Choosing Wisely: FFR vs. Anatomy Dilemma in LM PCI and Introduction to FATE-MAIN Trial

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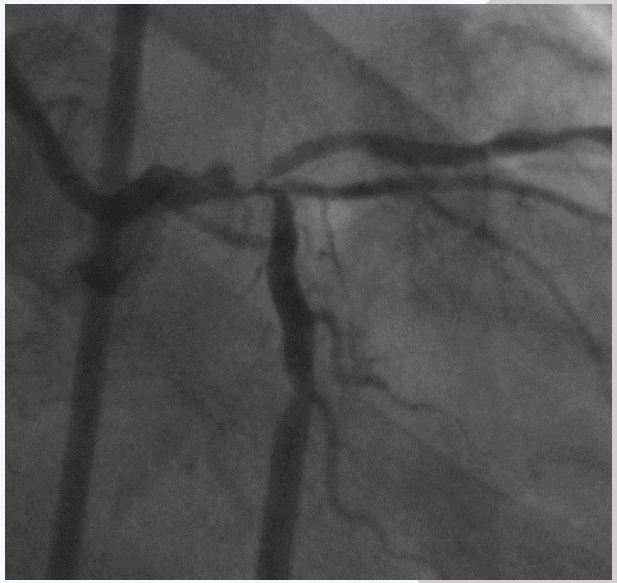
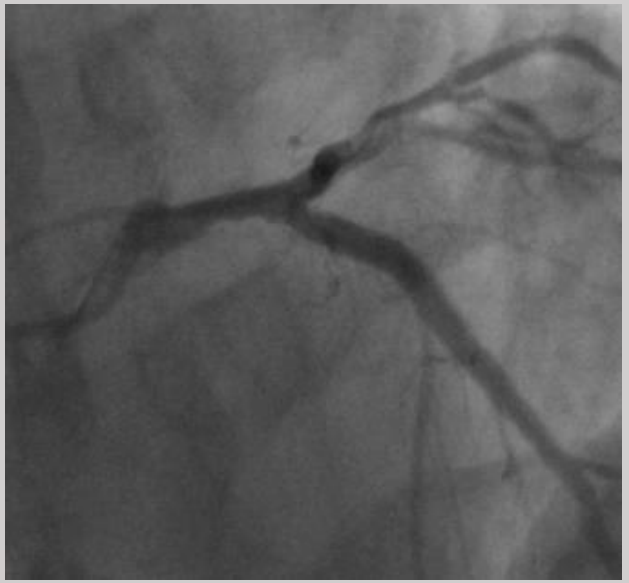
What is the Significant Stenosis of LM ?

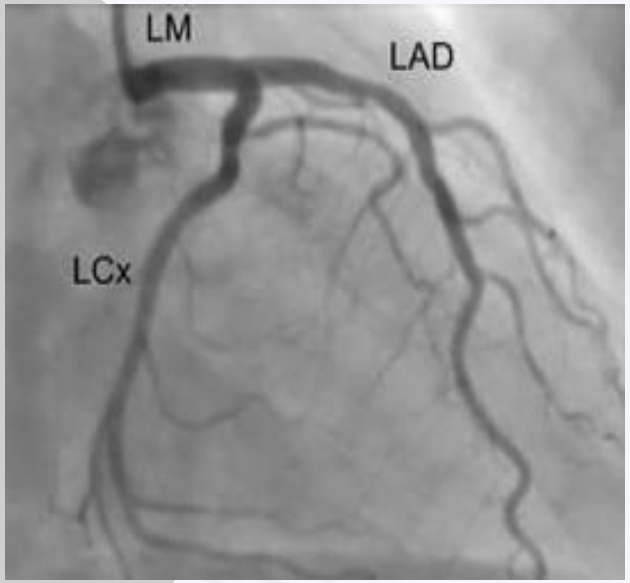
Grey Zone

Significant Stenosis

Non-Significant Stenosis







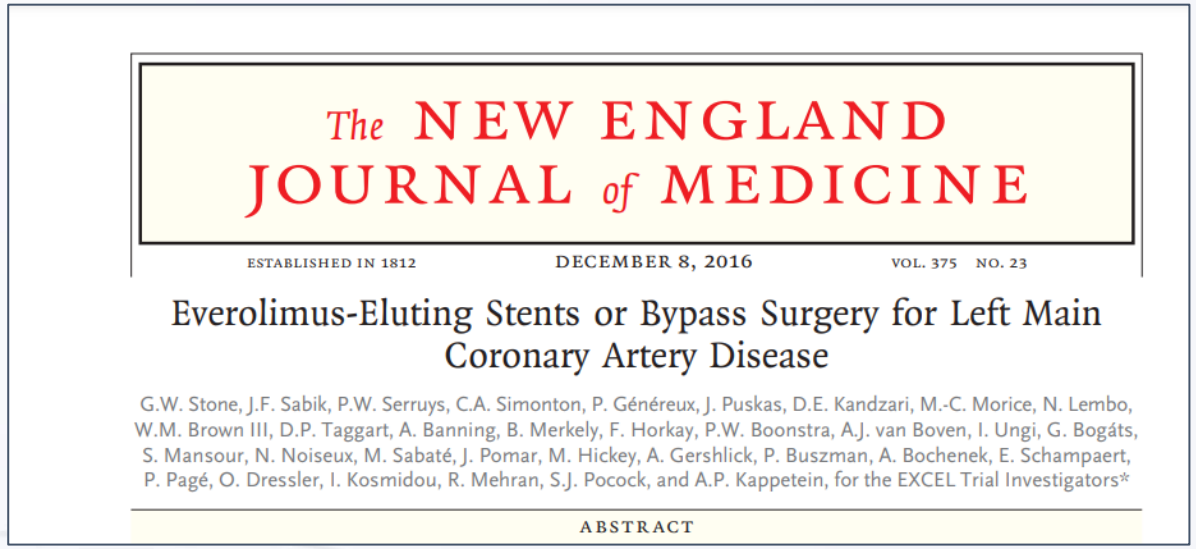
Significant Left Main Disease (DS>50%)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Stents versus Bypass Surgery for Left Main Coronary Artery Disease

Seung-Jung Park, M.D., Young-Hak Kim, M.D., Duk-Woo Park, M.D., Sung-Cheol Yun, Ph.D., Jung-Min Ahn, M.D., Hae Geun Song, M.D., Jong-Young Lee, M.D., Won-Jang Kim, M.D., Soo-Jin Kang, M.D., Seung-Whan Lee, M.D., Cheol Whan Lee, M.D., Seong-Wook Park, M.D., Cheol-Hyun Chung, M.D., Jae-Won Lee, M.D., Do-Sun Lim, M.D., Seung-Woon Rha, M.D., Sang-Gon Lee, M.D., Hyeon-Cheol Gwon, M.D., Hyo-Soo Kim, M.D., In-Ho Chae, M.D., Yangsoo Jang, M.D., Myung-Ho Jeong, M.D., Seung-Jea Tahk, M.D., and Ki Bae Seung, M.D.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2016 VOL. 375 NO. 23

Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease

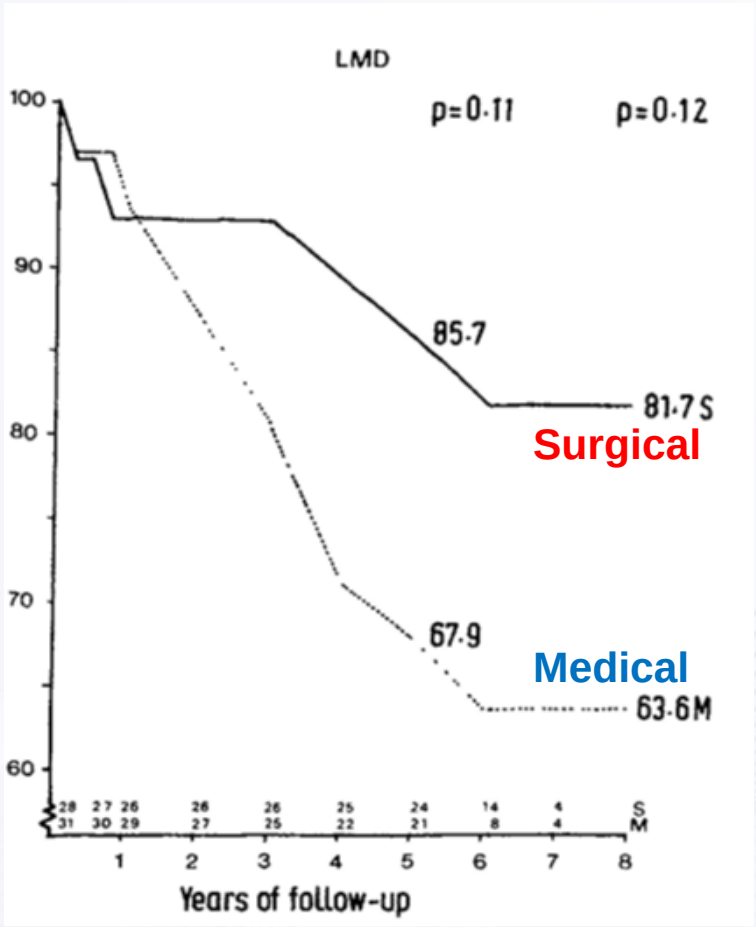
G.W. Stone, J.F. Sabik, P.W. Serruys, C.A. Simonton, P. Généreux, J. Puskas, D.E. Kandzari, M.-C. Morice, N. Lembo, W.M. Brown III, D.P. Taggart, A. Banning, B. Merkely, F. Horkay, P.W. Boonstra, A.J. van Boven, I. Ungi, G. Bogáts, S. Mansour, N. Noiseux, M. Sabaté, J. Pomar, M. Hickey, A. Gershlick, P. Buszman, A. Bochenek, E. Schampaert, P. Pagé, O. Dressler, I. Kosmidou, R. Mehran, S.J. Pocock, and A.P. Kappetein, for the EXCEL Trial Investigators*

ABSTRACT

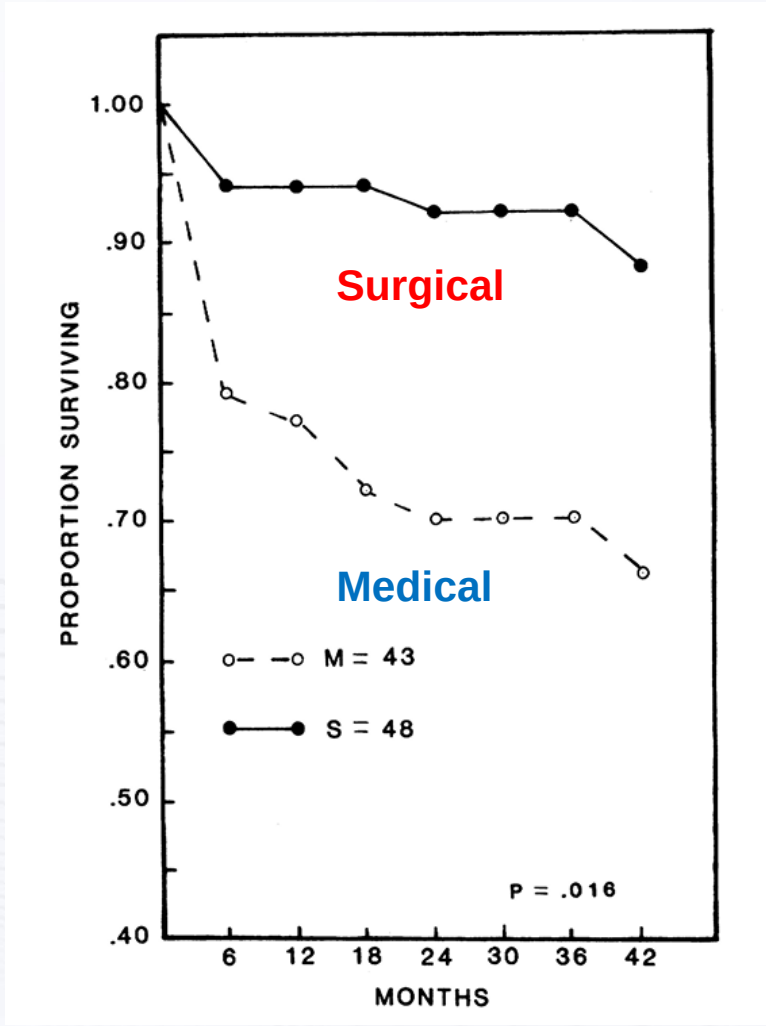
All patients had to have newly diagnosed unprotected stenosis of more than 50% of the diameter of the left main coronary artery, as estimated visually

Stenosis of the LMCA of 70% or more, as estimated visually, or stenosis of 50% to less than 70% if determined by means of noninvasive or invasive testing to be hemodynamically significant

Significant Left Main Disease (DS>50%)



ECSS Group Lancet 1982 Nov 27;2(8309):1173-80



Takaro et al. Circulation 1982;66:14-22

Prognostic Spectrum of LM Stenosis

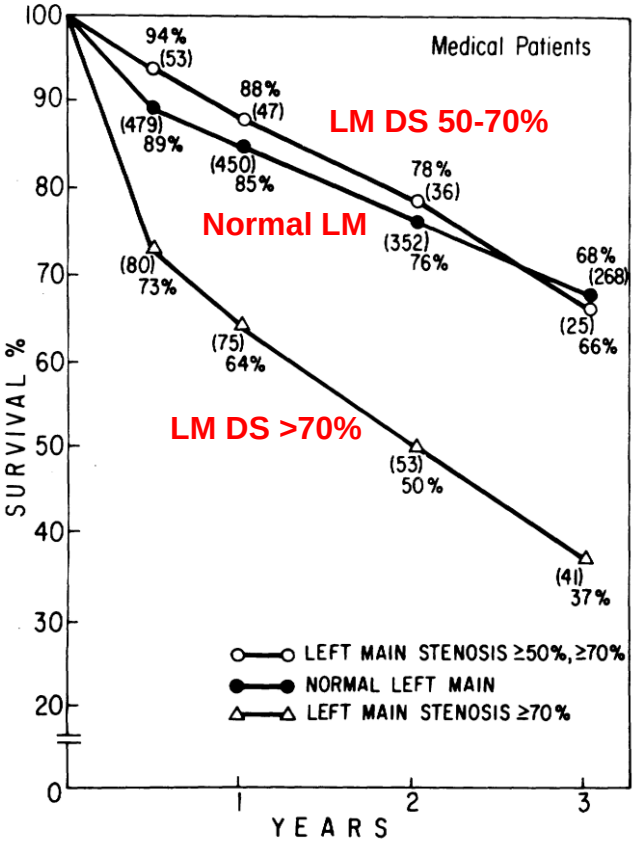


FIGURE 2. *Cumulative survival rates of medically treated patients with three-vessel coronary artery disease who had a normal left main coronary artery, who had 50 to 70% left main stenosis, and who had 70% or greater left main stenosis.*

LM DS >70%

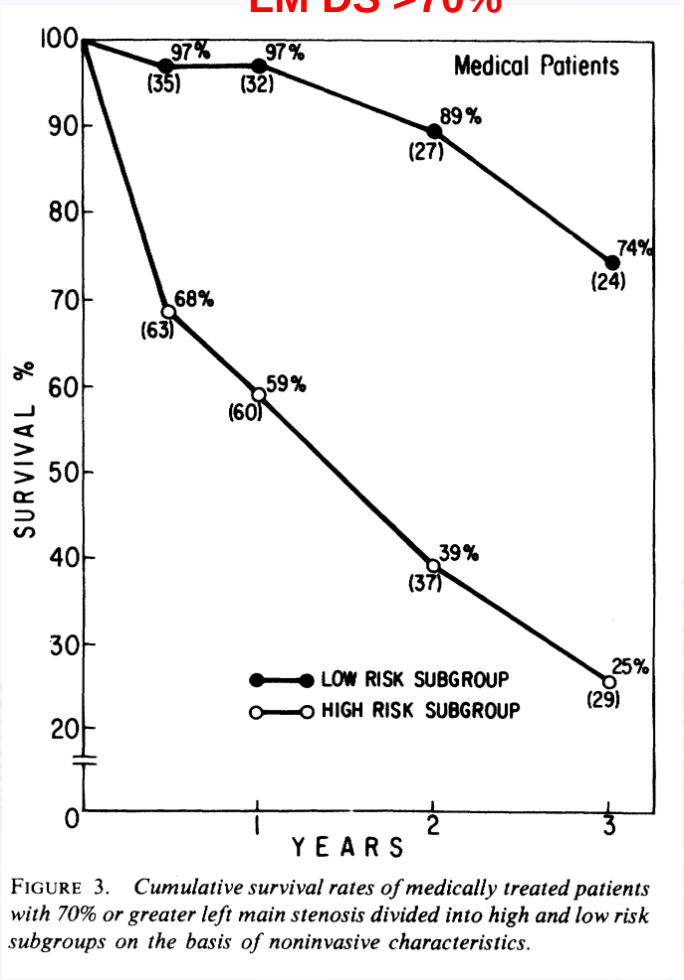


FIGURE 3. *Cumulative survival rates of medically treated patients with 70% or greater left main stenosis divided into high and low risk subgroups on the basis of noninvasive characteristics.*

Non-invasive Risk Factors

- History of congestive heart failure
- Chest pain at rest
- Cardiomegaly on chest X-ray
- ST-T wave change

Conley MJ, Ely RL, Kisslo J, Lee KL, McNeer JF, Rosati RA. Circulation. 1978;57:947–952

Survival in Subgroups of LM

TABLE 4. *Cumulative Survival Rates at 42 Months by Treatment Assigned (1972–1974 Left Main Lesion Cohort)*

Group	n	Cumulative survival rate: Medical	Surgical	Difference§	Treatment† effect *p*	Homogeneity‡ *p*
All patients	91	0.65	0.88	0.23	0.016	
Stenosis 50–75%	47	0.82	0.92	0.10	0.089	0.47
> 75%	44	0.48	0.83	0.35	0.036	
LV function						
Normal	23	0.71	0.78	0.07	0.10	0.27
Abnormal	67	0.62	0.89	0.27	0.012	
Tercile*						
Low	33	0.93	0.83	–0.10	>0.50	0.035
Middle	24	0.58	0.92	0.34	0.073	
High	33	0.44	0.88	0.44	0.004	

*Missing data on one patient for each factor.
†Test of overall difference in survival between treatment groups within a subgroup category.
‡Test of equality of treatment effects across subgroup categories.
§Surgical minus medical.

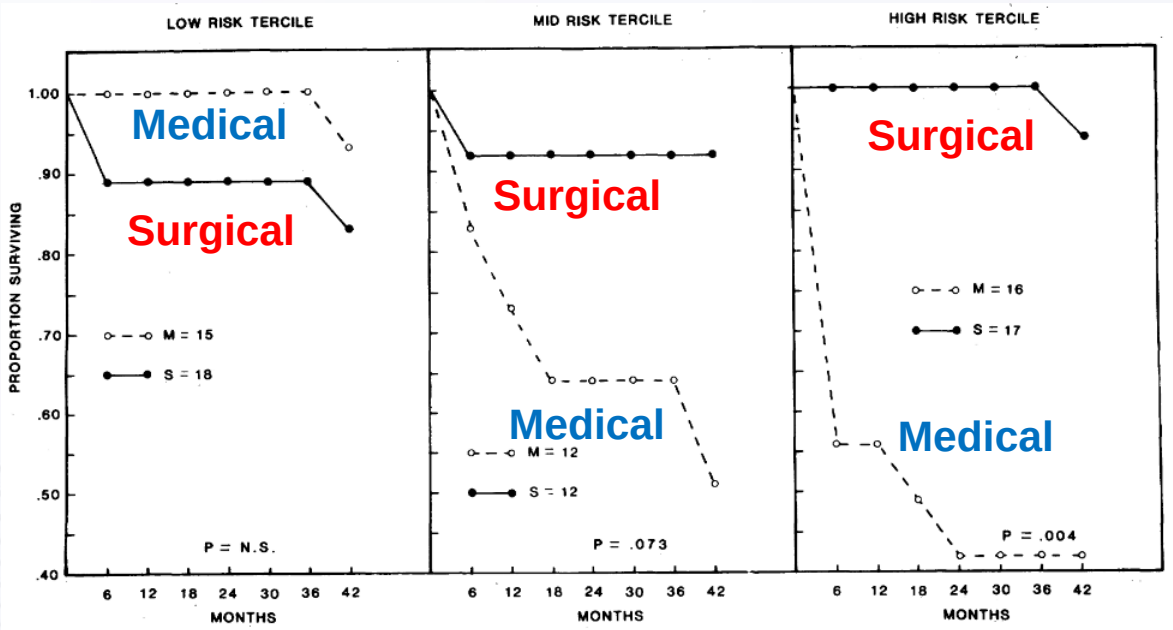


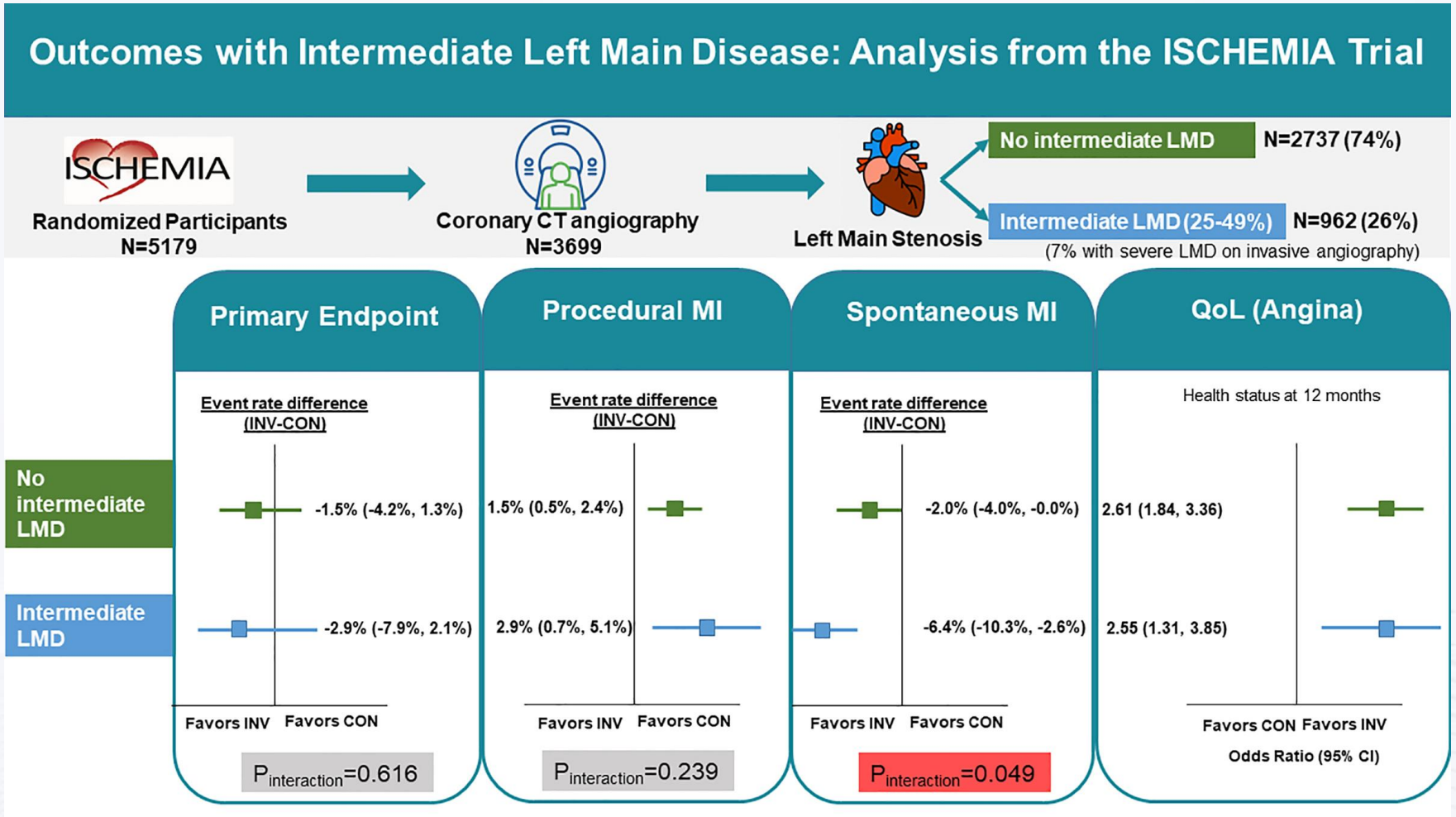
FIGURE 3. *Cumulative survival rates in risk terciles by treatment assigned. M = medical; S = surgical.*

Non-invasive Risk Factors

- History of MI
- History of Hypertension
- Resting ST depression
- NYHA III, IV

Takaro et al. Circulation 1982;66:14-22

Intermediate LMD (DS, 25%–49%) on outcomes



Circulation: Cardiovascular Interventions. 2022;15

CAG analysis for Left Main: Poor Reproducibility

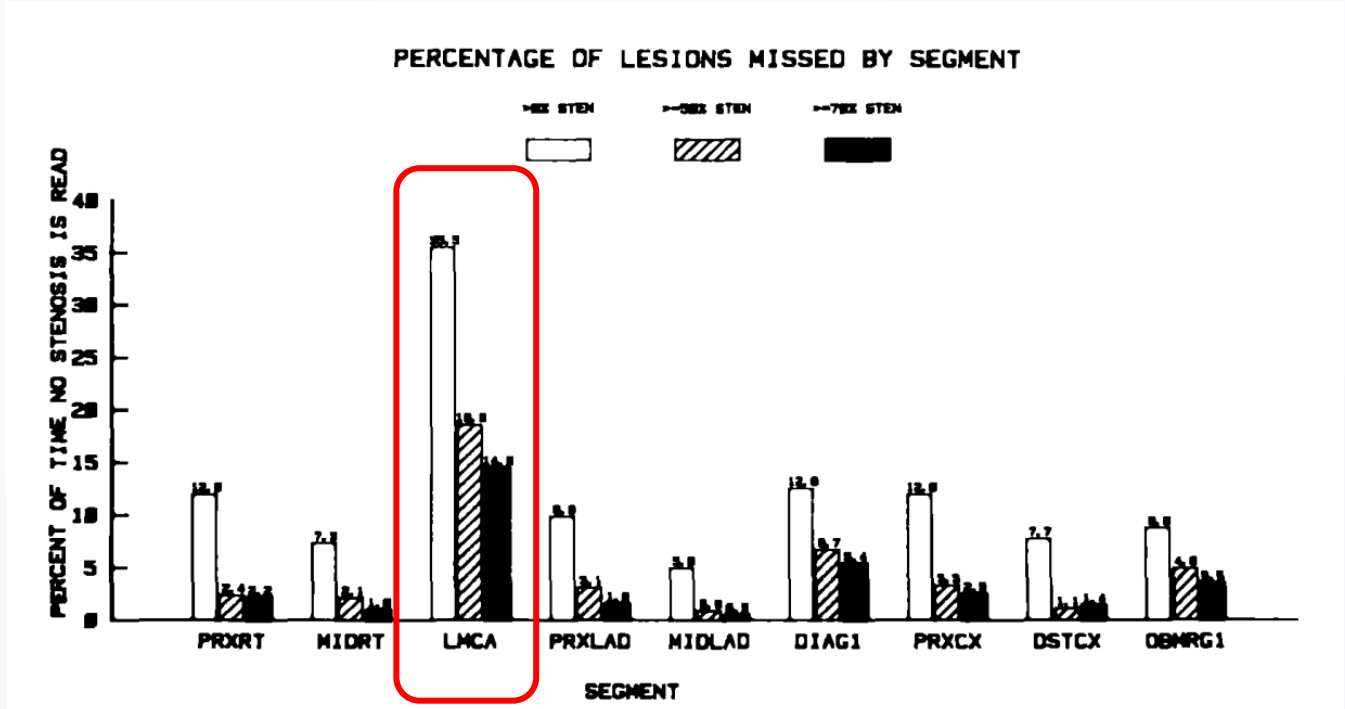
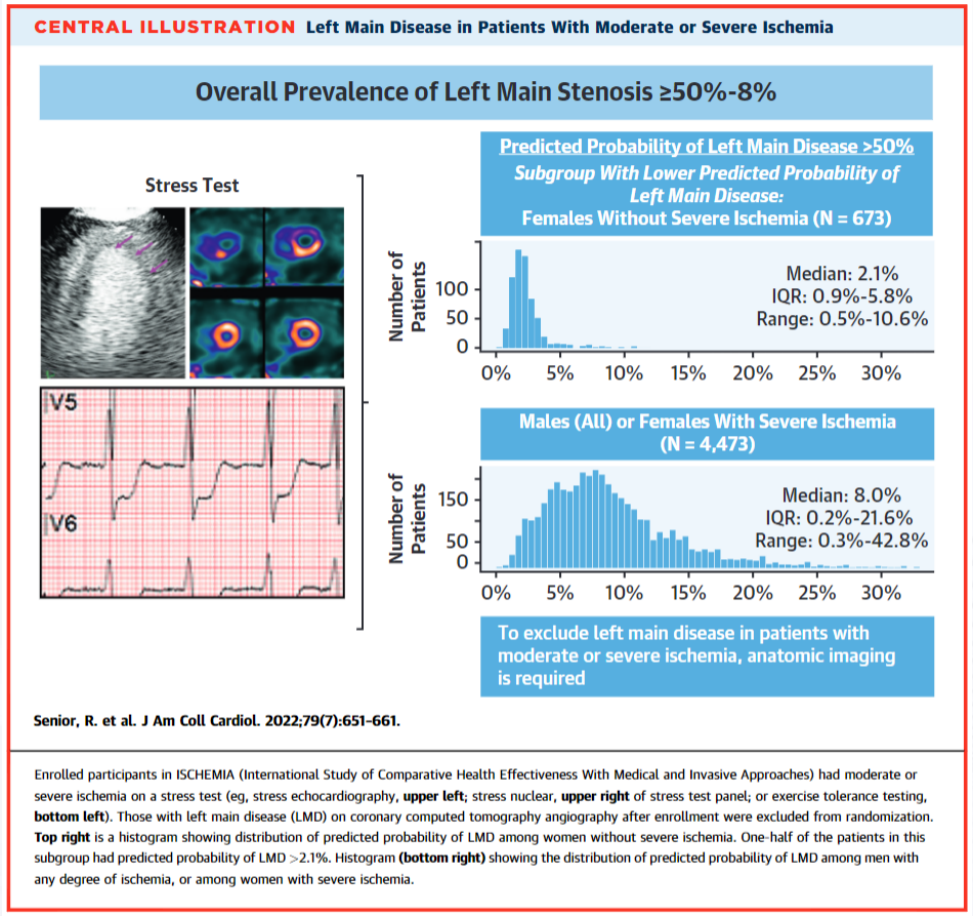


Fig. 3. Among cases with segments where one reader may read a stenosis of a fixed amount or more (>0% stenosis, ≥50% stenosis, ≥70% stenosis), the percent of the time a second reader will see no stenosis is estimated. Abbreviations: PrxRt, proximal right coronary artery; MidRt, middle right coronary artery; LMCA, left main coronary artery; PrxLAD, proximal left anterior descending coronary artery, MidLAD, middle left anterior descending coronary artery, 1stDiag, first diagonal branch; PrxCx, proximal circumflex coronary artery; DstCx, distal circumflex coronary artery; 1st Obt Marg, first obtuse marginal coronary artery.

Reproducibility of coronary arteriographic reading in the coronary artery surgery study (CASS)

Catheterization and Cardiovascular Diagnosis 1982

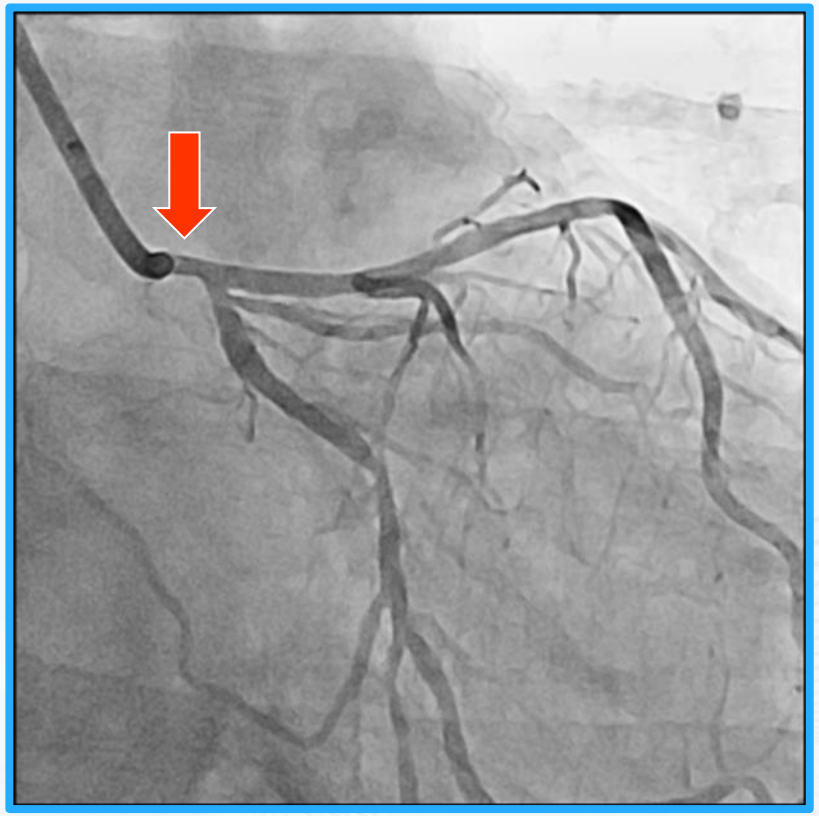
Predictors of LM Disease in the ISCHEMIA Trial



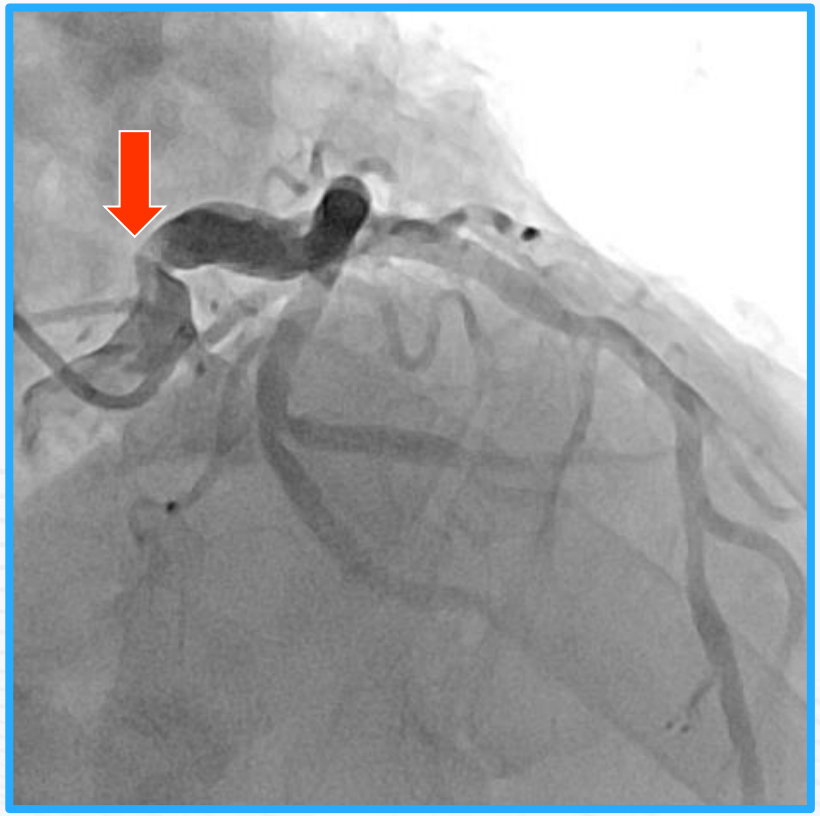
Predictors

- Older age
- Male sex
- Absence of prior MI
- Transient ischemic LV dilation on stress echo
- Magnitude of ST-segment depression on ETT
- peak METs achieved on ETT

Which is a Significant Stenosis ?

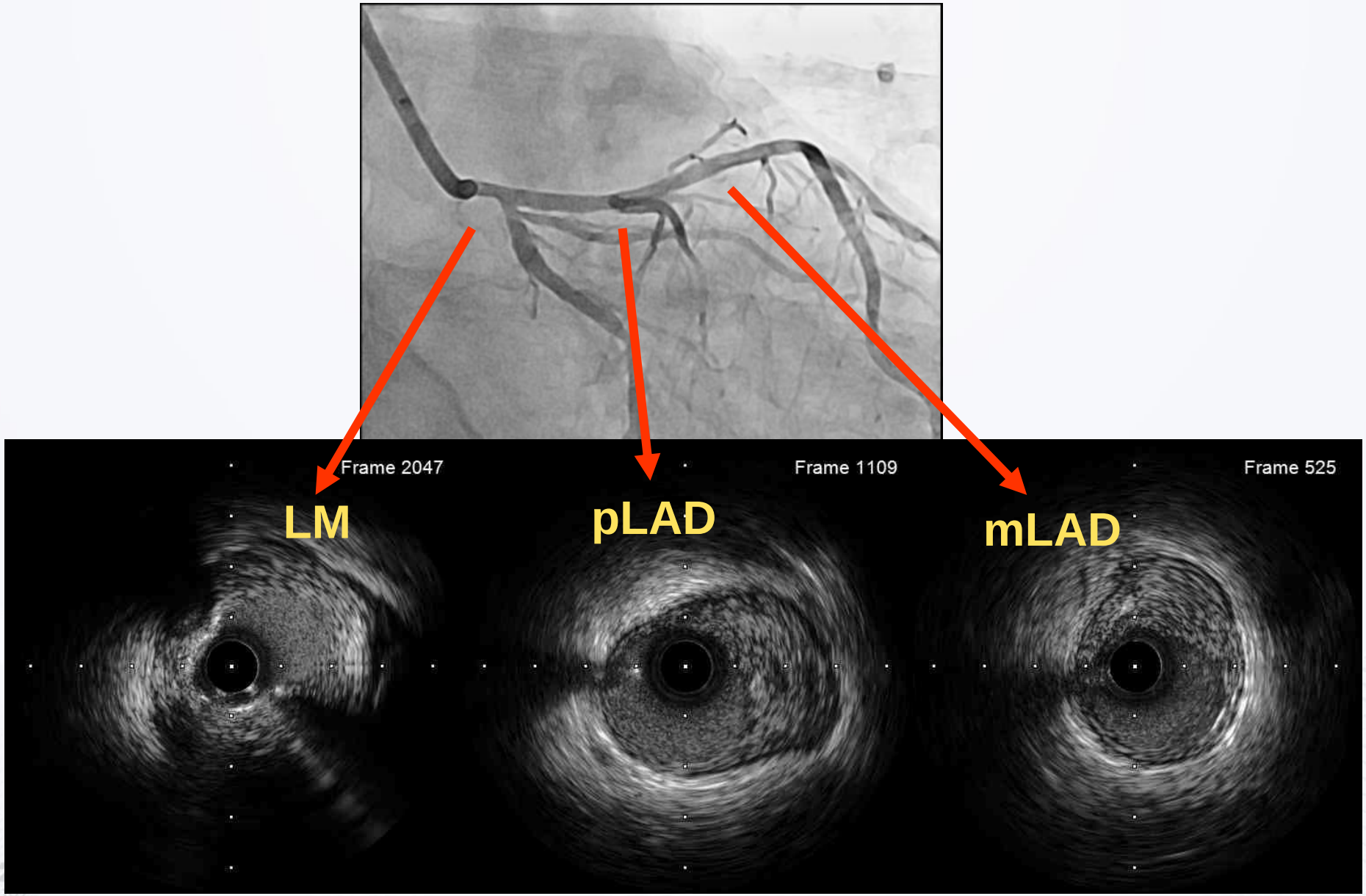


FFR 0.71

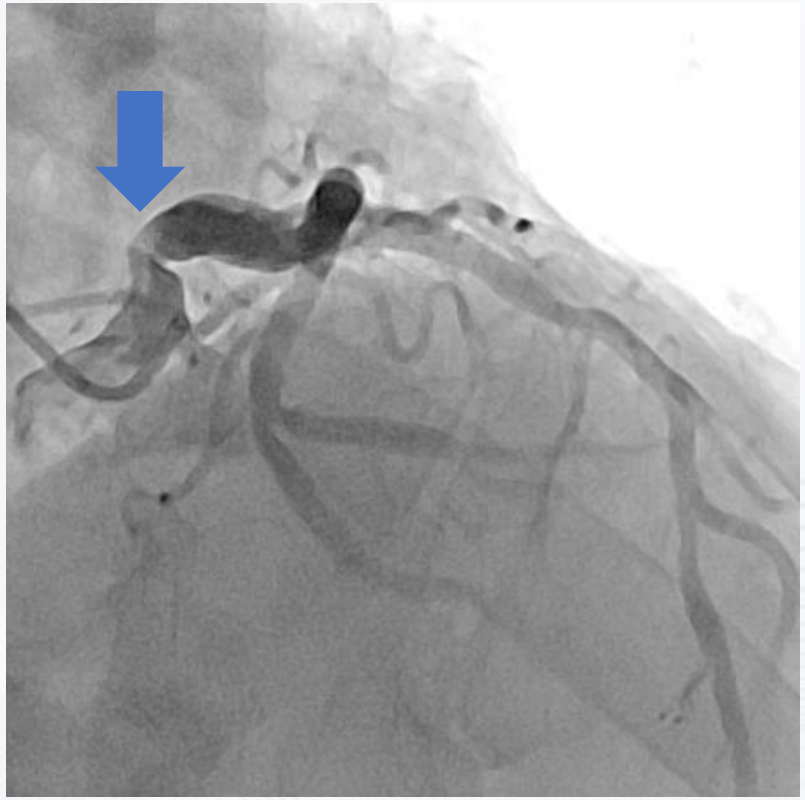


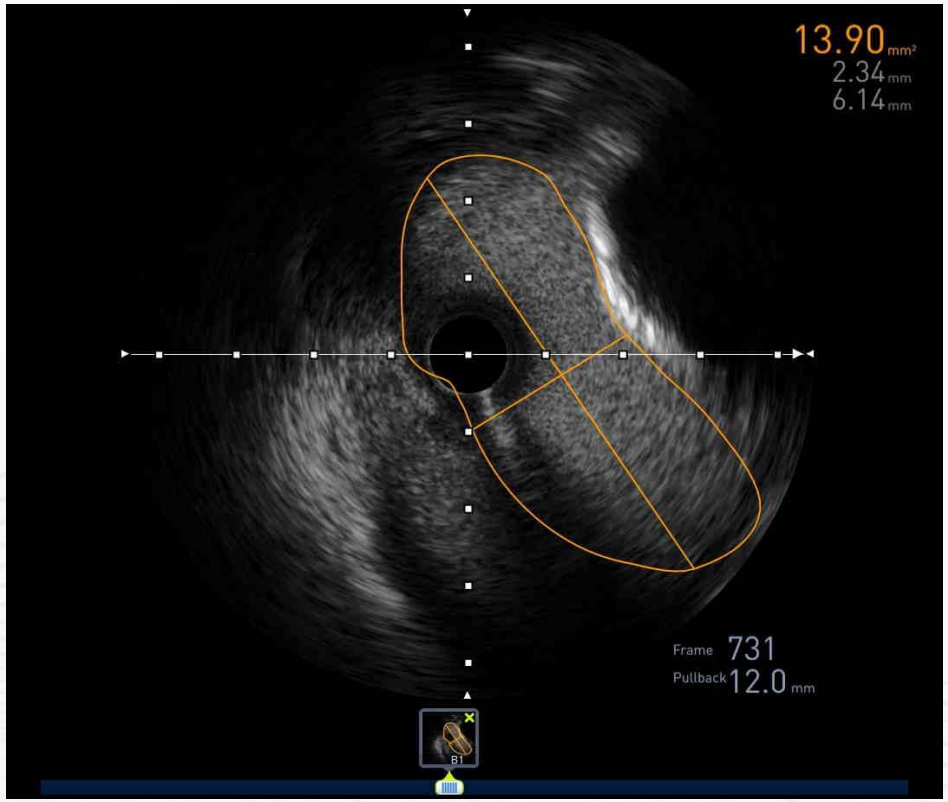
FFR 0.89

Diffuse Atherosclerosis

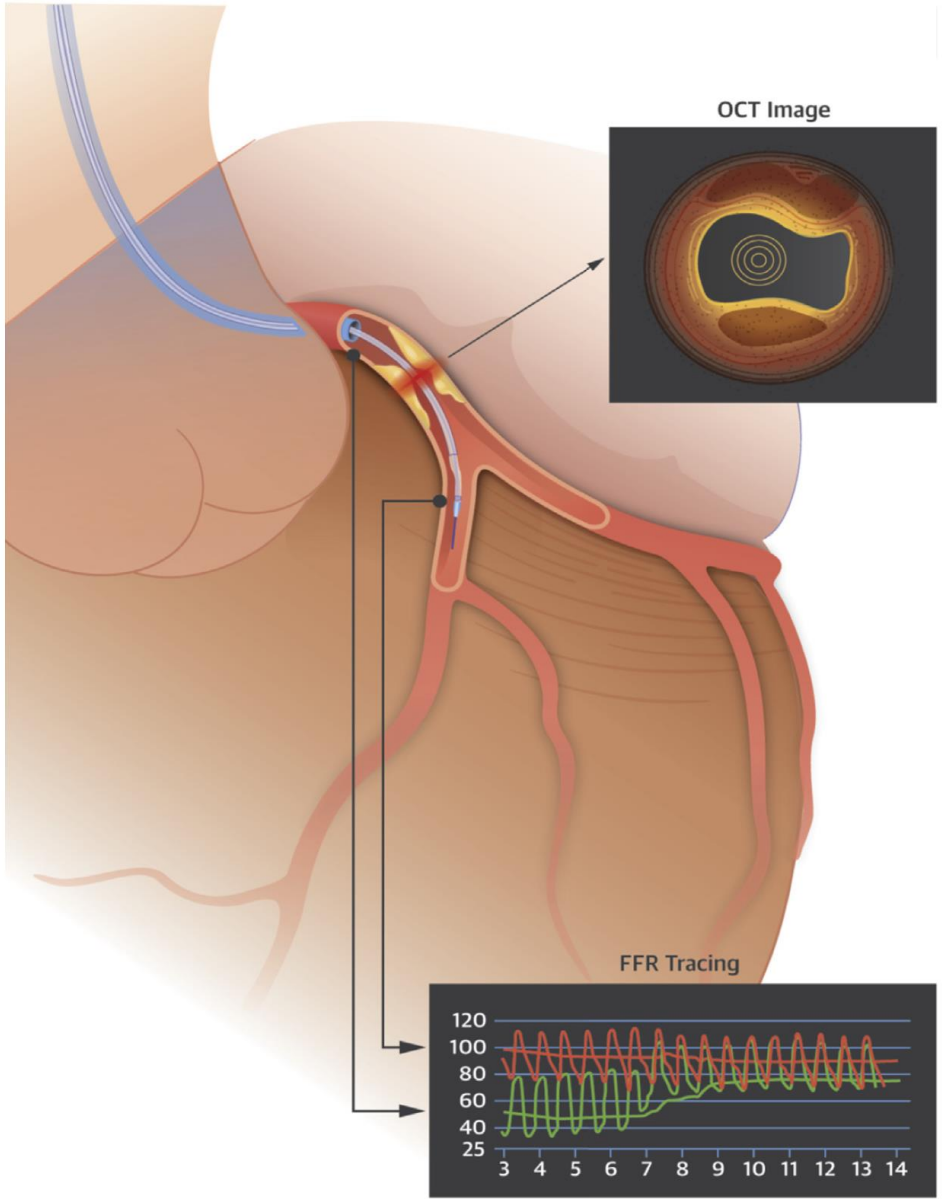


MLA 8.8-13.9mm²





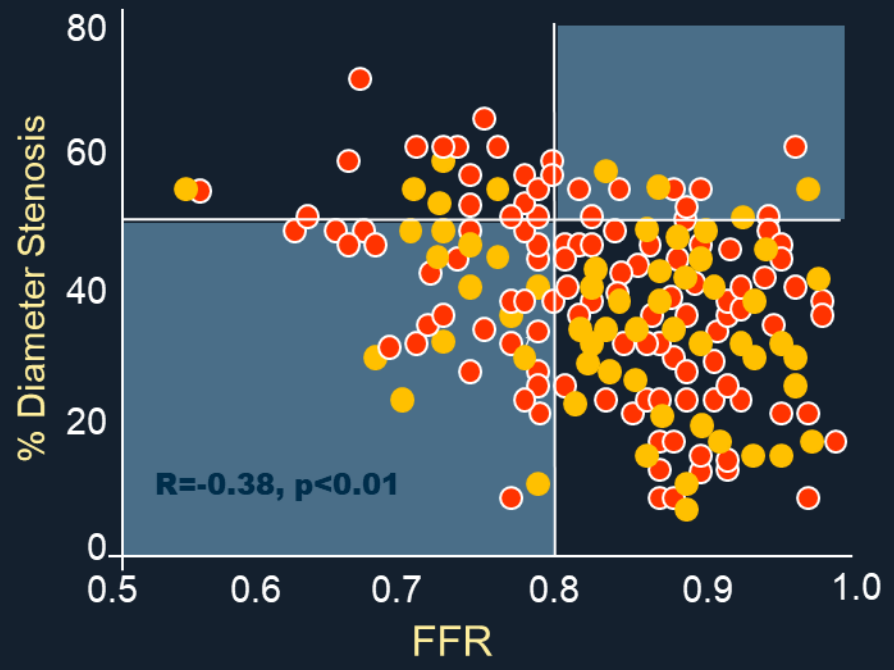
CENTRAL ILLUSTRATION **OCT/FFR Evaluation of Moderate LMCA Lesion**



Bing, R. et al. J Am Coll Cardiol Intv. 2015; 8(12):1529–39.

Inaccurate Coronary Angiography

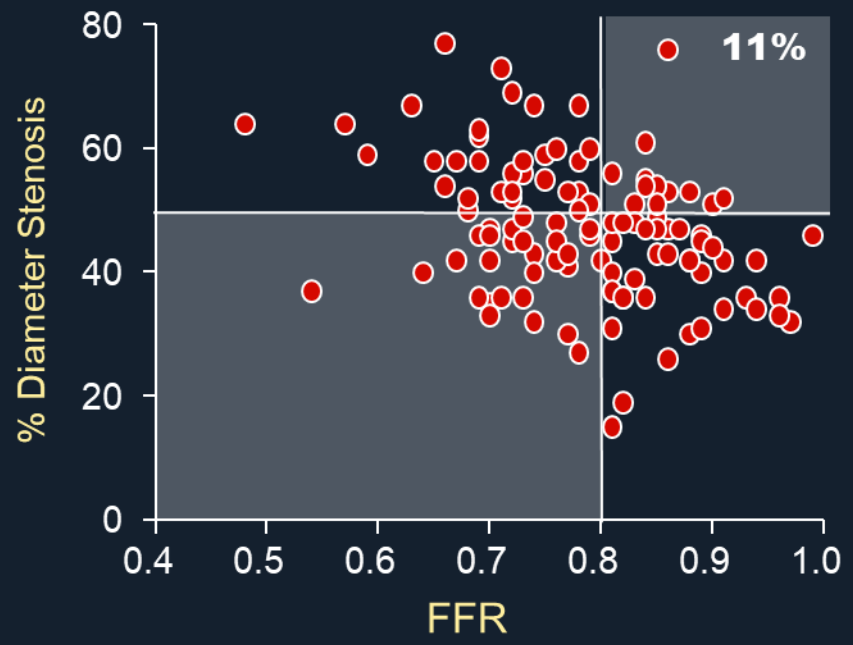
"Mismatch" is 29% in equivocal LMCA



Hamilos et al
Circulation 2009;120:1505-1512

● Isolated LMCA disease

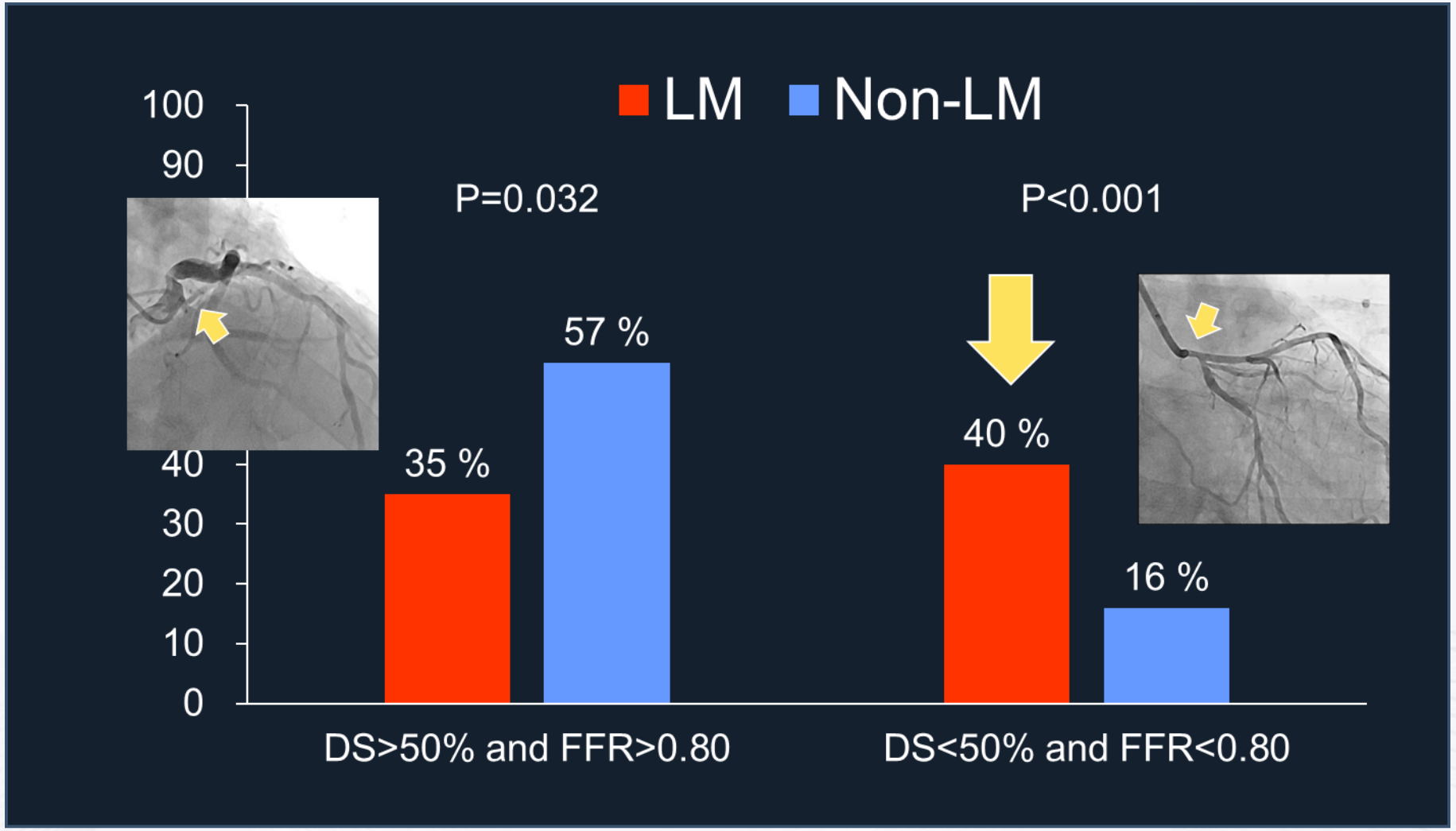
"Mismatch" is 37% in equivocal LMCA



Park SJ, Ahn JM et al
JACC Cardiovasc Interv. 2014 ;7(8):868-74

Left Main Supplies Large Myocardium

In symptomatic patients, ambiguous LM stenosis should be evaluated by FFR



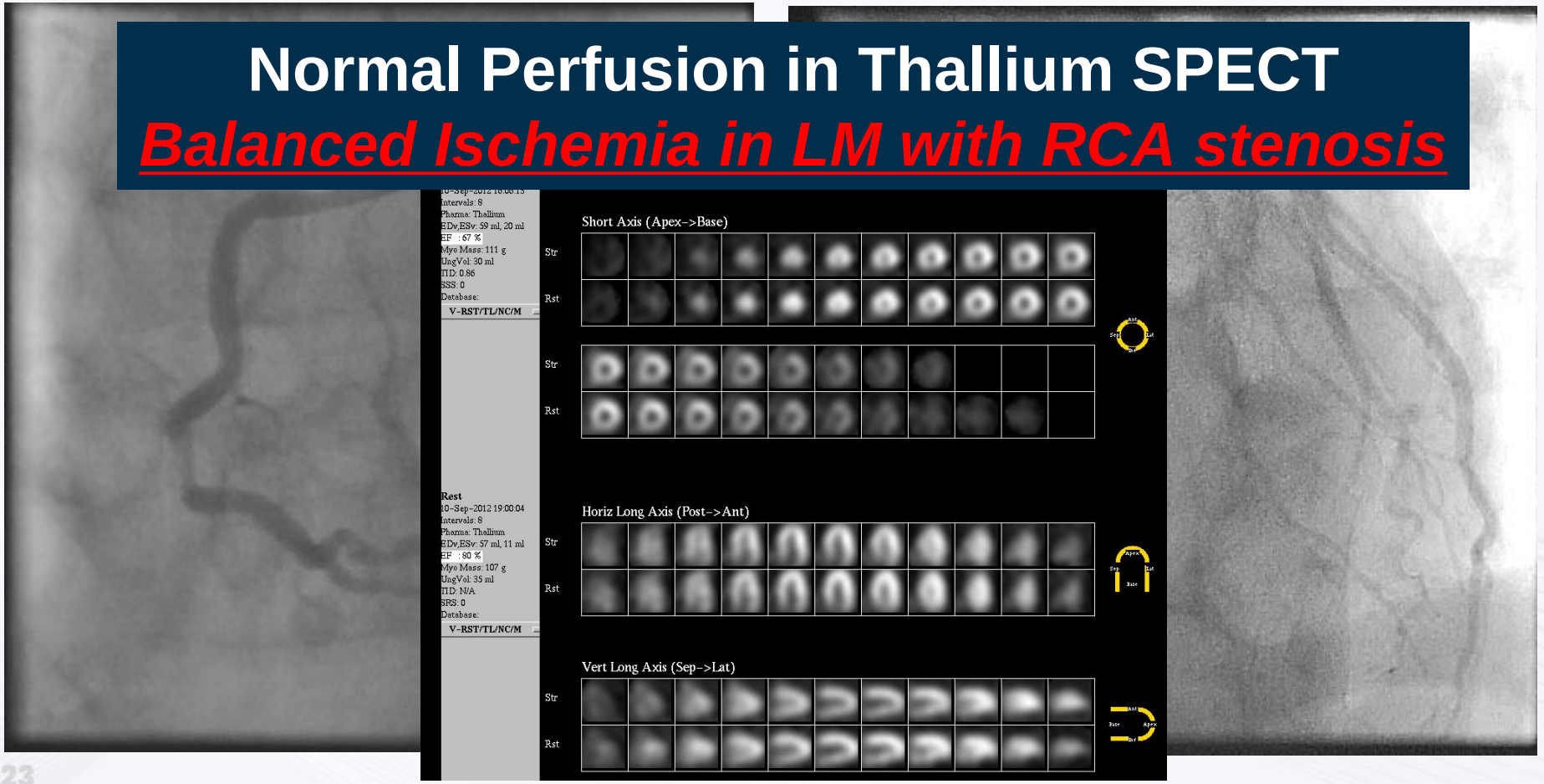
Park SJ et al JACC Cardiovasc Interv. 2012;5:1029-36

Left main stenosis with RCA disease

65yrs/M, Effort chest pain

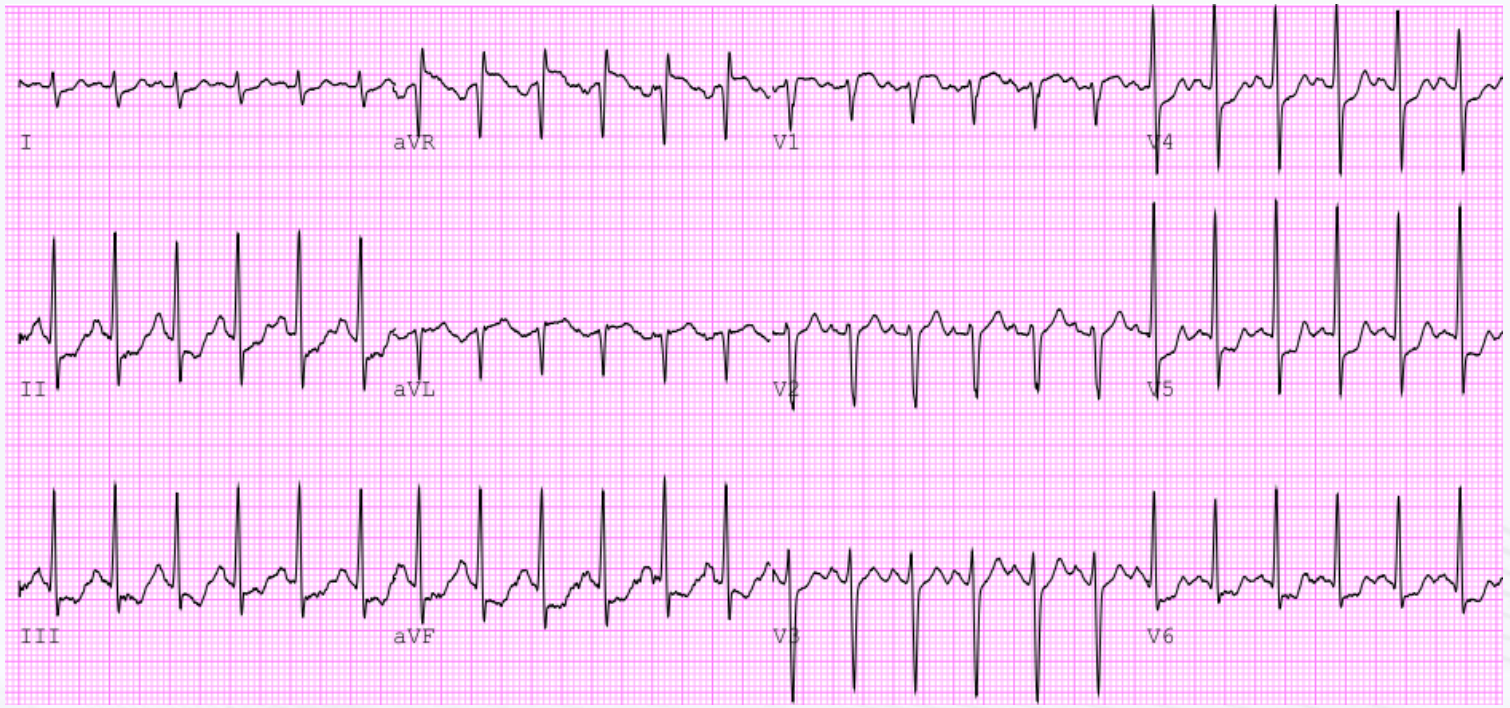
Right Coronary

Left Coronary



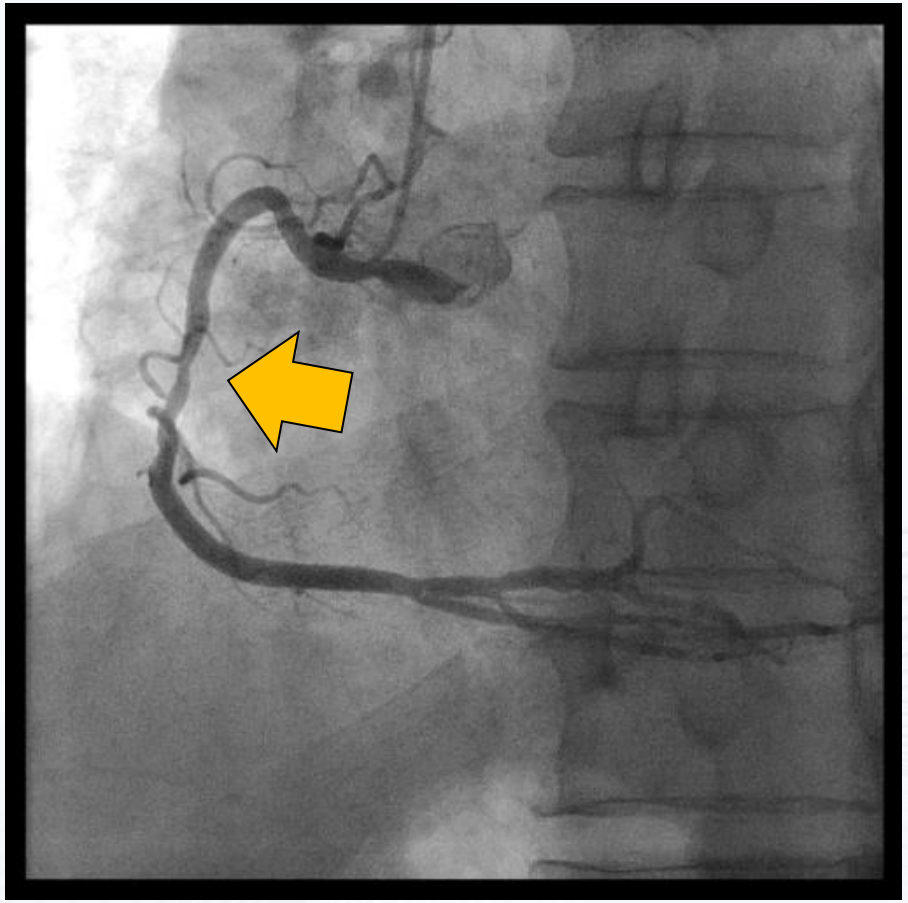
M/76, Effort Chest Pain

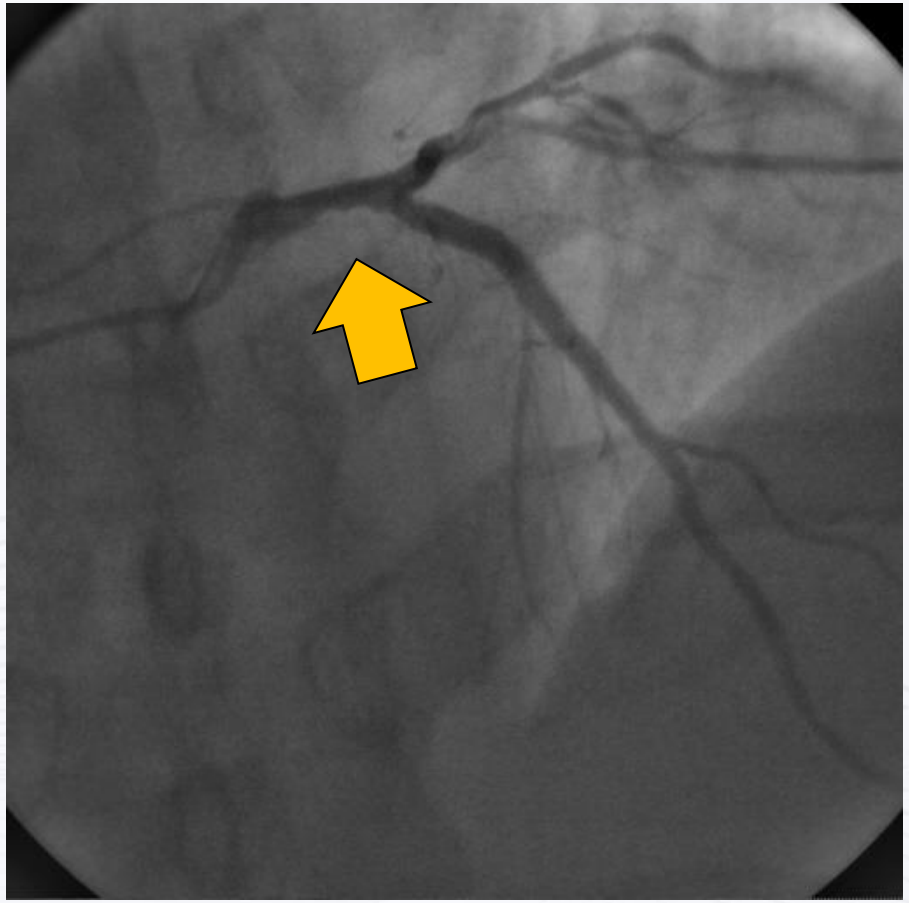
Treadmill Test



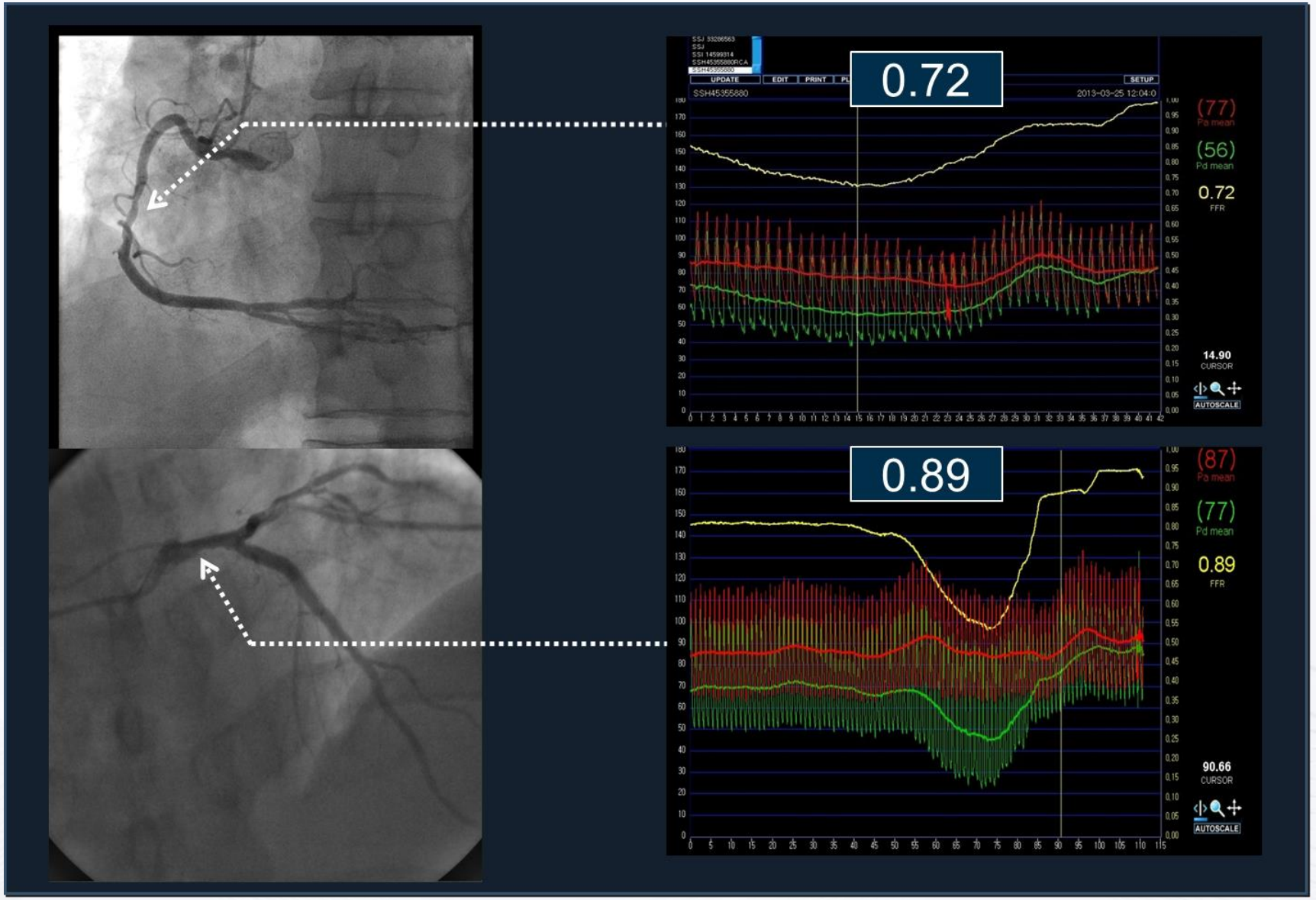
Positive at Stage 4

Coronary Angiography

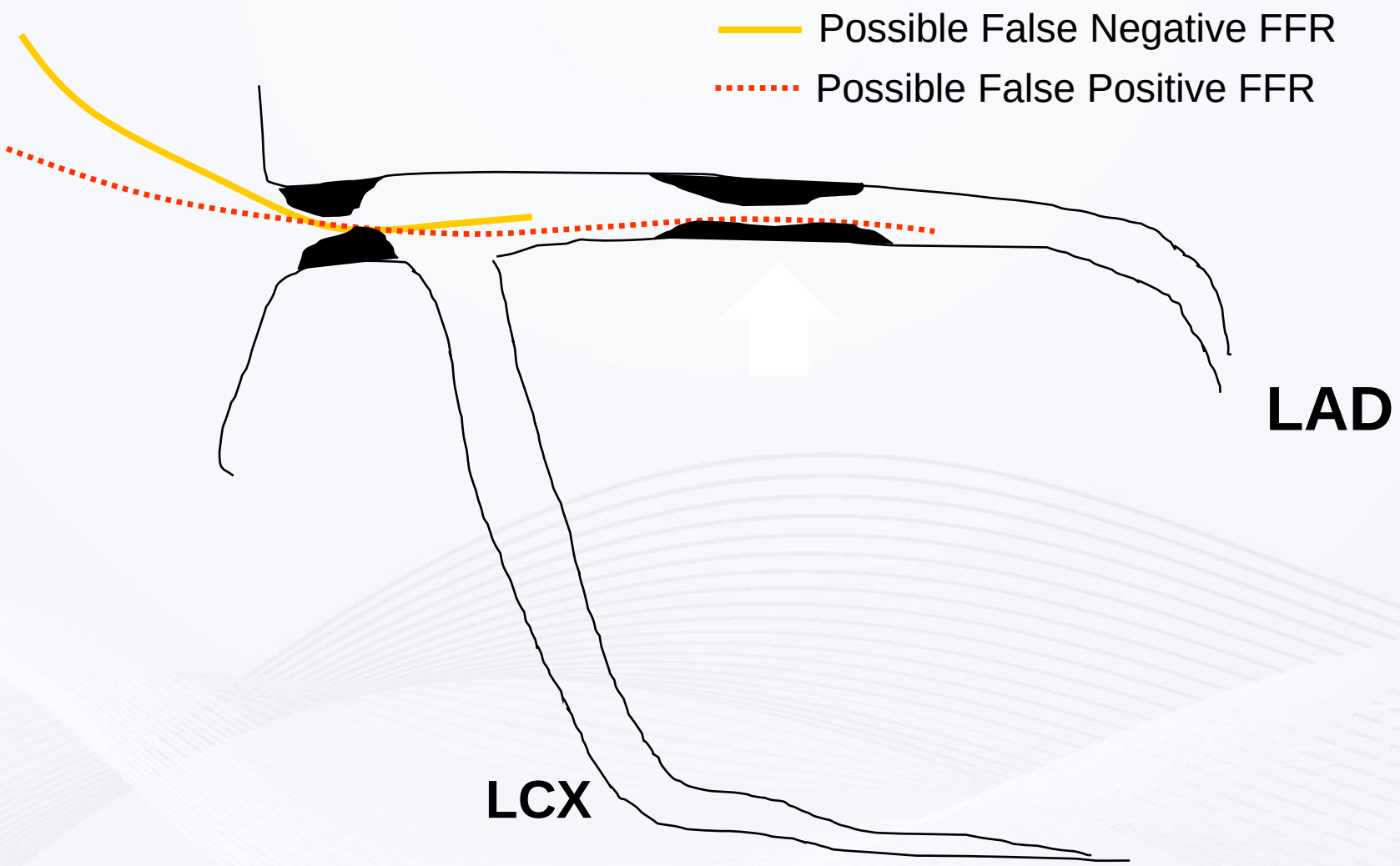




Fractional Flow Reserve

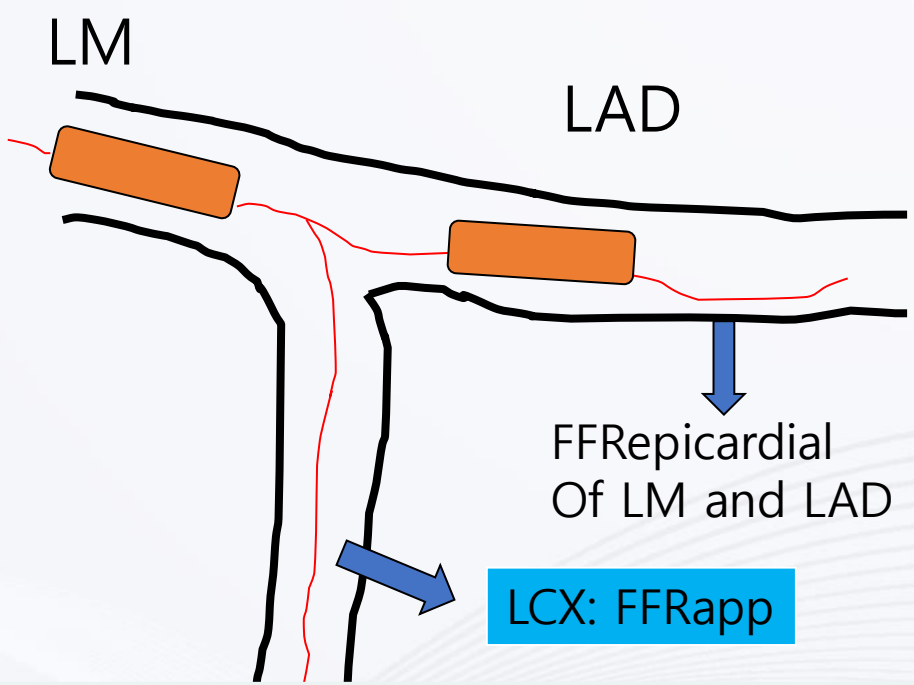


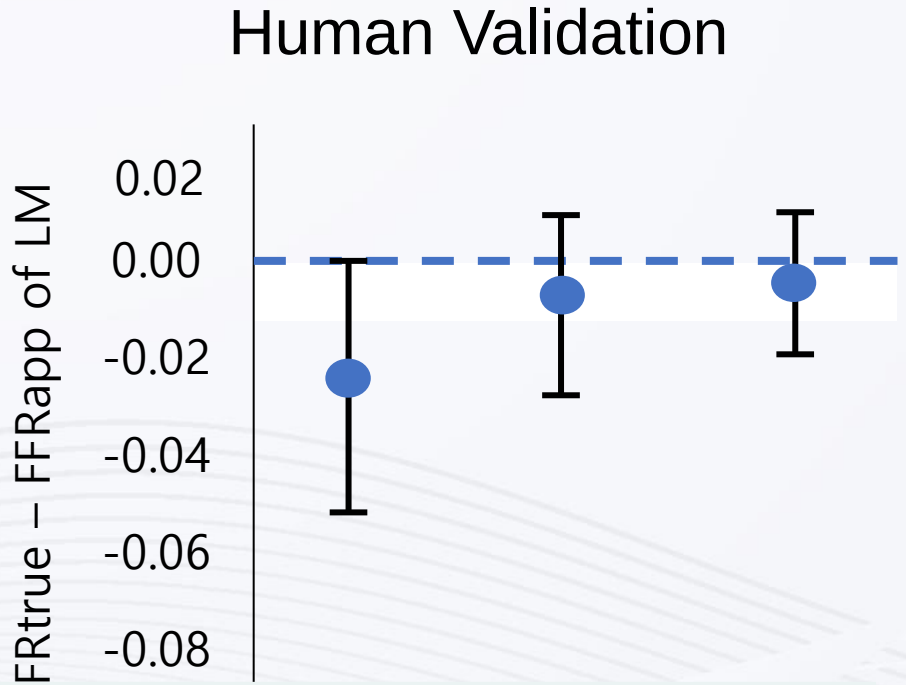
Down Stream Disease



Down Stream Disease

Unless downstream stenosis is very significant, its impact is mild





RESULTS In 25 patients, 91 pairs of measurements were made, 71 with LAD stenosis and 20 with LCx stenosis. FFR_{true} of the LMCA was significantly lower than FFR_{app} (0.81 ± 0.08 vs. 0.83 ± 0.08, $p < 0.001$), although the numerical difference was small. This difference correlated with the severity of the downstream disease ($r = 0.35$, $p < 0.001$). In all cases in which FFR_{app} was >0.85, FFR_{true} was >0.80.

Fearon WF, et al JACC Cardiovasc Interv. 2015 Mar;8(3):398-403

Clinical Outcomes After Deferral of LM Disease

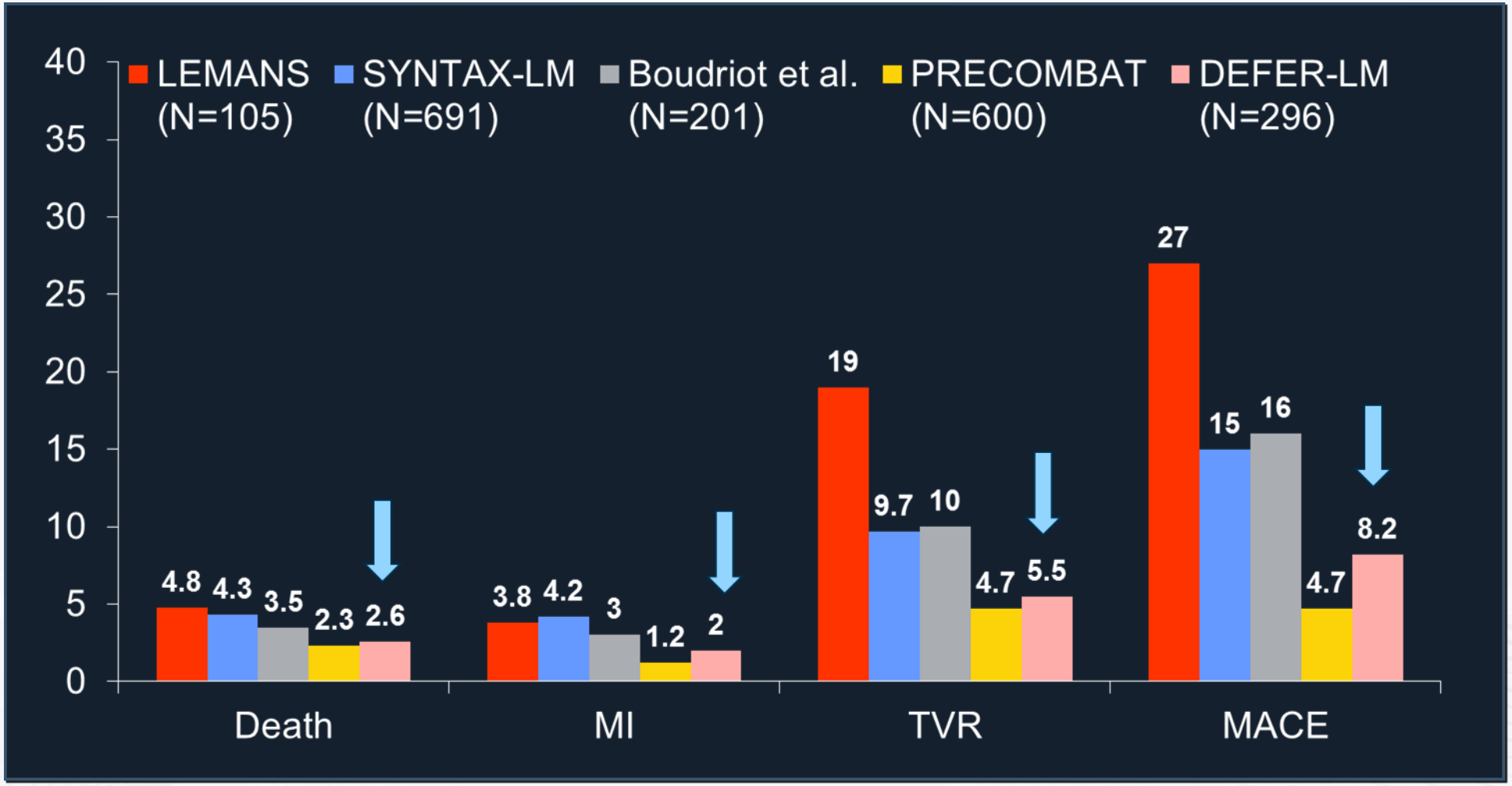
(6 studies, 296 patients)

Outcomes	Incidence (%/year)
All Death	2.6 (1.3-5.2)
Cardiac Death	2.6 (1.3-5.2)
Myocardial Infarction	2.0 (0.7-5.1)
TVR	5.5 (3.3-8.8)
MACE	8.2 (5.5-12.1)

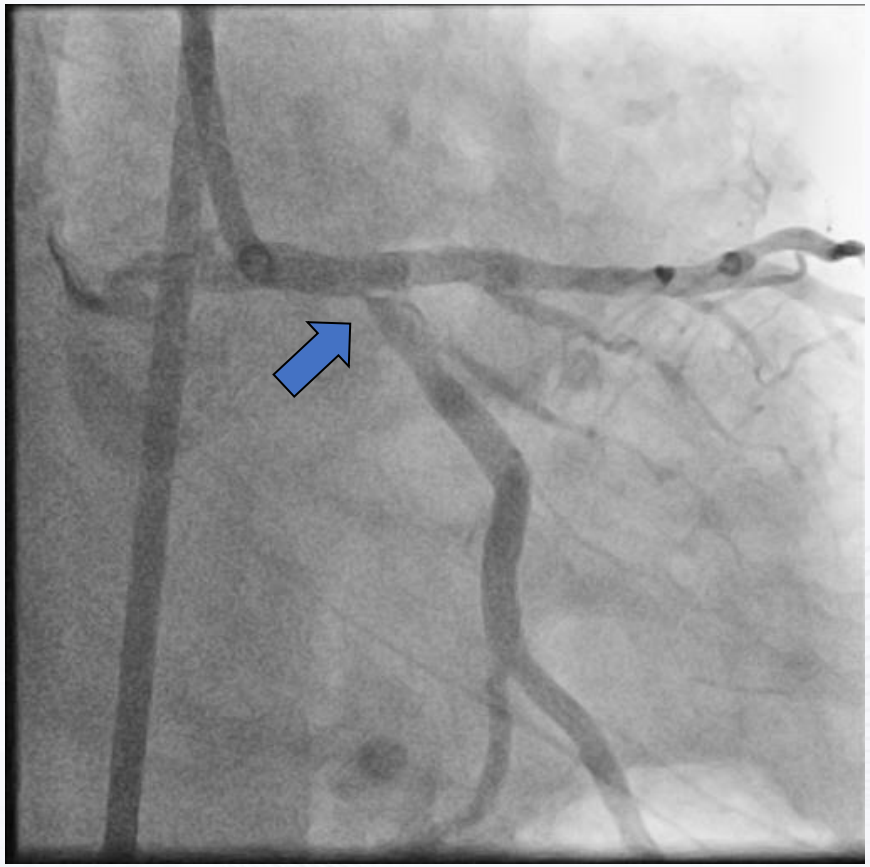
(6 studies, 296 patients)

Hamilos M, Circulation. 2009;120:1505-1512
Bech GJ, Heart. 2001;86:547-552
Courtis J, Am J Cardiol. 2009;103:943-949
Lindstaedt M, Am Heart J. 2006;152:151-159
Jasti V, Circulation. 2004;110:2831-2836
Sueman, Heart Vessels. 2005;20:271-7

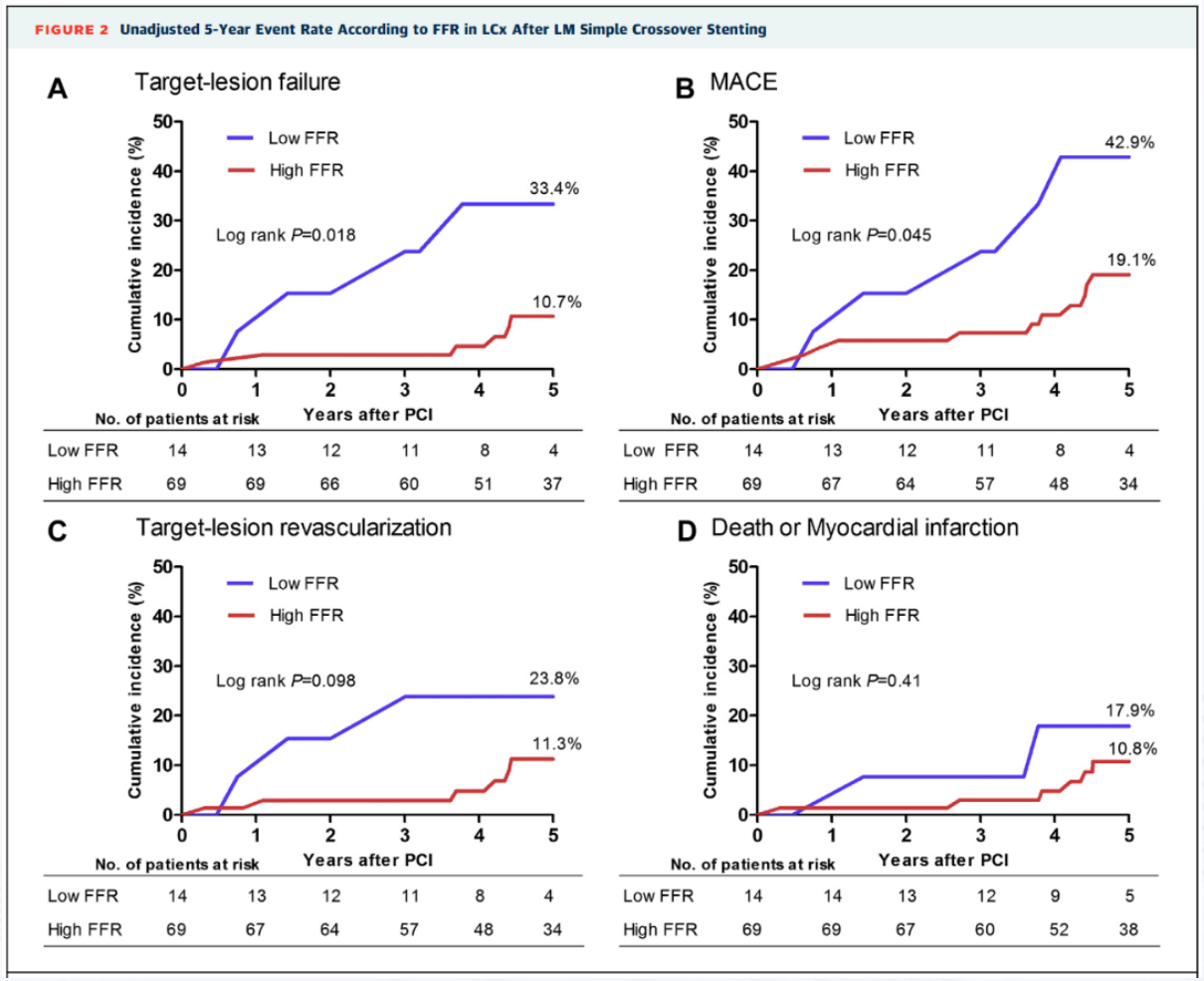
Safety of Deferred LM Disease



POST PCI LCX FFR 0.82



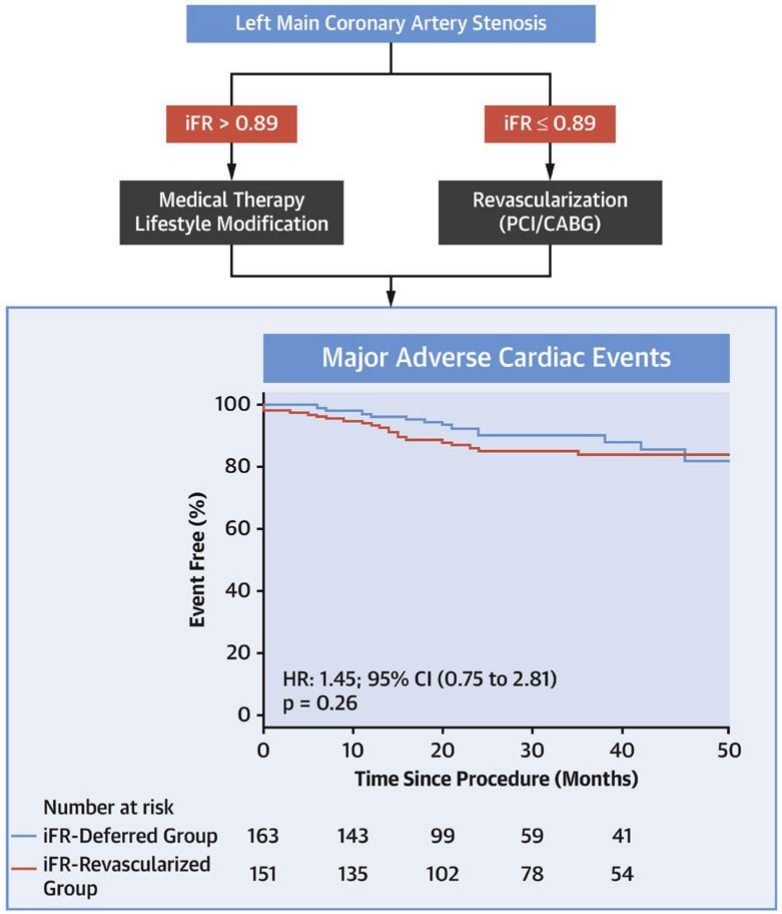
LCX FFR after Simple Cross Over



J Am Coll Cardiol Intv 2019;12:847–55

Deferred LM Disease By iFR

CENTRAL ILLUSTRATION: MACE in Patients With LM Stenosis: Kaplan-Meier Curves



Warisawa, T. et al. J Am Coll Cardiol Intv. 2020;13(14):1655-64.

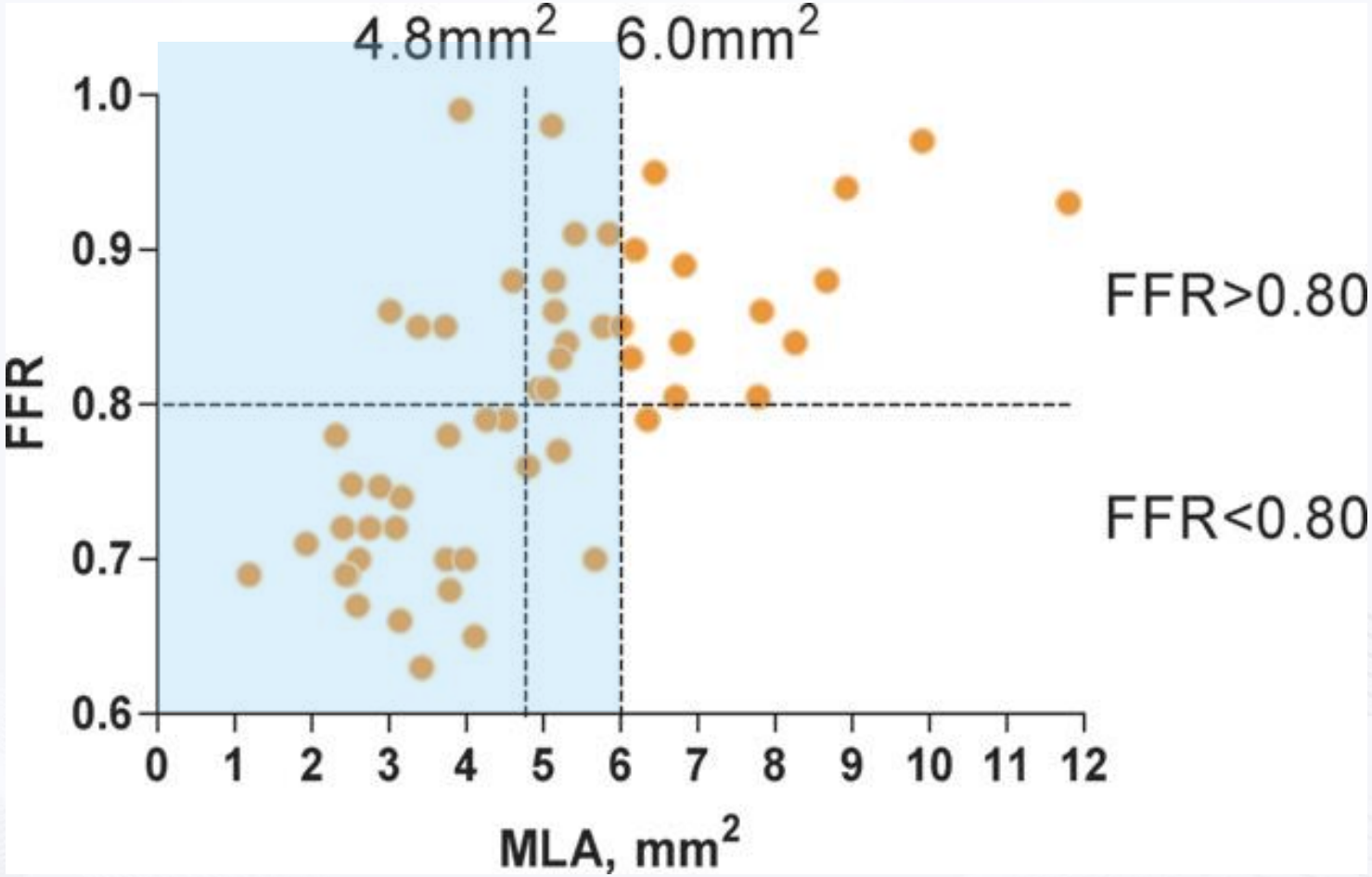
2018 ESC Guideline

Recommendations on functional testing and intravascular imaging for lesion assessment

Recommendations	Class[a]	Level[b]
When evidence of ischaemia is not available, FFR or iwFR are recommended to assess the haemodynamic relevance of intermediate-grade stenosis.[15,17,18,39]	I	A
FFR-guided PCI should be considered in patients with multivessel disease undergoing PCI.[29,31]	IIa	B
IVUS should be considered to assess the severity of unprotected left main lesions.[35–37]	IIa	B

FFR = fractional flow reserve; iwFR = instantaneous wave-free ratio; IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.

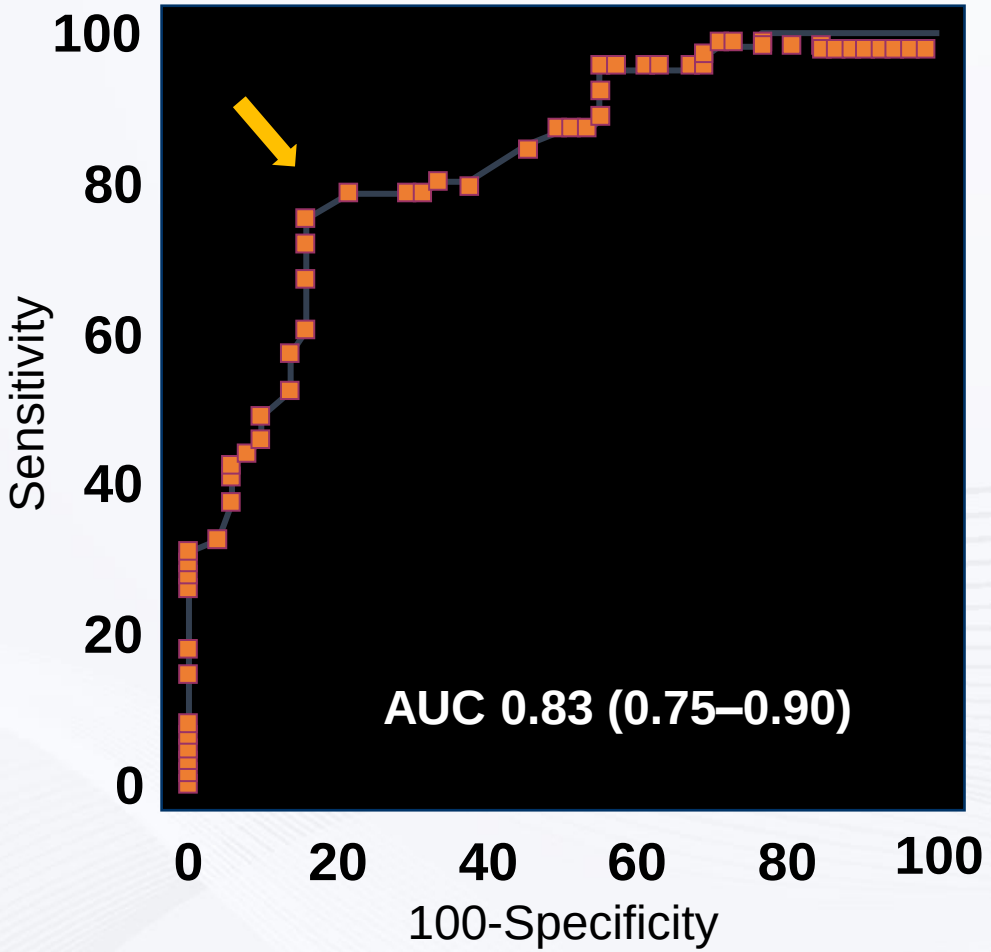
Correlation between MLA (IVUS) and FFR in intermediate LMCA disease



Park SJ et al. JAHA 2012 Dec;1(6):e004556

IVUS MLA

Matched with FFR <0.80 (N=112)



Cut-off = 4.5 mm²

Sensitivity	79%
Specificity	80%
PPV	83%
NPV	76%
Accuracy	80%

Park SJ, Ahn JM et al. *JACC Interv, 2014;7(8):868-874*

LITRO Study: Predefined MLA Criteria 6 mm²

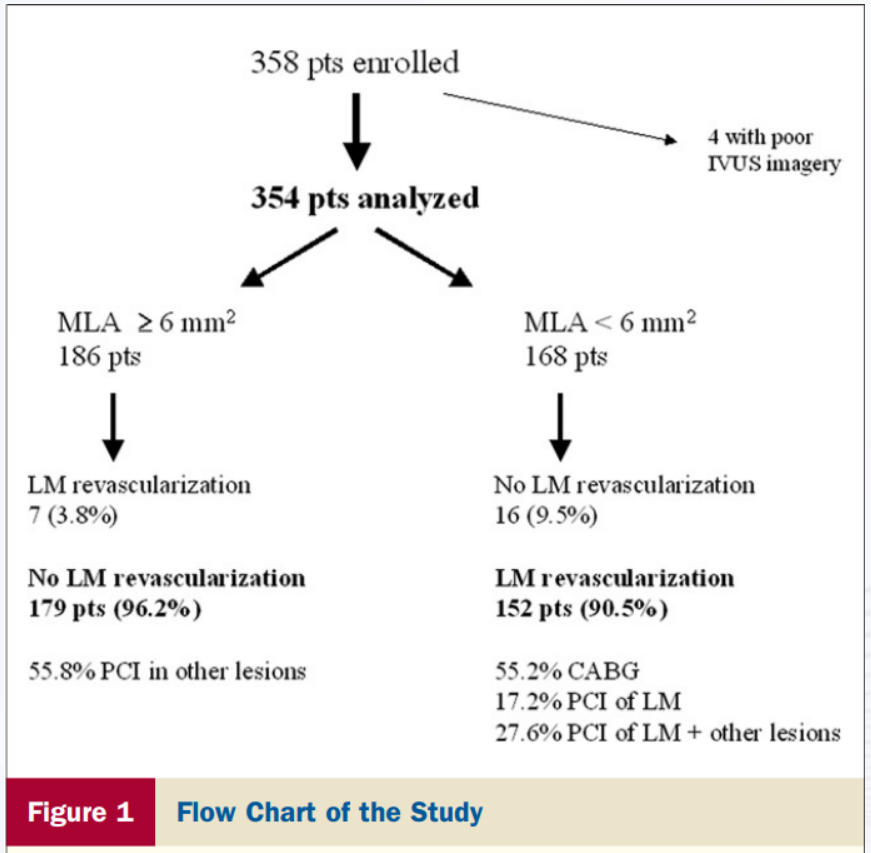


Figure 1 **Flow Chart of the Study**

CABG = coronary artery bypass graft; IVUS = intravascular ultrasound; LM = left main; MLA = minimum lumen area; PCI = percutaneous coronary intervention; pts = patients.

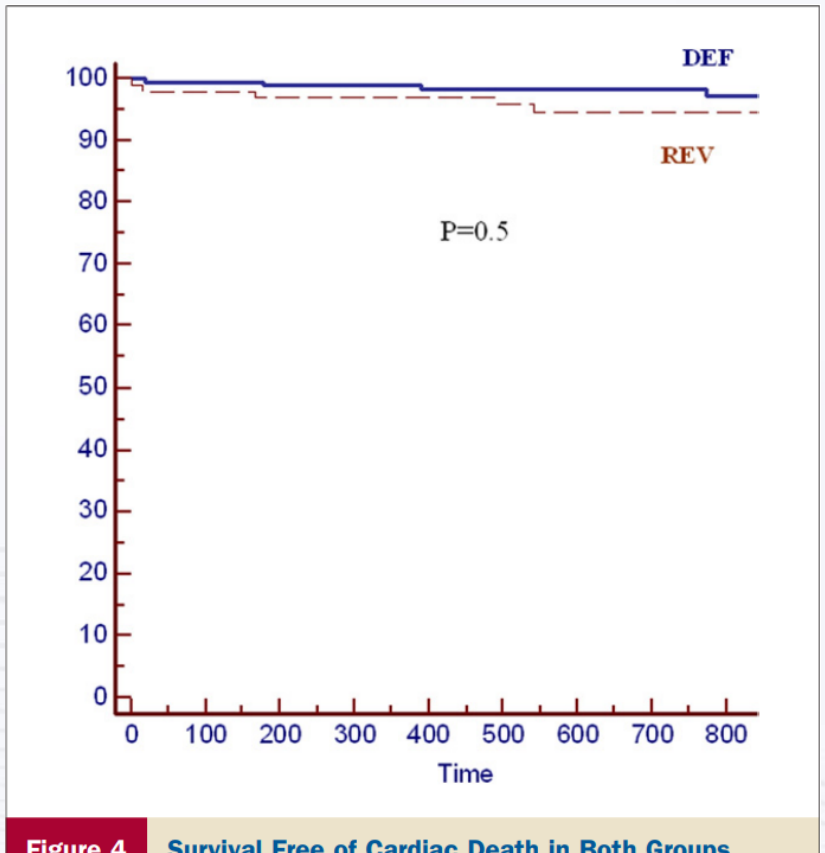


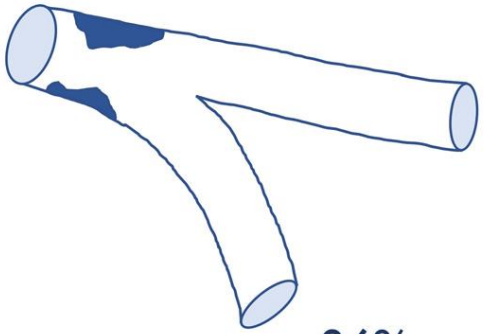
Figure 4 **Survival Free of Cardiac Death in Both Groups**

Survival free of cardiac death in the deferred (DEF) and revascularized (REV) groups.

FFR vs iFR in intermediate LMCA stenosis
iLITRO-EPIC 07 Study

FFR and iFR in 300 patients with intermediate LMCA stenosis – IVUS in 188 patients

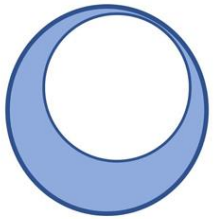
FFR / iFR agreement



80% from LAD

86% from LCX

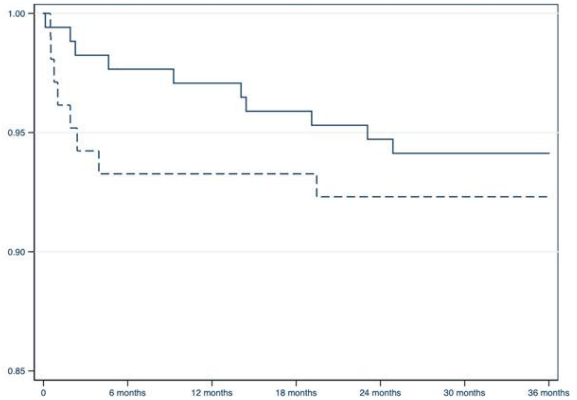
IVUS vs FFR/iFR



MLA<6mm²		MLA≥6mm²	
35%	FFR -	22%	FFR +
46%	iFR -	28%	iFR +

Clinical follow-up

LMCA revascularization deferred according to iFR and IVUS in 181 patients



At a median follow-up of 20 months, MACE incidence was 8.3% in the defer group and 13.3% in the revascularization group

HR 0.71, 95% CI [0.30-1.72], p=0.45

In patients with intermediate LMCA stenosis, a physiology-guided treatment decision is feasible either with FFR or iFR with moderate concordance between both indices. In case of disagreement, the use of IVUS may be useful to indicate revascularization. Deferral of revascularization based on iFR appears to be safe in terms of MACE

Circulation: Cardiovascular Interventions. 2022;15:861–871

Integrated use of FFR and IVUS in left main PCI

Park SJ et al. JAHA 2012 Dec;1(6):e004556

Intermediate LMCA stenosis (DS* 30-70%)

Ostial or Shaft Stenosis

- **Whether to Treat or Not: FFR guidance**
  - FFR measurement is crucial
- **How to Treat: IVUS guidance**
  - Pre-intervention IVUS evaluation
    Evaluate minimal lumen diameter, reference vessel diameter, lesion length, plaque burden and distribution.
  - Pre-intervention IVUS optimization
    MSA‡ >8.2mm^2 is important

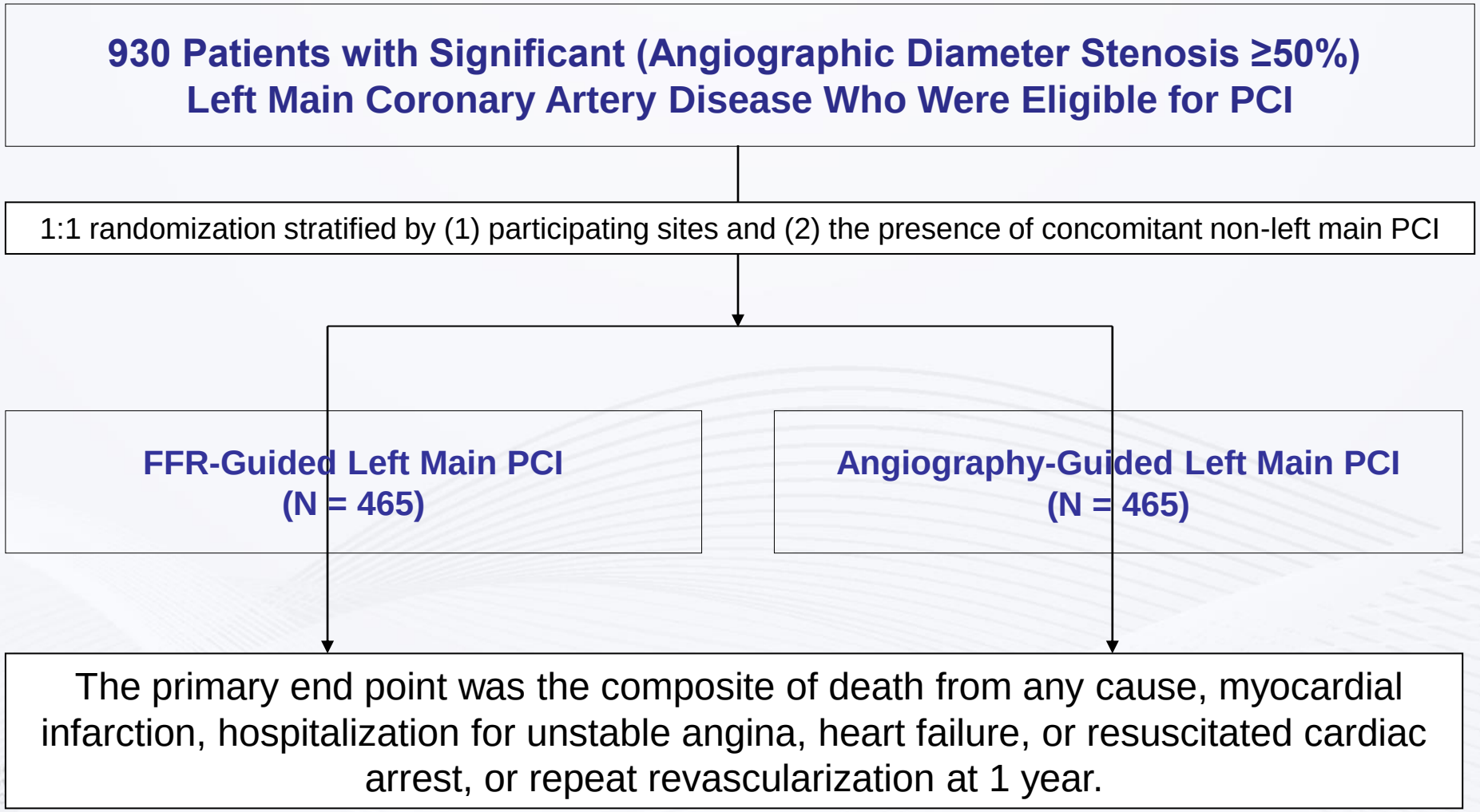
Bifurcation Stenosis

- **Whether to Treat or Not: FFR guidance**
  - FFR measurement is important
    Consider a bifurcation stenosis as a single unit of disease (see Figure 2.)
  - IVUS can assist the functional evaluation of bifurcation stenosis
    MLA†>4.8mm^2 (sensitivity 89%, specificity 83%) and plaque burden>72% (sensitivity 73%, specificity 79%) to predict FFR≤0.80 (see Figure 3.)
- **How to Treat: IVUS guidance**
  - Pre-intervention IVUS evaluation
    Evaluate anatomic features favoring single stent cross over stenting (see Table 4.)
  - Post-intervention IVUS optimization
    Evaluate MSA in every segment of LMCA (see Figure 5.)

* Visual estimated diameter stenosis; † Minimal lumen area; ‡Minimal stent area

Fractional Flow Reserve versus Angiography for Treatment-Decision and Evaluation of Significant Left MAIN Coronary Artery Disease

FATE-MAIN Trial



Inclusion criteria

Inclusion Criteria: subject must have met all of the following criteria to be eligible for treatment in the study:

1. The subject must be ≥20 years of age with angina and/or evidence of myocardial ischemia

2. Significant de novo LMCA disease (defined as ≥ 50% diameter stenosis by visual estimation) with or without concomitant non-left main major epicardial CAD, amenable to PCI with DES implantation.

4. The patient or guardian agrees to the study protocol and the schedule of clinical follow-up, and provides informed, written consent, as approved by the appropriate Institutional Review Board/Ethical Committee of the respective clinical site.

Exclusion criteria

1. Extremely calcified or tortuous vessels precluding FFR measurement
2. The presence of complex coronary disease anatomy or lesion characteristics or other cardiac condition(s) which leads the participating interventional cardiologist to believe that PCI is not suitable (i.e. the subject should be managed with CABG or medical the rapy alone)
3. Recent STEMI (<7 days prior to randomization)
4. Cardiogenic shock and/or need for mechanical/pharmacologic hemodynamic support
5. Severe left ventricular dysfunction (ejection fraction <30%)
6. Requirement for other cardiac surgical procedure (e.g., valve replacement or aorta su rgery)
7. Contraindication or inability to take aspirin or P2Y12 inhibitors (clopidogrel, ticagrelor, or clopidogrel)
8. Prior PCI of the left main trunk
9. Prior CABG

Study endpoints

Primary

The primary outcome was the composite of death from any causes, MI, or hospitalization for unstable angina, heart failure, resuscitated cardiac arrest, or repeat revascularization at 12 months after randomization.

Secondary

Each individual component of primary composite outcome; Composite of death or MI; Stent thrombosis (ARC definition): Bleeding complications (Bleeding Academic Research Consortium [BARC] criteria); Procedure time; Amount of contrast agent used; Length of hospital stay; Rehospitalization (any, cardiac, or noncardiac causes); Functional class (assessed by the CCS Classification); Angina-related quality of life index (by SAQ); Health-related quality of life index (by the EQ-5D); Number of anti-anginal medications used at each time point

Key Messages

- In the contemporary clinical practice, the goal of PCI is to achieve complete functional revascularization of ischemic territories. Thus, theoretical and practical concept of physiology-guided PCI will also work even in left main PCI setting.

- For all “borderline or intermediate” LMCA, it is strongly recommended to confirm physiologic lesion significance before treatment using FFR evaluation and non-ischemia-producing lesions should not be treated.

- **In the FATE-MAIN trial,** we assume that the improved outcomes with FFR-guided PCI are likely a result of more judicious PCI whereby ischemia-producing LMCA lesions are revascularized and non-ischemia producing LMCA lesions are treated with OMT alone.