and economic impacts of FFR\textsubscript{CT} as well as its downstream impact and net reclassification of subjects with abnormal FFR\textsubscript{CT} for adverse clinical outcomes (NCT02499679). Furthermore, a FAME-type randomized controlled trial is being discussed, which will evaluate the efficacy of an FFR\textsubscript{CT}-guided strategy to improve clinical outcomes beyond a stenosis-guided strategy in patients referred for invasive or noninvasive ischemia testing.

**CONTEXTUALIZATION OF FFR\textsubscript{CT} IN CAD IMAGING**

In recent years, there has been discussion regarding the strengths and limitations of diagnostic testing for CAD. Prior large-scale registry data for coronary CTA and stress testing have focused largely on the diagnostic and prognostic utility of imaging findings, with relatively little intertest comparisons. Indeed, only in the last several months have we witnessed the presentation of the first 2 large-scale, randomized controlled trials (PROMISE [Prospective Multicenter Imaging Study for Evaluation of Chest Pain] and SCOT-Heart [Scottish Computed Tomography of the Heart]) that directly compared functional versus anatomic testing strategies for downstream clinical outcomes. Both of these studies shared generally similar findings (38,39). With no significant differences noted in “hard” adverse clinical events between coronary CTA and stress testing, coronary CTA was associated with reduced ICA normalcy rates (fewer “false-positive” studies), greater diagnostic certainty, and increased use of primary prevention medications. Coronary CTA was also associated with an increase in coronary revascularization rates (particularly of surgical CABG), with a trend toward reduced death and myocardial infarction at 1 year. These data lend support to the clinical use of coronary CTA for evaluation of patients with suspected CAD. The coupling of FFR\textsubscript{CT} to coronary CTA now offers an additional pathway for diagnosis of CAD, thus expanding the anatomic capabilities offered by coronary CTA to include physiological information that allows for direct interrogation of the functional significance of any or all coronary artery lesions.

In the context of the recent approval of FFR\textsubscript{CT} by the U.S. Food and Drug Administration for routine clinical use for patients without known CAD, it is germane to consider the questions necessary to resolve when faced with a symptomatic patient with suspected CAD. The coupling of FFR\textsubscript{CT} to coronary CTA now offers an additional pathway for diagnosis of CAD, thus expanding the anatomic capabilities offered by coronary CTA to include physiological information that allows for direct interrogation of the functional significance of any or all coronary artery lesions.

In the context of the recent approval of FFR\textsubscript{CT} by the U.S. Food and Drug Administration for routine clinical use for patients without known CAD, it is germane to consider the questions necessary to resolve when faced with a symptomatic patient with suspected CAD and to also evaluate FFR\textsubscript{CT} in this context. Given the adverse prognosis that exists for even mild forms of coronary atherosclerosis, a sequential approach to CAD diagnostic evaluation sensibly begins with determination of whether any CAD exists (high sensitivity), whether any revascularizable coronary stenoses exist without overestimation of severity (high specificity), and whether visualized coronary stenoses impair coronary flow. The available clinical evidence supports FFR\textsubscript{CT} as fulfilling these criteria.
However, in addition to the susceptibility of FFRCT to impaired image quality, several additional limitations of this method should be considered. At present, little is known regarding the impact of FFRCT as a function of angina typicality. As such, whether typical angina can be discounted based on an FFRCT <0.80 (or vice versa) is unknown. The field should be careful to examine this noninvasive test in the context of clinical information. These include not only the symptom typicality of presenting patients but also stress imaging results. Only future studies examining the relationship of FFRCT to these data will reveal its precise role in clinical practice.

In addition to these diagnostic features, FFRCT has been shown capable of identifying ischemia which stems from coronary lesions that do not meet conventional definitions of “angiographically severe” (i.e., intermediate stenoses, diffuse atherosclerosis) (Figure 2B) and small vessels demonstrating inadequate vasodilation. Finally, FFRCT has the potential to predict the therapeutic benefit of coronary revascularization by “virtual stenting” or even the relative efficacy of revascularization strategy (Figure 2E). As an example of the latter, multivessel virtual stenting may be compared with “virtual bypass surgery” by using FFRCT to determine which method maximally reduces ischemia (Figure 2D). Whether these methods can more effectively reduce ischemia or improve clinical outcomes remains unknown but is currently being evaluated.

CONCLUSIONS

FFRCT is a novel method that uses CFD for determining the hemodynamic significance of coronary artery lesions by using patient-specific data extracted from typically acquired coronary CTA. Prior multicenter trials have shown a generally high diagnostic performance of FFRCT. Ongoing trials comparing the diagnostic performance of FFRCT versus stress imaging methods—as well as the clinical support and cost-effectiveness of FFRCT-based strategies compared with the usual care strategies—will inform its most appropriate use in clinical practice.

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