Approach the physiologic significance of a LMCA Stenosis In Interventional Cardiology

NGUYỄN THƯỢNG NGHĨA MD., PhD.

NGUYỄN HOÀNG TÀI MY MD

Interventional Department – Cho Ray Hospital – HCMC - Vietnam

CORONARY HEMODYNAMICS

1 Myocardial cell contraction and relaxation are aerobic, O_2-requiring processes.

2 O_2 extraction in the coronary bed is near maximal in the baseline state (80% vs 30–40% in skeletal muscle) -> **to increase O_2 delivery -> flow must increase.**

3 In the normal heart, major resistance to coronary flow in the **microvasculature** (small, distal arterioles) vs little resistance in the visible epicardial arteries.

4 The primary mechanism to **increase** coronary flow is via a **decrease** in microvascular resistance (regulated by metabolic demands).

5 The presence of hemodynamically significant epicardial disease reduces microvasculature resistance at baseline so that coronary blood flow is maintained. This **limits** the ability of the myocardium to increase flow in response to increased demand.

CORONARY BLOOD FLOW

- … under resting conditions is generally 15–20% of maximal blood flow in patients with normal coronary arteries and is not altered by gender or age.
- … increases **two- to fivefold** in the normal heart
- … is **primarily controlled** by local metabolites (Adenosine, NO), Hypoxia > hypercapnea or acidosis.

Neural influences: relatively **minor** (Sympathy, Parasympathy)

CORONARY BLOOD FLOW

- … is unique in that it primarily occurs during diastole (**diastole predominance)** -> myocardial ischemia during tachycardia.
- **Maximal** coronary blood flow can be achieved:

1. Reactive hyperemic flow
2. exercise or another physiologic stimulus to
3. microcirculation vasodilators (adenosine)

How to measure:
1. Clearance methods.
2 Thermodilution.
3 Flowmeter techniques.
4 Doppler wire (CFR)
5 Fractional flow reserve wire (FFR)

CORONARY FLOW RESERVE

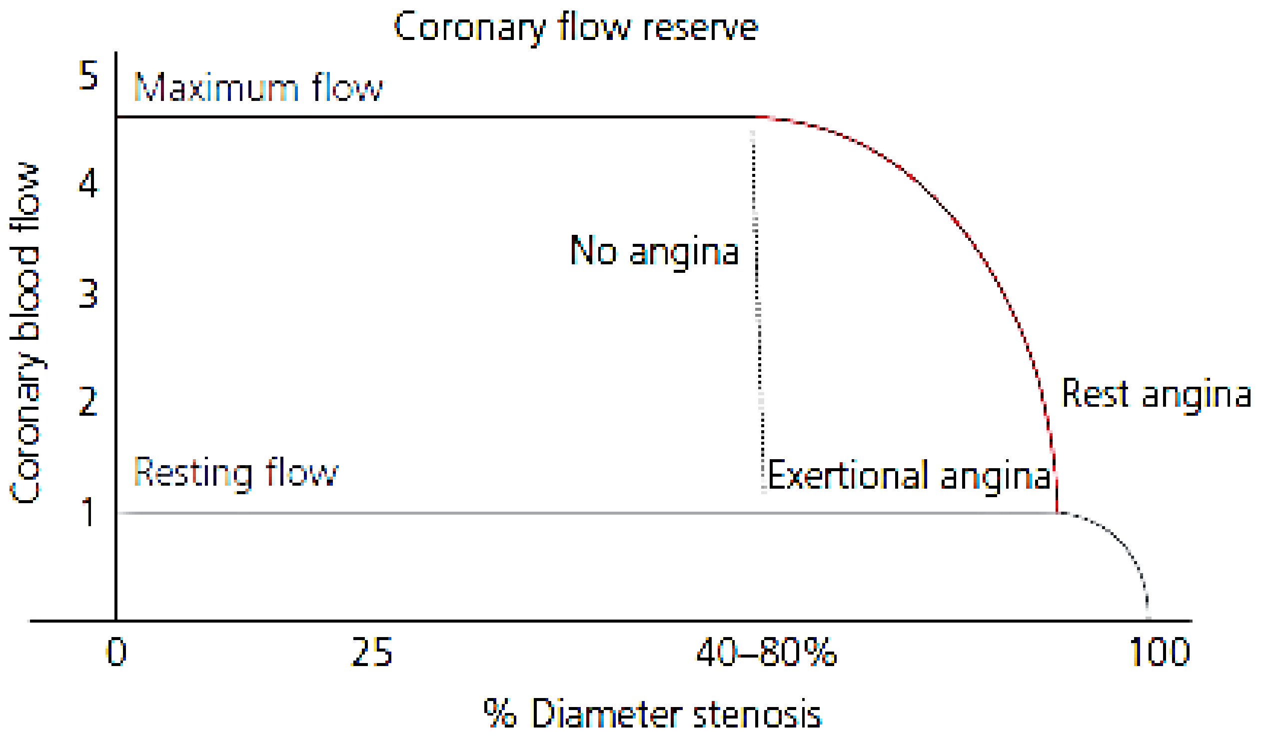


Figure 24.1 Simplified graph of coronary flow reserve. The ability to increase coronary flow is essential to meet metabolic demands during physiologic stress. Resistance to flow from a stenosis in an epicardial artery can compromise the ability of coronary flow to increase.

CORONARY FLOW RESERVE

- CFR: the ratio of maximal coronary flow to resting coronary blood flow

-> decrease with progressive obstruction of the lumen of an epicardial coronary artery by atherosclerosis.

- **Flow = velocity × area**
- Minimal changes in coronary diameter -> CFR: the ratio of maximal coronary velocity to resting coronary blood velocity
- Measured with 0.014 inch guidewire with a 12 mhz piezoelectric transducer

Limitations

- Conditions other than atherosclerosis can affect CFR
- Dependent on correct positioning of the doppler flow wire.
- Lack of consensus on what value of CFR is consistent with a hemodynamically significant lesion.
- Cannot discriminate between epicardial lesions and microvascular
- Dysfunction -> “relative CFR” (rCFR)

FRACTIONAL FLOW RESERVE

- Concept of using pressure gradient since the early days of endovascular intervention
- Ohm’s law: **flow= pressure / resistance**
- FFR is defined as maximum myocardial blood flow in the presence of a stenosis divided by the theoretical maximum flow in a normal vessel (i.e, the absence of any stenosis).
- **Independent** of changes in systemic blood pressure, heart rate, or myocardial contractility.

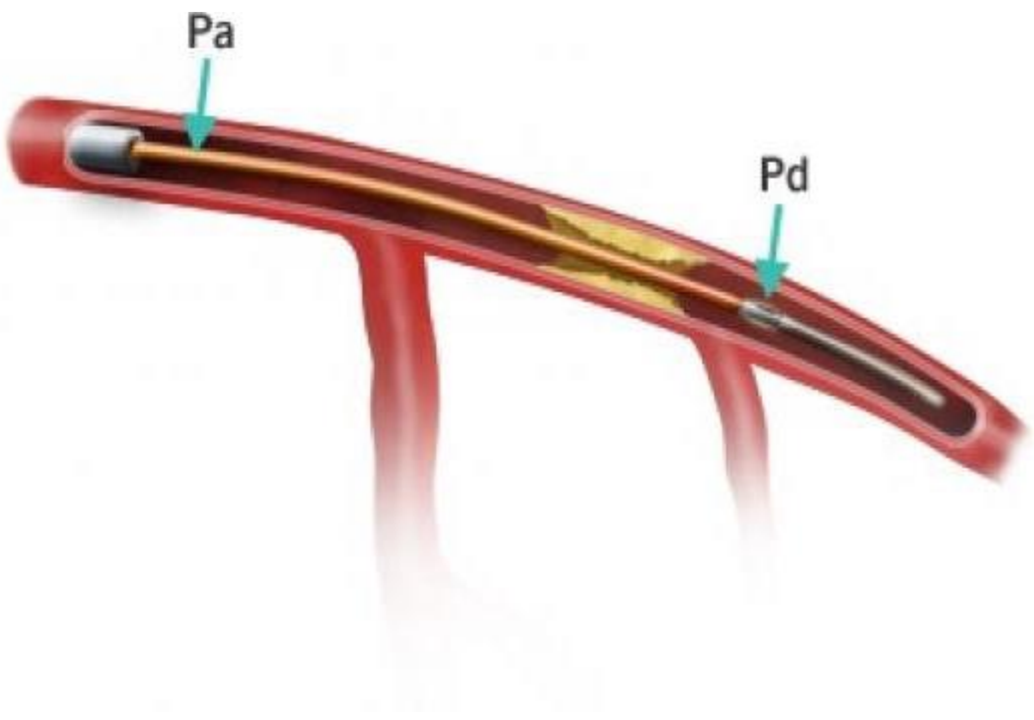
$$FFR = \frac{(P_d - P_v)/R_{min}}{(P_a - P_v)/R_{min}}$$

At maximal hyperemia, resistance of the myocardium is minimized

$$FFR = \frac{(P_d - P_v)}{(P_a - P_v)}$$

the venous pressure is minimal compared to the arterial pressure

$$FFR = \frac{P_d}{P_a}$$



FFR threshold of 0.80 as the gold standard

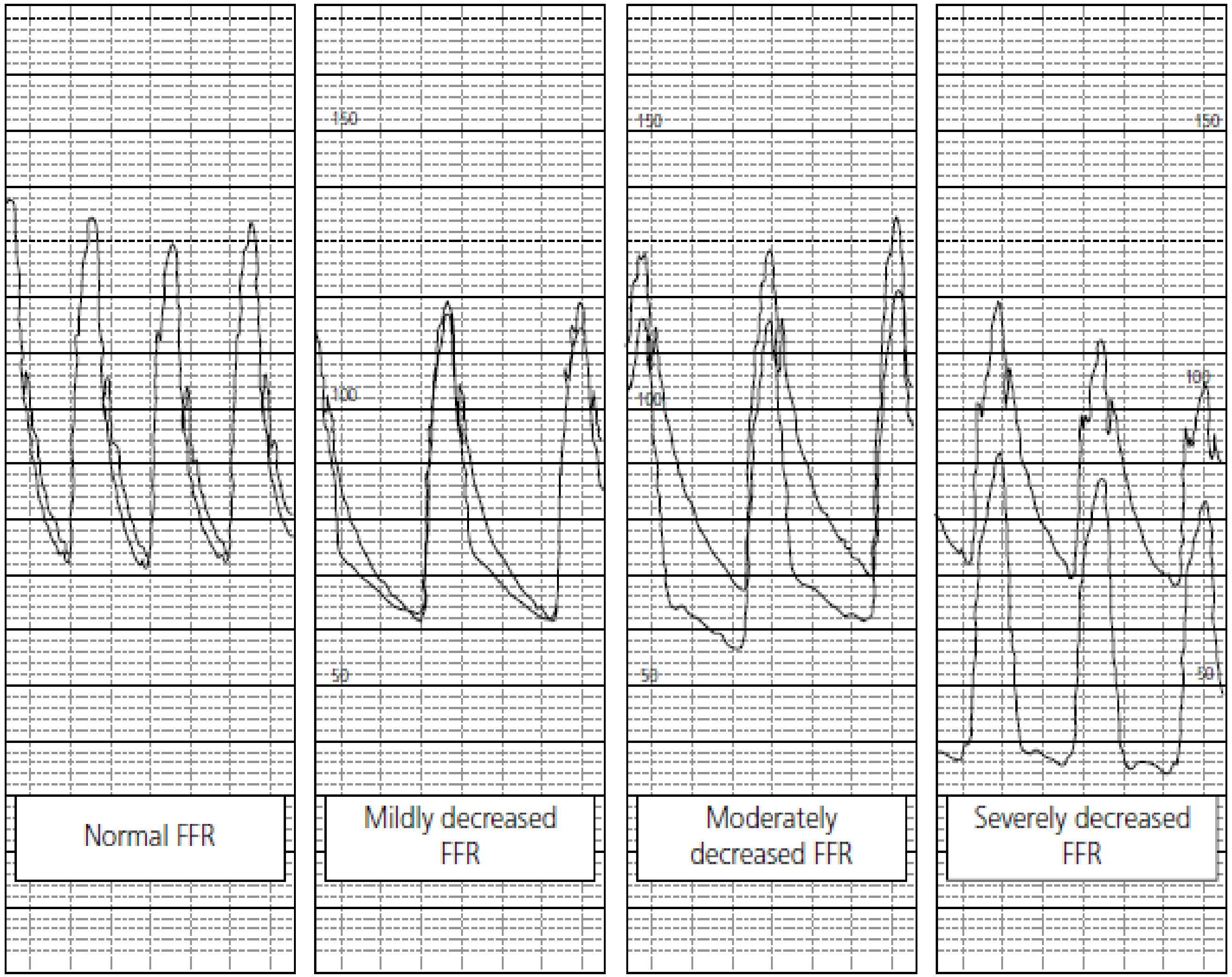


Figure 24.3 Examples of FFR measurements in four patients with coronary disease of different hemodynamic severity. Simultaneous pressure recordings, following intracoronary administration of adenosine, from the aorta and distal coronary artery in four different patients showing normal FFR and mildly, moderately, and severely decreased FFR.

Limitations of FFR

- Need for adenosine -> increases the time, cost, and risk of side effects.
- Technical aspects such as removing the introducer, clearing the guide of contrast, disengaging the guide for an ostial lesion
- Several assumptions to simplify the equation

$$FFR = \frac{(P_d - P_v)/R_{\min}}{(P_a - P_v)/R_{\min}} \text{ to } FFR = \frac{P_d}{P_a}$$

- Recent studies suggest that FFR has a continuous and independent relationship with clinical outcomes rather than a defined threshold value *

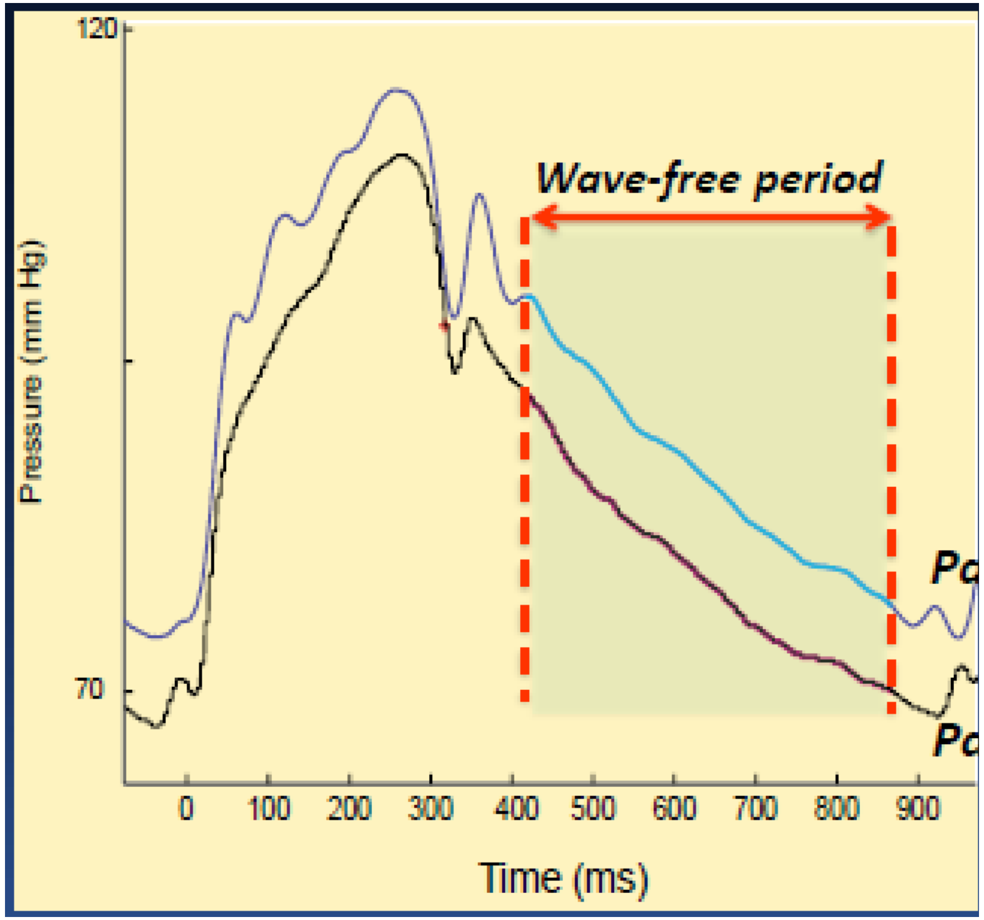
*Johnson NP *et al*. *J Am Coll Cardiol* 2014;**64**:1641–1654.

What is iFR ?
iFR = instantaneous wave-free ratio

Definition:

Instantaneous pressure ratio (iFR), across a stenosis during the wave-free period, when resistance is naturally constant and minimised in the cardiac cycle

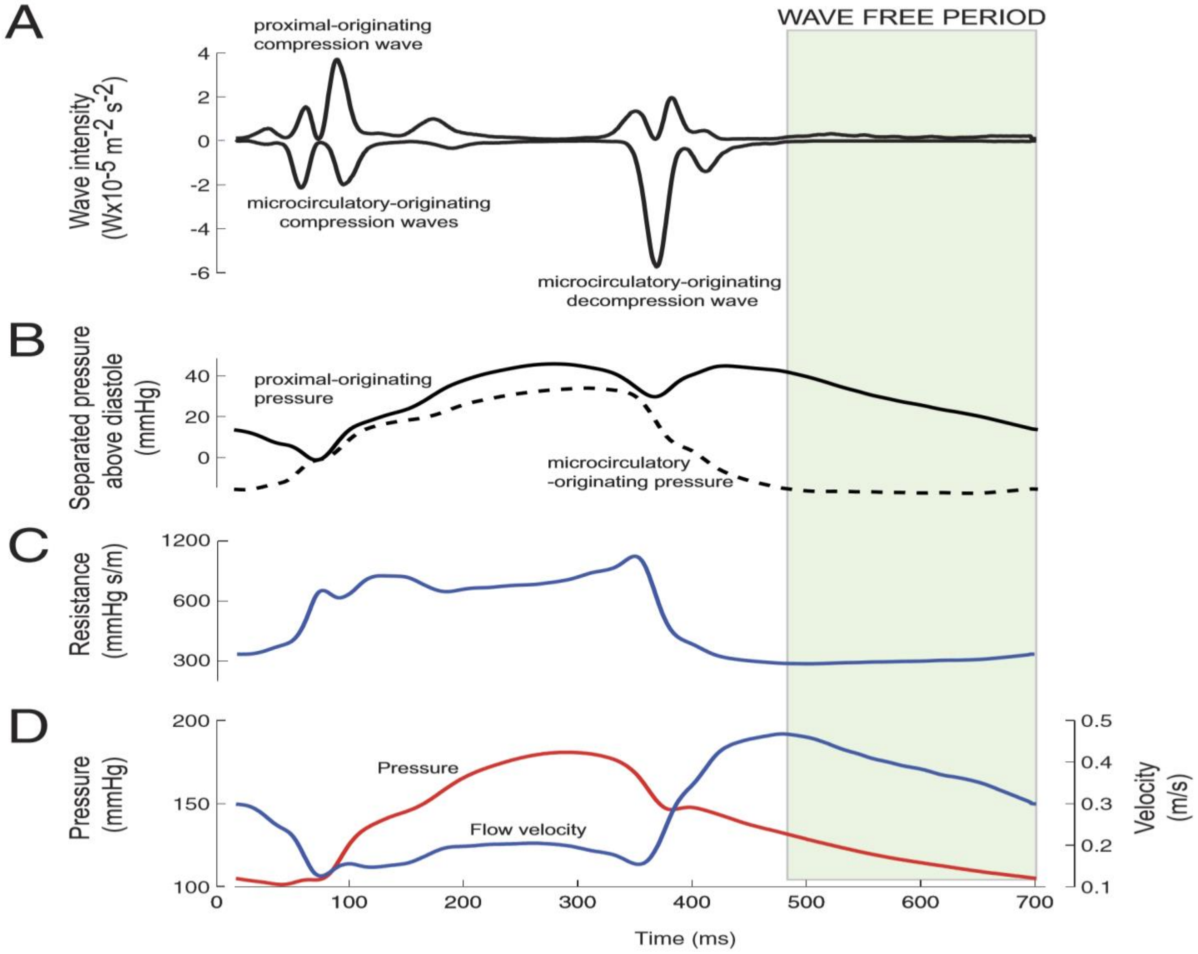
- iFR: comparison of pressures during diastole in the absence of hyperemia
- Measured during the wave-free period of mid to late diastole, when flow during the cardiac cycle is the highest and the microcirculatory resistance is the lowest.
- During this period, pressure and flow velocity are linearly related.
- **iFR threshold of <0.90** has been proposed for revascularization (**RESOLVE**)



Sen S. et al., J Am Coll Cardiol 2012;59:1392–402

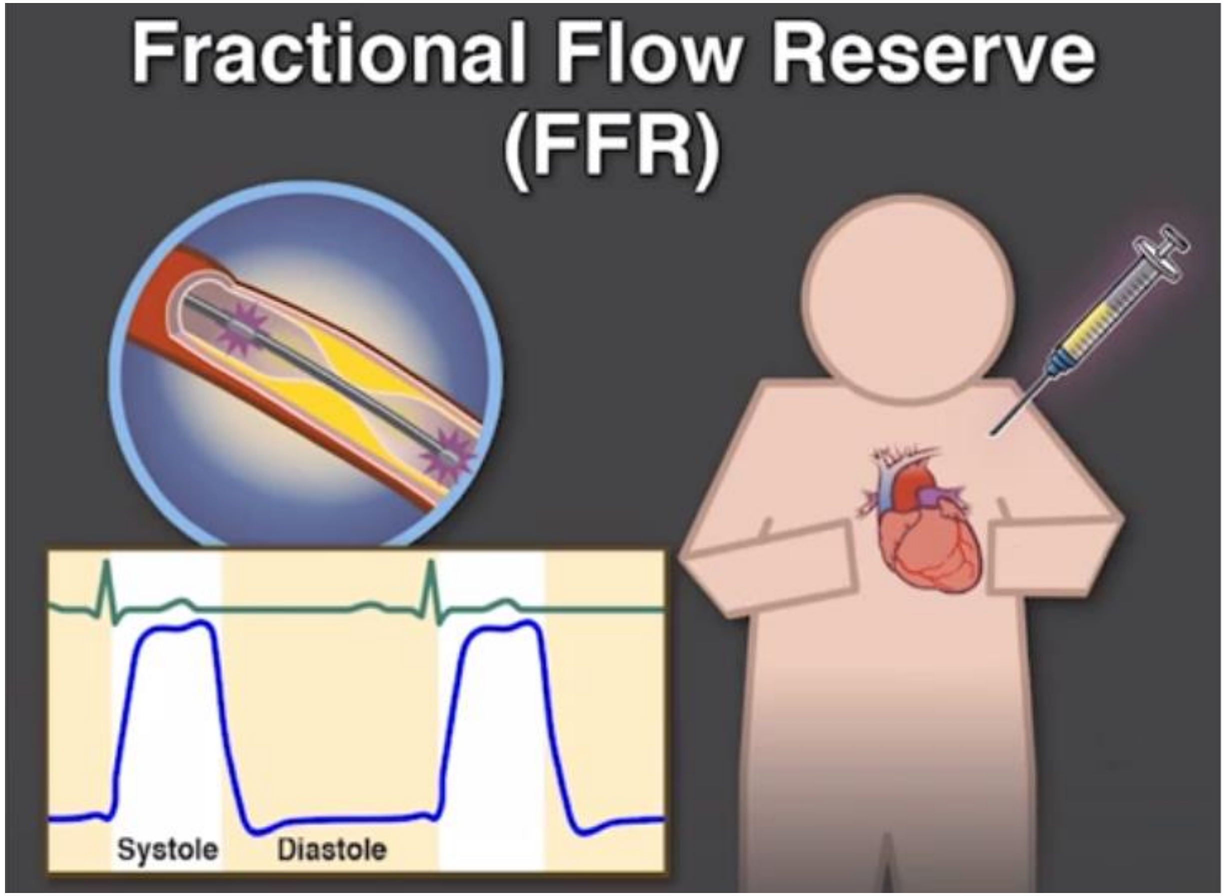
Identification of Wave-Free Period in the Cardiac Cycle

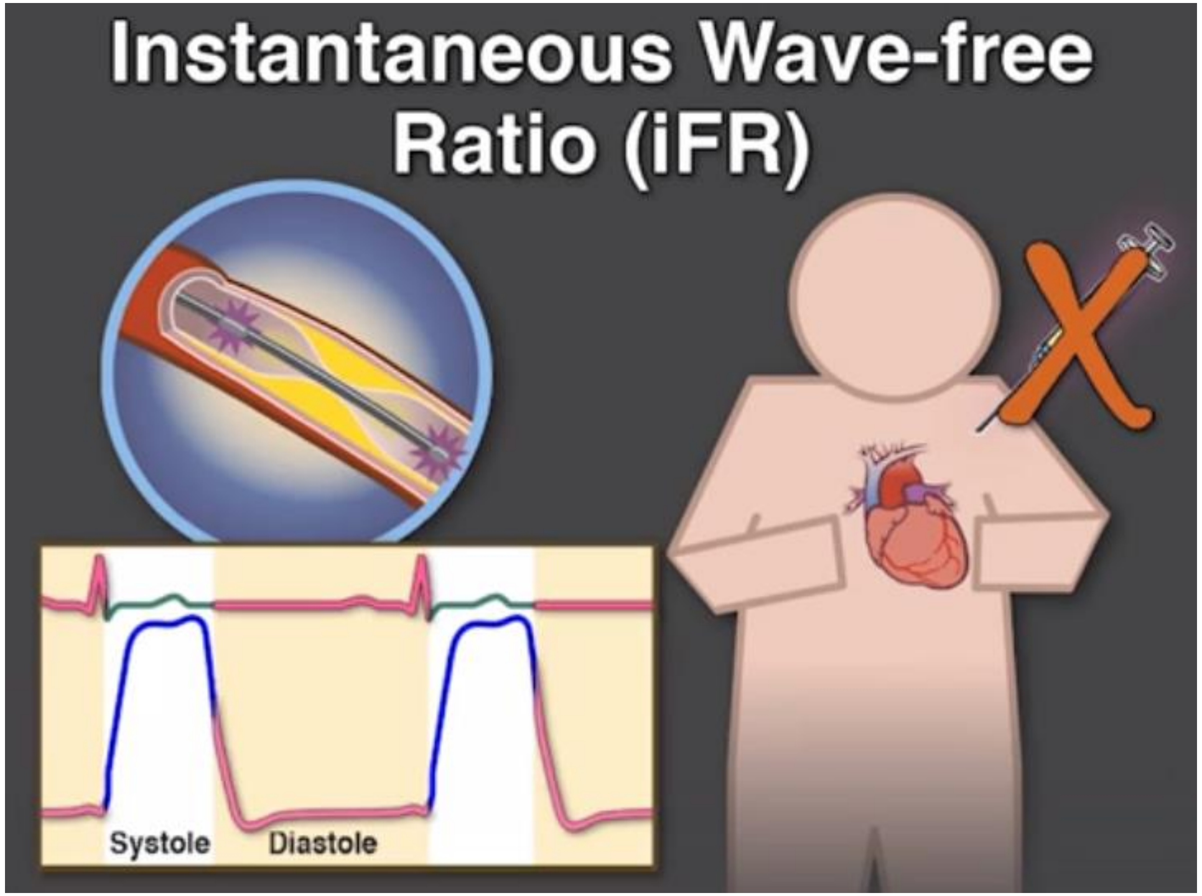
- (A) Wave-intensity analysis demonstrates the proximal and microcirculatory (distal) originating waves generated during the cardiac cycle. A wave-free period can be seen in diastole when no new waves are generated (shaded).
- (B) This corresponds to a time period in which there is minimal microcirculatory (distal)– originating pressure (B)
- (C) minimal and constant resistance (C)
- (D) a nearly constant rate of change in flow velocity (D)



Sen S. et al., J Am Coll Cardiol 2012;59:1392–402

FFR vs iFR


Fractional Flow Reserve (FFR)
Systole
Diastole


Instantaneous Wave-free Ratio (iFR)
Systole
Diastole

iFR-SWEDEHEART

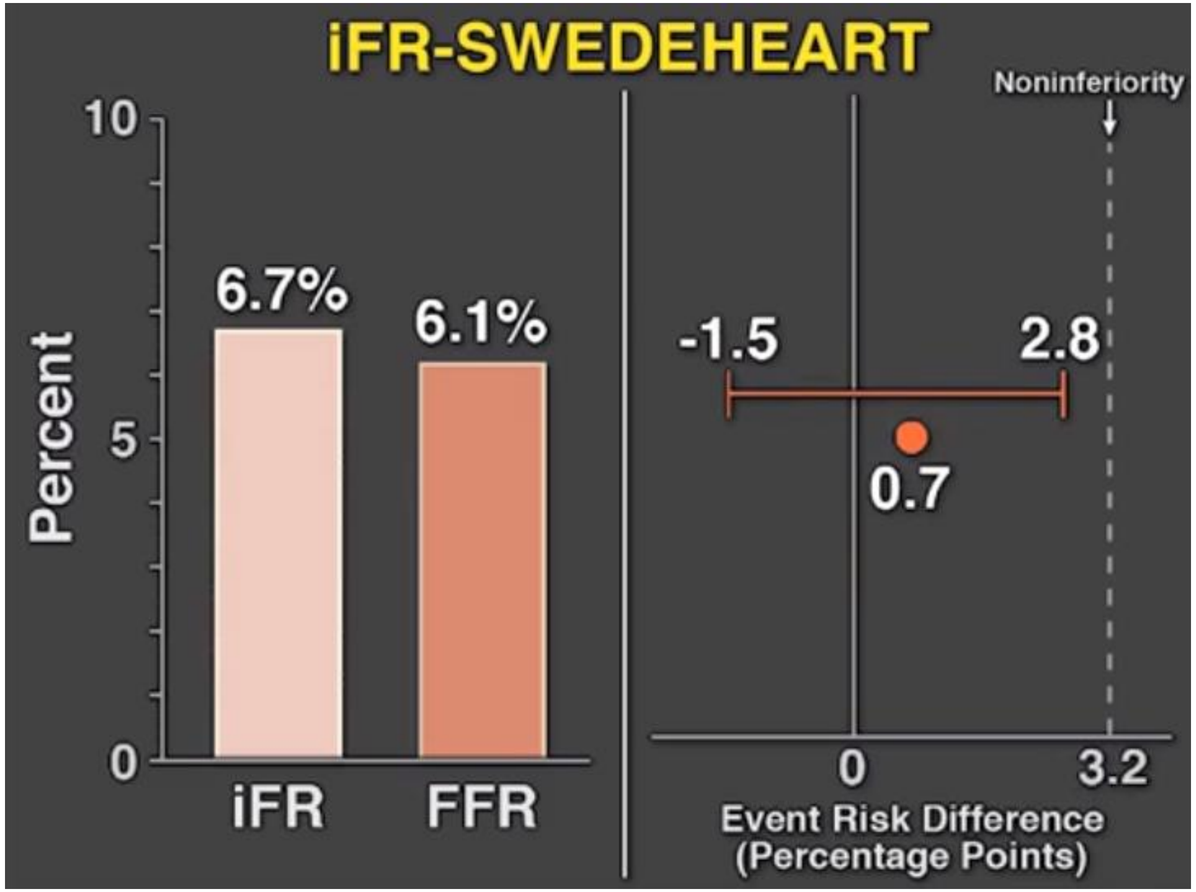
- Open-label
- Randomized
- 2037 Patients
- Stable angina or acute coronary syndrome

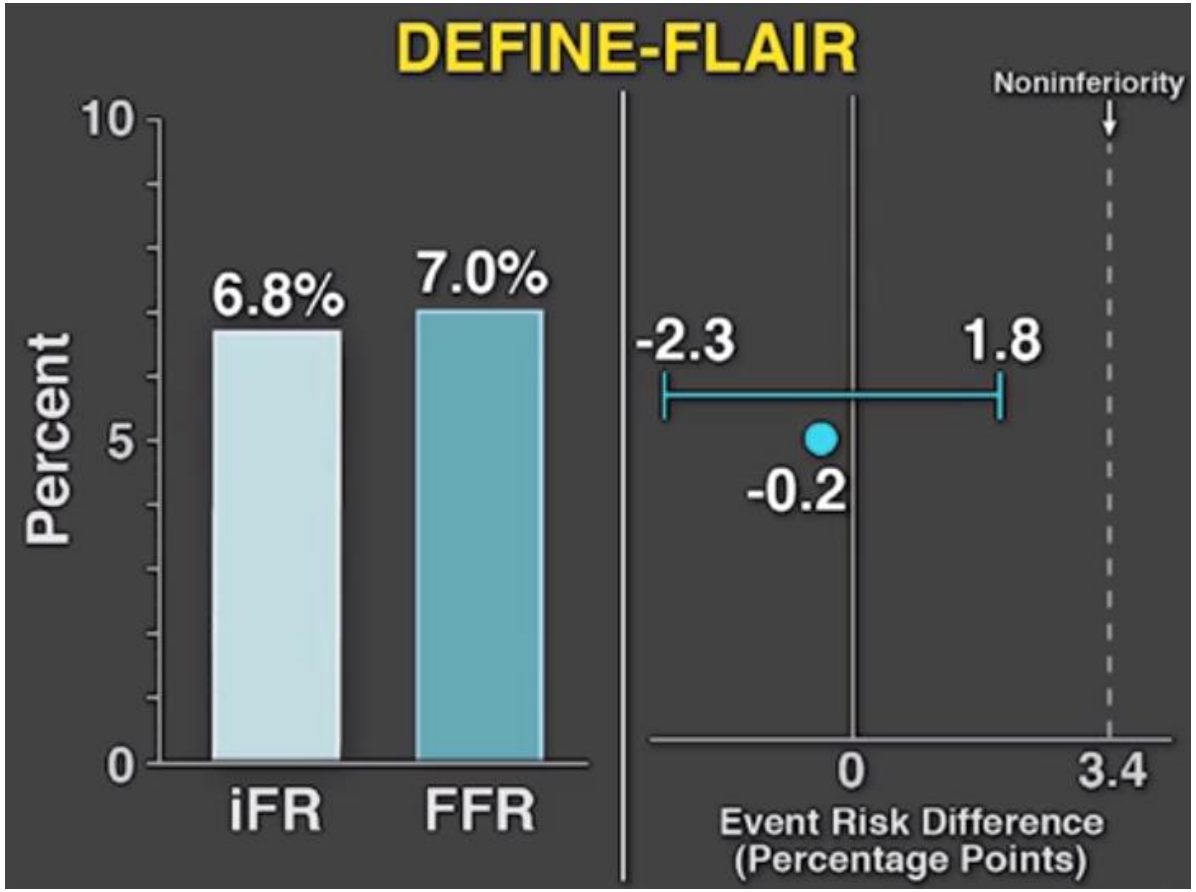
DEFINE-FLAIR

- Blinded
- Randomized
- 2492 Patients
- Coronary artery disease

OUTCOME: death, MI, and urgent revascularization at 12 months
NON-INFERIOR

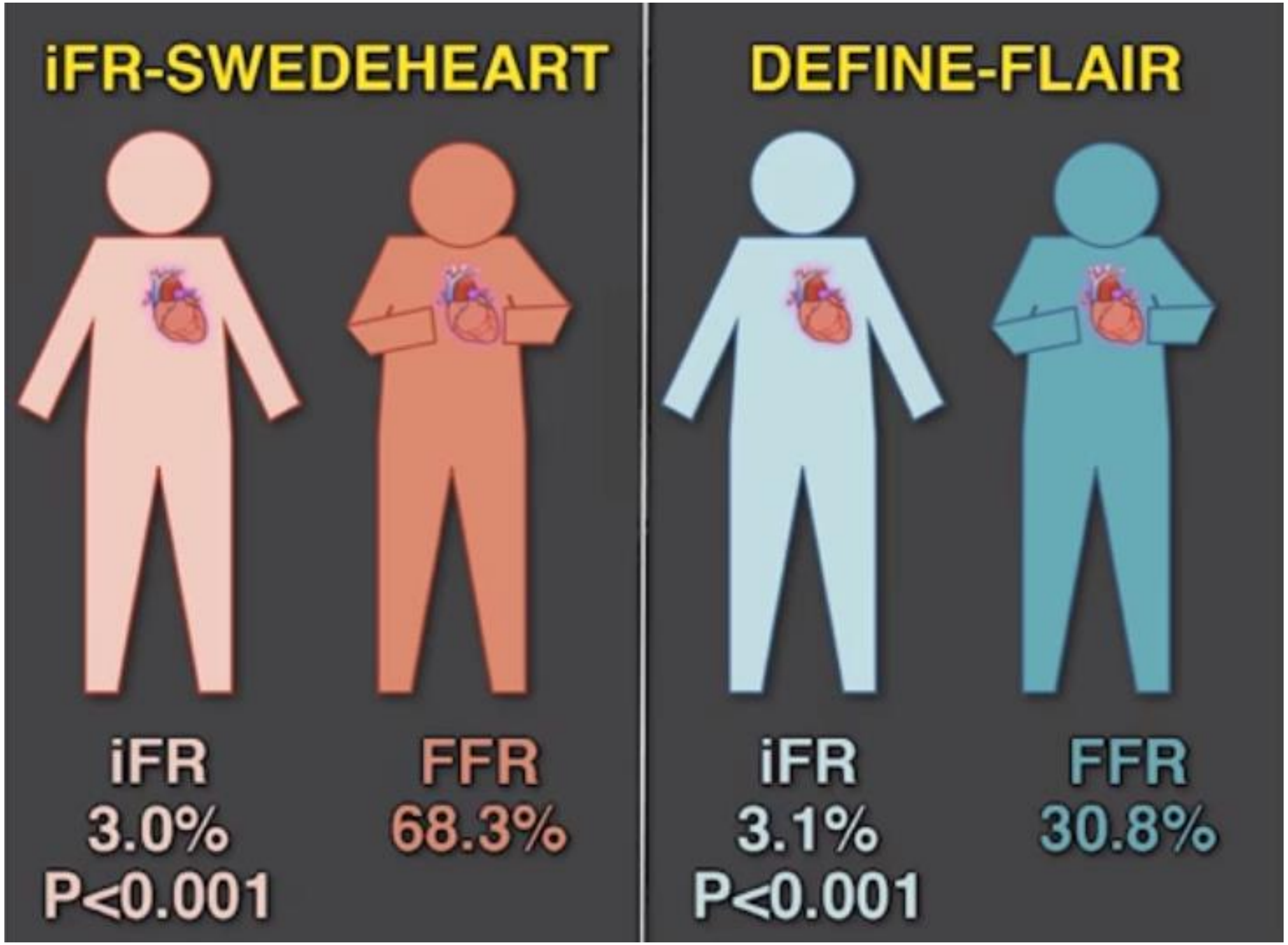
Death, MI, and urgent revascularization at 12 mths





1. *N Engl J Med*. 2017;376:1813–1823. doi: 10.1056/NEJMoa1616540.
2. *N Engl J Med*. 2017;376:1824–1834. doi: 10.1056/NEJMoa1700445.

Patient discomfort



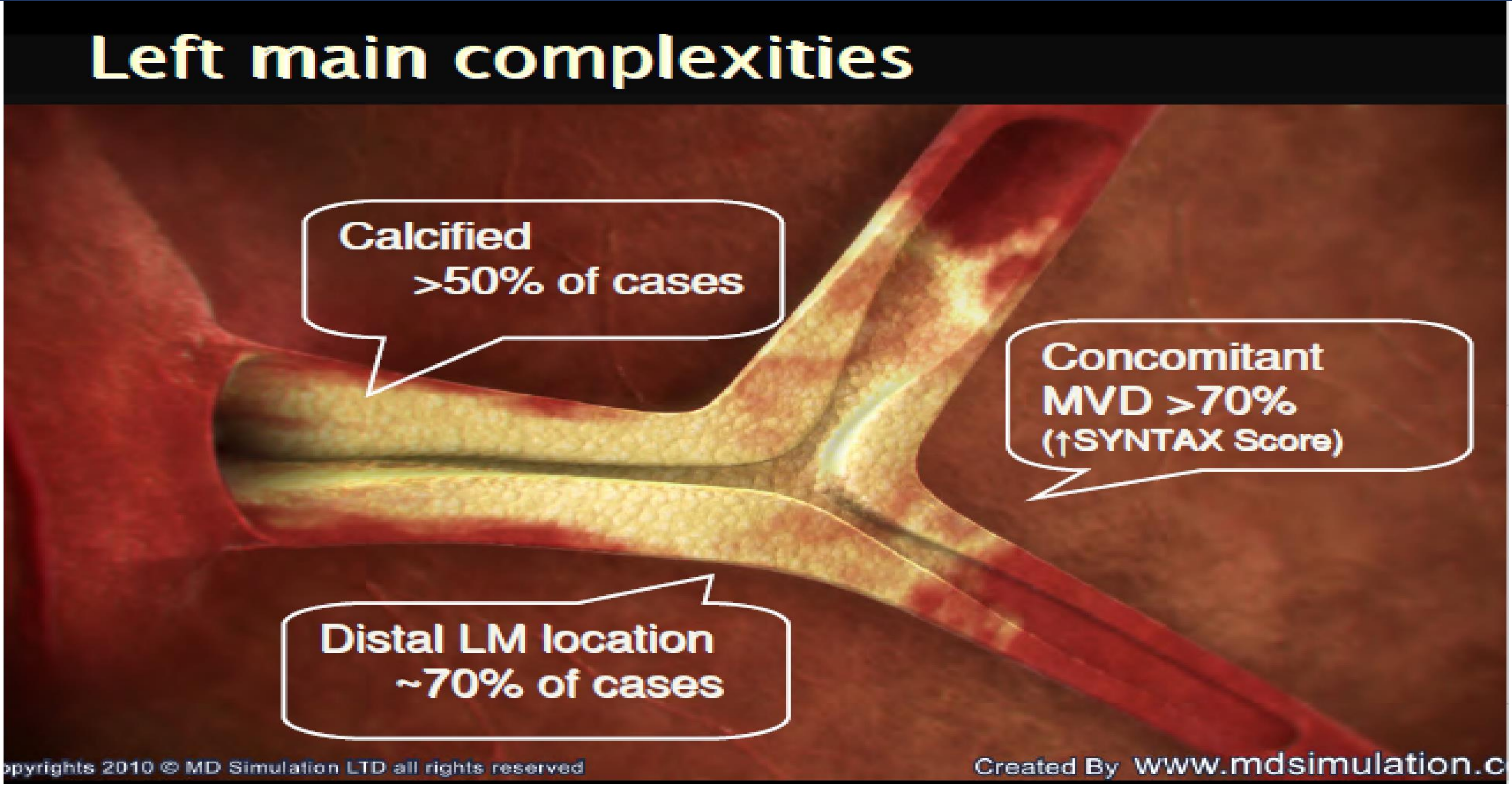
Meta-Analysis of Death and Myocardial Infarction in the DEFINE-FLAIR and iFR-SWEDEHEART Trials

FFR = iFR ?

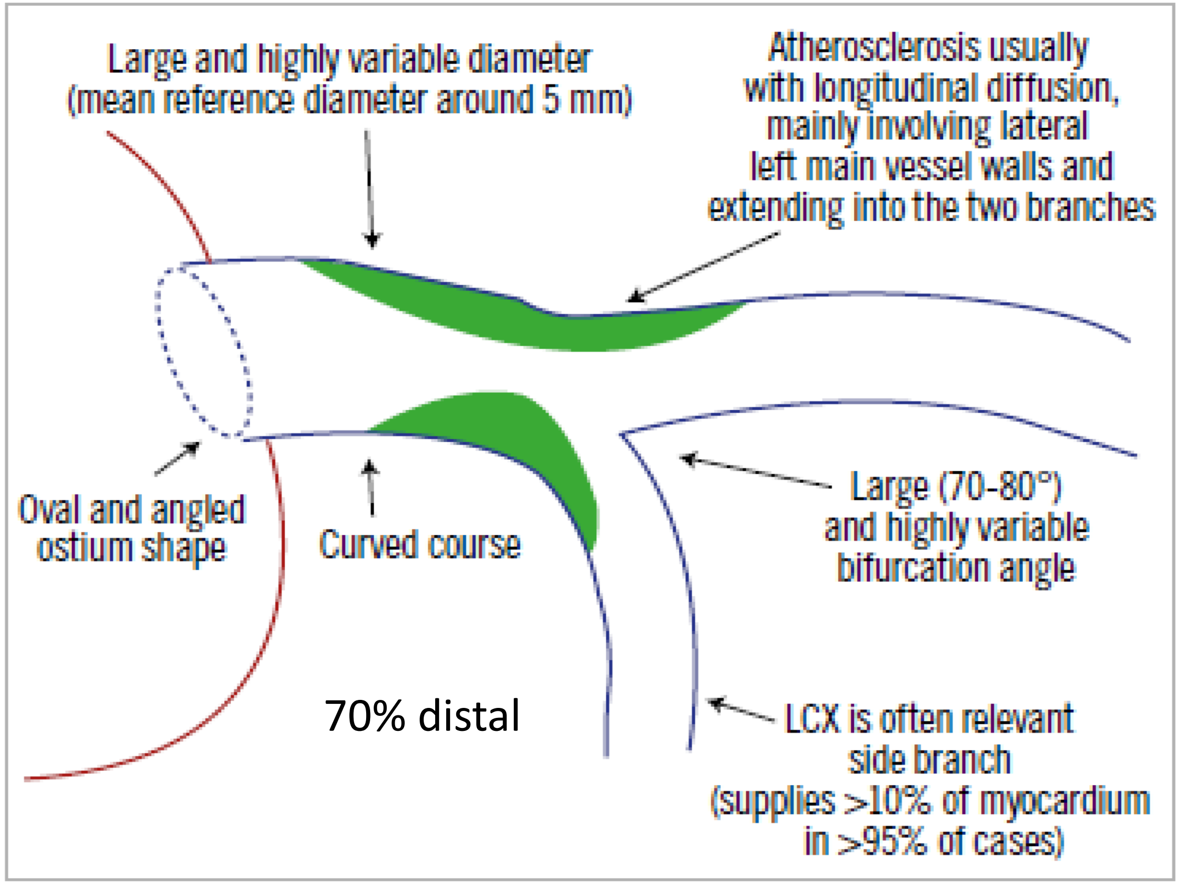
Table. Unplanned Revascularization and Spontaneous Adverse Outcomes at 12 Months in DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) and iFR-SWEDEHEART (Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome) Trials

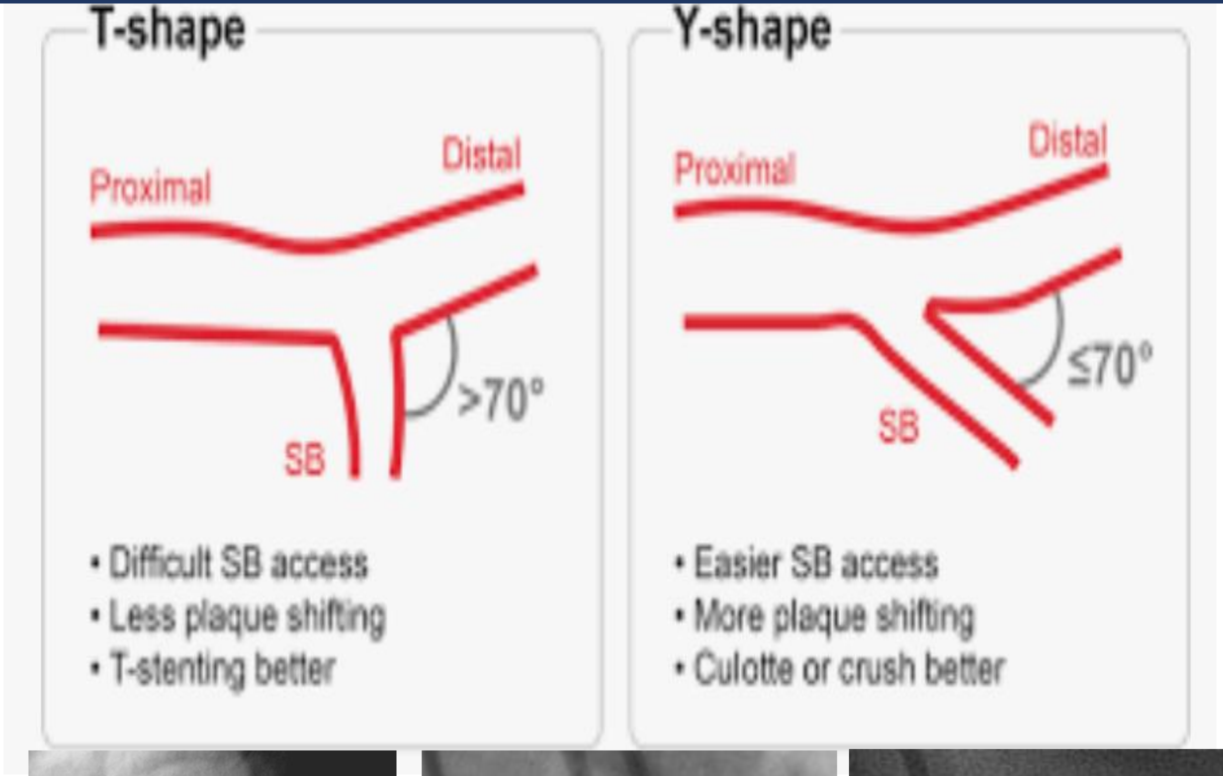
	iFR n (%)	FFR n (%)	Risk Ratio	95% CI	*P* Value
Unplanned revascularization					
DEFINE-FLAIR	46 (4.0)	63 (5.3)	0.75	(0.52–1.09)	0.13
iFR-SWEDEHEART	47 (4.6)	46 (4.6)	1.02	(0.68–1.51)	0.94
Overall			0.87	(0.65–1.16)	0.34
Test for heterogeneity: χ^2 = 1.18 df=1 (P=0.277), I^2 = 15.6%					
Nonfatal myocardial infarction					
DEFINE-FLAIR	31 (2.7)	28 (2.4)	1.14	(0.69–1.89)	0.61
iFR-SWEDEHEART	22 (2.2)	17 (1.7)	1.29	(0.69–2.41)	0.43
Overall			1.20	(0.81–1.77)	0.37
Test for heterogeneity: χ^2 = 0.09 df=1 (P=0.767), I^2 = 0%					
Death					
DEFINE-FLAIR	22 (1.9)	13 (1.1)	1.74	(0.88–3.44)	0.11
iFR-SWEDEHEART	15 (1.5)	12 (1.2)	1.24	(0.59–2.64)	0.57
Overall			1.50	(0.90–2.48)	0.12
Test for heterogeneity: χ^2 = 0.42 df=1 (P=0.516), I^2 = 0%					
Death or myocardial infarction					
DEFINE-FLAIR	53 (4.6)	41 (3.5)	1.33	(0.89–1.98)	0.16
iFR-SWEDEHEART	37 (3.7)	29 (2.9)	1.27	(0.79–2.05)	0.33
Overall			1.30	(0.96–1.77)	0.09

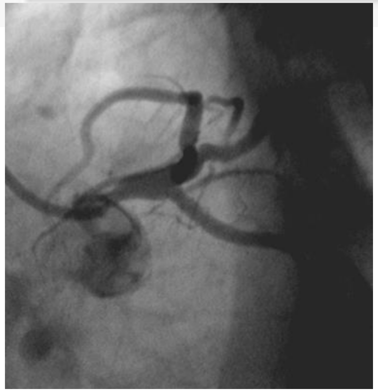
The importance of LMCA



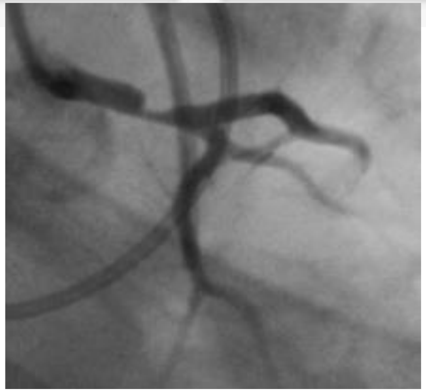
The importance of LM Birfurcation



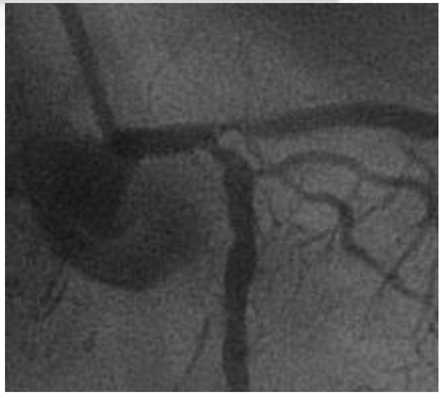




Ostial LM



Mid.LM



Distal LM

EBC Consensus 2018

Randomized FFR Trials in angiographically equivocal lesions
Question 1: Is this lesion LMCA flow-limiting ?

1. DEFER showed that it was safe to defer PCI in lesions with an FFR >0.75

- *Bech et al. Circulation 2001;103:2928-34*
- *Pijls et al. J am CollCardiol2007;49:2105-11*

2. **FAME-I showed that treating lesions with an FFR >0.80 with first generation DES was harmful and that a deferred PCI strategy was safer and cost-saving**

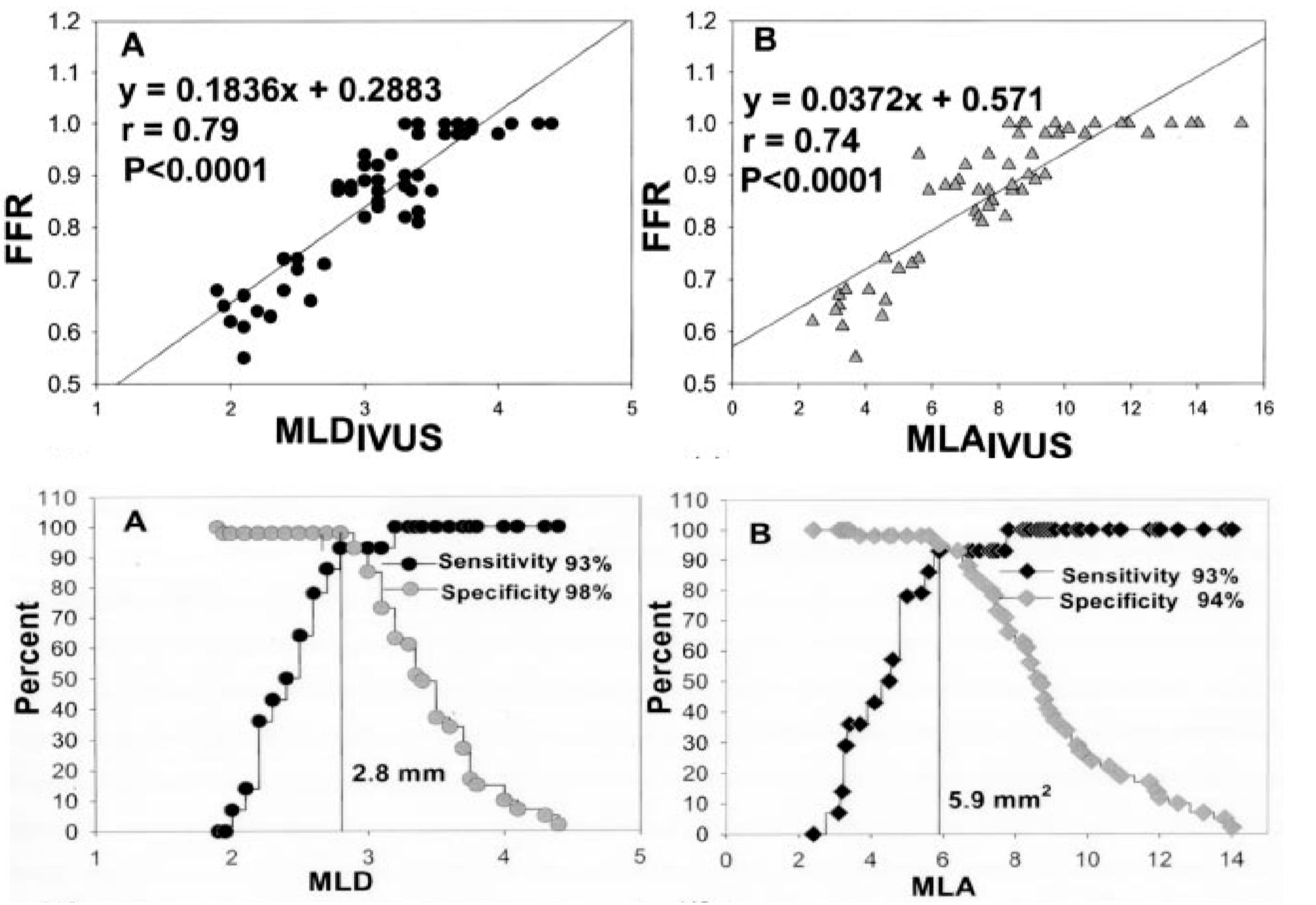
- *Toninoet al. N EnglJ Med. 2009;360:213-24*
- *Pijls et al. J am CollCardiol2010;56:177-84*
- *Fearon et al. Circulation 2010;122:2545-50*

3. **FAME-II showed that deferring PCI in lesions with an FFR <0.80 was harmful compared to optimal medical therapy. While more expensive at the beginning, the cost of this strategy decreased by 50% at 1 year. In addition, FAME-II confirmed the findings of DEFER**

- *De Bruyne et al. N EnglJ Med 2012;367:991-1001*
- *Fearonet al. Circulation 2013;17:1335-40*
- *De Bruyneet al. N EnglJ Med 2014;371:1208-17*

Adapted from G. Mintz, MD

Question 1: Is this lesion LMCA flow-limiting ?
How about role of FFR/iFR or IVUS?

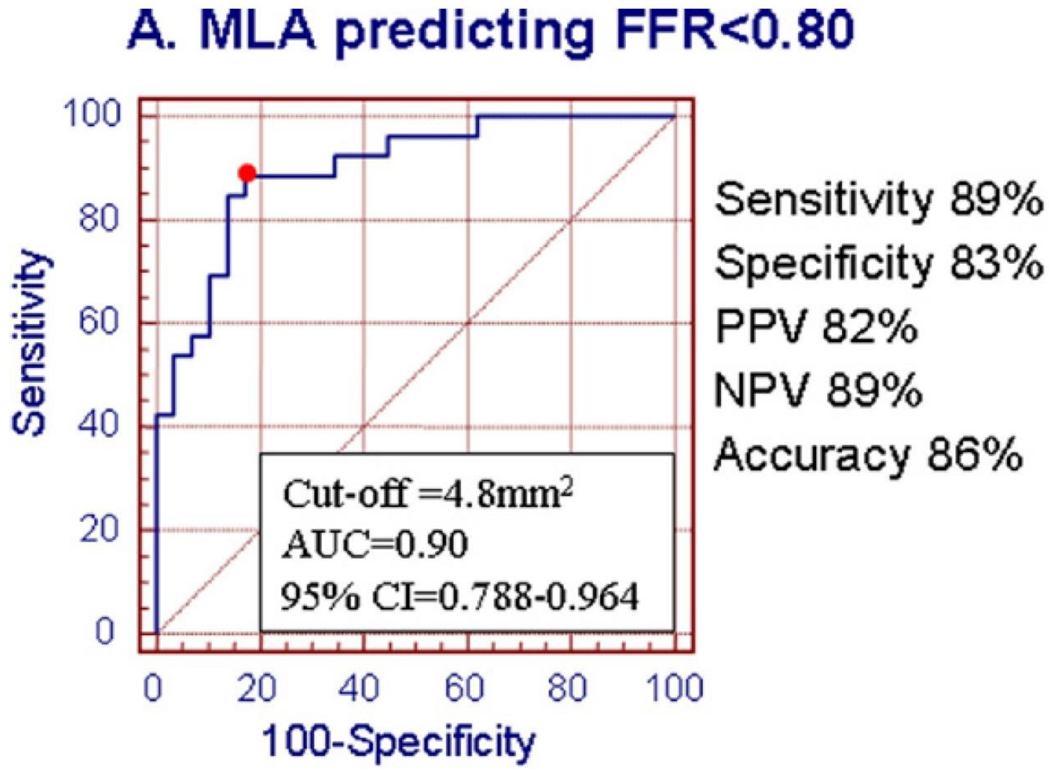


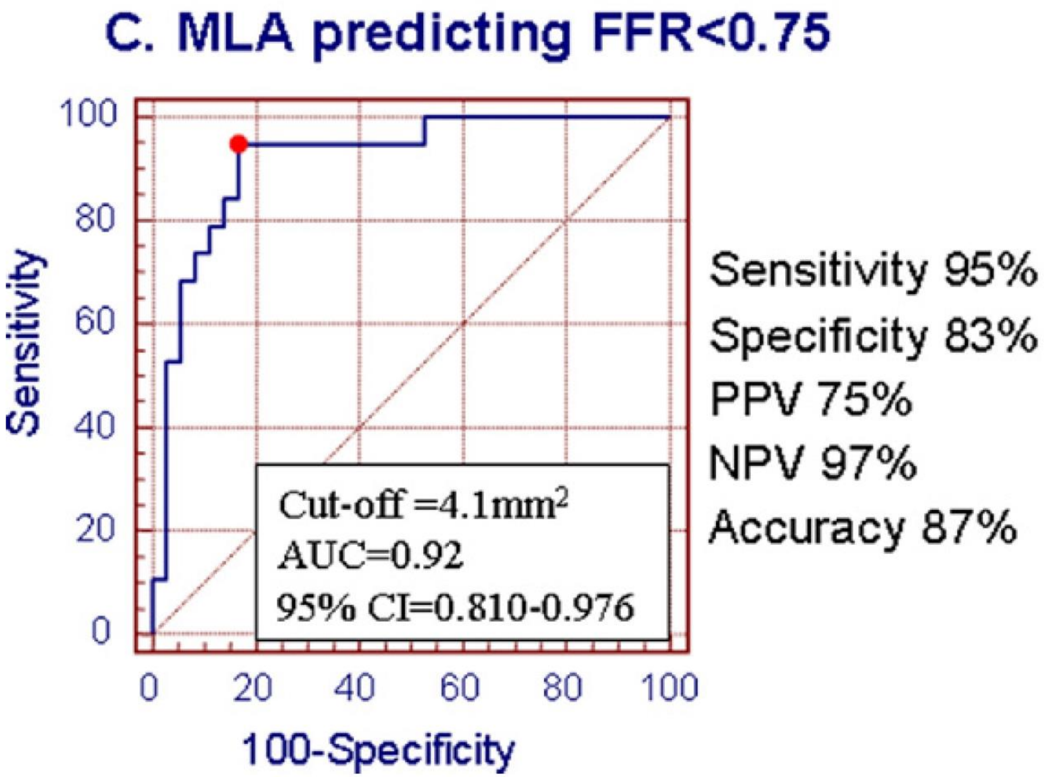
55 patients with angiographically equivocal left main disease

Jasti V et al.; Circulation November 2, 2004, Volume 110, Issue 18

Question 1: Is this lesion LMCA flow-limiting ?
How about role of FFR/iFR or IVUS?

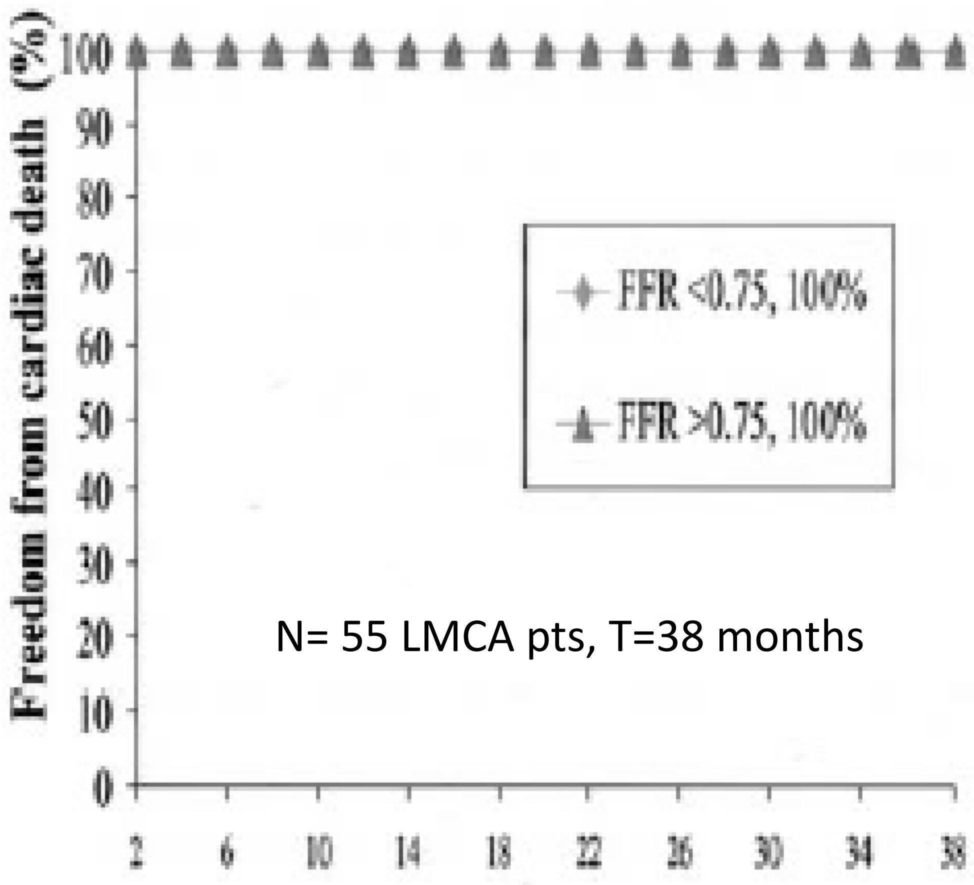
55 patients with 30-80% LM and FFR and IVUS



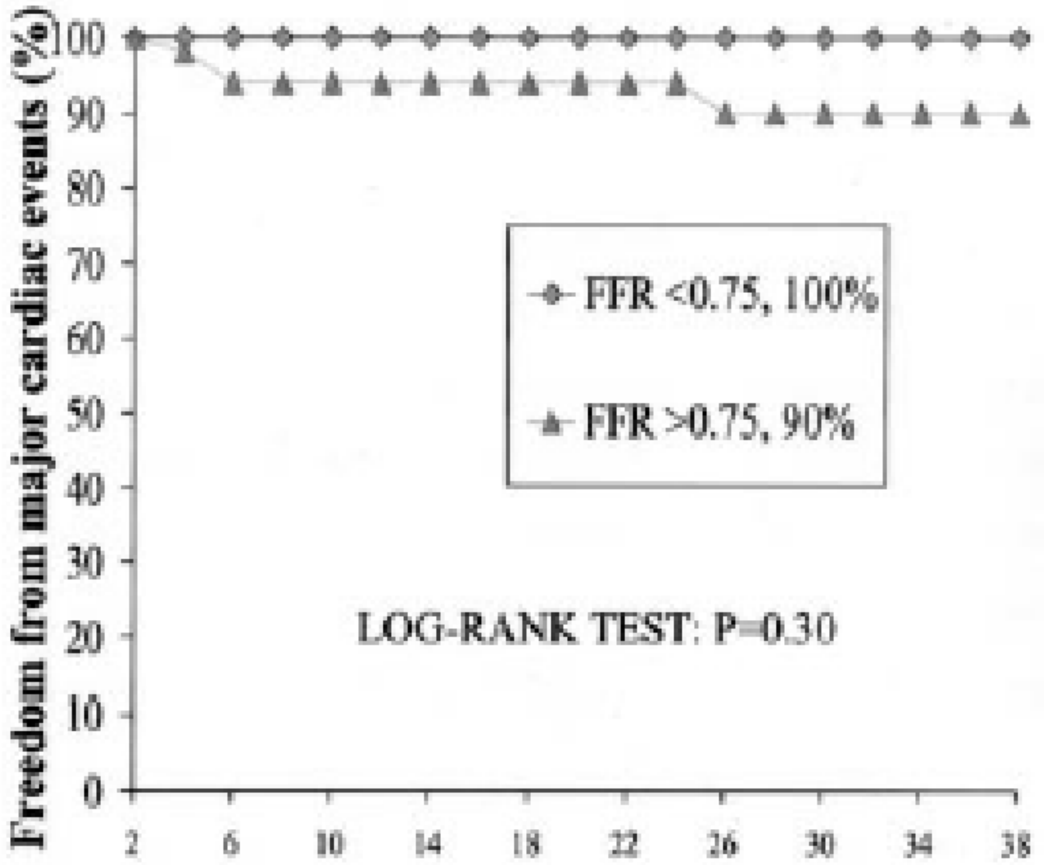


Kang et al.; J Am Coll Cardiol Intv 2011;4:1168–74

Question 2: Is it safe to defer LM Rx if FFR/iFR > 0.80?

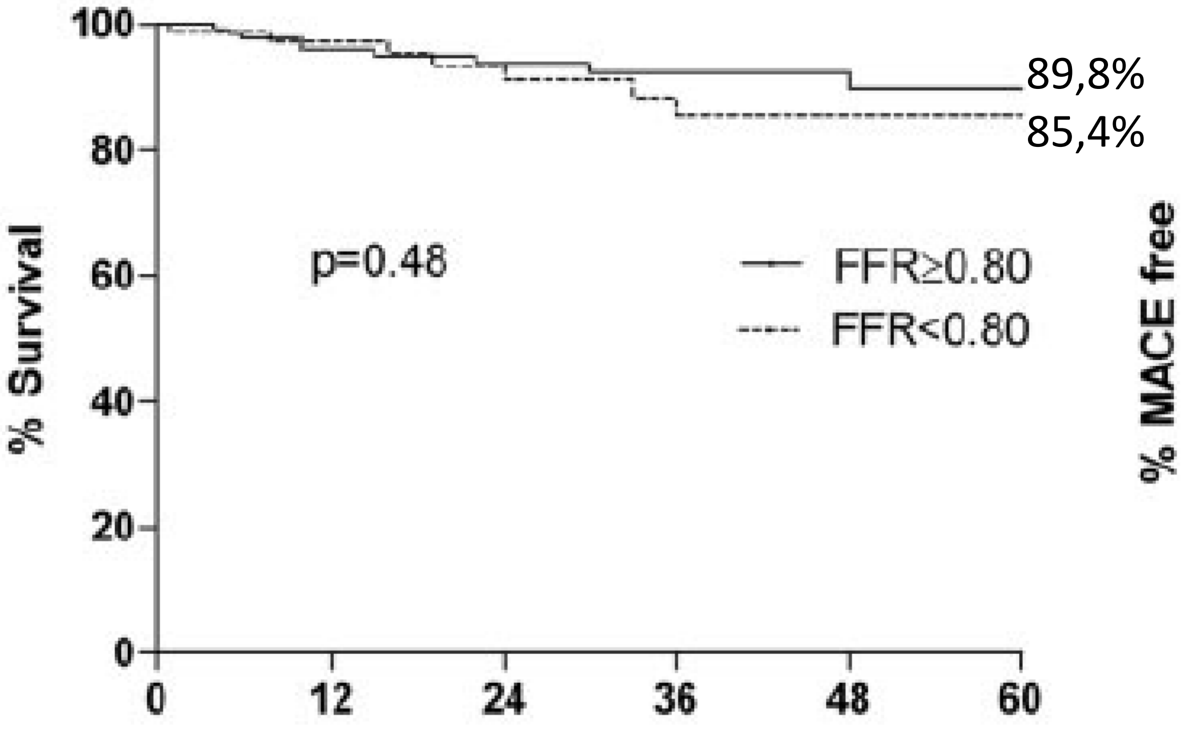


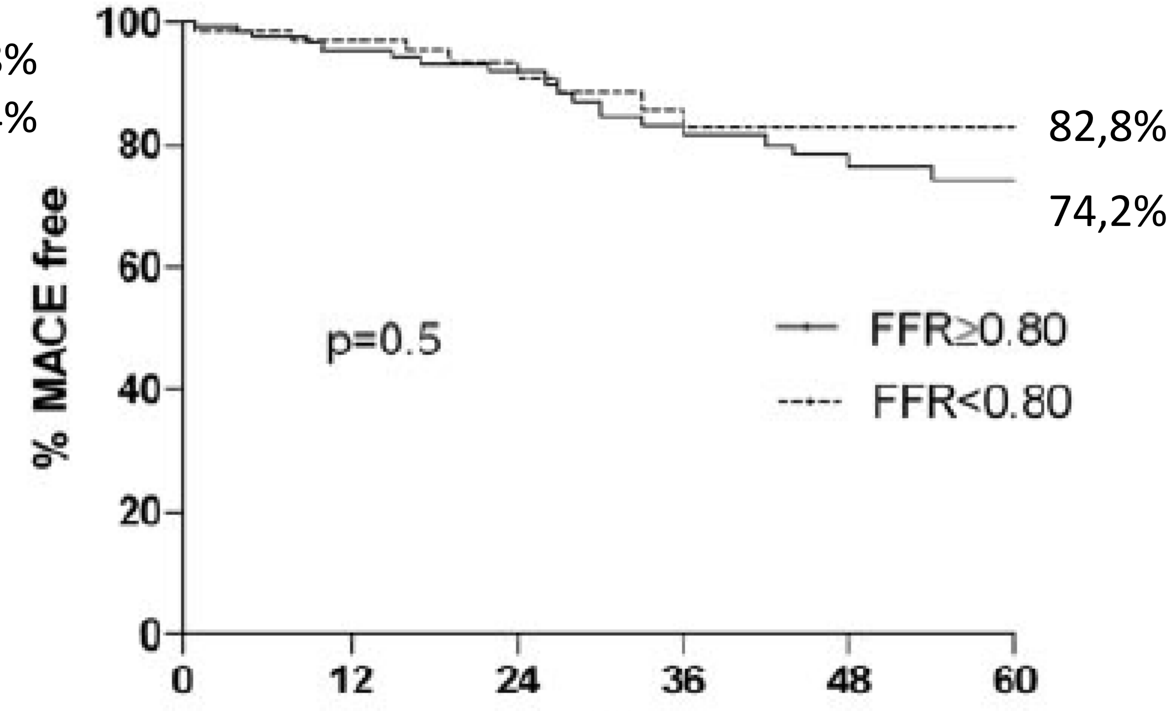
N= 55 LMCA pts, T=38 months



Jasti V et al.; Circulation November 2, 2004, Volume 110, Issue 18
Kang et al.; J Am Coll Cardiol Intv 2011;4:1168–74

Question 2: Is it safe to defer LM Rx if FFR > 0.8 ?



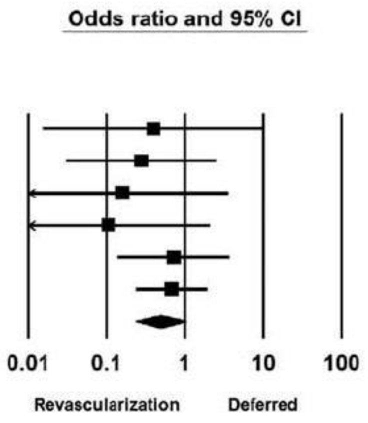


N=213 LMCA pts, T= 60 months

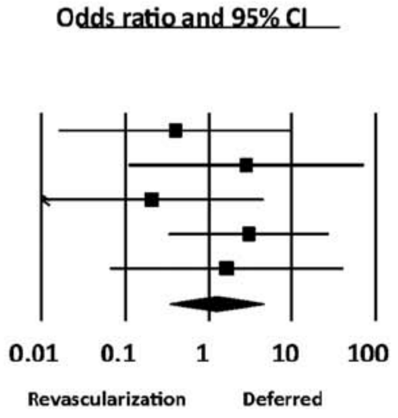
Hamilos M. et al. Circulation. 2009;120:1505-1512.)

Question 2: Is it safe to defer LM Rx if FFR/iFR > 0.80? Pooled meta-analysis of 6 studies, N=525 LMCA pts

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Bech	0.401	0.016	10.301	-0.551	0.581
Jimenez-Navarro	0.278	0.031	2.497	-1.143	0.253
Legutko	0.161	0.007	3.590	-1.153	0.249
Lindstaedt	0.107	0.005	2.090	-1.474	0.140
Courtis	0.722	0.140	3.705	-0.391	0.696
Hamilos	0.678	0.242	1.899	-0.740	0.459
	0.497	0.237	1.040	-1.856	0.063

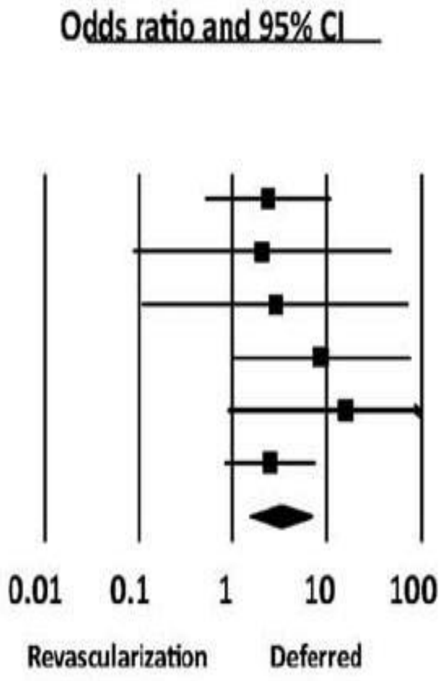


Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Bech	0.401	0.016	10.301	-0.551	0.581
Legutko	2.846	0.109	74.379	0.628	0.530
Lindstaedt	0.208	0.010	4.559	-0.997	0.319
Courtis	3.026	0.330	27.781	0.979	0.328
Hamilos	1.647	0.066	40.936	0.304	0.761
	1.225	0.335	4.481	0.306	0.760



Cardiac death,MI rate was similar between both groups when LM deferred based on FFR

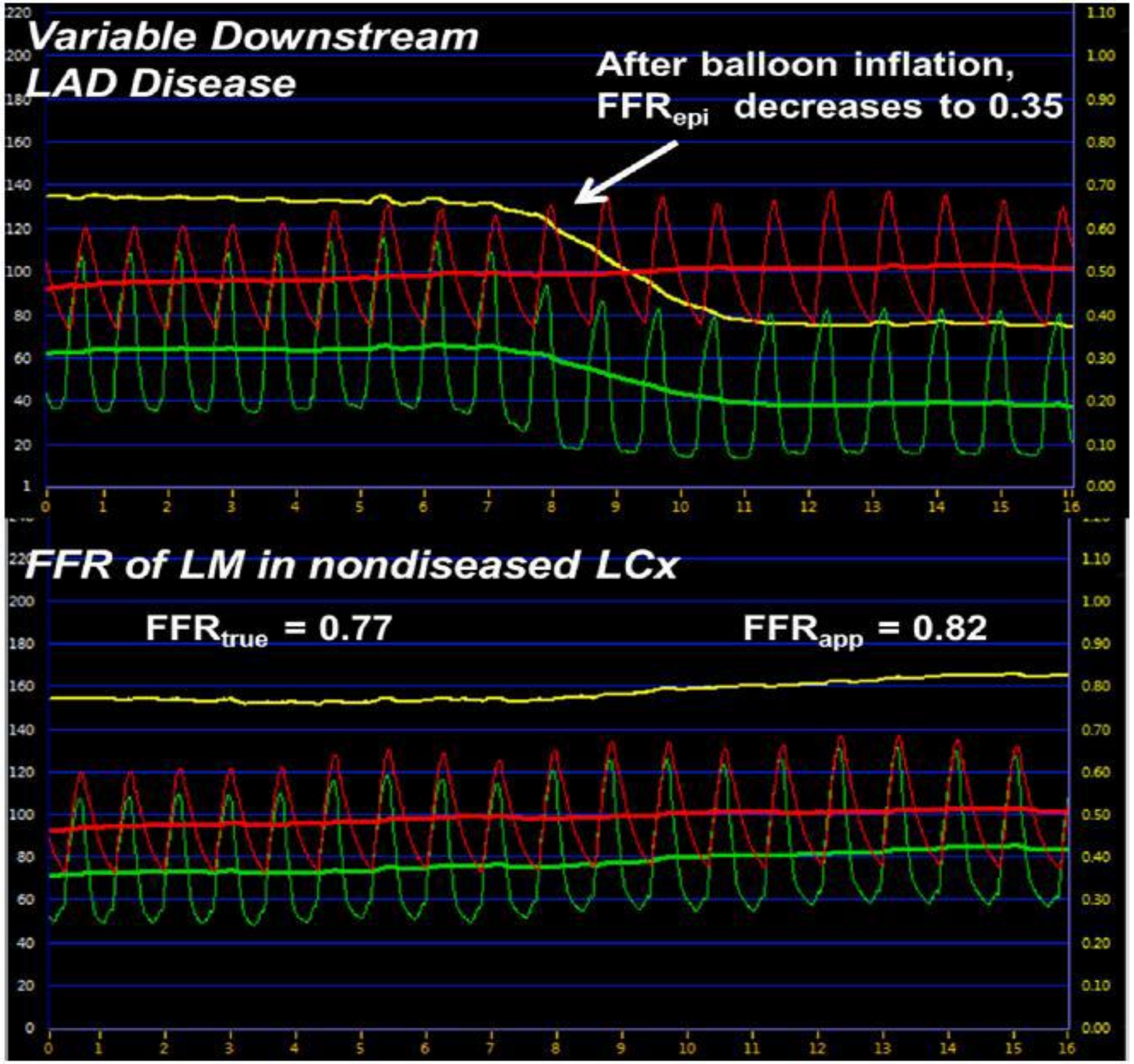
Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Bech	2.368	0.504	11.125	1.092	0.275
Jimenez-Navarro	2.027	0.087	47.429	0.439	0.660
Legutko	2.846	0.109	74.379	0.628	0.530
Lindstaedt	8.667	0.960	78.268	1.923	0.054
Courtis	15.639	0.892	274.209	1.882	0.060
Hamilos	2.494	0.807	7.704	1.588	0.112
	3.238	1.513	6.931	3.026	0.002



Revascularization rate was higher when LM deferred based on FFR

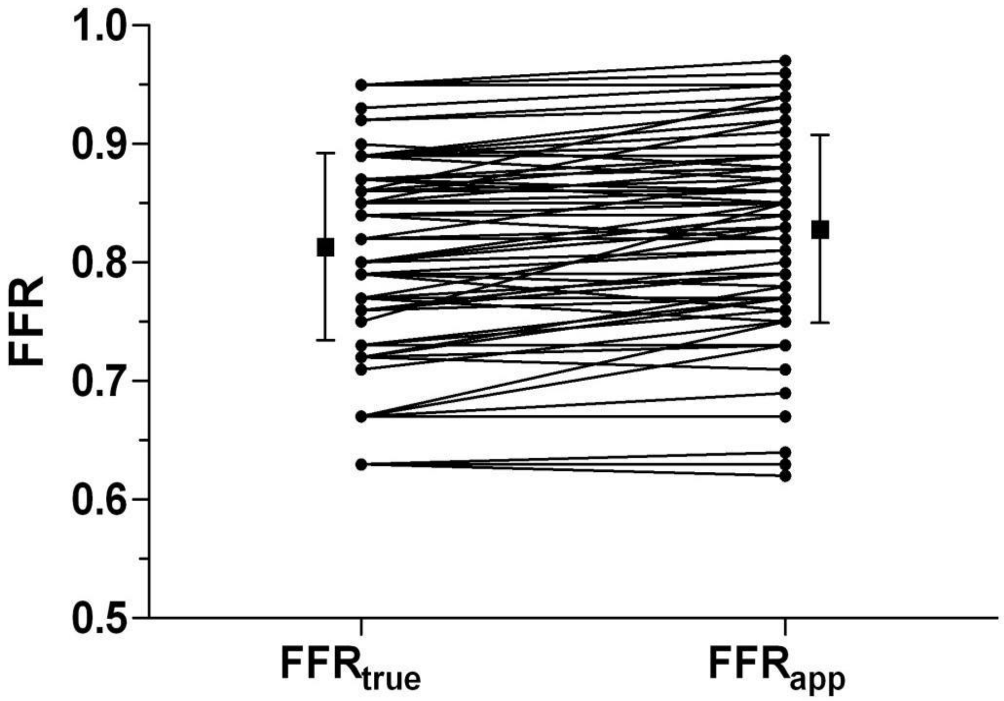
Mallidi J. et al. Catheter Cardiovasc Interv. 2015 Jul;86(1):12-8

Question 3: Does downstream Stenosis affect on LMCA FFR?



91 paired measurements obtained in 24 patients

0.81±0.08 vs. 0.83± 0.08, *P*<0.001

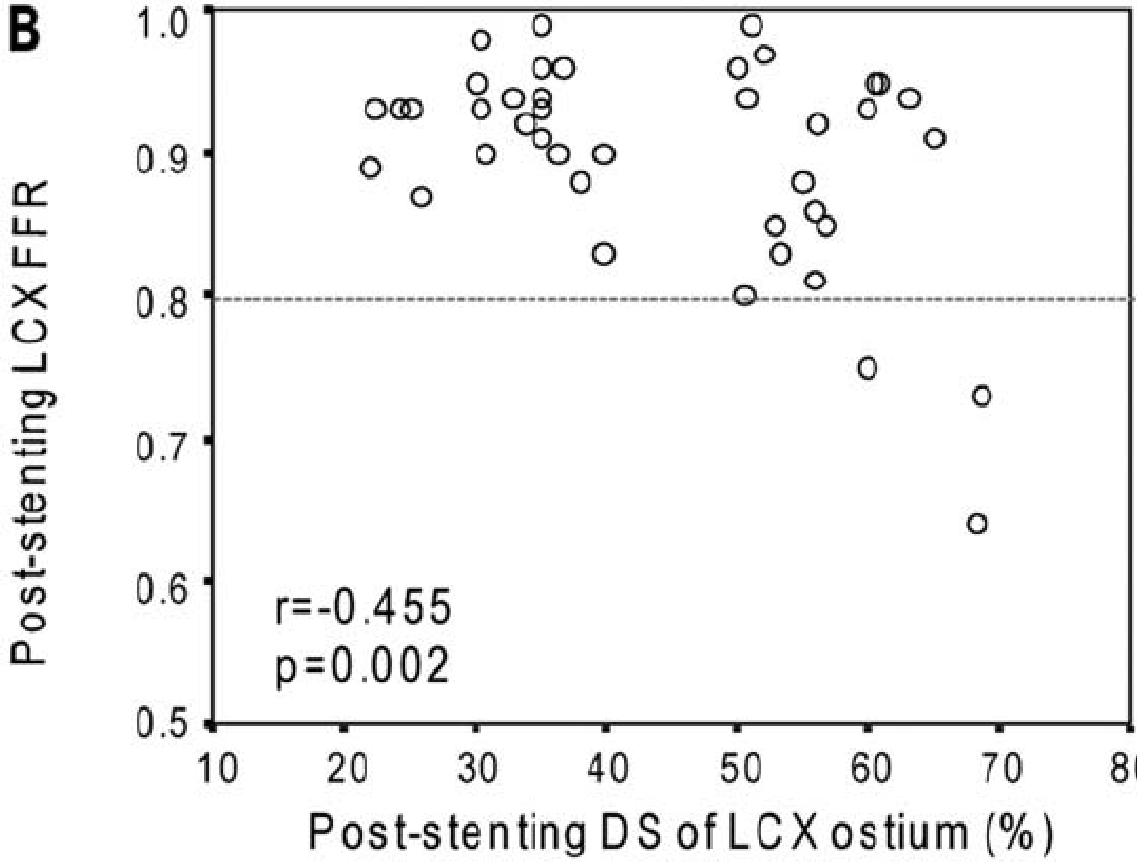


When FFRapp >0.85, FFRtrue >0.80

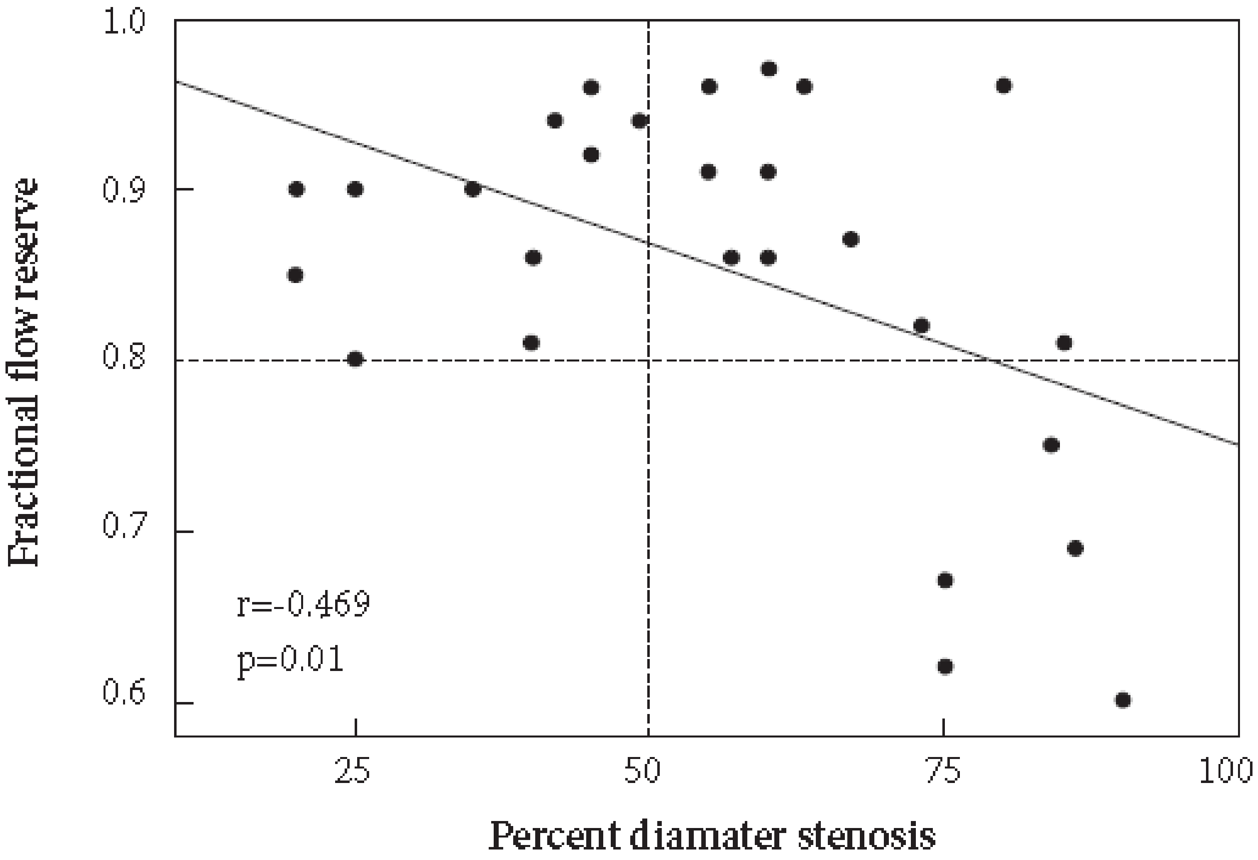
Fearon WF. et al. JACC CV Intervent 2015;8:398-403.

Question 4: Is this “jailed” LCx significant ?

43 patients with cross-over LM to LAD PCI
FFR of LCx, post PCI (pre LCx < 50%)



29 patients with LM/LAD crossover stenting
FFR of “jailed” Cx (pre LCx: 30 -40%)



Kang SJ, et al. Catheter Cardiovasc Intervent 2014;83:545-52.
Nam CW, et al. Korean Circ J 2011;41:304-7.

ROLE OF FFR/iFR

- In patients with stable angina when no other objective evidence of ischaemia is available.
- Not recommended to determine whether a single or two-stent approach.
- The evaluation is difficult since the pinching could be temporary, due to vascular wall oedema, minor intramural haematomas and plaque shift, prone to remodeling
  - ➢ An SB FFR value above 0.80 before MB stenting does not exclude a subsequent need for treating the SB.
  - ➢ An FFR/iFR value above 0.80 in a jailed SB indicates that further SB treatment may be safely deferred.

SUMMARY

- For most clinical scenarios, measuring one or the other index should be based on one individual's comfort level for each test. In some clinical circumstances, the argument can be made to obtain both measurements.
- The decision to revascularize lesions with discordant ifr and FFR results should be made carefully, and comprehensive physiologic evaluations would be needed to guide decisions on treatment strategies for these lesions.
- The available clinical evidence strongly supports the current practice of an ischemia-guided revascularization strategy

-> regardless of whether FFR or iFR is used for clinical decision- making

When you come to a fork in the road, take it.

—Yogi Berra

THE END