Beyond Stenosis: Ischemia and Plaque Assessments in Coronary CTA

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Controversies in Cardiovascular Disease 2016
DISCLOSURE

Daniel S. Berman, M.D.
declares the following relationships:

Consultant: Molecular-Dynamics
Royalties: Cedars-Sinai Medical Center
Beyond Stenosis: Ischemia and Plaque Assessments in Coronary CTA

- General considerations
- Stenosis
- Ischemia
- Plaque
Decisions of coronary revascularization should not be based upon anatomic stenosis alone

**COURAGE Trial**  
(D/MI/CVA)

- 2,287 individuals with angiographically obstructive CAD and ischemia assigned to PCI or medical tx and followed for 4.6 years

**BARI 2D Trial**  
(D/MI/CVA)

- 2,368 diabetic patients assigned to revascularization or medical tx and followed for 5 years

Source: Boden et al. NEJM 2007; BARI 2D Study Group, NEJM 2009
Primary Outcome

All-cause death, MI, or urgent revascularization

De Bruyne B et al. NEJM 2012
Multiple Features Beyond Stenosis Contribute to High-Risk Plaque

Assessable by OCTA
- Plaque burden
- Lipid core
- Spotty calcification
- Low endothelial shear stress (ESS)
- FFR

Beyond Stenosis: Ischemia and Plaque Assessments in Coronary CTA

- General considerations
- Stenosis
- Ischemia
- Plaque
Risk-stratification in CAD
Stenosis has been given a bad rap
Risk-stratification in CAD
Stenosis has been given a bad rap

- Most MI’s are caused by event in plaque with mild stenosis; but,
  - Mild stenoses: far more numerous
- Occlusive thrombosis: more likely in severely stenosed artery

Arbab-Zadeh, Fuster JACC 2015
Alderman, et al: CASS; JACC 1993
### CASS: Rate of Segment Occlusion by Baseline Stenosis Severity

<table>
<thead>
<tr>
<th>Stenosis at Baseline</th>
<th>Occlusion at Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-49%</td>
<td>2.3%</td>
</tr>
<tr>
<td>50-80%</td>
<td>10.1%</td>
</tr>
<tr>
<td>81-95%</td>
<td>23.6%</td>
</tr>
</tbody>
</table>

Follow-up angio (n=298):
- 42-66 months after randomization
- 3049 non-bypassed segments

Left Main Coronary Stenosis

CTA  CATH

BLUORB
Left Main Coronary Stenosis

- Left main CAD: excluded in COURAGE, BARI 2D, ISCHEMIA
Left Main Coronary Stenosis

- Left main CAD: excluded in COURAGE, BARI 2D, ISCHEMIA
- Frequency: 5-7% of invasive coronary angiograms (Fjedet EHJ2012)
Survival Probability

Survival Time (Years)

23,854 patients w/o known CAD (57±13 years), 2.3 year f/u

Source: CONFIRM Min et al. J Am Coll Cardiol 2011
Consistent findings in all populations studied to date

Source: CONFIRM Min et al. J Am Coll Cardiol 2011
CHD Death and MI in Scot Heart Trial
Post-hoc 50-Day Landmark Analysis

**Implementation Delay**

<table>
<thead>
<tr>
<th></th>
<th>Impact of Alterations in Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCA</td>
<td>Standard Care</td>
</tr>
</tbody>
</table>

Proportion of patients with an event (%)

- CTCA Performed
- Result Reviewed
- Management Changed
- Invasive Angiography Arranged
- Prescription issued

HR 0.50 [0.28-0.90]
P = 0.020

4416 patients with stable CP
85% had exercise testing

Williams..Newby, et al JACC2016
Beyond Stenosis: Ischemia and Plaque Assessments in Coronary CTA

- General considerations
- Stenosis
- Ischemia
- Plaque
Non-Invasive FFR\textsubscript{ct}

- From typically acquired CCTA
- Computational fluid dynamics
  - Stenosis
  - Vessel volume after lesion
  - Myocardial mass distal to lesion
- No additional acquisition, radiation
- No modification to imaging protocols
- No administration of medications

**Case 1**

- **LAD stenosis**
- FFR CT = 0.65
- FFRCT 0.62 = Lesion-specific ischemia

**Case 2**

- **RCA stenosis**
- FFR CT = 0.86
- FFRCT 0.87 = No ischemia
**FFR\textsubscript{CT}: Three (3) Prospective Multicenter Trials**

<table>
<thead>
<tr>
<th></th>
<th>DISCOVER-FLOW</th>
<th>DeFACTO</th>
<th>NXT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point</strong></td>
<td>Per pt. diag accuracy</td>
<td>Per pt. diag accuracy; lower limit 95% CI 0.7</td>
<td>Per pt. AUC</td>
</tr>
<tr>
<td><strong>Study sites/countries</strong></td>
<td>4 / 3</td>
<td>17 / 5</td>
<td>10 / 8</td>
</tr>
<tr>
<td><strong>Site expertise qualification</strong></td>
<td>FFR</td>
<td>CT or FFR</td>
<td>CT plus FFR</td>
</tr>
<tr>
<td><strong>CT training of site</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>FFR training of site</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>CT quality check</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>CT results reading</strong></td>
<td>Core lab</td>
<td>Core lab</td>
<td>Site</td>
</tr>
<tr>
<td><strong>FFR results report</strong></td>
<td>Site</td>
<td>Site</td>
<td>Site with core lab overview</td>
</tr>
<tr>
<td><strong>Vessel size for inclusion</strong></td>
<td>$\geq 2.0$ mm</td>
<td>$\geq 1.5$ mm</td>
<td>$\geq 2.0$ mm</td>
</tr>
<tr>
<td><strong>Use of NTG with CT</strong></td>
<td>?</td>
<td>75%</td>
<td>99.6%</td>
</tr>
<tr>
<td><strong>Software version*</strong></td>
<td>V 1.0 manual</td>
<td>V 1.2 partial automation approx 6 hours (this is specified in manuscript)</td>
<td>V 1.4 increased automation &lt;4 hours</td>
</tr>
</tbody>
</table>

Koo et al JACC 2011
Min et al JAMA 2013
Norgaard et al JACC 2014
NXTPer-Vessel: $\text{FFR}_{\text{CT}}$ vs. FFR and ICA

$\text{FFR}_{\text{CT}}$ diagnostic accuracy superior to both CT and ICA stenosis

Norgaard et al. JACC 2014
**NXTPer-Vessel: $\text{FFR}_{CT}$ vs. FFR and ICA**

<table>
<thead>
<tr>
<th></th>
<th>$\text{FFR}_{CT} \leq 0.80$</th>
<th>$CT \geq 50$</th>
<th>$ICA \geq 50$</th>
<th>N=484</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy</strong></td>
<td>81</td>
<td>65</td>
<td>64</td>
<td>95</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>84</td>
<td>83</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>60</td>
<td>51</td>
<td>61</td>
<td>93</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>61</td>
<td>33</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td>95</td>
<td>92</td>
<td>93</td>
<td></td>
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$\text{FFR}_{CT}$ diagnostic accuracy superior to both CT and ICA stenosis

*Norgaard et al. JACC 2014*
The FFRct RIPCORD Study

• 200 consecutive patients with stable chest pain undergoing CCTA then FFR by ICA) (from NXT)
• Management plans: consensus of 3 interventionalists
• Assumed that patients were suitable for any treatment:
  – OMT, PCI, CABG, more information needed
• Plan 1: based on CCTA
• Plan 2: based on CCTA + FFRct

Curzen..Rajani: JACC CV Imaging 2016
Recommended Management Plan on the Basis of CCTA with and without FFRct

<table>
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<tr>
<th>TABLE 1</th>
<th>Summary of Overall Changes to Management in Patients According to Treatment Plan on the Basis of CT Angiography Alone and of FFR_{CT} Data in Addition to CT Angiography</th>
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</tr>
<tr>
<td>More data required</td>
<td>38 (19.0)</td>
</tr>
<tr>
<td>Optimal medical therapy</td>
<td>67 (33.5)</td>
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<td>Percutaneous coronary intervention</td>
<td>87 (43.5)</td>
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<td>8 (4.0)</td>
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Values are n (%) or % (95% confidence interval). n = 200 patients; p < 0.001 for between group change, angio alone versus FFR_{CT}.

CT = computed tomography; FFR_{CT} = computer tomography-derived fractional flow reserve.

200 patients from NXT: All had subsequent ICA

The FFRct RIPOORD study

Curzen...Rajani: JACC CV Imaging 2016
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The FFR<sub>ct</sub> RIPOORD study

Curzen, Rajani: JACC CV Imaging 2016
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Recommended management plan: changed in 36% of cases

200 patients from NXT: All had subsequent ICA

The FFR\(_{CT}\) RIPCORD study

Ourzen...Rajani: JACC CV Imaging 2016
FFRct at Cedars-Sinai: Pilot Experience

- 1550 patients: CCTA from 2/19/16 to 11/4/16
- Research/hospital funding: No charge to patient or insurance
- 393 CCTA sent for FFRct (>25% stenosis)

<table>
<thead>
<tr>
<th>Maximal CT stenosis grade</th>
<th>N of Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1: 1-24%</td>
<td>3 1%</td>
</tr>
<tr>
<td>Grade 2: 25-49%</td>
<td>193 49%</td>
</tr>
<tr>
<td>Grade 3: 50-69%</td>
<td>109 28%</td>
</tr>
<tr>
<td>Grade 4: 70-89%</td>
<td>28 7%</td>
</tr>
<tr>
<td>Grade 5: 90-99%</td>
<td>14 4%</td>
</tr>
<tr>
<td>Grade 6: 100%</td>
<td>13 3%</td>
</tr>
<tr>
<td>Unevaluable</td>
<td>33 8%</td>
</tr>
</tbody>
</table>

Unpublished 2016
BRADER (79M): Recent onset exertional CP/SOB
Statin, ASA, ARB, BB

FFR 0.71
BAUSTE (59M) Non-exertional CP/SOB
DM/Insulin; Hypertension

Normal SPECT-MPI
Frequency of Abnormal FFRct Across Lesion by CCTA Stenosis Category (Cedars-Sinai)

810 vessels (393 patients) Maximal CT stenosis grade

Unpublished 2016
Frequency of Abnormal FFRct Across Lesion by CCTA Stenosis Category (Cedars-Sinai)

- 2.5% of vessels with 1-24% stenosis had FFRct ≤0.80
- 810 vessels (393 patients) Maximal CT stenosis grade

Unpublished 2016
Frequency of Abnormal SPECT by CCTA Stenosis Category

Nearly Identical to FFRct Findings

Tamarappoo, Berman et al JNC 2010
Use of FFRct at Cedars-Sinai
Algorithm According to % Stenosis and Plaque Features

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>FFRct</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25%</td>
<td>No</td>
</tr>
<tr>
<td>25-49%</td>
<td>Consider if closer to 50% and/or high risk plaque features</td>
</tr>
<tr>
<td>50-69%</td>
<td>FFRct</td>
</tr>
<tr>
<td>70-89%</td>
<td>Consider if closer to 50% and no high risk plaque features</td>
</tr>
<tr>
<td>≥90%</td>
<td>No</td>
</tr>
</tbody>
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Beyond Stenosis: Ischemia and Plaque Assessments in Coronary CTA

- General considerations
- Stenosis
- Ischemia
- Plaque
Positive remodeling (+), Soft plaque (+), Fibrous plaque (+), Calcification (-)

Motoyama et al. JACC 2007;50:319-26
Adverse Plaque Features: positive remodeling, low attenuation plaque, spotty calcification

Motoyama et al. JACC 2007;50:319-26
High risk plaque Features: Predict Ischemia

Shmilovich, Cheng, et al., Atherosclerosis 2011
Aggregate Plaque Volume: Predicts FFR Ischemia In Patients with Intermediate Stenosis

58 pts with intermediate stenosis on CCTA

Nakazato, et al JACC 2013
Automated quantitative plaque characterization*

- % Diameter Stenosis
- % Area Stenosis
- Total plaque volume/burden (CP, NCP)
- Low-density NCP plaque volume/burden
- % NCP/Total plaque Volume
- % Aggregate plaque volume
- Remodeling index
- Contrast density difference
- Minimum luminal area, lesion length

Automated quantitative plaque characterization*

- %Diameter Stenosis
- %Area Stenosis
- Total plaque volume/burden (CP, NCP)
- Low-density NCP plaque volume/burden
- %NCP/Total plaque Volume
- %Aggregate plaque volume
- Remodeling index
- Contrast density difference
- Minimum luminal area, lesion length

*Autoplaq

Dey et al. JCCT 2009, Dey et al. JCCT 2014,
Quantitative Plaque Assessment on CCTA Predicts PET Ischemia

Prediction of impaired MFR by coronary CTA (per-vessel)

153 vessels

- Composite Score 0.83 (0.79-0.91)
- Stenosis 0.66 (0.57-0.76)

p = 0.005*

Prediction of impaired MFR by coronary CTA (per-patient)

51 patients

- Composite Score 0.93 (0.86-1.0)
- Stenosis 0.69 (0.53-0.84)

p = 0.0016*

Autoplaq vs N-13 Ammonia PET

Dey, et al Circ CV Imaging 2015
Stenosis, Low-density Plaque, and FFRct Predict of FFR-Ischemia

N=484 vessels/254 pts (NXT); Autoplaque

Gaur...Norgard EHJ 2016
1,059 pts with CCTA followed up for 27 ± 10 months
ACS developed in 15 patients.
None had >75% stenosis in the culprit lesion at time of CCTA
Motoyama et al. JACC 2009;54:49-57
High risk plaque (HRP) Features: Predict ACS

HRP and Significant Stenosis: Complementary

N=3,158; 88 ACS in mean f/u 3.9 ± 2.1 years

HRP: positive remodeling or low attenuation plaque; SS: ≥70% stenosis

Motoyama, et al JACC 2015
Serial Quantitative Coronary Plaque Assessment
Assessing the Effects of Therapy

- Reproducible, quantitative assessments of global plaque burden and plaque features
- Potential important tool for serial assessment
  - Clinical trials
  - Clinical management
  - Could extend application of CCTA to asymptomatic patients
Endothelial Shear Stress (ESS) in Human Coronary Arteries

Left Main, Proximal LAD, and Proximal Circumflex

Undisturbed laminar flow
- Physiologic ESS
  - vasculoprotective

Low and oscillatory disturbed laminar flow
- Low ESS
  - pro-inflammatory
  - and atherogenic

Low Flow and Reversed Flow:
- outer waist of a bifurcation
- inner aspect of a curve,
- downstream from an obstruction

Courtesy: Peter Stone

Innovative Refinements to Enhance ESS Calculation by CCTA

Measuring coronary flow in major coronary artery and side branches

Stenosis, Ischemia, and Plaque in CCTA

- **Stenosis**: Definitive when severe
- **FFRct**
  - Provides lesion specific ischemia
  - Reduces need for stress imaging after CCTA
  - Decreases the rate of ICA after CCTA
- **Quantification of plaque**:
  - Adds to prognostic assessment
  - Potential to guide revascularization in asymptomatic patients
  - Valuable tool for assessment of therapy
- **Assessments of stenosis, plaque, and ischemia**: Complementary
Thank you very much