Coronary Physiology in the Cathlab

DEFER, SYNTAX, COURAGE and FAME's

A Synthesis

W. Wijns, Aalst (B)

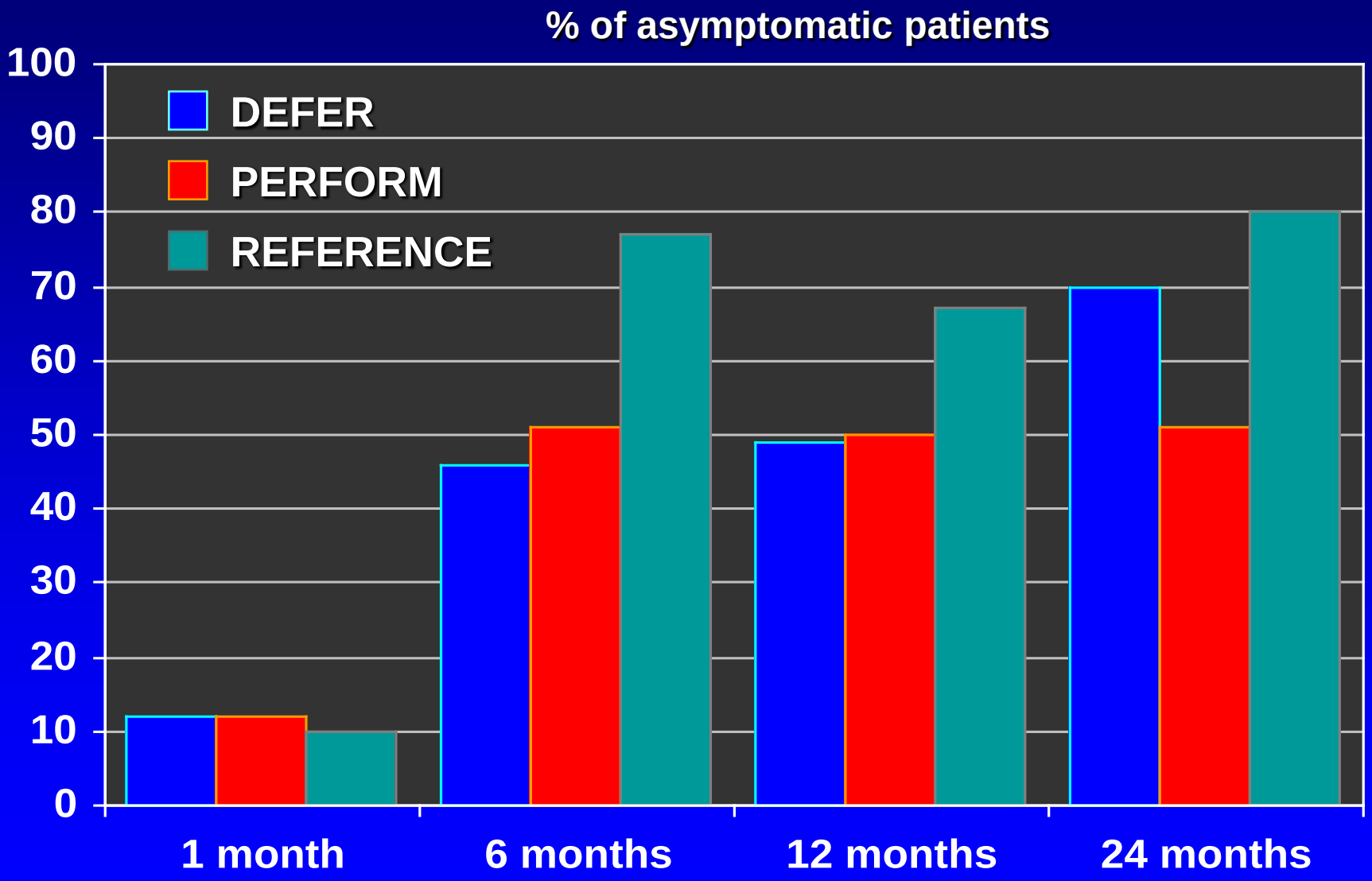
DEFER, SYNTAX, COURAGE and FAME's

What is your conclusion from …

- **DEFER**
- FAME 1
- SYNTAX

How does this trial influence your practice …

DEFER Study: Impact on Symptoms



Bech et al. Circulation 2001

DEFER Study Results at 5 years

FFR > 0.75

No PCI

PCI

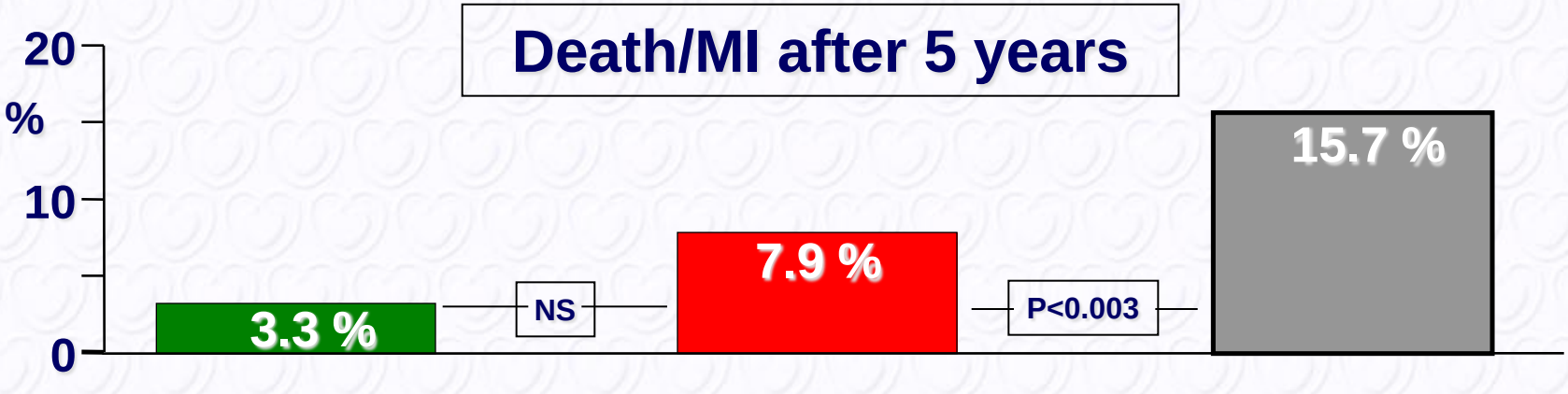
FFR < 0.75

PCI

DEFER

PERFORM

REFERENCE



When FFR > 0.75 Death and MI rate is < 1% per year

Pijls et al, JACC 2007;49:2105-1.

DEFER, SYNTAX, COURAGE and FAME's

What is your conclusion from …

- DEFER
- **FAME 1**
- SYNTAX

How does this trial influence your practice …

FAME 1 study: Study Population

The FAME study was designed to ***reflect daily practice*** in performing PCI in patients ***with multivessel disease***

Inclusion criteria:

- ***ALL*** patients with multivessel disease
- At least 2 stenoses ≥ 50% in 2 or 3 major epicardial coronary artery disease, amenable for stenting

Exclusion criteria:

- Left main disease or previous bypass surgery
- Acute STEMI
- Extremely tortuous or calcified coronary arteries

Note: patients with previous PCI were not excluded

FAME 1 study: Functional Class at 1 Year

	ANGIO-group N=496	FFR-group N=509	P-value
Patients without event and free from angina	326 (68)	360 (73)	0.07
Patients free from angina, No. (%)	374 (78)	399 (81)	0.20
Number of anti-anginal meds, No.	1.2 ± 0.7	1.2 ± 0.8	0.48
EQ-5D visual analogue scale	74 ± 16	75 ± 16	0.65

FAME 1 study: Adverse Events at 1 year

Events at 1 year, No (%)	ANGIO-group N=496	FFR-group N=509	P-value
Death, MI, CABG, or repeat-PCI	**91 (18.4)**	**67 (13.2)**	**0.02**
Death	15 (3.0)	9 (1.8)	0.19
Death or myocardial infarction	55 (11.1)	37 (7.3)	0.04
CABG or repeat PCI	47 (9.5)	33 (6.5)	0.08
Total no. of MACE	113	76	0.02
Myocardial infarction, specified			
All myocardial infarctions	43 (8.7)	29 (5.7)	0.07
Small periprocedural CK-MB 3-5 x N	16	12	
Other infarctions (“late or large”)	27	17	

DEFER, SYNTAX, COURAGE and FAME's

What is your conclusion from …

- DEFER
- FAME 1
- **SYNTAX**

How does this trial influence your practice …

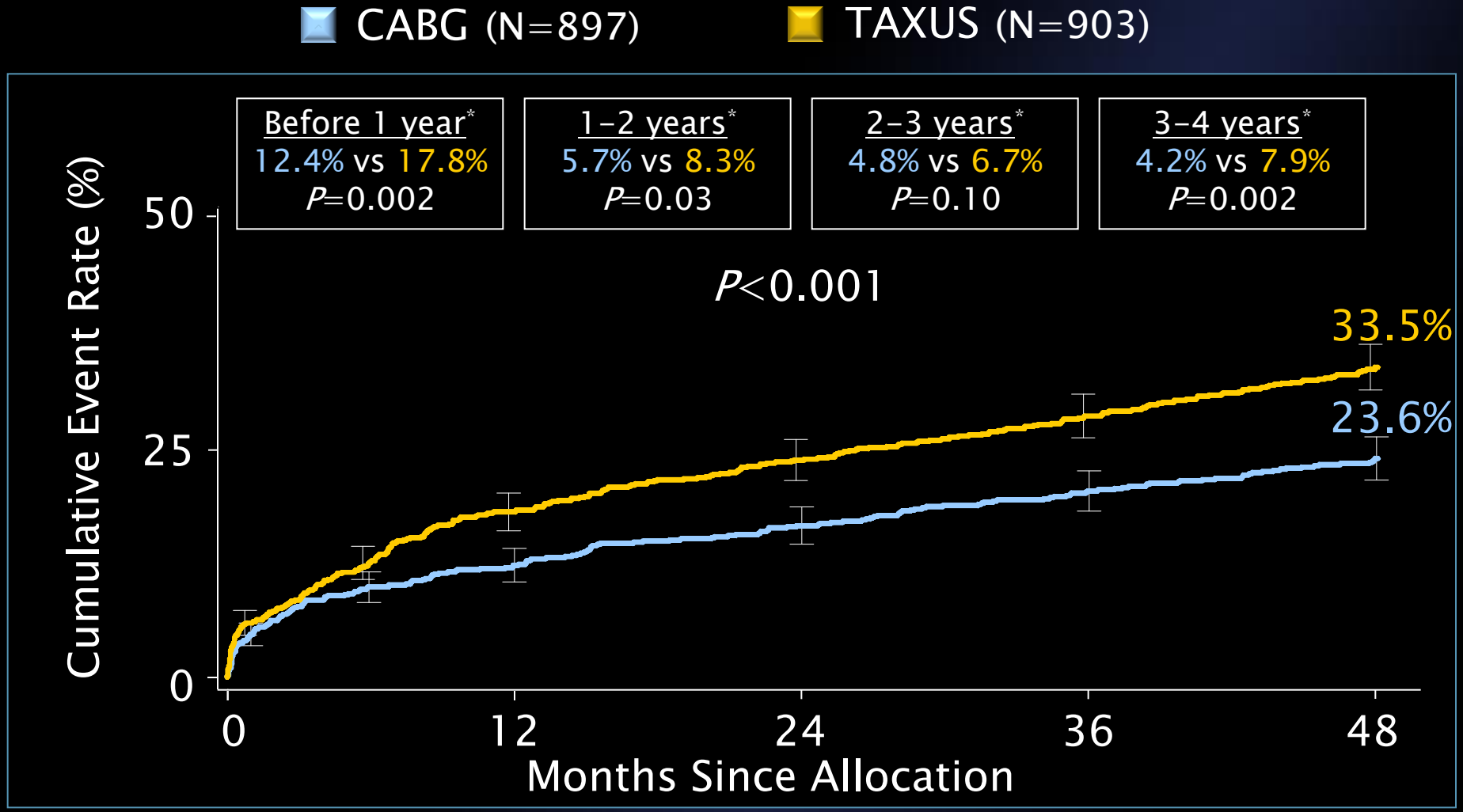
Patient in SYNTAX

Randomized Controlled Trial Intent-to-Treat

CABG	RCT	PCI*
n=897	**Enrolled** N=1800	n=903
n=849	**1 Year Follow-up** CABG 94.6% PCI 98.7%	n=891
n=836	**2 Year Follow-up** CABG 93.2% PCI 98.0%	n=885
n=827	**3 Year Follow-up** CABG 92.2% PCI 98.0%	n=885
n=819	**4 Year Follow-up** CABG 91.3% PCI 97.3%	n=879

*TAXUS Express

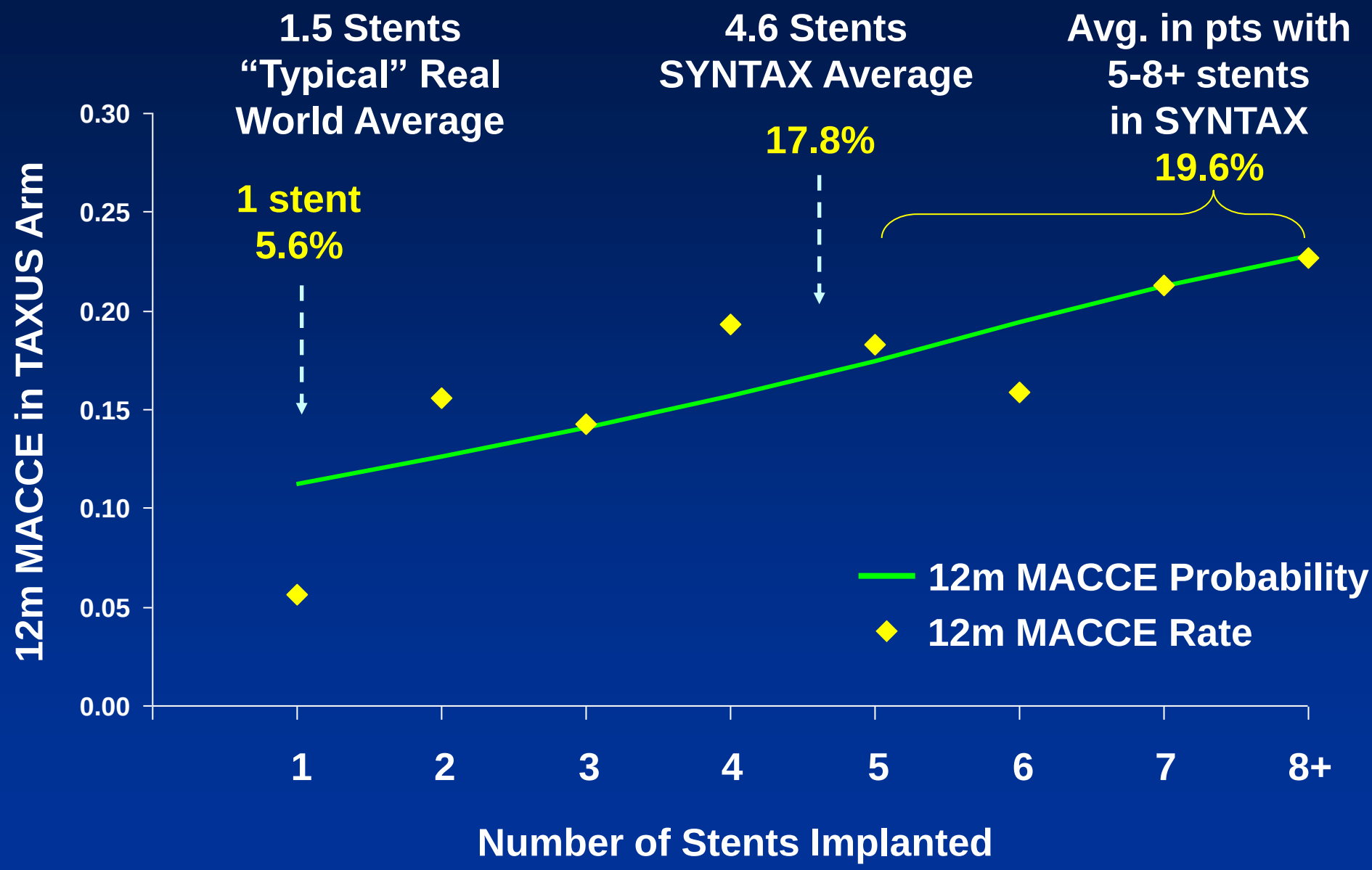
MACCE to 4 Years



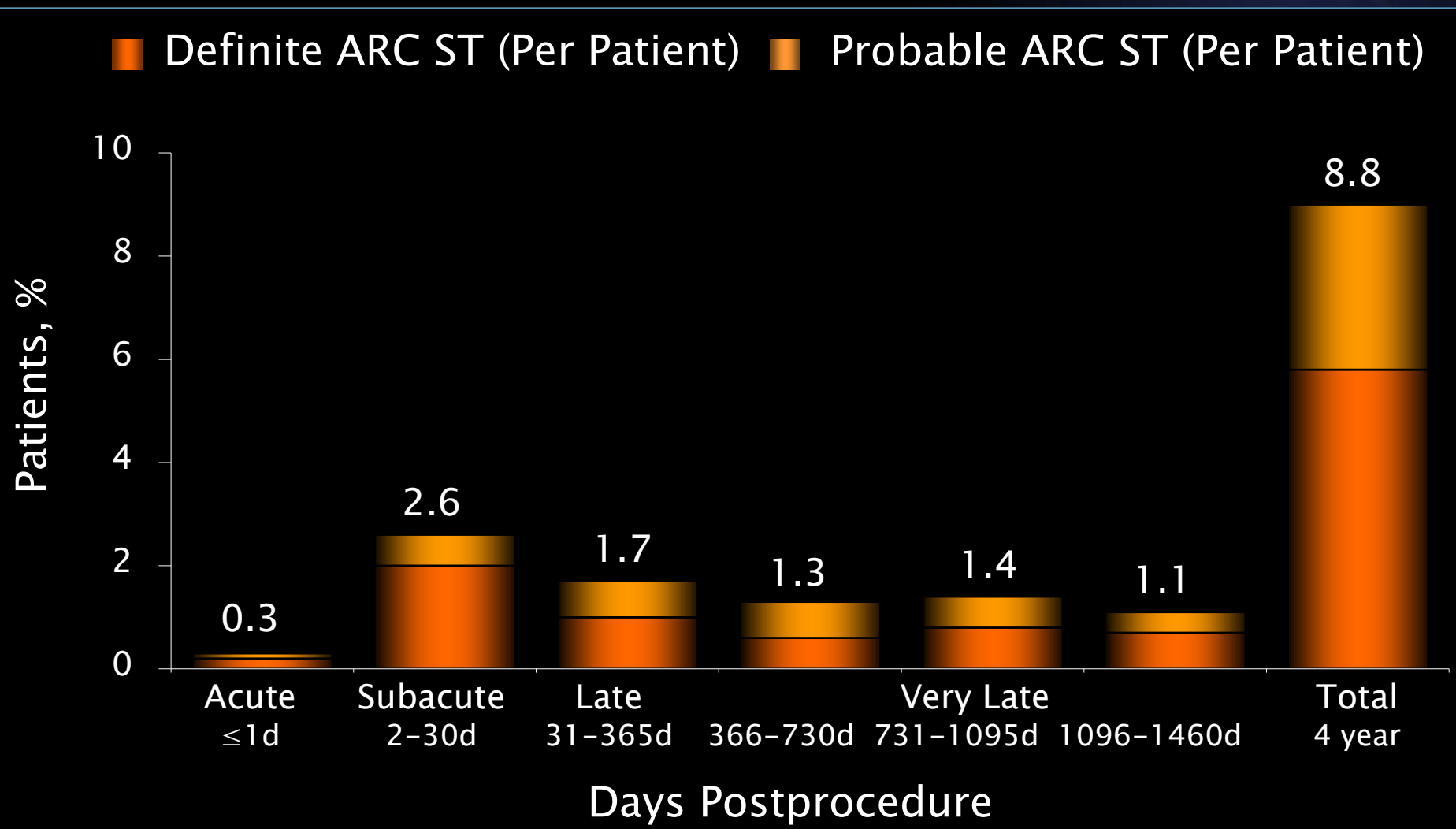
Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value;*Binary rates

ITT population

Linear Increase in MACCE by Number of Stents in the SYNTAX Trial



ARC ST



Definite plus probable per ARC definitions (Cutlip, et al. *Circulation* 2007;115:2344). 1PCI patient had an ST 1d and 6d post-procedure; therefore, counted in the ≤1d and 2-30d intervals but only once in the total.

DEFER, SYNTAX, COURAGE and FAME's

We conclude that …

Dual targeting (anatomy + function) is symptomatically equivalent and prognostically superior to single targeting (angio only)

Less is More (DEFER, FAME 1)

More is Less (SYNTAX)

DEFER, SYNTAX, COURAGE and FAME's

What is your conclusion from …

- **COURAGE**
- FAME 2

How does this trial influence your practice …

COURAGE Trial

Clinical Outcome Utilising Revascularisation and Aggressive DruG Evalution

Multicenter randomised trial testing the following hypothesis:

- **the best clinical outcome can be achieved by combining PCI with intensive medical therapy**
- **primary endpoint: death, MI, ACS (Tn+)**
- **N = 2287 pts: medical vs PCI + medical**

COURAGE: Study Overview

- 2287 patients randomised (after angiography) between BMS plus drug therapy vs. drug therapy alone
- The composite primary end point was all-cause death or acute MI
- Duration 2.5 - 7 years with on average 5 year follow-up

cumulative event rate	PCI	Med Rx
Death or MI	19.0%	18.5%
Death, MI, stroke	20.0%	19.5%
Hospitalization for ACS	12.4%	11.8%
MI	13.2%	12.3%

Trial conclusion

PCI did not reduce the risk of death or MI in this patient population

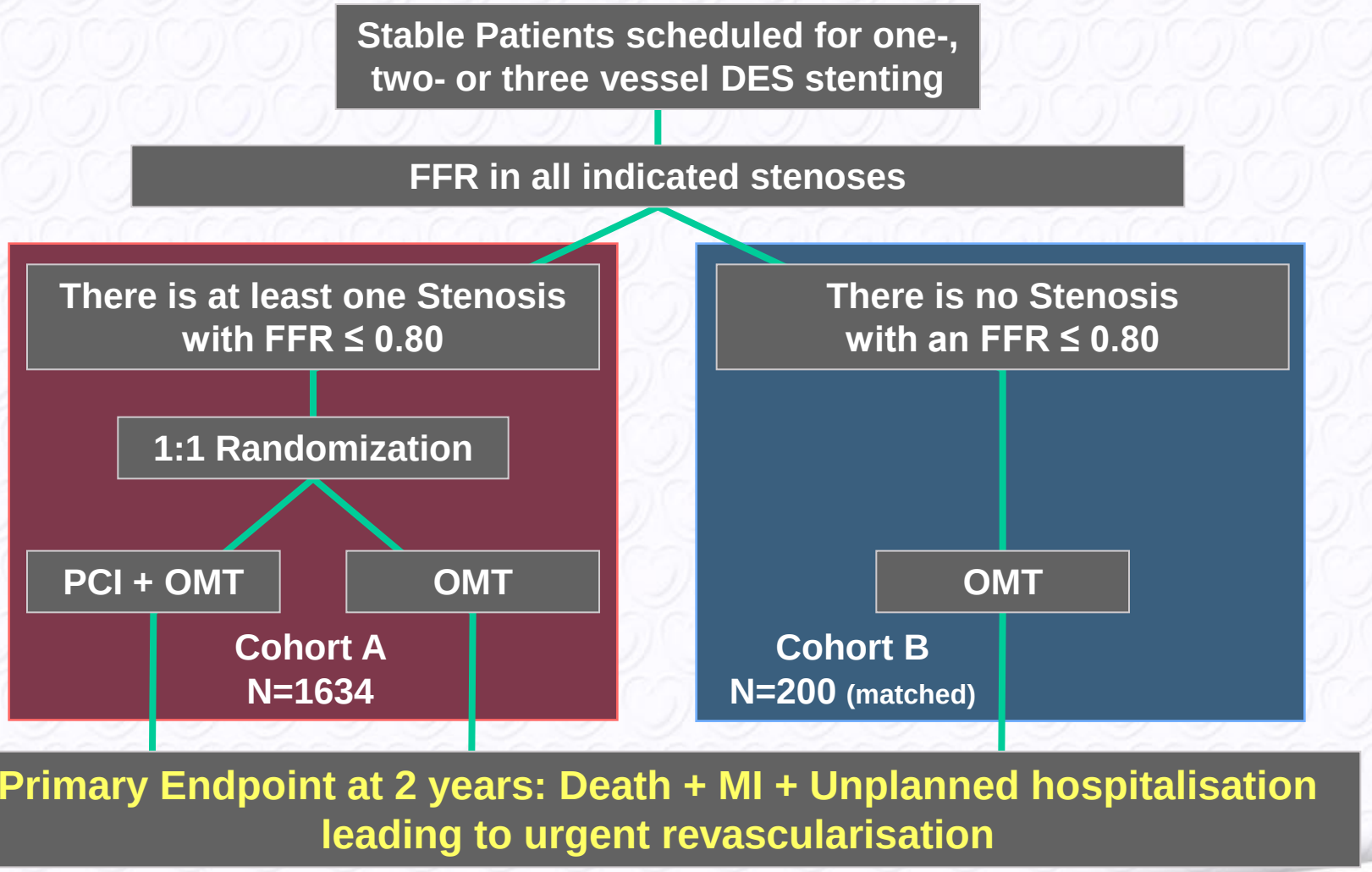
DEFER, SYNTAX, COURAGE and FAME's

What is your conclusion from …

- COURAGE
- **FAME 2**

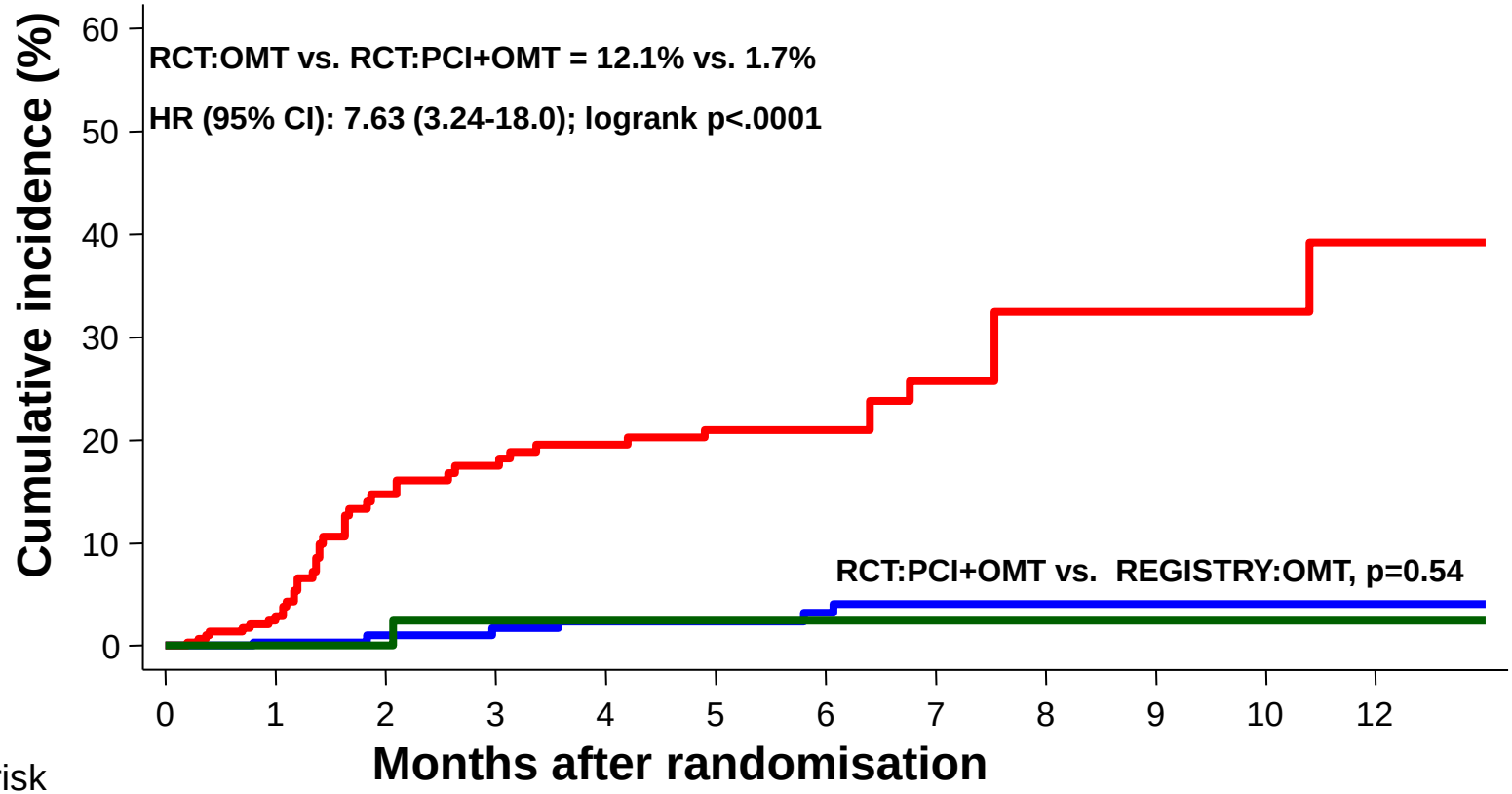
How does this trial influence your practice …

Study design of FAME II randomised clinical trial



Follow-up after 1, 6 months, 1, 2, 3, 4 and 5 years

Rate of Any Revascularisation



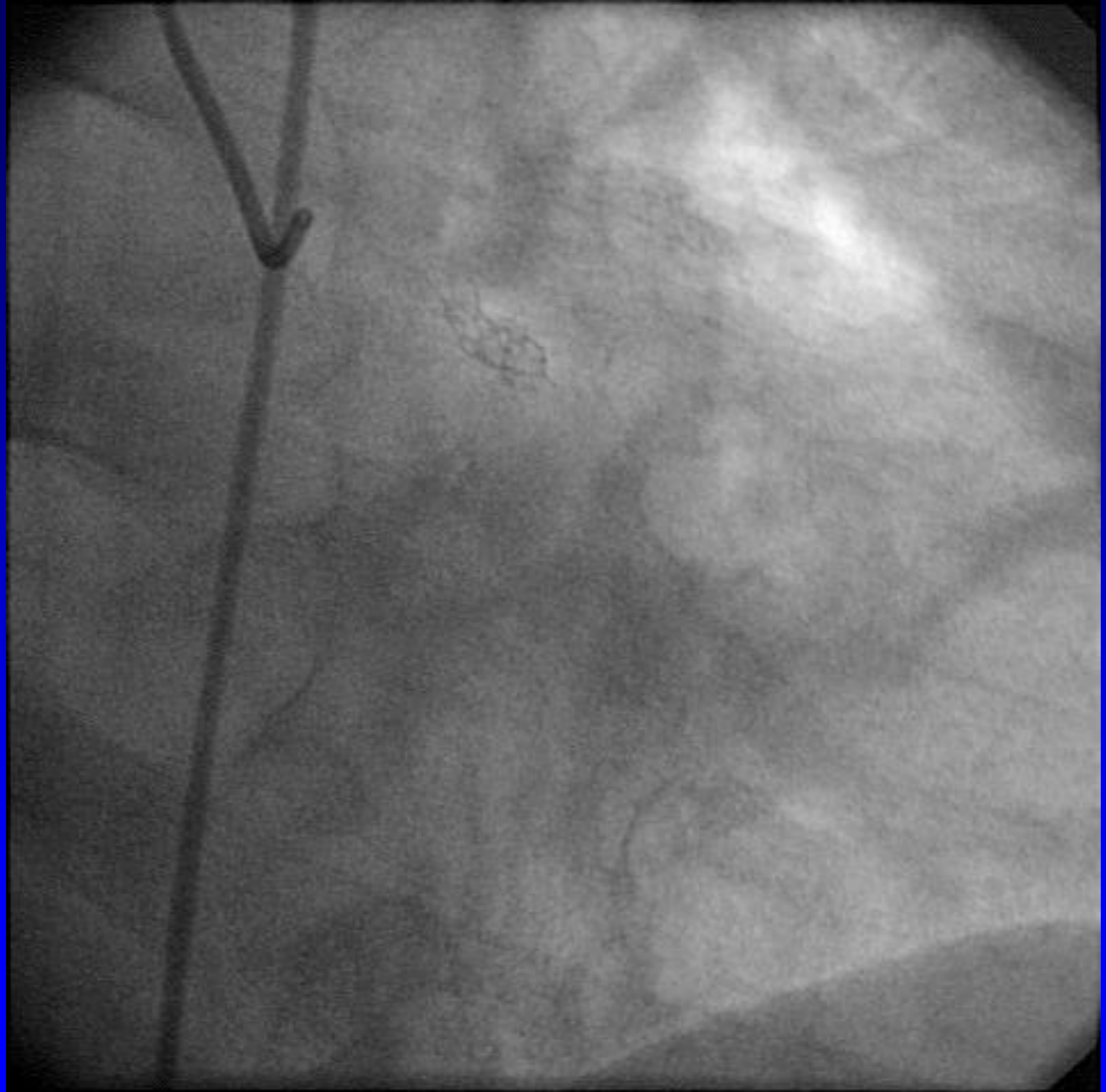
No. at risk												
RCT:OMT only	339	238	123	119	115	112	83	20	10	10	10	8
RCT:PCI+OMT	352	256	144	141	140	139	114	25	18	18	18	18
REGISTRY:OMT only	131	88	41	40	40	40	35	4	1	1	1	1

Coronary Physiology in the Cathlab

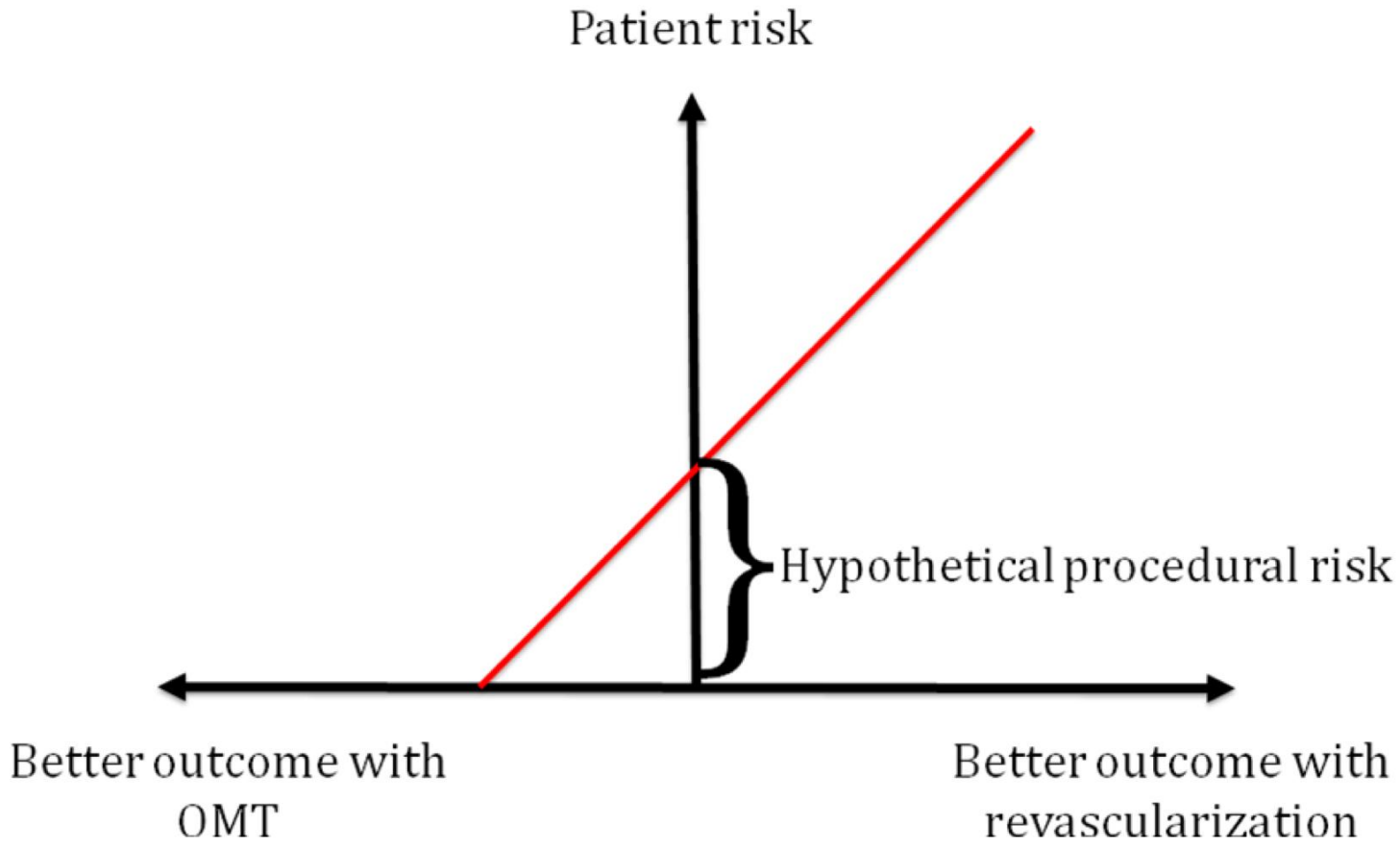
DEFER, SYNTAX, COURAGE and FAME's

Let's attempt a Synthesis

W. Wijns, Aalst (B)



Benefit of revascularization for stable ischaemic heart disease: the jury is still out



A-A Fassa et al. Eur H J 2013; ahead of print

Evidence basis for PCI vs. OMT

Evidence for benefit

If moderate / large ischemia

1997: ACIP trial

2003: Nuclear imaging studies

2008: Nuclear substudy COURAGE

2009: Substudy of BARI 2 D

2012: FAME 2 randomised trial

Evidence for lack of benefit

in the absence of ischemia

1998: Nuclear imaging studies

2005: Besançon randomised trial*

2007: Defer randomised trial

2010: FAME 1 randomised trial

*Legalery, EHJ 26:2623

Revascularisation versus Medical Therapy after Stress SPECT: Survival Analysis

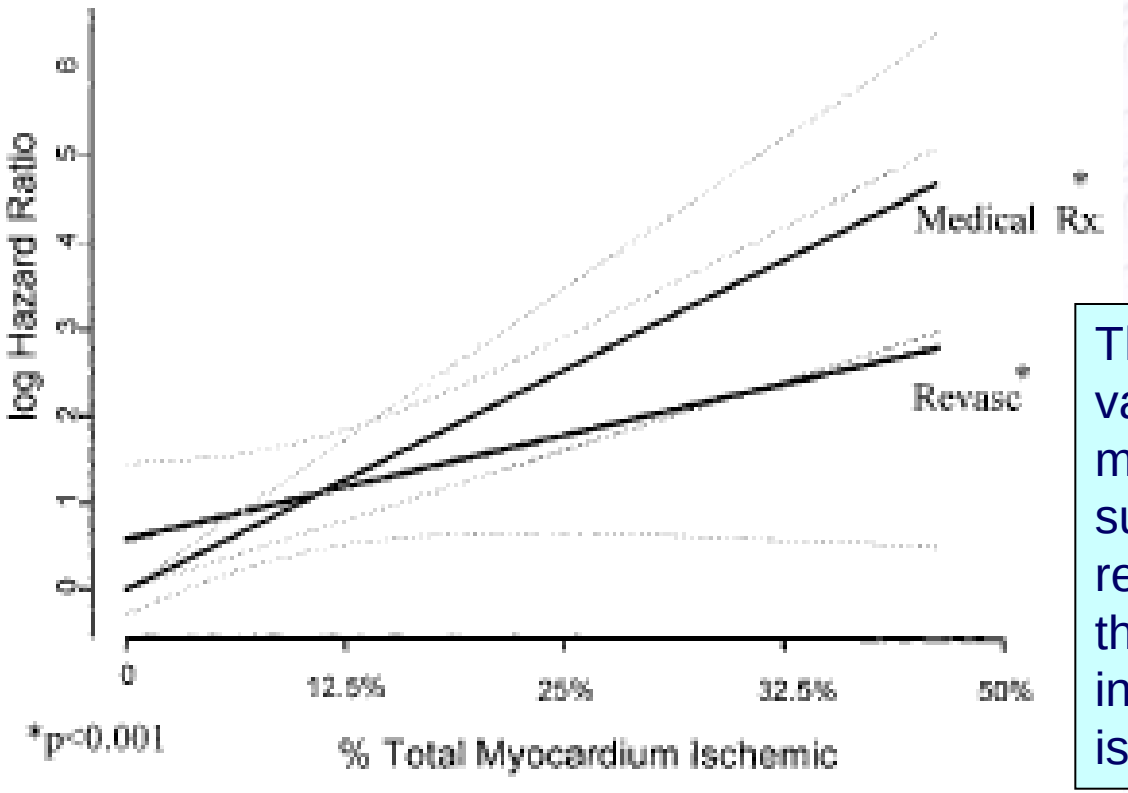


Figure 4. Log hazard ratio for revascularization (Revasc) vs medical therapy (Medical Rx) as a function of % myocardium ischemic based on final Cox proportional hazards model. Model, $P<0.0001$; interaction, $P=0.0305$.

These two lines intersect at a value of ~ 10% of ischaemic myocardium, above which the survival benefit for revascularization over medical therapy increases as a function of increasing amounts of inducible ischemia.

Hachamovitch et al. Circulation 2003;107:2900-6.

Indications for revascularisation in stable angina or silent ischaemia

	Subset of CAD by anatomy	Class	Level
For symptoms	Any stenosis > 50% with limiting angina or angina equivalent, unresponsive to OMT	I	A
	Dyspnoea/CHF and > 10% LV ischaema/viability supplied by > 50% stenotic artery	IIa	B
	No limit symptoms with OMT	III	C

	Subset of CAD by anatomy	Class	Level
For prognosis	Left main > 50%*	I	A
	Any proximal LAD > 50%*	I	A
	2VD or 3VD with impaired LV function*	I	B
	Proven large area of ischaemia (> 10% LV)	I	B
	Single remaining patent vessel > 50% stenosis*	I	C
	1VD without proximal LAD and without > 10% ischaemia	III	A

* With documented ischaemia or Fractional Flow Reserve (FFR) < 0.80 for % diameter stenosis by angiography between 50 and 90 %

Practical decision tree for the Management of patients with stable CAD

Two steps approach

1. **Is there an indication for revascularisation on top of OMT? For symptomatic and/or prognostic reasons?**

2. **If so, which is more appropriate: CABG or PCI?**

DEFER, SYNTAX, COURAGE and FAME's

Watch for …

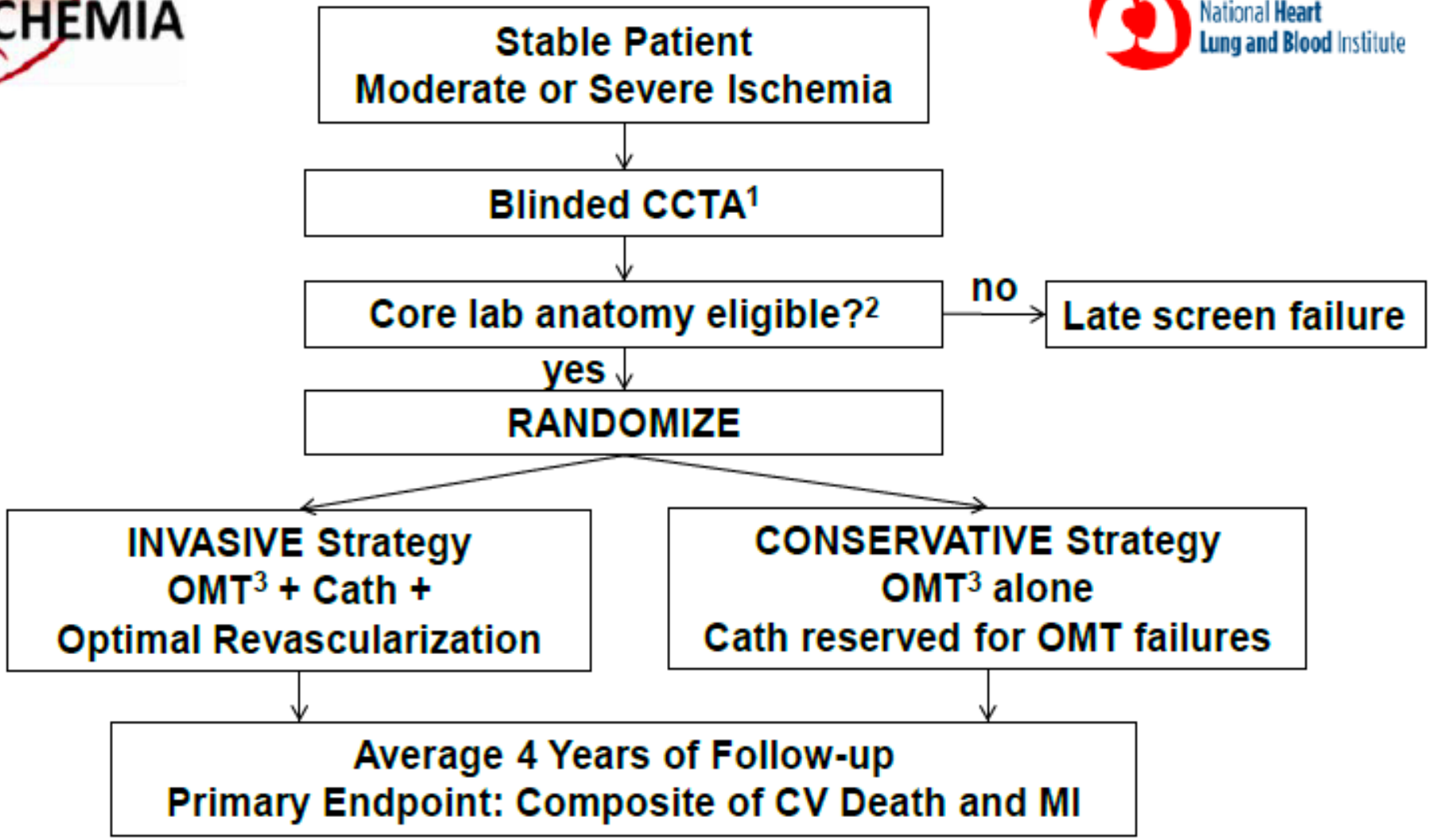
New ESC Guidelines on Stable Angina (september 2013)

Upcoming ESC Guidelines on Myocardial Revascularization (2014)

Ongoing ISCHEMIA trial

ISCHEMIA

National Heart Lung and Blood Institute



[1]CCTA will be performed in all patients with eGFR ≥60 mL/min
[2]Exclude patients with LM disease or no obstructive disease
[3]OMT=Optimal medical therapy

DEFER, SYNTAX, COURAGE and FAME's

- Angiographic guidance to revascularization results in inappropriate intervention in ~50% of cases
- Revascularization will only improve prognosis in patients with significant risk (ischemic burden)
- Indications for OMT or OMT + revascularization should be based on combined anatomic and functional evaluation
- Diagnostic value of FFR has reached the highest level of evidence (class I A recommendation) but remains poorly adopted

Disclosures for William Wijns
Cardiovascular Center Aalst, Belgium

Consulting Fees: on my behalf go to the Cardiovascular Research Center Aalst

Contracted Research between the Cardiovascular Research Center Aalst and several pharmaceutical and device companies, incl. St Jude and Volcano

Ownership Interest: Cardio³BioSciences, biotechnology start-up on regenerative medicine

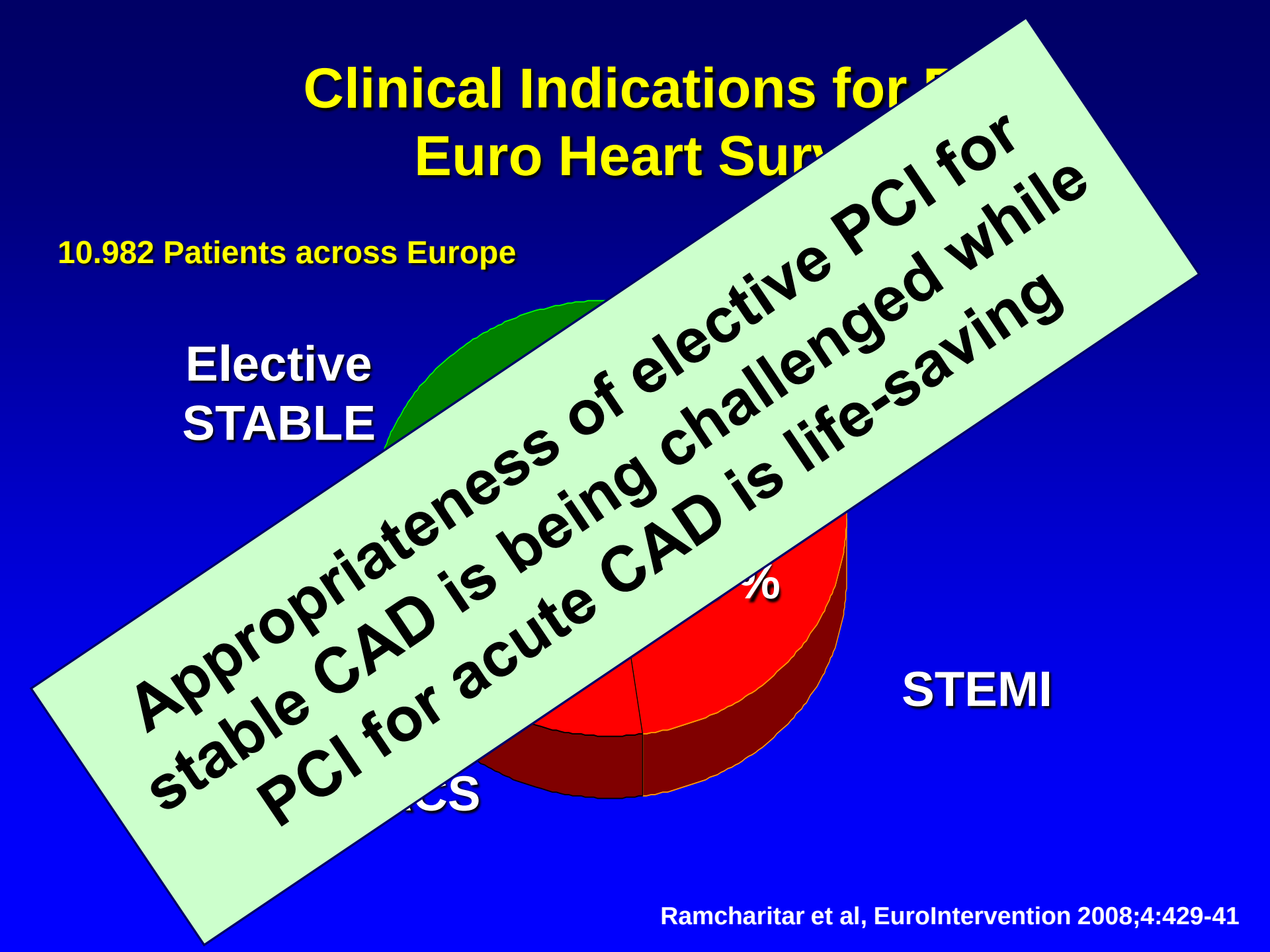
Chairman of PCR, Co-Chairman of EuroPCR and Africa PCR

DEFER, SYNTAX, COURAGE and FAME's and . . .

	N	cost
▸ DEFER	325	
▸ FAME 1	1.005	
▸ SYNTAX	1.800	100K+
▸ COURAGE	2.287	?
▸ FAME 2	691	
▸ ISCHEMIA	8.800	90K+

Clinical Indications for P
Euro Heart Surv

10.982 Patients across Europe

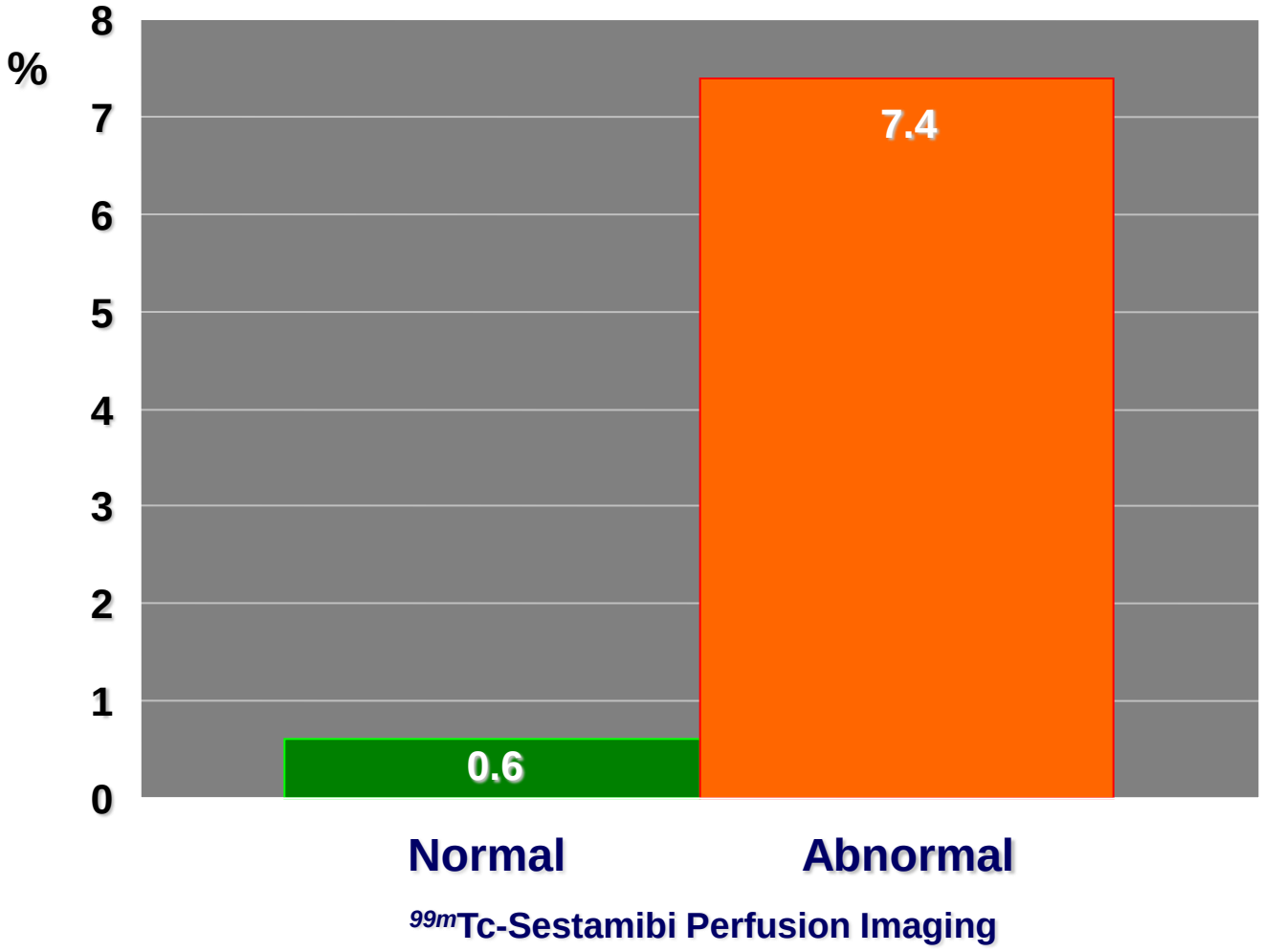


Appropriateness of elective PCI for stable CAD is being challenged while PCI for acute CAD is life-saving

Ramcharitar et al, EuroIntervention 2008;4:429-41

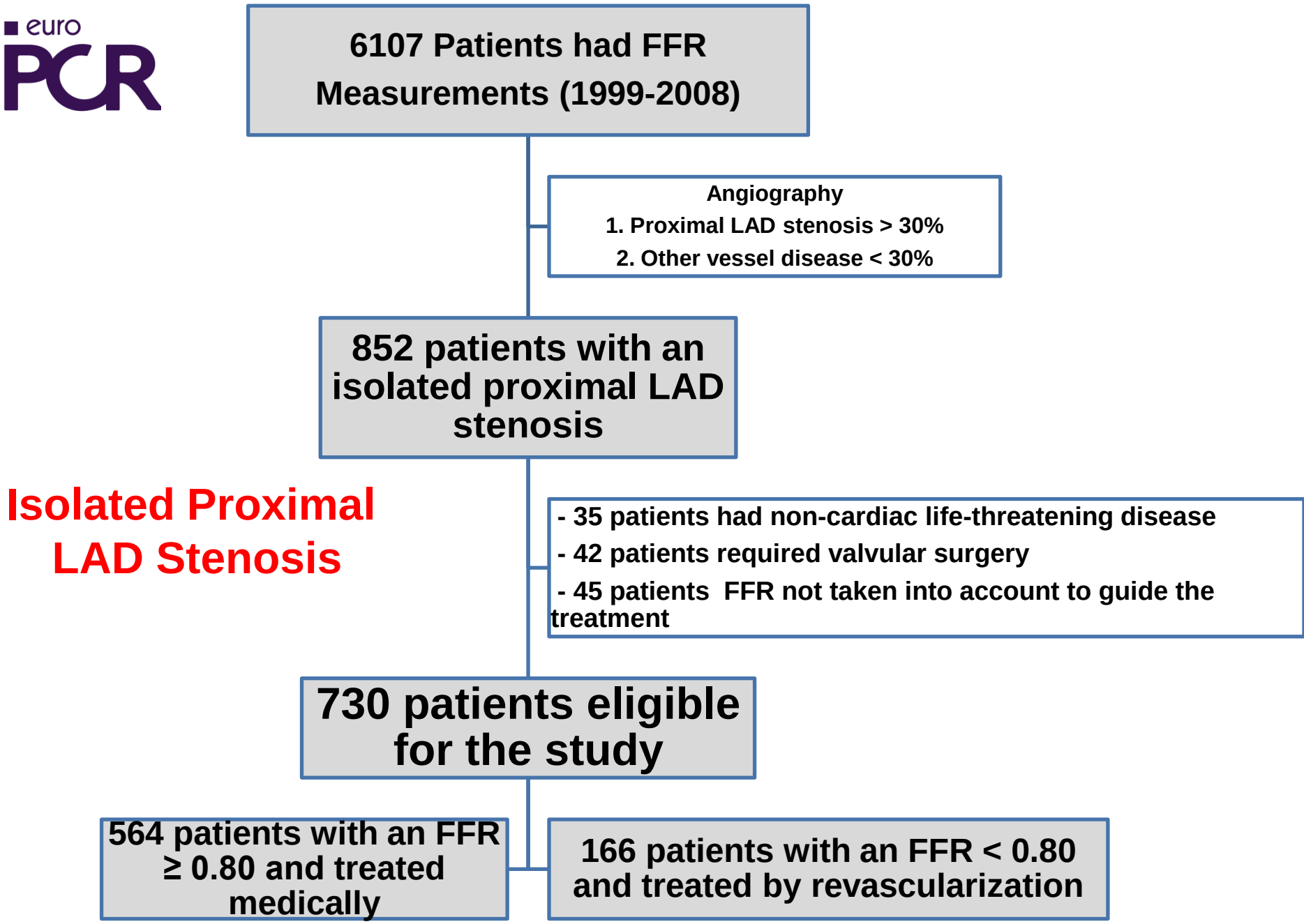
Prognostic Value of Stress 99mTc-sestamibi Perfusion Imaging

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

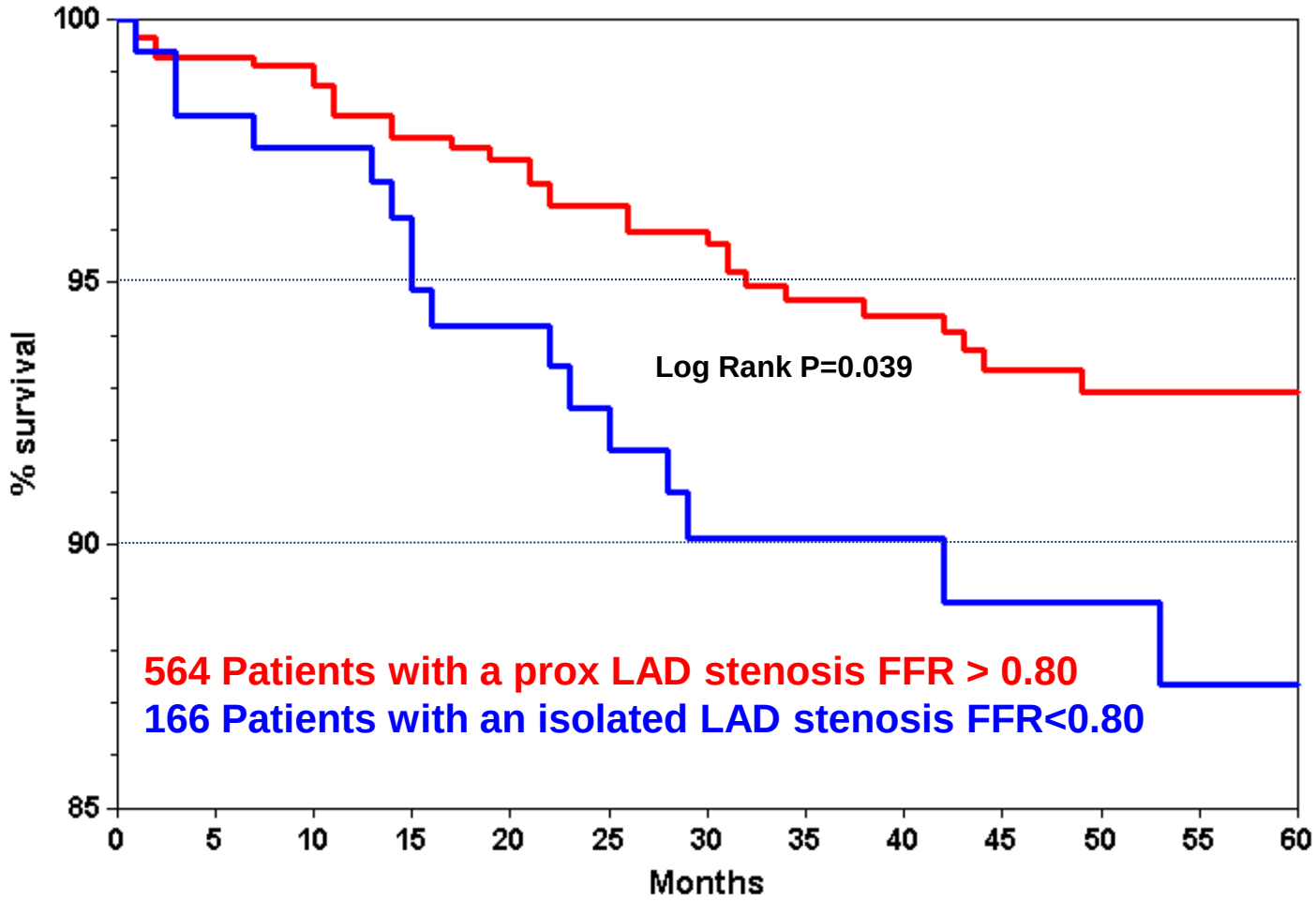


^{99m}Tc-Sestamibi Perfusion Imaging

Iskander S, Iskandrian A E JACC 1998


6107 Patients had FFR Measurements (1999-2008)
Angiography
1. Proximal LAD stenosis > 30%
2. Other vessel disease < 30%
852 patients with an isolated proximal LAD stenosis
Isolated Proximal LAD Stenosis
- 35 patients had non-cardiac life-threatening disease
- 42 patients required valvular surgery
- 45 patients FFR not taken into account to guide the treatment
730 patients eligible for the study
564 patients with an FFR ≥ 0.80 and treated medically
166 patients with an FFR < 0.80 and treated by revascularization

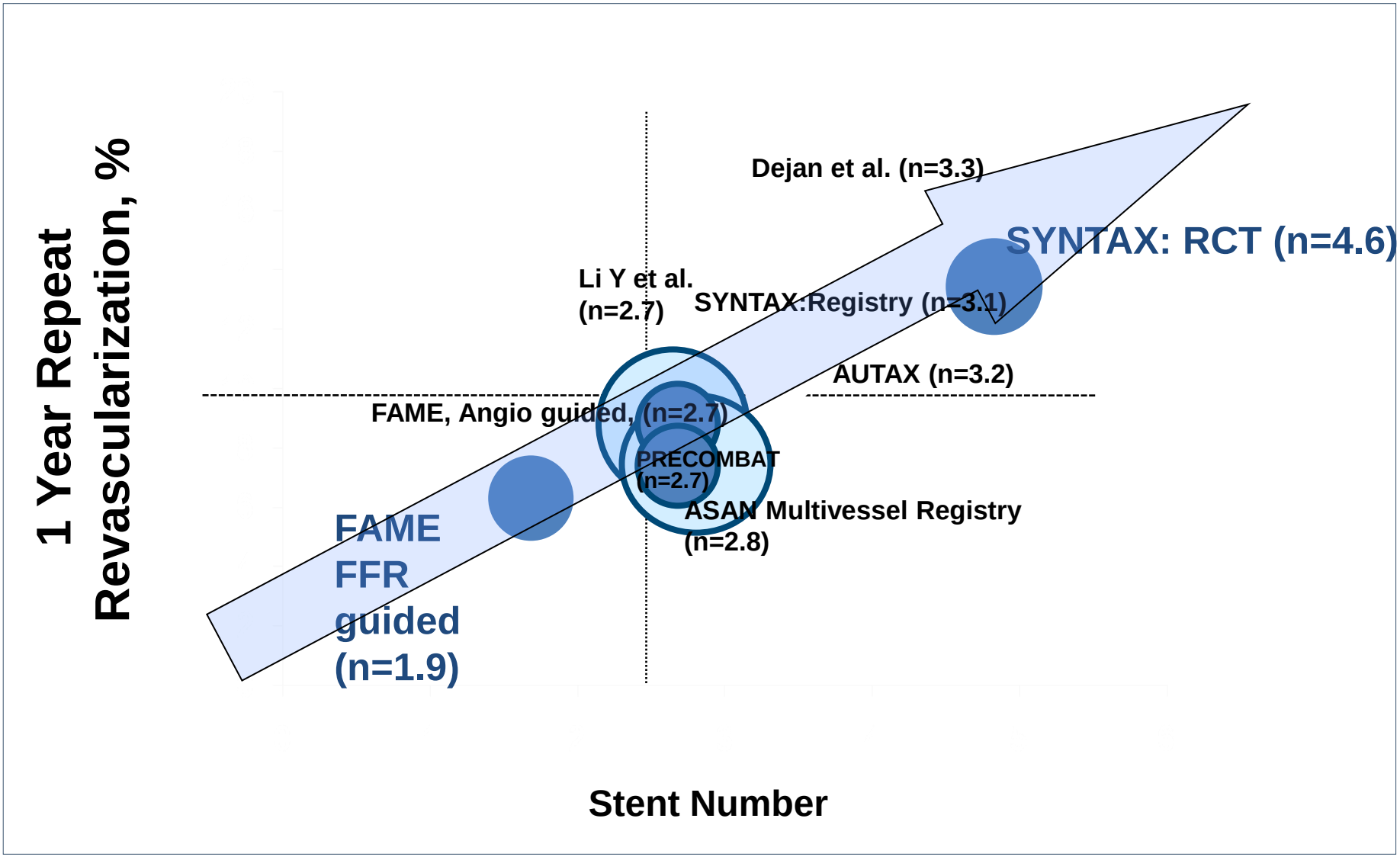
Proximal LAD Stenoses



O. Muller et al. JACC CV Interv 2010

Is More Stents More Care ?

in Left Main & Multivessel Stenting



What is the Next ?

Suggested Randomized Study, **FAME III**

Stable Patients with
Positive FFR (<0.80), 2-3 Vessel Disease

R

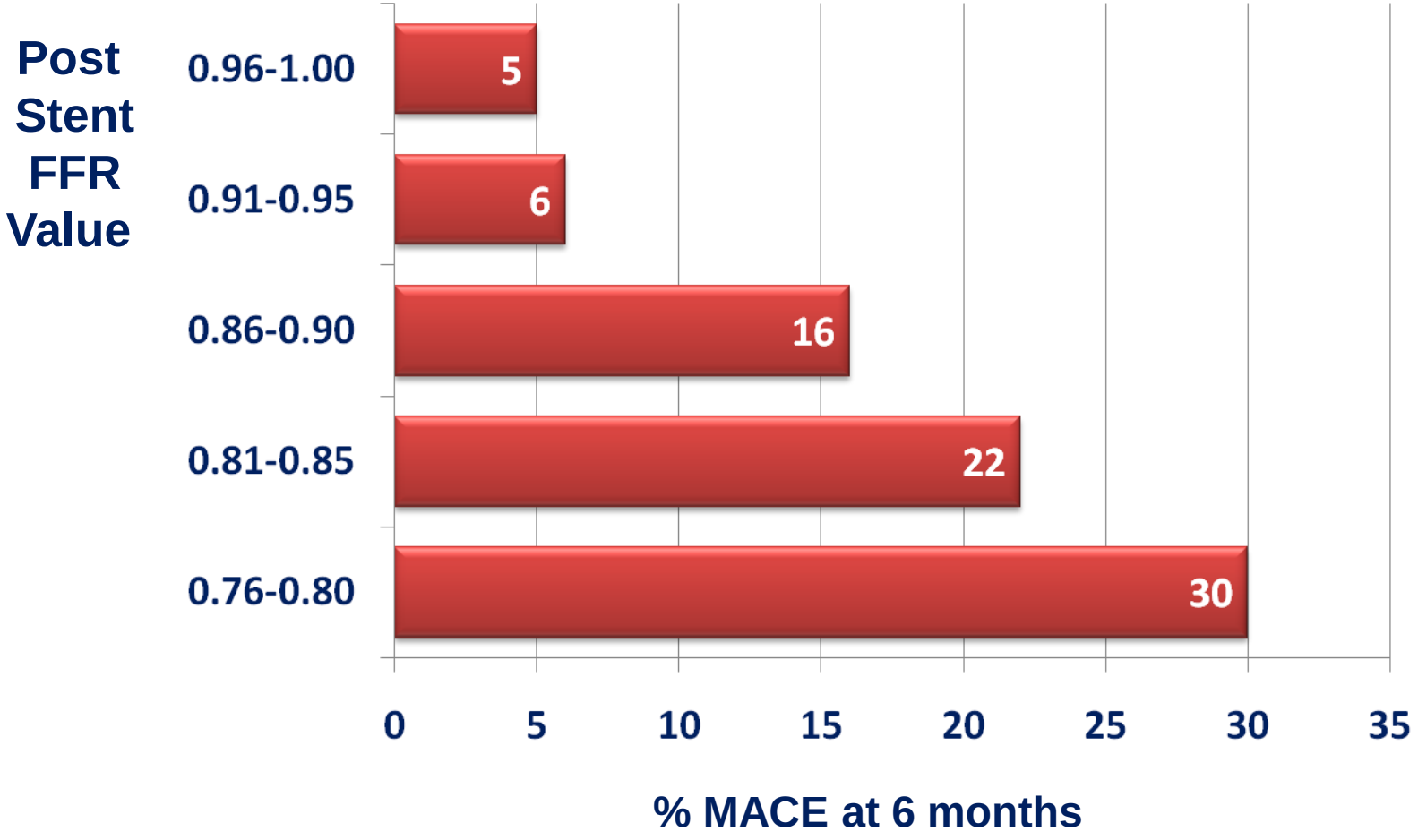
PCI + OMT

CABG

Primary Endpoint at 2 years:
Death + MI + Stroke

Does post-PCI FFR value predict outcome?

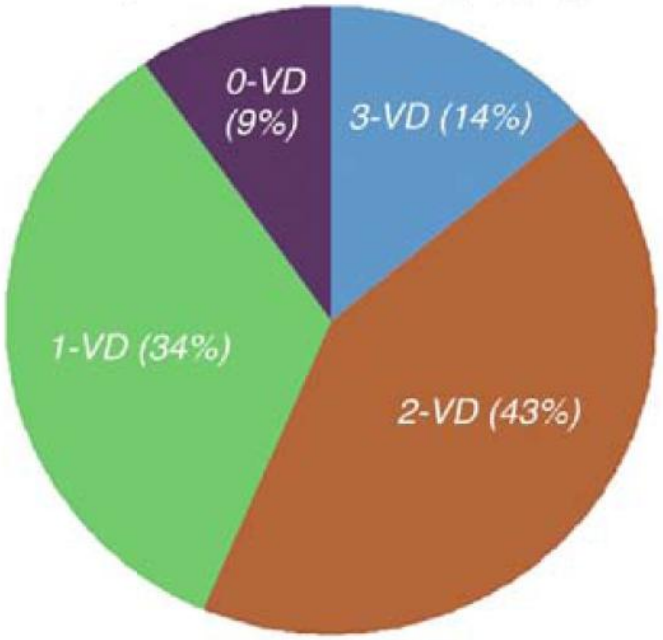
FFR Post Stent Registry: 750 patients post BMS



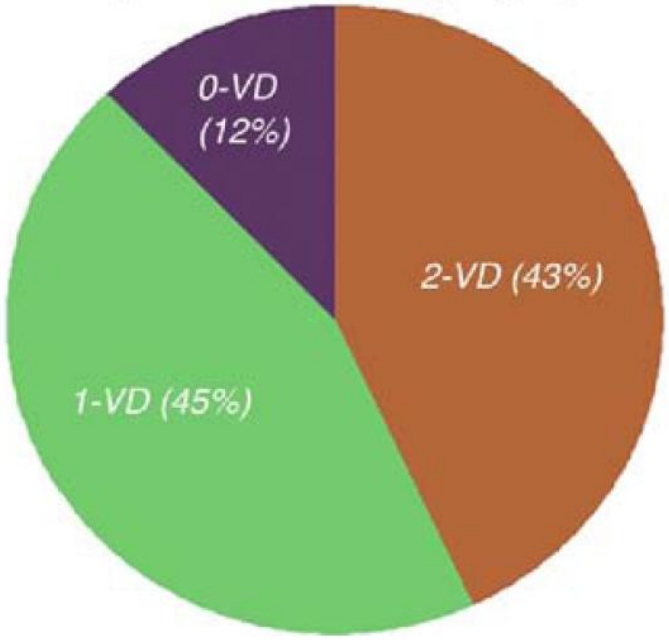
Pijls N.H.J. et al. , Circulation 2002

Proportion of Functionally Significant Stenoses in Patients with 3- or 2- Vessel Disease by Angiography

Angiographic 3-VD



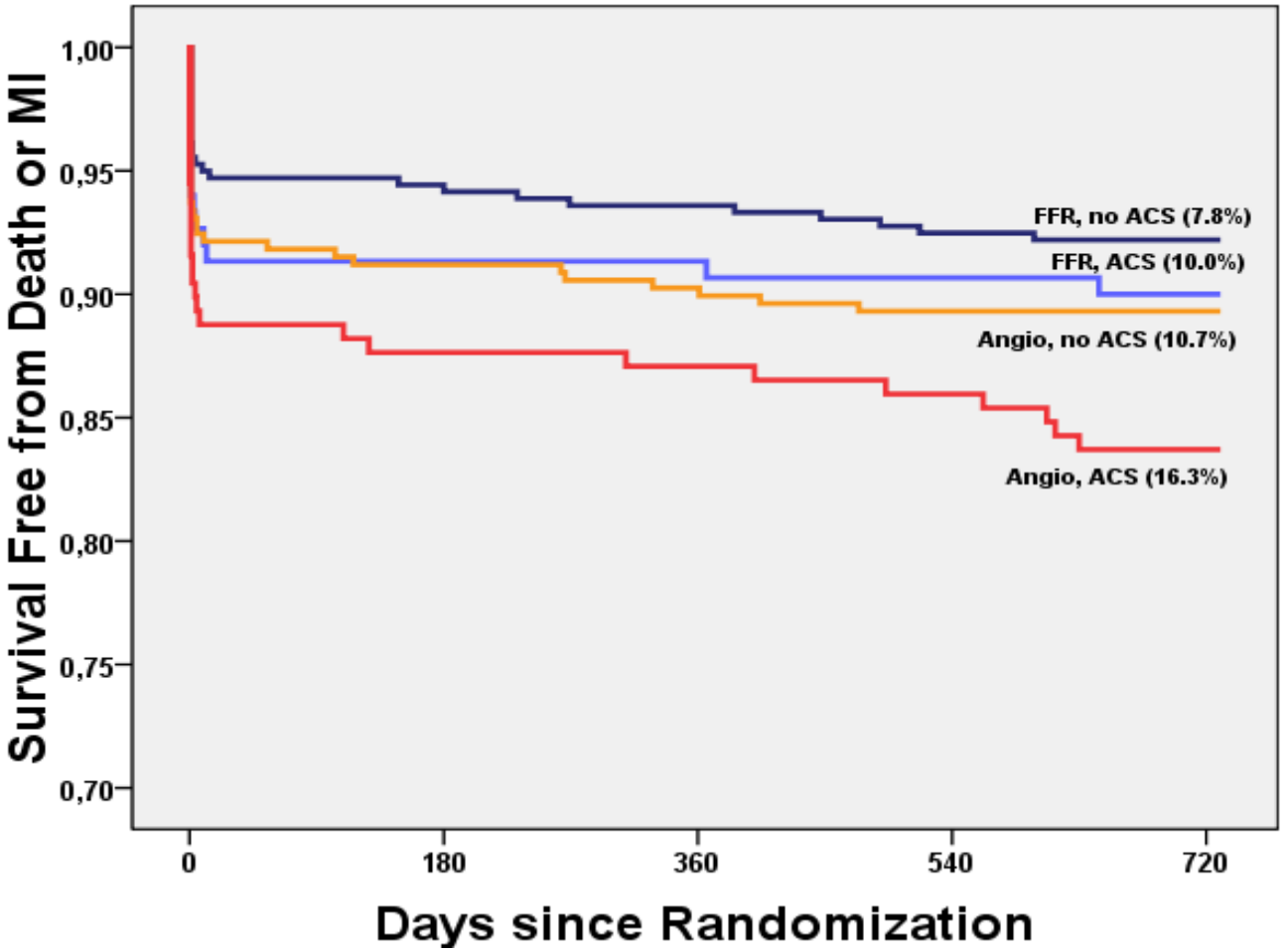
Angiographic 2-VD



Tonino P et al. *JACC* 2010

FFR NSTE ACS (Culprit + Non Culprit Vessel)

Comparison of MACE in FAME patients with and without ACS



Tonino et al, J Am Coll Cardiol 2011 (submitted)

Evidence basis for myocardial revascularisation vs. Optimal Medical Therapy

- Several meta-analyses since 2000

2000	Bucher
2004	Brener
2005	Hannan
2005	Katritsis
2008	Hannan
2008	Schomig
2009	Hlatky
2009	Trikalinos
2009	Jeremias

- Survival benefit from CABG vs OMT only

  HR 0.62 (0.50 – 0.77)

- Survival benefit from PCI vs OMT only

  HR 0.82 (0.68 – 0.99)

Jeremias. Am J Med. 2009;122:152-61.