SAFETY OF DEFERRING PCI BASED UPON FFR

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From a patient’s point of view, the wind tunnel for any index to be used in clinical medicine, is its *influence on outcome*

For most invasive indexes in the cath lab, no outcome studies have been performed or were “negative”

*FFR* is the only invasive index used which systematically improved outcome in RCT’s, which will be highlighted in the present session
FFR and Clinical Outcome:

3 important questions:

• Is it safe to defer PCI if FFR is negative?

• Is it indicated to perform PCI if FFR is positive?

• Does systematic use of FFR improve outcome of PCI?
Risk to die or experience myocardial infarction in the next 5 years related to a coronary stenosis:

- **non-ischemic stenosis:** < 1% per year *  
  (NUCLEAR studies, PET, MRI, DEFER, FAME)

- **ischemic stenosis, if left untreated:** 5-10% per year  
  (Many historical registries, nuclear studies, ACIP, CCTA, MRI, FFR)

- **stented stenosis:** 2-3% per year  
  (e.g DEFER, FAME, SYNTAX, many large studies and registries)
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
Events (within 1 year)

No events/1 year

- Calcium
- CTA
- SPECT
- MR-PERF
- DSMR
Is it important to detect ischemia?

Log hazard ratio for revascularization (Revasc) vs medical therapy (Medical Rx) as a function of % myocardium ischemic based on final Cox proportional hazards model

Above 10% ischemic myocardium, the survival benefit from revascularisation increases with the extent of ischemia


ETP, April 2011
The *DEFER* Study: Flow Chart

Patients scheduled for PCI without Proof of Ischemia (n=325)

**Randomization**

- **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
**DEFER: Cardiac Death And Acute MI After 5 Years**

- **non-ischemic stenosis, R/x**
- **non-ischemic stenosis, R/x + stent**
- **ischemic stenosis, R/x + stent**

P = 0.002

P = 0.003

P = 0.21

- DEFER
  - FFR ≥ 0.75: 3.3%
  - FFR < 0.75: 15.7%

- PERFORM
  - FFR ≥ 0.75: 7.9%

- REFERENCE

**DEFER-study, JACC 2007; 49 : 2105-2111**
**DEFER: Cardiac Death And Acute MI After 5 Years**

- non-ischemic stenosis, R/x
- non-ischemic stenosis, R/x + stent
- ischemic stenosis, R/x + stent

**DEFER-study, JACC 2007; 49 : 2105-2111**
Freedom From Chest Pain

[Graph showing differences between baseline, 1 month, 1 year, 2 years, and 5 years for Defer group, Perform group, and Reference group.]

- **Defer group** (blue bars) indicates FFR > 0.75 across all years.
- **Perform group** (red bars) also shows FFR > 0.75 at baseline and 1 month, dropping to FFR < 0.75 at 1 year, then back to FFR > 0.75 at 2 years and 5 years.
- **Reference group** (gray bars) consistently shows FFR < 0.75 across all years.
Stenting a functionally non-significant (FFR-negative) stenosis does NOT make any sense.

*It is unnecessary, expensive, and increases the risk of death and MI without any symptomatic benefit*

Further evidence from FAME, FAME-2 and (indirectly) from PROSPECT
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

FFR-guided PCI
- Measure FFR in all indicated stenoses
- Stent only those stenoses with FFR ≤ 0.80

follow-up at 1, 2, 5 year
Measuring FFR in Multivessel Disease: FAME Study (N=1005) : One Year Outcomes

- Death: 3, 1.8
- MI: 8.7, 5.7
- Repeat Revasc: 9.5, 6.5
- Death/MI: 11.1, 7.3
- MACE: 18.3, 13.2

- Angio-Guided: ~40% ↓
- FFR-Guided: ~35% ↓
- ~30% ↓
- ~35% ↓

\[ p=0.04 \] \[ p=0.02 \]

Outcome of Deferred Lesions:

513 Deferred Lesions and 901 stented lesions in 509 FFR-Guided Patients

2 Years

9 Late Myocardial Infarctions

8 Due to a New Lesion or Stent Related

1 Myocardial Infarction due to an Originally Deferred Lesion

Only 1/513 or 0.2% of deferred lesions resulted in a late myocardial infarction
Outcome of Deferred Lesions:

513 Deferred Lesions and 901 stented lesions in 509 FFR-Guided Patients

2 Years

53 Repeat Revascularizations

10 Originally Deferred Lesions with Clear Progression

37 in a New Lesion and/or in a Restenotic One

6 Without FFR or Despite an FFR > 0.80

Only 10/513 or 1.9% of deferred lesions clearly progressed requiring repeat revascularization
Risk for death or MI related to functionally non-significant stenosis:

- **DEFER study**: 0.6 % (follow-up of 5 years; *JACC* 2008)
- **FAME study**: 0.4 % per year (f.u. of 2 years; *NEJM* 2009)

Also with other modalities of investigation, outcome of non-significant lesions is excellent:

- **CCTA studies**: 0.7 % per year (*Min, JACC* 2011)
- **Prospect study**: 0.4 % per year (*Stone, NEJM* 2011)
CONCLUSION:

Deferring stenting of a functionally non-significant stenosis as indicated by FFR > 0.80, is safe and associated with an annual death & AMI infarction rate of < 1% with adequate medical therapy.

Stenting of such stenosis is unnecessary, expensive, and even sometimes hazardous with increase of the risk of adverse events.
The key issue in decision making whether and where to stent, is the presence and extent of inducible ischemia related to a particular stenosis.

No ischemia → no angina pectoris & favourable outcome
   no benefit by stenting

Ischemia → generally angina pectoris & unfavourable outcome
   proven benefit by stenting
**DEFER study (N=325):**
Cardiac death and Acute MI after 5 years

- **P< 0.03**

- **non-ischemic stenosis, treated medically**

- **ischemic stenosis, treatment by PCI & optimum R/x**

- **ischemic lesion is much more dangerous than non-ischemic lesion**

- **risk of individual non-ischemic lesion to cause death or AMI, is very small and < 1 % per year with R/x !!**

*JACC 2007; 49: 2105-2111*
Coronary Occlusion at 5 Years as a Function of Stenosis Severity

Stenosis Severity at Baseline

Coronary Occlusion at 5 Years as a Function of Stenosis Severity

Adapted from Alderman et al. J Am Coll Cardiol 1993
Paradox or antithesis?

Excellent outcome of medical treatment in non-ischemic stenosis (DEFER study, many non-invasive studies) versus concept of vulnerable plaque
today → ? → tomorrow

TCFA → ? → Plaque Rupture

Renu virmani, ETP course 2005
Let’s look a little bit more critical to such “plaques”.... What are the facts ?? What is the fiction ??
(Vulnerable) Plaque: Facts and Fiction

FACTS:
- plaques are very common
- majority of plaques has an excellent prognosis with medical treatment
- only few plaques are vulnerable
- strongest indicator with respect to prognosis is associated ischemia

FICTION:
- every plaque is vulnerable
- every vulnerable plaque leads to ACS
- most ACS occurs in mild plaques
- vulnerability can be assessed by imaging
Underlying Stenosis Severity of Abrupt Total Occlusions

Falk, Shah and Fuster, Circulation 1995

"Acute Coronary Syndromes most often occur at the site of mild stenoses"
Do Myocardial Infarctions Evolve from Mild Stenoses?

Serial Angiographic (Retrospective) Studies in Patients with MI and a Prior Coronary Angiogram

No QCA, No IVUS but unblinded “eyebolling”

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Delay Angio-MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrose et al. JACC 1988</td>
<td>23</td>
<td>1 month to 7 years</td>
</tr>
<tr>
<td>Little et al. Circulation 1988</td>
<td>42</td>
<td>4 days to 6.3 years</td>
</tr>
<tr>
<td>Giroud et al. AJC 1992</td>
<td>92</td>
<td>1 month to 11 years</td>
</tr>
<tr>
<td>Moise et al. AJC 1984</td>
<td>116</td>
<td>39 months</td>
</tr>
<tr>
<td>Webster et al. JACC 1990</td>
<td>30</td>
<td>55 months</td>
</tr>
<tr>
<td>Hackett et al. AJC 1989</td>
<td>10</td>
<td>21 months</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>313</strong></td>
<td><strong>A few days to 11 years</strong></td>
</tr>
</tbody>
</table>

(average 3.9 years !!!)
THE MYTHE OF
THE “DANGEROUS” PLAQUE

The hypothesis of the occurrence of acute MI on such previously non-significant plaque is based upon

- 6 small retrospective studies
- with a total of 313 patients
- in whom the “index” catherization was performed an average of 3.9 years before the acute event

All other literature (21 “meta-analyses” and hundreds of references), refer to these 6 studies !!!
Coronary Occlusion at 5 Years as a Function of Stenosis Severity

Adapted from Alderman et al. J Am Coll Cardiol 1993
**DEFER study (N=325)**:
Cardiac death and Acute MI after 5 years

![Graph showing risk of cardiac death and Acute MI after 5 years based on FFR values.](image)

- **non-ischemic stenosis, treated medically**: 3.3%
- **ischemic stenosis, treatment by PCI & optimum R/x**: 15.7%

**P< 0.03**

- ischemic lesion is much more dangerous than non-ischemic lesion
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*JACC 2007; 49: 2105-2111*
250 consecutive patients with ST-elevation MI in the Catharina Hospital:

• underlying stenosis angiographically significant in 92 % of the cases

• *At meticulous anamnesis, 80 % of patients had recurrent chest pain in the year before the acute myocardial infarction occurred !!*

*Frobert et al CCI, 2007, 70: 958-965*
Incidence of coronary artery disease in *asymptomatic*, apparently healthy persons

> 50 years old : 25%
> 60 years old : 40%

*Sims et al, Am Heart J 1983*
*Maseri, Ischemic Heart Disease 1995*

*What about the prognosis of these patients?*

*Related to inducibility of ischemia*
• structure of the coronary circulation
• relation between vessel size and perfusion area
• endothelium and development of atherosclerosis
• the 2 or 3 compartment model of the coron circulation
• collaterals
• why functional testing / FFR ?
• which lesions should be treated
• vulnerable plaques: facts & fiction
• ischemia & vulnerability: paradox or antithesis ?
"The missing link"

Is there a link between vulnerability and ischemia?

**Hypothesis:**

- repetitive ischemia *and*
- high shear stress / pressure gradients

*induce vulnerability*

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Supported by studies on the relation between vulnerability markers and low FFR: on-going work of Pasterkamp et.al. *Heart 2007*
TLR2 stimulation (Pam3Cys)

Versteeg et al, Heart 2007
Pro-inflammatory cytokines, activated monocytes, etc

Vulnerability ("out of the blue")
Concept of Tomorrow:

ischemic episodes

Pro-inflammatory cytokines, activated monocytes, etc

Vulnerability
Concept of today:

ischemic episodes

Pro-inflammatory cytokines etc

Vulnerability

by the way: 70% area Stenosis !!
new paradigm:

Plaque / stenosis

↓

Ischemic episodes

↓

production of remodelling-promoting substances

- successful remodelling, decrease of ischemia
- overshoot, plaque rupture

Searching for vulnerability starts with searching for ischemia
Suppose aliens would visit us and would like to investigate the determinants of a fire.

**Substance X**, always detected when there has been a fire

**Living unidentified object releasing the substance X**

“Substance X (also called “water”) must be a dangerous substance!”