Integrating IVUS, FFR, and Noninvasive Imaging to Optimize Outcomes

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Cardiovascular Research Foundation
COURAGE Nuclear Substudy (n=314)

Death/MI according the residual ischemia (SPECT)

- PCI+optimal medical therapy was associated with greater ischemia reduction overall and in pts with moderate/severe pre-treatment ischemia
- ≥5% ischemia reduction was associated with reduced death/MI compared to no ischemia reduction: 13.4% vs 27.4%, p=0.037 (overall) and 16.2% vs 32.4%, p=0.001 (in patients with moderate/severe pretreatment ischemia)

(Shaw et al. Circulation 2008;117:1283-91)
Relationship Between Extent of Ischemia and Cardiac Events (n=1689)

Progressive Manifestations of Myocardial Ischemia as Illustrated by Ischemic Cascade

Commonly Applied Noninvasive Testing

ECG
Gated SPECT, Echo
Echo
PET, CMR
PET, SPECT, CMR

Invasive Disease States Where Ischemia is Manifested

Severe Stenosis
Moderate Stenosis
Endothelial Dysfunction / Microvascular Disease

Decreased Perfusion
Metabolic Changes
Diastolic Dysfunction
Systolic Dysfunction
ST-T Wave Changes
Chest Pain

Exposure Time of Mismatch in Myocardial Oxygen Supply / Demand
Near Term
Prolonged

Asymptomatic Manifestations
Symptomatic Manifestations

(Shaw. TCT 2008)
In the United States, 44.5% of medicare pts underwent stress testing within the 90 days prior to elective PCI.

Factors Predicting Stress Test Prior to Elective PCI

Geographic Variation of Rates of Stress Testing Prior to Elective PCI

(Lin et al. JAMA 2008;300:1765-1773)
Use of MPS to localize CAD

<table>
<thead>
<tr>
<th></th>
<th>LAD</th>
<th>RCA</th>
<th>LCX</th>
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<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>DePasquale et al. Circulation 1988;77:316-27</td>
<td>78%</td>
<td>83%</td>
<td>89%</td>
</tr>
<tr>
<td>Borges-Neto et al. J Am Coll Cardiol. 1988;11:962-9</td>
<td>80%</td>
<td>84%</td>
<td>87%</td>
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</tbody>
</table>

As best at I have been able to determine, the use of myocardial perfusion scanning to guide PCI especially in the setting of multivessel disease is anectodal, is extrapolated from DEFER and FAME and the fact that FFR was originally validated against MPS, and is not supported by the literature.
Cardiac MR and Viability: Prediction of improved LV function by MRI

DEFER 5 Year Results

Event Free Survival

Cardiac Death and MI

(Pijls et al. J am Coll Cardiol 2007;49:2105-11)
FAME: FRACTIONAL FLOW RESERVE versus ANGIOGRAPHY FOR GUIDING PCI IN PATIENTS WITH MULTIVESSEL CORONARY ARTERY DISEASE

Late Breaking Trial at TCT, October 14th, 2008

Nico H.J. Pijls, MD, PhD
Catharina Hospital, Eindhoven
The Netherlands,
on behalf of the FAME investigators
## FAME study: Procedural Results

<table>
<thead>
<tr>
<th></th>
<th>ANGIO-group N=496</th>
<th>FFR-group N=509</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td># indicated lesions per patient</td>
<td>2.7 ± 0.9</td>
<td>2.8 ± 1.0</td>
<td>0.34</td>
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<tr>
<td></td>
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<tr>
<td><strong>FFR results</strong></td>
<td></td>
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</tr>
<tr>
<td>Lesions succesfully measured, No (%)</td>
<td>-</td>
<td>1329 (98%)</td>
<td>-</td>
</tr>
<tr>
<td>Lesions with FFR ≤ 0.80, No (%)</td>
<td>-</td>
<td>874 (63%)</td>
<td>-</td>
</tr>
<tr>
<td>Lesions with FFR &gt; 0.80, No (%)</td>
<td>-</td>
<td>513 (37%)</td>
<td>-</td>
</tr>
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<td></td>
<td></td>
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<tr>
<td><strong>Stents per patient</strong></td>
<td>2.7 ± 1.2</td>
<td>1.9 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lesions succesfully stented (%)</td>
<td>92%</td>
<td>94%</td>
<td>-</td>
</tr>
<tr>
<td>DES, total, No</td>
<td>1359</td>
<td>980</td>
<td>-</td>
</tr>
</tbody>
</table>
**FAME study: Event-free Survival**

The graph illustrates the absolute difference in MACE-free survival over time. The survival rates for FFR-guided and Angio-guided procedures are shown.

- **30 days**: FFR-guided 2.9%, Angio-guided 90 days 3.8%
- **180 days**: FFR-guided 4.9%, Angio-guided 360 days 5.3%

The graph also shows a comparison of survival rates at different time points, indicating a trend of higher survival in FFR-guided procedures compared to Angio-guided procedures.
IVUS determinants of LMCA FFR <0.75

(Jasti et al. Circulation 2004;110:2831-6)
IVUS Criteria for a ‘Significant’ LMCA Stenosis

- Most IVUS LMCA studies show either insignificant disease or critical disease
- Absolute lumen CSA <6.0mm² (or MLD <3.0mm) is the suggested criterion for a significant LMCA stenosis
  - Correlates with a LMCA FFR <0.75
  - Murray’s Law \( (\text{LMCA} r^3 = \text{LAD} r^3 + \text{LCX} r^3) \)
  - Does not depend on finding a disease-free reference segment
Attenuated Plaque

- Attenuated plaques were observed in 39.6% of STEMI, 17.6% of NSTEMI, and 0% of stable angina.
- Attenuated plaques were associated with more fibroatheromas and a larger necrotic core (on VH-IVUS).
- In ACS patients with attenuated plaques (1) the level of CRP was higher, (2) angiographic thrombus and initial coronary flow <TIMI 2 were more common, and (3) no-reflow or flow deterioration post-PCI were more common.

(Lee et al. JACC Cardiovasc Interv. 2009;2:65-72)
(Wu et al, Am J Cardiol 2010;105:48-53)
culprit of the culprit proximal to MLA

MLA
Numerous studies have shown a relationship between the maximum necrotic core and post-PCI distal embolization

- Kawaguchi et al. J Am Coll Cardiol. 2007;50:1641-6
  - ST re-elevation in 71 pts with STEMI
  - Doppler FloWire high intensity transit signals in 44 pts undergoing elective stenting resulting in poor recovery of CVFR
- Park et al. VH Summit 2007 (unpublished)
  - Largest NC independent predictor of CK-MB release (n=332)
- Hong et al. J Am Coll Cardiol Img, 2009;2:458-468
  - Troponin post elective stenting in 80 pts (29 stable and 51 unstable angina)
- Bose et al. Basic Res Cardiol 2008;103:587-97
  - CK and TnI in 55 pts undergoing direct stenting. Patients in the 4th quartile of NC volume had a particularly high increase in biomarkers.
  - No reflow in 49 pts with ACS undergoing PCI
- Hong et al. Eur Heart J, in press
  - No reflow in 190 pts with ACS undergoing stenting


Goldstein et al. JACC Cardiovasc Imaging. 2009;2:1420-4
IVUS guidance was associated with significantly lower rate of
- Angiographic restenosis (22.2% vs. 28.9%; OR 0.64, p=0.02)
- Repeat revascularization (12.6% vs. 18.4%; OR 0.66, p=0.004)
- Overall MACE (19.1% vs. 23.1%; OR 0.69, p=0.03)
but no significant effect on MI (p=0.51) or mortality (p=0.18).
Predictors of DES
Thrombosis & Restenosis

<table>
<thead>
<tr>
<th></th>
<th>DES Thrombosis</th>
<th>DES Restenosis</th>
</tr>
</thead>
</table>
| **Underexpansion** | • 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  
| **Edge problems** | • Fujii et al. J Am Coll Cardiol 2005;45:995-8)  
                           • Okabe et al., Am J Cardiol. 2007;100:615-20  
                           • Liu et al. Am J Cardiol 2009;103:501-6  
                           • Costa et al, Am J Cardiol, 2008;101:1704-11 |
| **(geographic miss, secondary lesions, large plaque burden, etc)** | | |

Edge problems: (geographic miss, secondary lesions, large plaque burden, etc)
By definition, sensitivity/specificity curve analysis “must” identify a single MSA that best separates restenosis from no restenosis. C-statistic for TAXUS was only 0.64.

(Hong et al. Eur Heart J 2006;27:1305-10)
(Doi et al. JACC Cardiovasc Interv. 2009;2:1269-75)
Does one size (\(\text{MSA}=5.0-5.5\text{mm}^2\)) fit all?

- Is an MSA of 5.0-5.5mm\(^2\) enough in big arteries? Probably not. There is a step-wise decrease in restenosis with increasing stent expansion (MSA)
- Is it achievable in small arteries? Also, probably not.
- If so, manufacturers would only need to make one size DES – i.e., a 2.75mm stent - and it would suffice in all situations.
Comparison of 9-month QCA edge restenosis vs reference lumen area and plaque burden in TAXUS-IV, V, and VI (n=810)

- Reference lumen area did not affect Taxus edge restenosis ($c=0.55$)
- Reference plaque burden had a moderate effect on Taxus edge restenosis; a cut-off of 42% best separated edge restenosis from no restenosis ($c=0.67$)

(Liu et al, Am J Cardiol 2009;103:501-6)
1296 IVUS-guided, DES-treated lesions in 884 pts vs 1312 propensity-score-matched, angio-guided, DES-treated lesions in 884 pts

<table>
<thead>
<tr>
<th></th>
<th>IVUS-guided</th>
<th>Angio-guided</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>30 day</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>2.8%</td>
<td>5.2%</td>
<td>0.01</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>0.5%</td>
<td>1.4%</td>
<td>0.045</td>
</tr>
<tr>
<td>TLR</td>
<td>0.7%</td>
<td>1.7%</td>
<td>0.045</td>
</tr>
<tr>
<td><strong>1 year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>14.5%</td>
<td>16.2%</td>
<td>0.3</td>
</tr>
<tr>
<td>Definite stent thrombosis</td>
<td>0.7%</td>
<td>2.0%</td>
<td>0.014</td>
</tr>
<tr>
<td>Probably stent thrombosis</td>
<td>4.0%</td>
<td>5.8%</td>
<td>0.08</td>
</tr>
<tr>
<td>TLR</td>
<td>5.1%</td>
<td>7.2%</td>
<td>0.06</td>
</tr>
<tr>
<td>Late definite stent thrombosis</td>
<td>0.2%</td>
<td>0.7%</td>
<td>0.3</td>
</tr>
</tbody>
</table>

(Roy et al. Eur Heart J 2008;29:1851-7)
All-Cause Mortality After LMCA DES Implantation: Impact of IVUS Guidance

Cumulative Incidence (%)

IVUS (n=595)
95.2%

No IVUS (n=210)
85.6%

HR=0.43, p=0.019

Other independent predictors were previous CHF, chronic renal failure, COPD, and EUROSCORE>6

“Optimal” MSA and TLR after LMCA DES Implantation (n=595)

Minimum stent area (mm$^2$)

(SJ Park. TCT 2007)
FFR Assessment of 97 Jailed Side Branch Lesions

- There was a negative correlation between the % stenosis on QCA and FFR ($r = -0.41$, $p < 0.001$).

- Only 27% of lesions with QCA $DS > 75\%$ were functionally significant as assessed by FFR ($<0.75$).

(Koo et al. J Am Coll Cardiol 2005;46:633-7)
Early

Late

Very Late

Impact

100%

Biologic causes (inflammation, remodeling, stent malapposition, etc)

Mechanical causes (underexpansion, inflow/outflow disease, etc)
Impact of DES underexpansion on early/late and very late thrombosis

Minimum stent CSA (mm\(^2\))

# with DES Thrombosis

ST <1yr (Okabe, n=14)
ST <1yr (Liu, n=20)
ST >1yr (Cook, n=13)

(Okabe et al. Am J Cardiol 2007;100:615-20)
(Cook et al. Circulation 2007;115:2426-34)
Months of follow-up

Stent-thrombosis Free Survival (%)

IVUS

No-IVUS

p=0.013

(Roy et al. Eur Heart J. 2008;29:1851-7)
Meta-Analysis of Late Stent Malapposition (LSM) Frequency

• 17 studies with 4648 patients
  - 2453 BMS and 2195 DES
  - 4 SES, 4 PES, 1 EES, 2 ZES, 3 DES vs DES, and 3 BMS only

• LSM more common in DES than BMS
  - OR=2.5, p=0.02 when both RCT and observational studies were included
  - OR=4.4, p=0.002 when only RCT were included
  - SES > PES > ZES > EES

(Hassan et al. Eur Heart J, in press)
Meta-Analysis of Very Late ST in LSM

- 5 studies with 2080 patients
  - 228 LSM and 1852 no LSM
  - 3 Late ST (<12 mos), none in LSM
  - 6 Very late ST (>12 mos), 4 in LSM
- Risk of very late ST was higher in LSM patients (OR=6.5, p=0.02).
- Based on the expected numbers of very late ST, 3 of 5 studies favored the relationship between LSM and very late ST.

*(Hassan et al. Eur Heart J, in press)*
Neoatherosclerosis with neointimal rupture was observed in 62.5% of DES patients with VLST and 100% of BMS patients with VLST.

(Lee et al. J Am Coll Cardiol 2010;55:1936-42)
Follow-up

- A decrease in specificity has been observed when myocardial perfusion imaging (MPI) is performed <2 months of PCI.
- The overall sensitivity and specificity of MPI for detecting myocardial ischemia ≥2 months after PCI are both 79%, and are roughly equivalent in all three vascular territories.
- Following PCI, progression of disease in untreated vessel segments occurs at rates approaching 7% per year in both symptomatic and asymptomatic patients. More than one-half of pts presenting with chest pain >1 year after PCI have a new lesion or significant worsening of a previously nonobstructive stenosis. During late follow-up, outcomes are more strongly correlated with disease progression than restenosis.
- Asymptomatic patients should initially be followed clinically and undergo MPI at 6-9 months. Patients with normal, low-risk, or intermediate-risk scans (small or medium-sized defects of mild-to-moderate severity) can be managed medically. Patients with high-risk scans (medium-sized severe defects, large defects of any severity, or scans showing stress-induced left ventricular failure) should undergo angiography.

(Giedd & Bergmann. J Am Coll Cardiol 2004;43:328-36)
In the ideal world...

- Pts would be screened pre-PCI using a technique that assessed stress-induced myocardial ischemia (or viability when treating CTOs).
  - Although the various techniques have their systematic differences, my experience is that the dedication of an institution to expertise in an individual technique is most important.
- FFR would be used to identify ischemia-producing lesions, especially in the setting of intermediate lesions or multivessel disease. The exception being intermediate LM lesions where IVUS has certain advantages over FFR, especially in the setting of LAD and/or LCX disease.
- Stent implantation would be IVUS-guided to optimize expansion and full lesion coverage, especially in high-risk pt and lesion subsets.
- After 6 months pts would have repeat assessment of stress-induced myocardial ischemia.