Intermediate lesion assessment-IVUS and FFR

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Agenda

- What is an intermediate lesion
- **Goals of assessment (Targets):** Physiologic and morphologic
- **Different modalities:**
  1. FFR and iFR
  2. IVUS and VH-IVUS
- **Different situations:** Elective, NSTEMI, STEMI, LM trunk
Why do we need assessment?

- Angiography demonstrates only a 2-dimensional view of coronary arteries and does not have the capability of providing information regarding vessel physiology.

- Lesions that appear to be similar may in fact look very different from a cross-sectional view and behave different from a physiologic standpoint.
Goals

I. To determine the functional significance of an angiographically intermediate (30 – 70%) lesion

II. To determine the stress on the heart from the lesion; to avoid expensive nuclear tests

III. To confirm therapeutic outcomes
Using FFR in the Cath Lab
FFR Definition:

- Ratio of distal mean coronary pressure to mean aortic pressure in the stenotic vessel during maximum hyperemia.

- Represents the very fraction of blood flow that still has been preserved despite the stenosis.

  \[ \text{FFR}_{\text{myo}} = \frac{P_d}{P_a} \]
Adenosine

- **I.C. (Intracoronary bolus)**
  - LCA: 40 – 60 μg
  - RCA: 30 – 40 μg
- **I.V. Infusion**
  - 140 μg/kg/min
  - Infuse in femoral or subclavian vein or in large peripheral vein

Pijls and DeBruyne, *Coronary Pressure*, 2000, pp. 100 – 19
Pressure Clinical Applications

- Single vessel intermediate lesions
- Dual lesions with uncertainty of culprit
- Multi-vessel disease (CABG vs. Angioplasty)
- SVG lesions
- Left Main disease
- IMA/Vein Graft
- Secondary lesions
- Re-stenosis/in stent stenosis
- Post infarct

(Pijls & DeBruyne, 1997)
Why FFR?

- PCI is performed to relieve symptoms of ischemia.
- Is there evidence showing that a stenosis is causing ischemia?
- Does a stenosis still cause ischemia after stenting?
- Studies show that FFR can answer these questions with a high level of reproducibility*

* Kern et al. Circulation 2006; 114:1321-1341
“Physicians are presented with the dilemma of balancing a positive CTA with a negative angiogram, then having to choose between intervention and medical therapy. Technologies like IVUS and FFR provide important objective measures of disease severity – essentially serving as the tie-breaker.”

- John Hodgson, M.D. and past President of the Society for Cardiovascular Angiography and Interventions


- 4 experienced cardiologists reviewed angio’s from 51 pts. with intermediate or equivocal LMCA disease

- Each reviewer’s angio interpretations were correct no more than 50% of the time when taking FFR as the gold standard for LMCA lesions

- Inter-observer variation was large – the 4 reviewers correctly agreed on only 29% of angio’s
Clinical Studies

- Defer
- Fame
- Fame 2
- Fame 3
- Famous
DEFER Study Breakdown

Randomized Patients Without Proof of Ischemia (325)

Deferral of PTCA (167)

- FFR $\geq$ 0.75 (91)
  - No PTCA
  - DEFER Group

- FFR < 0.75 (76)
  - PTCA
  - REFERENCE Group

Performance of PTCA (158)

- FFR < 0.75 (68)
  - PTCA

- FFR $\geq$ 0.75 (90)
  - PTCA
  - PERFORM Group
Event Free Survival Rates

Event-Free Survival Rate

Years of Follow-up

- DEFER
- PERFORM
- REFERENCE (FFR < 0.75)

p=0.52
p=0.17
p=0.03
DEFER Results

**Composite Mortality Rates**

- **DEFER (FFR > 0.75):** 3.3%
- **PERFORM (FFR < 0.75):** 7.9%
- **REFERENCE (FFR < 0.75):** 15.7%

**P-values:**
- P = 0.21
- P = 0.002
- P = 0.003
DEFER Results

Risk of stenosis causing death or AMI is <1% per year when FFR is greater than 0.75 and stenting is deferred.

- There is no clinical benefit to stenting patients with stable ischemia whose FFR measures greater than 0.75.
Fractional Flow Reserve versus Angiography for Multivessel Evaluation

FRACTIONAL FLOW RESERVE versus ANGIOGRAPHY FOR GUIDING PCI IN PATIENTS WITH MULTIVESSEL CORONARY ARTERY DISEASE
Patient with stenoses ≥ 50% in at least 2 of the 3 major epicardial vessels

Indicate all stenoses ≥ 50% considered for stenting

Randomization

Angiography-guided PCI

Stent all indicated stenoses

1-year follow-up

FFR-guided PCI

Measure FFR in all indicated stenoses

Stent only those stenoses with FFR ≤ 0.80

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FAME study: Event-free Survival

**absolute difference in MACE-free survival**

- 30 days: 2.9%
- 90 days: 3.8%
- 180 days: 4.9%
- 360 days: 5.3%
FAME study: CONCLUSIONS (1)

Routine measurement of FFR during PCI with DES in patients with multivessel disease, when compared to current angiography guided strategy

• reduces the rate of the composite endpoint of death, myocardial infarction, re-PCI and CABG at 1 year by ~ 30%

• reduces mortality and myocardial infarction at 1 year by ~ 35%
FAME study: CONCLUSIONS (2)

Routine measurement of FFR during PCI with DES in patients with multivessel disease, when compared to current angiography guided strategy, furthermore:

- is cost-saving and does not prolong the procedure
- reduces the number of stents used
- decreases the amount of contrast agent used
- results in a similar, if not better, functional status
Routine measurement of FFR during DES-stenting in patients with multivessel disease is superior to current angiography guided treatment.

It improves outcome of PCI significantly.

It supports the evolving paradigm of “Functionally Complete Revascularization”, i.e. stenting of ischemic lesions and medical treatment of non-ischemic ones.
Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease

Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D.,
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Pim A.L. Tonino, M.D., Ph.D., Zsolt Piroth, M.D., Nikola Jagic, M.D.,
Sven Mobius-Winkler, M.D., Gilles Rioufol, M.D., Ph.D., Nils Witt, M.D., Ph.D.,
Petr Kala, M.D., Philip MacCarthy, M.D., Thomas Engström, M.D.,
Keith G. Oldroyd, M.D., Kreton Mavromatis, M.D., Ganesh Manoharan, M.D.,
Peter Verlee, M.D., Ole Frobert, M.D., Nick Curzen, B.M., Ph.D.,
Jane B. Johnson, R.N., M.Sc., Peter Jüni, M.D., and William F. Fearon, M.D.,
for the FAME 2 Trial Investigators*
In patients with stable coronary disease, PCI has not been shown to improve prognosis.

FAME 1 demonstrated the superiority of FFR-guided over angiography-guided PCI.

In previous trials, revascularization has been guided by the angiographic appearance of the lesions.

It is likely that in previous trials a sizable proportion of patients had no or little ischemia.
Flow Chart

Stable CAD patients scheduled for 1, 2 or 3 vessel DES-PCI
N = 1220

FFR in all target lesions

Randomized Trial

At least 1 stenosis with FFR ≤ 0.80 (n=888)

Randomization 1:1

PCI + MT

MT

73%

Registry

When all FFR > 0.80 (n=332)

MT

27%

Follow-up after 1, 6 months, 1, 2, 3, 4, and 5 years

Registry

50% randomly assigned to FU

FAME 2: FFR-Guided PCI versus Medical Therapy in Stable CAD
Kaplan-Meier plots of Landmark Analysis of Death or MI

≤7 days: HR 7.99 (0.99-64.6); p=0.038
> 8 days: HR 0.42 (0.17-1.04); p=0.053
p-interaction: p=0.003
Conclusions

• In patients with stable coronary artery disease, FFR-guided PCI, improves patient outcome as compared with medical therapy alone

• This improvement is driven by a dramatic decrease in the need for urgent revascularization for ACS

• In patients with functionally non-significant stenoses medical therapy alone resulted in an excellent outcome, regardless of the angiographic appearance of the stenoses
Objective:

The primary objective of the FAME 3 Trial is to demonstrate that FFR-guided PCI with the 2nd generation Resolute DES is non-inferior to CABG in patients with multivessel CAD.

Major Endpoints

- **Primary Endpoint:**
  One year rate of Death, MI, Stroke and Revascularization

- **Key Secondary Endpoint:**
  Three year rate of Death, MI and Stroke
Study Flow:

All Comers with 3 V CAD (not involving LM)

Heart team identifies lesions for PCI/CABG and then patient is randomized

FFR-Guided PCI with Resolute DES
Stent all lesions with FFR ≤ 0.80 (n=750)

Perform CABG based on coronary angiogram (n=750)

Primary: One Year follow-up for Death, MI, CVA, Revascularization
Key Secondary: Three Year follow-up for Death/MI/CVA

Non-inferior Design
Different situations

- SCAD
- STEMI
- NSTEMI
FAMOUS-NSTEMI

Trial design: Participants with NSTEMI were randomized to an FFR-guided strategy (n = 176) vs. a coronary angiography-guided strategy (n = 174).

Results

- Proportion of patients medically treated: 22.7% in the FFR group vs. 13.2% in the angiography group (p = 0.022)
- MACE at 12 months: 8.0% vs. 8.6% (p = 0.89), respectively
- Freedom from revascularization at 12 months: 21.0% vs. 13.2% (p = 0.054)

Conclusions

- Among NSTEMI patients, an FFR-guided strategy was feasible, resulting in a larger proportion of patients treated medically
- FFR-guided strategy was associated with similar MACE, but a marginal reduction in revascularization

Layland J, et al. Eur Heart J 2014;Sep 1:[Epub]
Identification of wave-free period

Fully automated algorithms

Identification of naturally low resistance period

Uses pressure only

Sen S, Escaned J, Davies JE et al. JACC (in press 2011)
Davies JE et al. Circulation 2006;113:1767-1778
FFR is established in clinical practice

*At best* it is only used in 6% of PCI in USA\(^1\)

One barrier is the current *requirement* for vasodilator drugs such as adenosine

*Contraindicated* or *disliked* by patients

Adds to procedural *time*

Adds to procedural *costs*

\(^1\) Kleiman NS. J Am Coll Cardiol 2011; 58:1291-21
PRIMARY Results of ADVISE
ADenosine Vasodilation
Independent Stenosis Evaluation

Dr Justin Davies MD, PhD
Imperial College London
on behalf of the ADVISE investigators
Summary

Identified a *wave-free period* in cardiac cycle when resistance is naturally *stabilized* and *minimal* avoiding the need for administration of adenosine
Summary

iFR measured during this wave-free period gives a **measure of stenosis severity similar to FFR**
iFR Evidence

- ADVISE and ADVISE II
- CLARIFY study
- RESOLVE study
- VERIFY and VERIFY 2
IVUS in intermediate lesions

- Left Main Trunk
- Other epicardial coronary arteries
IVUS in LM assessment

- FAME and FAME 2 excluded LM lesions

- Difficulties in assessment of LM ostial lesions
IVUS Assessment of Left Main Disease
Suggested IVUS Criteria for a ‘Significant’ LMCA Stenosis

- Most IVUS LMCA studies show either insignificant disease or critical disease, only a minority require careful quantification.
- Although there are no prospective studies, the following criteria for a significant LMCA stenosis are suggested:
  - \( MLD = 2.8-3.0 \text{mm} \)
  - \( \text{Lumen CSA} < 6.0-7.5 \text{mm}^2 \) –
    - in general, the sum of the lumen areas of the two daughter vessels (LAD and LCX, each of which should be 4.0\( \text{mm}^2 \))
    - it correlates with a LMCA FFR<0.75
IVUS Provides Prognostic Data for LM Disease

Independent predictors of MACE @11.7 months: DM (P=0.004), any untreated lesion >50% (p=0.037), and IVUS MLD (P=0.005).

AS Abizaid et al JACC 1999;34:707-15
43 patients with single lesion 50%DS, short 8.5 mm, reference 3.1 mm

Am J Cardiol 2001;87:136-141
IVUS vs FFR
WHC: Ben-Dor et al. AHA 09

42 (67.7%) with MLA<4mm^2 had non ischemic FFR>0.8
47 (75.8%) with MLA<4mm^2 had non ischemic FFR>0.75

1 (37.5%) with MLA<3mm^2 had non ischemic FFR>0.8
17 (63.6%) with MLA<3mm^2 had non ischemic FFR>0.75
Plaque composition and vulnerability:

What do you mean …?!

**Plaque Vulnerability**

1- Morphologic vulnerability
2- Functional vulnerability
Can IVUS characterize vulnerable plaque?

IVUS can characterize multiple features of vulnerable plaque, including:

- Plaque progression and regression
- Ulceration
- Plaque Burden
- Arterial Remodeling
The risk for death or acute myocardial infarction in the next five years is **20 times higher** for an ischemic lesion compared to a non-ischemic lesion !!!

Iskander S, Iskandrian A E  JACC 1998
Summary

- Angiography limited
- For questions of ischemia use FFR
- Use IVUS for PCI guidance
  - Reference lumen diameter-stent size
  - Minimal stent area-expansion
- Act on evidence, don’t guess
Where do we stand?

### Recommendations for the clinical value of intracoronary diagnostic techniques

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<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
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<tr>
<td>FFR to identify haemodynamically relevant coronary lesion(s) in stable patients when evidence of ischaemia is not available.</td>
<td>I</td>
<td>A</td>
<td>50,51,713</td>
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<td>FFR-guided PCI in patients with multivessel disease.</td>
<td>Ila</td>
<td>B</td>
<td>54</td>
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<td>IVUS in selected patients to optimize stent implantation.</td>
<td>Ila</td>
<td>B</td>
<td>702,703,706</td>
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<td>IVUS to assess severity and optimize treatment of unprotected left main lesions.</td>
<td>Ila</td>
<td>B</td>
<td>705</td>
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<td>IVUS or OCT to assess mechanisms of stent failure.</td>
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<td>OCT in selected patients to optimize stent implantation.</td>
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Thank you