FFR – Incorporating & Expanding it’s use in Clinical Practice

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Concept of FFR

• Maximum flow down a vessel in the presence of a stenosis…

…compared to the maximum flow in the hypothetical absence of the stenosis
Concept of FFR

$$\text{FFR} = \frac{Q_{\text{stenosis}}}{Q_{\text{normal}}} = \frac{\text{Stenotic perfusion press.}}{\text{Normal perfusion press.}} = \frac{P_d}{P_a}$$
Technical Aspect

- Sensor tipped angioplasty guidewires have been developed and are used to measure pressure and flow across a coronary stenosis.
- Safe and typically adds a few minutes to the total procedure time for the assessment of each lesion.
- Maximal blood flow (hyperemia) is most commonly induced by intravenous (140 mcg/kg/min) or intracoronary adenosine (right coronary artery 50 to 100 mcg, left coronary artery 100 to 200 mcg bolus).
FFR Validation

- A normal value is 1, while values <0.80 are associated with provokable ischemia with an accuracy > 90% and a specificity of 100%
- The occurrence of false negative and false positive FFR values is rare

Why Do We Need FFR?

• MPI lacks spatial resolution, particularly in MVD
• In the majority of patients undergoing PCI, noninvasive stress imaging has not been performed

PET-CT vs FFR

• 2 studies comparing FFR and nuclear perfusion scanning in patients with MVD, both of which demonstrated significant discordance between the 2 modalities

Am J Cardiol. 2007;99:896–902
Figure Legend:

Respective Proportion of Number of Vascular Abnormalities as Described at Coronary Angiography, MPI, and FFR

FFR = fractional flow reserve; MPI = myocardial perfusion imaging.
Coronary Angio vs FFR

• Fractional Flow Reserve Versus Angiography for Multi-vessel Evaluation (FAME) trial
FAME Trial

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

Tonino et al, NEJM 2009
FAME primary end point

FAME: FFR-guided PCI was superior to Angio-guided PCI in MVD

Tonino et al, NEJM 2009
### FAME

|                           | ANGIO-group N=496 | FFR-group N=509 | p-value  
|---------------------------|-------------------|-----------------|--------
| Stents per patient        | 2.7 ± 1.2         | 1.9 ± 1.3       | <0.001 |
| Contrast agent used (ml)  | 302 ± 127         | 272 ± 133       | <0.001 |
| Materials used at procedure (US $) | 6007       | 5332            | <0.001 |
| Length of hospital stay (days) | 3.7 ± 3.5 | 3.4 ± 3.3 | 0.05   |

Tonino et al, NEJM 2009
Kaplan–Meier Survival Curves According to Study Group.

(P = 0.20)
Approximately one fourth of the deferred lesions appeared >70% narrowed on visual interpretation of the angiogram!
IVUS vs FFR

- FFR is a physiologic assessment, whereas IVUS/OCT are highly accurate for vessel sizing and confirming stent expansion and strut apposition.

- In a report of 25 IVUS or OCT imaging studies correlated to FFR, MLA >4 mm² had FFR > 0.8 in 91% of cases with a strong negative correlation.

- An MLA <4 mm² had poor correlation to FFR, with most studies reporting a roughly 50% chance of having an FFR <0.8.

*J Am Coll Cardiol. 2012 Mar;59(12):1080-9*
Data supporting FFR Guided PCI
DEFER study

325 patients

181 patients FFR > 0.75 => No ischaemia

Randomisation

144 patients FFR < 0.75 => Ischaemia

Performance of PTCA
90 patients

Deferral of PTCA
91 patients

2 yr follow-up

Bech et al, Circulation 2001
DEFER: 2 year follow-up: event-free survival

Bech et al, Circulation 2001

FFR $\geq 0.75$. Geen PTCA
FFR $\geq 0.75$. Wel PTCA
DEFER Study Result at 5 years

In patients with proven CAD WITHOUT ischemia, annual death/MI rate is 1% and NOT improved by PCI

Pijls et al, JACC 2007
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., Bindu Kalesan, M.P.H., Emanuele Barbato, M.D., Ph.D., Pim A.L. Tonino, M.D., Ph.D., Zsolt Piroth, M.D., Nikola Jagic, M.D., Sven Möbius-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., B.S.N., Peter Jüni, M.D., and William F. Fearon, M.D., for the FAME 2 Trial Investigators*
FAME 2 Trial

• In patients with stable coronary artery disease for whom PCI was being considered, all stenoses were assessed by FFR

• Patients in whom at least one stenosis was functionally significant (FFR, ≤0.80) were randomly assigned to FFR-guided PCI plus OMT (PCI group) or OMT alone (medical-therapy group)
FAME 2 Trial

A Primary End Point
- PCI vs. medical therapy:
  - Hazard ratio, 0.32 (95% CI, 0.19–0.53); P<0.001
- PCI vs. registry:
  - Hazard ratio, 1.29 (95% CI, 0.49–3.39); P=0.61
- Medical therapy vs. registry:
  - Hazard ratio, 4.32 (95% CI, 1.75–10.70); P<0.001

B Death from Any Cause
- PCI vs. medical therapy:
  - Hazard ratio, 0.33 (95% CI, 0.03–3.17); P=0.31
- PCI vs. registry:
  - Hazard ratio, 1.12 (95% CI, 0.05–27.33); P=0.54
- Medical therapy vs. registry:
  - Hazard ratio, 2.66 (95% CI, 0.14–51.18); P=0.30

C Myocardial Infarction
- PCI vs. medical therapy:
  - Hazard ratio, 1.05 (95% CI, 0.51–2.19); P=0.89
- PCI vs. registry:
  - Hazard ratio, 1.61 (95% CI, 0.48–5.37); P=0.41
- Medical therapy vs. registry:
  - Hazard ratio, 1.65 (95% CI, 0.50–5.47); P=0.41

D Urgent Revascularization
- PCI vs. medical therapy:
  - Hazard ratio, 0.13 (95% CI, 0.06–0.30); P<0.001
- PCI vs. registry:
  - Hazard ratio, 0.63 (95% CI, 0.19–2.03); P=0.43
- Medical therapy vs. registry:
  - Hazard ratio, 4.65 (95% CI, 1.72–12.62); P<0.001

No. at Risk
- Medical therapy
  - PCI: 447, Registry: 166
  - PCI: 414, Registry: 156

No. at Risk
- PCI
  - PCI: 447, Registry: 166
  - PCI: 414, Registry: 156
Moderate LM Stenosis

• Hamilos and colleagues reported 213 patients with moderate left main disease in whom FFR was measured
• FFR was nonischemic in 138 of these patients, and revascularization was deferred
• In this study, as in previous ones, experienced interventional cardiologists were unable to predict accurately which lesions would have a significant FFR on the basis of their interpretation of the angiogram

Circulation. 2009;120:1505–1512
Kaplan–Meier mortality curves showing percent survival (A) and major adverse cardiac events (MACE; B) in the 2 study groups.

FFR for Risk Stratification (FSS)
Proportions of Study Population

Proportions of the study population according to the tertiles of the classic SYNTAX score (SS) (A) and those of the functional SYNTAX score (FSS) (B). After incorporating FFR into the SS to calculate FSS, 32% of patients moved from a higher-risk group to a lower-risk group as follows: 38% of the highest SS tertile moved to the medium- or lowest-risk FSS group, whereas 59% of the medium-risk SS tertile moved to the lowest-risk FSS group.
Outcomes According to the SS

The rates of death or myocardial infarction (MI) (A), and the rates of major adverse cardiac events (MACE), as composite of death, MI, or any repeat revascularization including repeat percutaneous coronary intervention and coronary artery bypass graft (B) according to the tertiles of SS and FSS. The rate of death or MI as a critical hard endpoint was significantly different in the FSS groups unlike the SS groups. The rate of MACE was accordingly increased for the highest-risk group; this trend was attenuated in the FSS groups compared with the classic SS groups. *p < 0.01, **p < 0.001. Abbreviations as in Figure 1.
Figure 1. Rate of patients with multivessel disease before (A) and after (B) fractional flow reserve (FFR) measurement. Rate of patients with 1, 2 to 3, and ≥4 anastomoses (C). Angio indicates angiography.
## Table 3. Clinical End Points at the 36-Month Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Angiography-Guided Group (n=429), n (%)</th>
<th>FFR-Guided Group (n=198), n (%)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>31 (7)</td>
<td>7 (4)</td>
<td>1.712 (0.843–3.475)</td>
<td>0.137</td>
</tr>
<tr>
<td>MI</td>
<td>25 (6)</td>
<td>12 (6)</td>
<td>0.913 (0.453–1.841)</td>
<td>0.780</td>
</tr>
<tr>
<td>TVR</td>
<td>14 (3)</td>
<td>9 (5)</td>
<td>0.671 (0.276–1.630)</td>
<td>0.378</td>
</tr>
<tr>
<td>MACEs</td>
<td>52 (12)</td>
<td>22 (11)</td>
<td>1.030 (0.627–1.692)</td>
<td>0.908</td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; FFR, fractional flow reserve; HR, hazard ratio; MACEs, major adverse cardiovascular event; MI, myocardial infarction; and TVR, target vessel revascularization.
Rate of patients with symptoms at baseline and at the last clinical follow-up

<table>
<thead>
<tr>
<th></th>
<th>ANGIO</th>
<th>FFR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASELINE</strong></td>
<td>377 [88%]</td>
<td>174 [88%]</td>
</tr>
<tr>
<td></td>
<td><strong>FOLLOW-UP</strong></td>
<td></td>
</tr>
<tr>
<td>ANGIO</td>
<td>201 [47%]</td>
<td></td>
</tr>
<tr>
<td>FFR</td>
<td>62 [31%]</td>
<td></td>
</tr>
</tbody>
</table>

OR=1.000, 95% C.I. 0.597 to 1.675; p=1.000

OR=1.948, 95% C.I. 1.362 to 2.786; p<0.001

Patients (%) with CCS class II-IV
Graft Patency

Overall occlusion-free graft survival

- Angio-guided
- FFR-guided

Log Rank 6.297, p=0.012

Follow-up (months)

Angio-guided: 174 128 83 39
FFR-guided: 60 47 26 16

Circulation 2013 Sep;128(13):1405-11
At subsequent multivariate analysis, the only independent variables predicting adverse events were:

- FFR category ($P < 0.001$)
- Length of stent ($P < 0.01$).

**TABLE 4.** Crude and Stent Length–Adjusted ORs for Adverse Events With 95% CIs for the 5 Categories of FFR

<table>
<thead>
<tr>
<th>FFR Category</th>
<th>Crude OR</th>
<th>Adjusted OR for Stent Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR &gt;0.95</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>FFR 0.91–0.95</td>
<td>1.28 (0.60–2.75)</td>
<td>1.25 (0.58–2.70)</td>
</tr>
<tr>
<td>FFR 0.86–0.90</td>
<td>3.71 (1.79–7.67)</td>
<td>3.71 (1.79–7.71)</td>
</tr>
<tr>
<td>FFR 0.81–0.85</td>
<td>5.10 (2.23–11.67)</td>
<td>4.91 (2.13–11.31)</td>
</tr>
<tr>
<td>FFR &lt;0.80</td>
<td>7.44 (3.12–17.75)</td>
<td>7.35 (3.04–17.73)</td>
</tr>
<tr>
<td>Stent length, per 5 mm</td>
<td>...</td>
<td>1.27 (1.08–1.51)</td>
</tr>
</tbody>
</table>

_Circulation_. 2002;105(25):2950
Jailed Side Brach and FFR
Jailed Side Brach and FFR

<table>
<thead>
<tr>
<th>% Stenosis</th>
<th>≥50, &lt;75</th>
<th>≥75</th>
</tr>
</thead>
<tbody>
<tr>
<td>All lesions (n = 94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFR &lt;0.75</td>
<td>0</td>
<td>20 (27%)</td>
</tr>
<tr>
<td>FFR ≥0.75</td>
<td>20</td>
<td>53</td>
</tr>
<tr>
<td>Vessel size ≥2.5 mm (n = 28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFR &lt;0.75</td>
<td>0</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>FFR ≥0.75</td>
<td>7</td>
<td>13</td>
</tr>
</tbody>
</table>

(J Am Coll Cardiol 2005;46:633–7)
Challenges: Serial stenoses
Challenges: Serial stenoses

\[
\text{FFR(A)}_{\text{app}} = P_m / P_a
\]
\[
\text{FFR(A)}_{\text{true}} = P_m' / P_a' = P_d' / P_a'
\]
\[
\text{FFR(A)}_{\text{pred}} = \frac{P_d - [(P_m / P_a) \times P_w]}{(P_a - P_m) + (P_d - P_w)}
\]

\[
\text{FFR(B)}_{\text{app}} = P_d / P_m
\]
\[
\text{FFR(B)}_{\text{true}} = P_d' / P_m' = P_d' / P_a'
\]
\[
\text{FFR(B)}_{\text{pred}} = 1 - \frac{(P_m - P_d) \cdot (P_a - P_w)}{P_a \times (P_m - P_w)}
\]

(Circulation. 2000;102:2371-2377.)
Coronary Pressure & FFR: Pull-Back Curve

pressure wire pulled back from distal LAD to ostium of LCA during sustained hyperemia

$\Delta P(A+B)$

$\Delta P(B)$

$\Delta P(A)$

PROXIMAL STENOSIS (A)

DISTAL STENOSIS (B)

mm Hg

150

100

50

0

10 sec

guiding catheter

pressure wire
Distal: 0.45

Prox: 0.88
Pred: 0.74

Prox: 0.75

Final: 0.84
Diffuse coronary disease: gradual increase of pressure.
Challenges: Downstream Stenosis and intermediate LM disease

**FIGURE 2** Case Example of the Effect of Complete LAD Occlusion

Variable Downstream LAD Disease

After balloon inflation, $FFR_{\text{epi}}$ decreases to 0.35

**FIGURE 1** Experimental Layout

$FFR_{\text{true}} = 0.77$  
$FFR_{\text{app}} = 0.82$

(J Am Coll Cardiol Intv 2015;8:398–403)
**LM-CLINICAL IMPLICATIONS**

- FFR in the nondiseased vessel is <0.80 Significant
- If the FFR is >0.85 it can be assumed that the true FFR will be >0.80.
- If the FFR is between 0.81 -0.85 and the FFRepi is < 0.45, then it is possible that the true FFR will be < 0.80 after revascularization of the downstream epicardial disease

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*(J Am Coll Cardiol Intv 2015;8:398–403)*
Why we should use FFR

• Accuracy / extremely reproducible
• Independent of hemodynamic changes
• Superb spatial resolution
• Accounts for collateral flow
• Safety
• Cost reduction
• Better/complete relief of ischemia
• Risk Stratification (FSS)
Conclusions

• Should FFR be measured in all cases of PCI?
• If a patient has typical angina and SVD with a significant-appearing lesion that is ischemic on a noninvasive stress imaging study, then FFR measurement is not necessary.
• If a patient is having an acute MI with significant SVD, FFR is not necessary.
• The vast majority of cases in the cath lab involve patients with MVD, lesions of indeterminate severity, or discordant or absent stress imaging data.
• In these scenarios, there is now a wealth of data supporting the routine measurement of FFR to guide PCI.