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

James K. Min1; Jonathon Leipsic2; Michael J. Pencina3; Daniel S. Berman1; Bon-Kwon Koo4; Carlos van Mieghem5; Andrejs Erglis6; Fay Y. Lin7; Allison M. Dunning7; Patricia Apruzzese3; Matthew J. Budoff8; Jason H. Cole9; Farouc A. Jaffer10; Martin B. Leon11; Jennifer Malpeso8; G.B. John Mancini12; Seung-Jung Park13, Robert S. Schwartz14; Leslee J. Shaw15, Laura Mauri16 on behalf of the DeFACTO Investigators

1Cedars-Sinai Heart Institute, Los Angeles, CA; 2St. Paul's Hospital, Vancouver, British Columbia; 3Harvard Clinical Research Institute, Boston, MA; 4Seoul National University Hospital, Seoul, Korea; 5Cardiovascular Center, Aalst, Belgium; 6Pauls Stradins Clinical University Hospital, Riga, Latvia; 7Cornell Medical College, New York, NY; 8Harbor UCLA, Los Angeles, CA; 9Cardiology Associates, Mobile, AL; 10Massachusetts General Hospital, Harvard Medical School, Boston, MA; 11Columbia University Medical Center, New York, NY; 12Vancouver General Hospital, Vancouver, British Columbia; 13Asan Medical Center, Seoul, Korea; 14Minneapolis Heart Institute, Minneapolis, MN; 15Emory University School of Medicine, Atlanta, GA; 16Brigham and Women's Hospital, Boston, MA
Disclosures

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Background

• **Coronary CT Angiography:**
  - High diagnostic accuracy for anatomic stenosis
  - Cannot determine physiologic significance of lesions

• **Fractional Flow Reserve (FFR):**
  - Gold standard for diagnosis of lesion-specific ischemia
  - Use improves event-free survival and cost effectiveness

• **FFR Computed from CT (FFR\textsubscript{CT}):**
  - Novel non-invasive method for determining lesion-specific ischemia

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Overall Objective

• To determine the diagnostic performance of $\text{FFR}_{\text{CT}}$ for detection and exclusion of hemodynamically significant CAD
Study Endpoints

• **Primary Endpoint**: Per-patient diagnostic accuracy of FFR\textsubscript{CT} plus CT to diagnose hemodynamically significant CAD, compared to invasive FFR reference standard
  
  – Null hypothesis rejected if lower bound of 95% CI > 0.70
  
  • 0.70 represents 15% increase in diagnostic accuracy over myocardial perfusion imaging and stress echocardiography, as compared to FFR\textsuperscript{1,2}
  
  – 252 patients: >95% power

• **Secondary Endpoint**:
  
  – Diagnostic performance for intermediate stenoses (30-70%)

\textsuperscript{1}Mellikan N et al. JACC: Cardiovasc Inter 2010, 3: 307-314; \textsuperscript{2}Jung PH et al. Eur Heart J 2008; 29: 2536-43
Study Criteria

Inclusion Criteria:
• Underwent >64-row CT
• Scheduled for ICA within 60 days of CT
• No intervening cardiac event

Exclusion Criteria:
• Prior CABG
• Suspected in-stent restenosis
• Suspected ACS
• Recent MI within 40 days of CT

ICA = Invasive coronary angiography; CABG = coronary artery bypass surgery; ACS = acute coronary syndrome; MI = myocardial infarction
Study Procedures

• **Intention-to-Diagnose Analysis**
  – Independent blinded core laboratories for CT, QCA, FFR and FFR\textsubscript{CT}
  – FFR\textsubscript{CT} for all CTs received from CT Core Laboratory

• **CT:** Stenosis severity range\textsuperscript{1}
  – 0%, 1-29%, 30-49%, 50-69%, 70-89%, \geq90%

• **QCA:** Stenosis severity (%)

• **FFR:** At maximum hyperemia during ICA
  – Definition: (Mean distal coronary pressure) / (Mean aortic pressure)

• **Obstructive CAD:** \geq50%stenosis (CT and QCA)

• **Lesion-Specific Ischemia:** \leq0.80 (FFR and FFR\textsubscript{CT})\textsuperscript{2}

\textsuperscript{1}Raff GL et al. J Cardiovasc Comp Tomogr 2009; 3: 122-36; \textsuperscript{2}Tonino PA et al. N Engl J Med 2009; 360: 213-24; FFR, subtotal / total occlusions assigned value of 0.50; FFR\textsubscript{CT}, subtotal / total occlusions assigned value of 0.50, \(<30\%\) stenosis assigned value of 0.90
Study Procedures: $\text{FFR}_{\text{CT}}$

$\text{FFR}_{\text{CT}}$: Derived from typical CT

- No modification to imaging protocols
- No additional image acquisition
- No additional radiation
- No administration of adenosine
- Selectable at any point of coronary tree

Patient-Specific Coronary Pressure:

- Image-based modeling
- Heart-Vessel Interactions
- Physiologic conditions, incl. Hyperemia
- Fluid dynamics to calculate $\text{FFR}_{\text{CT}}$
1. **Image-Based Modeling** – Segmentation of patient-specific arterial geometry
2. **Heart-Vessel Interactions** – Allometric scaling laws relate caliber to pressure and flow
3. **Microcirculatory resistance** – Mophometry laws relate coronary dimension to resistance
4. **Left Ventricular Mass** – Lumped-parameter model couples pulsatile coronary flow to time-varying myocardial pressure
5. **Physiologic Conditions** – Blood as Newtonian fluid adjusted to patient-specific viscosity
6. **Induction of Hyperemia** – Compute maximal coronary vasodilation
7. **Fluid Dynamics** – Navier-Stokes equations applied for coronary pressure
Patient Enrollment

• Study Period
  – October 2010 – 2011

• Study Sites
  – 17 centers from 5 countries

• Study Enrollment (n=285)
  – n=33 excluded

• Final study population
  – Patients (n=252)
  – Vessels (n=407)
## Patient and Lesion Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 ± 9</td>
</tr>
<tr>
<td>Prior MI</td>
<td>6</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>6</td>
</tr>
<tr>
<td>Male gender</td>
<td>71</td>
</tr>
<tr>
<td>White</td>
<td>67</td>
</tr>
<tr>
<td>Asian</td>
<td>31</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>71</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>80</td>
</tr>
<tr>
<td>Family history</td>
<td>20</td>
</tr>
<tr>
<td>Current smoker</td>
<td>18</td>
</tr>
</tbody>
</table>

- **ICA**
  - Stenosis ≥50% 47%
  - Mean Stenosis 47%

- **FFR**
  - FFR ≤ 0.80 37%

- **CT**
  - Stenosis ≥50% 53%
  - Calcium Score 381
  - Location
    - LAD 55%
    - LCx 22%
    - RCA 23%

Abbreviations: MI = myocardial infarction; PCI = percutaneous intervention; FH = family history; CAD = coronary artery disease; FFR = fractional flow reserve; CACS = coronary artery calcium score; LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery.
Per-Patient Diagnostic Performance

<table>
<thead>
<tr>
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<th>FFR(_{\text{CT}}) &lt;0.80</th>
<th>CT ≥50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>73</td>
<td>64</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>90</td>
<td>84</td>
</tr>
<tr>
<td>Specificity</td>
<td>54</td>
<td>42</td>
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<tr>
<td>PPV</td>
<td>67</td>
<td>61</td>
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<tr>
<td>NPV</td>
<td>84</td>
<td>72</td>
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</table>

95% CI:
- FFR\(_{\text{CT}}\) <0.80: 67-78, 60-74, 74-90
- CT ≥50%: 84-95, 46-83, 34-51

N=252
Discrimination

**Per-Patient**

- FFR\(_{\text{CT}}\) 0.81 (95% CI 0.75, 0.86)
- CT 0.68 (95% CI 0.62, 0.74)

**Greater discriminatory power for FFR\(_{\text{CT}}\) versus CT stenosis**

- Per-patient (\(\Delta 0.13, p<0.001\))
- Per-vessel (\(\Delta 0.06, p<0.001\))

*AUC = Area under the receiver operating characteristics curve*
Case Examples: Obstructive CAD

**Case 1**
- **CT**
- LAD stenosis
- FFR 0.65 = Lesion-specific ischemia

**Case 2**
- **CT**
- RCA stenosis
- FFR 0.86 = No ischemia

**FFR\_CT**
- FFR 0.62 = Lesion-specific ischemia
- FFR\_CT 0.87 = No ischemia
Per-Patient Diagnostic Performance for Intermediate Stenoses by CT (30-70%)

<table>
<thead>
<tr>
<th></th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<tr>
<td>N=83</td>
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<td></td>
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<tr>
<td>FFR_{CT} &lt; 0.80</td>
<td>73</td>
<td>82</td>
<td>66</td>
<td>54</td>
<td>88</td>
</tr>
<tr>
<td>CT ≥ 50%</td>
<td>57</td>
<td>37</td>
<td>66</td>
<td>34</td>
<td>68</td>
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95% CI

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<tr>
<th></th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>N=83</td>
<td>61-80</td>
<td>63-92</td>
<td>53-77</td>
<td>39-68</td>
<td>75-95</td>
</tr>
<tr>
<td>FFR_{CT}</td>
<td>46-67</td>
<td>22-56</td>
<td>53-77</td>
<td>20-53</td>
<td>55-79</td>
</tr>
</tbody>
</table>
Case Example: Intermediate Stenosis

31-49% stenosis
CT Core Lab

50-69% stenosis
QCA Core Lab

FFR 0.74
= Lesion-specific ischemia

FFR_{CT} 0.71
= Lesion-specific ischemia
Limitations

• Did not interrogate every vessel with invasive FFR

• Did not solely enroll patients with intermediate stenosis\(^1,2\)

• Did not test whether FFR\(_{CT}\) -based revascularization reduces ischemia\(^3\)

• Did not enroll prior CABG / In-Stent Restenosis / Recent MI

Conclusions

- FFR\textsubscript{CT} demonstrated improved accuracy over CT for diagnosis of patients and vessels with ischemia
  - FFR\textsubscript{CT} diagnostic accuracy 73\% (95\% CI 67-78\%)
    - Pre-specified primary endpoint >70\% lower bound of 95\% CI
    - Increased discriminatory power

- FFR\textsubscript{CT} superior to CT for intermediate stenoses

- FFR\textsubscript{CT} computed without additional radiation or imaging

- First large-scale demonstration of patient-specific computational models to calculate physiologic pressure and velocity fields from CT images

- Proof of feasibility of FFR\textsubscript{CT} for diagnosis of lesion-specific ischemia
Thank you.