Milestone for Left Main PCI: Upcoming EXCEL Trial

Gregg W. Stone MD
Columbia University Medical Center
The Cardiovascular Research Foundation

SYNTAX Eligible Patients

SYNTAX

De novo disease (n=1800)

Limited Exclusion Criteria

- Previous interventions
- Acute MI with CPK>2x
- Concomitant cardiac surgery

Left Main Disease (isolated, +1, +2 or +3 vessels)	3 Vessel Disease (revasc all 3 vascular territories)
N=705	N=1095

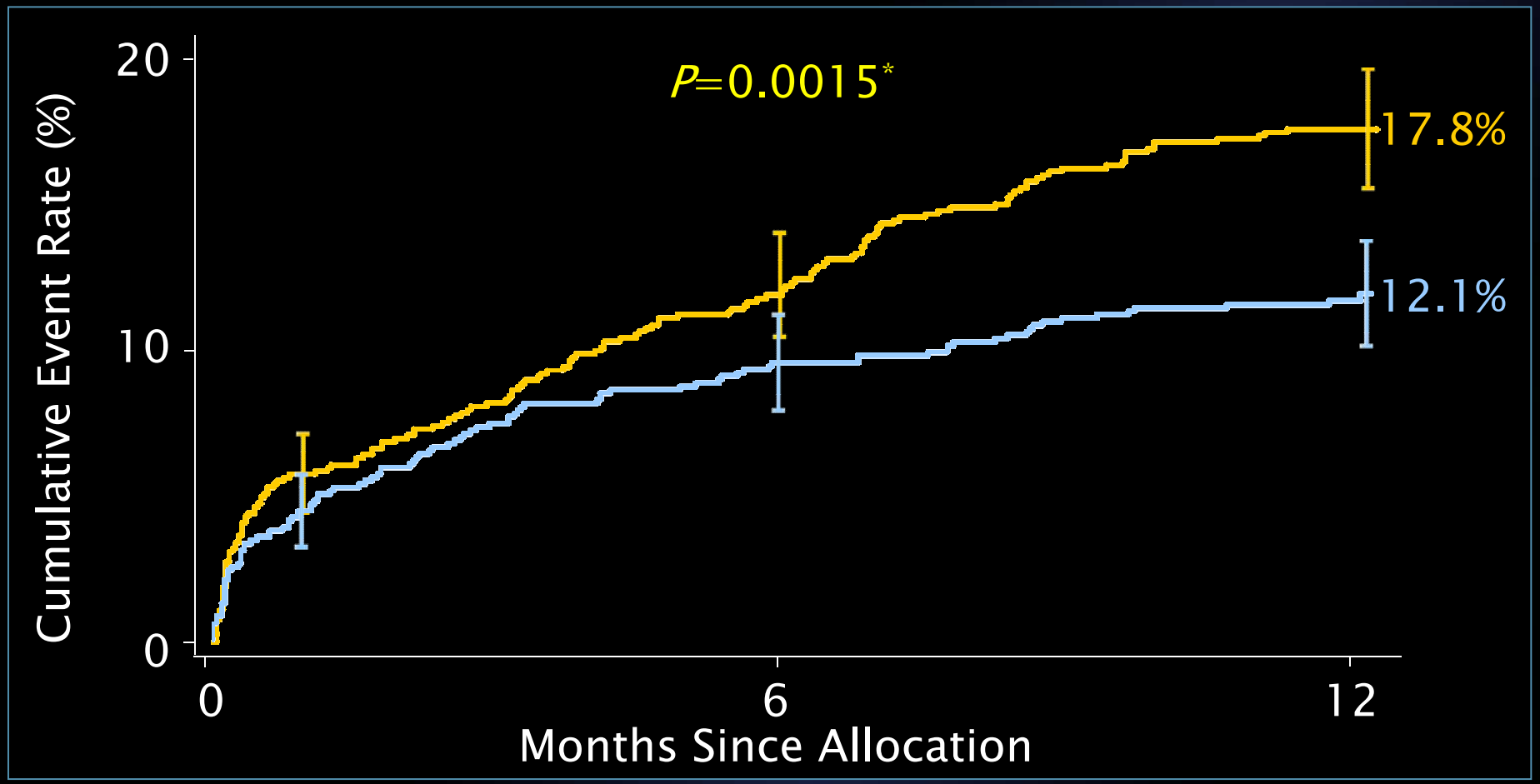
Primary endpoint = death/MI/stroke/repeat revasc at 1 year

Serruys PW et al. NEJM 2009;360:961-72

MACCE to 1 Year *(primary endpoint)*

(All-cause death, stroke, MI, any repeat revasc)

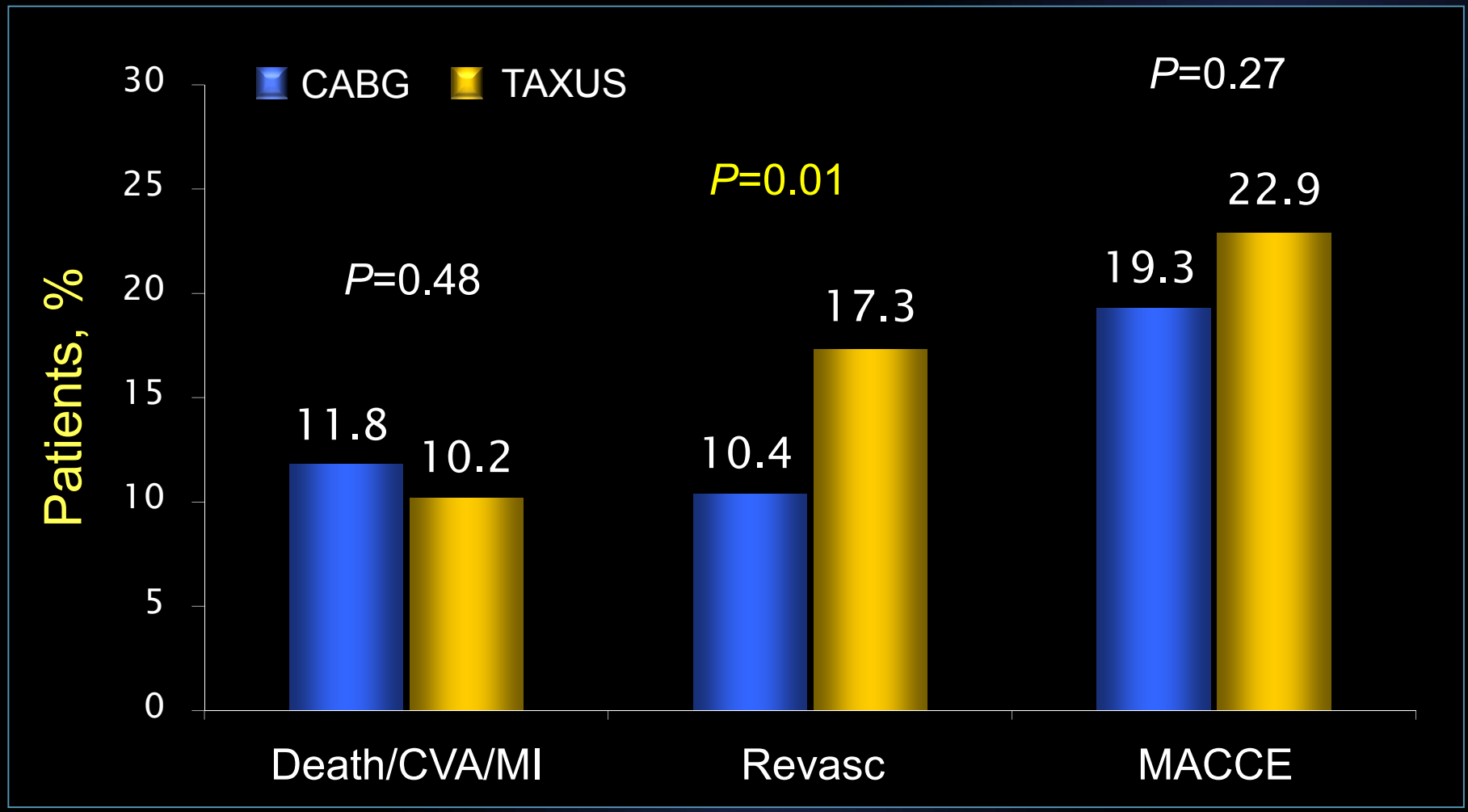
SYNTAX



ITT population

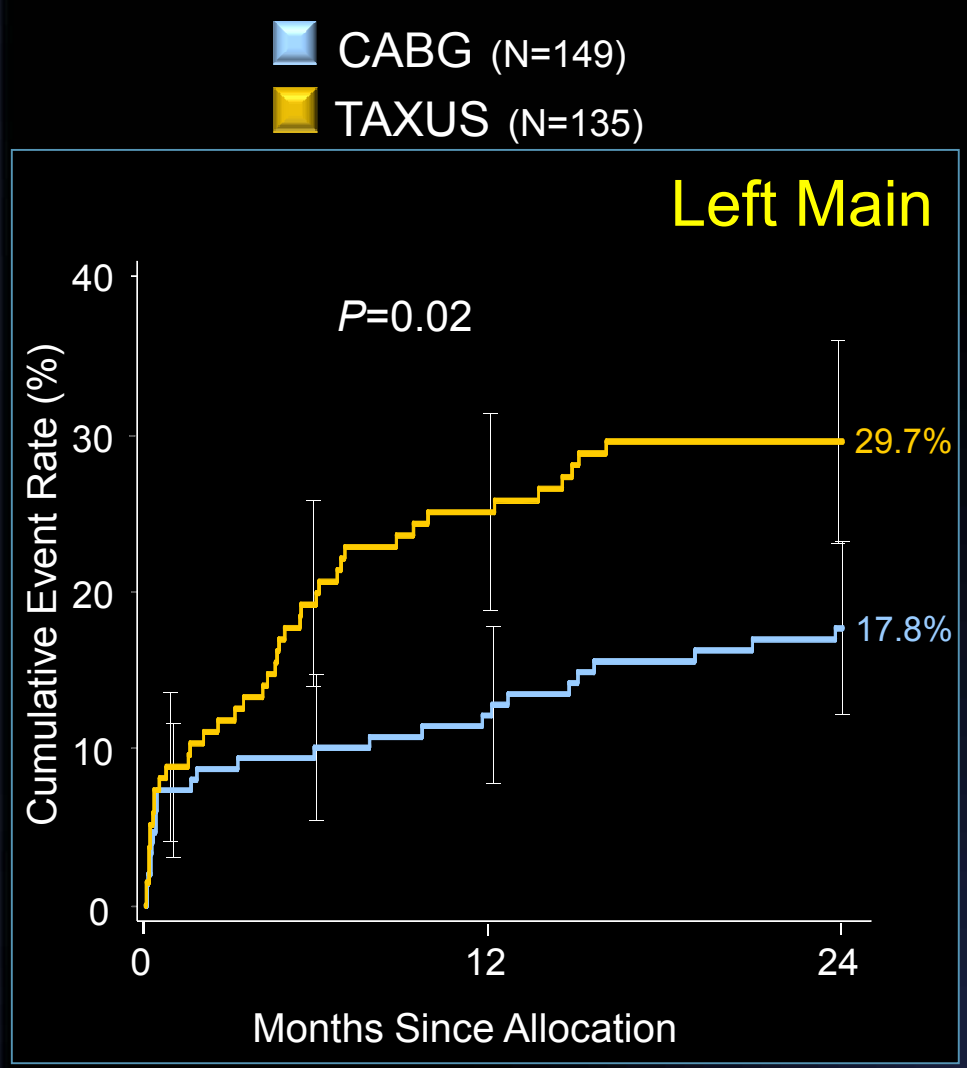
Serruys PW et al. NEJM 2009;360:961-72

SYNTAX: 2 Year Outcomes in the LM Subgroup (N=705)



MACCE to 2 Years by SYNTAX Score Tercile

Left Main SYNTAX Score ≥33

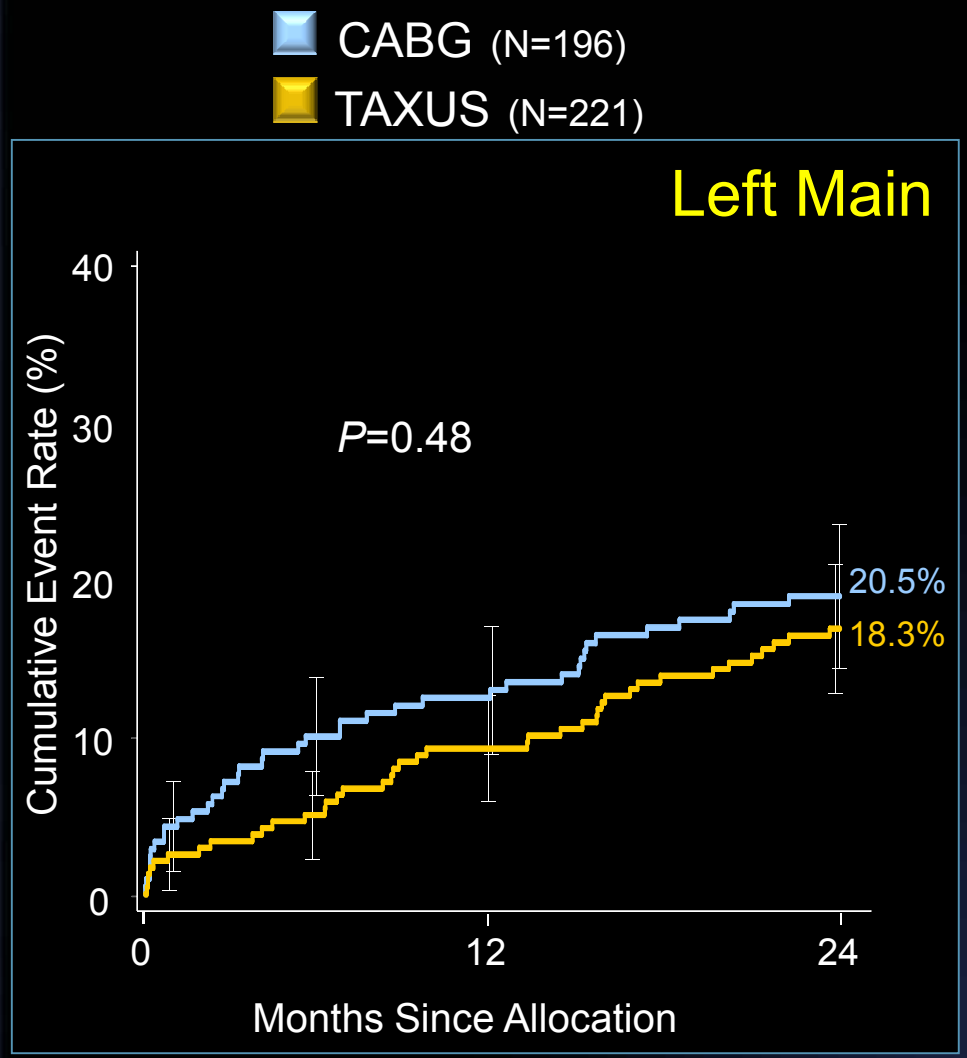


	CABG	PCI	*P*-value
Death	4.1%	10.4%	0.04
CVA	4.2%	0.8%	0.08
MI	6.1%	8.4%	0.48
Death, CVA or MI	11.5%	15.6%	0.32
Revasc.	9.2%	21.8%	0.003

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value

Site-reported data; ITT population

MACCE to 2 Years by SYNTAX Score Tercile *Left Main SYNTAX Scores 0–32*



	CABG	PCI	*P*–value
Death	7.9%	2.7%	0.02
CVA	3.3%	0.9%	0.09
MI	2.6%	3.8%	0.59
Death, CVA or MI	12.1%	6.9%	0.06
Revasc.	11.4%	14.3%	0.44

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value

Site-reported Data; ITT population

ACC/AHA Guidelines Post SYNTAX

Stenting of the LMCA as an alternative to CABG may be considered in pts with anatomic conditions that are associated with a low risk of PCI procedural complications and clinical conditions that predict an increased risk of adverse surgical outcomes

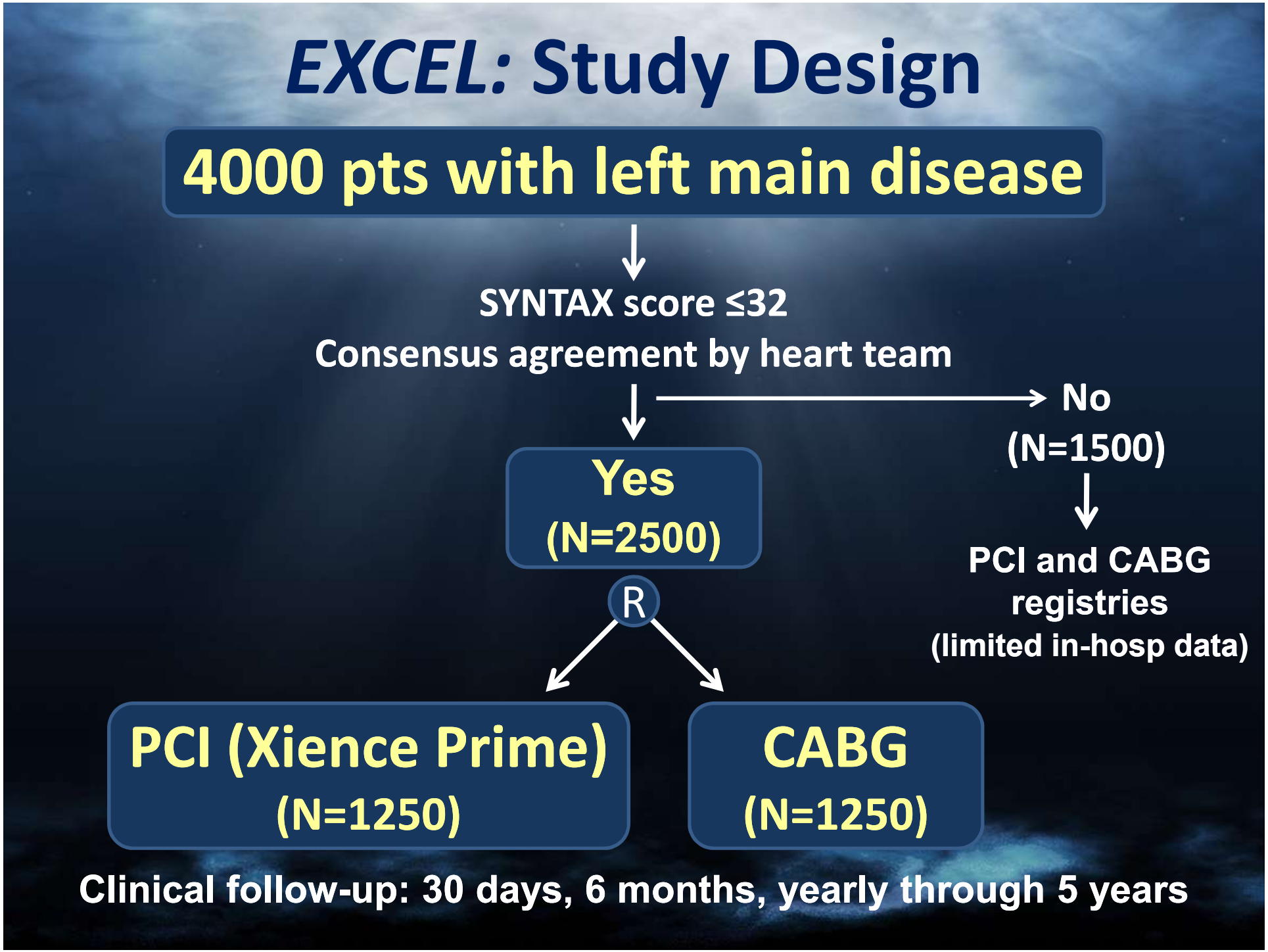
IIb = “may or might be considered; may or might be reasonable; usefulness/effectiveness is unknown/unclear/uncertain or not well established”

ACC/AHA 2009 Focused Updates for STEMI and PCI. Circulation 2009;120:2271–2306

What Would an Informative Trial of Left Main DES vs. CABG Look Like?

- It wouldn't be an all-comers trial!
  - Exclude pts who clearly should go to CABG, e.g. high SYNTAX scores
- Optimize PCI technique
  - Pre-specify when/how to use IVUS, staged procedures, RX of distal bifurcation, no routine angio FU, etc.
  - Use the best stent and adjunctive pharmacology
- Optimize CABG technique
  - Minimize waiting time to CABG, maximize pan-arterial revascularization, adjunctive pharmacology, etc.
- Use a meaningful 1º endpoint: Death, CVA or MI
- ~2500 randomized pts

EXCEL: Study Design

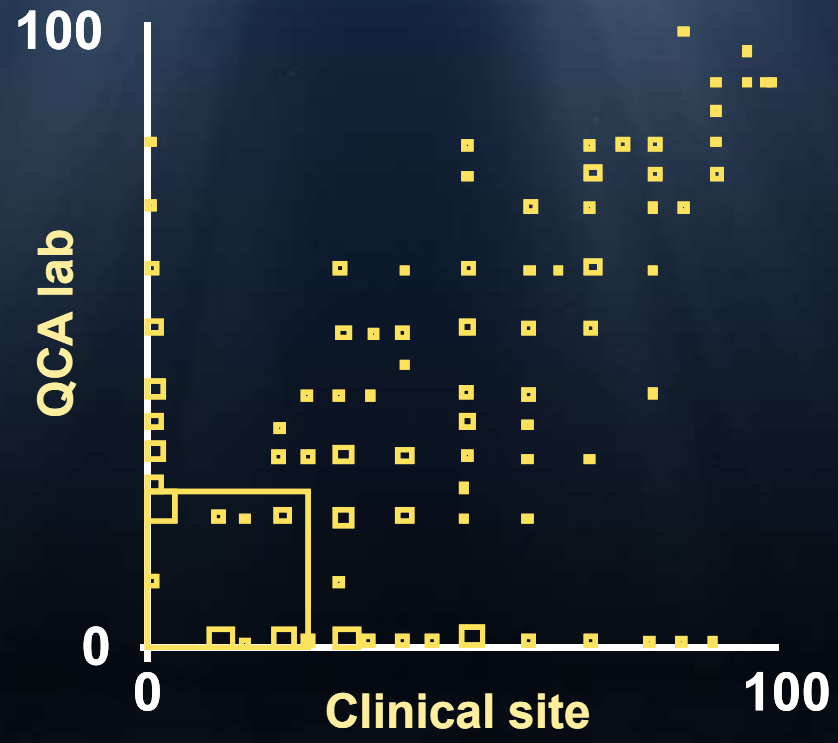


EXCEL: Inclusion Criteria

- Clinical and anatomic eligibility for both PCI and CABG by heart team consensus
- Silent ischemia, stable angina, unstable angina or recent MI
- Significant LM ds. by heart team consensus
  - Angiographic DS ≥70%, or
  - Angiographic DS ≥50% to <70% with
    - a markedly positive noninvasive study, and/or
    - IVUS MLA <6.0 mm^2, and/or
    - FFR <0.80

Of all the coronary segments, the LMCA has the greatest angiographic variability

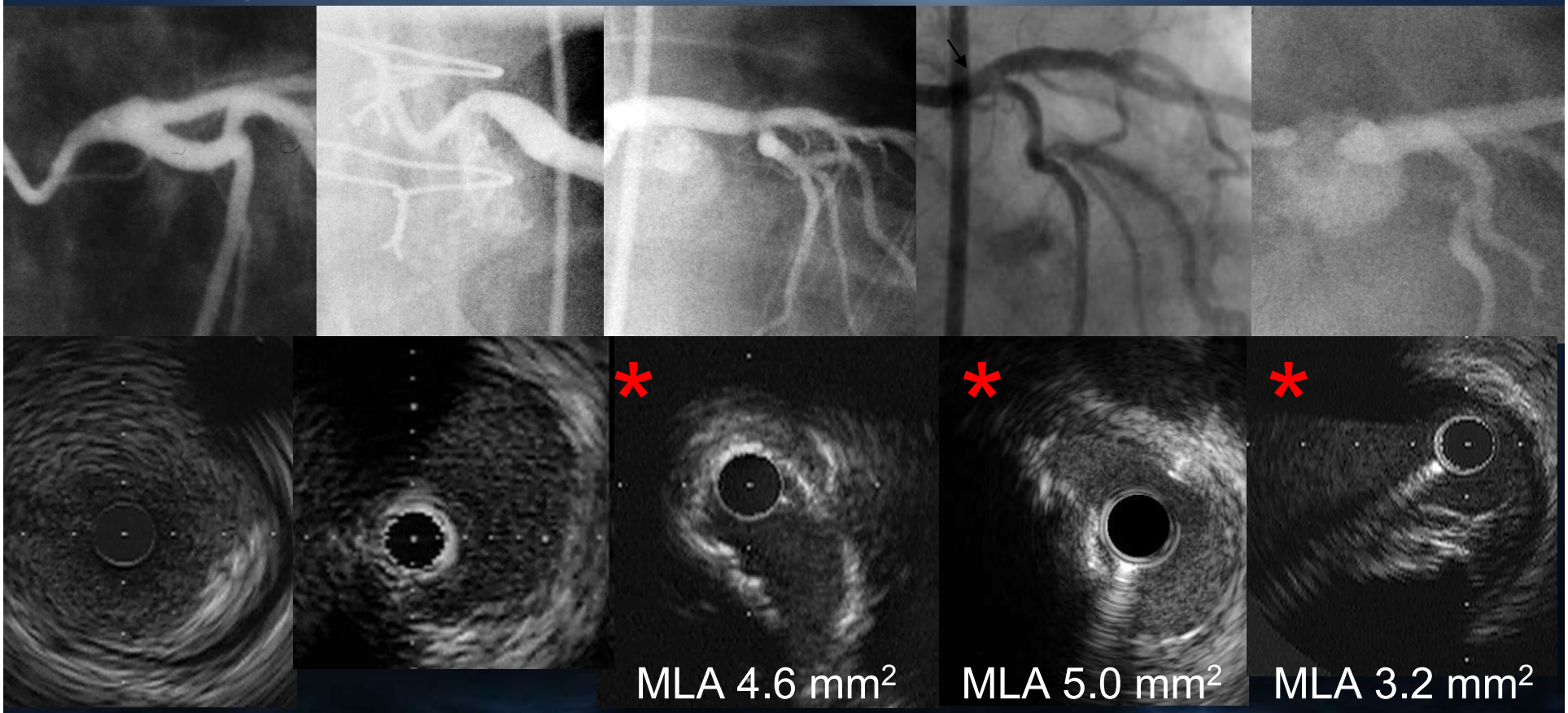
Comparison in DS% assessment from the core lab (QCA) vs the clinical site (CASS Study)



*area of the square is proportional to the number of cases

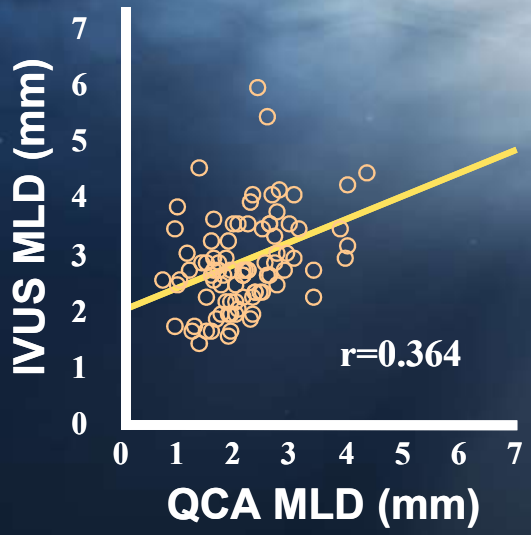
Fisher et al. Cathet Cardiovasc Diagn 1982;8:565-75

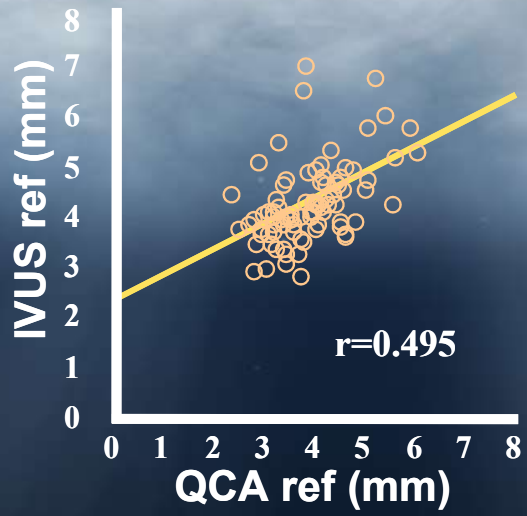
Which of these LMCA lesions are significant and therefore should be treated? And which are not??

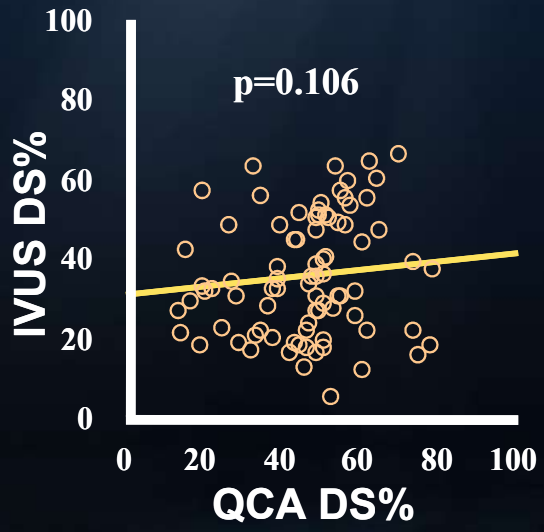


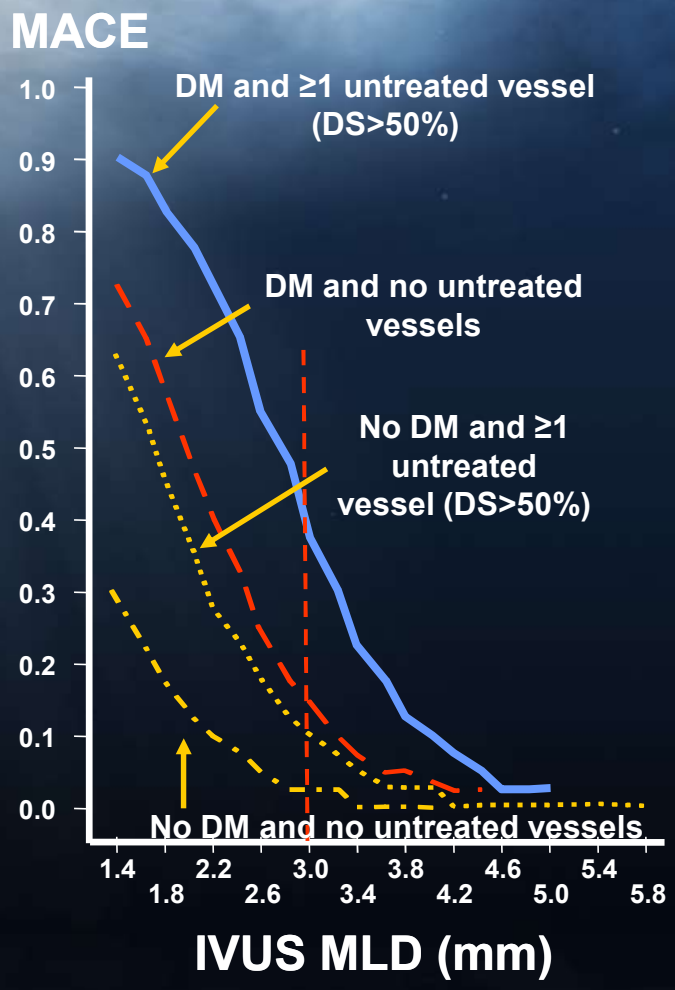
LMCA IVUS usually shows either insignificant or critical disease

1-Year FU of 122 pts with moderate LM disease





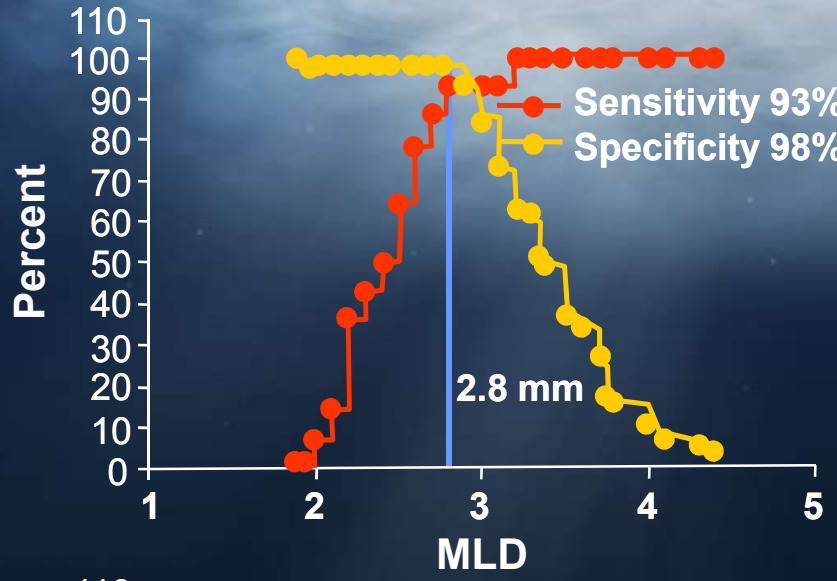


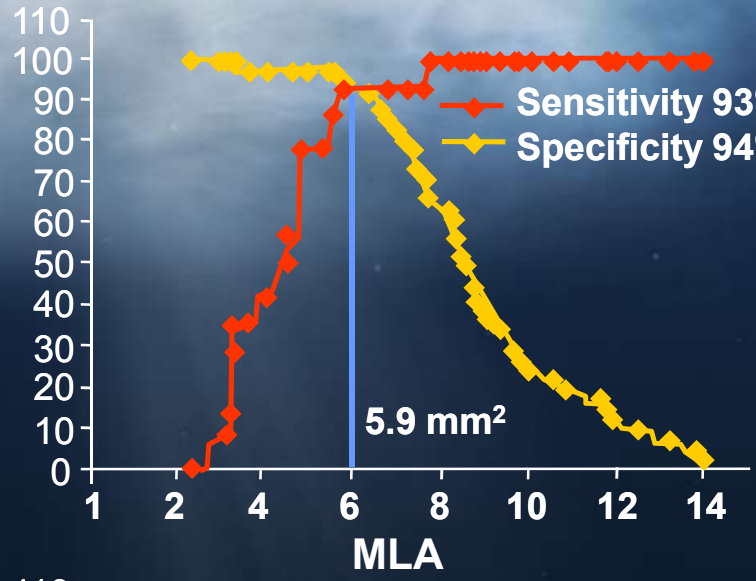


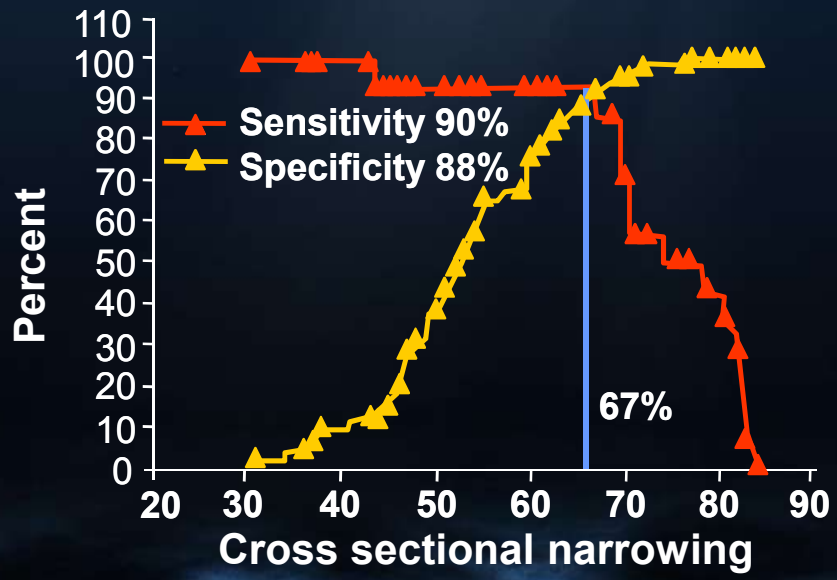
Independent predictors of MACE @11.7 months: DM (p=0.004), untreated lesion >50% (p=0.037), and IVUS MLD (p=0.005)

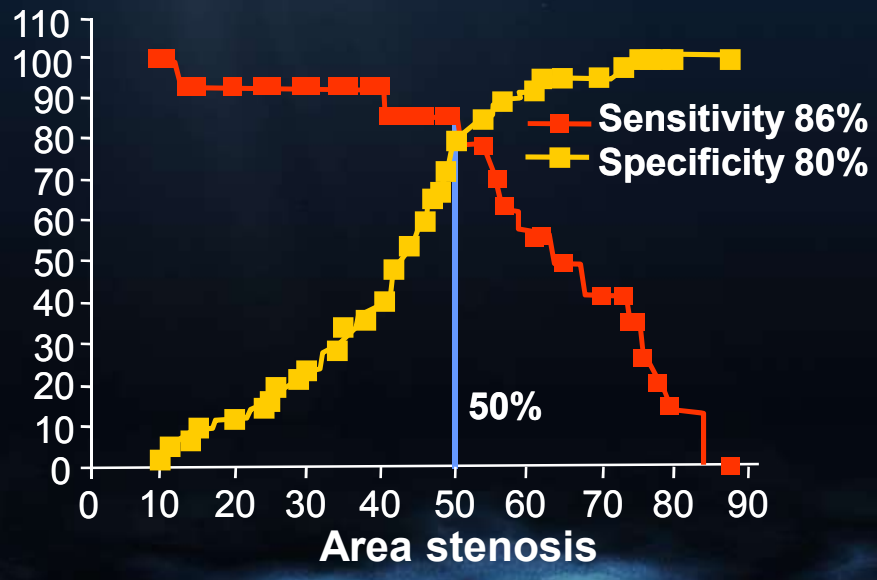
Abizaid et al. JACC 1999;34:707-15

IVUS determinants of LMCA FFR <0.75







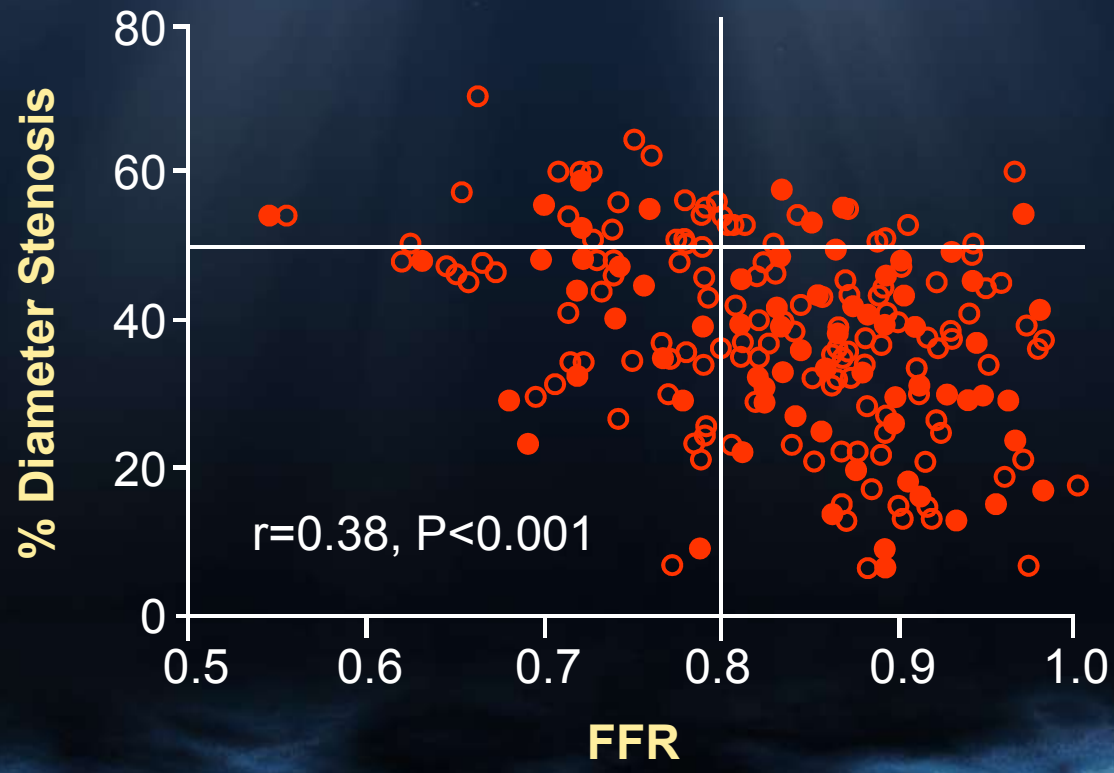


MLA <6.0 mm² (or MLD <3.0 mm) is the suggested criterion for significant LMCA stenosis. **Jasti et al. Circulation 2004;110:2831-6**

FFR Guidance for Left Main Treatment

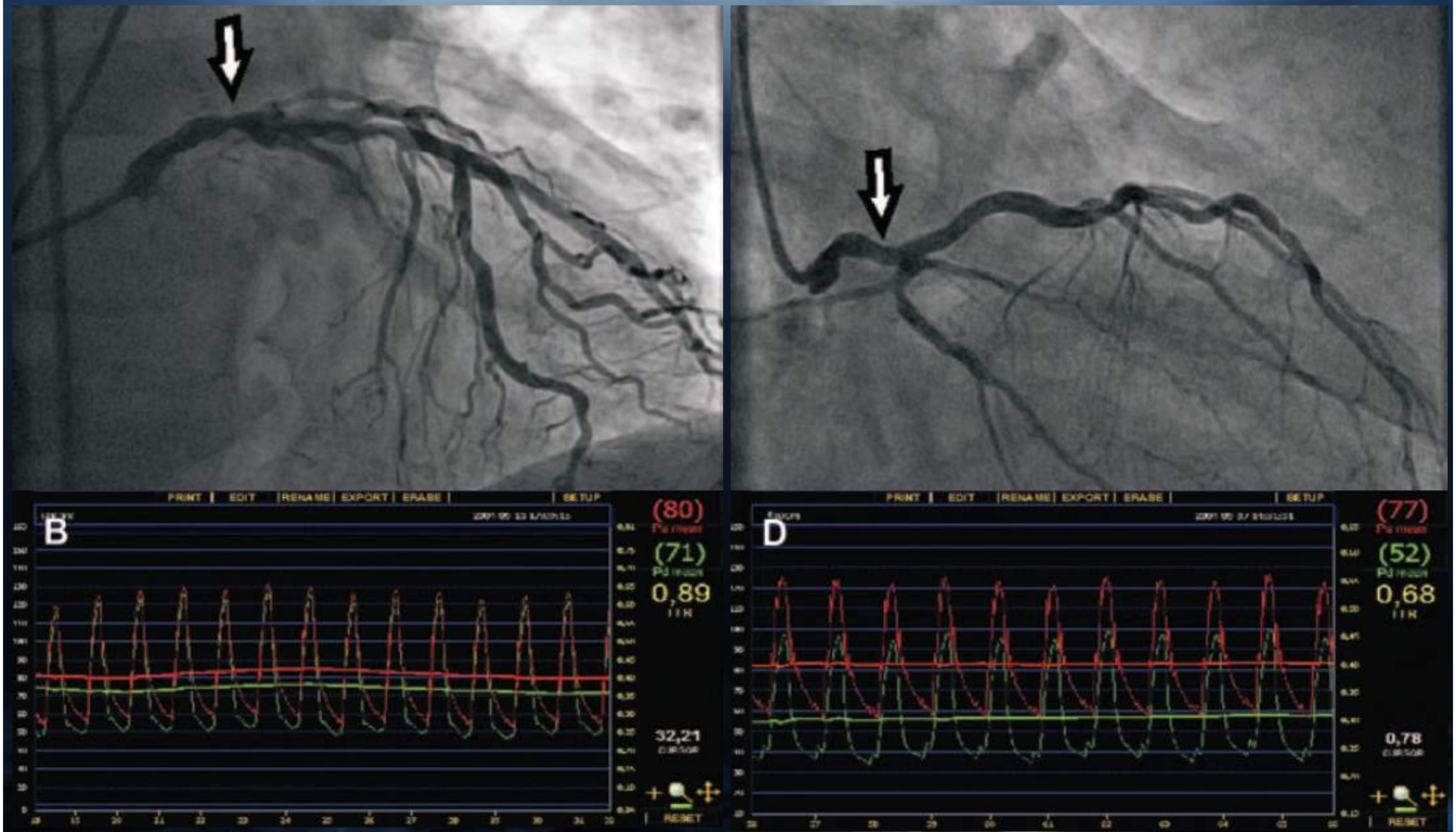
FFR was performed in 213 pts with angiographically borderline (DS 30% - 70%) LM lesions

FFR ≥0.80 ⇒ medical Rx (n=138); FFR <0.80 ⇒ CABG (n=75)



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

Correlation between angiography and FFR in unprotected left main disease

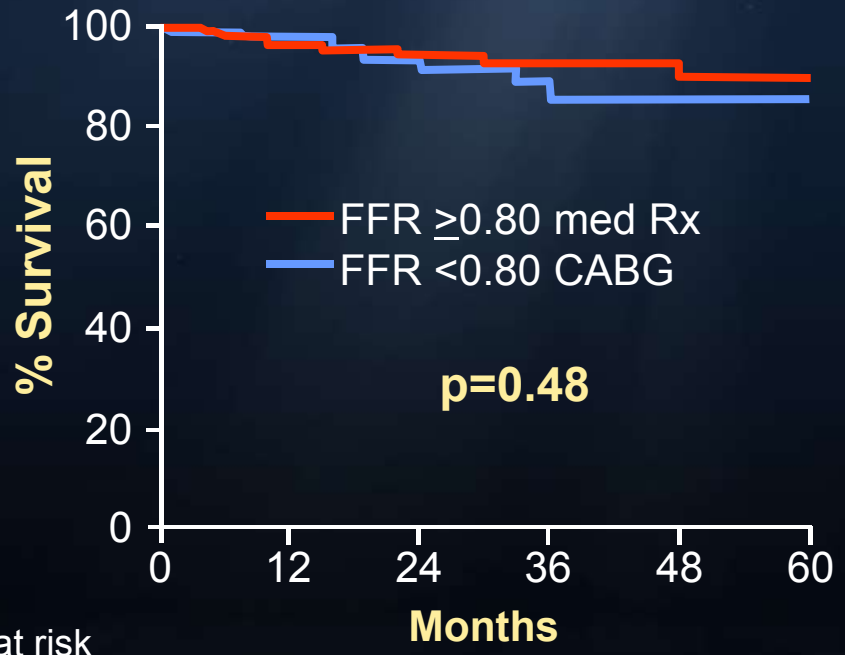


Hamilos M et al. Circulation. 2009;120:1505-1512.

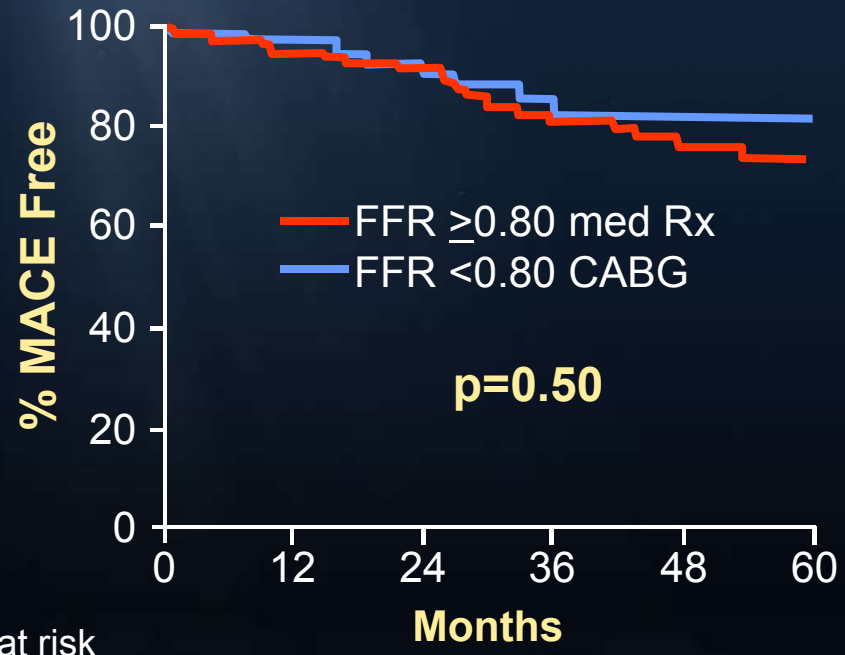
FFR Guidance for Left Main Treatment

FFR was performed in 213 pts with angiographically borderline (DS 30% - 70%) LM lesions

FFR ≥0.80 ⇒ medical Rx (n=138); FFR <0.80 ⇒ CABG (n=75)



No. at risk						
FFR ≥0.80	136	103	72	52	38	26
FFR <0.80	73	56	41	30	14	10



No. at risk						
FFR ≥0.80	136	106	77	57	42	30
FFR <0.80	73	56	40	29	15	10

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

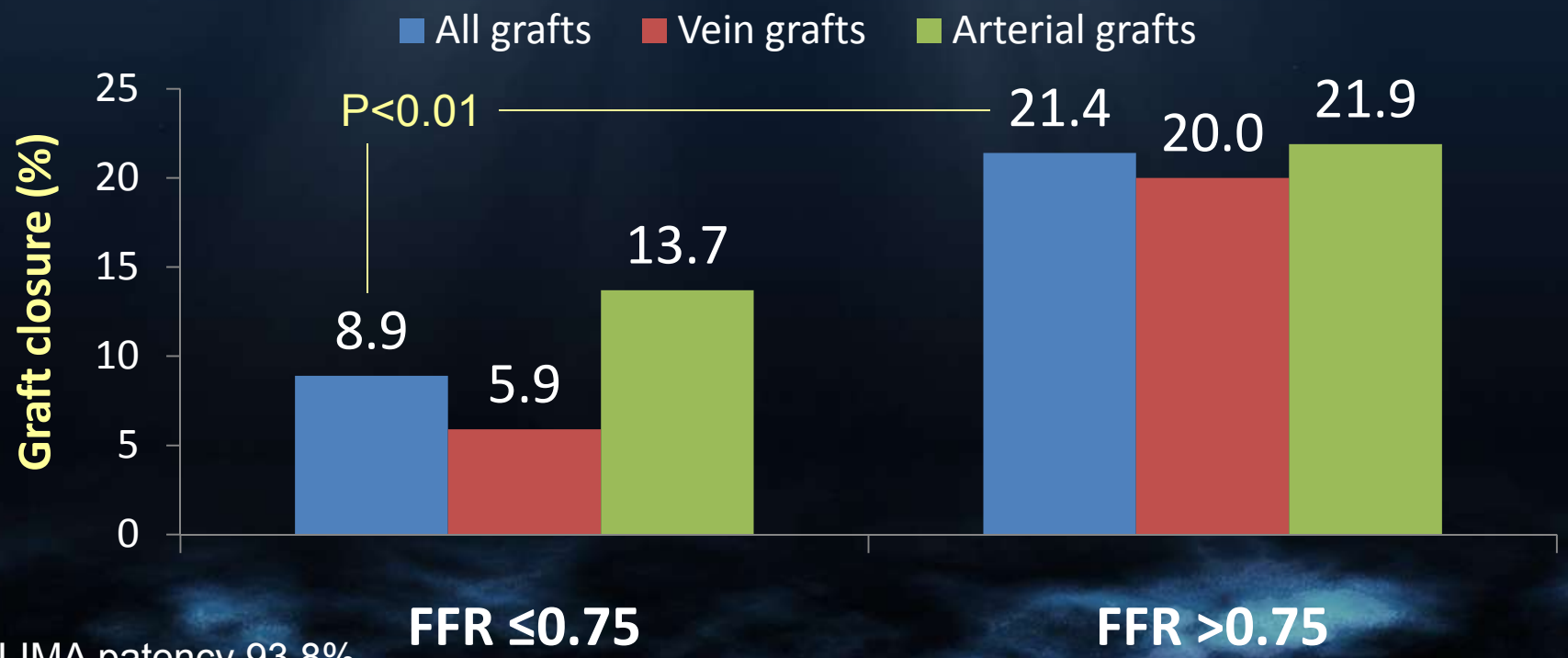
Why not revascularize pts with borderline LM lesions in the absence of ischemia?≤

FFR was performed in 525 lesions in 153 pts before bypass

Baseline FFR was ≤0.75 in 337 (64%) and >0.75 in 168 (36%)

Repeat angiography was performed at 1-year

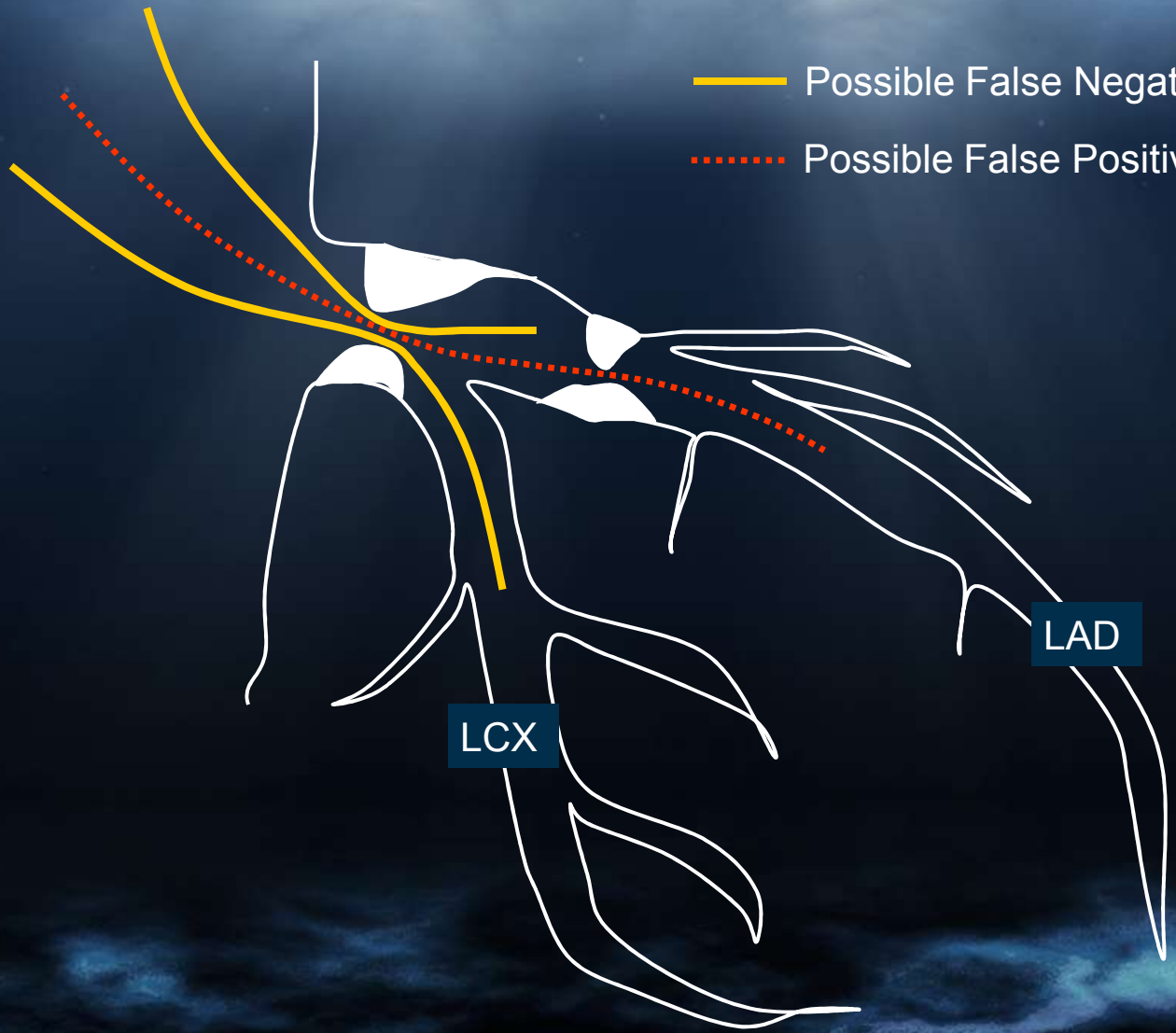
Graft closure at 1-year according to baseline native cor FFR:



1-yr LIMA patency 93.8%
1-yr radial patency 71.0%

Botman CJ et al. Ann Thorac Surg 2007;83:2093–7.

EXCEL: IVUS is recommended over FFR for invasive evaluation of intermediate LM ds.



EXCEL: Clinical Exclusion Criteria

- Prior PCI within 1 year, or prior LM PCI anytime
- Prior CABG anytime
- Need for any cardiac surgery other than CABG
- Additional surgery required within 1 year
- Unable to tolerate, obtain or comply with dual antiplatelet therapy for 1 year
- Non cardiac co-morbidities with life expectancy < 3 years
- Clinical equipoise not present

EXCEL: Angiographic Exclusion Criteria

- Left main DS <50% (visually assessed)
- SYNTAX score ≥33
- Left main RVD <2.25 mm or >4.5 mm

EXCEL: Use of XIENCE Prime

Enhanced stent
New SDS

-More flexible and deliverable

- Shorter balloon tapers

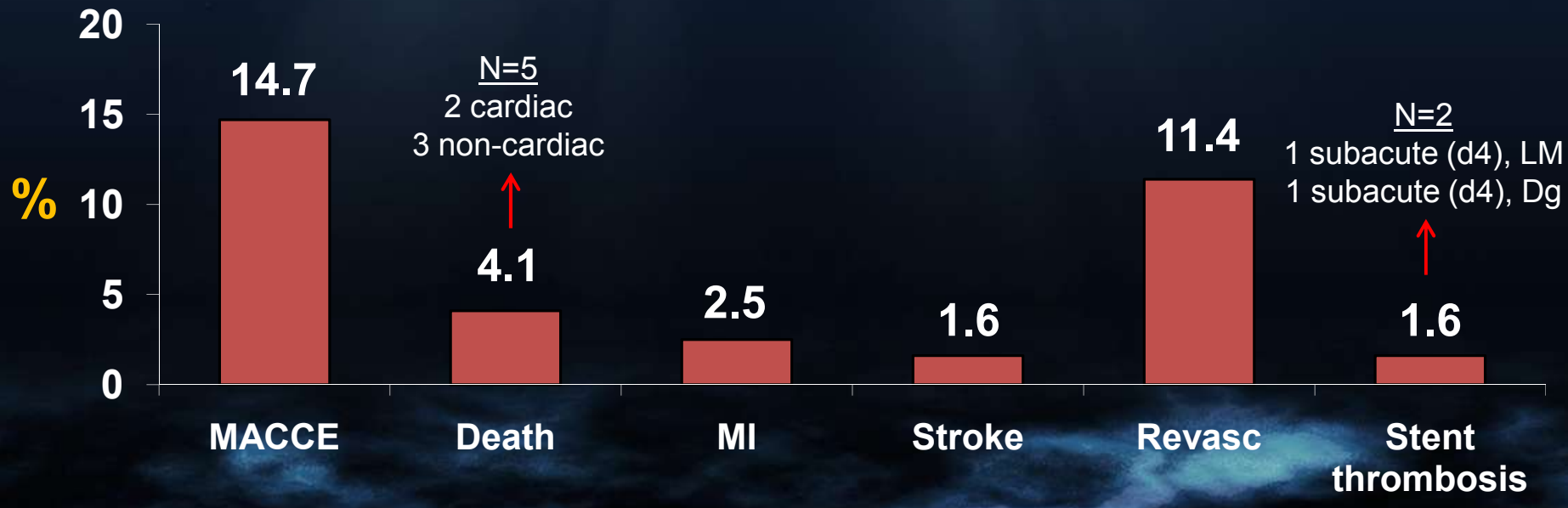
- Higher RBP

XIENCE Prime for LM Ds: LeMaX Pilot

174 pts with ULM ds. were treated with XIENCE Prime at 4 French centers between 12/07 and 5/09

- All-comers, except STEMI and shock excluded
- Mean age 69, 42% NSTEMI, 46% 3VD, mean 2.1 lsns/pt
- Mean SYNTAX score 25.1, 81% distal bifurcation

One-year MACE (in 122 eligible pts)

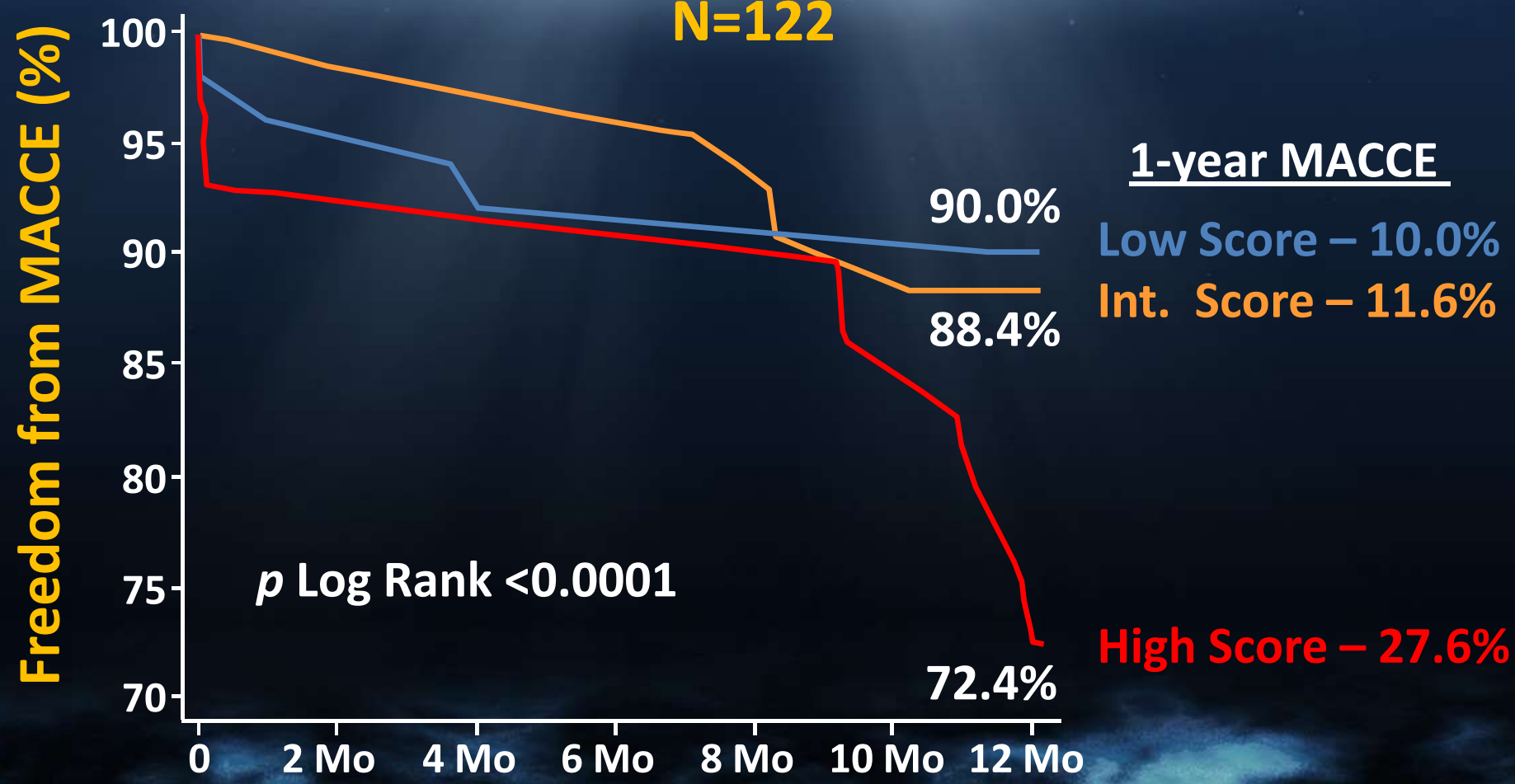


Salvatella N. AHA 2009

XIENCE Prime for LM Ds: LeMaX Pilot

174 pts with ULM ds. were treated with XIENCE Prime

- Mean SYNTAX score 25.1 ± 10.1 -



Salvatella N. AHA 2009

EXCEL: Endpoints

- Primary endpoint: Death, MI, or stroke at median follow-up of 3 years
- Major secondary endpoint: Death, MI, stroke or unplanned revascularization at median follow-up of 3 years
  - ❖ Power analysis: Both endpoints are powered for sequential noninferiority and superiority testing
- Quality of life and cost-effectiveness assessments: At regular intervals

EXCEL: Organization (i)

Academically driven study; 50% interventionalists, 50% cardiac surgeons

- Principal Investigators:
  - Interventional: Patrick W. Serruys, Gregg W. Stone
  - Surgical: A. Pieter Kappetein, Joseph F. Sabik
- Executive Operations Committee:
  - 4 principal investigators, Peter-Paul Kint, Martin B. Leon, Alexandra Lansky, Roxana Mehran, Marie-Angèle Morel, Chuck Simonton, David Taggart, Lynn Vandertie, Gerrit-Anne van Es, Jessie Coe, Poornima Sood, Ali Akavand, Krishnankutty Sudhir, Thomas Engels
- Optimal Therapy Committee Chairs
  - PCI: Martin B. Leon
  - Surgery: David Taggart
  - Medical: Bernard Gersh

EXCEL: Organization (ii)

- Countries and Country Leaders (PCI and CABG)
  - United States: David Kandzari and John Puskas
  - Europe (10): Marie-Claude Morice and David Taggart
  - Brazil: Alex Abizaid and Luis Carlos Bento Sousa
  - Argentina: Jorge Belardi and Daniel Navia
  - Canada: Erick Schampaert and Marc Ruel
  - S. Korea: Seung-Jung Park and Jay-Won Lee
- Statistical Committee
  - Stuart Pocock, Chair
- Data Safety and Monitoring Board
  - Lars Wallentin, Chair
- Academic Research Organizations
  - Cardiovascular Research Foundation and Cardialysis
- Sponsor: Abbott Vascular

EXCEL: Status

- After 12 months of preparation the protocol is finalized
- The site selection process is underway
- FDA meetings and global regulatory submissions are being prepared
- First patient enrolled: 3rd Quarter 2010