Diagnostic Accuracy of Fractional Flow Reserve from Anatomic Computed TOMographic Angiography: The DeFACTO Study

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Disclosures

- **Research Support:** NHLBI (R01HL115150-01; U01 HL105907-02 [Contract]); QNRF (NPRP 09-370-3-089); GE Healthcare (significant); Philips Healthcare (modest); Vital Images (modest)

- **Equity Interest:** TC3, MDDX, Cedars-Sinai Medical Center

- **Medical Advisory Board:** GE Healthcare, Arineta

- **Study Funding:** This study was funded by HeartFlow, Inc. HeartFlow, Inc. worked with the steering committee for study design and provided blinded FFR\textsubscript{CT} analyses for the study. HeartFlow, Inc. did not have involvement in the statistical data analysis, manuscript preparation, and review or authorization for submission.

- No study investigator had any financial interest related to the study sponsor
Background

- Coronary CT angiography is a non-invasive test that demonstrates high accuracy to invasive angiography but cannot determine the hemodynamic significance of a coronary lesion\(^1\)
- Fractional flow reserve (FFR) is the gold standard for diagnosis of lesion-specific ischemia\(^2\), and its use to guide coronary revascularization improves event-free survival and lowers healthcare costs\(^3,4\)
- Computational fluid dynamics is a novel technology that enables calculation of FFR from CT (FFR\(_{\text{CT}}\)), and may represent a non-invasive method for determination of lesion-specific ischemia\(^5\)
- To date, the diagnostic performance of FFR\(_{\text{CT}}\) has not been tested in a large-scale prospective multicenter study

Objective

- The **OVERALL OBJECTIVE** of the DeFACTO study was to determine the diagnostic performance of FFR\textsubscript{CT} for the detection and exclusion of hemodynamically significant CAD in a prospective multicenter international study.
Study Endpoints

**Primary**: Per-patient diagnostic accuracy of $\text{FFR}_{\text{CT}}$ plus CT to determine the presence or absence of at least one hemodynamically significant coronary stenosis, as compared to an invasive FFR reference standard*
  
  - Study hypotheses tested at one-sided 0.05 Type I error rate, with null hypothesis to be rejected if lower bound of 95% CI $> 0.70$
  
  - 0.70 threshold chosen b/c this represented the mid-point of test accuracy for stress imaging testing\(^1\), 3-fold higher accuracy than recent large-scale reports of “real world” testing\(^2\), and higher than the point of concordance of stress imaging testing with invasive FFR
  
  - Assuming 0.35 rate of CAD, 238 patients (assuming 11% rate of nonevaluable CTs\(^3\)) needed to achieve 95% statistical power

**Secondary**:
  
  - Additional diagnostic performance characteristics (e.g., sensitivity / specificity)
  
  - Diagnostic performance for lesions of intermediate stenosis severity
  
  - Per-vessel correlation of $\text{FFR}_{\text{CT}}$ value to FFR measured value

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Inclusion / Exclusion Criteria

Inclusion Criteria:
• Age > 18 years
• Providing written informed consent
• Scheduled to undergo clinically-indicated non-emergent ICA
• >64-row CT within 60 days prior to ICA
• No cardiac interventional therapy between CT and ICA

Exclusion Criteria (Cardiac-specific):
• Prior coronary artery bypass surgery
• Prior PCI with suspected in-stent restenosis
• Suspicion of acute coronary syndrome
• Prior myocardial infarction within 40 days of ICA
Study Procedures

All studies (CT, QCA, FFR, FFR<sub>CT</sub>) interpreted in blinded fashion by 4 independent core labs.

- **CT**: Image acquisition / interpretation in accordance with societal guidelines on >64-row CT
- **QCA**: % diameter stenosis determined in standard fashion using commercially available software
- **FFR**: Standard fashion by commercially available equipment after administration of nitroglycerin and intravenous adenosine at rate of 140 mcg/kg/min through a central vein
  - FFR = (mean distal coronary pressure) / (mean aortic pressure) during hyperemia
- **Definitions**: Anatomic obstructive CAD defined as >50% diameter stenosis for CT and QCA; Lesion-specific ischemia defined as <0.80 for both FFR and FFR<sub>CT</sub><sup>1</sup>
  - FFR: Per protocol, subtotal (99%) or total (100%) occlusions assigned value of 0.50
  - FFR<sub>CT</sub>: Per protocol, subtotal / total occlusions assigned value of 0.50, and vessels with <30% maximal stenosis assigned value of 0.90

Computation of $\text{FFR}_{\text{CT}}$

$\text{FFR}_{\text{CT}}$ performed by HeartFlow scientists in blinded fashion.

1. **Image-based Modeling** – Comprehensive segmentation of coronary arteries and aorta to determine patient-specific coronary geometry
2. **Heart-Vessel Interactions** – At aortic and coronary outlets, enforced relationships b/w pressure and flow (e.g., aortic impedance)
3. **Segmentation of Left Ventricular Myocardial Mass** – Relate time-varying coronary resistance (i.e., pulsatile) to intramyocardial pressure
4. **Calculation of microcirculatory resistance** – Use of allometric scaling laws to relate patient-specific “form – function relationships (e.g. mass / size of object related to physiology)
5. **Patient-specific Physiologic Conditions** - Fluid viscosity (hematocrit), blood pressure
6. **Modeling of Hyperemia** – Standard prediction model to “virtually” force complete smooth muscle cell relaxation (arteriolar vasodilatation)
7. **Calculation of Fluid Dynamic Phenomena** – Application of universality of fluid dynamics, based upon Conservation of mass and momentum balance (e.g., airflow over jet; water flow in a river, etc.)
Computation of $\text{FFR}_{\text{CT}}$

**Patient-Specific Hyperemic Flow and Pressure:**
1. Numerical method using governing equations
2. Obtain solution for velocity and pressure throughout coronary vascular bed
3. Simultaneous solution of millions of non-linear partial differential equations
4. Repeat process thousands of time intervals within cardiac cycle

$\text{FFR}_{\text{CT}},$ does not require:
1. Modification to imaging protocols (i.e., prospective /retrospective ECG gating; fast pitch helical; FBP or IR)
2. Administration of adenosine
3. Additional image acquisition (i.e., no additional radiation)
4. Single-point assessment (i.e., $\text{FFR}_{\text{CT}}$ selectable on any point in coronary vascular bed)

$\text{FFR}_{\text{CT}}$ derived from a typically acquired CT

$\text{FFR}_{\text{CT}} = 0.72$
(can select any point on model)
Enrollment occurred between October 2010 – October 2011 at 17 centers in 5 countries [Belgium (1), Canada (1), Latvia (1), South Korea (2), United States (12)]

33 patients excluded due to non-evaluable CTs as determined by the CT Core Laboratory (n=31), and inability to integrate CT / FFR wire placement as determined by the Integration Core Core Laboratory (n=20)
### Study Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD or N (%)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>62.9 ± 8.7</td>
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<tr>
<td><strong>Prior MI</strong></td>
<td>15 (6.0)</td>
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<tr>
<td><strong>Prior PCI</strong></td>
<td>16 (6.3)</td>
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<tr>
<td><strong>Symptoms</strong></td>
<td></td>
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<tr>
<td>Stable</td>
<td>201 (79.7)</td>
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<tr>
<td>Worsening</td>
<td>43 (17.2)</td>
</tr>
<tr>
<td>Other (e.g., silent ischemia)</td>
<td>8 (3.1)</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>178 (70.6)</td>
</tr>
<tr>
<td><strong>Race / Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>169 (67.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>78 (31.0)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>53 (21.2)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>179 (71.2)</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td>201 (79.8)</td>
</tr>
<tr>
<td><strong>FH of CAD</strong></td>
<td>50 (19.9)</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
<td>44 (17.5)</td>
</tr>
</tbody>
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**Invasive Test Characteristics**

- **Stenosis >50%**              | 190 (46.5)         |
- **Average stenosis (%)**      | 46.8 ± 15.7        |
- **FFR <0.80**                 | 151 (37.1)         |

**Non-invasive Test**

- **Stenosis >50%**              | 216 (53.2)         |
- **>90% Stenosis**             | 79 (19.5)          |
- **Coronary Calcium (Agatston units)** | 381.5 ± 401.0 |

*N=408 vessels from 252 patients; ^N=406 vessels from 252 patients*
Per-Patient Diagnostic Performance

<table>
<thead>
<tr>
<th></th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FFRct</strong></td>
<td>73 95% CI</td>
<td>90 95% CI</td>
<td>84 95% CI</td>
<td>67 95% CI</td>
<td>84 95% CI</td>
</tr>
<tr>
<td><strong>CT</strong></td>
<td>64 95% CI</td>
<td>84 95% CI</td>
<td>77 95% CI</td>
<td>61 95% CI</td>
<td>72 95% CI</td>
</tr>
</tbody>
</table>

95% CI:
- FFRct: 67-78
- CT: 58-70
- Sensitivity: 84-95
- Specificity: 46-83
- PPV: 60-74
- NPV: 74-90
• Greater discriminatory power for FFR_{CT} compared to CT stenosis on per-patient (Δ = 0.13) and per-vessel basis (Δ = 0.06)
Per-Patient Diagnostic Performance for Intermediate Stenoses by CT (30-70%)
Case Examples

A. CT stenosis of the proximal LAD

B. FFR$_{CT}$ of 0.62, indicating vessel ischemia

C. ICA stenosis of LAD, and FFR of 0.65, indicating vessel ischemia

D. CT stenosis of the mid RCA

E. FFR$_{CT}$ of 0.87, indicating no vessel ischemia

F. ICA stenosis of mid RCA, and FFR of 0.88, indicating no vessel ischemia
Limitations

• Enrollment criteria disqualified individuals with prior CABG or suspected in-stent restenosis after PCI

• Not every vessel was interrogated in study participants
  – Only vessels deemed clinically-indicated for evaluation

• Unknown whether revascularization of ischemic lesions by FFR\textsubscript{CT} reduces ischemia
  – FFR\textsubscript{CT} algorithms enable calculation after “virtual” revascularization\textsuperscript{1}

• Study did not exclusively enroll patients considered anatomically indeterminate by CT (30-70%)\textsuperscript{2,3}
  – FFR\textsubscript{CT} compared favorably to CT stenosis in subset

Conclusions

• In stable patients with suspected CAD, $\text{FFR}_{\text{CT}}$ demonstrated **improved diagnostic accuracy** over CT stenosis for diagnosis of both patients and vessels who manifest ischemia
  – Did not satisfy its pre-specified primary endpoint of Dx accuracy $>70\%$ of lower bound of the one-sided 95% CI
  – High sensitivity and NPV implies low rate of FN
  – Considerable increase in discriminatory power

• In patients with **stenoses of intermediate severity** by CT—which are the most clinically ambiguous for ischemia determination—$\text{FFR}_{\text{CT}}$ demonstrated higher diagnostic performance compared to CT alone

• Proof of feasibility of $\text{FFR}_{\text{CT}}$, and represent **first large-scale prospective demonstration of use of computational models** to accurately calculate FFR from typically acquired CT images
Thank you.