

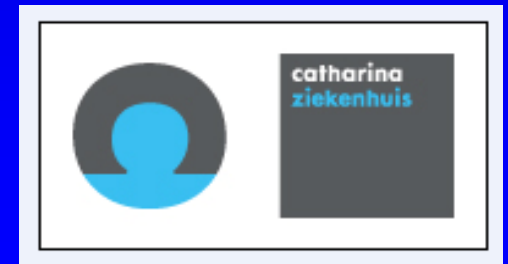
# *Imaging & Physiology Summit*

**FFR & LONG-TERM OUTCOME:  
15 year DEFER, 5 year FAME, and 5 year LAD's**

*Seoul, Korea, december 3rd, 2015*



Nico H. J. Pijls, MD, PhD  
Catharina Hospital,  
Eindhoven, The Netherlands



Speaker's name: NICO H J PIJLS

I have the following potential conflicts of interest to report:

- Research contracts : **grant support from St Jude Medical**
- Consulting: **St Jude Medical, Boston Sc, Opsens**
- Employment in industry
- Stockholder of a healthcare company: **Heartflow, Philips, ASML**
- Owner of a healthcare company
- Other(s)

*From a patient's point of view , the wind tunnel  
for any index to be used in clinical medicine,  
is its **influence on outcome***

## FFR and Clinical Outcome:

### 3 important questions:

- Is it safe to defer PCI if FFR is negative ?
- Is it indicated to perform PCI if FFR is positive ?
- Does systematic use of FFR improve outcome of PCI ?

# ***DEFER study***

## **Primary objective**

***To test safety of deferring PCI of non-ischemic stenosis as indicated by  $FFR \geq 0.75$***

*First randomized controlled trial using FFR with longest follow-up ever (17 years)*

# ***DEFER study: endpoints***

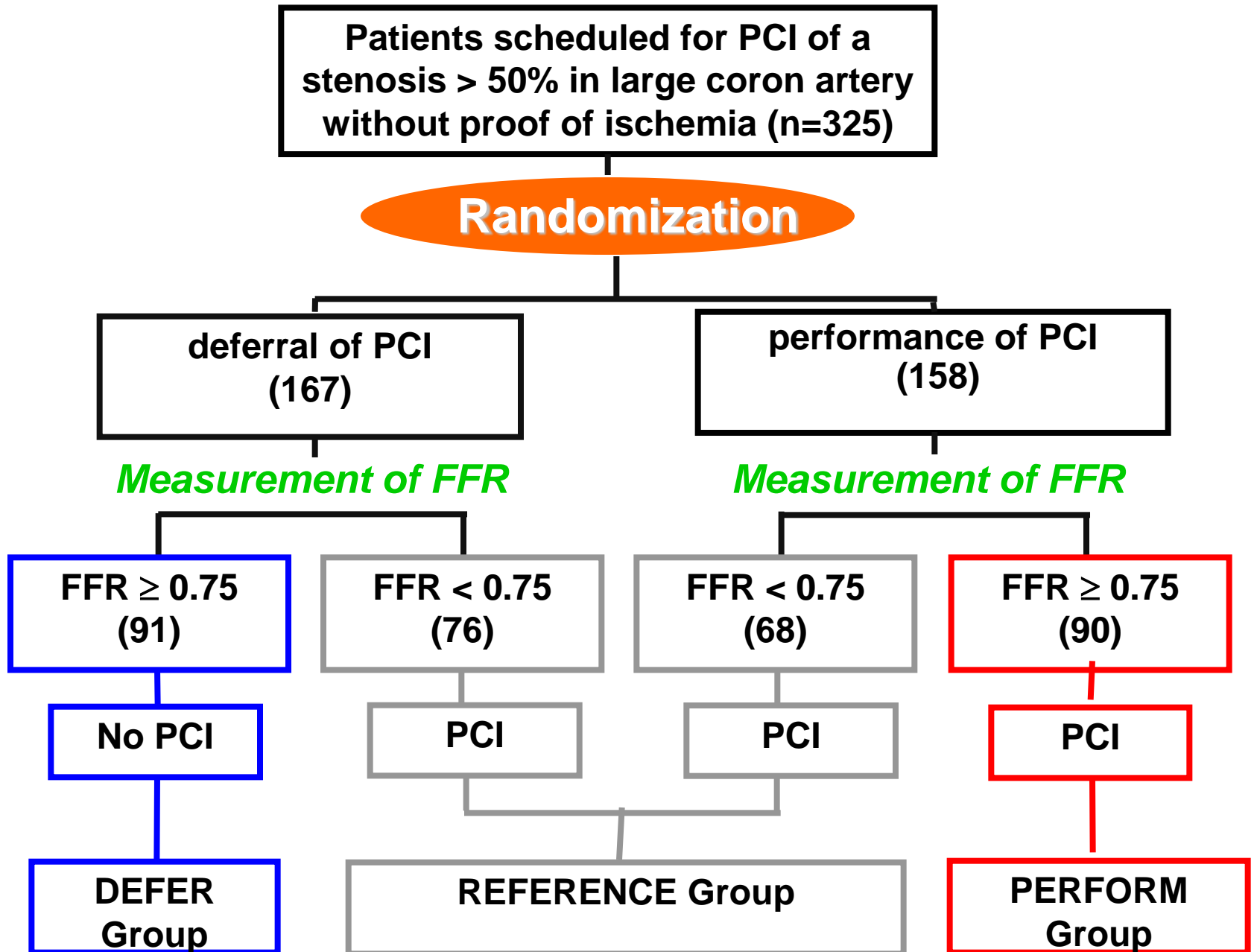
**Primary endpoint:** - MACE at 2 years

**Secondary endpoints:**

- MACE at 5 years
- individual components of MACE at 2 and 5 years
- functional class at 2 and 5 years

***15-year follow-up was not a pre-defined endpoint***

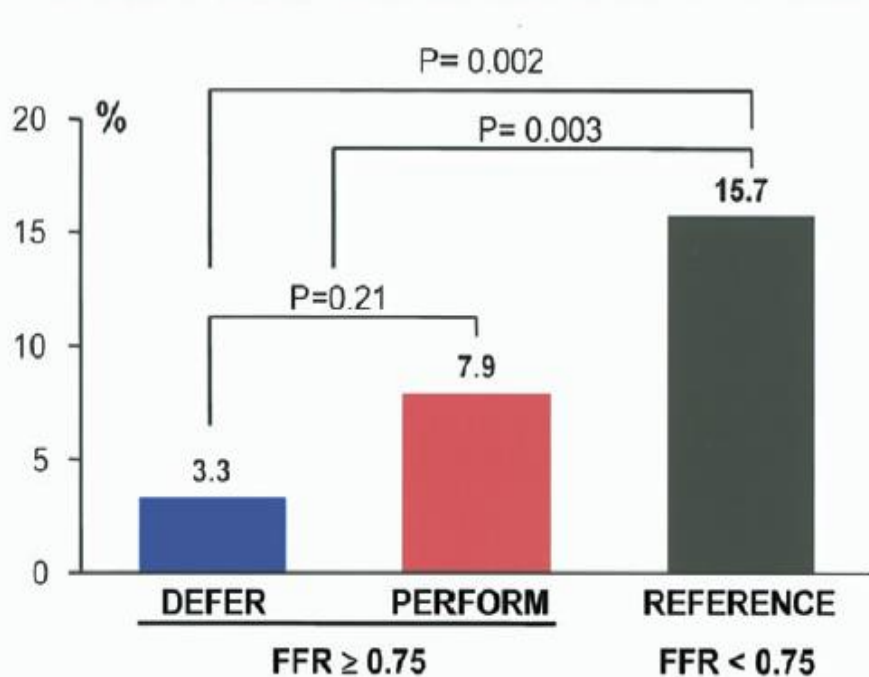
# The *DEFER* Study: Flow Chart



# 5-year follow-up

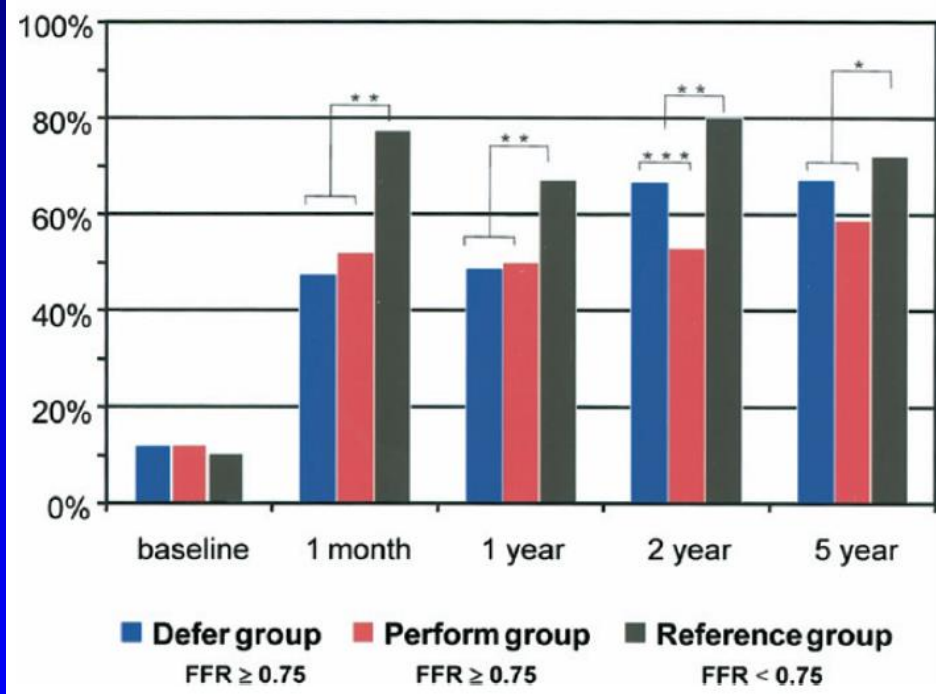
## Outcome

### Cardiac Death and Acute MI after 5 Years



## Symptoms

### % Patients Free from Chest Pain





# ***15-year follow-up***

## ***Follow-up was achieved as follows:***

- Complete follow-up in **92%** of all patients
- Follow-up with respect to mortality in **97%** of all patients
  
- Median follow-up of **16.8** years  
(interquartile range 15.3 -17.3 years)

## Results 15-year follow-up

### All cumulative events

	Any death	Any MI	Any revascularization
Defer	30	2	60
Perform	28	13	53
Reference	52	19	86

Comparison between Defer and Perform:
   
 - Any death: NS (30 vs 28)
   
 - Any MI: \* (2 vs 13)
   
 - Any revascularization: NS (60 vs 53)

\* p < 0.02

# MORTALITY

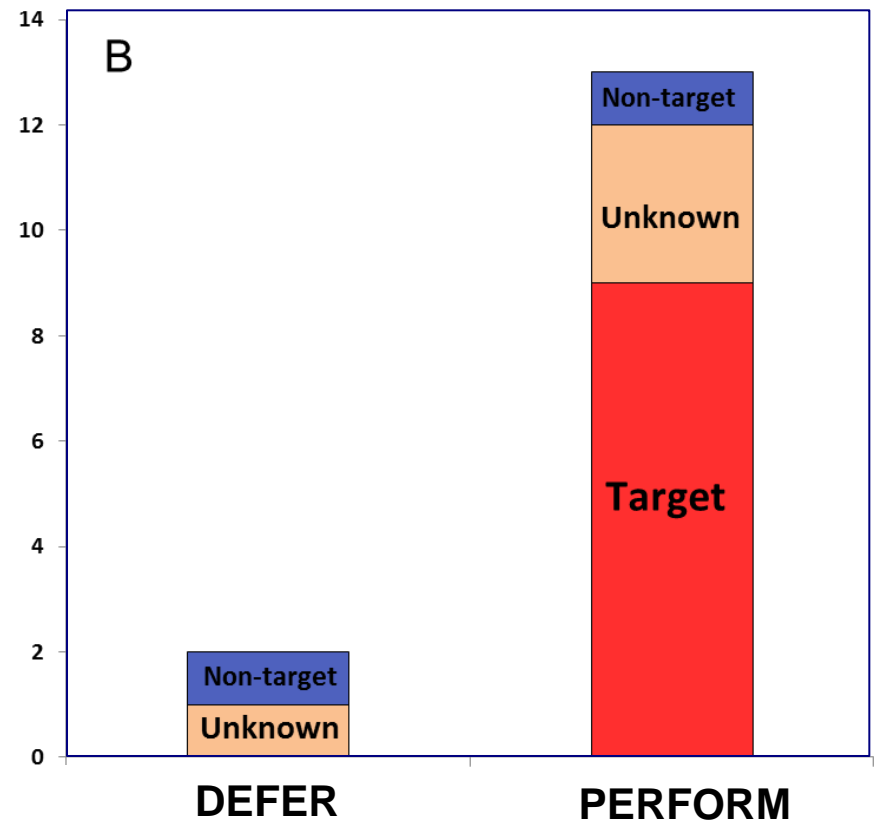
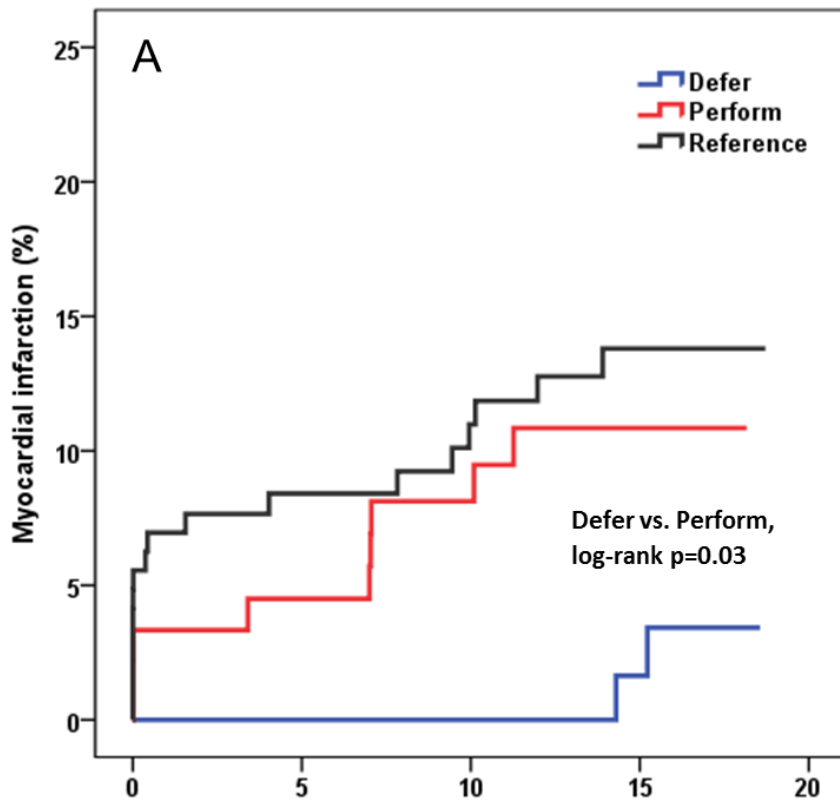
	Cardiac	Unknown	Non-cardiac	Total
<b>Defer</b>	5 (5%)	13 (14%)	12 (13%)	30 (33%)
<b>Perform</b>	4 (4%)	11 (12%)	13 (14%)	28 (31%)
<b>Reference</b>	15 (10%)	10 (7%)	27 (19%)	52 (36%)

• ***No statistical differences between groups***

• ***Mortality mainly related to advanced age (79 y at last follow-up)\****

\* In a completely healthy cohort of Dutch patients aged 62 years, expected mortality at 17 years of follow-up, is 28 %

# Myocardial infarction



- **Significant higher infarct rate in perform group ( $p < 0.03$ )**
- **Most infarctions related to target vessel**

# SUMMARY OF DEFER STUDY

**Deferral vs Performance of PCI in non-ischemic stenosis**  
(based upon FFR > 0,75) **gives the following very long term (> 15 years) outcome:**

- **Mortality:**  
no difference in mortality
- **Myocardial Infarction:**  
significant advantage in favour of Defer Group
- **Repeated PCI/CABG:**  
no differences

# Is it safe to defer PCI if FFR is negative ? → YES !!!

*Risk for death or MI related to functionally non-significant stenosis:*

- **FAME study** : 0.4 % per year (f.u. of 2 years; *NEJM 2009*)

*Also with other modalities of investigation, outcome of non-significant lesions is excellent:*

- **CCTA studies**: 0.7 % per year (*Min, JACC 2011*)
- **Prospect study**: 0.4 % per year (*Stone, NEJM 2011*)

# FUNCTIONALLY **NON-SIGNIFICANT** STENOSIS

→ **Stenting a functionally non-significant (FFR-negative) stenosis does NOT make any sense.**

*It is unnecessary, expensive, and increases the risk of death and MI without any symptomatic benefit*

# FUNCTIONALLY **SIGNIFICANT** STENOSIS

*IF ischemia is present, does (FFR guided) PCI improve outcome ?*

→ **FAME STUDIES**

Tonino et al: New Engl J Med 2009.

Pijls et al: JACC 2011

De Bruyne et al: New Engl J Med 2012 & 2014

Van Nunen et al: The Lancet, 2015 (today)





# ***FAME study: HYPOTHESIS***



***FFR - guided Percutaneous Coronary Intervention (PCI) in multivessel disease, is superior to angiography - guided PCI***

**FAME 1 study; N= 1006  
5 - year follow up presented today  
and published in Lancet today  
(van Nunen L, Zimmermann F, Tonino P, et al)**



# FLOW CHART

(N = 1006)

Patient with stenoses  $\geq 50\%$   
in at least 2 of the 3 major  
epicardial vessels

Indicate all stenoses  $\geq 50\%$   
considered for stenting

Randomization

Angiography-guided PCI

FFR-guided PCI

Stent all indicated  
stenoses

Measure FFR in all  
indicated stenoses

Stent only those  
stenoses with  $FFR \leq 0.80$

1, 2, 5-year follow-up

# *FAME study: **ENDPOINTS (1)***



## **PRIMARY ENDPOINT**

*Composite of death, myocardial infarction,  
or repeat revascularization (“MACE”)  
at 1 year*

## **SECONDARY ENDPOINTS**

*“MACE” and its individual components at  
2 years and at 5 years*

# FAME study: *Baseline Characteristics (2)*



	ANGIO-group N=496	FFR-group N=509	P-value
<b># indicated lesions per patient</b>	<b>2.7±0.9</b>	<b>2.8±1.0</b>	0.34
50-70% narrowing, No (%)	550 (41)	624 (44)	-
70-90% narrowing, No (%)	553 (41)	530 (37)	-
90-99% narrowing, No (%)	207 (15)	202(14)	-
Total occlusion, No (%)	40 (3)	58 (4)	-
Patients with ≥1 total occlusion (%)	7.5	10.6	0.08
Patients with prox LAD involved, No (%)	186 (38)	210 (41)	0.39
% lesions in segment 1,2,3,6,7,or11	960 (71)	1032 (73)	0.42



# FAME study: Procedural Results (1)

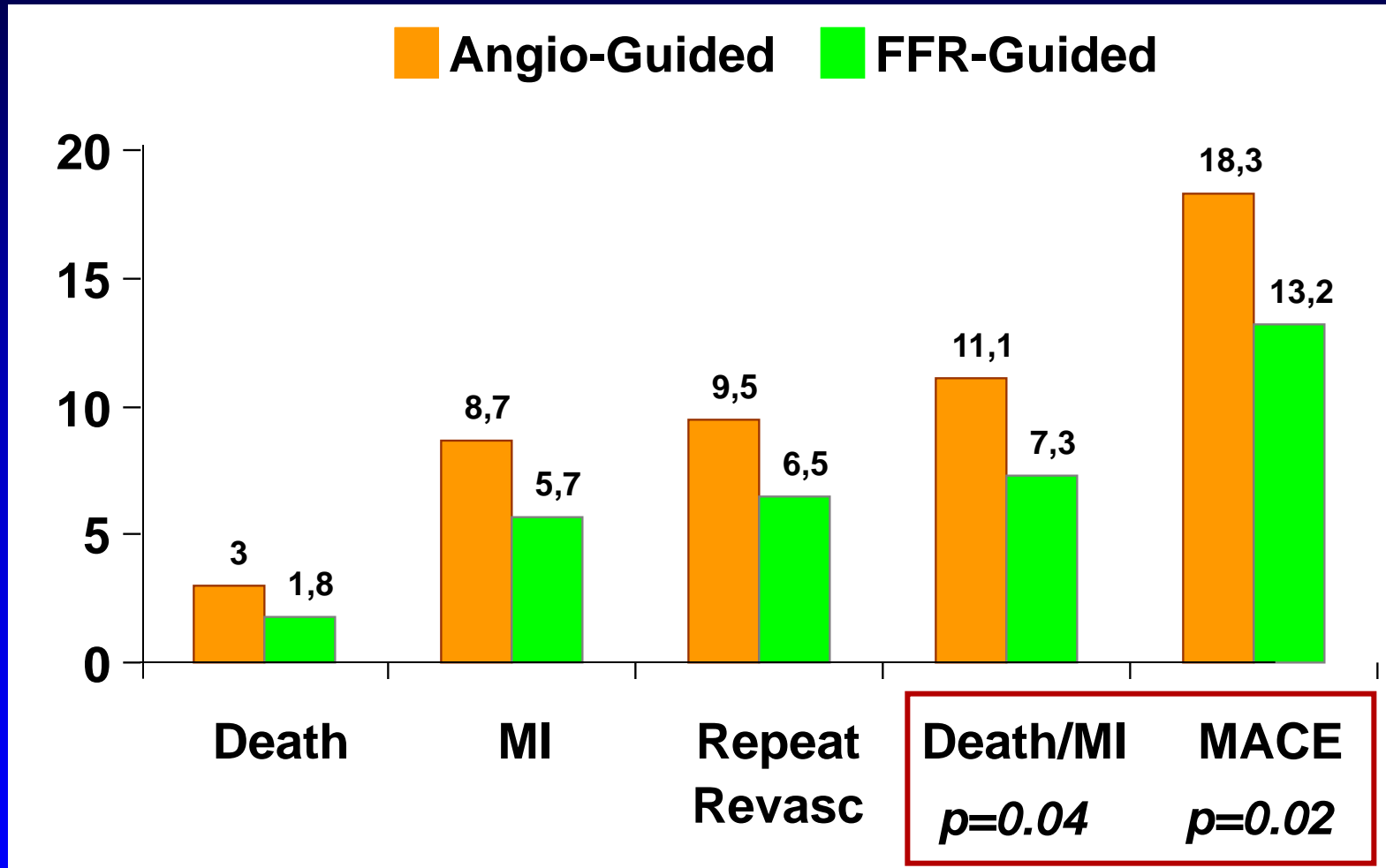
	ANGIO-group N=496	FFR-group N=509	P-value
<b># indicated lesions per patient</b>	<b>2.7 ± 0.9</b>	<b>2.8 ± 1.0</b>	<b>0.34</b>
<b>FFR results</b>			
Lesions successfully measured, No (%)	-	<b>1329 (98%)</b>	-
Lesions with FFR ≤ 0.80 ,No (%)	-	<b>874 (63%)</b>	-
Lesions with FFR > 0.80 ,No (%)	-	<b>513 (37%)</b>	-
<b>Stents per patient</b>	<b>2.7 ± 1.2</b>	<b>1.9 ± 1.3</b>	<b>&lt;0.001</b>
Lesions successfully stented (%)	<b>92%</b>	<b>94%</b>	-
DES, total, No	<b>1359</b>	<b>980</b>	-



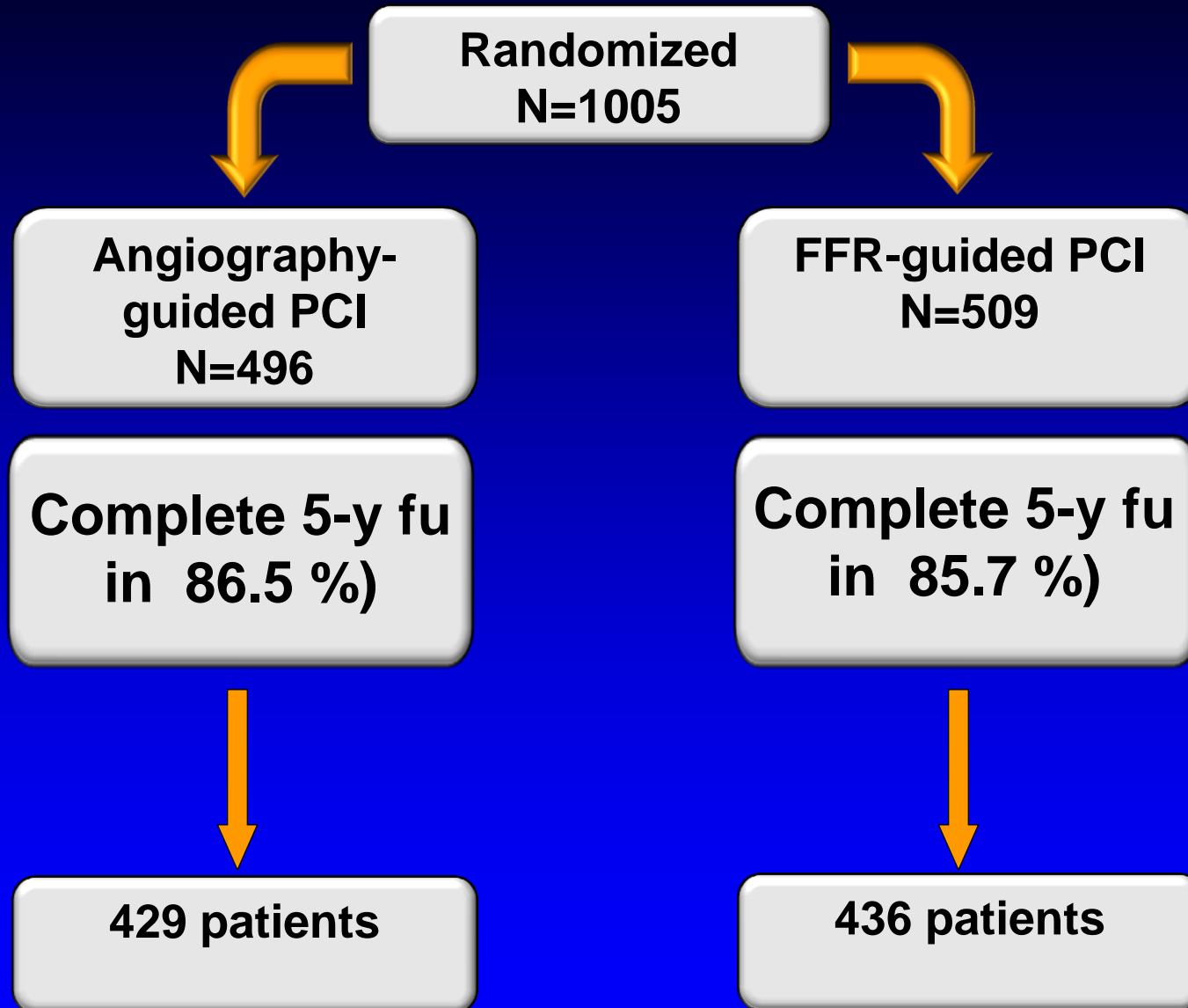
# ***FAME study: Procedural Results (2)***

	<b>ANGIO-group N=496</b>	<b>FFR-group N=509</b>	<b>P-value</b>
<b>Procedure time (min)</b>	<b>70 ± 44</b>	<b>71 ± 43</b>	<b>0.51</b>
<b>Contrast agent used (ml)</b>	<b>302 ± 127</b>	<b>272 ± 133</b>	<b>&lt;0.001</b>
<b>Materials used at procedure (US \$)</b>	<b>6007</b>	<b>5332</b>	<b>&lt;0.001</b>
<b>Length of hospital stay (days)</b>	<b>3.7 ± 3.5</b>	<b>3.4 ± 3.3</b>	<b>0.05</b>

# Measuring FFR in Multivessel Disease: FAME Study (N=1005) : One Year Outcomes

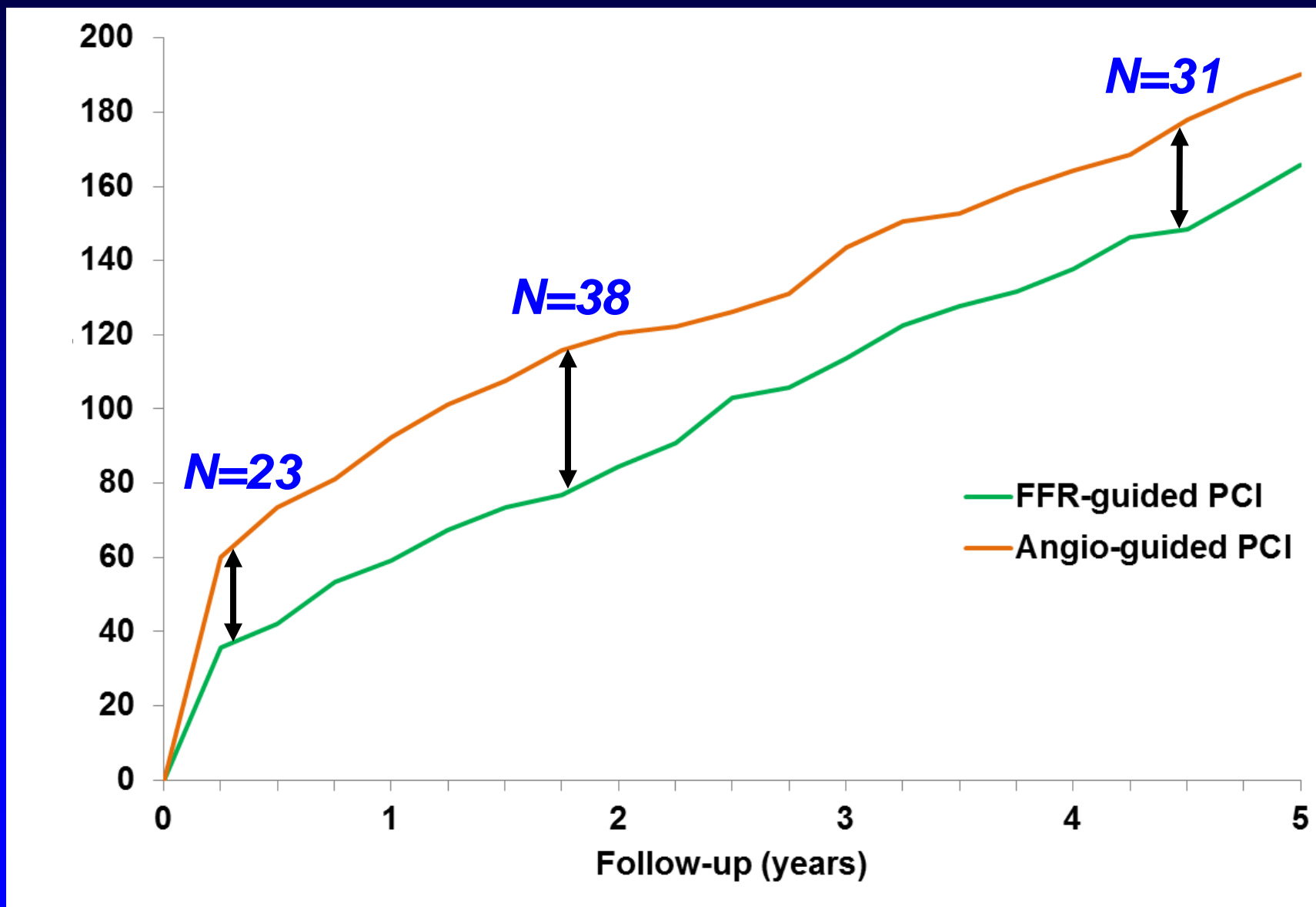


# 5 year follow-up

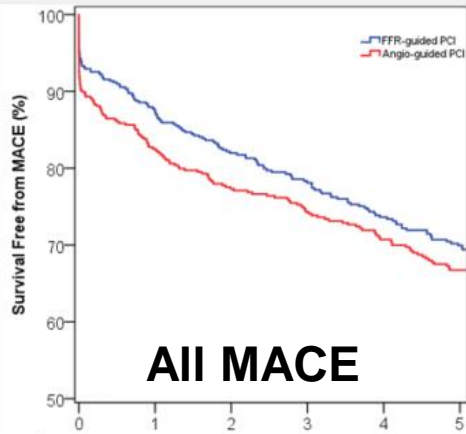




# FAME study: cumulative events during 5-year follow-up

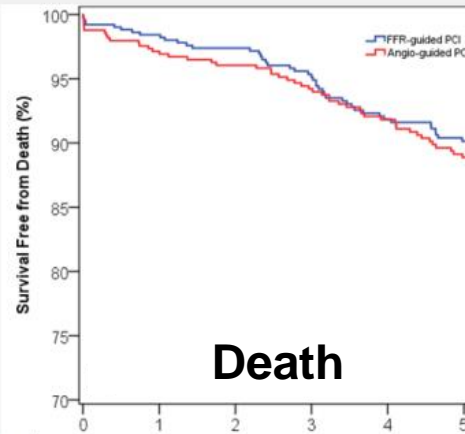


# FAME study: 5 - year Kaplan Meier survival curves



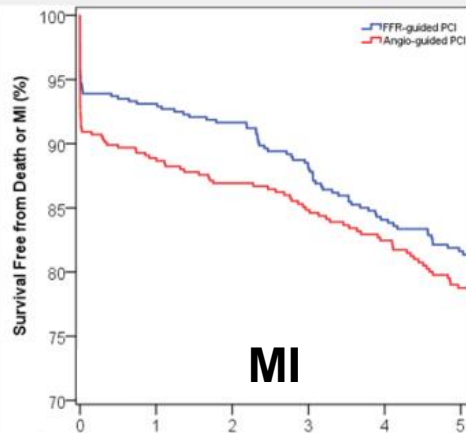
**All MACE**

No. at risk	Follow-up (years)					
	0	1	2	3	4	5
Angio	496	393	350	319	293	257
FFR	509	434	389	341	310	263



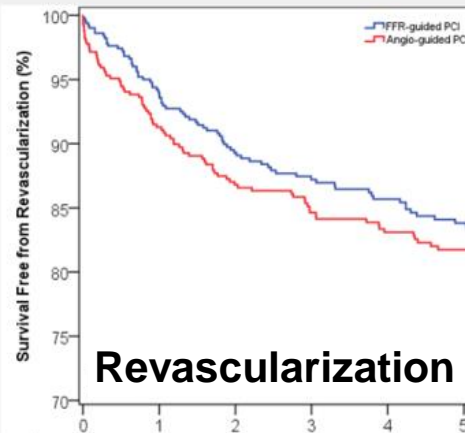
**Death**

No. at risk	Follow-up (years)					
	0	1	2	3	4	5
Angio	496	460	435	406	383	344
FFR	509	488	462	417	388	344



**MI**

No. at risk	Follow-up (years)					
	0	1	2	3	4	5
Angio	496	423	394	366	344	304
FFR	509	461	435	387	356	311



**Revascularization**

No. at risk	Follow-up (years)					
	0	1	2	3	4	5
Angio	496	423	380	346	319	281
FFR	509	458	412	362	333	285



# *FAME study: **Some prominent numbers***



## Absolute Reduction of **All-cause** Mortality:

*at 1 year: **1.2 %***

*at 2 years: **1.2 %***

*at 5 years: **1.3%***

## Relative Reduction of **Cardiac** Mortality:

*at 1 year: **30 %***

*at 2 years: **25 %***

*at 5 years: **27%***

## Multivariate Analysis of “**Primary Endpoint**” at 5 years:

*despite the lower number of patients at risk, significant decrease of MACE at 5 years in **male gender** (P=0.027)*

# **FAME study: Conclusions of 5-y Follow-up**



- *In patients with multivessel disease, FFR-guided PCI compared to angiography-guided PCI results in a significant decrease of adverse events up to 2 years, **while thereafter the risk of both groups evolves in parallel***
- *This clinical benefit is achieved with **fewer stents and less resource utilisation.***
- *This 5-y follow-up confirms the **long-term benefit and safety of FFR-guided PCI in patients with multivessel disease***



**EXPEDITED PUBLICATION: CLINICAL RESEARCH**

## **Long-Term Follow-Up After Fractional Flow Reserve–Guided Treatment Strategy in Patients With an Isolated Proximal Left Anterior Descending Coronary Artery Stenosis**

Olivier Muller, MD, PhD,\* Fabio Mangiacapra, MD,\* Argyrios Ntaliansis, MD, PhD,\*  
Katia M. C. Verhamme, MD, PhD,† Catalina Trana, MD,\* Michalis Hamilos, MD, PhD,\*  
Jozef Bartunek, MD, PhD,\* Marc Vanderheyden, MD,\* Eric Wyffels, MD,\*  
Guy R. Heyndrickx, MD, PhD,\* Frank J. A. van Rooij, DSC,‡  
Jacqueline C. M. Witteman, MSc, PhD,‡ Albert Hofman, MD, PhD,‡  
William Wijns, MD, PhD,\* Emanuele Barbato, MD, PhD,\* Bernard De Bruyne, MD, PhD\*

*Aalst, Belgium; and Rotterdam, the Netherlands*

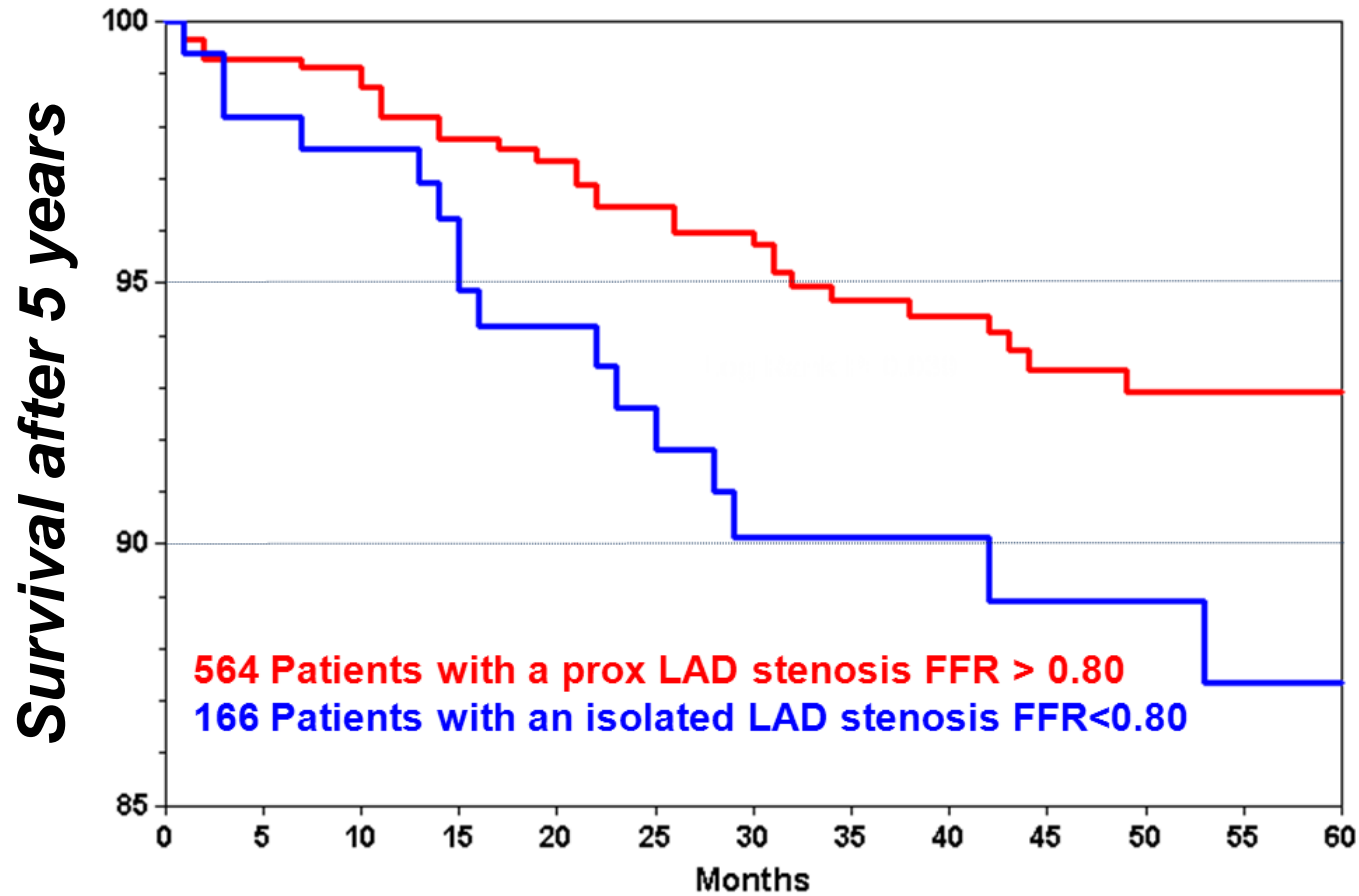
730 patients with proximal LAD stenosis 30-70%, referred for PCI

$FFR \leq 0.80 \rightarrow$  PCI or CABG : N = 166

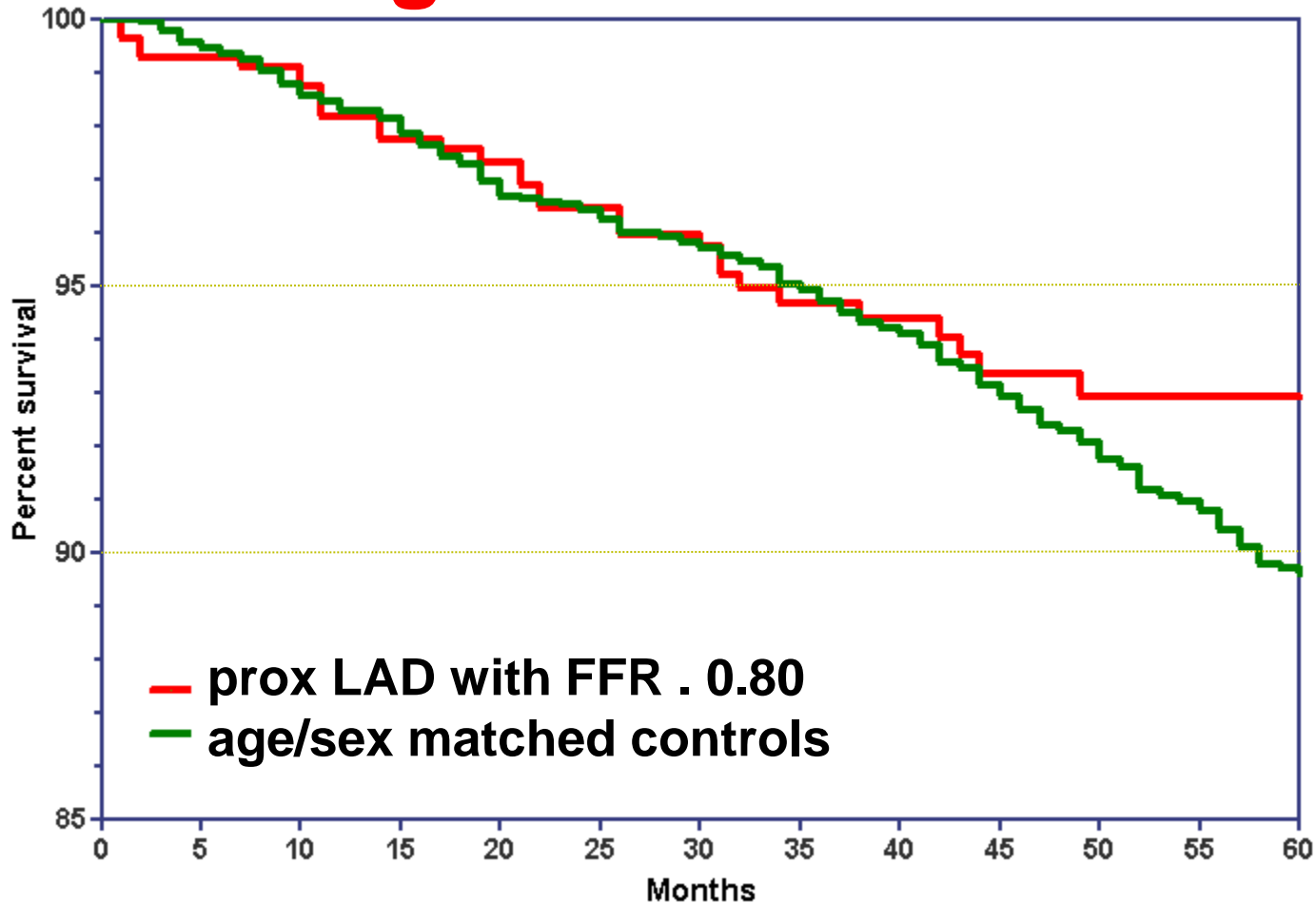
$FFR > 0.80 \rightarrow$  medical treatment, based upon FFR

*Follow up for 5 years, 1868 age & sex matched controls without  
known coronary disease*

# Proximal LAD Stenoses



# Clinical Outcome in FFR-Negative LAD Stenoses



**No ischemia, no revascularization  
regardless of the angio**



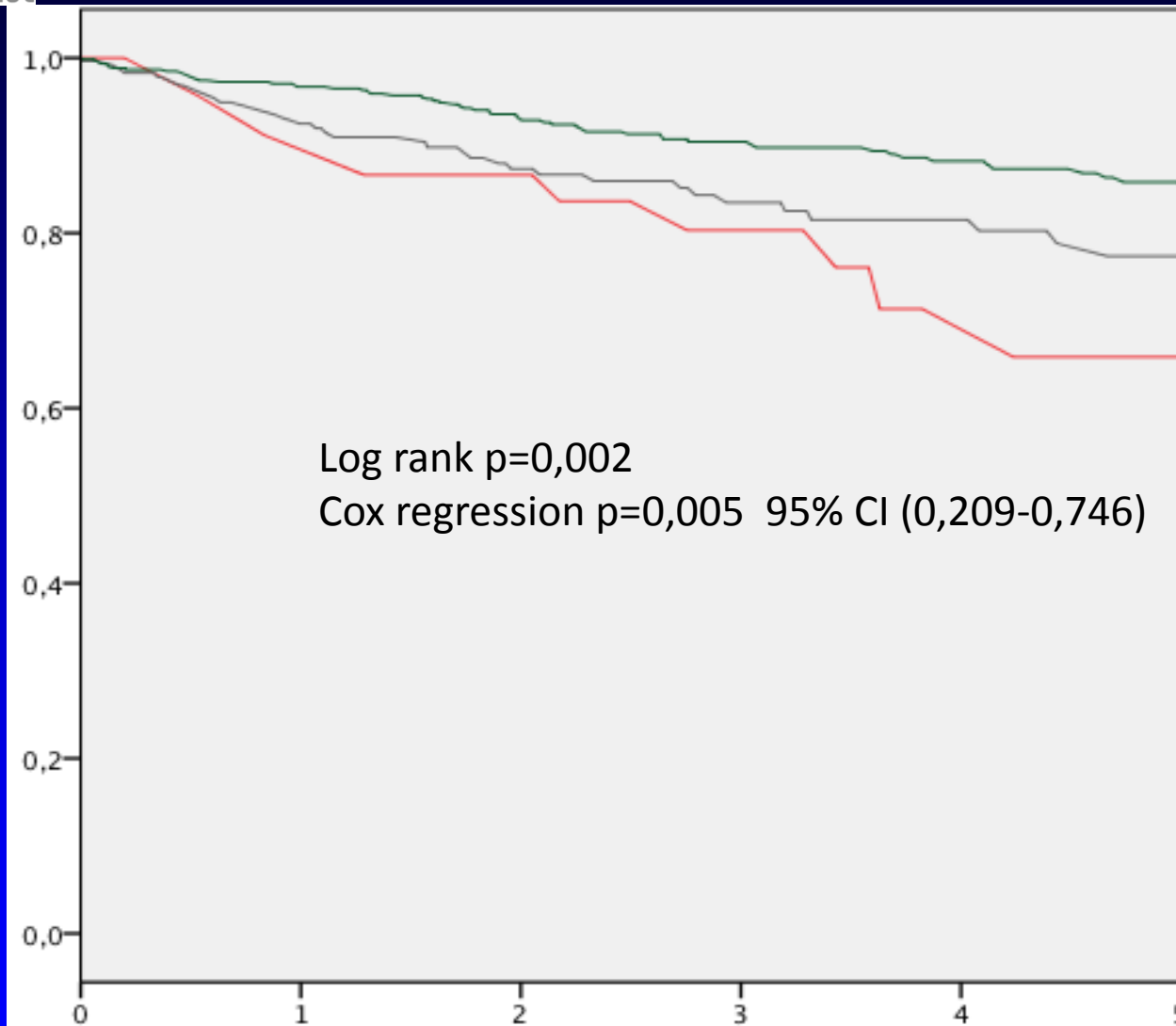
# Optimal cut-off value

## *evaluation of 'grey zone'*

- **1459 patients**
  - single-vessel disease
  - isolated de novo stenosis
  - FFR 0.70 – 0.85
- Categorized as
  - **FFR 0.70 – 0.75**
  - **FFR 0.76 – 0.80**
  - **FFR 0.81 – 0.85**
- Compared revascularization versus medical therapy
- Endpoint was **MACE at 5 years**



# MACE in medical therapy group



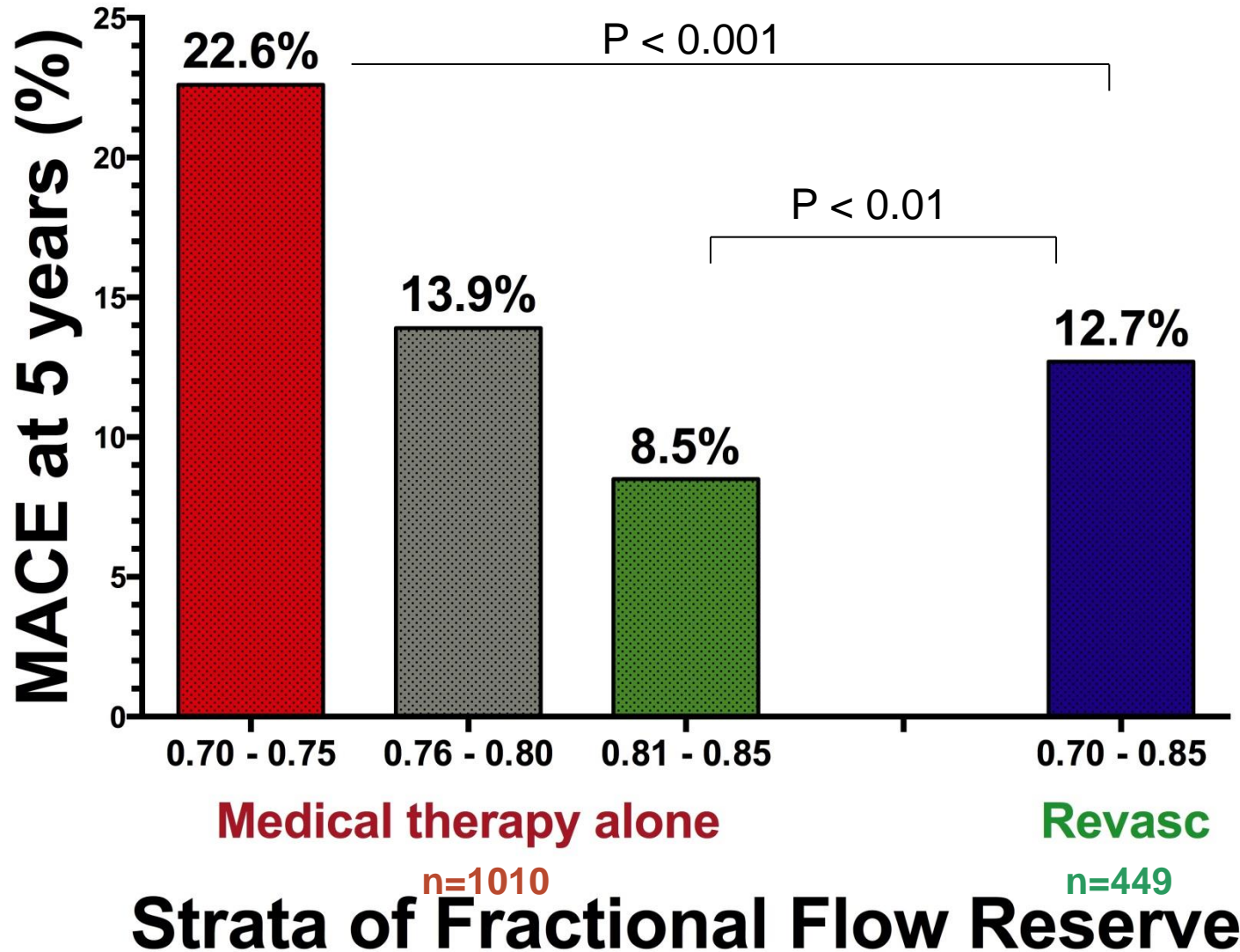
FFR  
 0,81-0,85 }  $p=0,009$   
 0,76-0,80 }  $p=0,287$   
 0,70-0,75 }

**MACE n 0**                      40                      68                      84                      95                      104

**Free of Mace n**            739                    555                    386                    289                    203

1010

# Optimal cut-off value *evaluation of 'grey zone'*



## **FFR and Clinical Outcome: 3 important questions:**

- **Is it safe to defer PCI if FFR is negative ? → YES !**  
*(together, in the 3 RCT's DEFER , FAME, and FAME 2 almost 2000 lesions were non-significant by FFR and consequently deferred. In these patients long-term rate of death & MI is 0.6 % per year ! (up to 15 years )*
- **Is it indicated to perform PCI if FFR is positive ?**  
**→ YES !** *( FAME -2 , less events, survival benefit)*
- **Does systematic use of FFR improve PCI outcome**  
**→ YES !** *(FAME, persistent superiority of FFR-guided PCI)*