Current Use of IVUS & FFR

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In patients with normal myocardial perfusion scan, even in the presence of angiographically proven CAD

0.6% / year, Cardiac Death and MI

Although FFR can be simply measured (and described) by pressure drop, FFR represents multi-factorial, spatial flow dynamics, and more integrated summation of physiological and anatomical aspects of a stenosis such as:

- Diameter stenosis
- Reference vessel diameter
- Lesion morphology and eccentricity
- Lesion length
- Plaque burden
- Different plaque characteristics
- Surface roughness
- Flow separation, turbulence, and eddies
FFR Original Validation Study

Compared to non-invasive stress test results (n=45 patients, intravenous adenosine infusion)

FFR <0.75

- Sensitivity: 88%
- Specificity: 100%
- Positive PV: 100%
- Negative PV: 88%
- Accuracy: 93%

Pijls NHJ, NEJM 1996;334:1703-8
### IVUS Cutoff Value Published Data Review

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Cut-off of MLA (mm²)</td>
<td>&lt;4.0 (Thallium +)</td>
<td>&lt; 4.0 (FFR&lt;0.75)</td>
<td>&lt;3.0 (FFR&lt;0.75)</td>
<td>&gt; 4.0 (CFR &gt;2.0)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>80%</td>
<td>92%</td>
<td>83 %</td>
<td>Accuracy 92%</td>
</tr>
<tr>
<td>Specificity</td>
<td>90%</td>
<td>54%</td>
<td>92.3 %</td>
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<tr>
<td>QCA VD (mm)</td>
<td>3.08±0.3</td>
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<tr>
<td>DS (%)</td>
<td>52±11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLA (mm²)</td>
<td>3.3±2.3</td>
<td>3.9±2.5</td>
<td>3.9±2.0</td>
<td>4.4±2.0</td>
</tr>
<tr>
<td>MVA (mm²)</td>
<td>12.0±4.6</td>
<td></td>
<td></td>
<td>13.2±4.4</td>
</tr>
<tr>
<td>Area stenosis%</td>
<td>65±18</td>
<td>55±24</td>
<td>43±24</td>
<td></td>
</tr>
</tbody>
</table>
Proposed IVUS MLA matched with FFR < 0.80

2.4 mm²

IVUS Minimal lumen area, mm²

FFR

IVUS Minimal lumen area, mm²

FFR

Plaque burden, %

r=0.507, p<0.001

r=-0.387, p<0.001

Area stenosis, %

r=-0.388, p<0.001

r=-0.472, p<0.001

Length of MLA <3mm², mm
IVUS MLA (2.4mm²) can not predict functional significance of coronary stenosis (FFR <0.8).

Sensitivity=90%
Specificity=60%
PPV=37%
NPV=96%
Accuracy=68%

Courtesy of Seung-Jung Park, MD, PhD
Heart Institute, Asan Medical Center, Seoul, Korea
Angiographic Functional Mismatch in intermediate Left Main Disease
IVUS MLA < 6.0 mm$^2$ is Matched with FFR <0.75

Prediction of FFR (0.75) with IVUS parameter

AMC Prospective Cohort Registry (n=47 lesions), 2011

Proposed IVUS MLA
Matched with FFR <0.80 in Left Main Disease

4.5 mm²

Courtesy of Seung-Jung Park, MD, PhD
Heart Institute, Asan Medical Center, Seoul, Korea
A. MLA predicting FFR<0.80

Sensitivity 83%
Specificity 83%
PPV 83%
NPV 83%
Accuracy 83%

Cut-off =4.5mm²
AUC=0.89
95% CI=0.759-0.960

B. MLA predicting FFR<0.75

Sensitivity 94%
Specificity 84%
PPV 75%
NPV 96%
Accuracy 87%

Cut-off =3.8mm²
AUC=0.92
95% CI=0.797-0.976

C. PB predicting FFR<0.80

Sensitivity 78%
Specificity 75%
PPV 75%
NPV 78%
Accuracy 77%

Cut-off =72%
AUC=0.77
95% CI=0.624-0.880

D. PB predicting FFR<0.75

Sensitivity 81%
Specificity 81%
PPV 68%
NPV 89%
Accuracy 81%

Cut-off =78%
AUC=0.82
95% CI=0.682-0.918
Impact of IVUS on Early and Late Clinical Outcomes Following PCI with DES

Of 1,504 pts in the MATRIX registry, 548 who underwent IVUS guidance were propensity-matched with controls.

<table>
<thead>
<tr>
<th>30-Day Outcomes</th>
<th>IVUS (n = 548)</th>
<th>No IVUS (n = 548)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/MI</td>
<td>1.5%</td>
<td>4.6%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>MACE (Cardiac Death, MI, Clinically Driven TVR)</td>
<td>2.2%</td>
<td>4.8%</td>
<td>0.04</td>
</tr>
<tr>
<td>MI</td>
<td>1.5%</td>
<td>4.0%</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Death/MI and MI also reduced at 2 years (both P < 0.01).

Conclusion: In an all-comers registry, IVUS guidance to optimize DES implantation improved short- and long-term outcomes.

Percutaneous Coronary Intervention of Functionally Non-Significant Stenosis: 5-year follow-up DEFER Study

Event Free Survival

Cardiac Death and MI

J Am Coll Cardiol. 2007 May 29;49(21):2105-11.
Lesions warranting PCI identified

PCI performed on indicated lesions only if FFR ≤0.80

Angio-Guided
PCI performed on indicated lesions

Randomized

Primary Endpoint
Composite of death, MI and repeat revasc. (MACE) at 1 year

Key Secondary Endpoints
Individual rates of death, MI, and repeat revasc., MACE, and functional status at 2 years

FFR-Guided

2 Year Survival Free of MACE

- **FFR-Guided**
- **Angio-Guided**

730 days
4.5%

_J Am Coll Cardiol._ 2010 Jul 13;56(3):177-84.
Diffuse long lesion
Defined by lesions requiring > 2 DES, which **can not be divided** by a normal looking area

Tandem lesion
Defined by lesions requiring > 2 DES, which **can be divided** by normal looking area.

Role of FFR
Measurement of **functional significance** and **functional lesion length** with pullback maneuver during continuous adenosine infusion (140 ug/kg/min).
Assessing FFR in Long Lesions
“Functional Lesion Length”

Pull-back during continuous hyperemia

Courtesy of Seung-Jung Park, MD, PhD
Heart Institute, Asan Medical Center, Seoul, Korea
FFR Intravenous adenosine(140ug/kg/min), pull-back maneuver, Pa, Pm, Pd and delta pressure measurement

ΔP1 = Pa - Pm

ΔP2 = Pm - Pd

Proximal: Pa, Pm, Pd

Distal

Courtesy of Seung-Jung Park, MD, PhD
Heart Institute, Asan Medical Center, Seoul, Korea
Rule of Big Delta

Tight Proximal

Treat Proximal lesion First!

$P_a$  Big $\Delta P_1$  $P_m$  $\Delta P_2$  $P_d$
Rule of Big Delta

Treat Distal lesion First!

$P_a$  $\Delta P1$  $P_m$  Big $\Delta P2$  $P_d$
Bifurcations and FFR

FFR of the **Jailed Side Branch**

Angiographic DS (%) of SB after MB stenting **can not predict** functional significance (FFR<0.75).
FFR in Unstable Angina and NSTEMI: Experience from the FAME Study

Subanalysis comparing FFR vs. angiography alone in 328 pts who had an initial diagnosis of UA or NSTEMI with 677 who had stable angina.

- No evidence of heterogeneity among subgroups for any outcome variable
- Similar risk reductions of MACE and its components (absolute risk reduction 5.1% for UA/NSTEMI vs. 3.7% for stable angina; \( P = 0.92 \))
- Number of stents used reduced without increase in hospital stay or procedure time; less contrast used

**Implications:** The benefit of FFR-guided PCI in multivessel disease does not differ between pts with UA/NSTEMI compared with stable angina.

Long-term Follow-up After Fractional Flow Reserve (FFR)-Guided Treatment Strategy in Patients with an Isolated Proximal LAD Coronary Artery Stenosis

730 pts assigned to medical management or revascularization based on FFR < or ≥ 0.80.

<table>
<thead>
<tr>
<th>5-Year Kaplan-Meier Estimate</th>
<th>Medical Mgmt (n = 564)</th>
<th>Revascularization (n = 166)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>92.9%</td>
<td>87.4%</td>
<td>0.0392</td>
</tr>
<tr>
<td>Survival Free of Death/MI</td>
<td>92.0%</td>
<td>84.9%</td>
<td>0.0155</td>
</tr>
<tr>
<td>Survival Free of Death/MI/TVR</td>
<td>89.7%</td>
<td>68.5%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Conclusion: Medical treatment of pts with a hemodynamically nonsignificant stenosis in the proximal LAD is associated with an excellent long-term clinical outcome.

Long-term Clinical Outcome After FFR-Guided PCI in Patients with Small-Vessel Disease

Retrospective registry study with aged-matched controls who underwent angiography-guided PCI.

<table>
<thead>
<tr>
<th>3-Year Follow Up</th>
<th>FFR (n = 222)</th>
<th>Angiography (n = 495)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or Nonfatal MI</td>
<td>6%</td>
<td>14%</td>
<td>0.004</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>1%</td>
<td>7%</td>
<td>0.007</td>
</tr>
<tr>
<td>MACE (Cardiac Death, Nonfatal MI, and TVR)</td>
<td>14%</td>
<td>28%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Conclusion:** FFR-guided PCI of small coronary arteries is safe and results in better clinical outcomes compared with angiography-guided PCI.

Primary Outcomes

PCI+MT vs. MT: HR 0.32 (0.19-0.53); p<0.001
PCI+MT vs. Registry: HR 1.29 (0.49-3.39); p=0.61
MT vs. Registry: HR 4.32 (1.75-10.7); p<0.001

Cumulative incidence (%) vs. Months after randomization

No. at risk
- MT: 441, 414, 370, 322, 283, 253, 220, 192, 162, 127, 100, 70, 37
- PCI+MT: 447, 414, 388, 351, 308, 277, 243, 212, 175, 155, 117, 92, 53
- Registry: 166, 156, 145, 133, 117, 106, 93, 74, 64, 52, 41, 25, 13
In 497 pts from the FFR arm of FAME, Syntax score was calculated normally and then recalculated only for lesions with FFR < 0.80.

<table>
<thead>
<tr>
<th>1-Year Death/MI by Risk Tertile</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syntax</td>
<td>5.4%</td>
<td>6.0%</td>
<td>11.7%</td>
<td>NS</td>
</tr>
<tr>
<td>Functional Syntax</td>
<td>4.8%</td>
<td>7.5%</td>
<td>15.8%</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Over 30% of patients with a Syntax score > 22 (indicating more complex CAD) moved to Functional Syntax score below that cutoff.

**Conclusion:** Incorporating FFR into the Syntax score of patients with multivessel disease may help improve risk stratification and predict 1-year outcomes after PCI.
DISCOVER-FLOW: Diagnosis of Ischemia-Causing Stenoses by Noninvasive Fractional Flow Reserve

Experimental FFR method compared with coronary CTA (≥ 64 slice scanner) in 103 pts (159 vessels) with stenosis in a major epicardial coronary artery.

<table>
<thead>
<tr>
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<th>Noninvasive FFR</th>
<th>Coronary CTA</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>87.9%</td>
<td>91.4%</td>
</tr>
<tr>
<td>Specificity</td>
<td>82.2%</td>
<td>39.6%</td>
</tr>
<tr>
<td>Diagnostic Accuracy</td>
<td>84.3%</td>
<td>58.5%</td>
</tr>
</tbody>
</table>

**Conclusion:** A method that calculates FFR based on coronary CTA accurately assesses the functional significance of CAD noninvasively. But further research is required before it can be used in a real-world setting.

Prospective Application of Predefined IVUS Criteria for Assessment of Intermediate Left Main Lesions

354 pts from the LITRO study; revascularization performed if minimum lumen area below 6 mm², deferred if above cutoff.

<table>
<thead>
<tr>
<th>2-Year Follow-up</th>
<th>Deferred (n = 179)</th>
<th>Revascularized (n = 152)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival Free from Cardiac Death</td>
<td>97.7%</td>
<td>94.5%</td>
<td>NS</td>
</tr>
<tr>
<td>Event-Free Survival</td>
<td>87.3%</td>
<td>80.6%</td>
<td>NS</td>
</tr>
</tbody>
</table>

The level of angiographic stenosis varied widely across the 2 groups.

Conclusion: An IVUS-derived cutoff can safely determine which intermediate left main lesions require revascularization.

Optimal Intravascular Ultrasound Criteria and Their Accuracy for Defining the Functional Significance of Intermediate Coronary Stenoses of Different Locations

- IVUS and FFR measurement were performed in 267 intermediate lesions
- Optimal IVUS criteria for significant stenosis FFR (value of <0.8) were assessed

**Conclusion:** When IVUS parameters are used to determine the functional significance, different criteria should be used according to lesion locations.

**Diagnostic accuracy of MLA for FFR of <0.8**

<table>
<thead>
<tr>
<th>MLA cutoff value (mm²)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prox LAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid LAD</td>
<td></td>
<td></td>
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<tr>
<td>RCA</td>
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MLA cutoff value in proximal LAD: MLA = 3.0mm² at different locations

## IVUS Predictors of BMS Thrombosis & Restenosis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Thrombosis</th>
<th>Restenosis</th>
</tr>
</thead>
</table>
## Predictors of DES Thrombosis & DES Restenosis

### Small MSA or MLA
- Fujii et al. J Am Coll Cardiol 2005;45:995-8
- Okabe et al., Am J Cardiol. 2007;100:615-20
- Hong et al. Eur Heart J 2006;27:1305-10
- Doi et al JACC Cardiovasc Interv. 2009;2:1269-75
- Choi et al. HORIZONS, unpublished

### Edge problems (geographic miss, secondary lesions, large plaque burden, dissections, etc)
- Fujii et al. J Am Coll Cardiol 2005;45:995-8
- Okabe et al., Am J Cardiol. 2007;100:615-20
- Costa et al, Am J Cardiol, 2008;101:1704-11
IVUS Predictors of Very Late DES Thrombosis

- Late DES Thrombosis (n=13)
- Controls (n=175)

Expansion was assessed at follow-up. “Underexpansion” probably represented an increase in reference vessel size (positive remodeling) rather than true underexpansion.

(Cook et al. Circulation 2007;115:2426-34)
Manufacturer’s Compliance Charts Cannot Be Used to Guarantee Adequate Stent Expansion

Comparison of IVUS-measured minimum stent diameter (MSD) and minimum stent area (MSA) with the predicted measurements from Cordis (Cypher in yellow, n=133) and BSC (Taxus in red, n=67).

DES achieve an average of only 75% of the predicted MSD (66% of MSA). Ratio of measured to predicted MSD/MSA is a measure of lesion compliance.

Meta-analysis of Incidence, Clinical Characteristics and Implications of Stent Fracture

• Eight studies with 108 stent fractures in 5,321 patients
• The mean incidence of stent fracture per patient was 4.0% (95% confidence interval 0.4% to 16.3%). All cases, except 1, were reported with sirolimus-eluting stents.
• The probability of stent fracture was significantly higher in
  - RCA than in the LAD and LCX lesions (p < 0.01). The probability of stent fracture was significantly increased in
    - Overlapping stents (7.5% vs 2.1%, p = 0.01) and long stents (46 vs 32.5mm, p < 0.01).
• Lesions with stent fractures had higher rates of ISR (38% vs 8.2%, p < 0.01) and TLR (17% vs 5.6%, p < 0.01); and the probability of stent fractures was higher in patients with ISR (12.8% vs 2.1%, p < 0.01) and TLR (8.8% vs 2.7%, p < 0.01).
Correlation of IVUS Findings With Aspirates in 28 Pts with Very Late DES Thrombosis

- 28 pts with very late DES ST and 26 controls
- LSM in 73% of very late DES ST segments. Maximal LSM area measured 6.2±2.4mm², and length measured 9.4±9.5mm. LSM area exceeded 5.0mm² in 5 of 8 segments (63%)

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<thead>
<tr>
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<th>WBCs</th>
<th>p</th>
<th>Eos</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Spontaneous MI</td>
<td>291±94</td>
<td></td>
<td>7±10</td>
<td></td>
</tr>
<tr>
<td>Early ST-BMS</td>
<td>146±117</td>
<td></td>
<td>1±1</td>
<td></td>
</tr>
<tr>
<td>Early ST-DES</td>
<td>73±117</td>
<td></td>
<td>1±2</td>
<td></td>
</tr>
<tr>
<td>Very late ST-BMS</td>
<td>84±50</td>
<td>0.000</td>
<td>2±3</td>
<td>0.038</td>
</tr>
<tr>
<td>Very late ST-DES</td>
<td>283±14</td>
<td>1</td>
<td>20±24</td>
<td></td>
</tr>
</tbody>
</table>

- LSM area correlated with total eosinophil count (p=0.008)

(Cook et al. Circulation 2009;120:391-9)
Percentage of Patients With Atherosclerotic Changes in DES Versus BMS in Relation to Duration of Implant at Autopsy
Pathology of In-stent Neoatherosclerosis in BMS and DES

- 197 BMS, 103 SES, and 106 PES with implant duration >30 days
- The incidence of neoatherosclerosis was significantly greater in DES (31%) than BMS (16%; p < 0.001).
- Median stent duration with neoatherosclerosis was shorter in DES than BMS (420 days v 2,160 days, p < 0.001).

<table>
<thead>
<tr>
<th></th>
<th>≤2 yrs</th>
<th>2-6 yrs</th>
<th>&gt;6 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td>0%</td>
<td>22%</td>
<td>42%</td>
</tr>
<tr>
<td>DES</td>
<td>29%</td>
<td>41%</td>
<td></td>
</tr>
</tbody>
</table>

- 7 BMS and 3 DES had TCFA or plaque rupture occurring with shorter implant durations for DES (1.5 ± 0.4 years) compared to BMS (6.1 ± 1.5 years).
Conclusions

- FFR has become a very useful tool in the diagnosis of functional ischemia in the catheterization laboratory.
- Although FFR can be simply described as a pressure drop or gradient, FFR represents (multi-factorial) a more integrated summation of physiological and anatomical aspects of a stenosis.
- Emerging data suggests that angiographic severity does not seem to correlate with its ischemic potential (angiographic-functional mismatch).
- Emerging data suggests that the IVUS-derived MLA commonly thought to correlate with ischemia appears to be smaller than previously described.
- IVUS can be very useful in optimizing stent implantation results, evaluating LM, and imaging stent restenosis and thrombosis cases in order to allow a mechanism-derived method of treatment.