CORONARY PHYSIOLOGY IN THE CATHLAB:

SAFETY OF DEFERRING PCI BASED UPON FFR

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

For most invasive indexes in the cath lab, no outcome studies have been performed or were "negative"

FFR is the only invasive index used which systematically improved outcome in RCT's, which will be highlighted in the present session

FFR and Clinical Outcome:

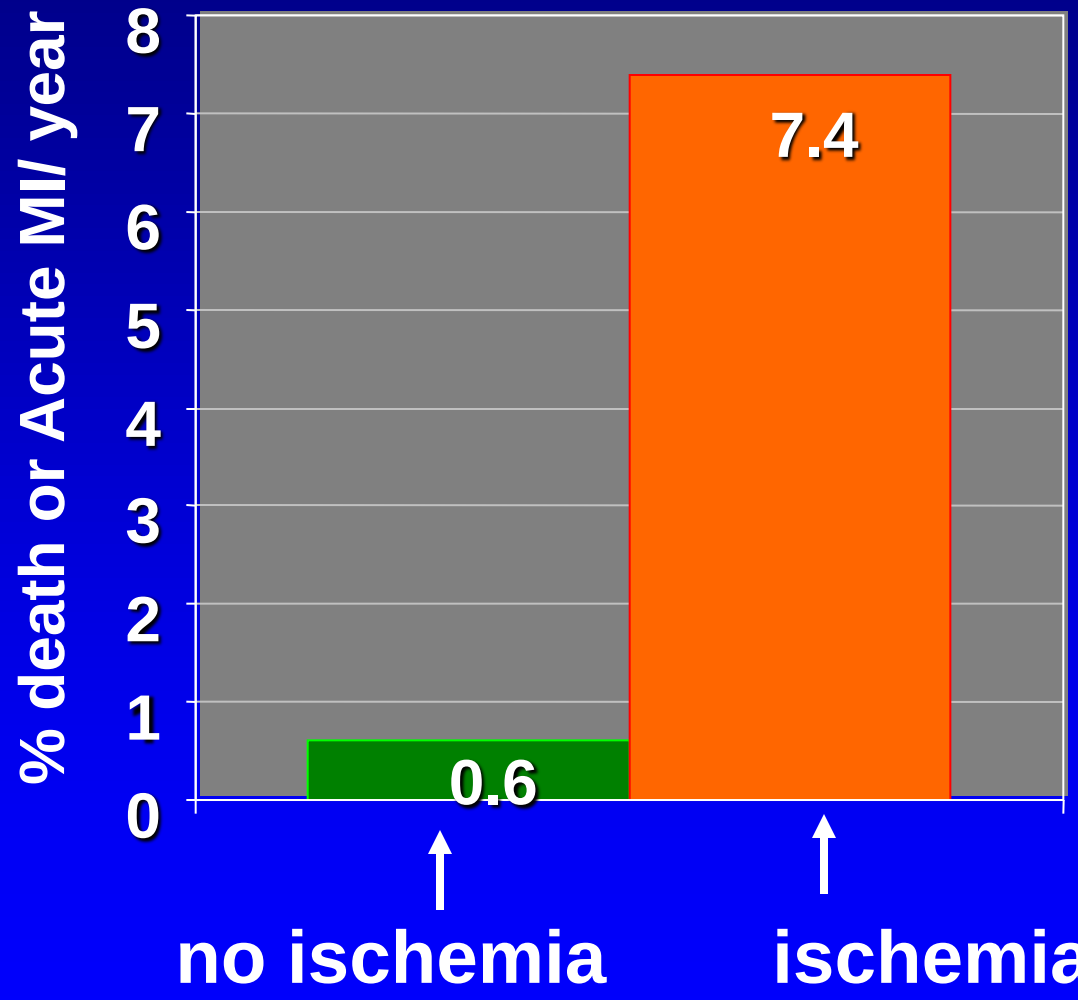
3 important questions:

- 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 ?

Risk to die or experience myocardial infarction in the next 5 years related to a coronary stenosis:

- **non-ischemic stenosis: < *1% per year ****
  (NUCLEAR studies, PET, MRI, DEFER, FAME)
- **ischemic stenosis, if left untreated: *5-10% per year***
  (Many historical registries, nuclear studies, ACIP, CCTA, MRI, FFR)
- **stented stenosis: *2-3% per year***
  (*e.g DEFER, FAME, SYNTAX,many large studies and registries)*

The risk for death or acute myocardial infarction in the next five years is 20 times higher for an ischemic lesion compared to a non-ischemic lesion !!!



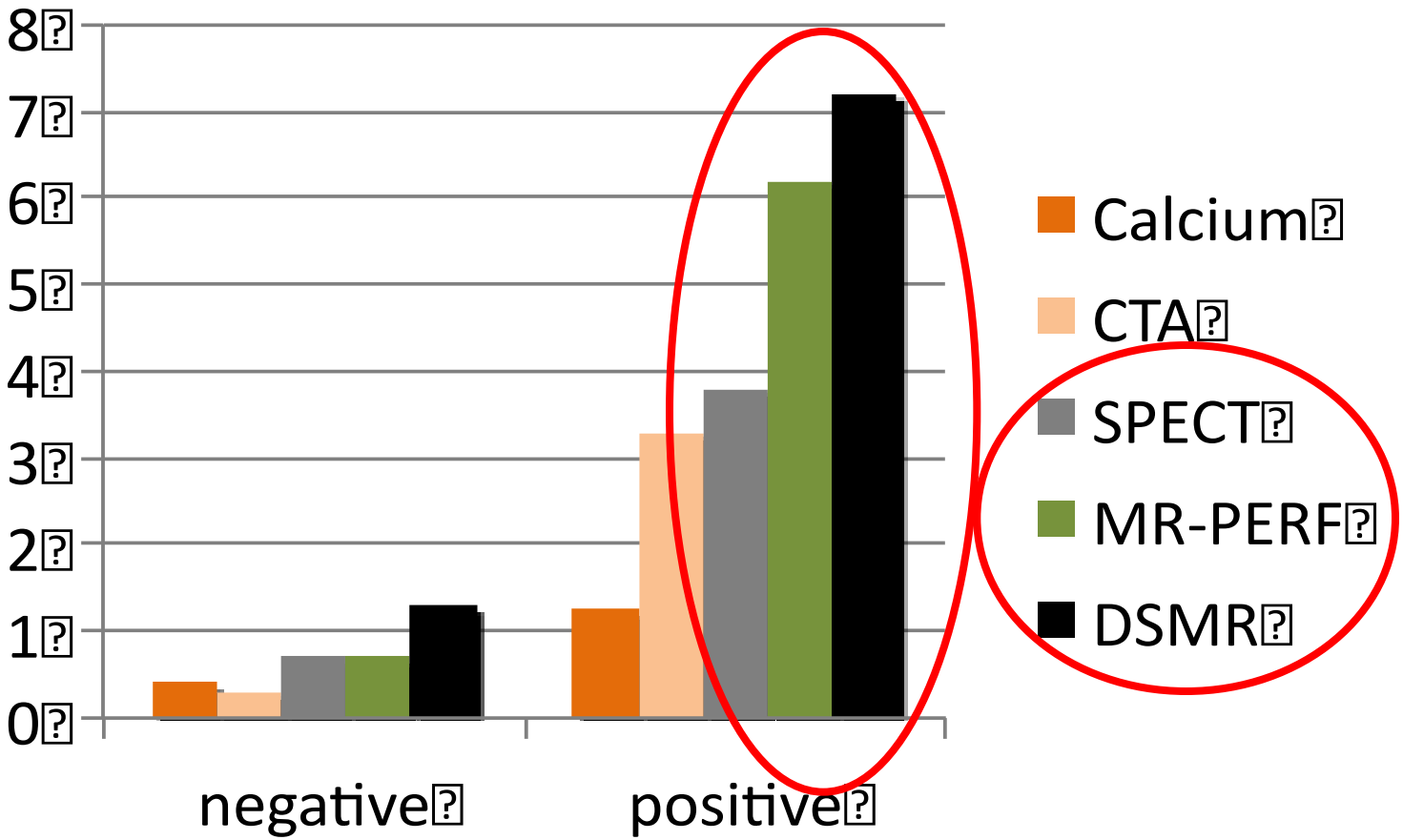
12000 Patients (2 x 6000)

similar stenosis severity by coronary angio

Iskander S, Iskandrian A E JACC 1998

Events (within 1 year)

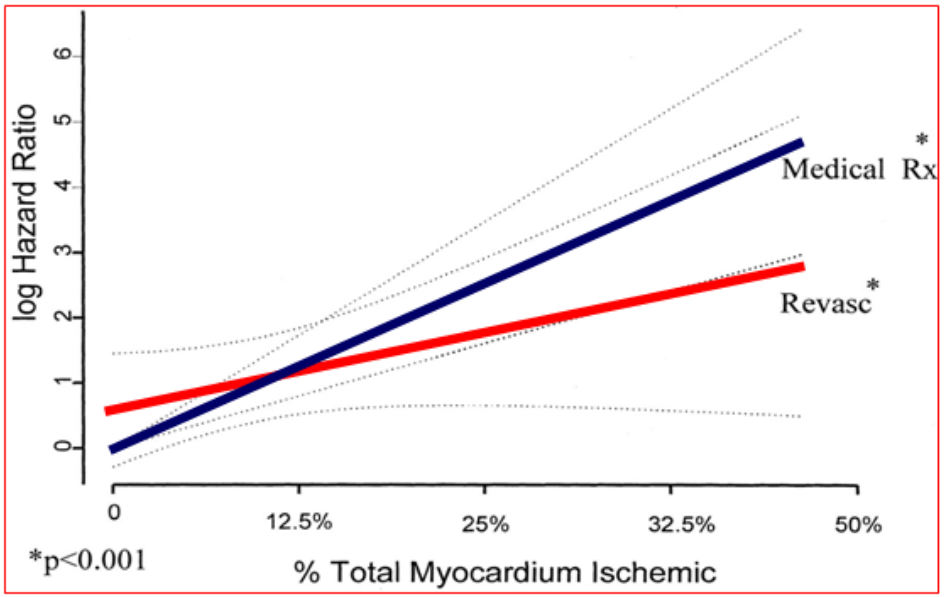
No events/1 year



Nagel; JACC Imaging 2009

Is it important to detect ischemia ?

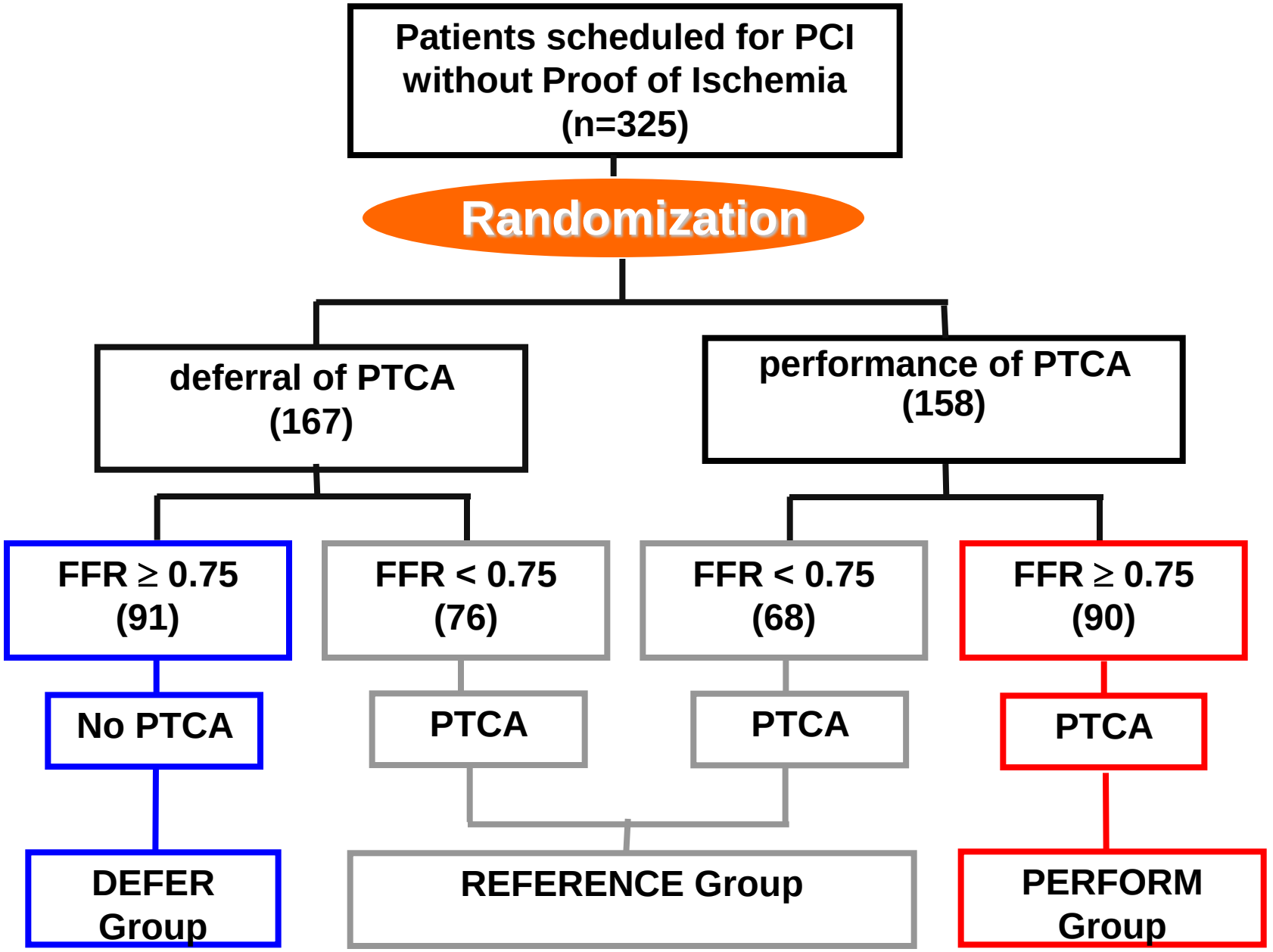
Log hazard ratio for revascularization (Revasc) vs medical therapy (Medical Rx) as a function of % myocardium ischemic based on final Cox proportional hazards model



Above 10% ischemic myocardium, the survival benefit from revascularisation increases with the extent of ischemia

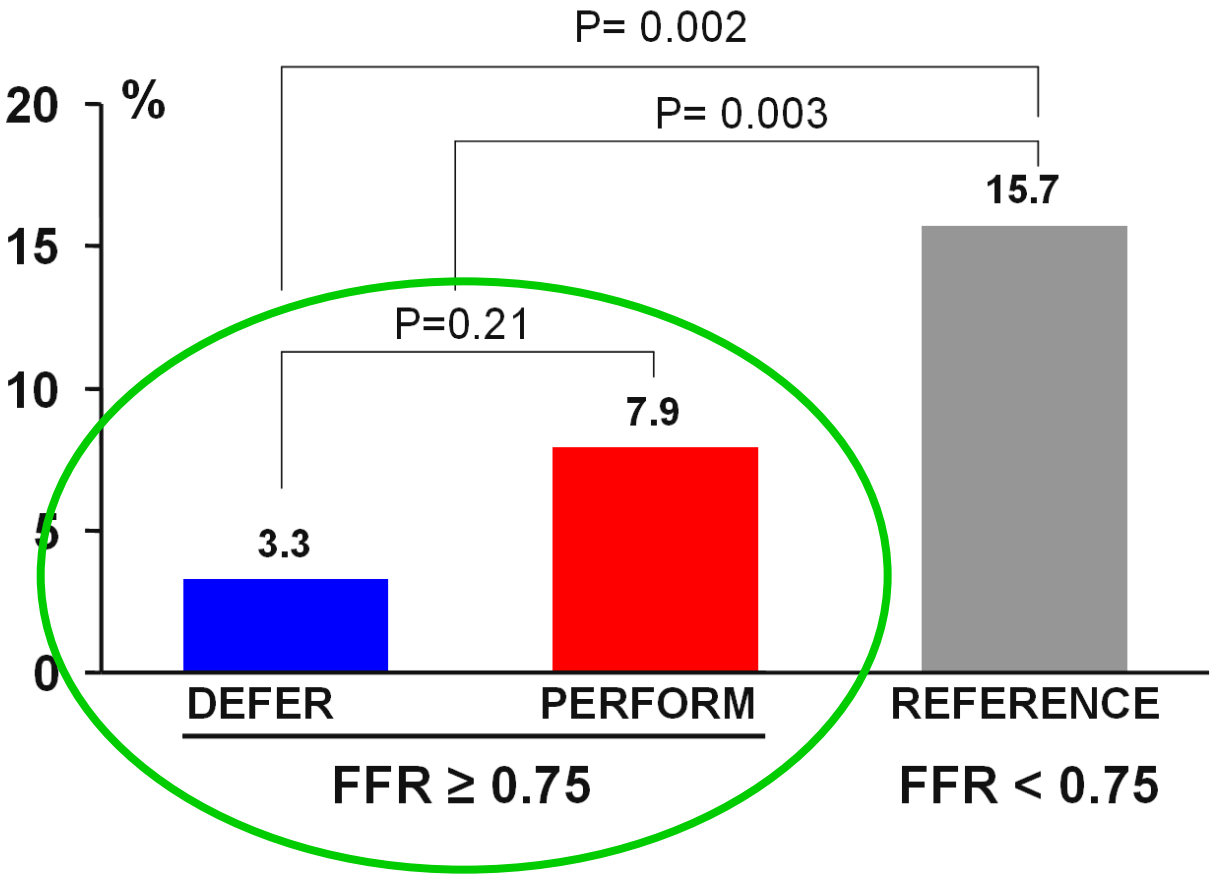
Hachamovitch, R. et al. Circulation 2003

The *DEFER* Study: Flow Chart



DEFER: Cardiac Death And Acute MI After 5 Years

non-ischemic stenosis, R/x
non-ischemic stenosis, R/x + stent
ischemic stenosis, R/x + stent



DEFER-study, JACC 2007; 49 : 2105-2111

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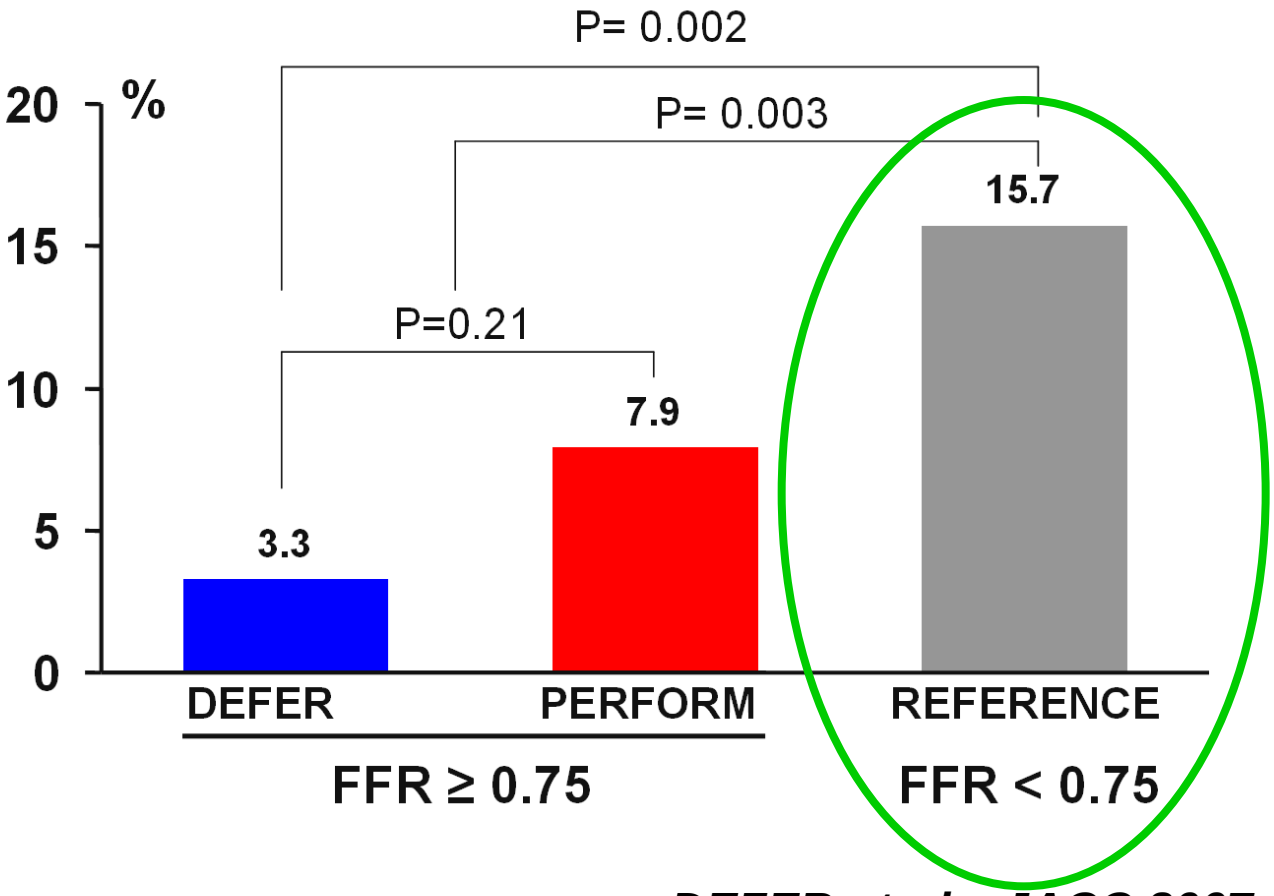
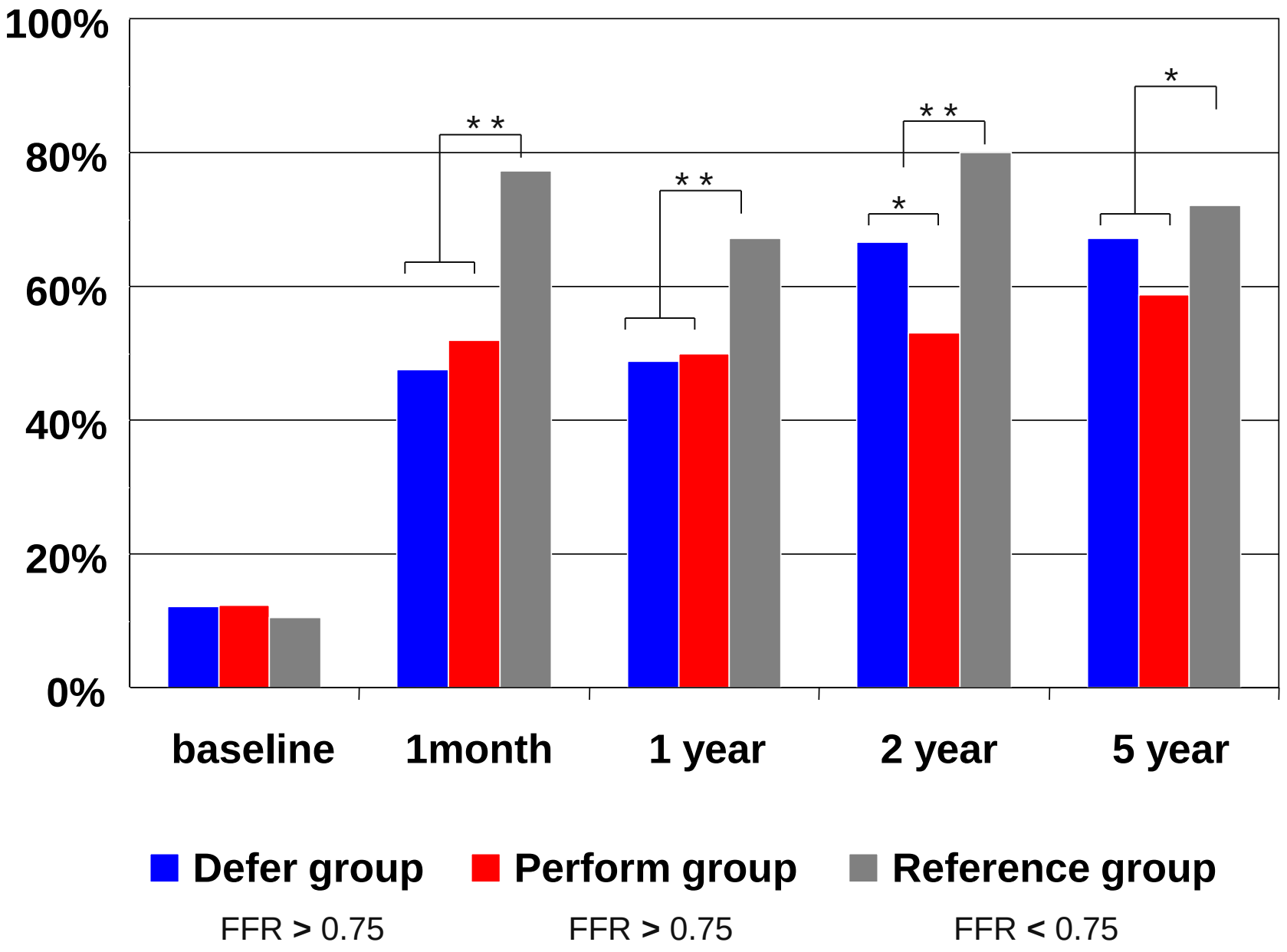


DEFER-study, JACC 2007; 49 : 2105-2111

Freedom From Chest Pain



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

Further evidence from FAME, FAME-2 and (indirectly) from PROSPECT

DEFER, FAME, Nuclear; Prospect

FLOW CHART

Patient with stenoses ≥ 50% in at least 2 of the 3 major epicardial vessels

Indicate all stenoses ≥ 50% considered for stenting

Randomization

Angiography-guided PCI

Stent all indicated stenoses

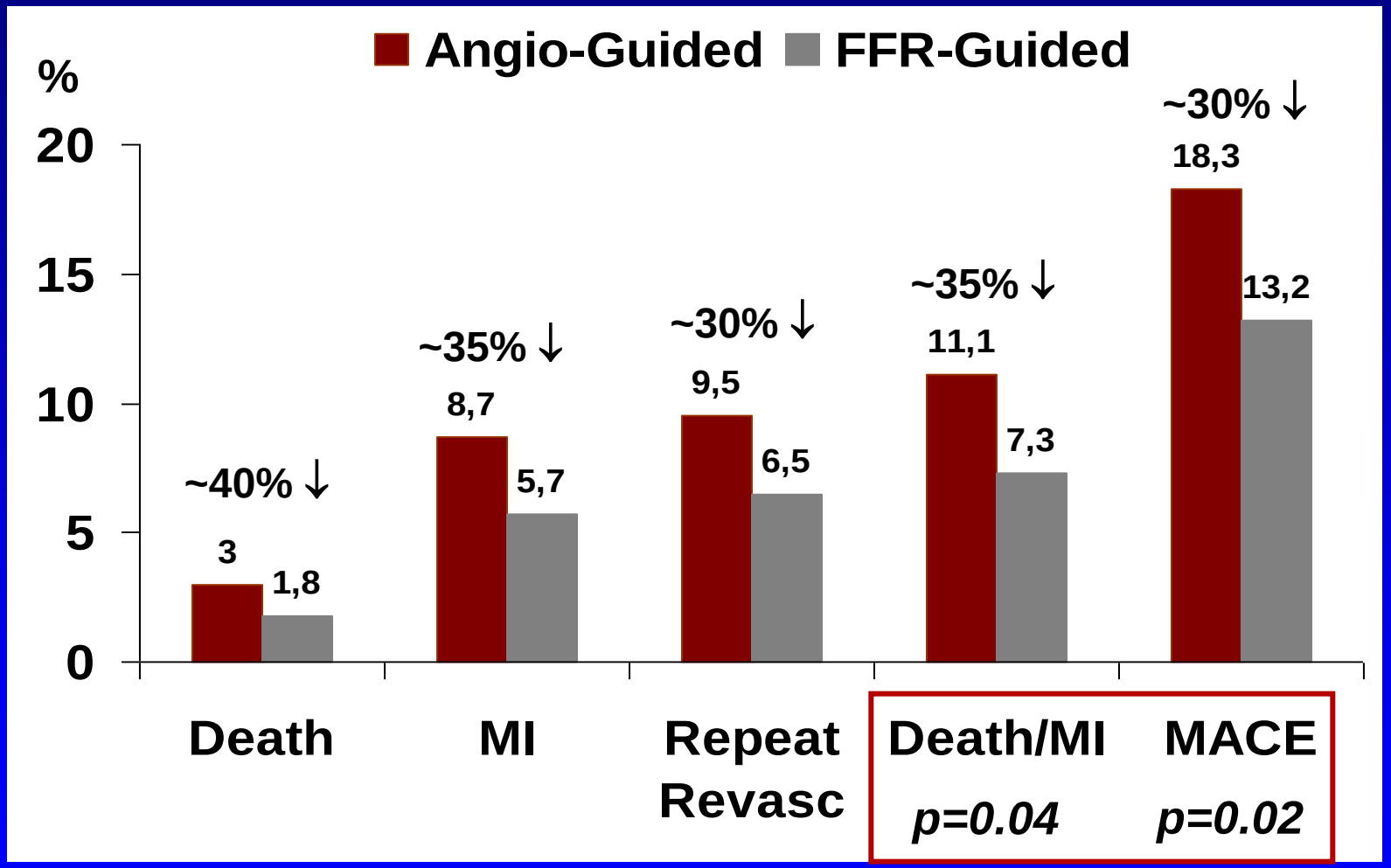
FFR-guided PCI

Measure FFR in all indicated stenoses

Stent only those stenoses with FFR ≤ 0.80

follow-up at 1,2,5 year

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



Tonino et al: New Engl J Med 2009;360:213-24.

Outcome of Deferred Lesions:

513 Deferred Lesions and 901 stented lesions in 509 FFR-Guided Patients

2 Years

9
Late Myocardial Infarctions

8
Due to a New Lesion or Stent Related

1
Myocardial Infarction due to an Originally Deferred Lesion

Only 1/513 or 0.2% of deferred lesions resulted in a late myocardial infarction

Outcome of Deferred Lesions:

513 Deferred Lesions and 901 stented lesions in 509 FFR-Guided Patients

2 Years

53 Repeat Revascularizations

37
in a New Lesion and/or in a Restenotic One

6
Without FFR or Despite an FFR > 0.80

10
Originally Deferred Lesions with Clear Progression

Only 10/513 or 1.9% of deferred lesions clearly progressed requiring repeat revascularization

SUMMARY

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

- DEFER study: 0.6 % (follow-up of 5 years; *JACC 2008)*
- 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)*

CONCLUSION:

Deferring stenting of a functionally non-significant stenosis as indicated by FFR > 0.80, is safe and associated with an annual death & AMI infarction rate of < 1% with adequate medical therapy.

Stenting of such stenosis is unnecessary, expensive, and even sometimes hazardous with increase of the risk of adverse events

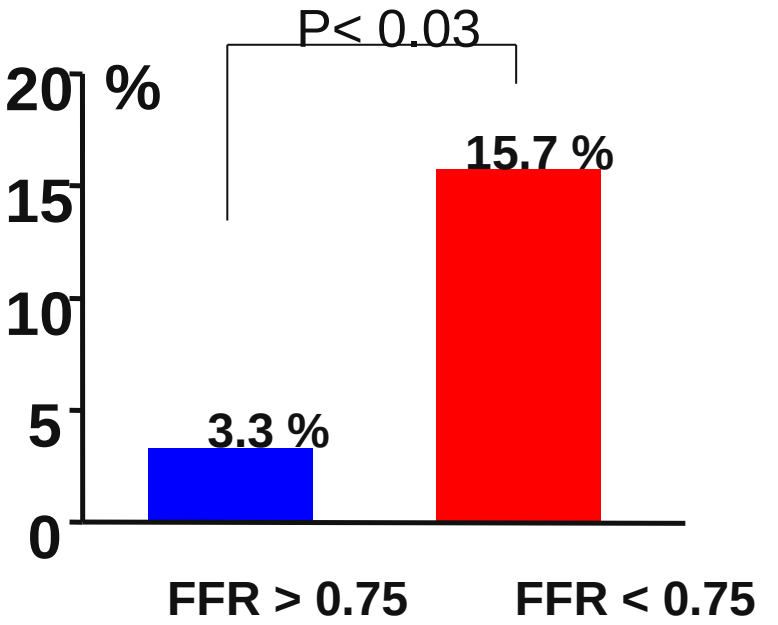
The key issue in decision making whether and where to stent, is the presence and extent of inducible ischemia related to a particular stenosis

No ischemia → ***no angina pectoris & favourable outcome***
no benefit by stenting

Ischemia → ***generally angina pectoris & unfavourable outcome***
proven benefit by stenting

DEFER study (N=325) :

Cardiac death and Acute MI after 5 years



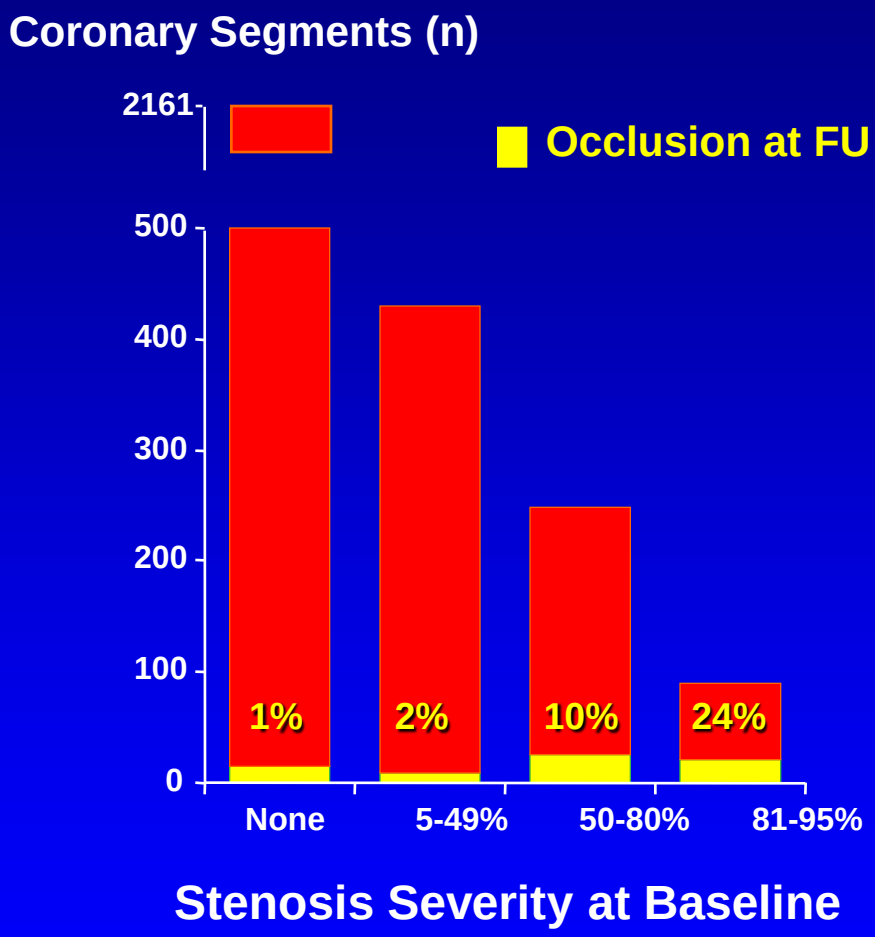
- non-ischemic stenosis, treated medically
- ischemic stenosis, treatment by PCI & optimum R/x

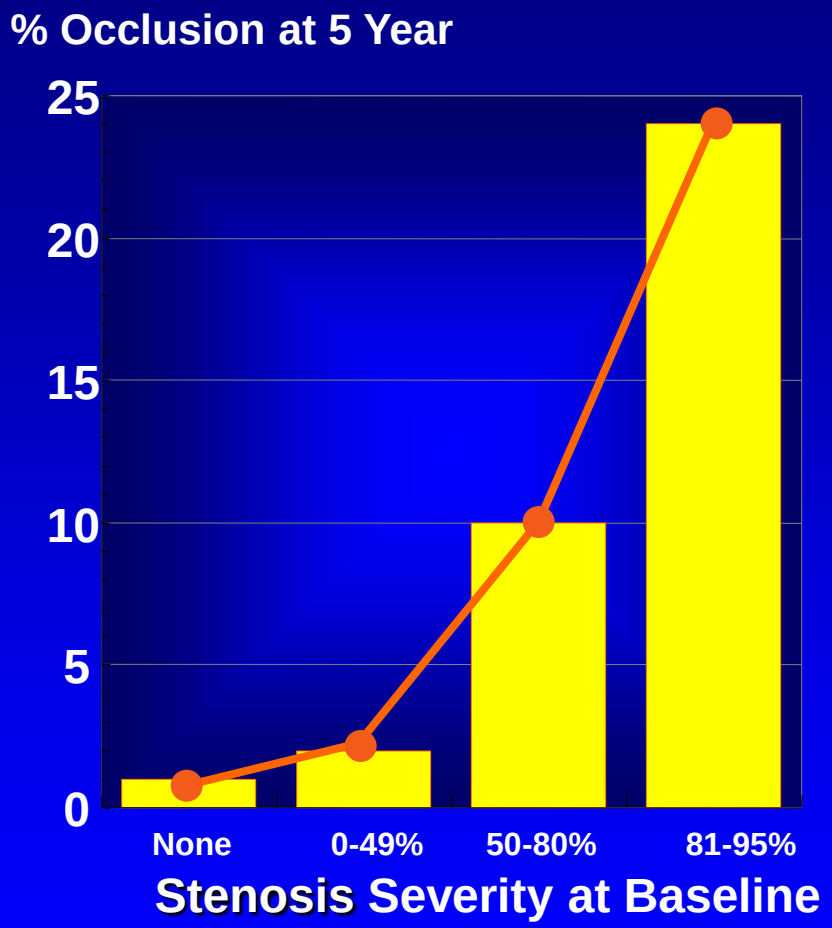
→ ischemic lesion is much more dangerous than non-ischemic lesion

→ risk of individual <u>non-ischemic</u> lesion to cause death or AMI, is very small and < 1 % per year with R/x !!

JACC 2007; 49: 2105-2111

Coronary Occlusion at 5 Years as a Function of Stenosis Severity





Adapted from Alderman et al. J Am Coll Cardiol 1993

Paradox or anthithesis ?

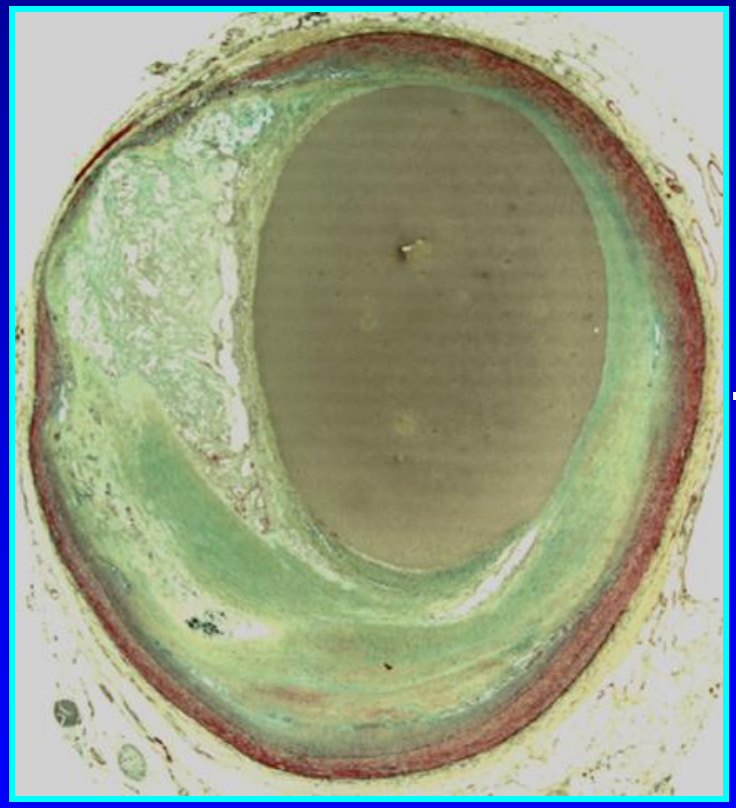
Excellent outcome of medical treatment in non-ischemic stenosis
(DEFER study, many non-invasive studies)

versus

concept of vulnerable plaque

today ? tomorrow

TCFA



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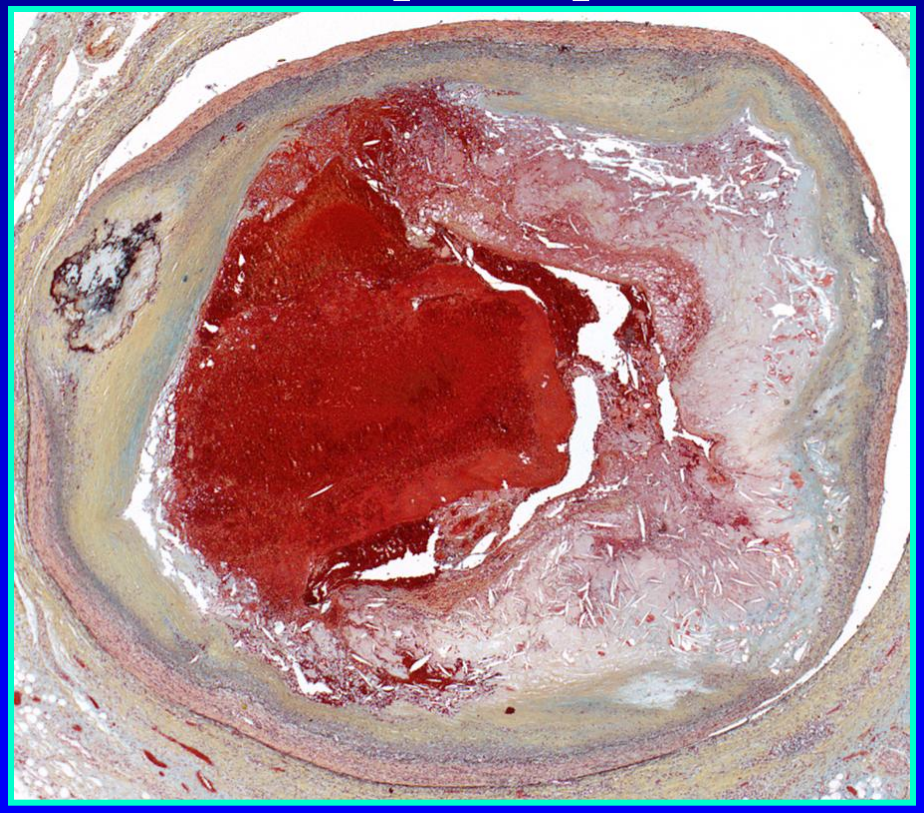
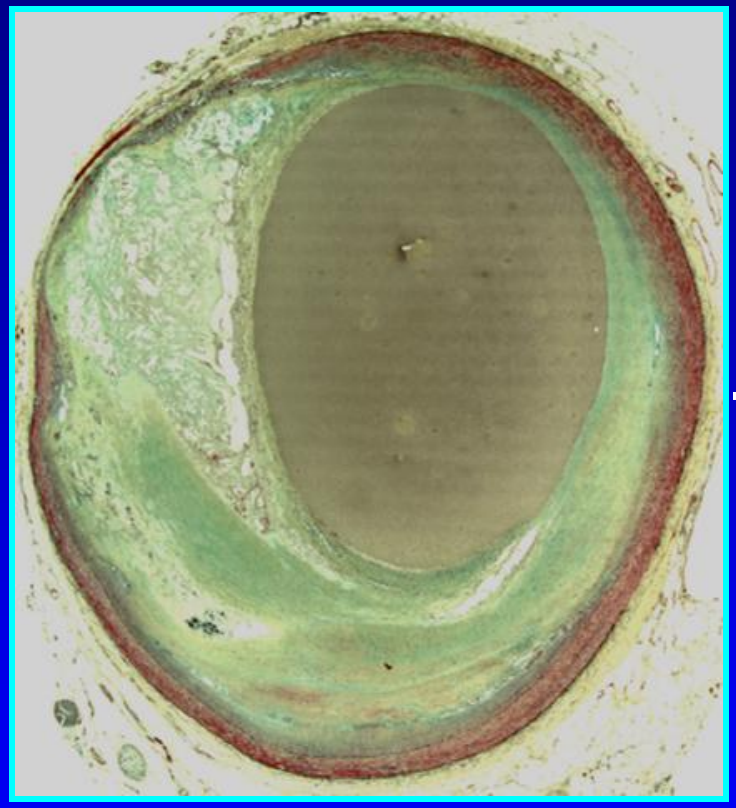
Plaque Rupture



Renu virmani, ETP course 2005

today ? tomorrow

TCFA



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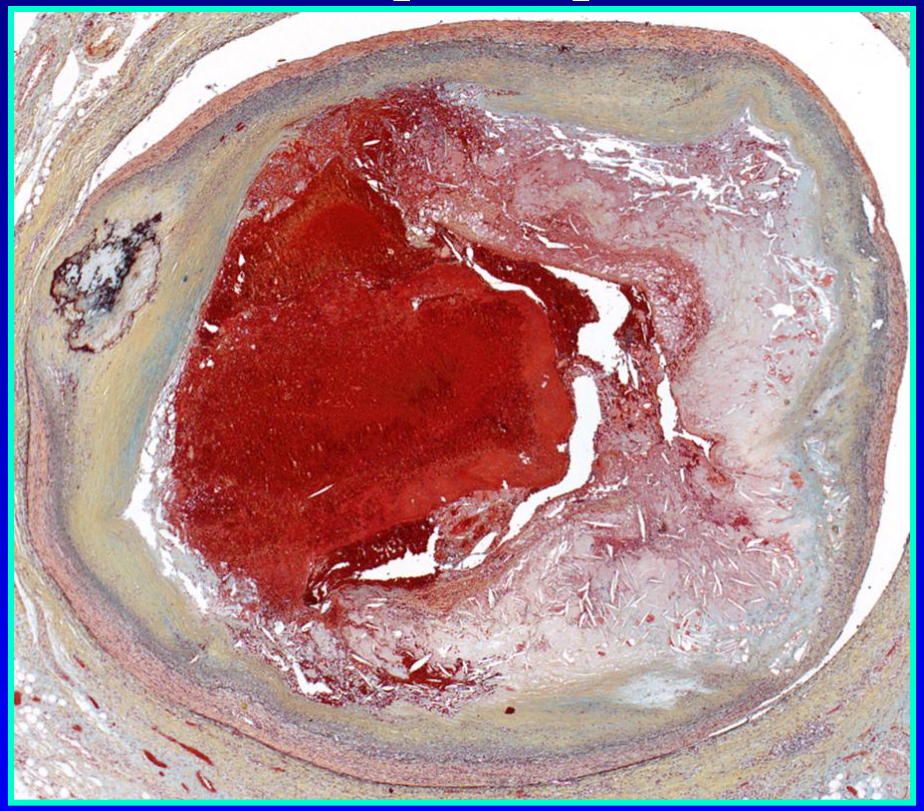


Let's look a little bit more critical to such "plaques"….
What are the facts ?? What is the fiction ??

(Vulnerable) Plaque: Facts and Fiction

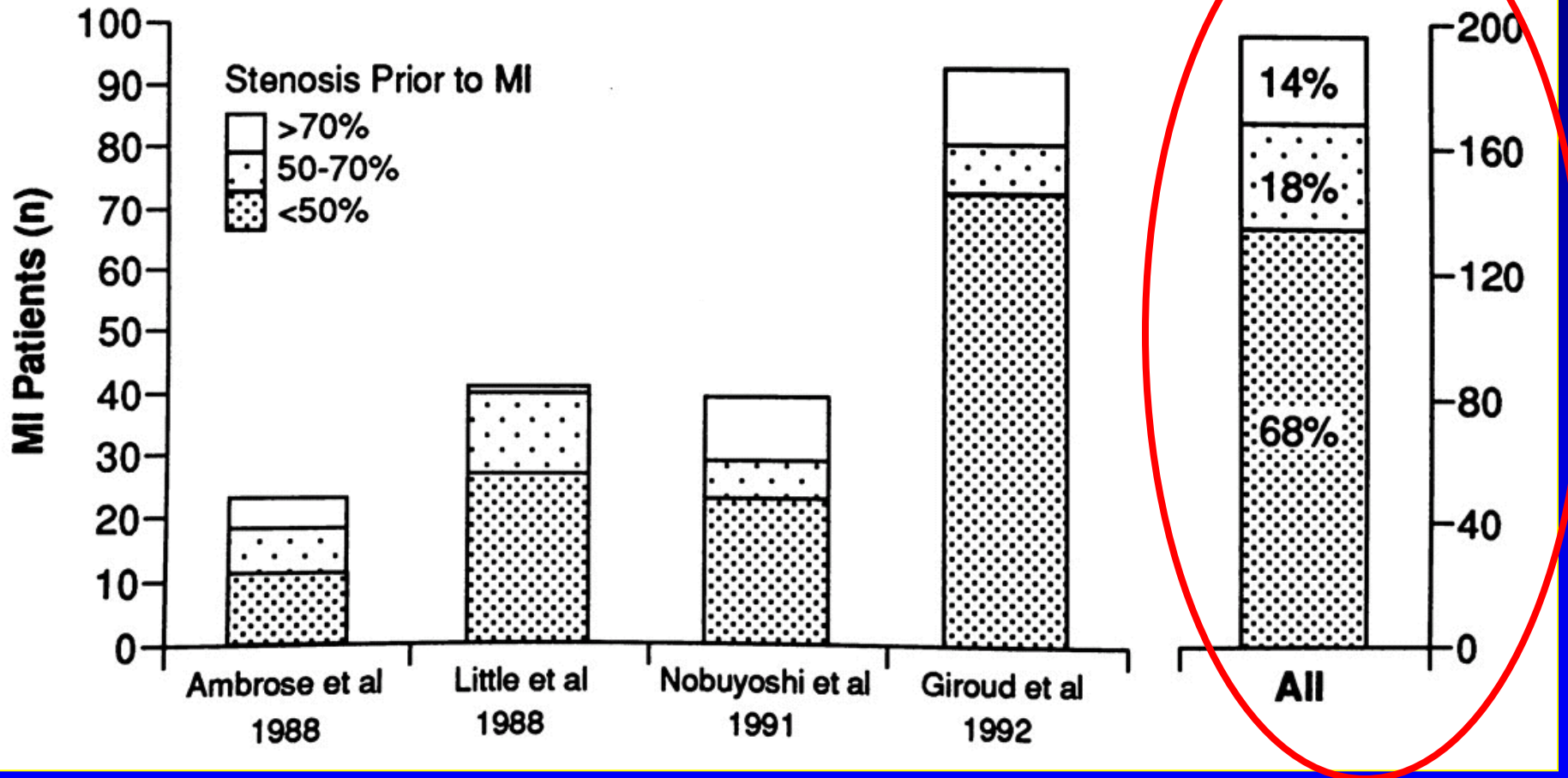
FACTS:

- plaques are very common
- majority of plaques has an excellent prognosis with medical treatment
- only few plaques are vulnerable
- strongest indicator with respect to prognosis is *associated ischemia*

FICTION:

- every plaque is vulnerable
- every vulnerable plaque leads to ACS
- most ACS occurs in mild plaques
- vulnerabilty can be assessed by imaging

Underlying Stenosis Severity of Abrupt Total Occlusions



Falk, Shah and Fuster, Circulation 1995

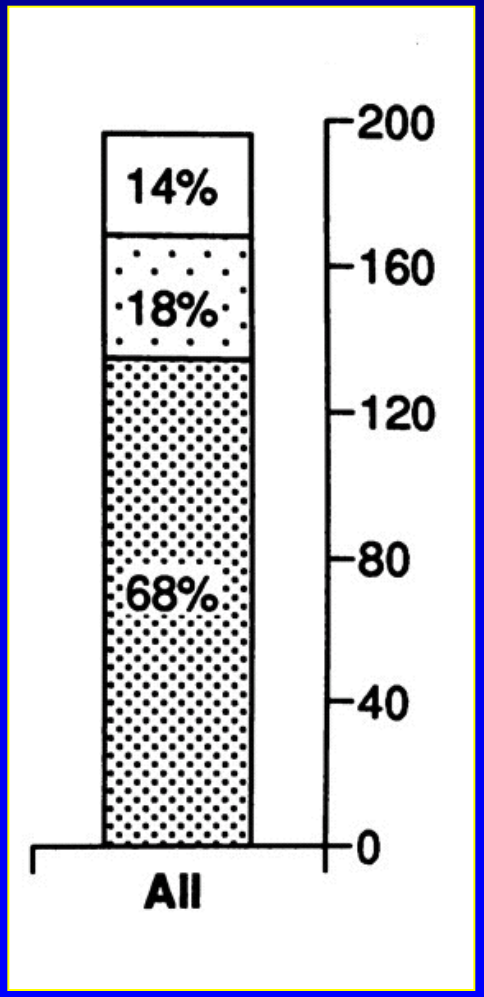
"Acute Coronary Syndromes most often occur at the site of mild stenoses"

Do Myocardial Infarctions Evolve from Mild Stenoses ?

Serial Angiographic (Retrospective) Studies in Patients with MI and a Prior Coronary Angiogram

No QCA, No IVUS but unblinded "eyebolling"

	Number of Patients	Delay Angio-MI
Ambrose et al *JACC* 1988	23	1 month to 7 years
Little et al *Circulation* 1988	42	4 days to 6.3 years
Giroud et al *AJC* 1992	92	1 month to 11 years
Moise et al. AJC 1984	116	39 months
Webster et al JACC 1990	30	55 months
Hackett et al AJC 1989	10	21 months
Total	**313**	**A few days to 11 years (average 3.9 years !!!)**



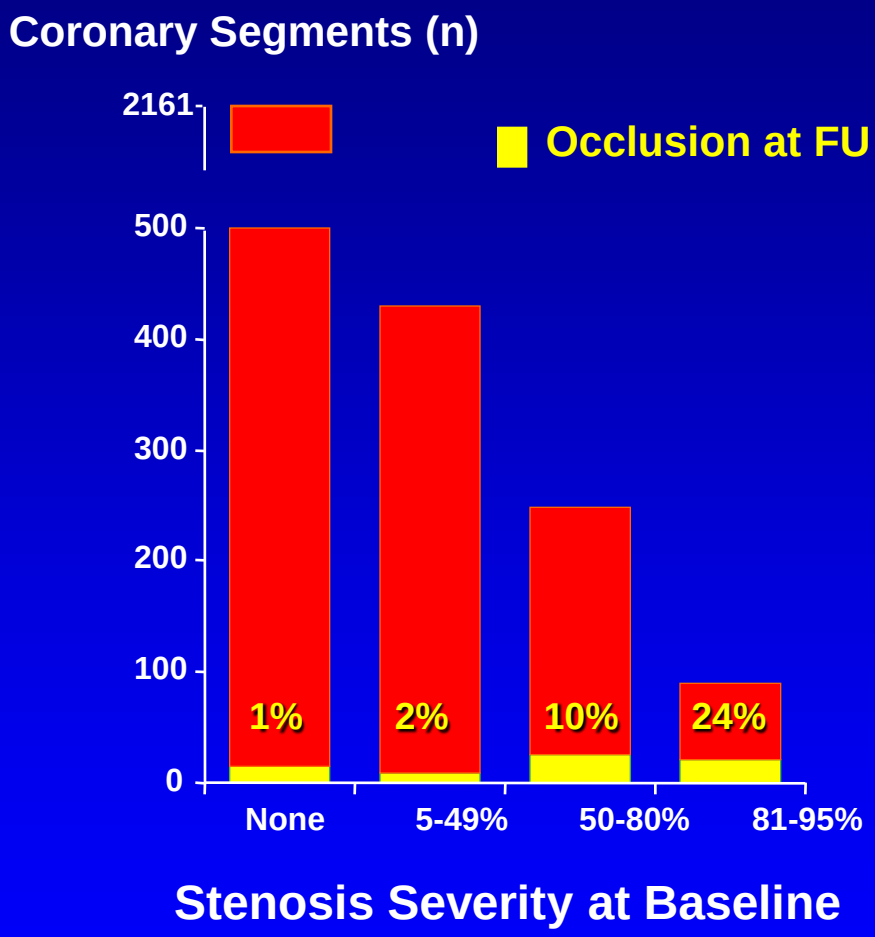
THE MYTHE OF THE "DANGEROUS" PLAQUE

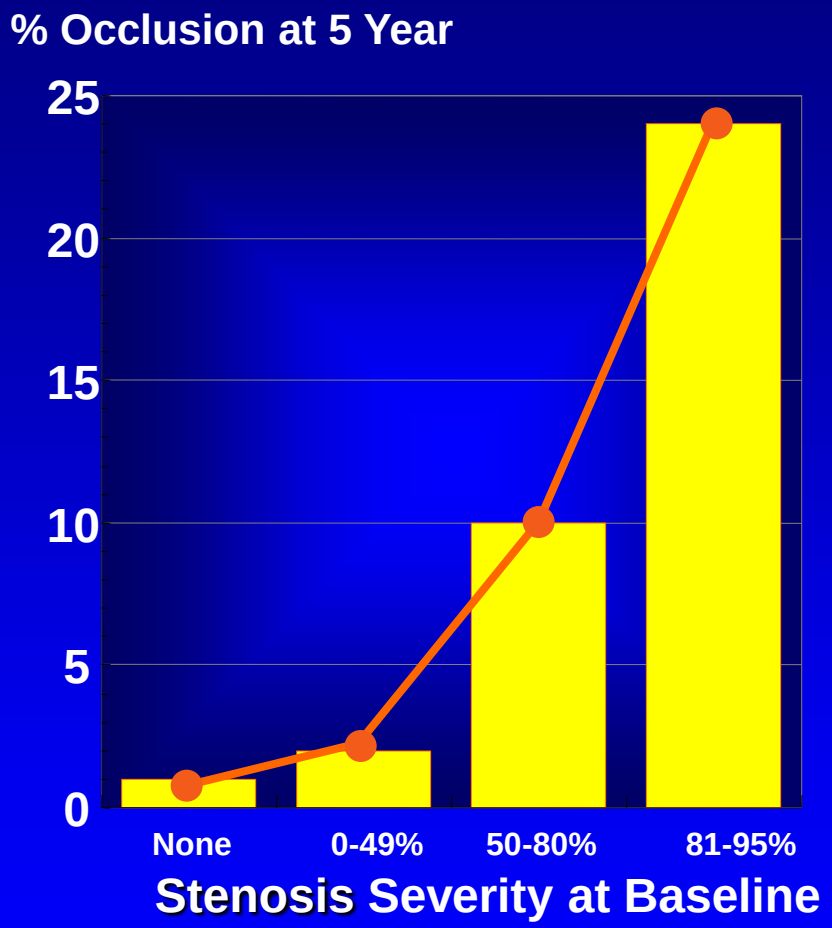
The hypothesis of the occurrence of acute MI on such previously non-significant plaque is based upon

- **6 small retrospective studies**
- **with a total of 313 patients**
- in whom the "index" catherization was performed an average of ***3.9 years*** before the acute event

All other literature (21 "meta-analyses" and hundreds of references), refer to these 6 studies !!!

Coronary Occlusion at 5 Years as a Function of Stenosis Severity





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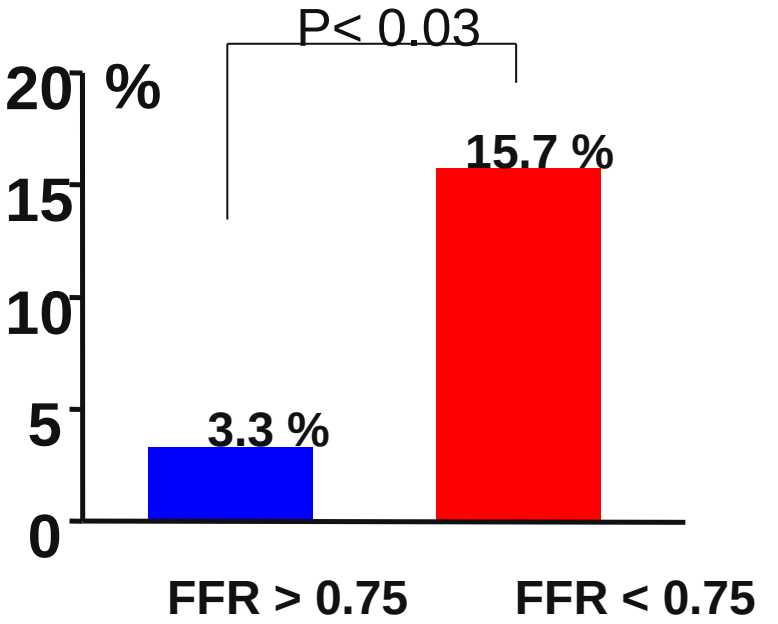

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JACC 2007; 49: 2105-2111

250 consecutive patients with ST-elevation MI in the Catharina Hospital:

- underlying stenosis angiographically significant in 92 % of the cases
- *At meticulous anamnesis, 80 % of patients had recurrent chest pain in the year before the acute myocardial infarction occurred !!*

Frobert et al CCI, 2007, 70: 958-965

INCIDENCE OF CORONARY STENOSIS IN A GENERAL POPULATION

Incidence of coronary artery disease in *asymptomatic*, apparently healthy persons

> 50 years old : 25%
> 60 years old : 40%

Sims et al, Am Heart J 1983
Maseri, Ischemic Heart Disease 1995

What about the prognosis of these patients ?

⟶ **Related to inducibility of ischemia**

- structure of the coronary circulation
- relation between vessel size and perfusion area
- endothelium and development of atherosclerosis
- the 2 or 3 compartment model of the coron circulation
- collaterals
- why functional testing / FFR ?
- which lesions should be treated
- vulnerable plaques: facts & fiction
- ***ischemia & vulnerability: paradox or antithesis ?***

"The missing link"

Is there a link between vulnerabilty and ischemia ?

Hypothesis:

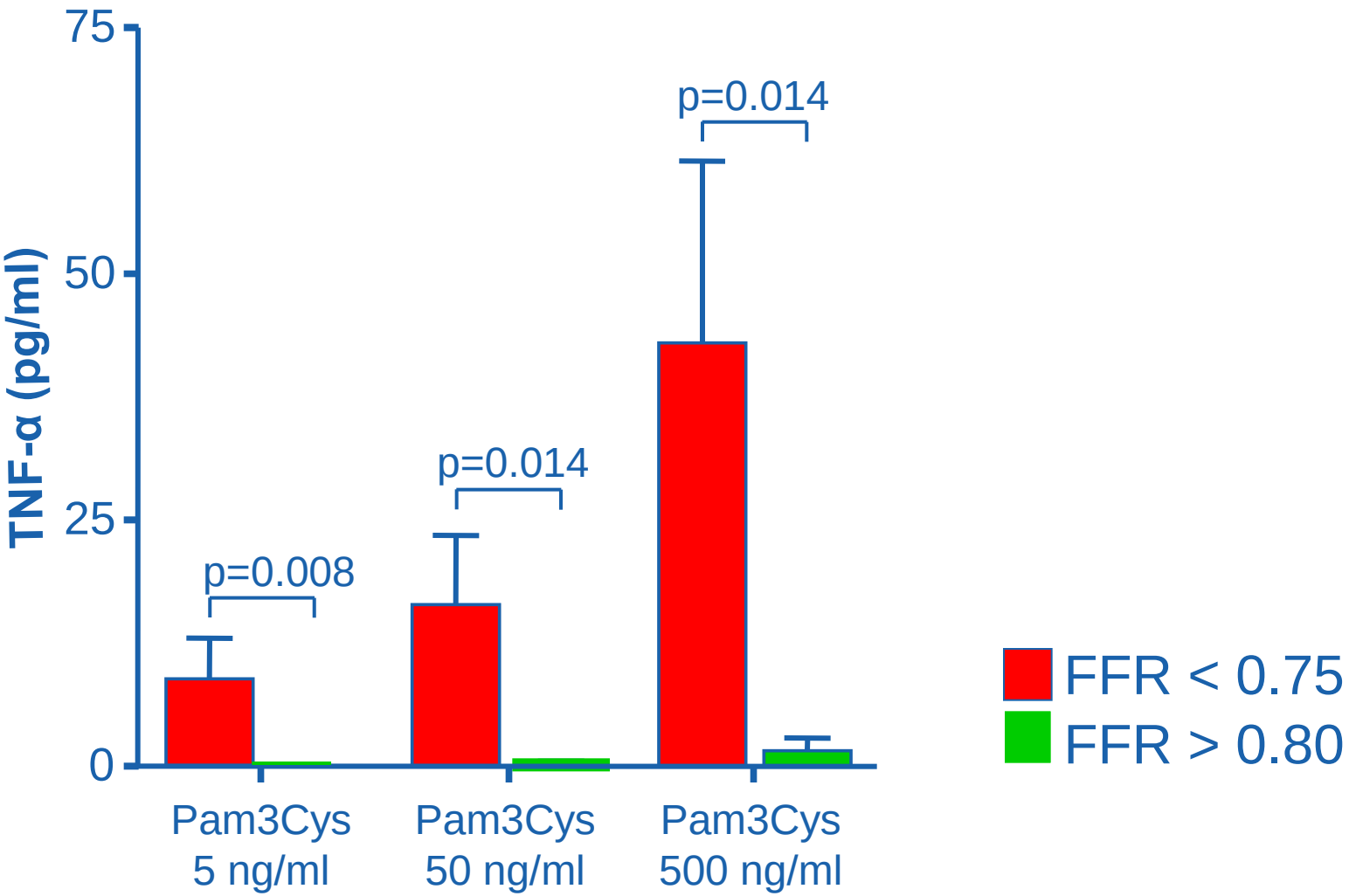
- repetitive ischemia *and*
- high shear stress / pressure gradients

induce vulnerability

→ *Supported by studies on the relation between vulnerability markers and low FFR: on-going work of Pasterkamp et.al.*

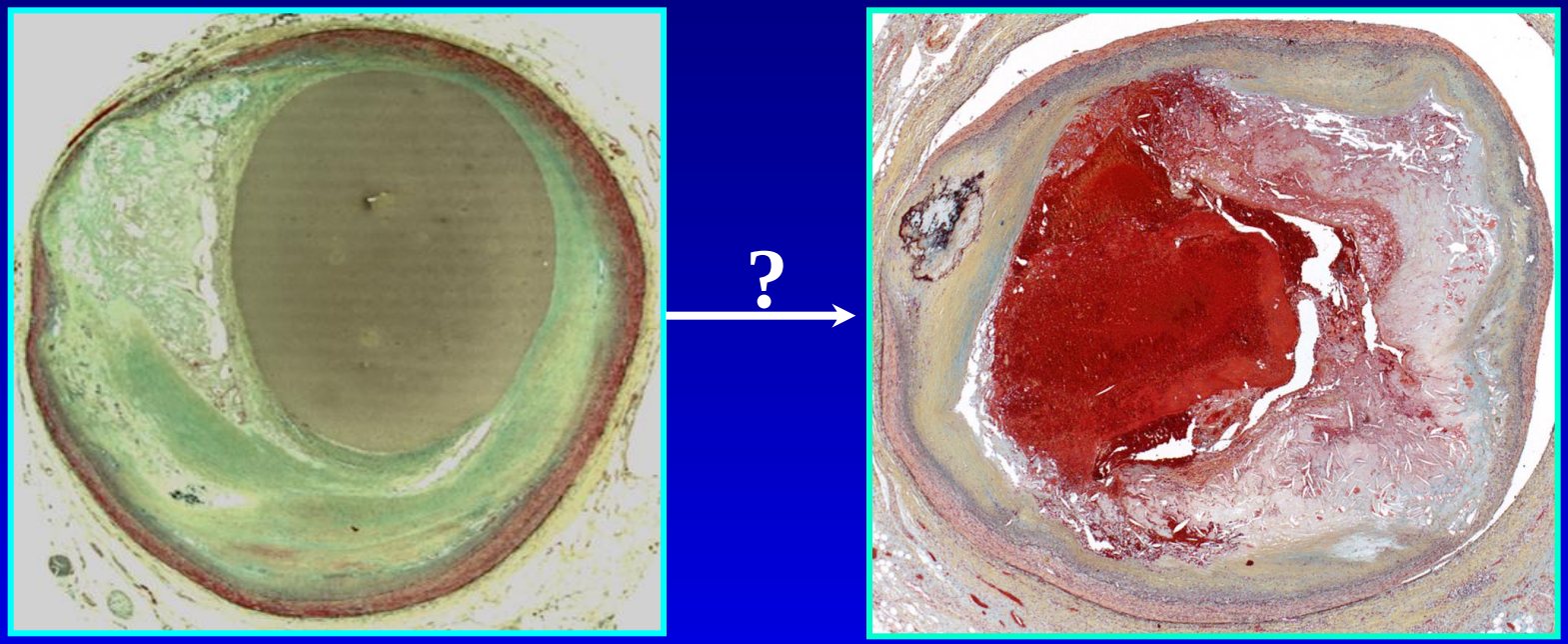
Heart 2007

TLR2 stimulation (Pam3Cys)



Versteeg et al, Heart 2007

Concept of Yesterday:



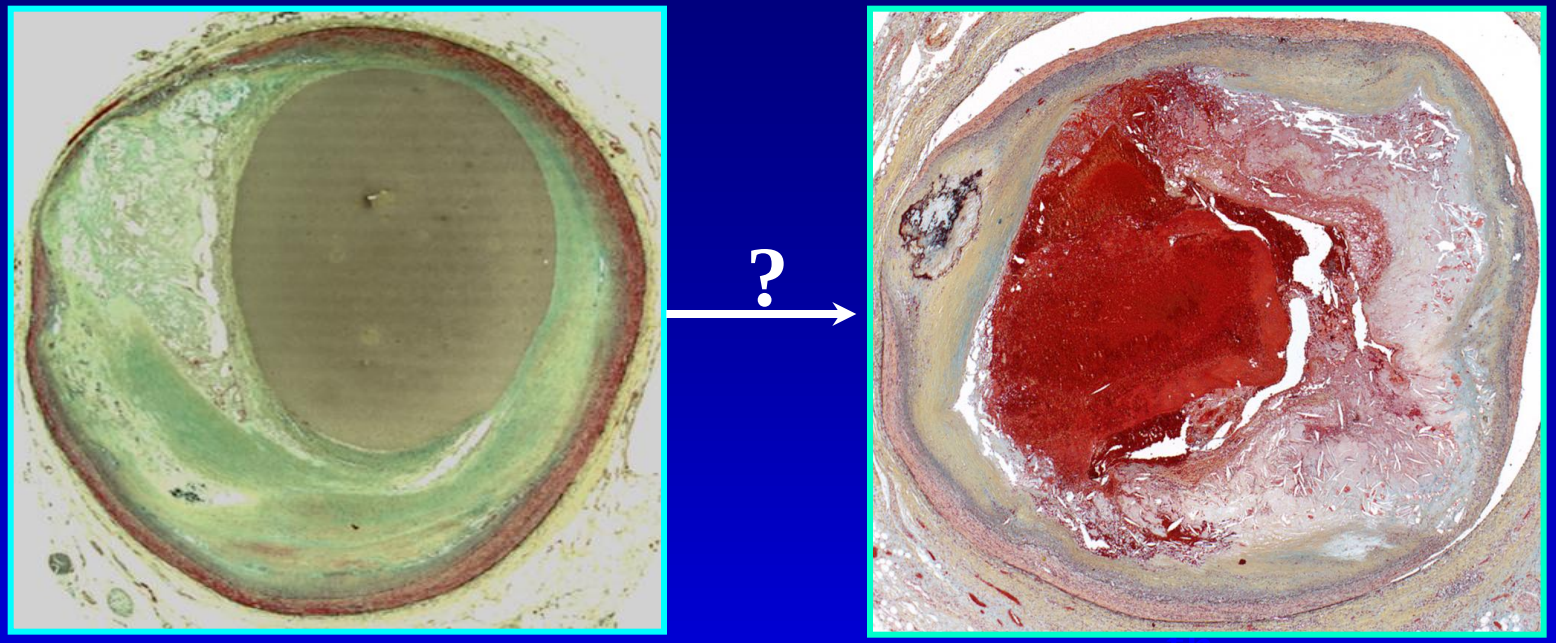
Pro-inflammatory cytokines,activated monocytes, etc

↓

Vulnerability

(“out of the blue”)

Concept of Tomorrow:



ischemic episodes

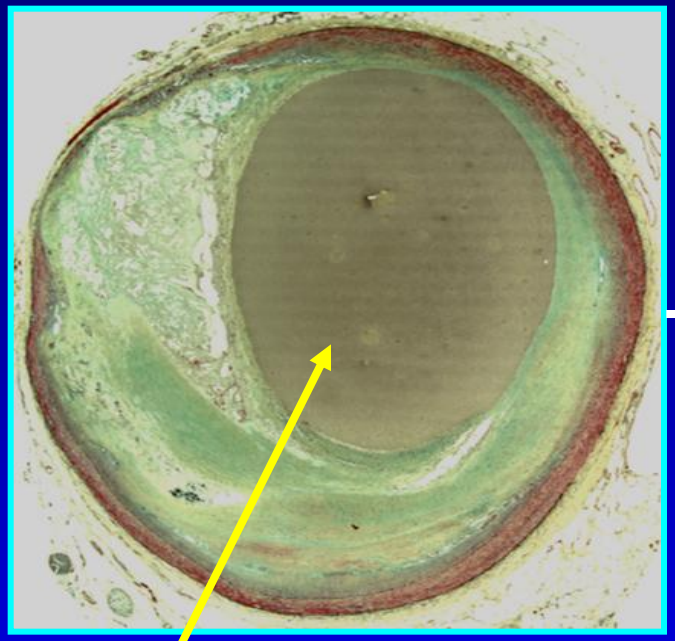
↓

Pro-inflammatory cytokines, activated monocytes, etc

↓

Vulnerability

Concept of today:



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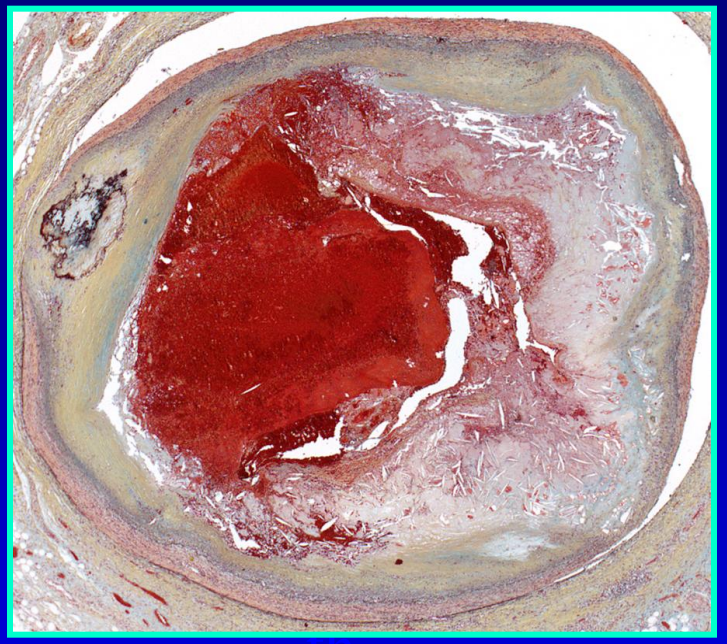

by the way:
70% area
Stenosis !!

ischemic episodes

↓

Pro-inflammatory cytokines etc

↓

Vulnerability

new paradigm:

Plaque / stenosis

↓

Ischemic episodes

↓

production of remodelling-promoting substances

↙ successful remodelling, decrease of ischemia

↘ overshoot, plaque rupture

Searching for vulnerability starts with searching for ischemia

Suppose aliens would visit us and would like to investigate the determinants of a fire.

"Substance X (also called "water") must be dangerous substance !"