Coronary computed tomographic angiography (CCTA) has developed into an accurate and effective tool for the detection of anatomical coronary artery disease (CAD). The diagnostic performance of CCTA has been validated in numerous single- and multicenter trials. Although it is an effective tool for stenosis evaluation and plaque detection, CCTA has been shown to provide limited information regarding the hemodynamic significance of a stenosis, with ischemia almost equally likely to be present or absent when an obstructive lesion is identified on CCTA. Because of this, many patients with stable angina and obstructive disease detected on CCTA undergo additional ischemia testing to discern the hemodynamic significance of a stenosis, which results in delayed diagnosis and increased costs. In addition, it has also been shown that traditional noninvasive ischemia testing performs poorly for the localization of ischemic lesions.

The importance of lesion-specific ischemia for the guidance of coronary revascularization has never been clearer. The prospective multicenter Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial revealed that fractional flow reserve (FFR) guidance in lesions with FFR ≤ 0.8 was associated with a 28% lower rate of major adverse clinical events compared to the previous gold standard non-FFR guided angiography procedure. Building upon these results, FAME II documented a significant reduction in downstream major adverse clinical events for those who underwent coronary revascularization for FFR-positive lesions versus optimal medical therapy. The totality of data published thus far support ischemia, and FFR-guided revascularization in particular, over angiography alone. These emerging data have spurred growing interest in FFRct as a potential all-in-one noninvasive tool for the detection of both anatomical coronary artery disease and ischemia.

It has recently been shown that FFR can be derived from a resting CCTA through the integration of computational fluid dynamics. This derived FFR, or FFRct, builds upon the anatomic model provided by an accurate CCTA and integrates advances in computational fluid dynamics and image-based modelling that allow for the calculation of coronary flow and pressure fields at both rest and hyperemia. The derivation and calculation of FFRct can be performed without any additional imaging or radiation; the modification of CCTA acquisition protocols, or the administration of medications such as adenosine or regadenoson to achieve hyperemia.

The calculation of FFRct from CCTA depends on several factors. These include the construction of an accurate anatomic model of the epicardial coronary arteries; a mathematical model of coronary physiology to derive boundary conditions representing cardiac output, aortic pressure, and microcirculatory resistance; and the numerical solution of the laws of physics governing.

It has recently been shown that FFR can be derived from a resting CCTA through the integration of computational fluid dynamics.
erning fluid dynamics. The CCTA examinations need to be acquired with the administration of nitroglycerin, as is done with invasively measured FFR, to ensure optimization of the diagnostic accuracy of FFRct. The complexities of calculating an FFR from a resting CCTA go beyond the scope of this review but have been described in detail elsewhere.

In short, by integrating computational fluid dynamics and solving the Navier-Stokes equations for incompressible fluids and integrating a number of other known relationships such as those between myocardial mass and total coronary blood flow at rest, the adaptation of luminal caliber in response to flow, pressure, and velocity across the coronary tree can be calculated (Table 1).

**EARLY EXPERIENCES WITH FFRct**

The prospective, multicenter, international Diagnosis of Ischemia-Causing Stenoses Obtained Via Non-Invasive Fractional Flow Reserve (DISCOVER-FLOW) trial was the first large-scale validation of FFRct. The trial was powered to evaluate the performance of FFRct on a per-vessel basis. FFRct displayed significant improvement in all measures of diagnostic performance for the detection of lesion-specific ischemia as defined as an FFR < 0.8 compared to CCTA-defined stenosis alone (Table 1). In fact, FFRct yielded a 25% improvement in overall diagnostic accuracy. Furthermore, FFRct provided significantly improved discriminatory capabilities as compared to CCTA (area under the receiver-operating characteristic curve, 0.9 vs 0.75; P < .001) and good correlation with FFR (r = 0.72).

In an important subanalysis of the DISCOVER-FLOW trial, Min et al found that only 25.5% of patients who were categorized as having intermediate stenosis of 50% to 69%, as defined by CCTA, exhibited ischemia. These intermediate lesions represent a difficult subset of disease for CT, owing to limitations in spatial resolution and anatomical confidence and the intermediate likelihood of a positive FFR with stenosis in this range. Interestingly, within this category of intermediate stenosis (50%–69%), FFRct demonstrated a diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of 83%, 66.7%, 88.6%, 66.7%, and 88.6%, respectively.

Recently, the large-scale, multicenter, international Determination of Fractional Flow Reserve By Anatomic Computed Tomographic Angiography (DeFACTO) study was published. The primary aim of DeFACTO was to evaluate the accuracy of FFRct compared to the standard reference of FFR by invasive coronary angiography (ICA) in the diagnosis of hemodynamically significant CAD on a per-patient basis. The DeFACTO trial included patients with suspected native CAD who were then referred for clinically indicated nonemergent ICA within 60 days of CCTA. Diagnostic accuracy for FFRct plus CT was 73% (95% confidence interval, 67%–78%), whereas accuracy for CT alone was 64%. The diagnostic performance of FFRct was more modest than shown in DISCOVER-FLOW, which at least in part reflects the varied CCTA data acquisitions. In DeFACTO, CCTA protocols could not be mandated with the administration of nitroglycerin and β-blockade at the discretion of the site. As a result, 14% of patients included in the analysis did not receive nitroglycerin for their CCTA examination, which is an essential element for FFRct derivation. Although the study did not meet the prespecified primary endpoint of diagnostic accuracy of > 70% of the lower bound of the one-sided 95% confidence interval, it did represent the first large-scale validation of FFRct and confirmed that when compared to CCTA alone, FFRct demonstrates improved diagnostic accuracy in the diagnosis of ischemia-causing lesions. At the per-patient level, FFRct together with CT (compared to CT alone) improves diagnostic accuracy as seen by an improvement in sensitivity and specificity and was found to demonstrate higher discriminatory power than CCTA alone in those vessels directly interrogated by FFR. Importantly, in the clinically relevant and challenging intermediate stenoses on CCTA (30%–70%), all measures of diagnostic performance improved with the use of FFRct over CCTA alone.
DISCUSSION

With the recent introduction of FFRct through the integration of computational fluid dynamics, the potential for a single noninvasive test to provide both anatomical and hemodynamic data is being realized. Given the growing evidence that FFR-guided revascularization improves outcomes as compared to both angiography alone and optimal medical therapy, the need for a noninvasive tool for the detection of lesion-specific ischemia has never been greater.

The potential and early results of FFRct suggest that it may in fact be such a tool for the complete evaluation of CAD identified on CCTA, allowing for improved decision making and providing valuable guidance regarding the need for revascularization.

As with any new technique, continued technological improvements are needed to further improve on the accuracy of FFRct, which will require further validation. In addition, further studies are needed to determine the potential cost effectiveness of FFRct in the context of other diagnostic algorithms for the evaluation of CAD.

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**TABLE 1. SUMMARY OF FINDINGS FROM THE DISCOVER-FLOW TRIAL**

<table>
<thead>
<tr>
<th></th>
<th>Per Vessel (n = 159)</th>
<th>Per Patient (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FFRct</td>
<td>CCTA Stenosis</td>
</tr>
<tr>
<td>≤ 0.8</td>
<td>84.3 (77.7–90)</td>
<td>58.5 (50.4–66.2)</td>
</tr>
<tr>
<td>≥ 0.5</td>
<td></td>
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<tr>
<td>Accuracy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>87.9 (76.7–95)</td>
<td>91.4 (81–97.1)</td>
</tr>
<tr>
<td>Specificity</td>
<td>82.2 (73.3–89.1)</td>
<td>39.6 (30–49.8)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>73.9 (61.9–83.7)</td>
<td>46.5 (37.1–56.1)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>92.2 (84.6–96.8)</td>
<td>88.9 (75.9–96.3)</td>
</tr>
</tbody>
</table>

Values are presented as median (range).

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