THE COMPLEX RELATION BETWEEN VULNERABILITY AND ISCHEMIA

a paradigm shift

Angioplasty Summit TCT ASIA
Seoul, Korea, april 23rd, 2008

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

Paradox or anthithesis ?

Two apparently contradictory concepts:

1. ***The most important prognostic factor in coronary artery disease, is the presence and extent of inducible ischemia:***
   ischemic lesions → *poor prognosis*
   non-ischemic lesions → *excellent outcome with medical treatment*

versus

2. ***concept of vulnerable plaque***:
   plaque rupture occurs on non-significant lesions and is unpredictable

INCIDENCE OF CORONARY STENOSIS IN A GENERAL POPULATION

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

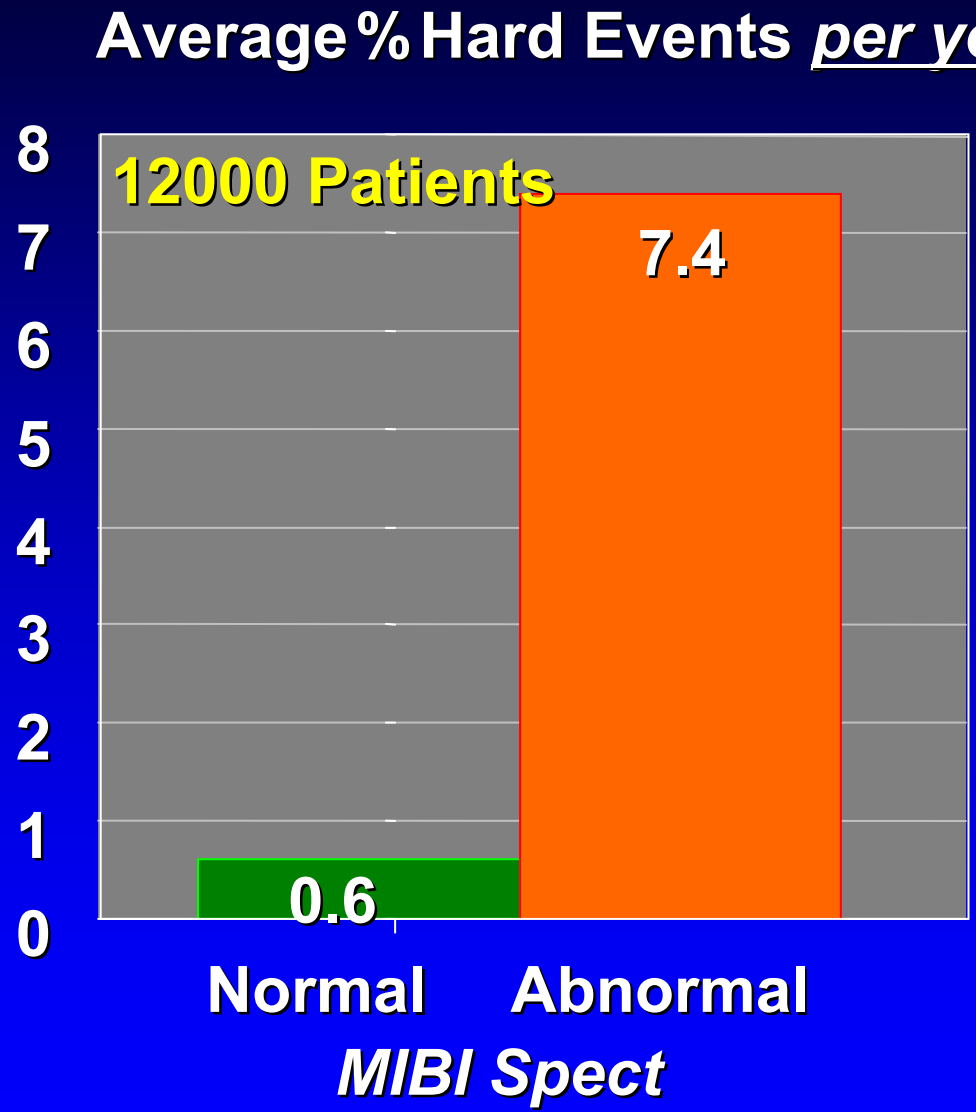
> 50 years old : 25%
> 60 years old : 40%

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

What about the prognosis of these patients ?

⟶ **Related to inducibility of ischemia**

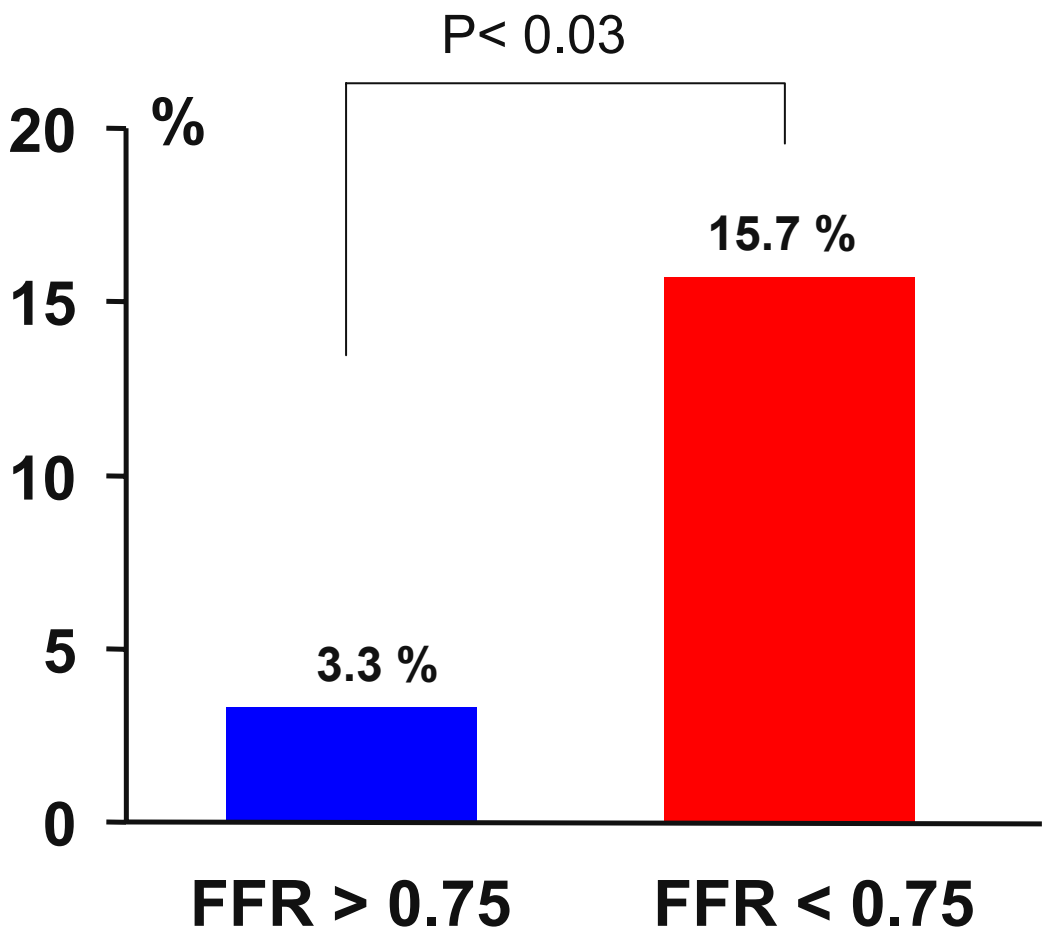
Prognostic significance of reversible ischemia at MIBI-Spect



risk of death or AMI from an ischemic stenosis is 20 x higher than from a non-ischemic stenosis of similar angiographic severity !!!!!

Iskander S, Iskandrian A E JACC 1998

DEFER study (N=325) :
Cardiac death and Acute MI after 5 years



non-ischemic stenosis, treated medically

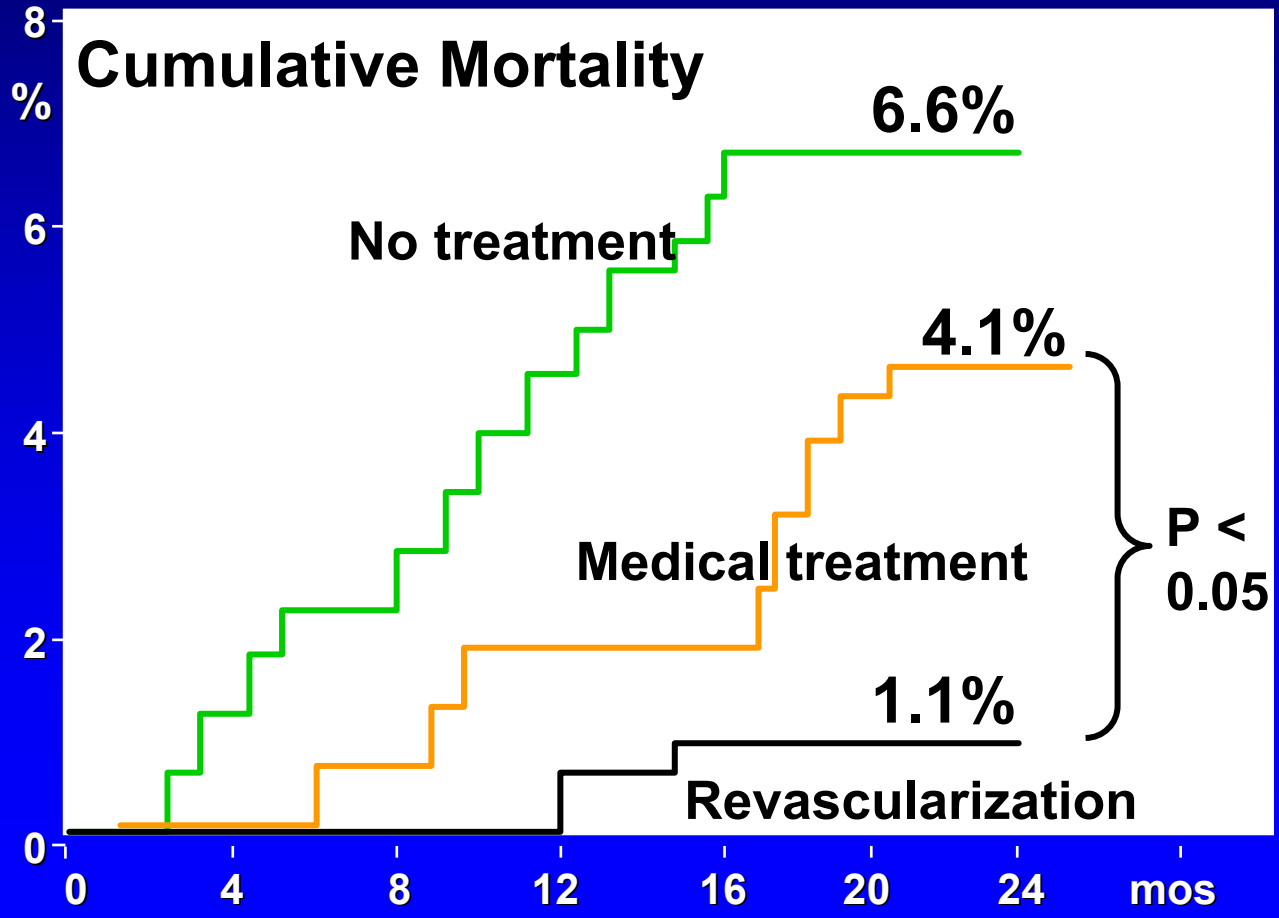
ischemic stenosis, treatment by PCI

ischemic lesion is much more dangerous than non-ischemic lesion

JACC 2007; 49: 2105-2111

PCI OF ISCHEMIC LESION IMPROVES OUTCOME !

558 patients , functionally significant stenosis without symptoms: randomization in 3 treatments strategies



Davies et al. Circulation. 1997

EVIDENCE-BASED MEDICINE:

- ***prognosis is related to inducibility of ischemia***
- ***PCI of "ischemic" lesions (lesions associated with reversible ischemia) makes sense and improves symptoms and outcome***
- ***PCI non-ischemic lesions is questionable and not better than medical treatment***

BUT……

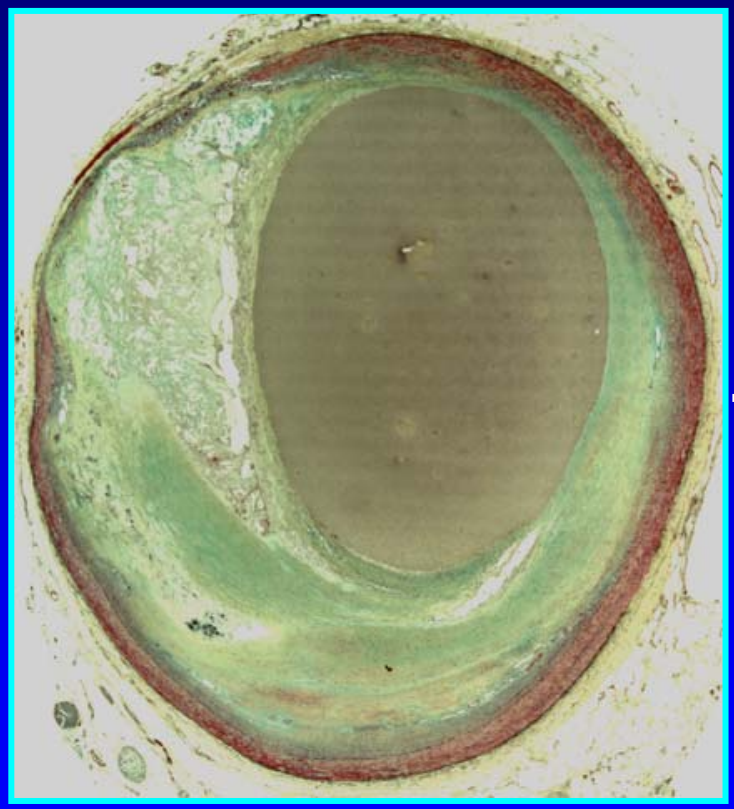
HOW DOES THIS RELATE TO THE CONCEPT OF

“MILD BUT DANGEROUS VULNERABLE PLAQUE”

?

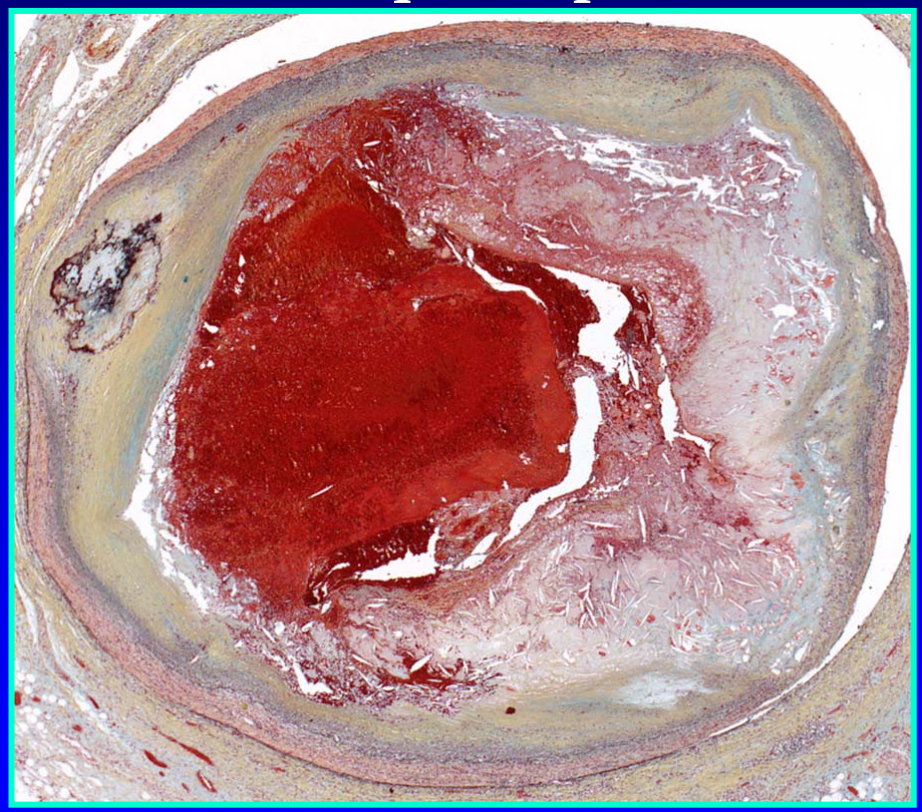
today ? tomorrow

TCFA



?

Plaque Rupture

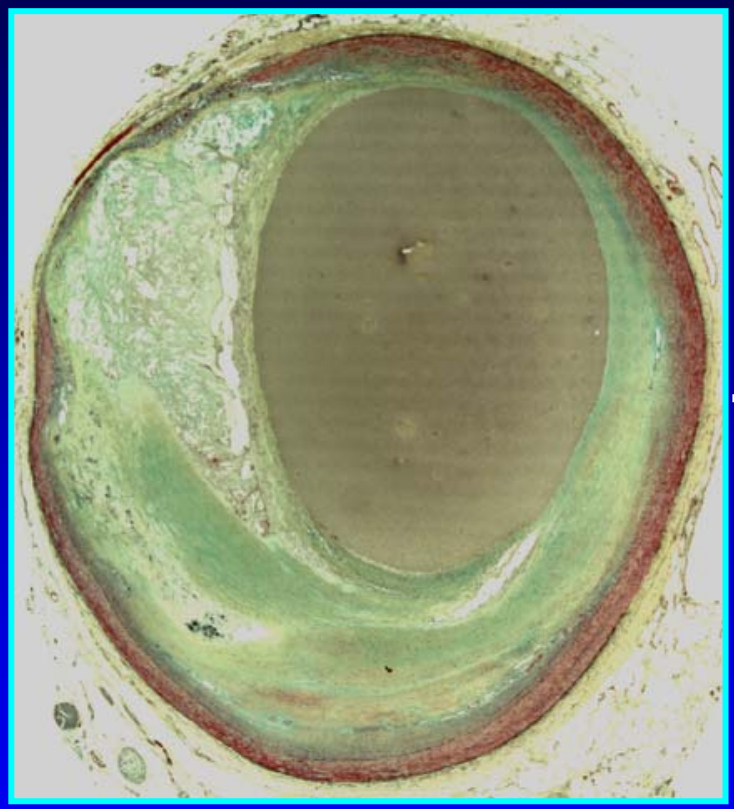


Renu virmani, ETP course 2005

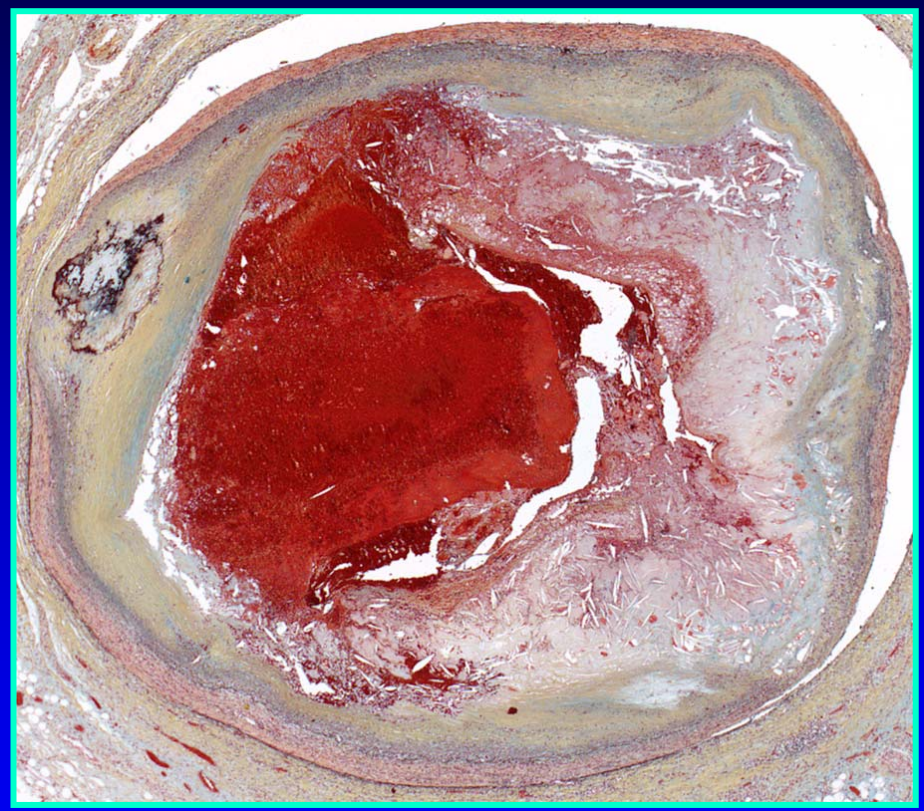
today ? tomorrow

TCFA

Plaque Rupture



?



Let's be a little bit more critical now ……. and distinguish facts and fiction….

Renu virmani, ETP course 2005

(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
- screening of vulnerability can be done by imaging

Screening for vulnerable plaque? How to start ?

- Suppose you have a method (whether invasive or not) with a sensitivity and specificity of 95 % (***utopic***, but let's assume).

- In the city of Eindhoven (250.000 citizins), the total number of citizins with hidden or overt CAD is at least 25.000, corresponding with at least 100.000 non-significant plaques.
- In the next 3 month, only 300 patients will develop ACS

Suppose you screen all patients with plaques for "vulnerability":
285 will be discovered correctly (true positives)
5000 will be "false" positive

⟶ **predictive value is 5 % !!**
you will place 20 unnecessary stents to prevent 1 ACS

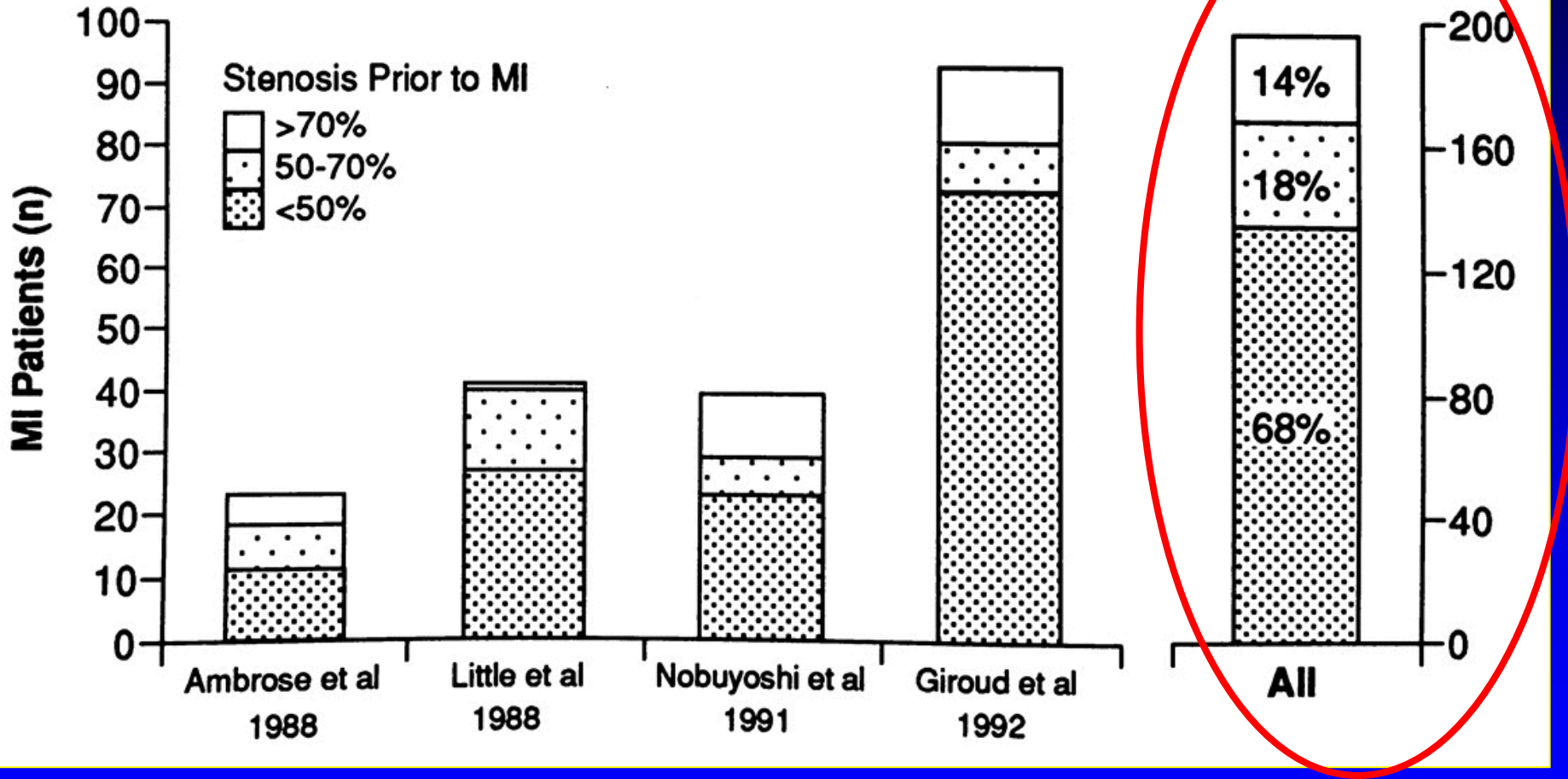
The majority of ACS occur

at the site of mild lesions

?

The mythe of the "dangerous" plaque

Underlying Stenosis Severity of Abrupt Total Occlusions



Falk, Shah and Fuster, Circulation 1995

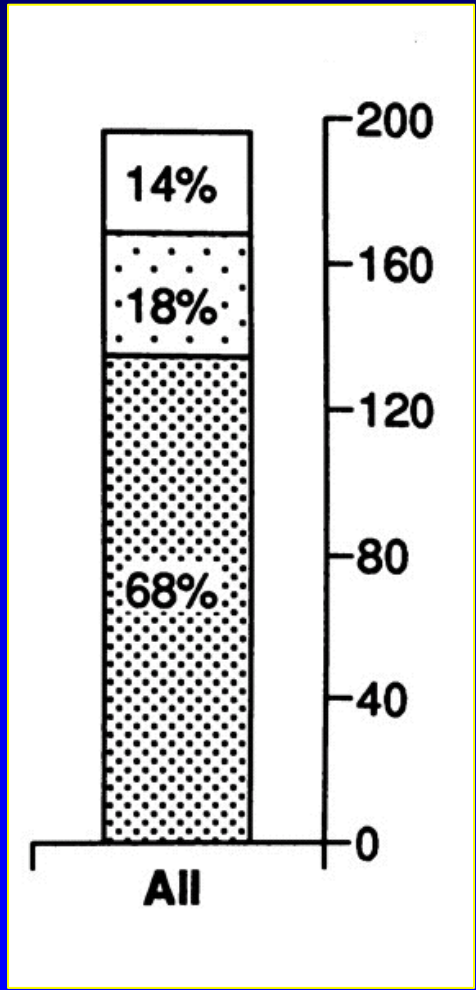
"Acute Coronary Syndromes most often occur at the site of mild stenoses"

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 !!!)**



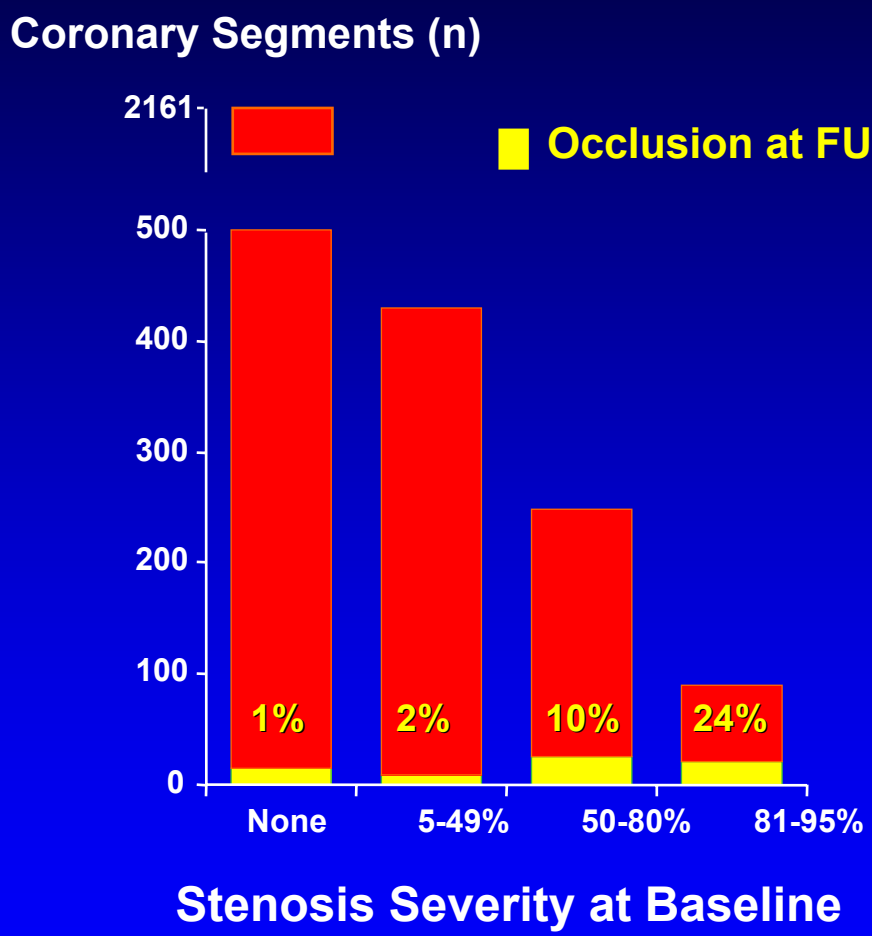
THE MYTHE OF THE "DANGEROUS" PLAQUE

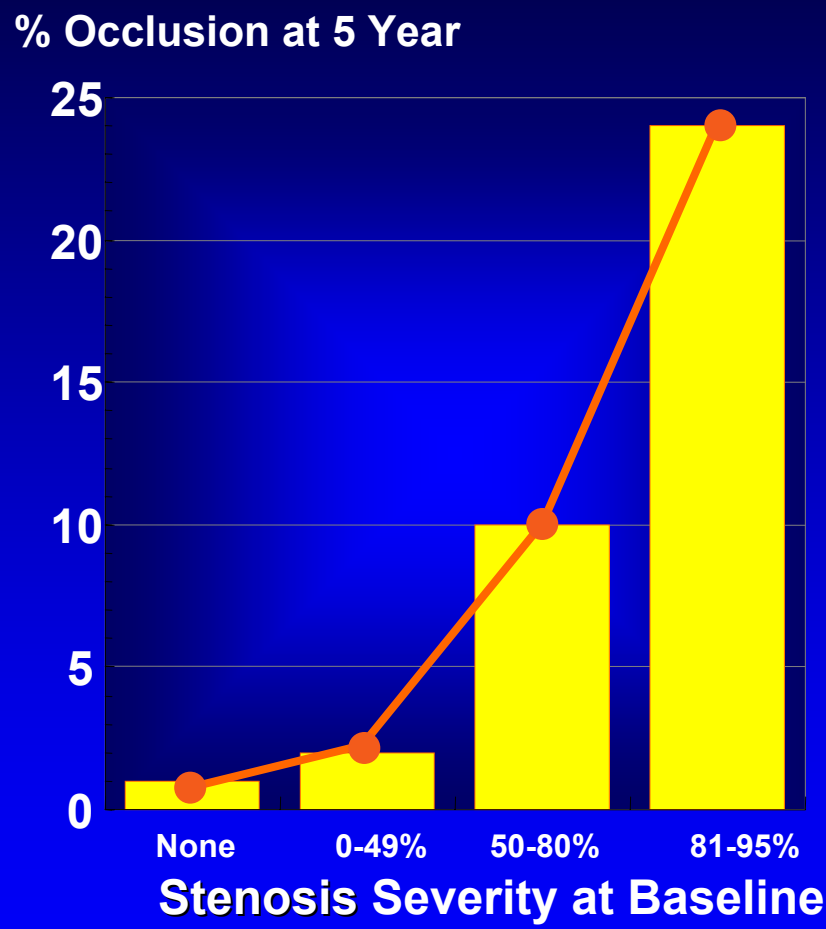
The hypothesis of the occurrence of acute MI on such previously non-significant plaque is based upon

- **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

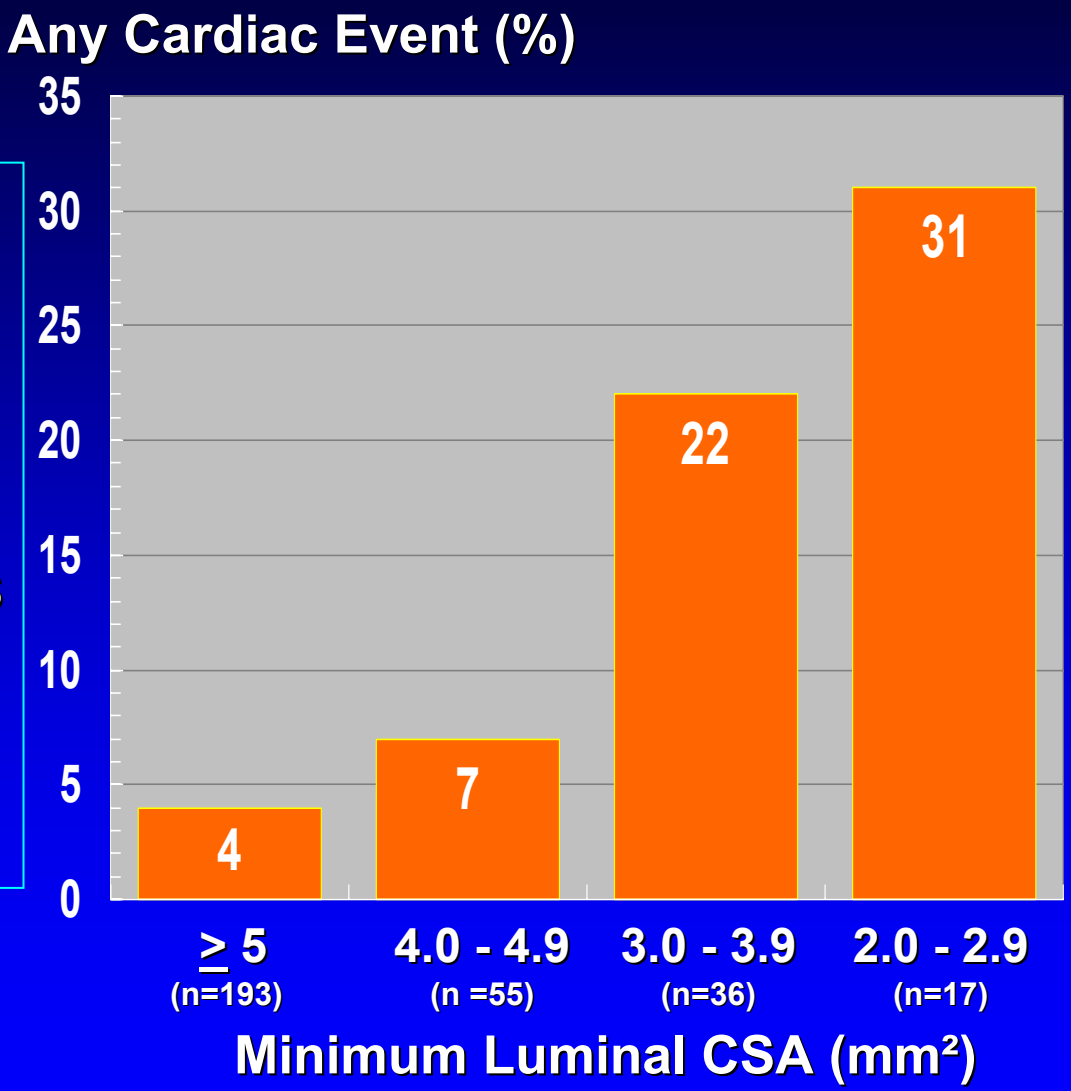




Adapted from Alderman et al. J Am Coll Cardiol 1993

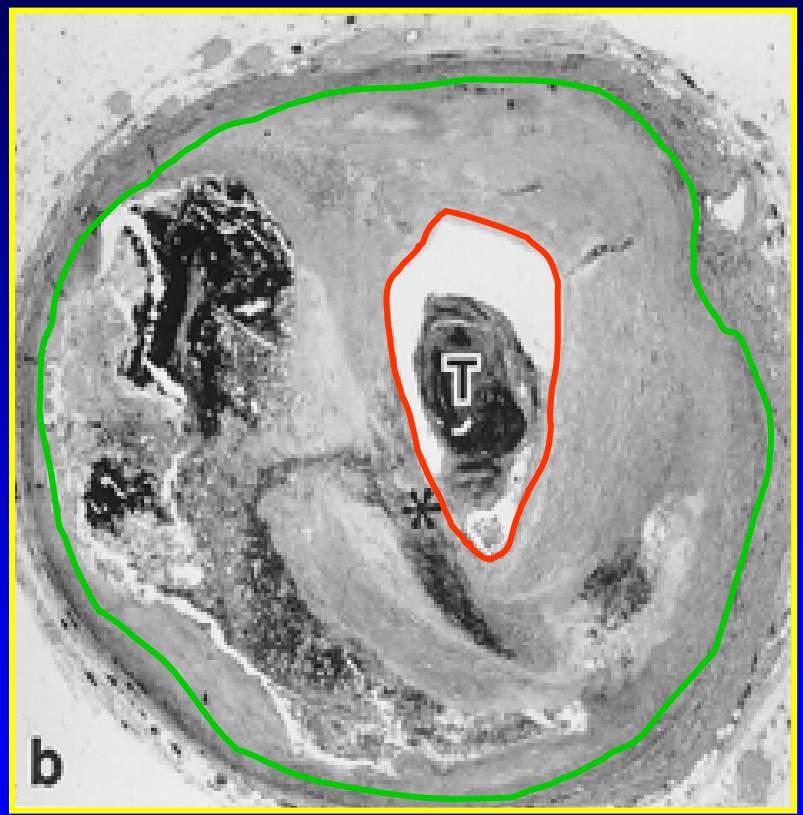
IVUS Examination: Clinical Outcome after Deferred Interventions

- 300 pts; 13 mos F-U
- CSA = only independent predictor of events
- Independent predictors of TLR: diabetes, min CSA, AS
- When CSA > 4 mm²:
  - event rate: 4%
  - TLR: 2.8%

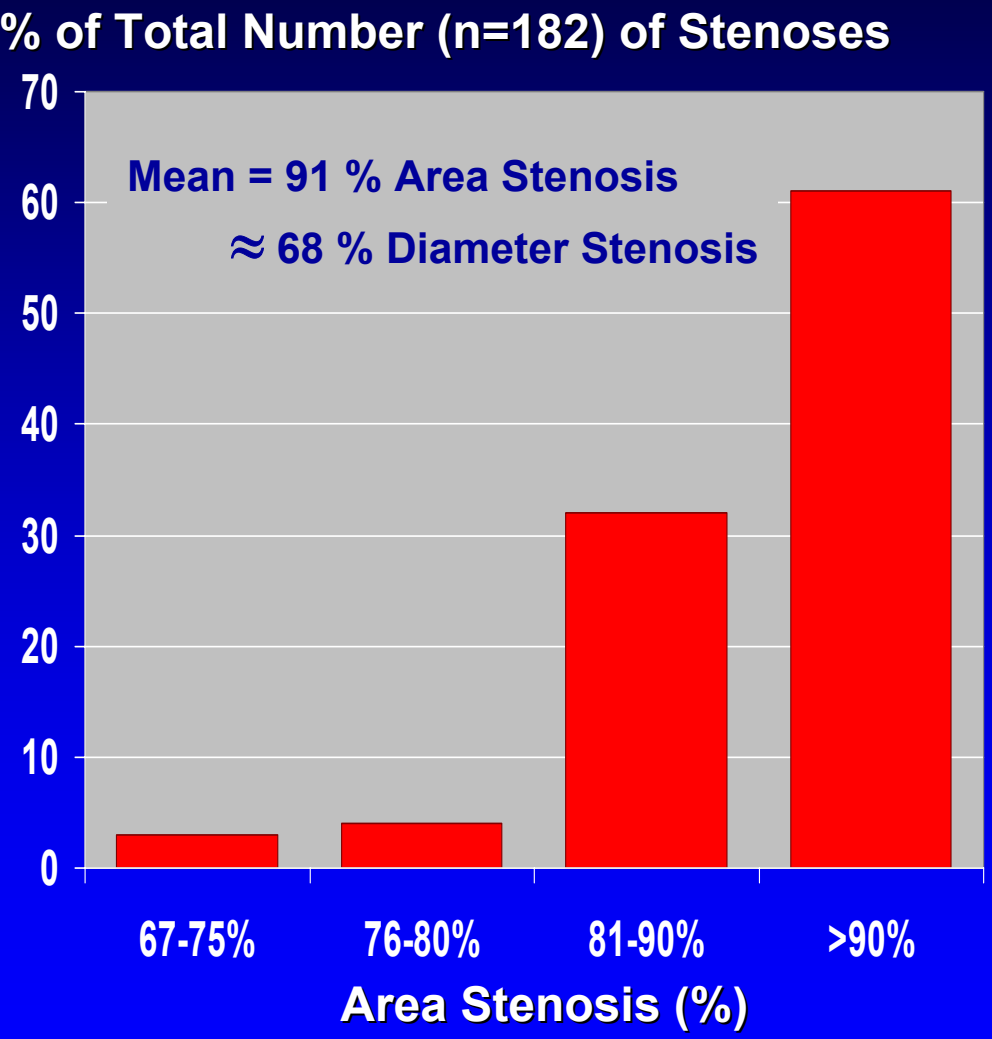


Abizaid AS et al. Circulation, 1999

Severity of Coronary Atherosclerosis at Sites of Plaque Rupture with Occlusive Thrombosis



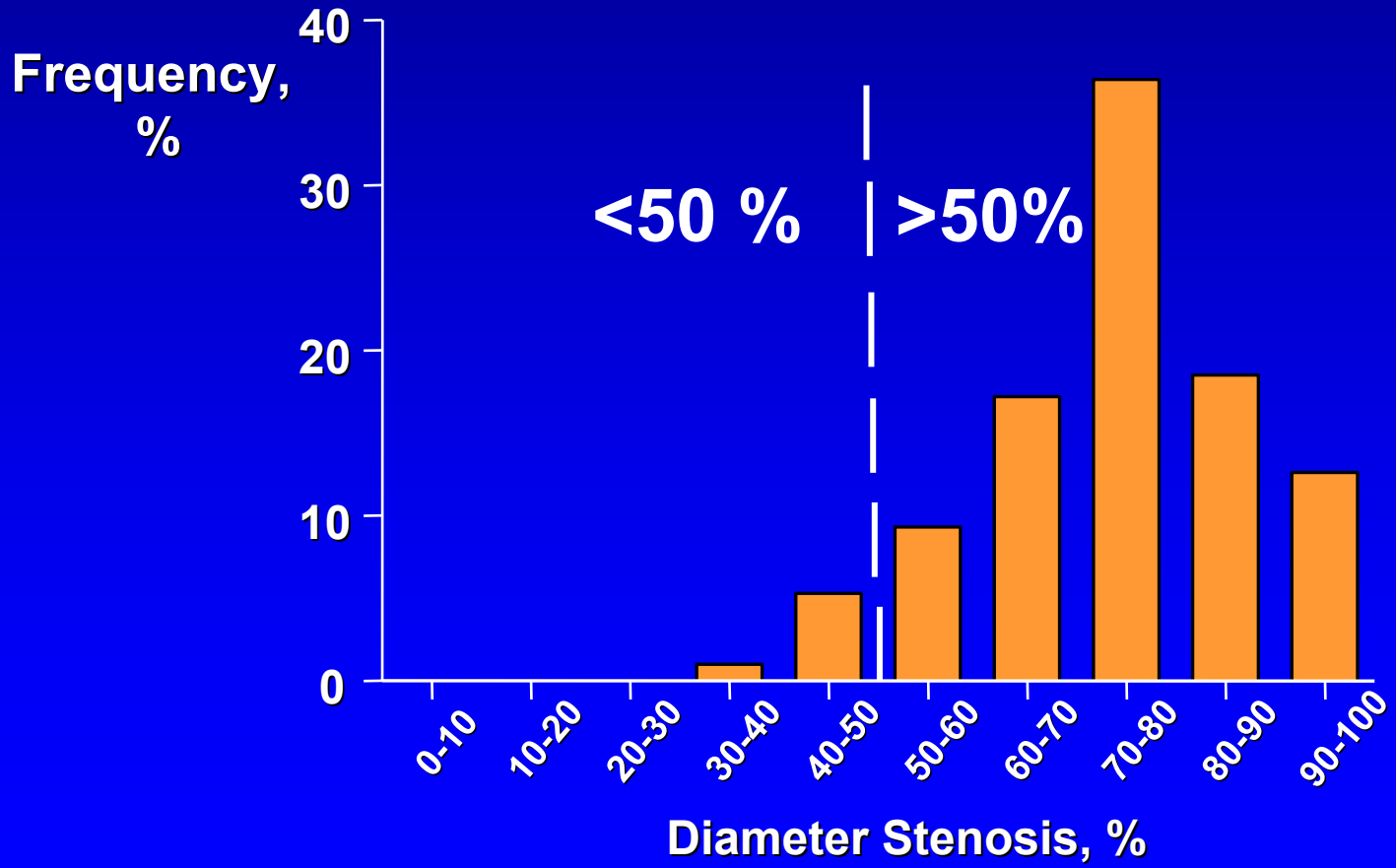
Area Stenosis = $\frac{\text{Vessel area} - \text{lumen area}}{\text{Vessel area}}$



Qiao J-H et al. JACC 1991

Stenosis Severity at Primary PCI in AMI

- 156 stenoses with distal flow enabling accurate QCA out of 250 consecutive Acute MI's
- In 92 %, underlying stenosis was > 50%
- In 71 %, underlying stenosis was > 70%



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

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

The fact that acute coronary syndromes "sometimes" occur in relation to a previously insignificant plaque, does not mean that a plaque is more dangerous than a severe stenosis, *because*:

Non-significant "plaques" :

Are 20 x more frequent than severe lesions. So, even if 50% of ACS would be related to such plaque, its *individual risk* is 20 times lower than the risk of a severe stenosis

Non-significant "plaques" :

Are often not giving complaints and therefore not treated in a similar way as a physiologically significant stenosis (aspirin, statines, stenting)

Paradox or anthithesis ?

Ischemia-related concept of prognosis

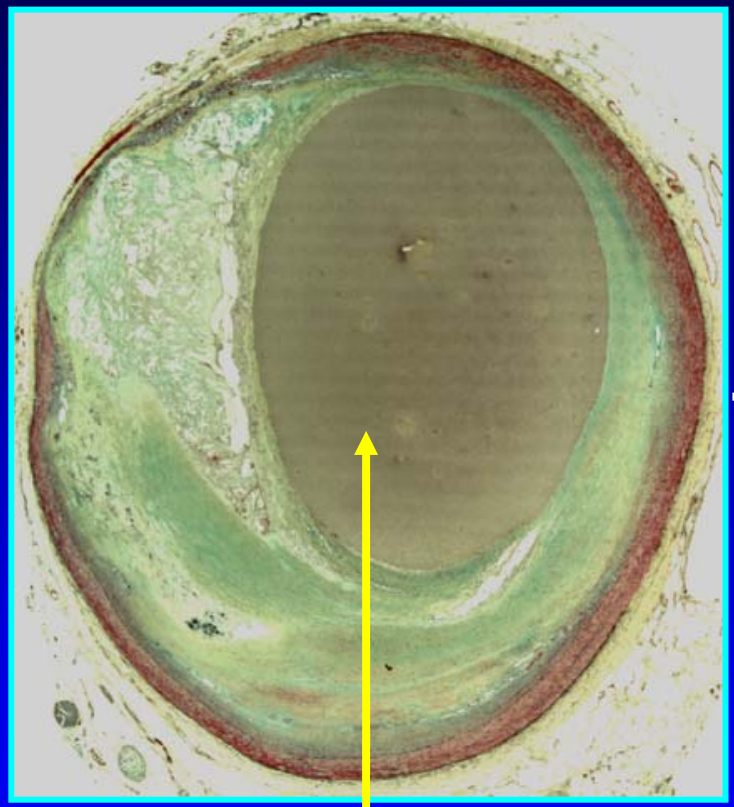
- Excellent outcome of medical treatment in non-ischemic stenosis
- Dangerous lesions are those associated with reversible ischemia

versus

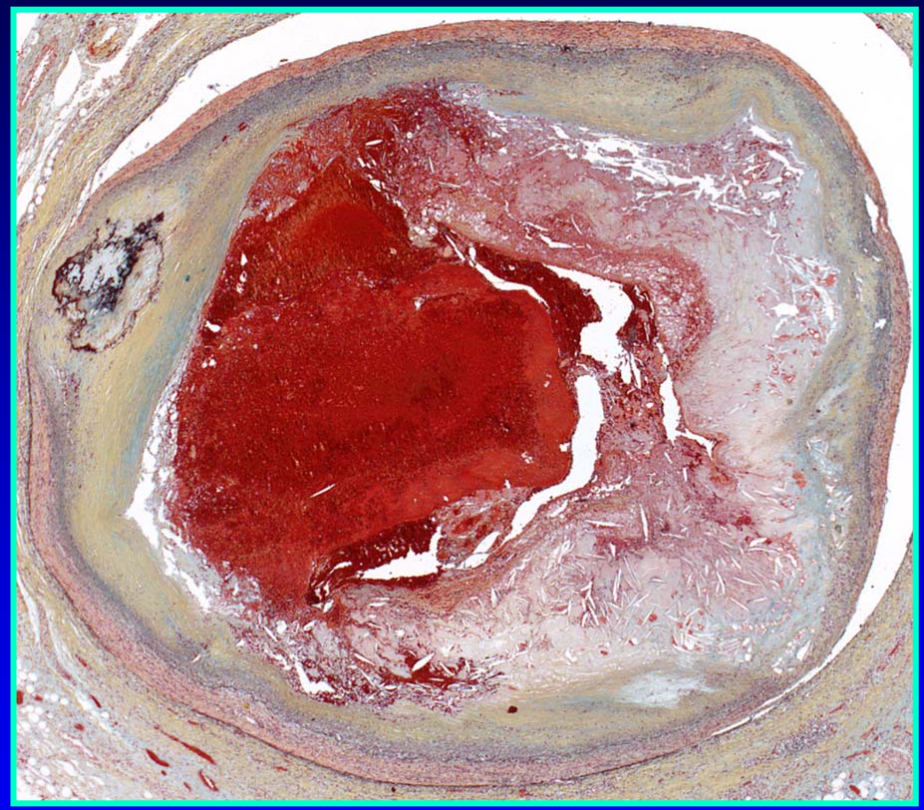
concept of vulnerable plaque

→ ***relation between vulnerabilty and ischemia !?!***

today ? tomorrow



?



This is not a mild plaque but a 70% area stenosis !!!

→ *Low FFR*

Renu virmani, ETP course 2005

"The missing link"

Is there a link between vulnerabilty and ischemia ?

Hypothesis:

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

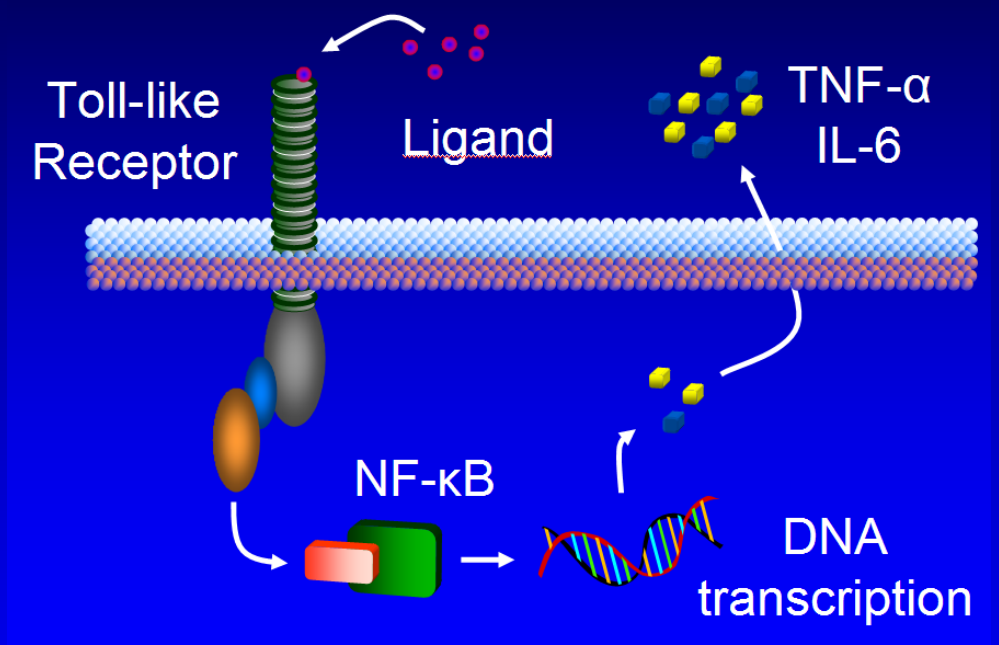
induce vulnerability

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

Heart 2007

TOLL-LIKE RECEPTORS ON LEUCOCYTES AND VULNERABILITY MARKERS

- Toll-like receptors (TLRs) are part of innate immune system
- ***Activation of TLRs results in production of pro-inflammatory cytokines, TNF-α, and other markers of vulnerabilty***



- In animal models, ***ischemia triggers TLR expression*** with increased production of TNF-α and other pro-inflammatory substances

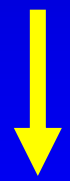
Medzhitov R, Nat Rev Immunol. 2001 Nov;1(2):135-45

J Cereb Blood Flow Metab. 2004 Nov;24(11):1288-304

PLAQUE VULNERABILITY & ISCHEMIC FFR:

If it is realized that also in humans

- coronary ischemia induces activation of TLRs
- ischemic coronary lesions can be detected by FFR



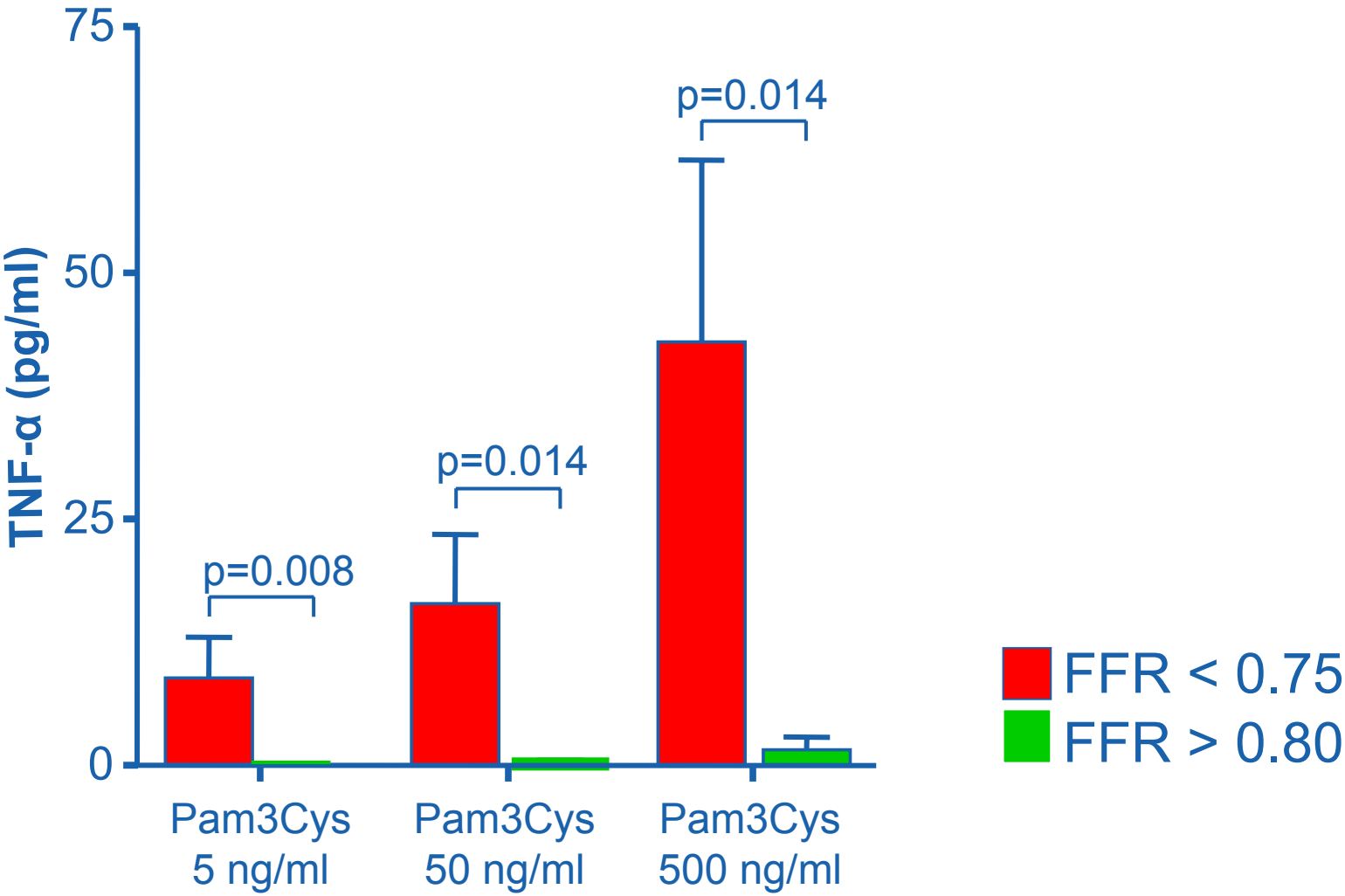
Is FFR related to TLR activity ?

Pilot Study in 50 humans:Methods

- Patients undergoing FFR measurement included in study
- Arterial blood sample drawn immediately following sheath insertion
- Blood sample transferred to lithium-heparin tube and placed on ice to prevent preliminary TLR activation
- Samples incubated overnight with TLR ligands
- TLR2 stimulation: 500, 50 and 5 ng/ml Pam3Cys
- TLR4 stimulation: 100, 10 and 1 ng/ml lipopolysaccharide
- ELISA for TNF-α and other cytokines in stimulated samples

Steeg et al, Heart 2007

TLR2 stimulation (Pam3Cys)



Steeg et al, Heart 2007

Results of that pilot study

- TNF-α production following stimulation of TLRs in whole blood is significantly higher if FFR<0.75

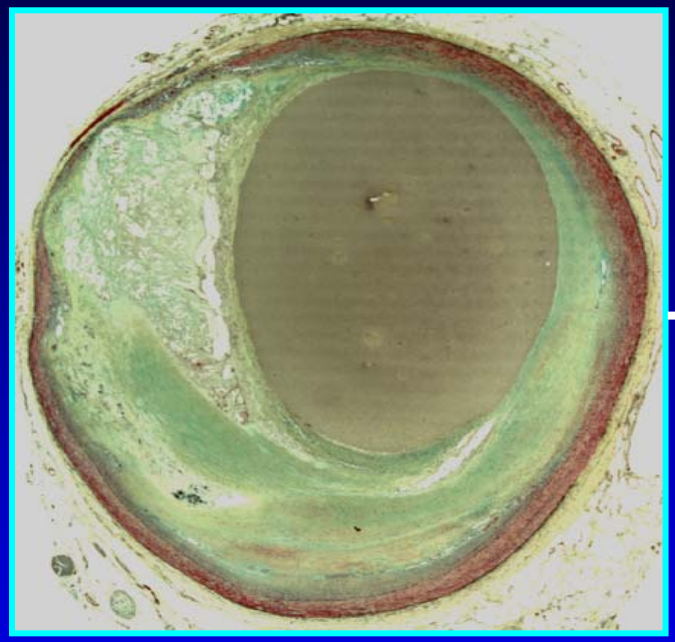
- Episodes of myocardial ischemia trigger for enhanced sensibility of TLRs and production of markers of inflammation

2 running studies:

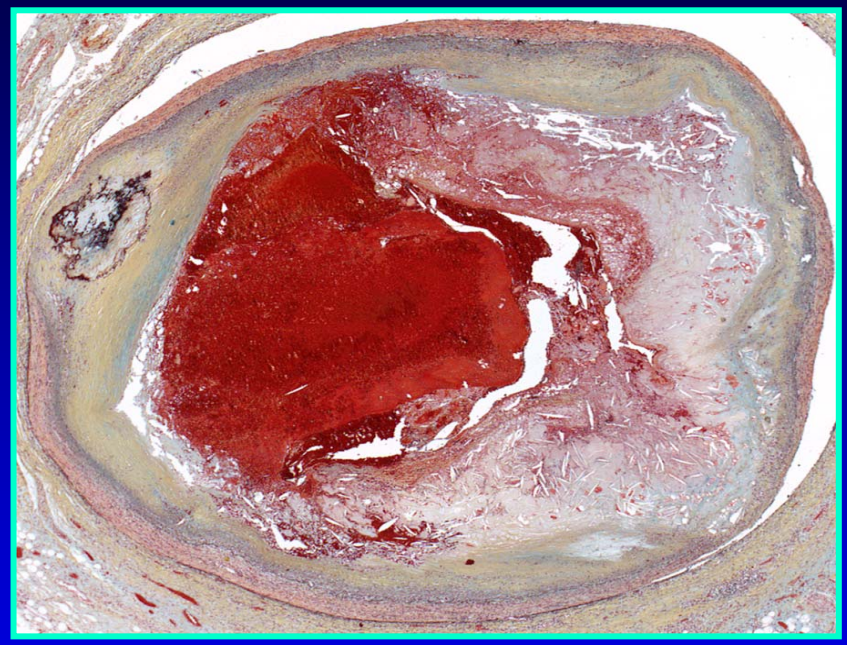
- TERMS study: Toll-like receptor expression and response in patients undergoing myocardial SPECT (100 patients, currently running)

- CTMM: Large multicenter trial to establish relation between FFR and vulnerabilty markers (800 patients)

Yesterday:



?



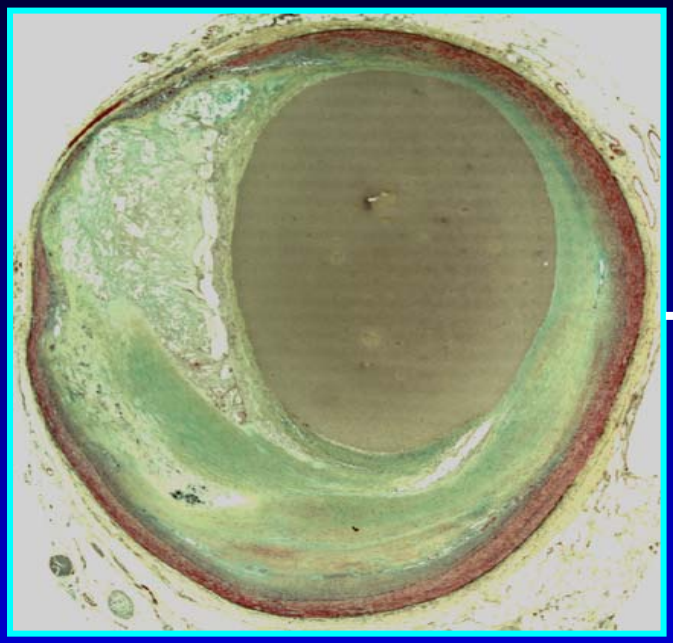
Pro-inflammatory cytokines etc

↓

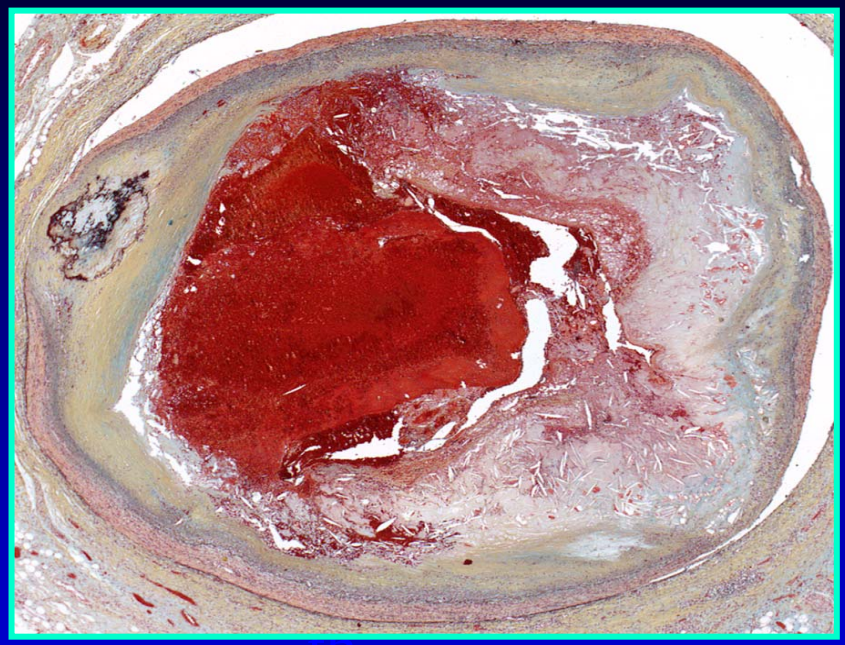
Vulnerability

("out of the blue")

Today / Tomorrow:



?



ischemic episodes

↓

Pro-inflammatory cytokines etc

↓

Vulnerability

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

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

new paradigm:

Plaque / stenosis

↓

Repetitive ischemic episodes

↓

production of remodelling-promoting substances

↙ successful remodelling, relieve of ischemia

↘ overshoot, plaque rupture

Searching for vulnerability starts with searching for ischemia

Screening for vulnerable plaque? How to continue?

- Strongest indicator with respect to prognosis, is inducible ischemia.

- Historical data & ACIP-trial: in asymptomatic patients with proven ischemia (ET / MIBI-Spect / FFR) but without intervention, at least **5** % (50/1000) will develop ACS within the next year.

- *suppose you screen 1000 patients with ischemic lesions:*
  45 will be discovered correctly ("true"-positives)
  45 will be "false" positive

predictive value is 50 % !!

you will place 1 unnecessary stent to prevent 1 ACS

Bayes theorema, Melin et.al, Circulation 1981

IN SUMMARY:

- There is a relation between vulnerabilty and ischemia, although complex and not yet completely understood

- Vulnerability does not occur “out-of-the-blue” , but is promoted in many cases by repetitive episodes of ischemia

- searching for vulnerable plaques in general, is searching for the needle in the haystack

- However, the haystack can be made much smaller (*and the screening process made more effective*), by first searching for ischemia !