Fractional Flow Reserve

A physiological approach to guide complex interventions

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What is FFR?

- Fractional Flow Reserve (FFR) is a lesion specific, physiological index determining the hemodynamic severity of intracoronary lesions[1].

- FFR can accurately identify lesions responsible for ischemia which in many cases would have been undetected or not correctly assessed by angiography or IVUS[2].

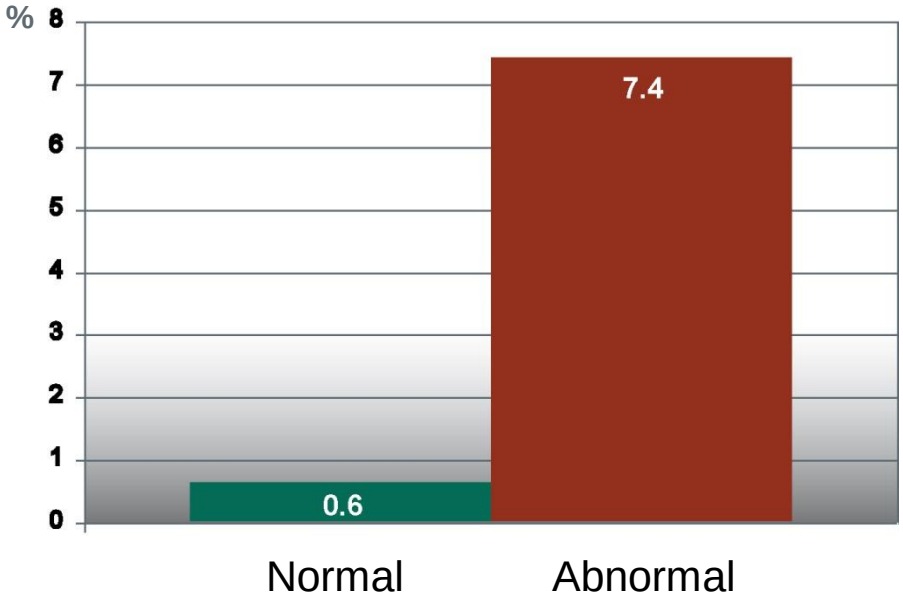
- FFR is measured at maximum hyperemia[1].

[1] De Bruyne B, et al, Heart 2008;94:949-959.

[2] Tonino PM, et al. NEJM, 2009; 360:213-224 .

Inducible ischemia

- Studies such as Iskander et al have shown that a person is significantly more likely to die or have a myocardial infarction (MI) if they have a lesion causing inducible ischemia than if they do not.
- Therefore it is essential to differentiate between both types of lesions.



Average Annual Hard Events
(Death or MI) in > 12000 Patients

Iskander S, et al J. Am. Coll. Cardiol. 1998;32;57-62

Inducible ischemia

- Treating a non-ischemic lesion does NOT relieve symptoms or prevent future cardiac events.
- FFR is an excellent way to provide proof of ischemia.

Pijls et al. J Am Coll Cardiol 2007;49:2105–11.

Treatment strategy

- If a lesion(s) is causing inducible ischemia
  then it is contributing to the patient's symptoms of angina – by treating with a stent there, is a high probability that this will relieve the patient's symptoms, improve quality of life and potentially reduce long-term risk of events.

Pijls et al. J Am Coll Cardiol 2007;49:2105–11.

What's wrong with angiography?

- 54-y-o man,
  PTCA prox LAD 8 years ago,
  stable angina, occluded distal LCx.

- 48-y-o man,
  aborted sudden death.
  No other stenosis at angio.

What about other methods?

- Other testing methods such as IVUS[1], stress testing[2] and even perfusion scanning[3] are not as specific as FFR in determining the functional significance of a particular lesion on blood flow to the myocardium.

- FFR is also a cost-effective, time-efficient and practical method of assessment that can be used easily in a busy cardiac catheterization laboratory[4].

[1] Briguori, C et al, American Journal of Cardiology: 2001; 87: 2: 136-141

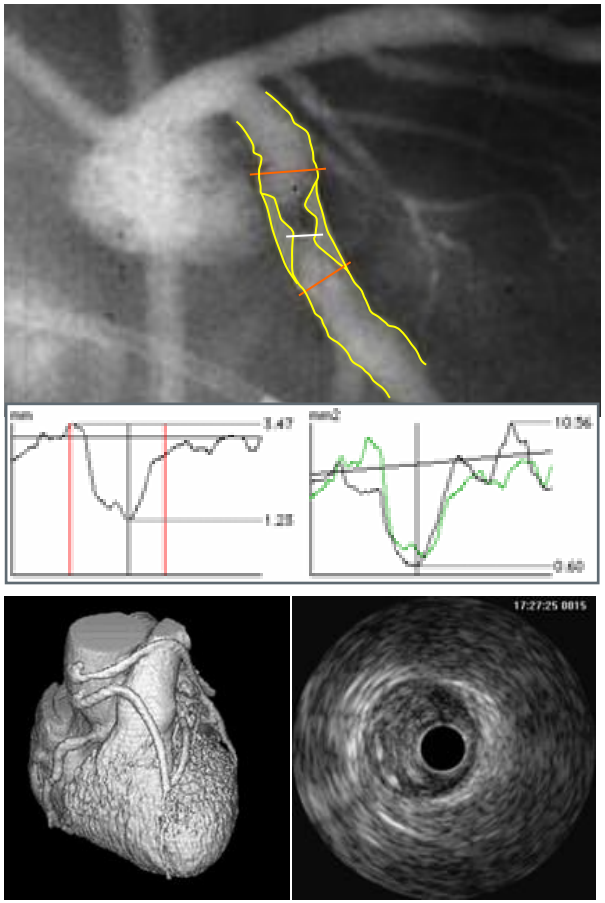
[2] Smart et al, JACC 2000;36:1265-1273.

[3] Melikian et al, J. Am. Coll Cardiol. Intv. 2010;3;307-314

[4] Tonino, P, et al. NEJM, Feb 2009; 360:213-224

Why guide coronary interventions with FFR?

- Imaging/morphologic modalities such as Angio, MSCT, IVUS cannot identify which individual lesion/lesions that are the cause of the patient's ischemia
- Imaging modalities can both over- and underestimate lesion severity, either leaving significant lesions untreated or causing excess stenting
- Imaging modalities do not take into account collateral flow or abnormal/impaired myocardium
- Non-invasive stress techniques are often in-conclusive and do not give physicians the detailed information needed to pinpoint significant lesions.



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European Guidelines

- Cardiologists and thoracic surgeons have written recommendations together, for when a patient should be revascularized (treated by PCI or CABG) rather than treated by optimal medical therapy alone.

- New guidelines: Functional testing (using a non-invasive test or FFR) is key in determining whether or not a patient should be revascularized*.

- FFR has been given the highest possible recommendation:

Class I
Level of Evidence A

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* Wijns, et al., *Eur Heart J (2010) 31(20): 2501-2555 first published online August 29, 2010*

FFR – Strongly Recommended

Table 33 Recommendations for specific percutaneous coronary intervention devices and pharmacotherapy

	Class[a]	Level[b]	Ref.[c]
FFR-guided PCI is recommended for detection of ischaemia-related lesion(s) when objective evidence of vessel-related ischaemia is not available.	I	A	15, 28
DES[d] are recommended for reduction of restenosis/re-occlusion, if no contraindication to extended DAPT.	I	A	45, 46, 55, 215

Table 1 Classes of recommendations

Classes of recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.

FFR Should be Used Before Deciding on Treatment

Table 8 Indications for revascularization in stable angina or silent ischaemia

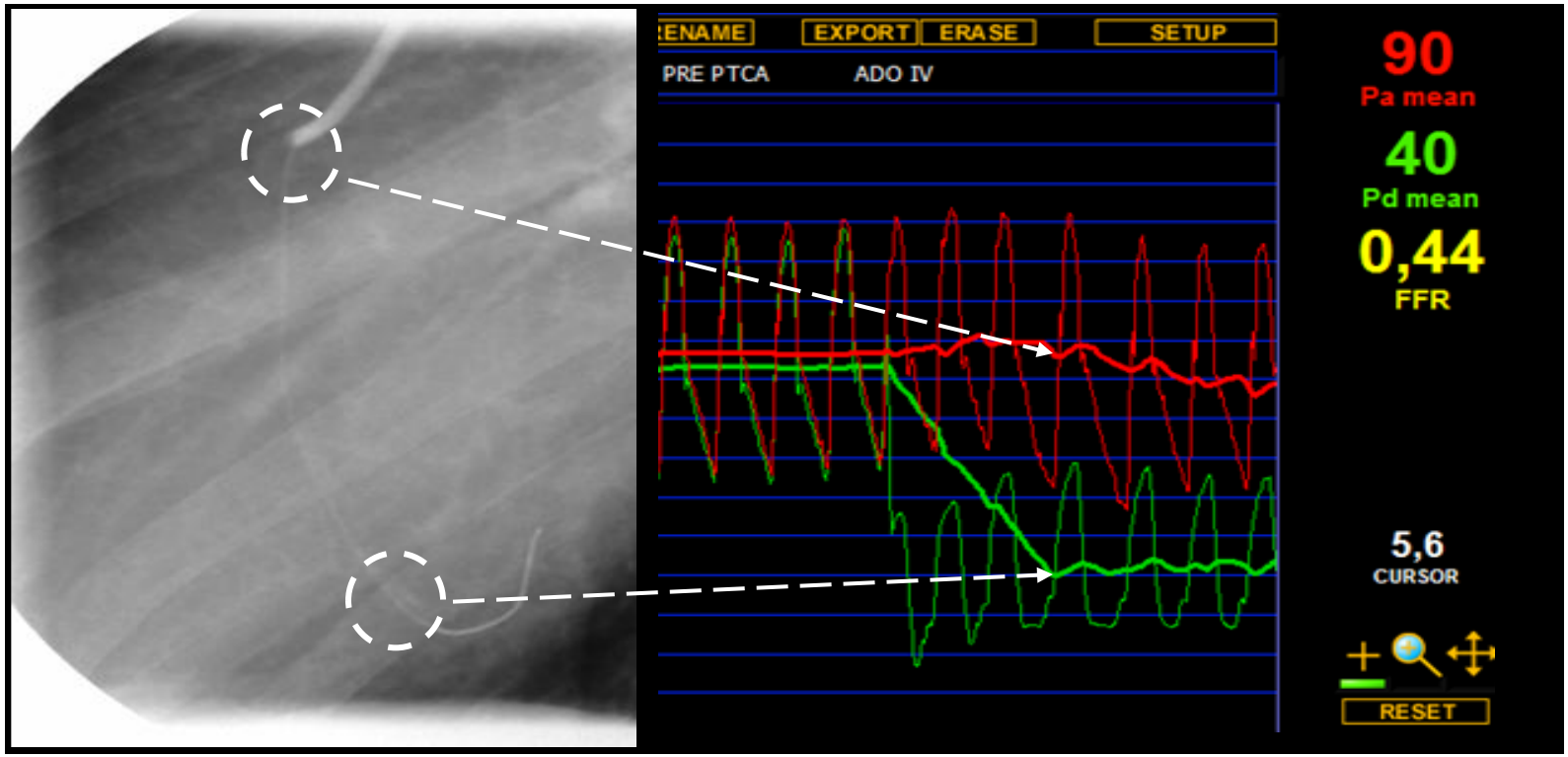
	Subset of CAD by anatomy	Class[a]	Level[b]	Ref.[c]
For prognosis	Left main >50%[d]	I	A	30, 31, 54
	Any proximal LAD >50%[d]	I	A	30–37
	2VD or 3VD with impaired LV function[d]	I	B	30–37
	Proven large area of ischaemia (>10% LV)	I	B	13, 14, 38
	Single remaining patent vessel >50% stenosis[d]	I	C	—
	1VD without proximal LAD and without >10% ischaemia	III	A	39, 40, 53
For symptoms	Any stenosis >50% with limiting angina or angina equivalent, unresponsive to OMT	I	A	30, 31, 39–43
	Dyspnoea/CHF and >10% LV ischaemia/viability supplied by >50% stenotic artery	IIa	B	—
	No limiting symptoms with OMT	III	C	—

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]With documented ischaemia or FFR <0.80 for angiographic diameter stenoses 50–90%.
CAD = coronary artery disease; CHF = chronic heart failure; FFR = fractional flow reserve; LAD = left anterior descending; LV = left ventricle; OMT = optimal medical therapy; VD = vessel disease.

For the treating physician, the new guidelines mean that FFR should be measured before a decision is made either to perform PCI or send the patient to surgery, in patients who come to the cath lab without a prior functional test and with a stenosis(es) 50-90% by angiography.

This is regardless of whether the patient has single-vessel disease, multivessel disease, or if the vessel is especially important, eg. proximal LAD or LMCA.

How does FFR work?



FFR_{myo} = Pd/Pa at hyperemia
FFR_{myo} = 40/90 = 0.44

Calculating FFR

Understanding the theory behind FFR helps you to trouble-shoot

FFR is measured during maximum hyperemia,
i.e. when there is maximum blood flow to the myocardium

Maximum hyperemia is important for two reasons:

- It is necessary to stress the heart to determine the presence and extent of inducible ischemia.

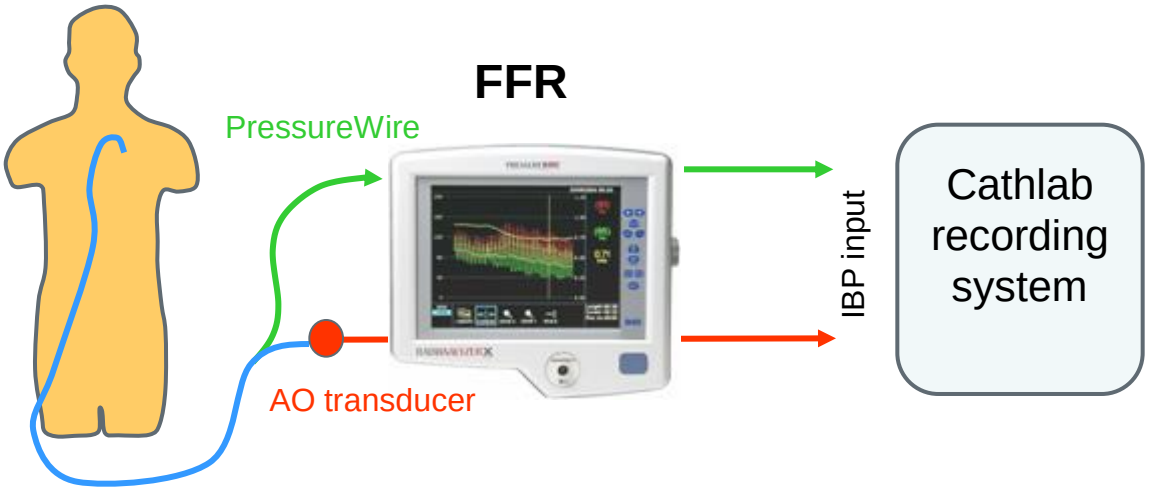
- We are measuring pressure to measure blood flow; pressure and flow in the coronary arteries are proportional ONLY at the point of maximum hyperemia. It is therefore only at this point that FFR is accurate.

PressureWire

- The distal pressure in the coronary artery is measured by a miniature pressure sensor located 3 cm from the tip of an 0.014” guidewire, called PressureWire™.

RadiAnalyzer Xpress

- PressureWire is connected to RadiAnalyzer Xpress, an interface which makes the FFR calculations automatically during the procedure.
  It displays both aortic and distal pressure wave curves.



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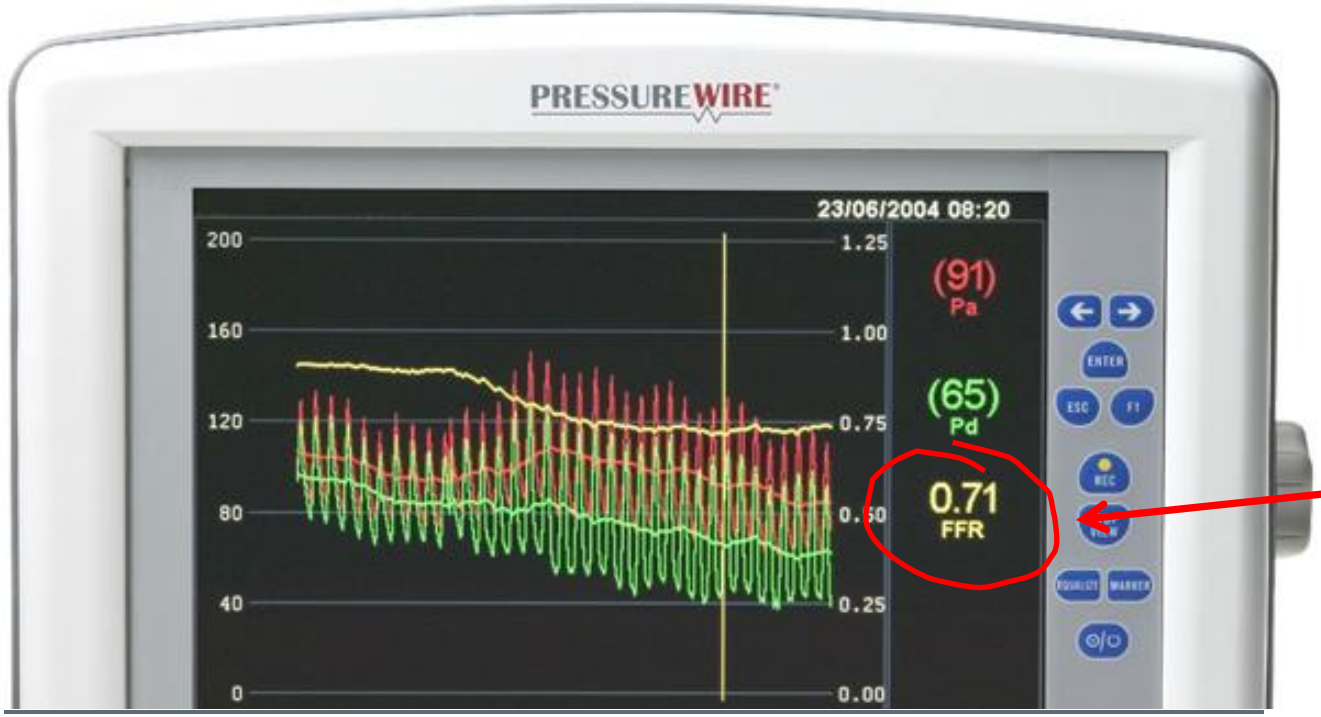
What does the FFR value mean?



FFR result = 71% of normal

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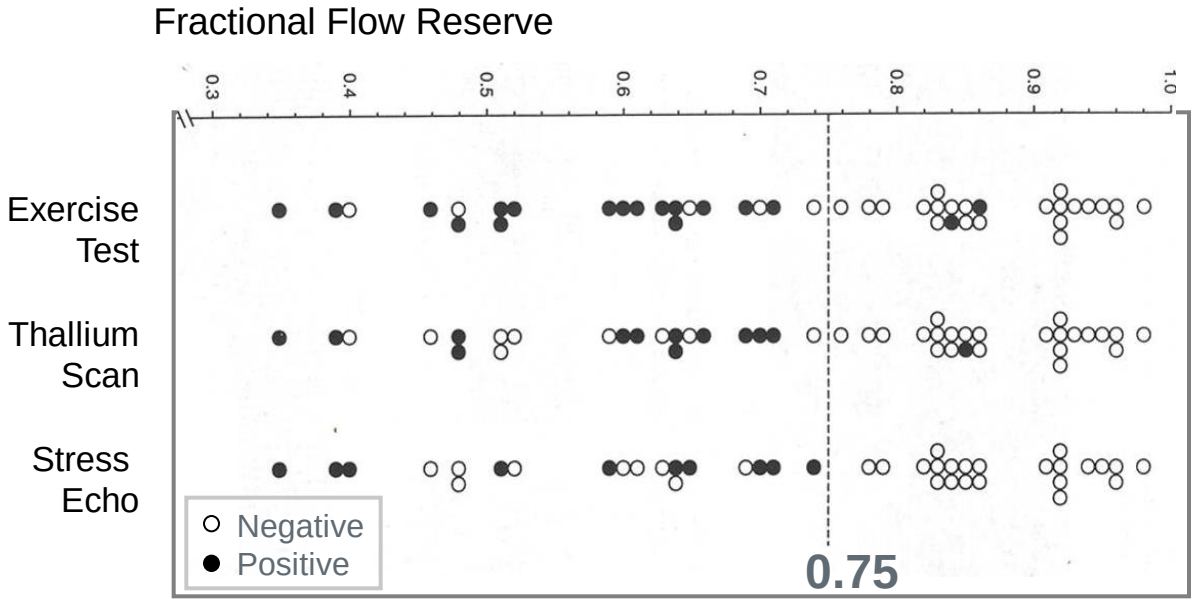
What does the FFR value mean (cont'd)?

During conditions of maximum hyperemia, only 71% of normal blood flow is able to reach the myocardium, due to one or more stenoses obstructing the flow in this vessel.

How accurate is FFR?

FFR < 0.75:

- Sensitivity = 88%
- Specificity = 100%



FFR has been validated against a "gold standard" for reversible ischemia, composed of 3 non-invasive tests.

Pijls NHJ ,et al. N Eng J Med 1996;334;26:1703-08.

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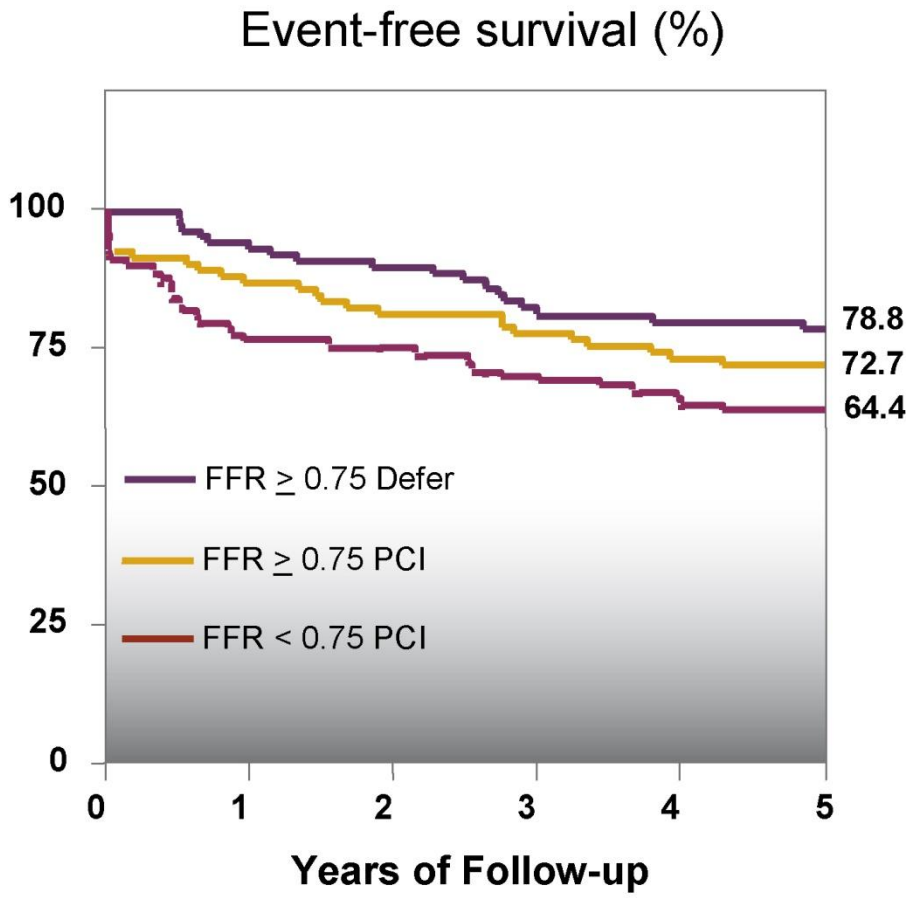
Prognosis - The DEFER Study

In the case of a coronary stenosis, where it is unclear if it can be held responsible for inducible ischemia, measuring FFR has important prognostic implications:

- FFR < 0.75 →
  Intervention is appropriate and results in significant improvement.
- FFR > 0.75 →
  No benefit from intervention, neither in terms of functional class nor in terms of adverse events.

Pijls, et al. J Am Coll Cardiol 2007;49:2105–11.

The DEFER Study: Five-year follow-up



The risk of "non-significant" stenoses to cause death or AMI is < 1 % per year

Pijls et al, J Am Coll Cardiol 2007;49:2105–11

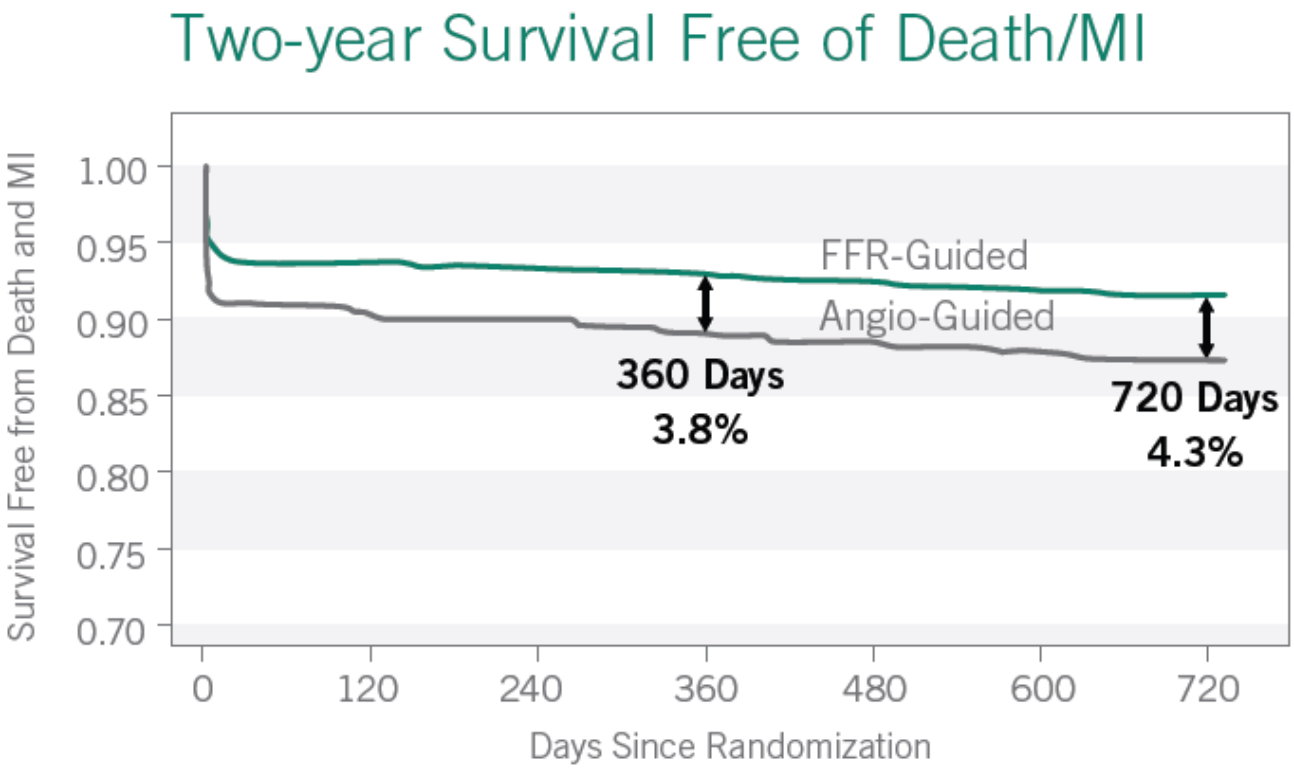
Improved Outcomes - The FAME Study[1]

- The results of the FAME Study validated PressureWire's clinical benefits by establishing that, compared to angiography alone, FFR measurement significantly reduces major adverse coronary events, is cost-saving and does not increase procedure time.

- **FAME Study Methods**
  - Randomized, prospective study – angiography only or angiography plus FFR
  - 20 centers in Europe and U.S.
  - 1,005 PCI patients undergoing DES stenting for multivessel disease

[1]Tonino et al. N Engl J Med 2009; 360:213-224;
Pijls et al. J Am Col. Cardiol 2010; 56: 177 - 184.

The FAME Study – Outcome Data



Tonino et al. N Engl J Med 2009; 360:213-224;
Pijls et al. J Am Col. Cardiol 2010; 56: 177 - 184.

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The FAME Study – Cost Savings Data

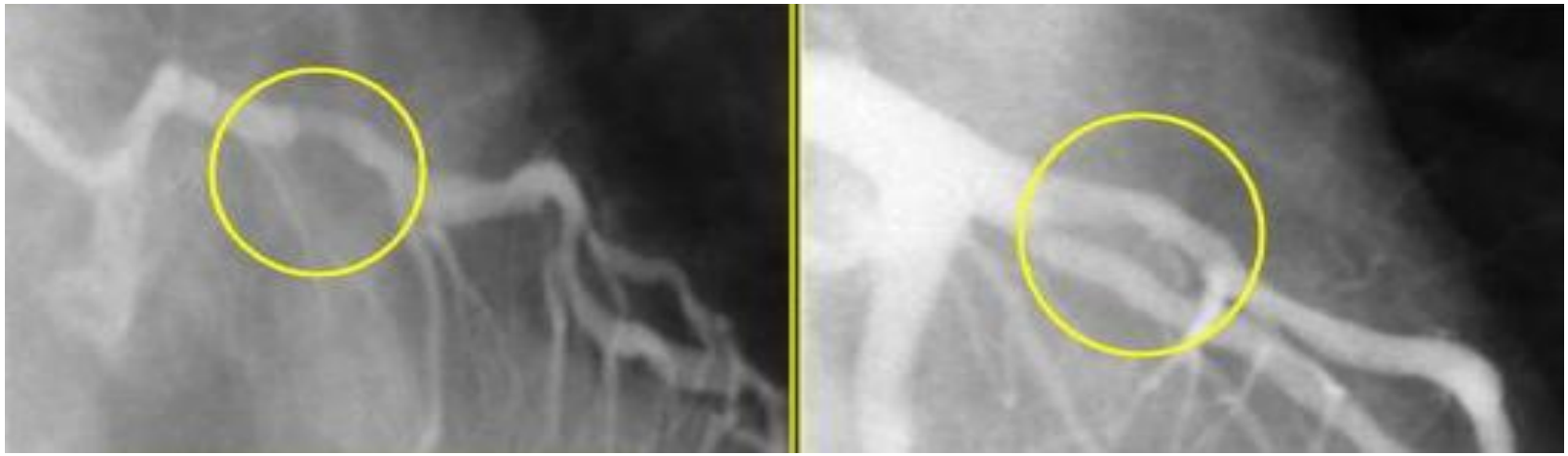
Improved Outcomes at Lower Costs

Bootstrap simulation indicated that the FFR-guided strategy was cost-saving in 99.8% and cost-effective in all 1,000 scenarios.

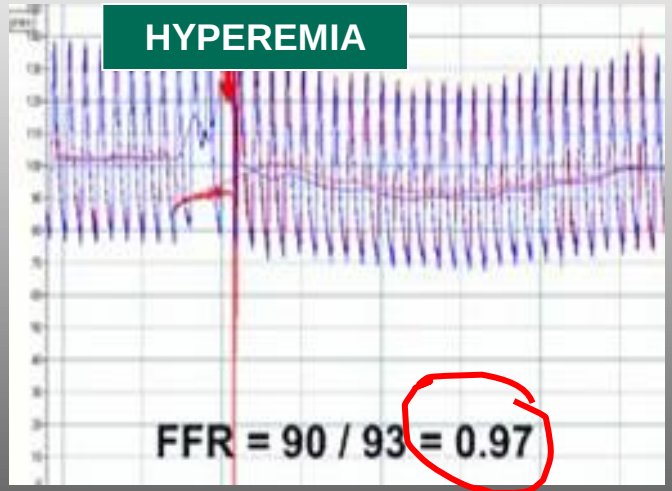
Tonino et al. N Engl J Med 2009; 360:213-224;
Pijls et al. J Am Col. Cardiol 2010; 56: 177 - 184.

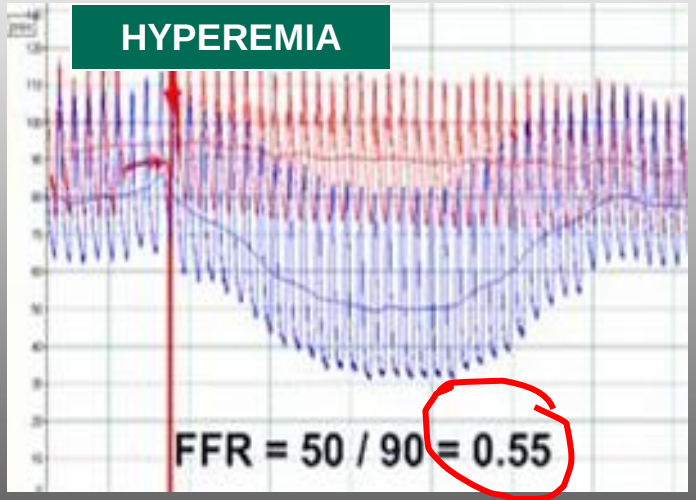
FFR provides the answer

- Which of these lesions *looks* flow limiting?



FFR can change the treatment strategy





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FFR provides the answer

Whatever the stenosis might *look* like…

- To understand the meaning of the stenosis for the patient, the only important number to know is the resulting distal perfusion pressure at hyperemia, as a fraction of normal perfusion pressure.

- This ratio determines the physiologic significance of the stenosis and its consequences for the patient, no matter what the stenosis looks like on angiography.

Unique features of FFR

- Normal value = 1.0 for every patient and every artery
- FFR is not influenced by changing hemodynamic conditions (heart rate, blood pressure, contractility)
- FFR specifically relates the influence of the epicardial stenosis to the myocardial perfusion area and blood flow
- FFR accounts for collaterals
- FFR has a circumscript threshold value (~0.75 – 0.80) to indicate ischemia
- FFR is easy to measure (success rate 99%) and extremely reproducible
- Pressure measurement has an unequal spatial resolution

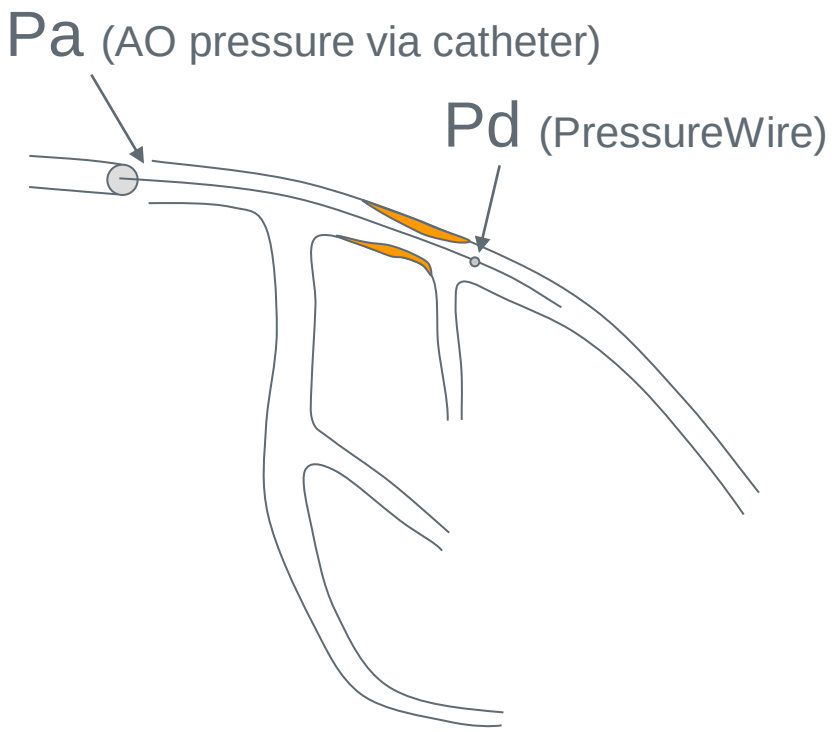
[1] De Bruyne, B et al, Heart; July 2008;94:949-959

The true definition

Definition of FFR
"Maximum achievable blood flow in stenotic coronary artery
divided by
Maximum blood flow in the same artery without stenosis"

$$FFR = \frac{Pd}{Pa}$$

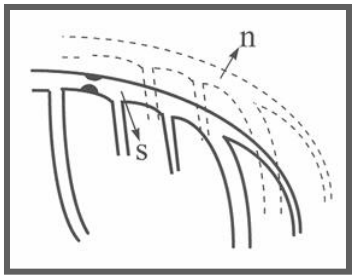
At maximum hyperemia



Clinical equivalence

It is important to remember that we are measuring pressure to measure blood flow:

- An FFR of 0.90 equates to 90% of normal maximum flow.
- An FFR of 0.80 equates to 80% of normal maximum flow.
- By changing the FFR from e.g. 0.50 to 0.95 by stenting the affected lesion then you are increasing blood flow from 50% to 95% of normal maximum flow.
- This is called Clinical Equivalence.

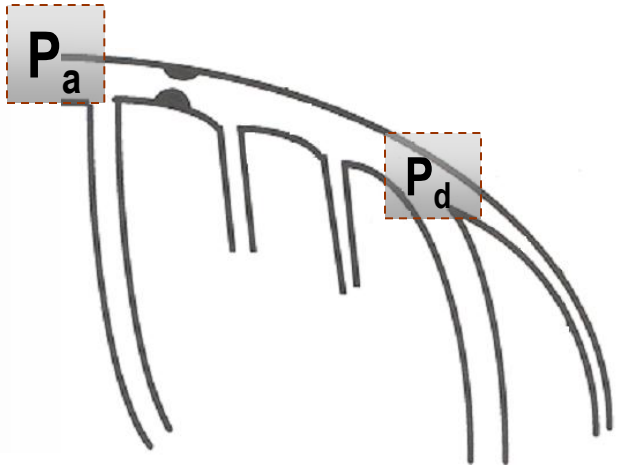


Pijls and De Bruyne, Coronary Pressure Kluwer Academic Publishers, 2000

Detailed Physiology

FFR = Fractional Flow Reserve

$$FFR_{myo} = \frac{P_d}{P_a}$$



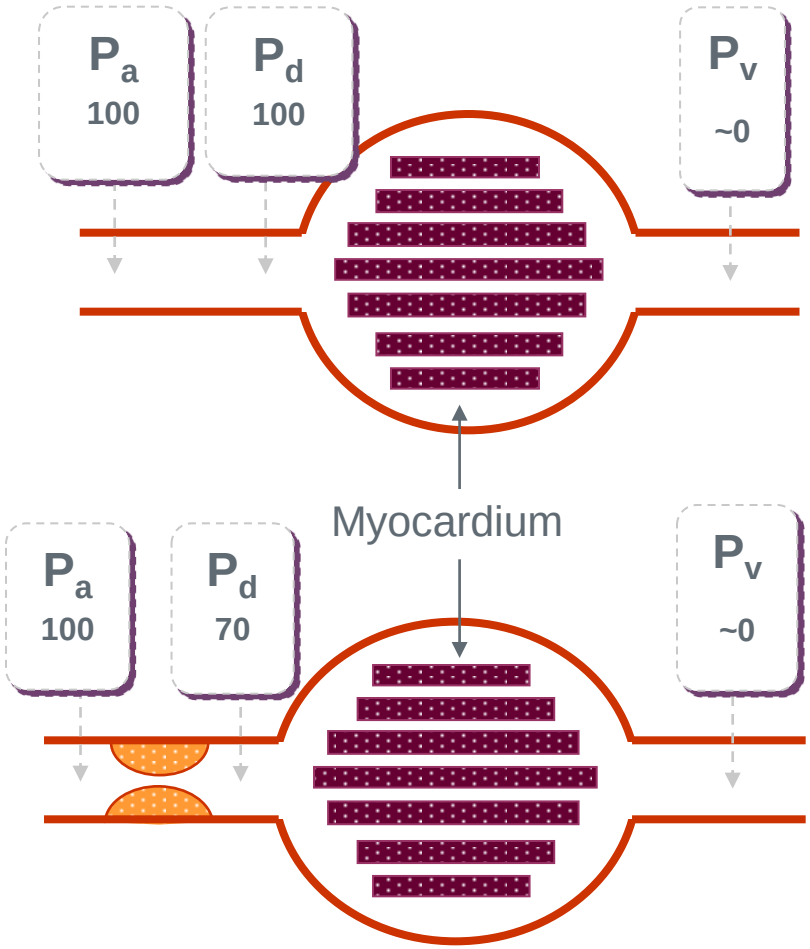
…in the presence of maximum flow

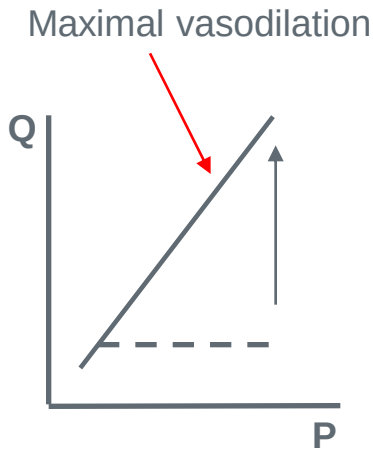
Detailed Physiology

FFR = Fractional Flow Reserve

$$FFR_{myo} = \frac{\text{Max } \textbf{flow} \text{ in presence of a stenosis}}{\text{Normal maximum } \textbf{flow}}$$

Detailed Physiology





During maximal vasodilation, the ratio of *stenotic flow* to n*ormal flow* is proportional to their respective driving pressures.

This is exactly the definition of the FFR: the ratio of *distal coronary pressure* to *aortic pressure*.

Detailed Physiology - (flow and pressure)

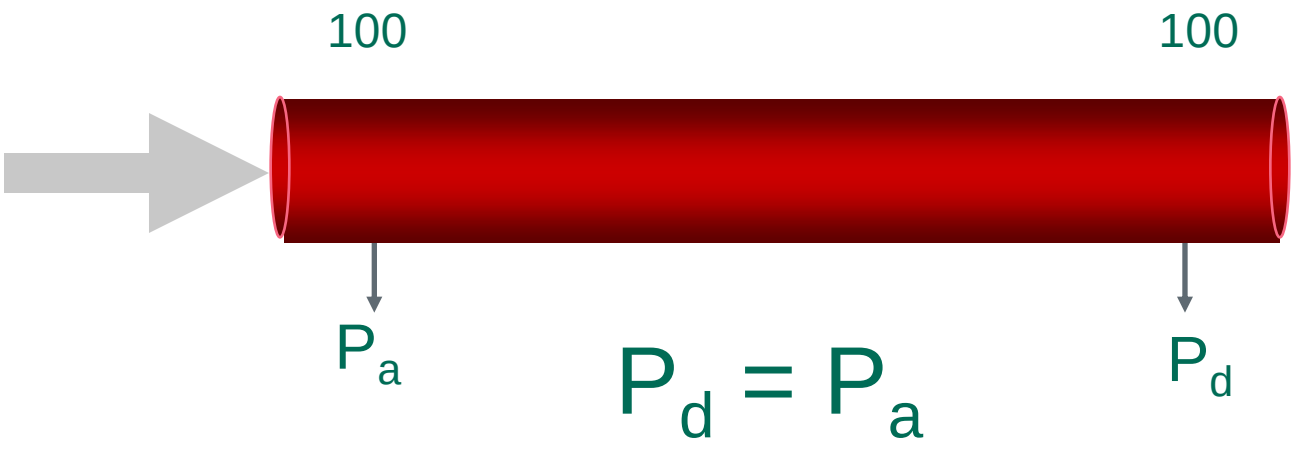
$$FFR_{myo} = \frac{Q^{s}_{max}}{Q^{n}_{max}} = \frac{(P_d - P_v)/R_{myo}}{(P_a - P_v)/R_{myo}}$$

Detailed Physiology

At maximal hyperemia: Coronary flow ≈ pressure

$$FFR_{myo} = \frac{P_d}{P_a} = \frac{(P_d - \cancel{P_v})/\cancel{R_{myo}}}{(P_a - \cancel{P_v})/\cancel{R_{myo}}}$$

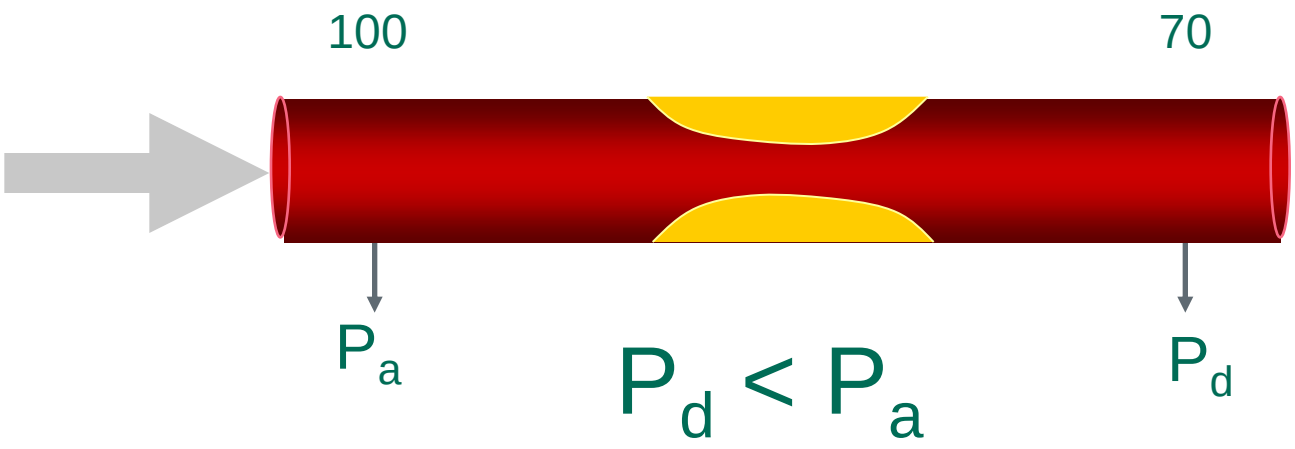
Normal FFR = 1.0



$$P_d = P_a$$

$$FFR_{myo} = \frac{P_d}{P_a} = 1$$

FFR in the presence of a stenosis

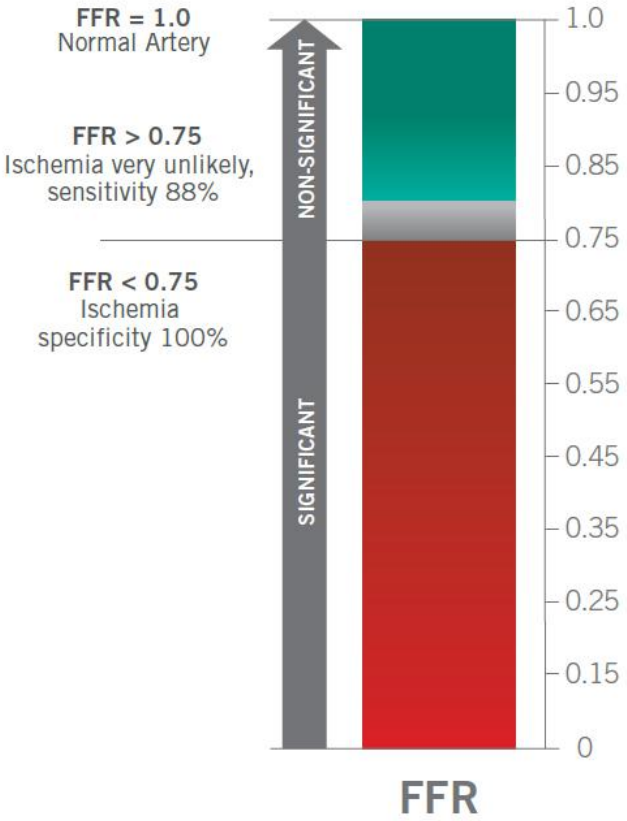


$$FFR_{myo} = \frac{P_d}{P_a} < 1$$

Significant or not?

The reduction in myocardial blood flow by a stenosis, as indicated by FFR, can be closely correlated to Ischemia.

FFR = 1.0	→	Normal artery
FFR > 0.75	→	Ischemia very unlikely, sensitivity 88%
FFR < 0.75	→	Ischemia, specificity 100%



"Measurement of Fractional Flow Reserve to asses the Functional Severity of Coronary Artery Stenoses",
Pijls *et al;* The New England Journal of Medicine;
Vol 334: 1703-1708 (1996)

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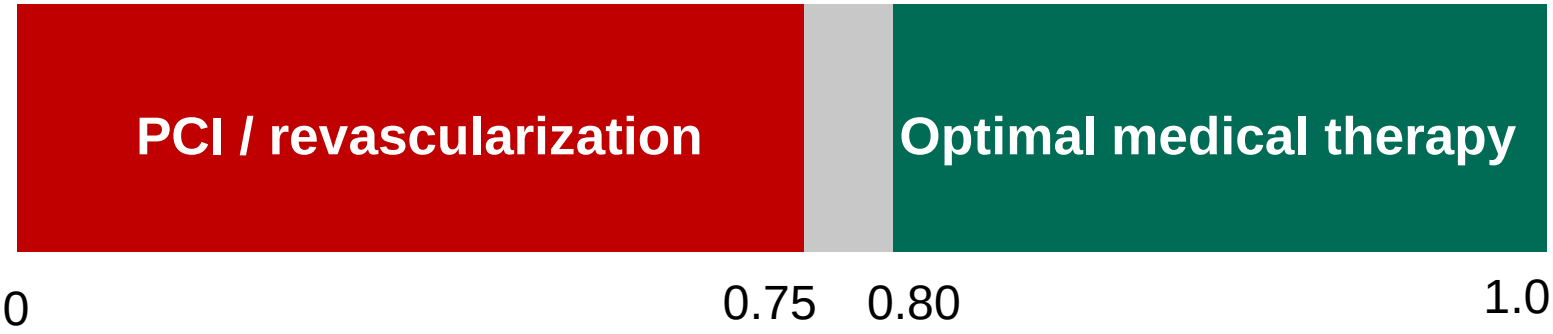
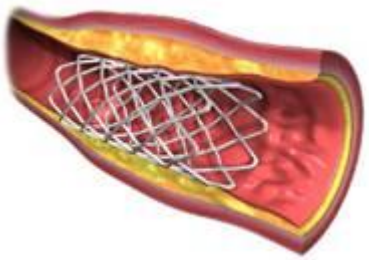
Intervention or not ?





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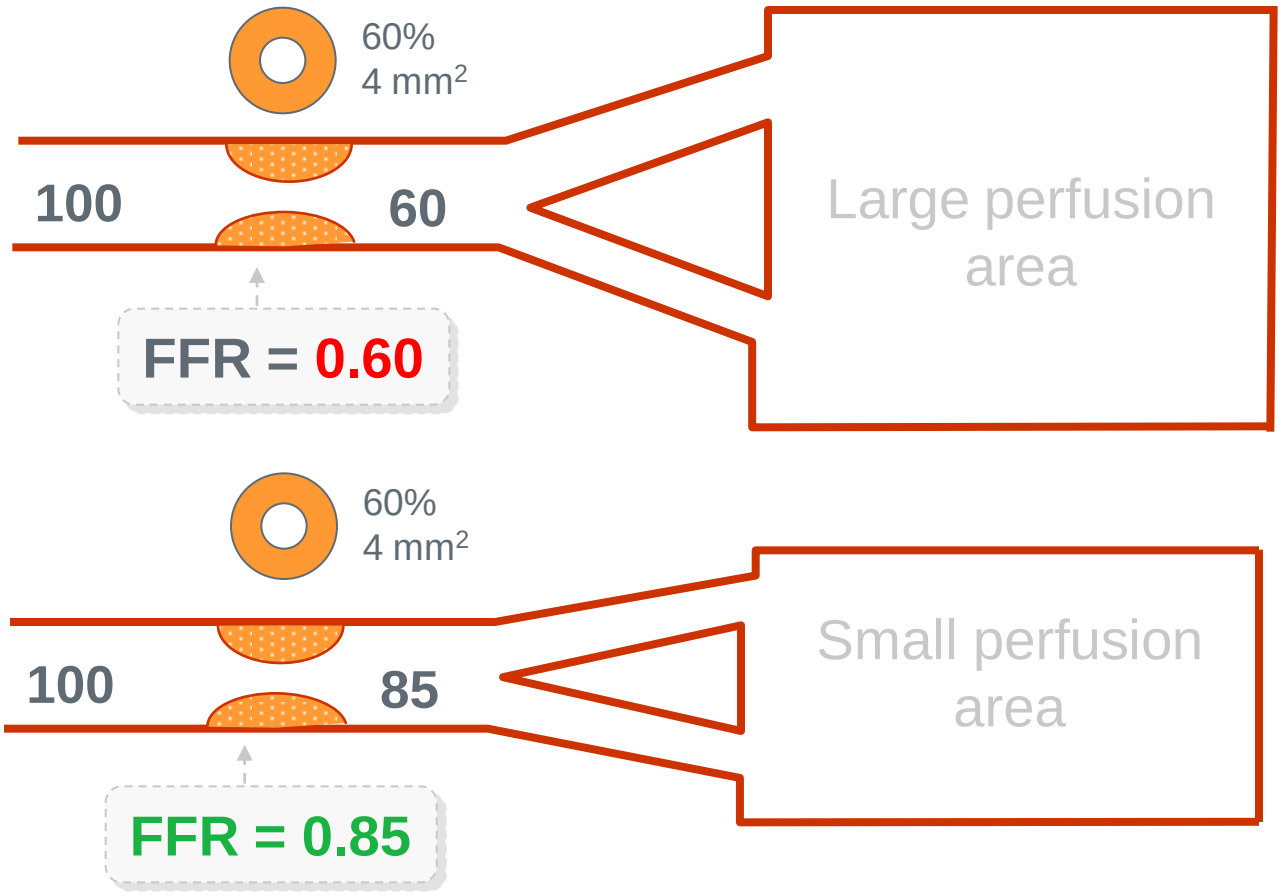
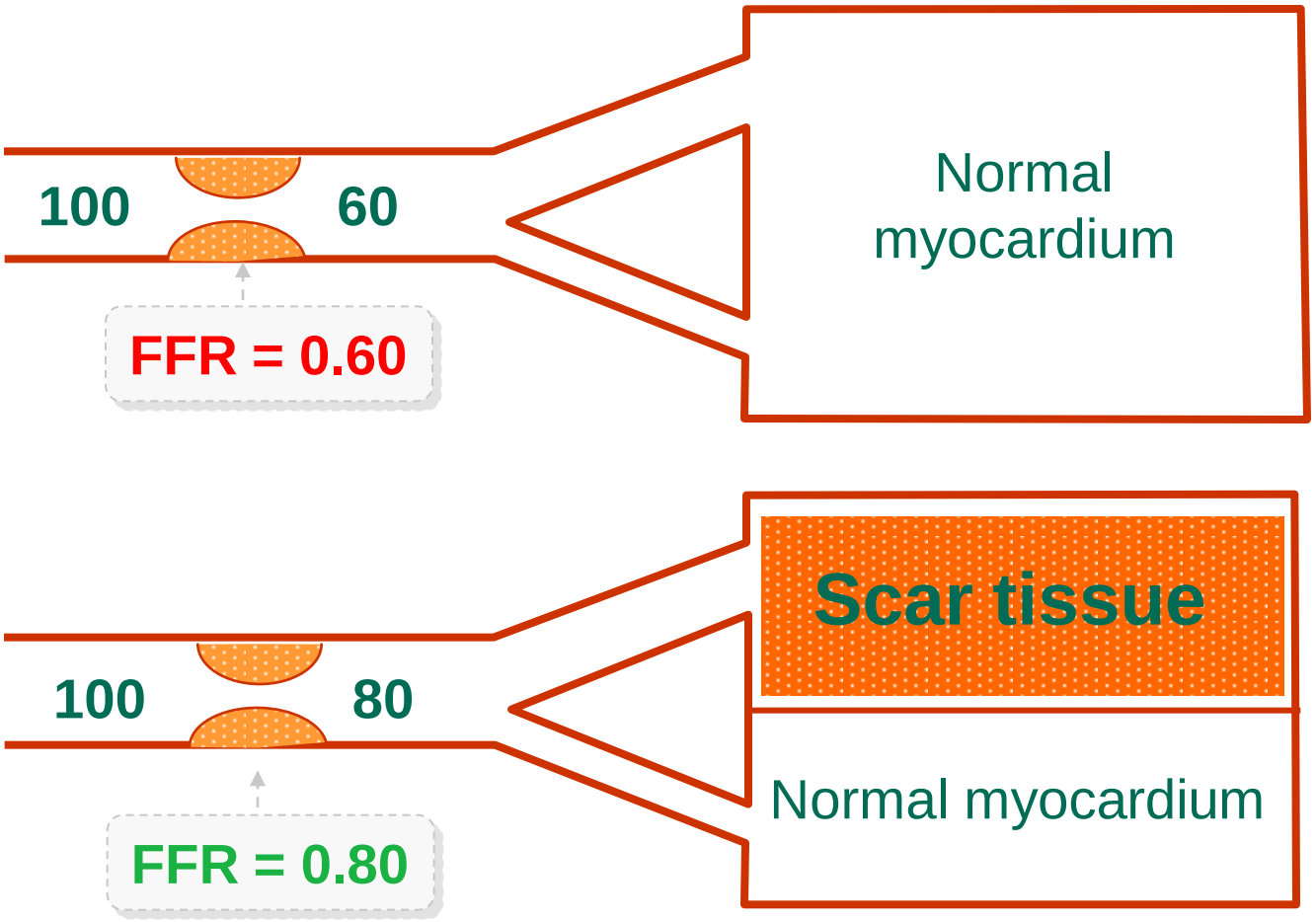
FFR accounts for the *interaction between*:

- Epicardial stenosis severity
- Extent of perfusion territory
- Myocardial blood flow
- Inducible ischemia

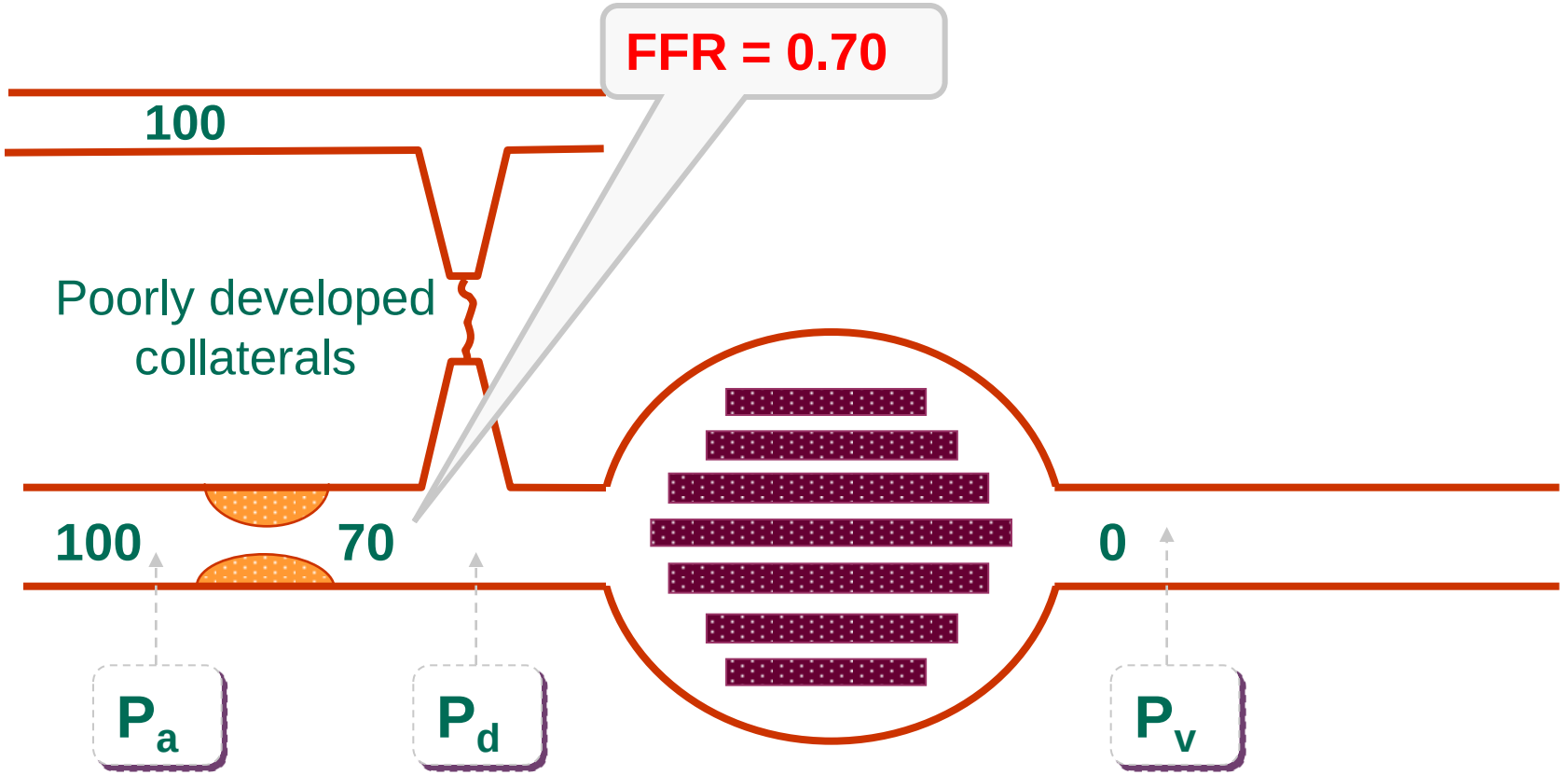
FFR accounts for size of perfusion area



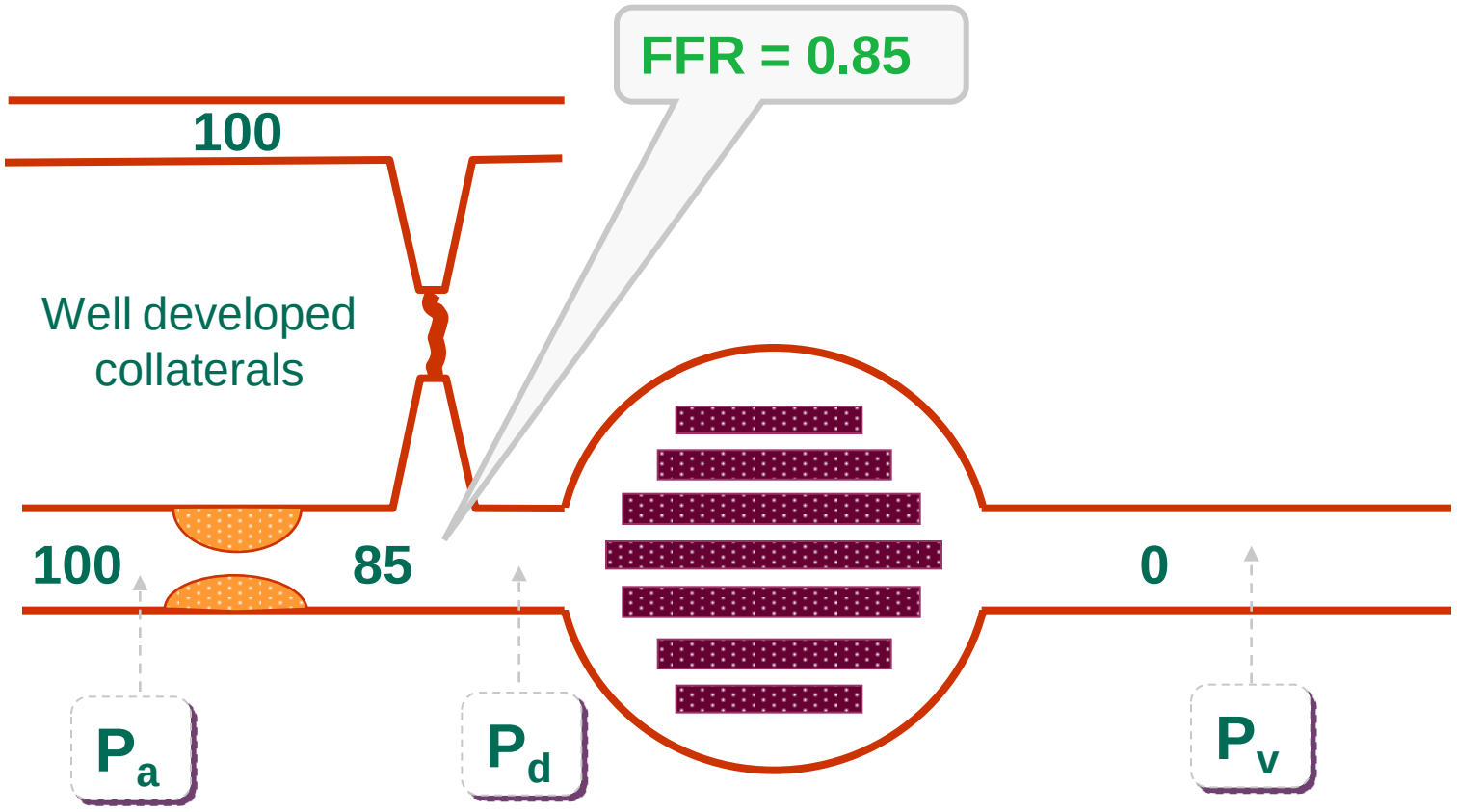
FFR accounts for size of perfusion area



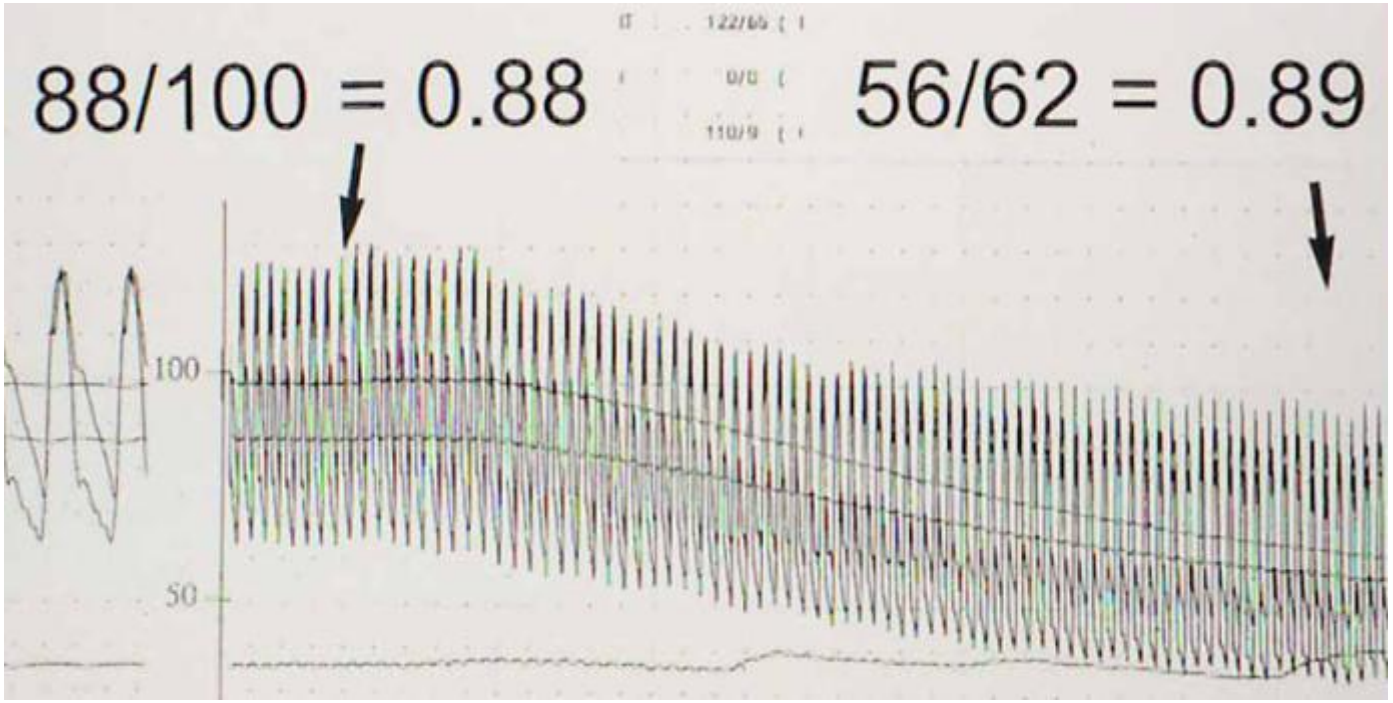
FFR accounts for contribution of collaterals



FFR accounts for contribution of collaterals



FFR - independent of blood pressure changes



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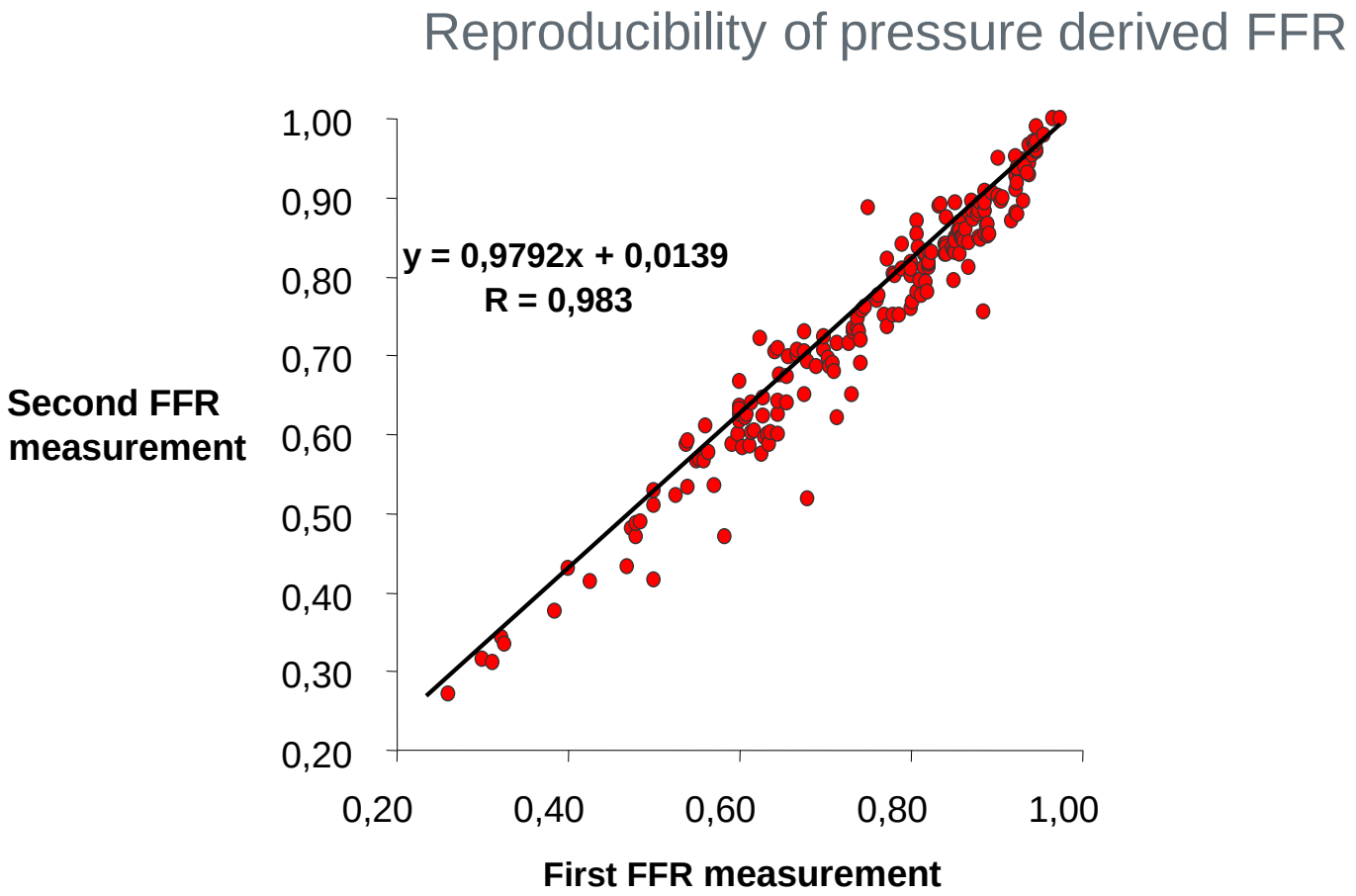
FFR - highly reproducible



Bech, G. J et al, Circulatio, 2001:103; 24: 2928-2934

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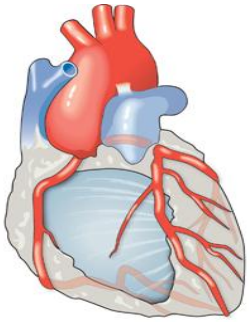
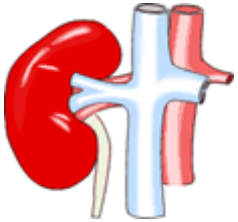
PressureWire clinical usage areas

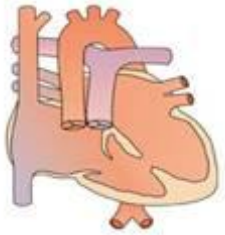
Coronaries
Lesion assessment, FFR
CFR, IMR



Peripheral vasculature
Renal, Iliacs



Ventricles
CRT optimization, valve assessment



Cerebral
Carotids

MAIN FOCUS
95% of use

ok

ok

Contraindicated

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Clinical Guide

Assess stenosis severity and guide treatment

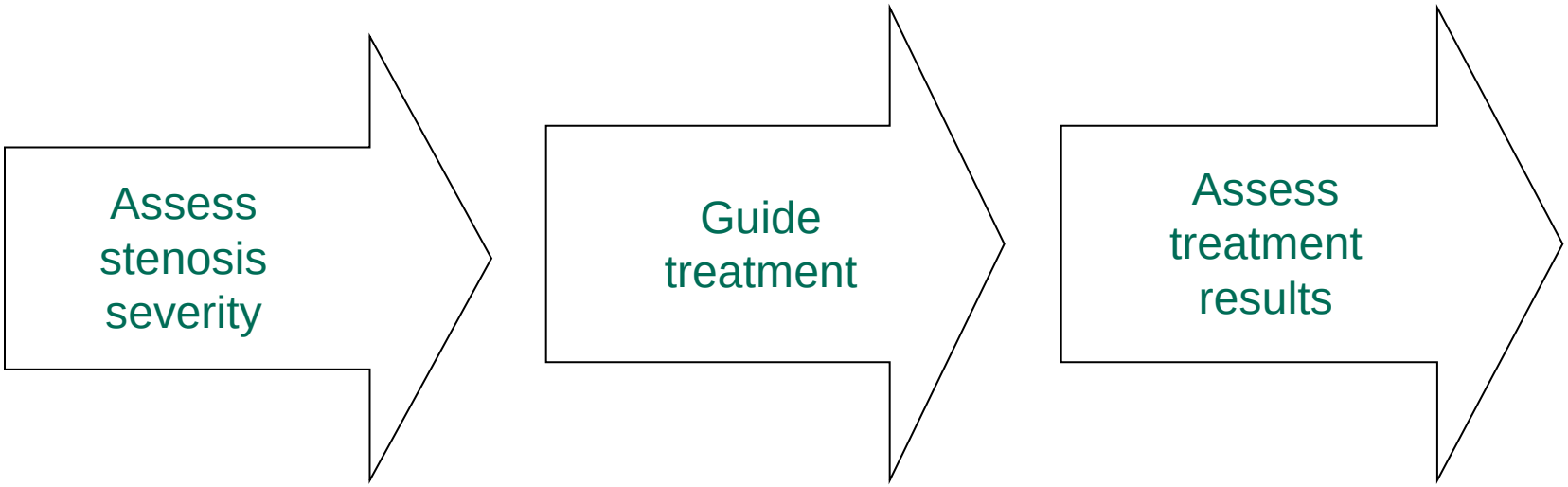
- Intermediate stenosis
  (in one or more coronary arteries, even bypass grafts)
- Serial lesions
- Diffuse disease
- Ostial or distal LM and ostial right lesions
- Sidebranch lesions
- Multivessel disease
- In-stent restenosis
- Prior MI

Clinical Guide

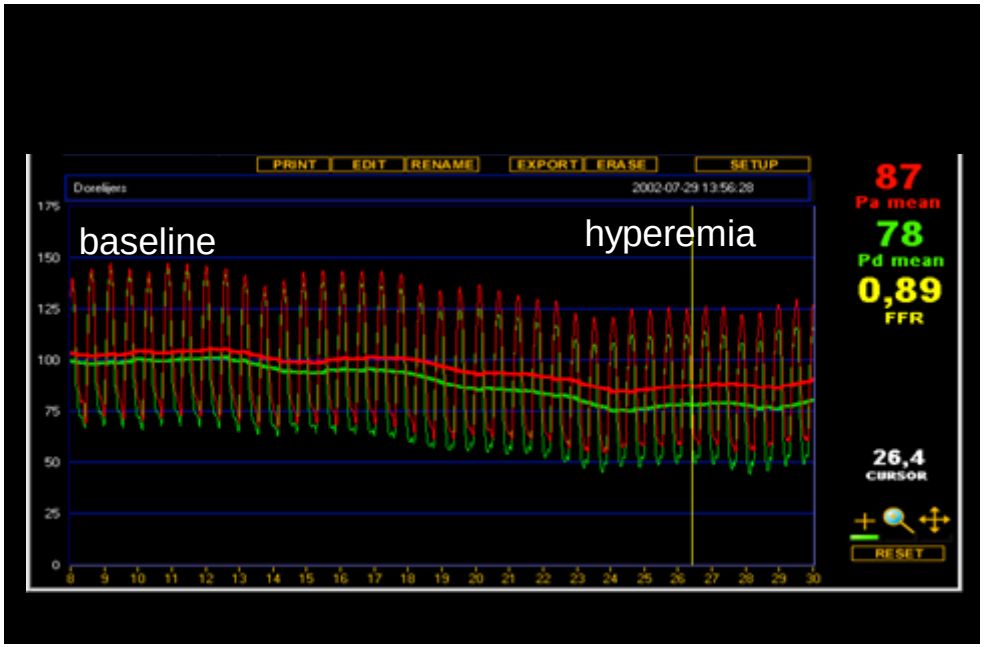
Assess treatment results

- Effect of the stent on stenosis
- Effect of the stent on the remaining vessel

FFR to improve clinical decision-making



Intermediate stenoses (40-60%)



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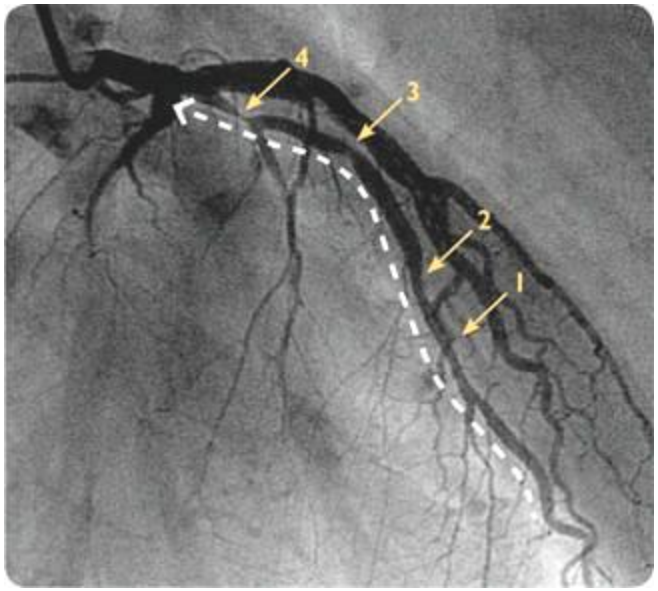
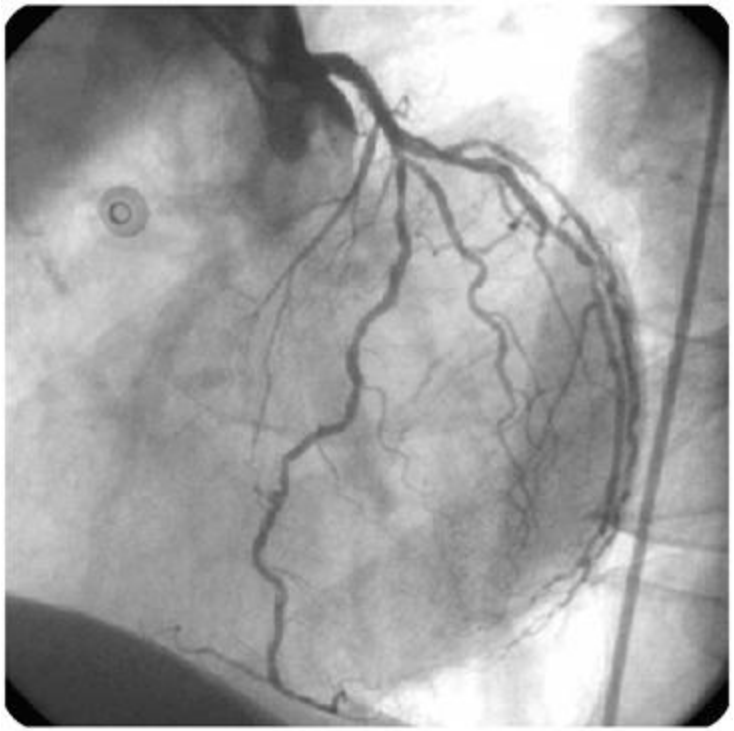
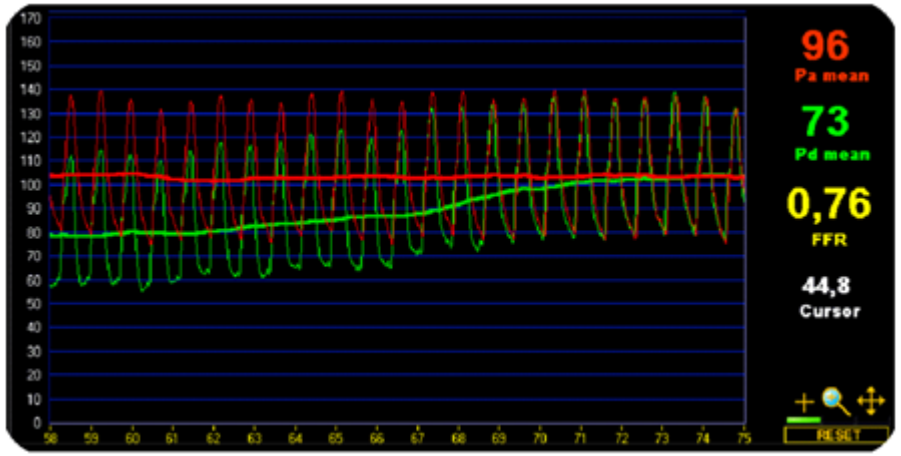
Serial stenoses



By performing a **pullback** over the stenoses the ”culprit lesion” can be identified.

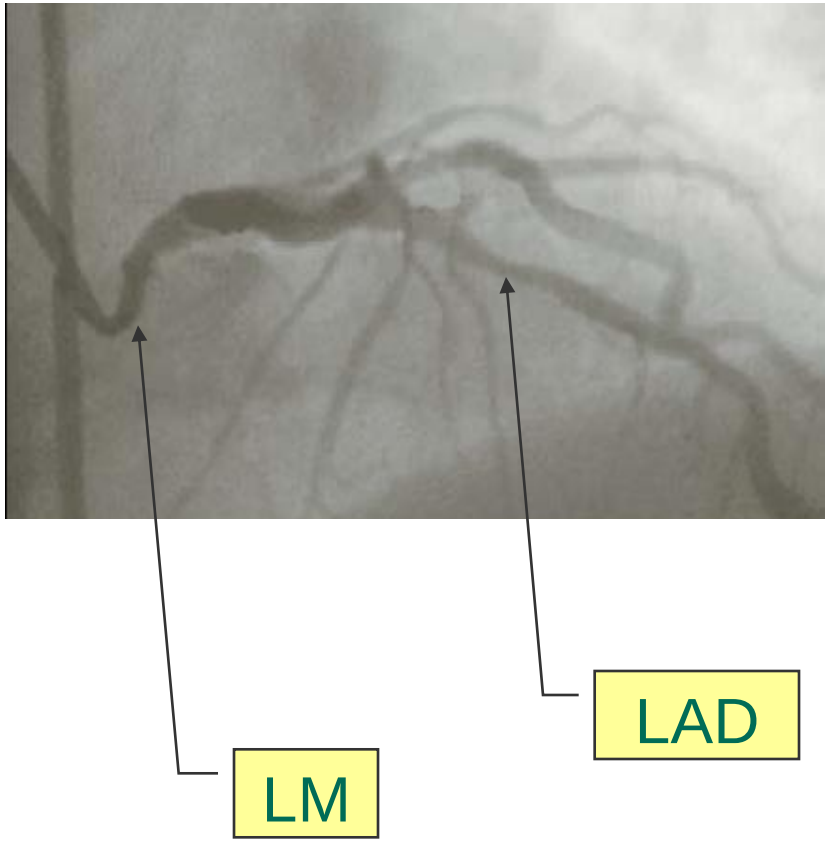
Diffuse disease





A **pullback** identifies the culprit lesion or reveals diffuse disease in the vessel.

Left Main Stenosis

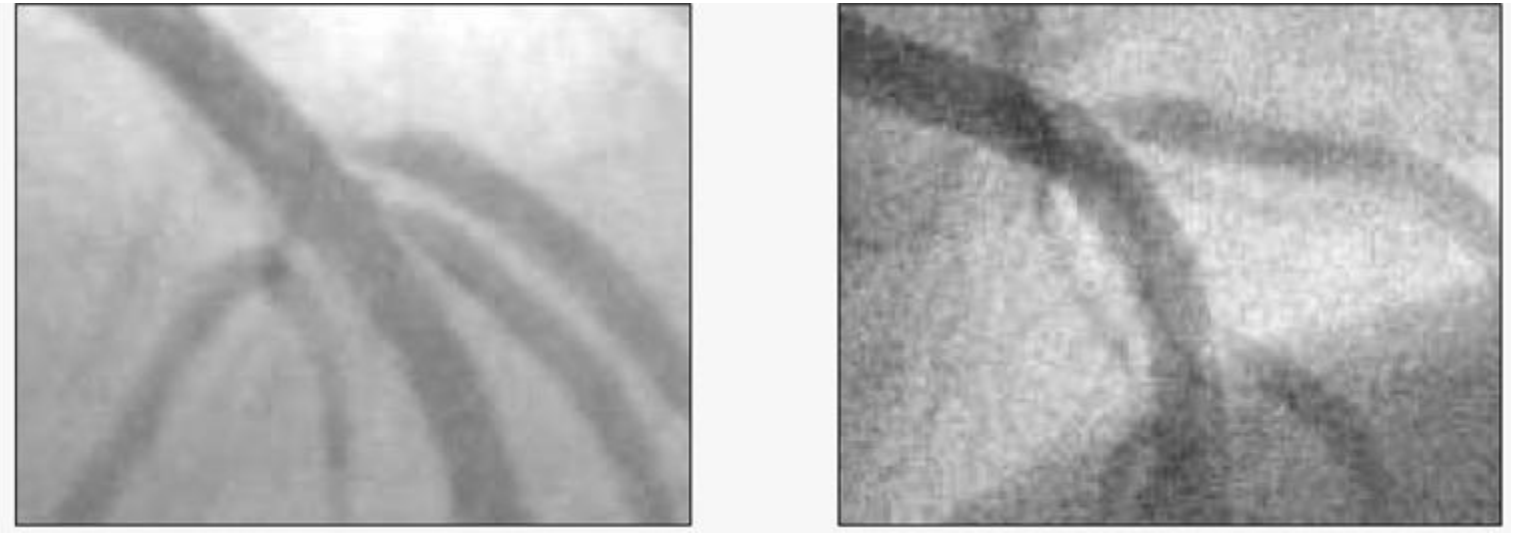


Surgery or not?

Measure pressure and the patient might avoid CABG

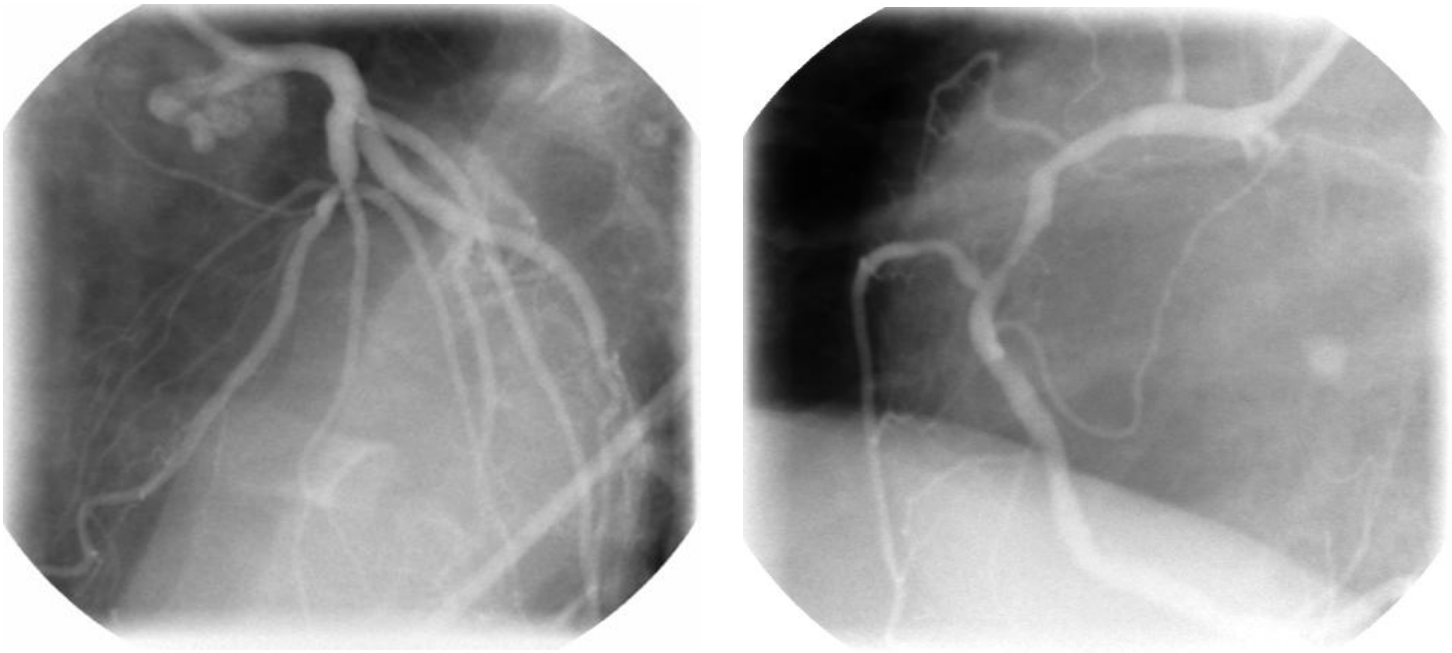
Side branch lesions

Measurement of FFR in side branch lesions suggests that most of these lesions do NOT have functional significance, despite morphologic appearance.
When in doubt, measure FFR.



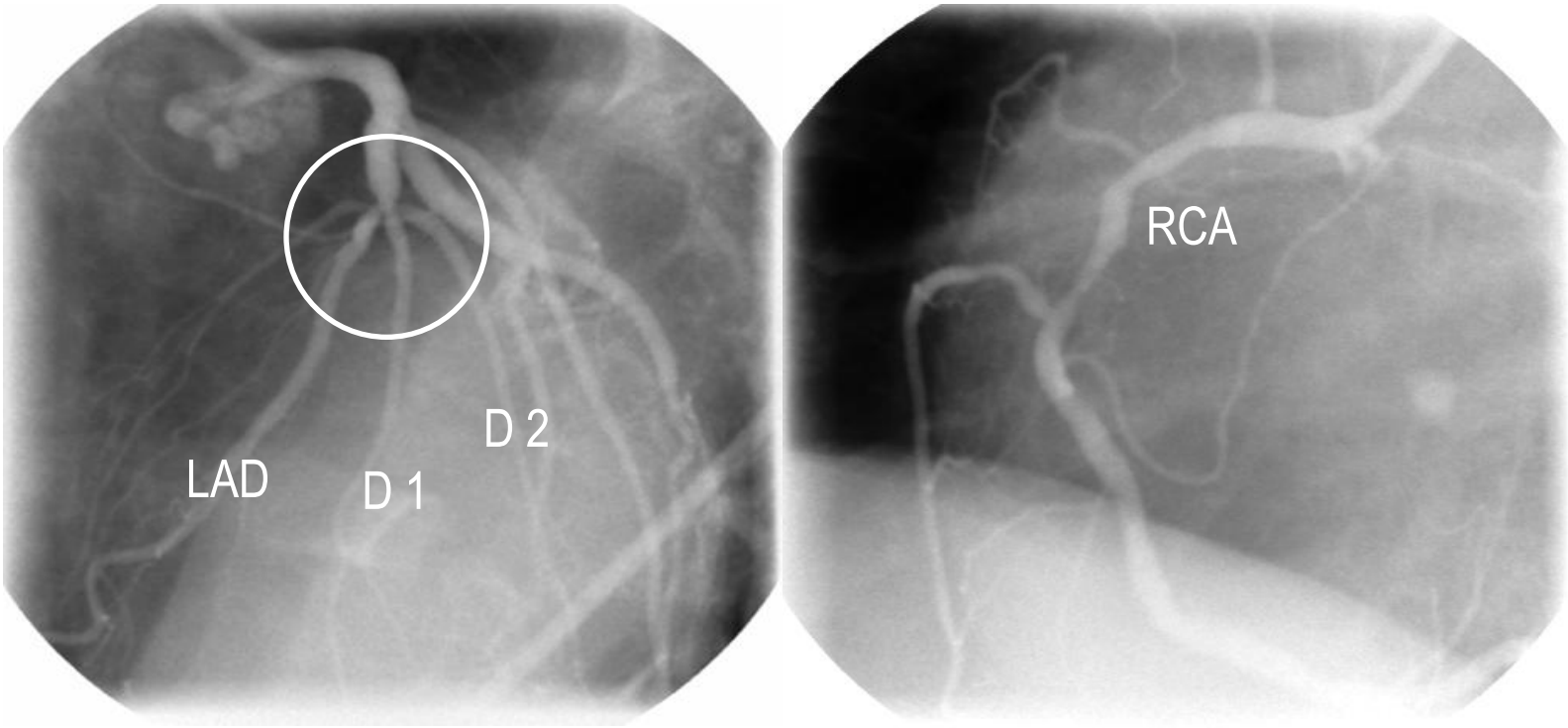
Koo et al. J Am Coll Cardiol. 2005;46: 633-7

MVD - Multivessel Disease

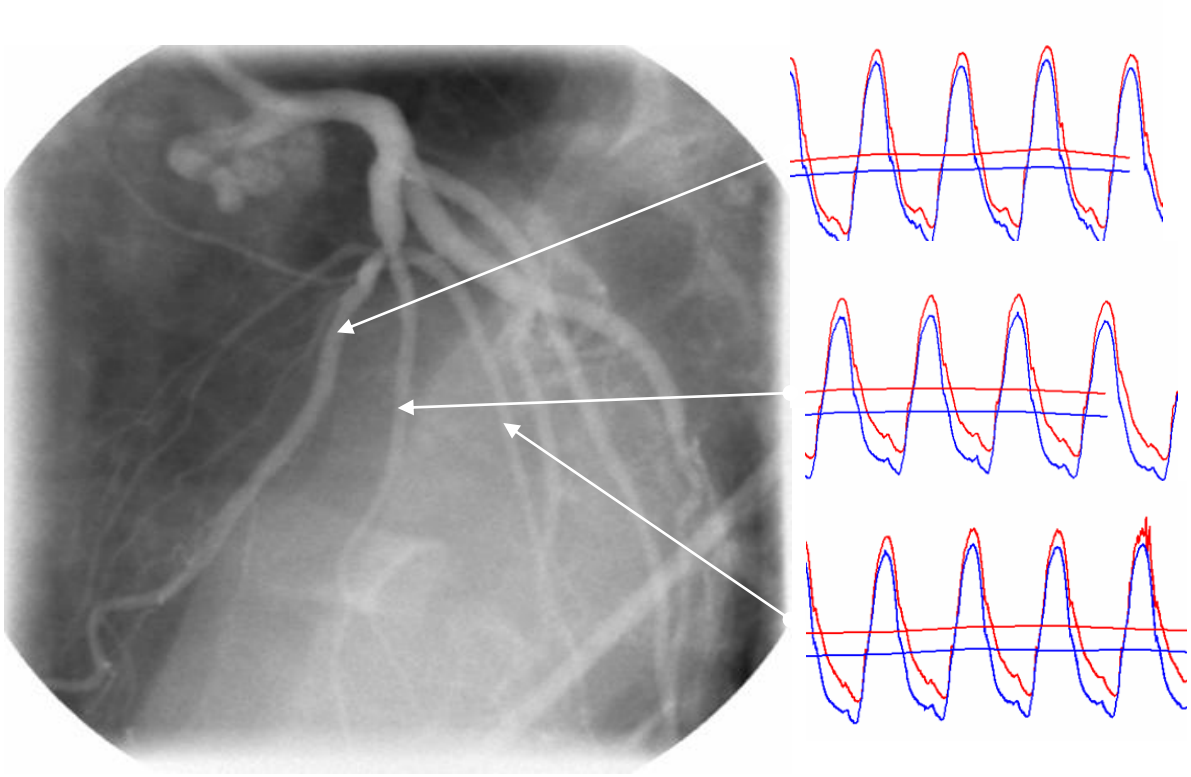


- Measure all suspected lesions
- Use long-lasting hyperemic stimulus – time for pullback
- Place stents only in stenoses where FFR is below 0.75

Where to intervene?



Where to intervene?



FFR = **0.94** >0.75

FFR = **0.89** >0.75

FFR = **0.90** >0.75

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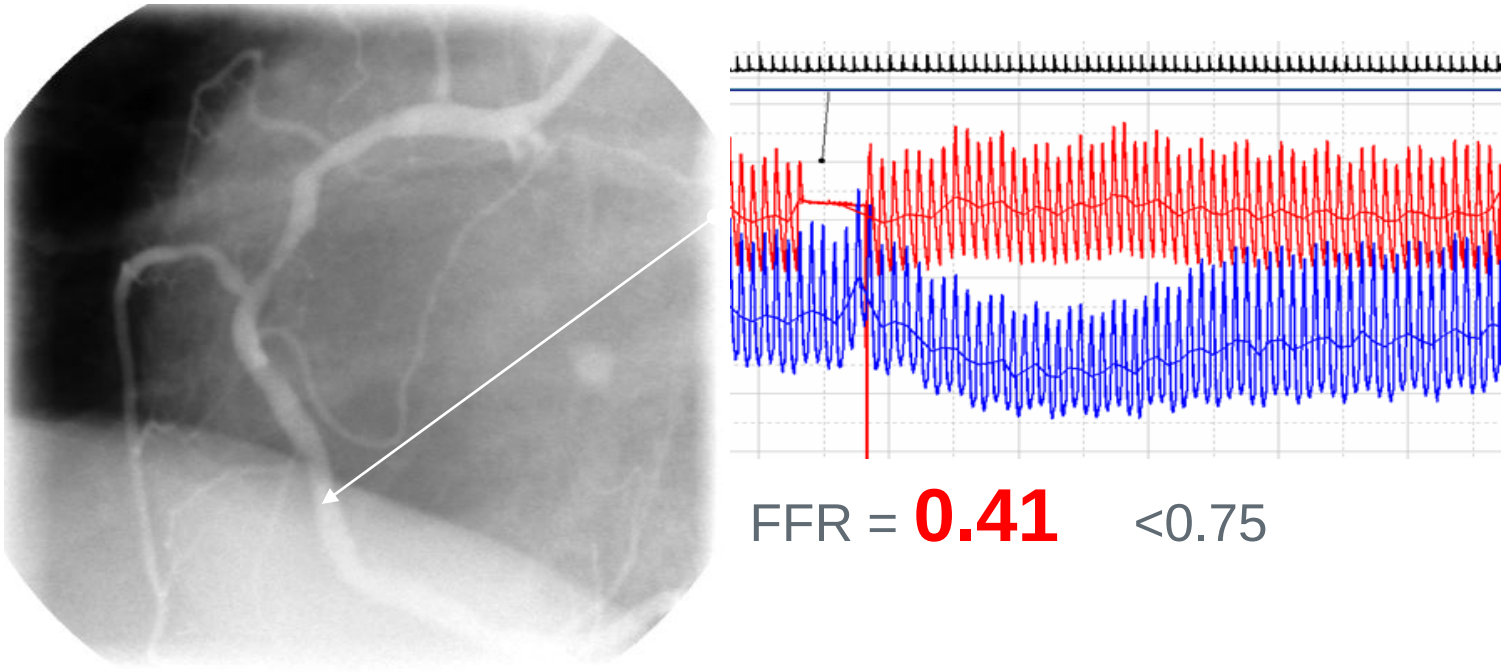
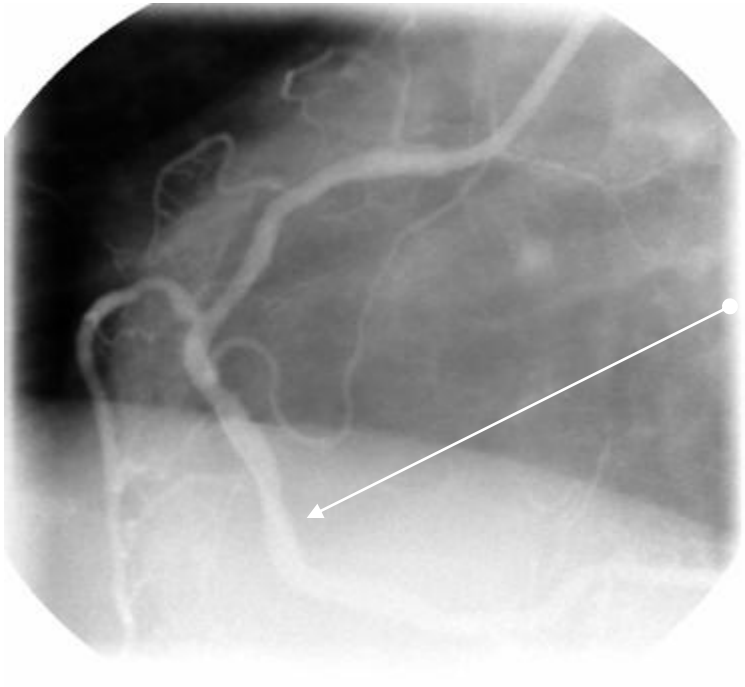
Where to intervene?

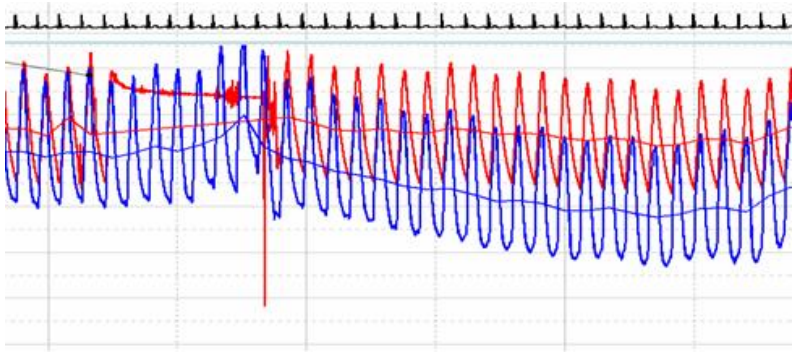


FFR = **0.41** <0.75

Where to intervene?

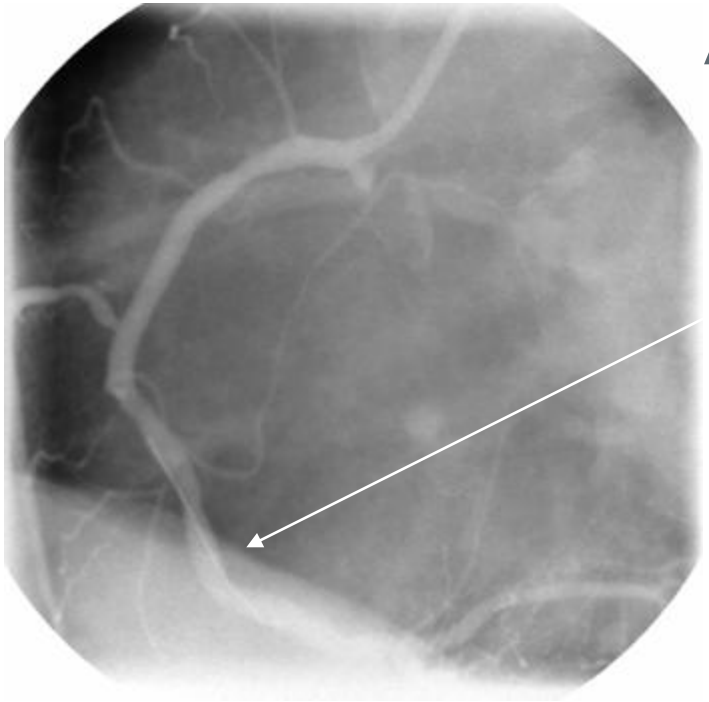


After balloon inflation
3.0 balloon 12 atm (mid-RCA)

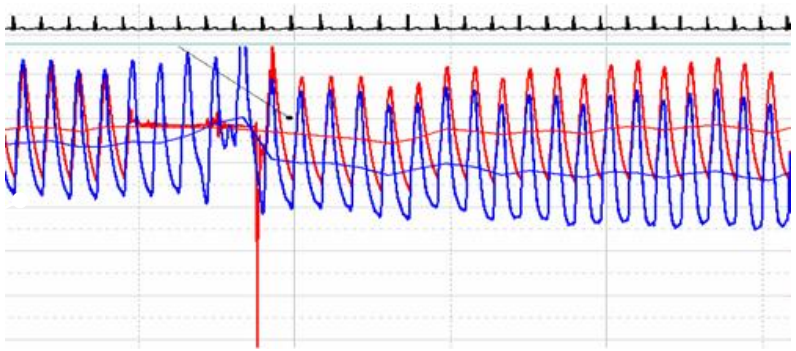


FFR = **0.67** <0.75

Where to intervene?

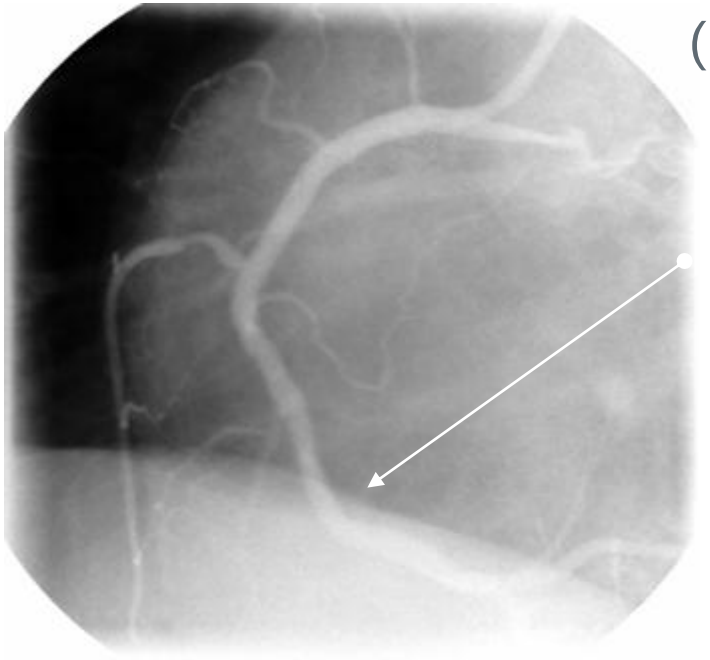


After stent 3.5 mm (mid-RCA)

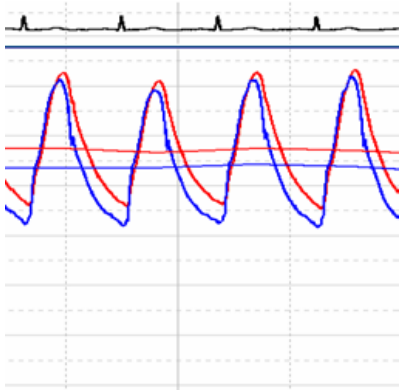


FFR = **0.80** Not optimal post stent result

Where to intervene?

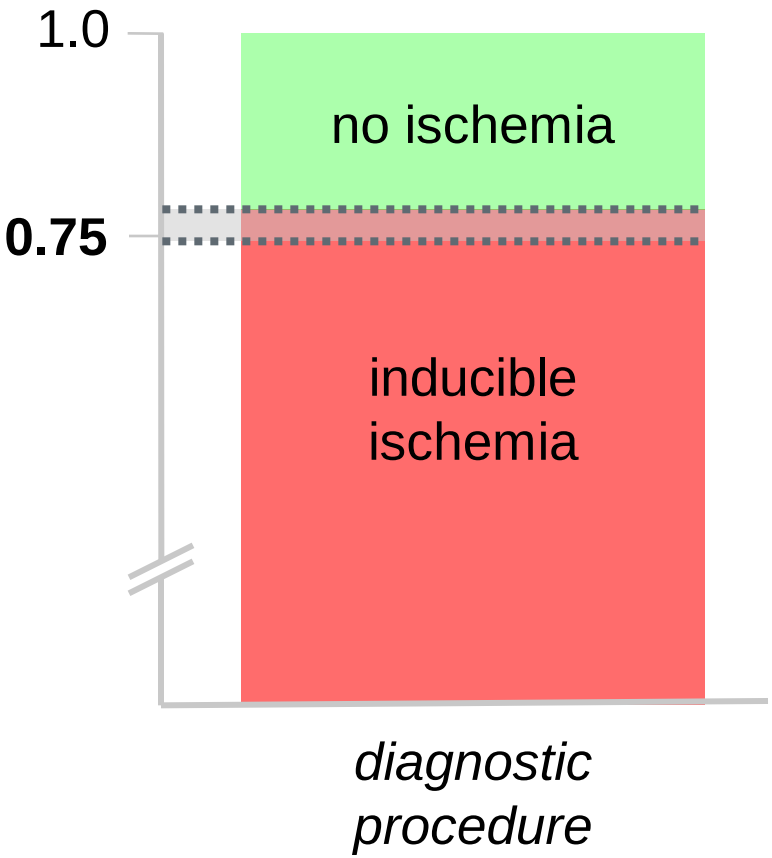


Stent 3.5 mm (mid-RCA) + Stent 3.5 mm (prox-RCA)

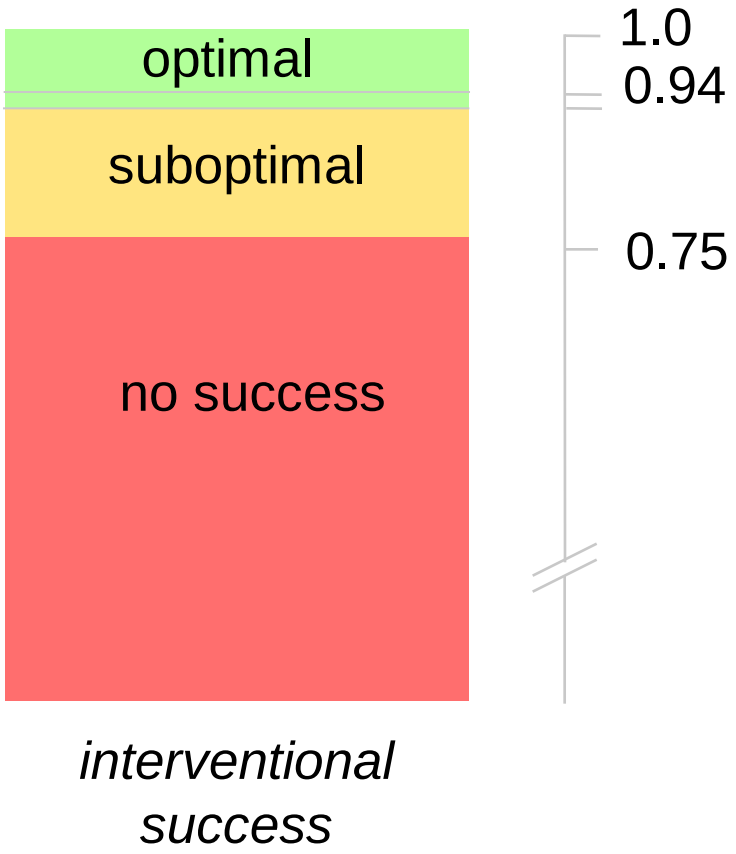


FFR = **0.94** Optimal post stent result

Decision-making



Assessing results of intervention



After stent implantation

FFR ≥ 0.94 = Optimum stent result

After balloon angioplasty

FFR < 0.75 = Unsuccessful PTCA
FFR 0.75-0.89 = Moderate result
FFR > 0.90 = Excellent result

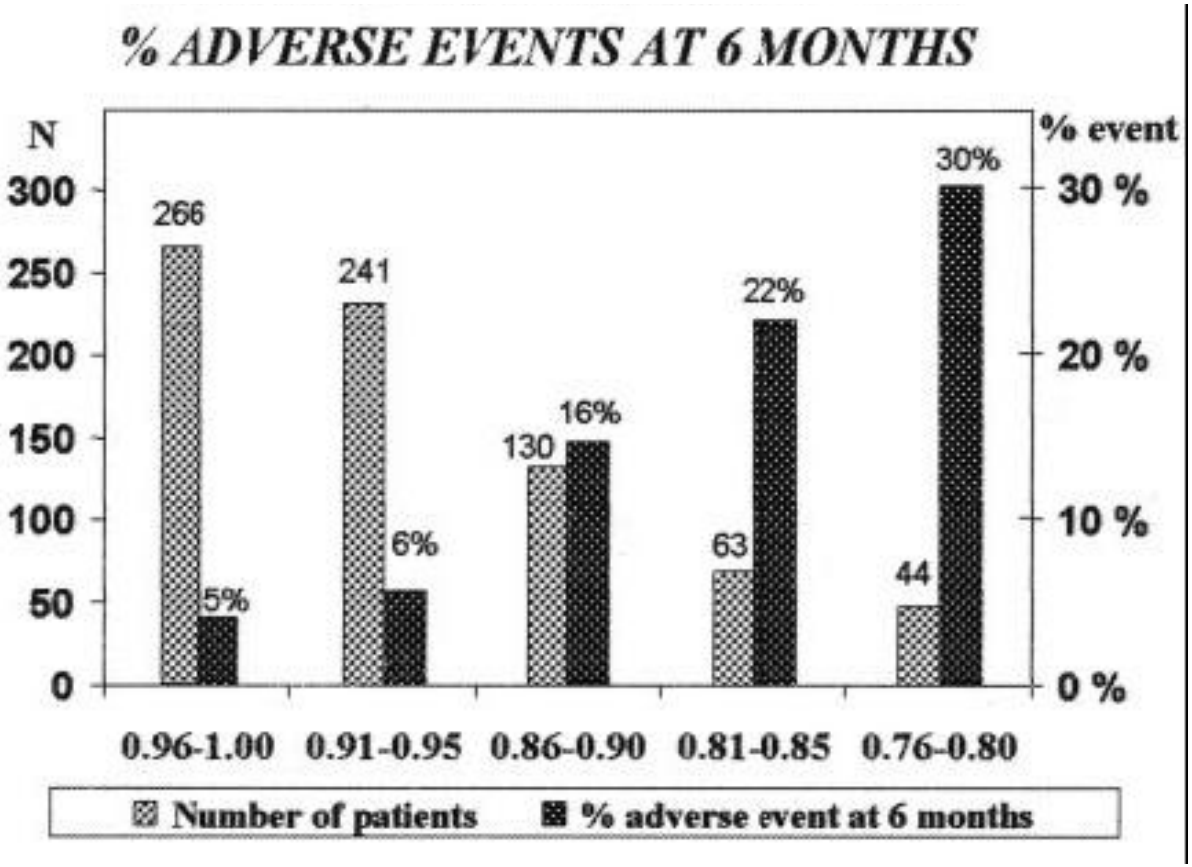
Assessing results of intervention

FFR after stent* deployment	Restenosis frequency (TVR) 6 months follow-up
>0.96	4,9%
0.91 - 0.95	6,2%
0.86 - 0.90	16,2%
0.81 - 0.85	22,2%
0.75 - 0.80	29,5%

* Bare metal stents

Pijls et al. Circulation, 2002; 105: 2950-2954

FFR measurement post-stenting



FFR-Post-Stent Registry (N=750).
Pijls et al. Circulation, 2002; 105: 2950-2954

Summary

The value of FFR:

- Invasive techniques are needed to help guide decision-making in the catheterization laboratory due to:
  - Limitations of angiography
  - Discrepancy between morphology and function
  - Limitations of noninvasive evaluation
  - Potential downside to indiscriminate DES use

- Measuring FFR can be a useful technique in this setting

Rx Only
Please review the Instructions for Use prior to using these devices for a complete listing of indications, contraindications, warnings, precautions, potential adverse events and directions for use.

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