Imaging & Physiology Summit

FUNCTIONALLY INSIGNIFICANT, VULNERABLE PLAQUE: DO YOU WANT TO TREAT?

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main arena

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(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 *inducible* ***ischemia***

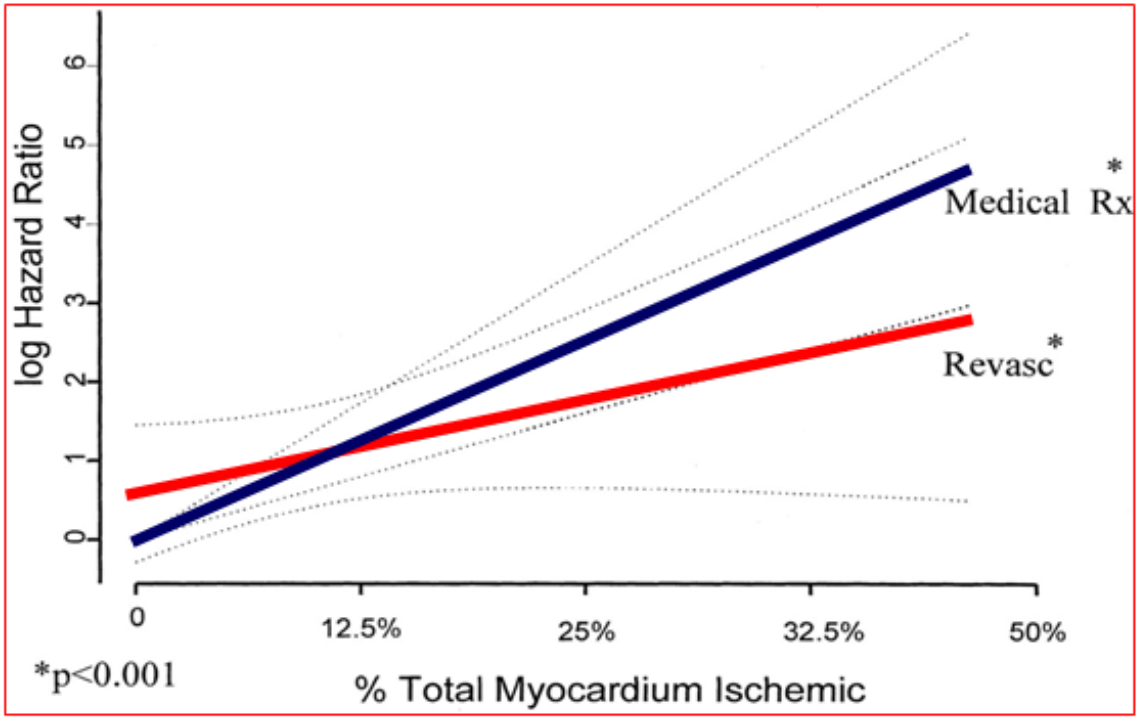
FICTION:

- every plaque is vulnerable
- every vulnerable plaque leads to ACS
- most ACS occurs in mild plaques
- screening of vulnerability can be done by imaging

Is it important to detect ischemia ?

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

Mortality



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

Hachamovitch, R. et al. Circulation 2003

Paradox or antithesis ?

Two apparently contradictory concepts:

1. ***The most important prognostic factor in coronary artery disease, is the presence and extent of inducible ischemia:***

versus

2. ***(presumed) concept of vulnerable plaque***:
   plaque rupture occurs on non-significant (non-ischemic ???) lesions and is unpredictable

Paradox or anthithesis ?

- **Is our idea about "vulnerability" correct or too much "coloured" by appealing but unproven visual impressions?**

- **What if "morphology" has little to do with vulnerability ?**

  (It has NEVER been shown in a prospective RCT that any morphologic feature of a plaque bears prognostic risk for death or MI)

- **What if *"vulnerability"* is determined by *repetitive inducible ischemia?***

PROSPECT STUDY (Stone et al, NEJM 2011)

- 697 patients with ACS in whom “non-culprit” lesions were investigated for concomittant “vulnerable” plaques by angiography, IVUS, and VH

- after 3 years, rate of death + AMI related to such “plaque” was ~ 1% per year ; “progression of angina” ~ 3% per year

- predictors for an “event” were not only specific plaque features (such as TCFA, plaque burden, etc) but ***stenosis severity !***

→ ***Excellent prognosis of deferred non-significant plaque***

→ ***If any morphologic aspect predicts vulnerability, it is severity (a surrogate of functional significance!)***

BUT……

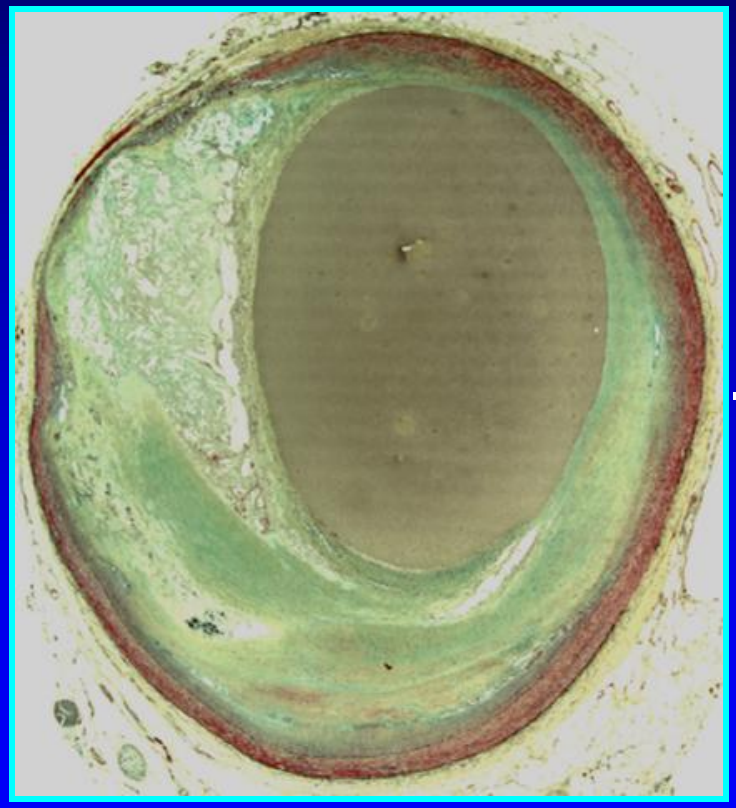
HOW DOES THIS RELATE TO THE CONCEPT OF

“MILD BUT DANGEROUS VULNERABLE PLAQUE”

?

today ? tomorrow

TCFA



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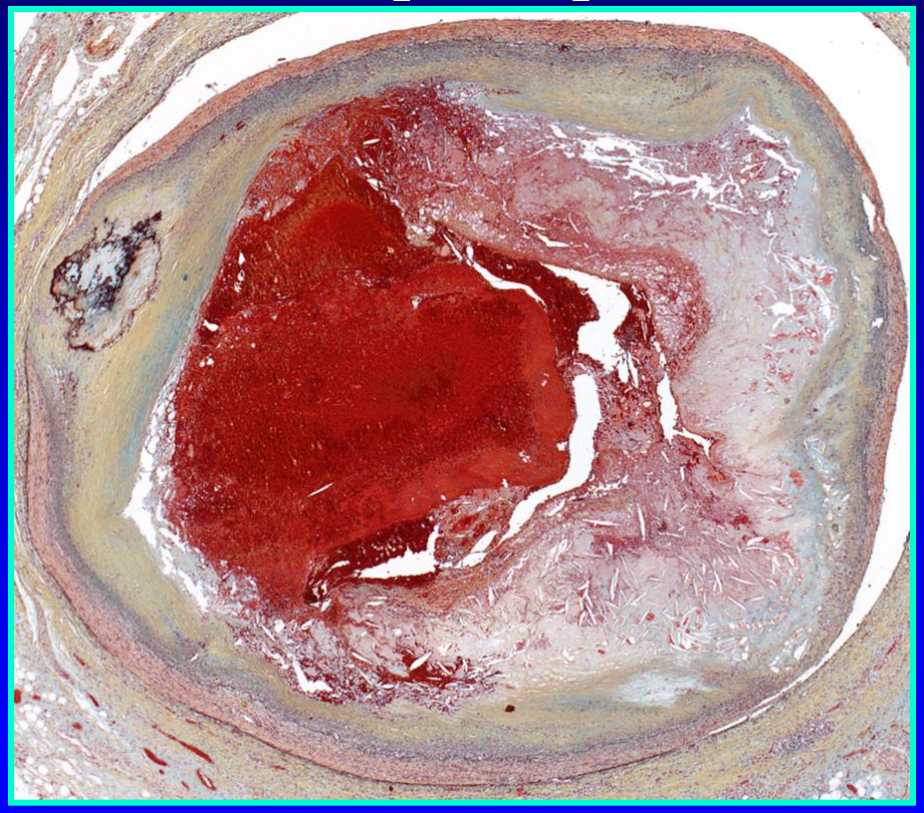
Plaque Rupture



Renu virmani, ETP course 2005

So, we need to reconsider what we mean by

“vulnerable plaque” !

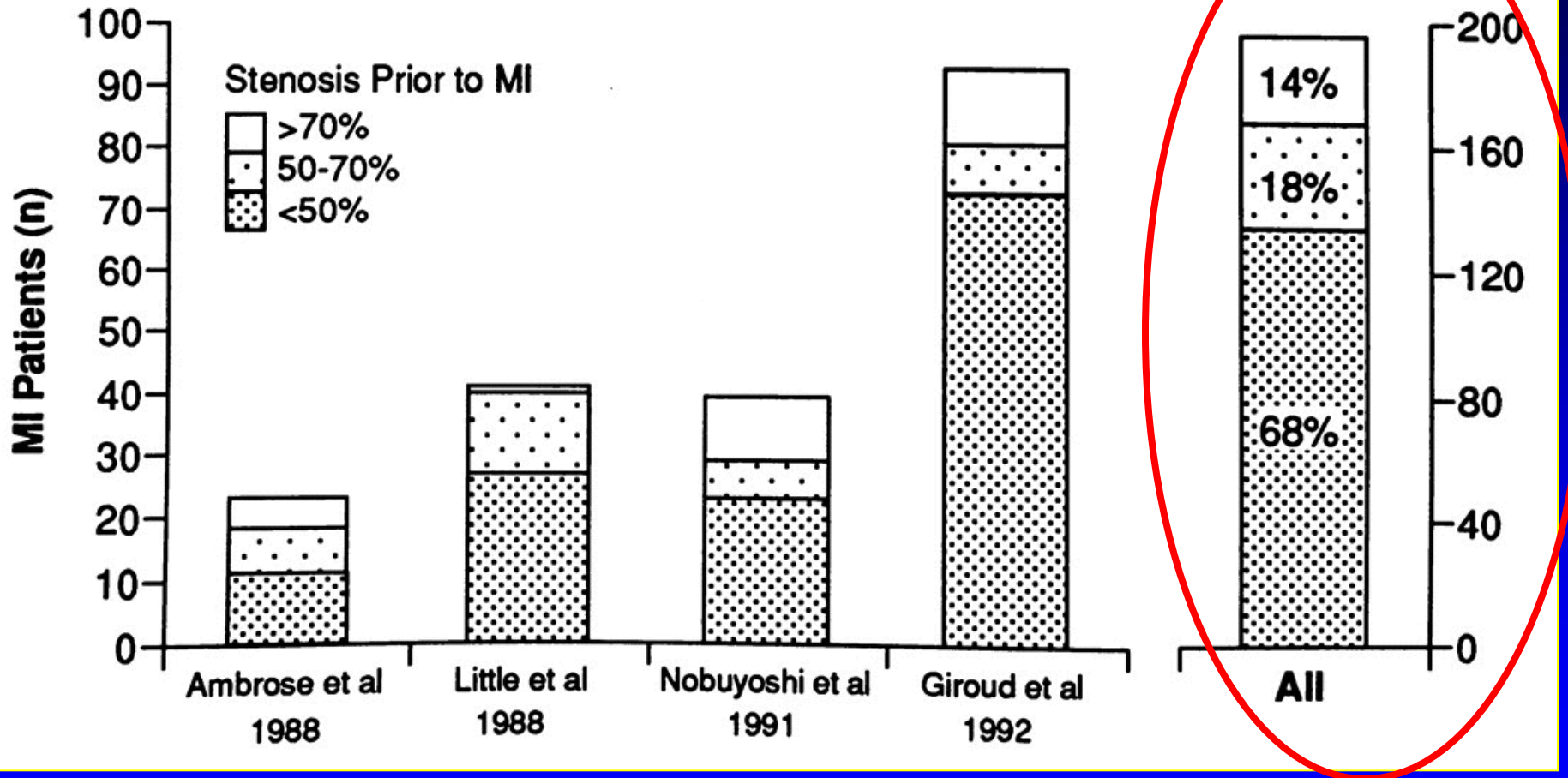
The majority of `vulnerable` plaques

consist of mild, non/significant lesions

?

The mythe of the "dangerous" plaque: Where does it come from ?

Underlying Stenosis Severity of Abrupt Total Occlusions



Falk, Shah and Fuster, Circulation 1995

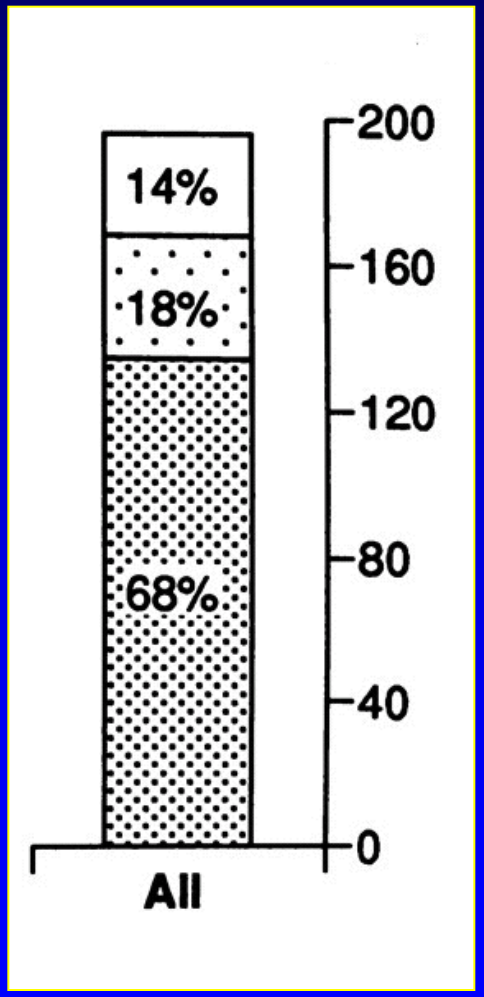
"Acute Coronary Syndromes most often occur at the site of mild stenoses"

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

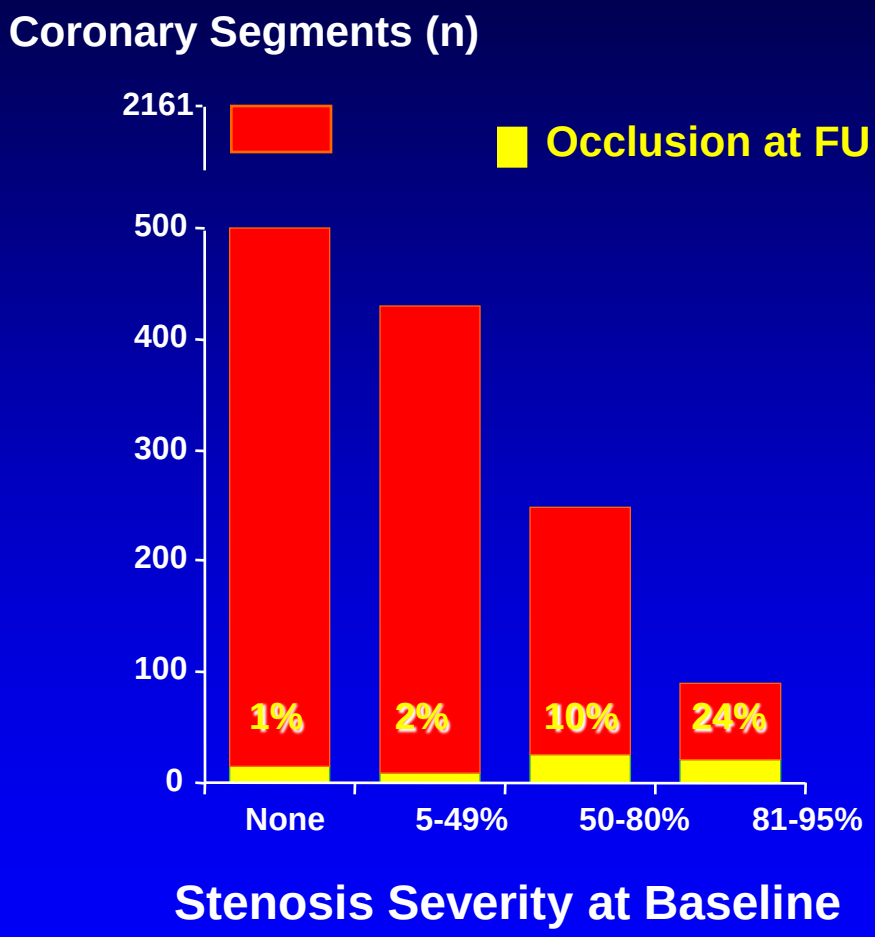
The hypothesis of the occurrence of acute MI on such previously non-significant plaque is based upon

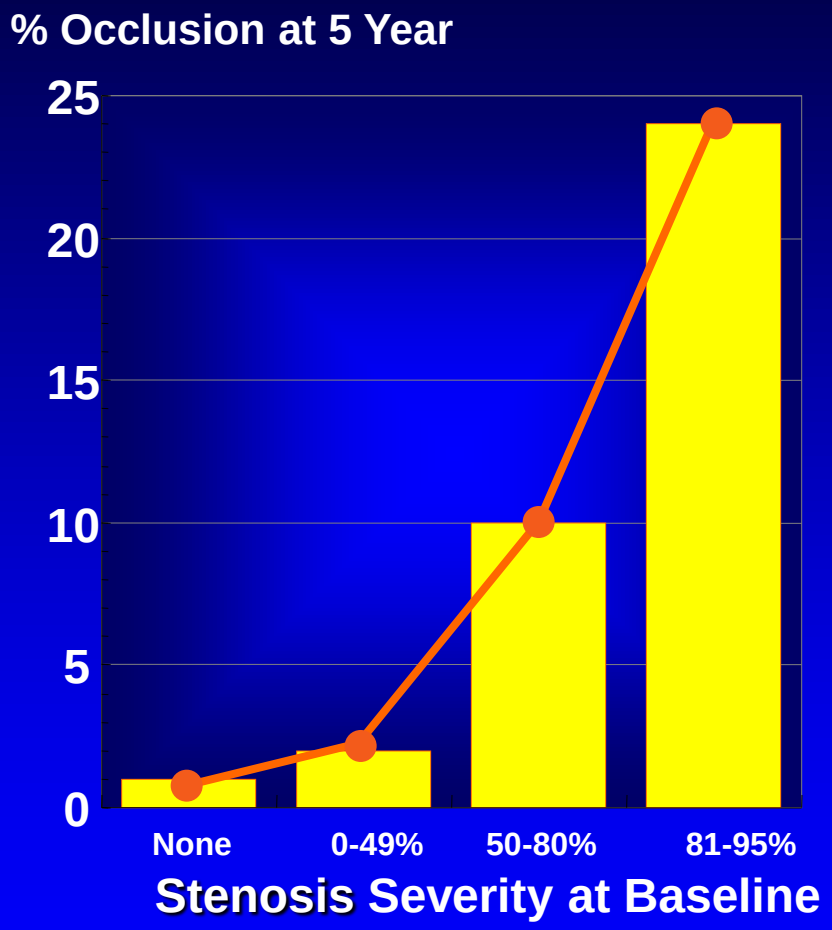
- **6 small retrospective studies**
- **with a total of 313 patients**
- in whom the "index" catherization was performed an average of ***3.9 years*** before the acute event
- in an era when no statins were available

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

*What do **PROSPECTIVE** STUDIES tell us ?*

Coronary Occlusion at 5 Years as a Function of Stenosis Severity

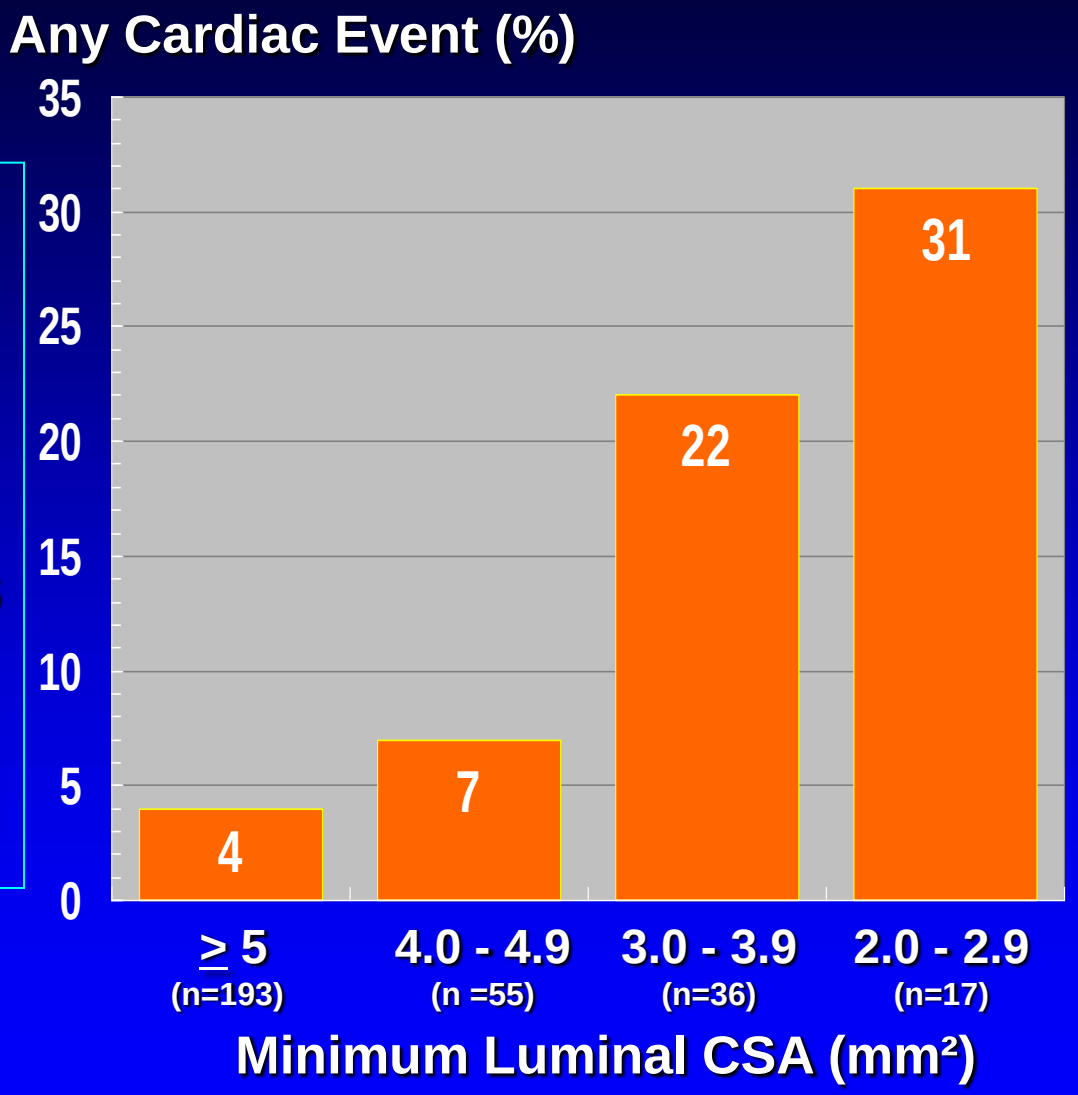




Adapted from Alderman et al. J Am Coll Cardiol 1993

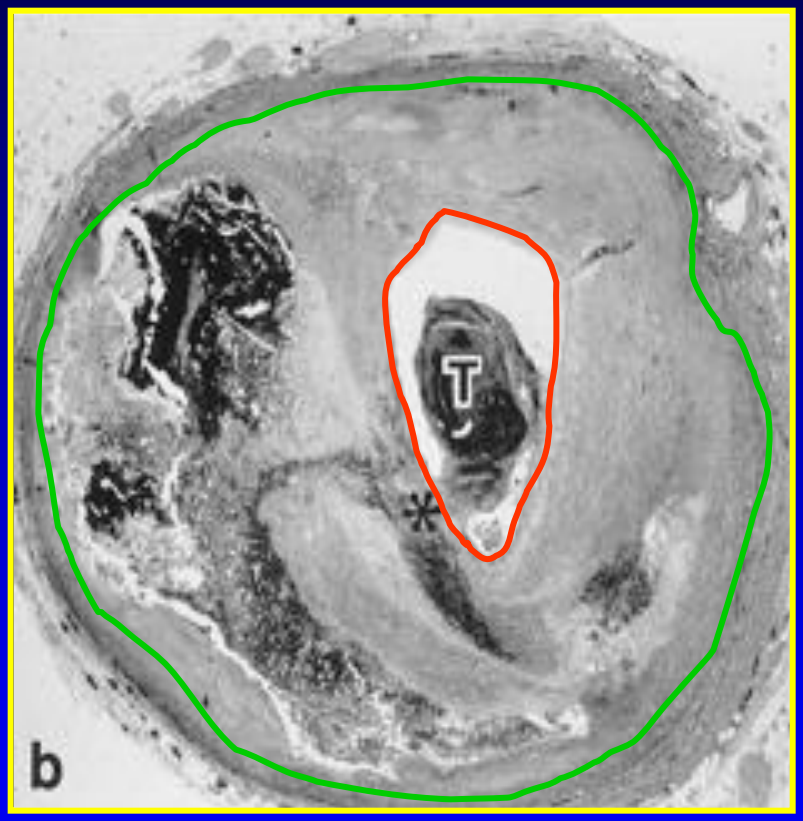
IVUS Examination: Clinical Outcome after Deferred Interventions

- 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%

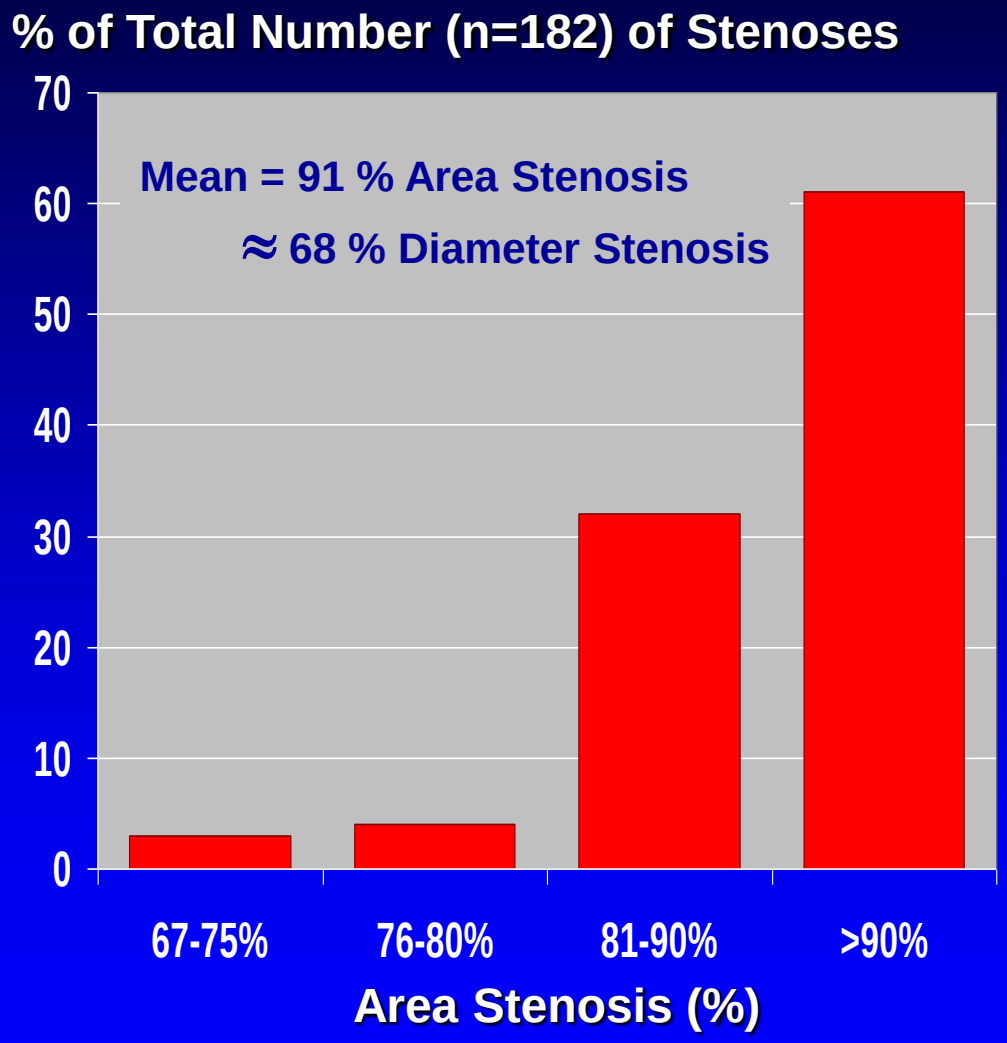


Abizaid AS et al. Circulation, 1999

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



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

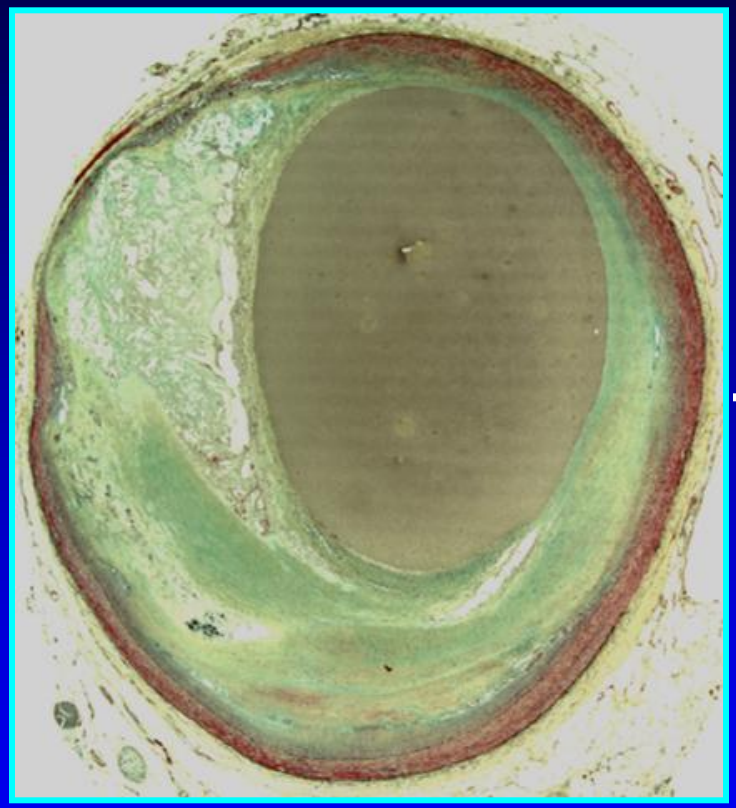


Qiao J-H et al. JACC 1991

today ? tomorrow

TCFA

Plaque Rupture



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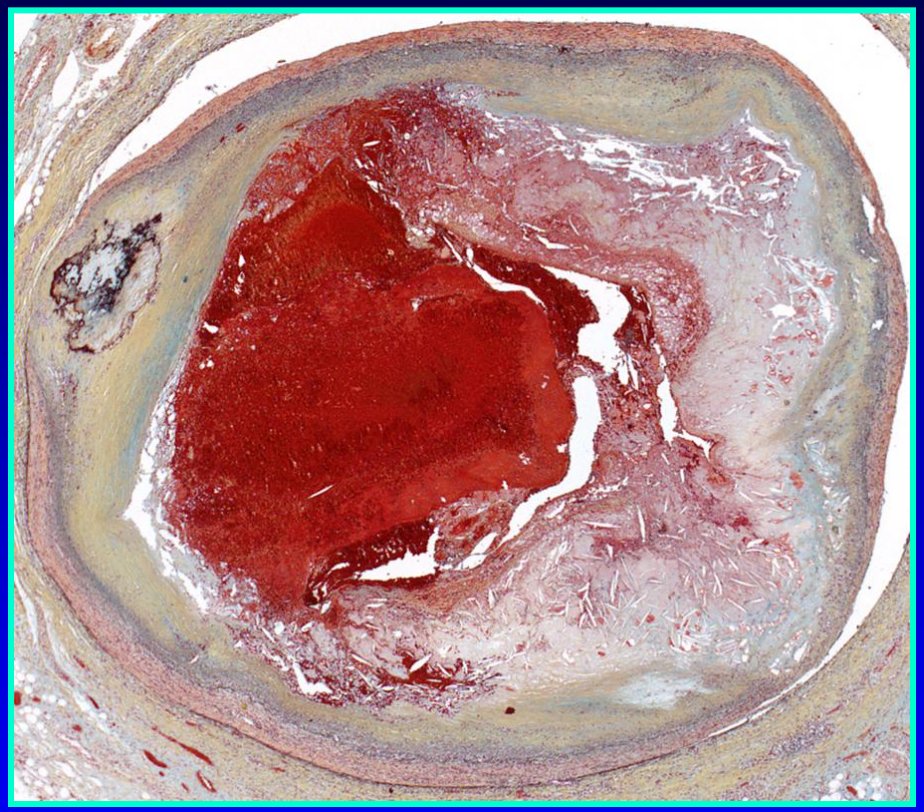
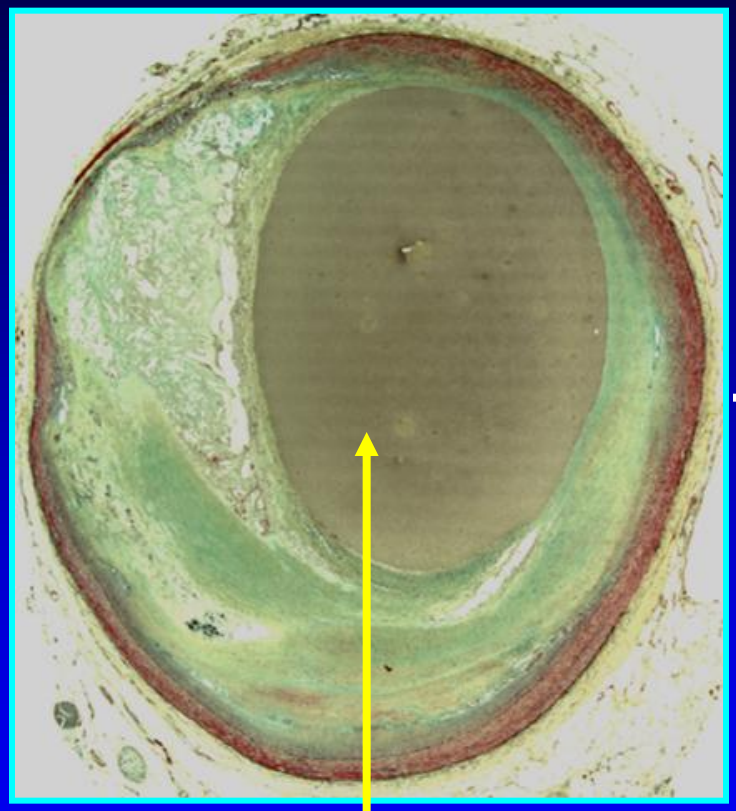


Let's be a little bit more critical now ……. and look a little bit better….

Renu virmani, ETP course 2005

today ? tomorrow



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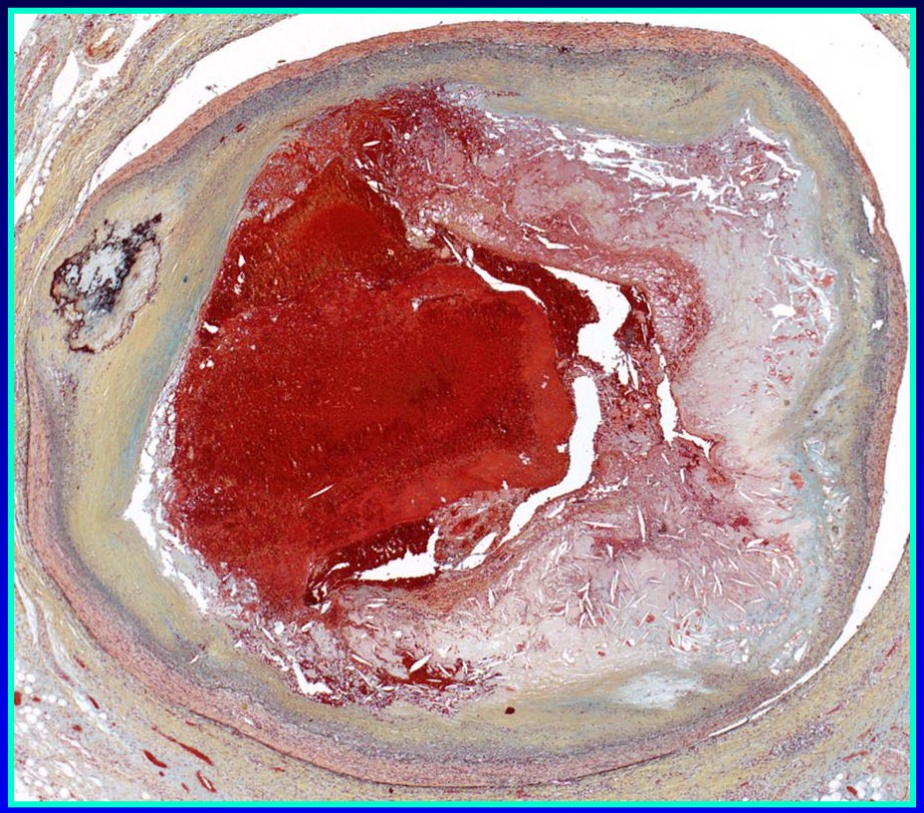
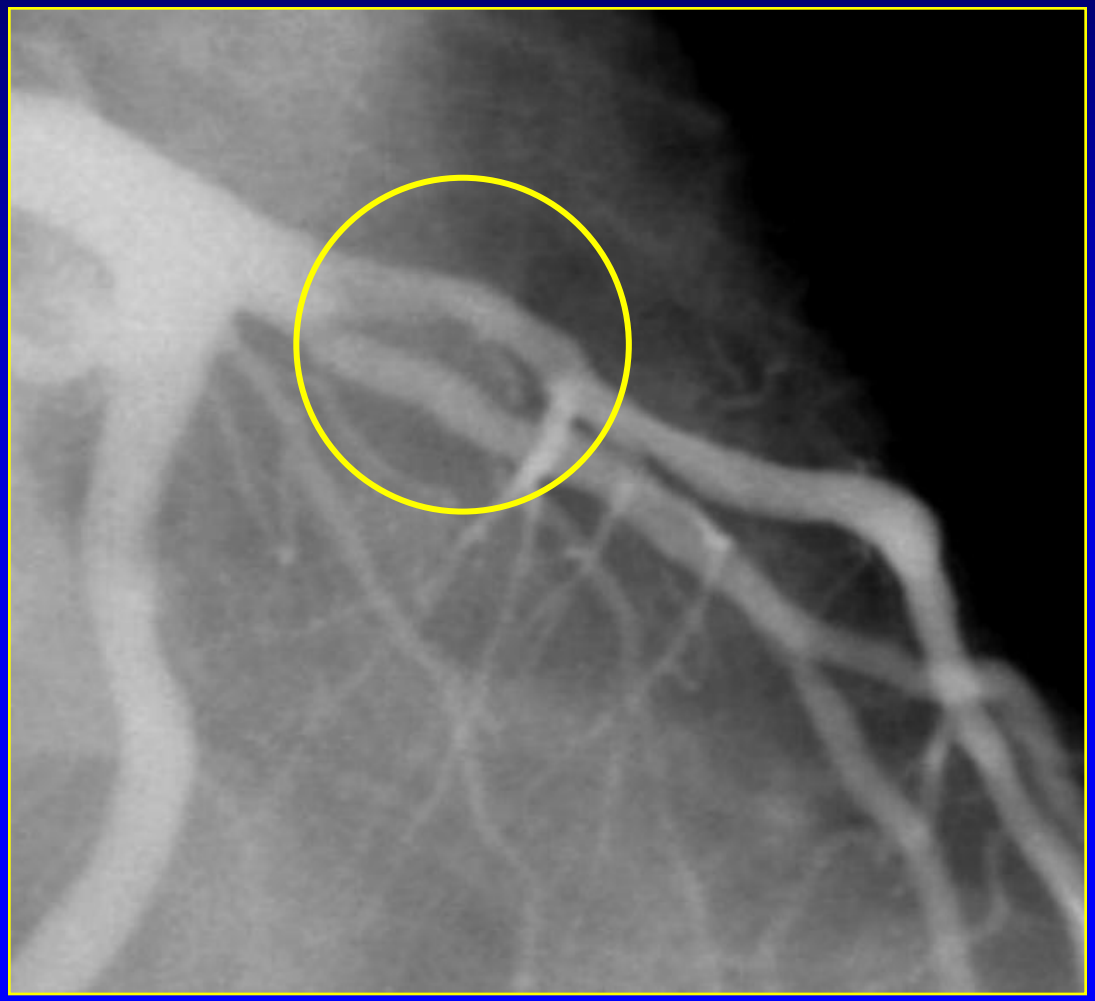


This is not a mild plaque but a 70% area stenosis !!!

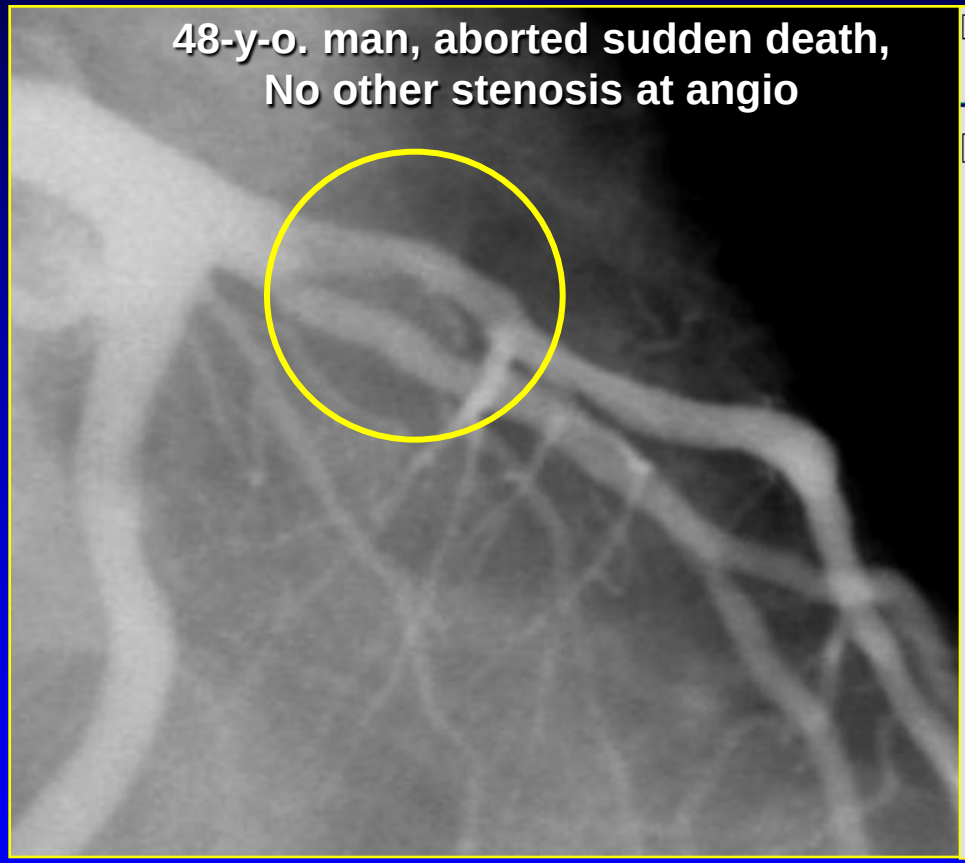
→ *Low FFR*

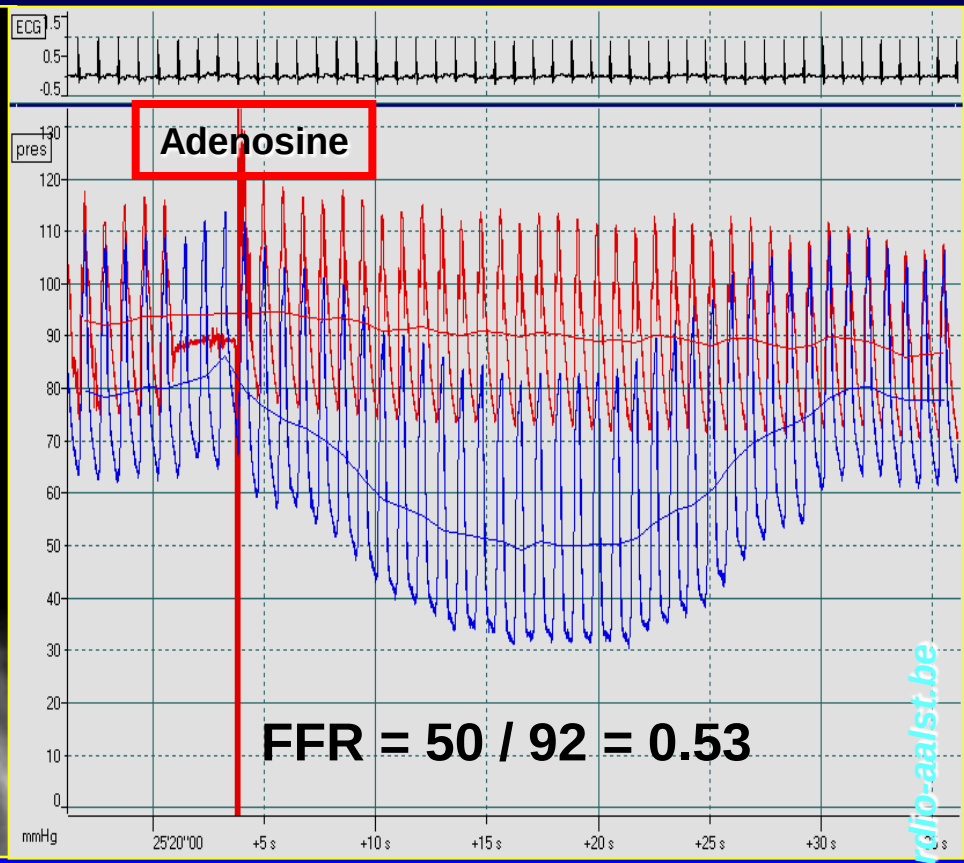
Renu virmani, ETP course 2005

- 48-y-old man
- Resuscitated sudden death
- *is this a mild plaque ?*



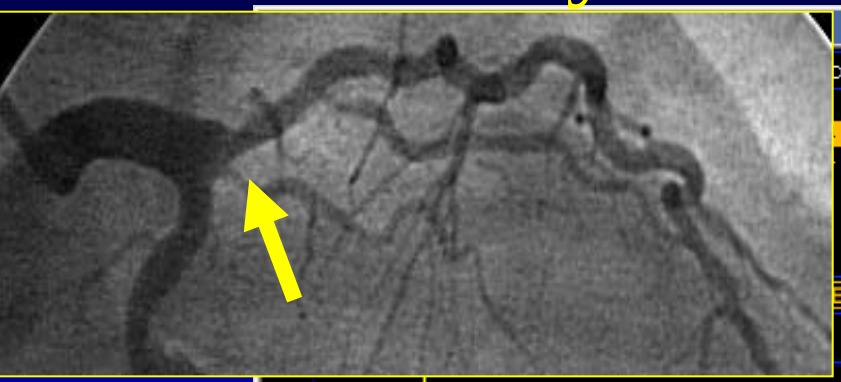
Do Acute Coronary Syndromes Occur at the Level of Mild Stenoses?





"Pseudo-Mild Stenosis" (unmasked by FFR)

57 year-old man with ACS



CSA:	**5.5 mm²**
Area Stenosis:	**72%**
Necr Core:	**13%**
Calcium:	**2.3%**

"The missing link"

Is there a link between vulnerabilty and ischemia ?

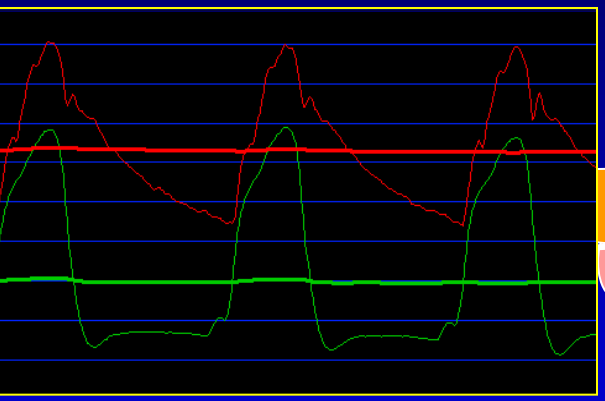
Hypothesis:

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

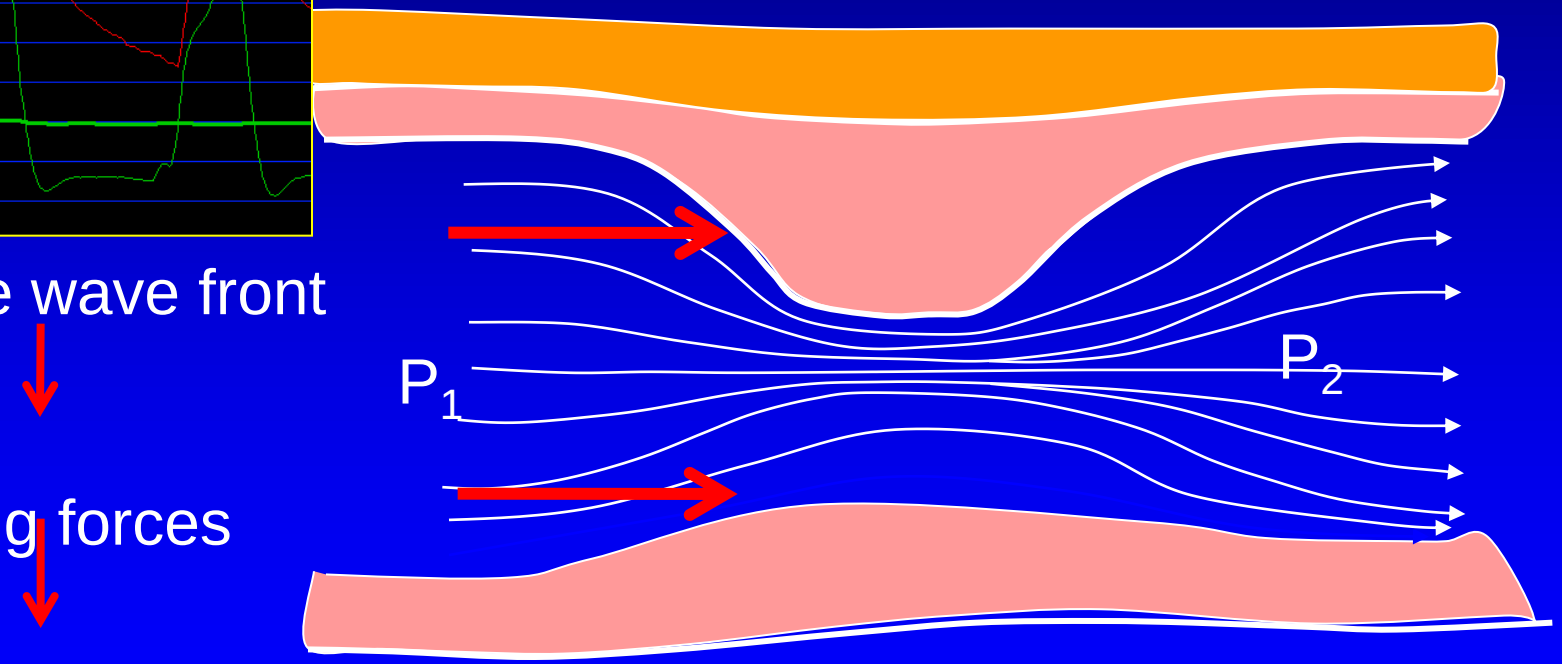
induce vulnerability

Mechanical constraints on coronary stenoses

Water hammer: 40.000.000 / year



Pressure wave front

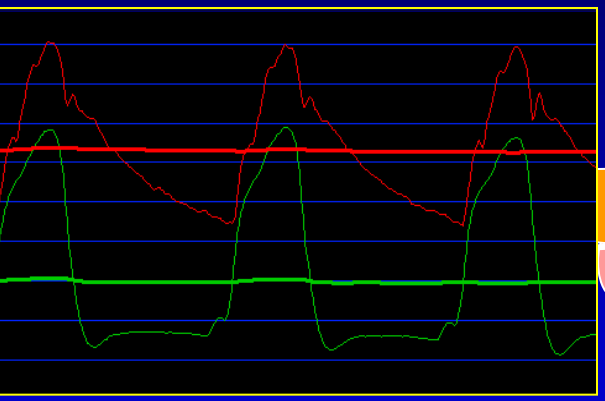


Slicing forces

Plaque fatigue

Mechanical constraints on coronary stenoses

Low lateral pressure (Venturi effect)



Pressure wave front

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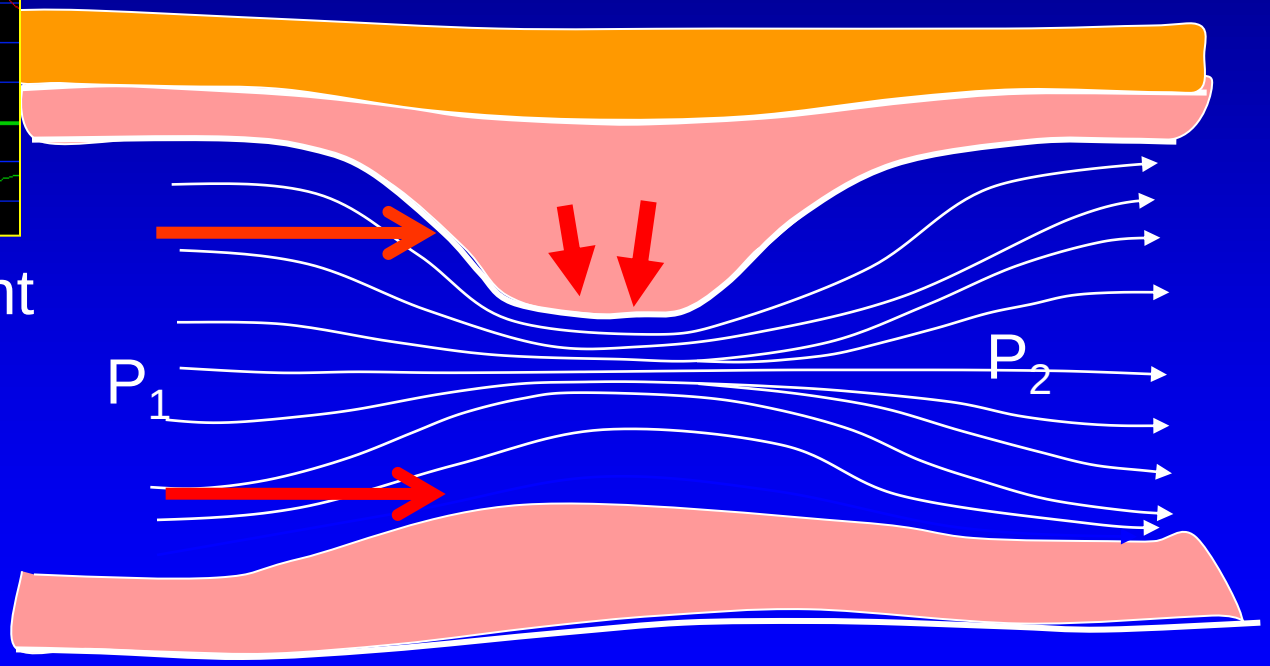
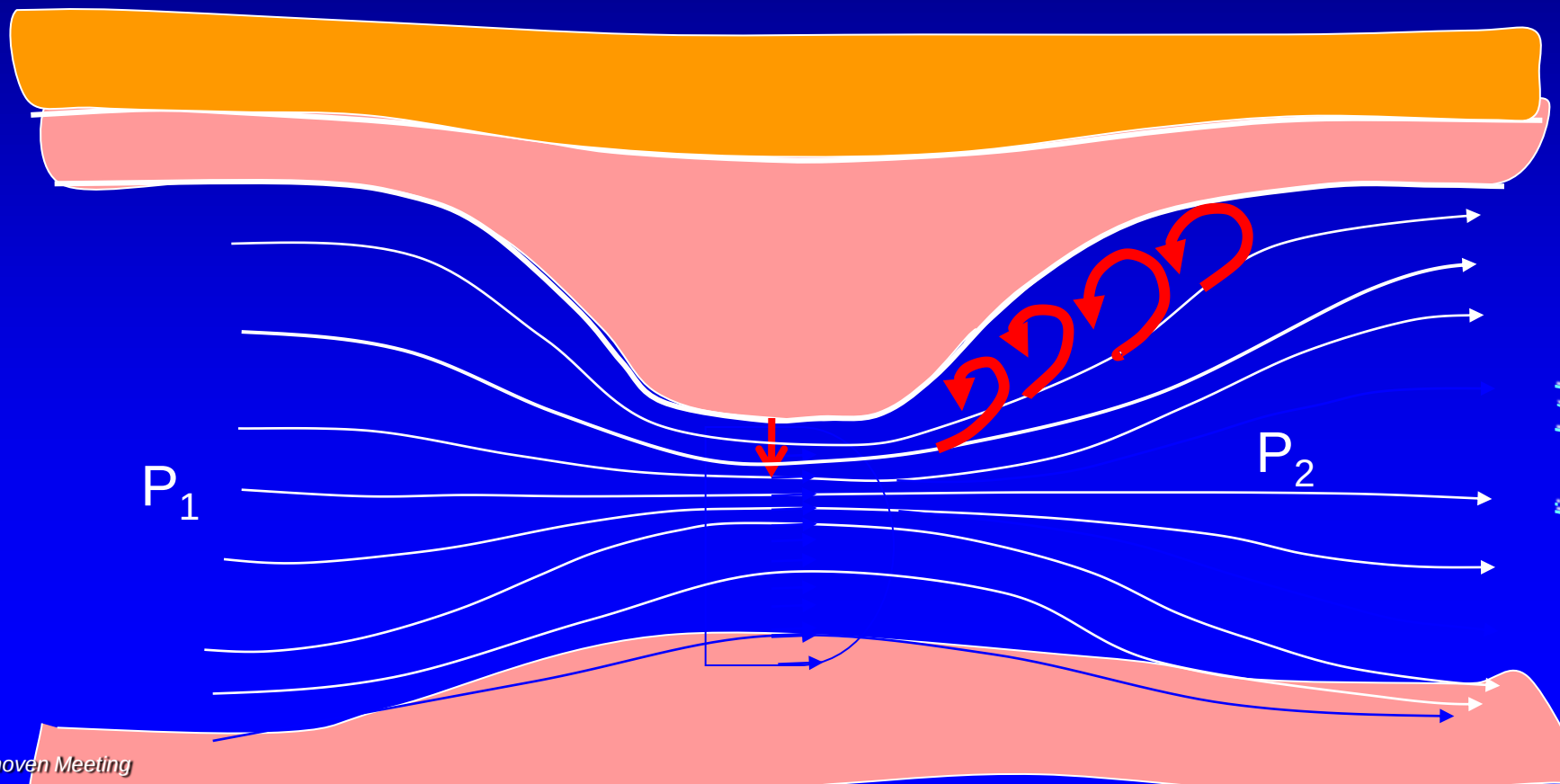


Mechanical constraints on coronary stenoses

Turbulences = unfavorable rheologic conditions at the shoulder of the plaque



Mechanical constraints on coronary stenoses

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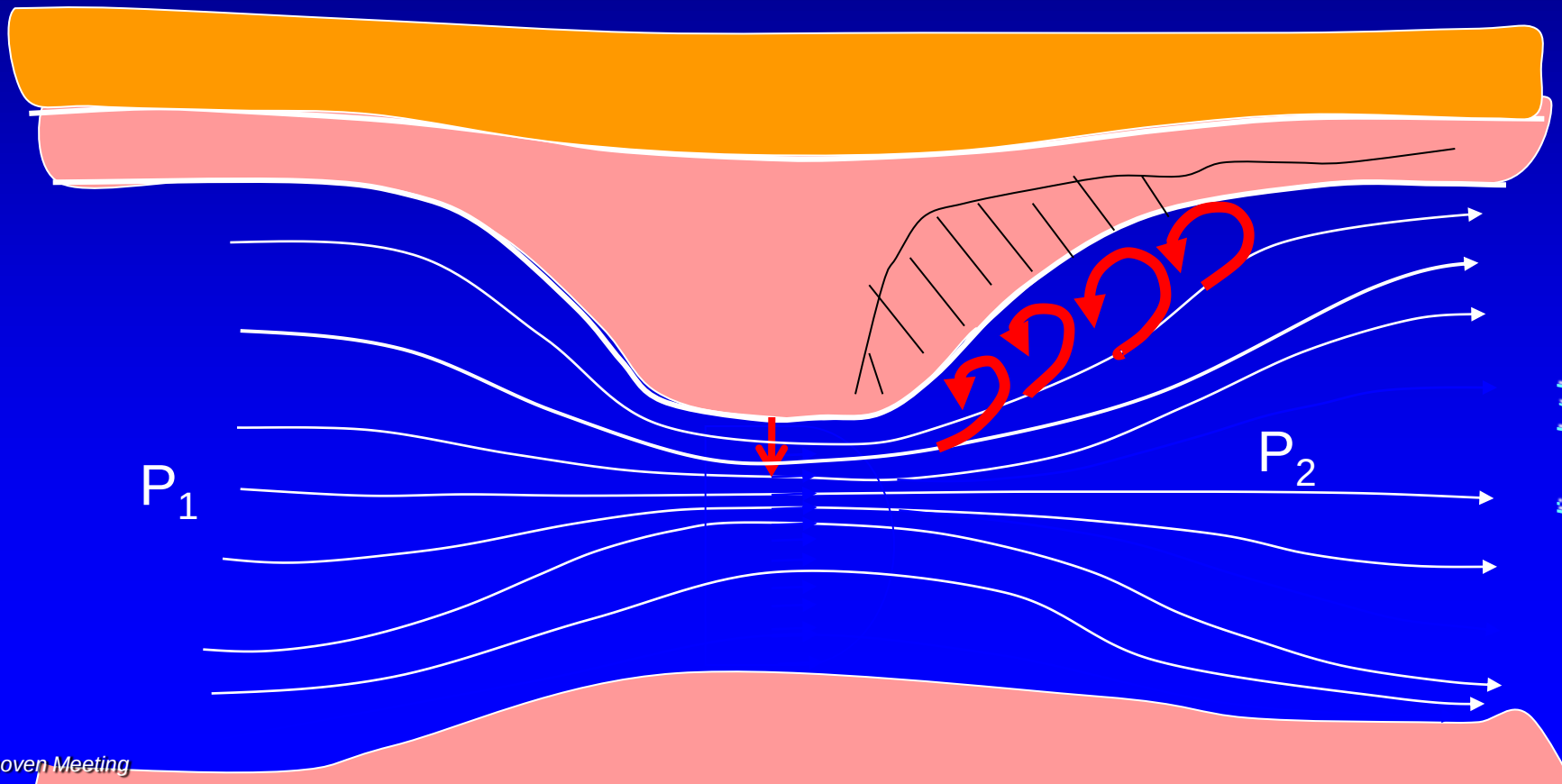
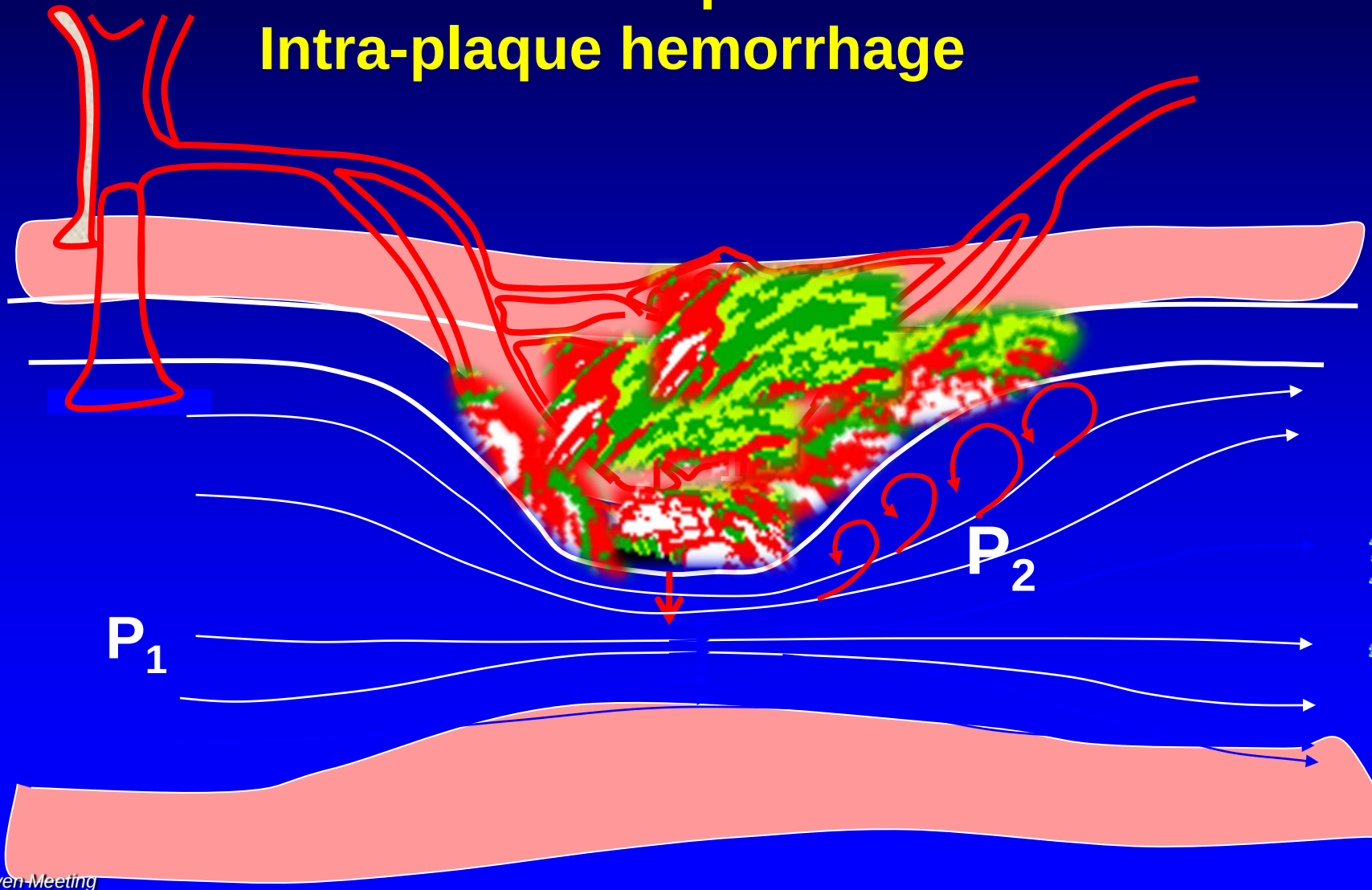


Importance of Vasa Vasorum And Vasa Plaquorum: Intra-plaque hemorrhage



"The missing link"

Is there a link between vulnerabilty and ischemia ?

Hypothesis:

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

induce vulnerability

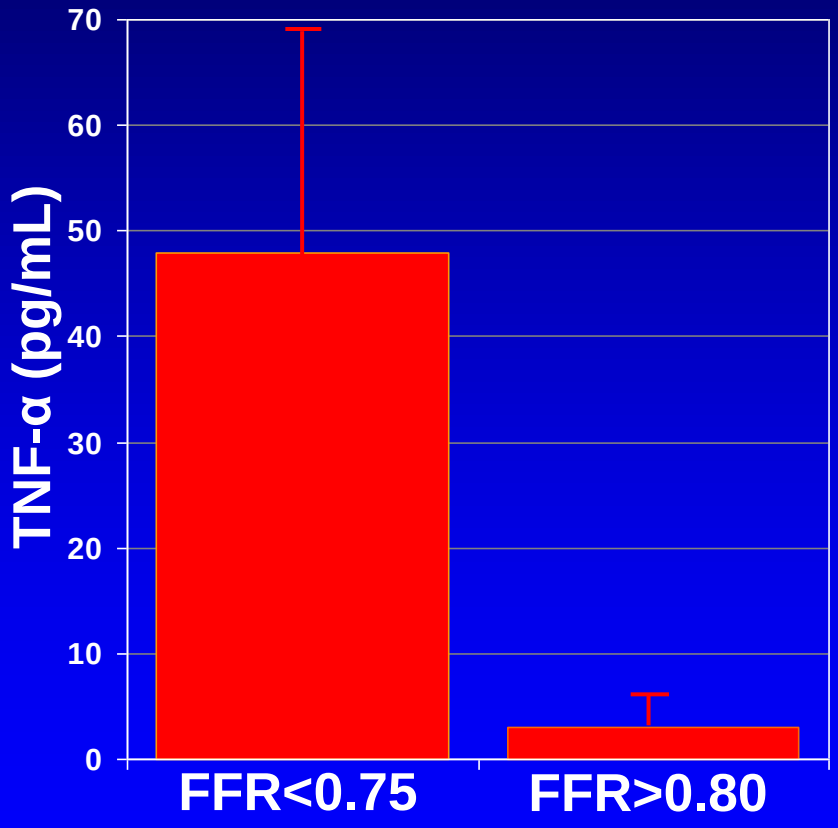
→ *Supported by studies on the relation between vulnerability markers and low FFR:*

Versteegh et al, Heart 2007

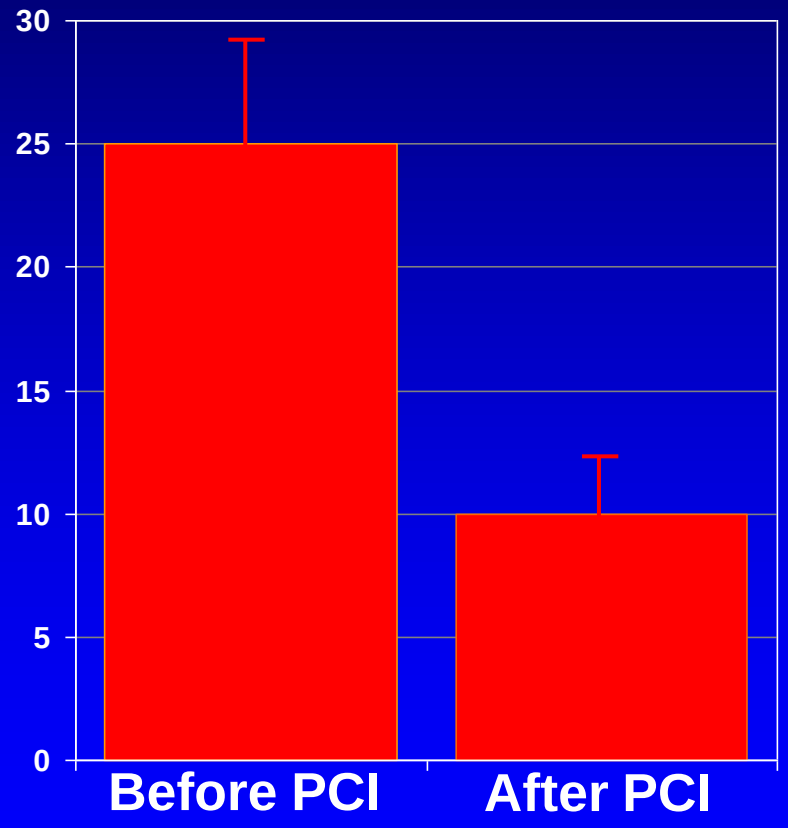
Cross-talks between hemodynamics and biology

Low FFR -> high vulnerability

TOLL-like receptors 2 and stenosis severity



TOLL-like receptors 2 before and after PCI



Adapted from D. Versteeg et al Heart Aug 2007

Repetitive ischemia
(with large pressure gradients)
promotes “vulnerability”

IN SUMMARY:

- There is a strong relation between vulnerabilty and ischemia, both mechanically and biochemically

- Vulnerability does not occur “out-of-the-blue” , but is promoted in many cases by repetitive episodes of ischemia (*high gradients, mech. stress)*

- *searching for vulnerable plaques by morphologic methods, is searching for the needle in the haystack* (cf Prospect Study)

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

“Severity”

“Vulnerability”

Functional Severity and Vulnerability: separate features?

With a few exceptions, ***vulnerable plaques are functionally significant***

(*or vice versa:*
if a plaque is functionally non-significant,
it is very rarely vulnerable)

IN CONCLUSION:

- There is no dispute between Akiko and me about necessity to treat ***true*** vulnerable plaque
- Of course we treat!
- *But the issue is how to discrimate vulnerability !*
- And the strongest indicatior for vulnerability, is inducible and repetitive ischemia
- Which can most simply be detected by FFR !

“NO GRADIENT, NO WORRIES !!!”