FFR in multivessel disease
&
FAME study

Coronary Physiology in the Catheterization Laboratory

European Heart House

April 7-9, 2011

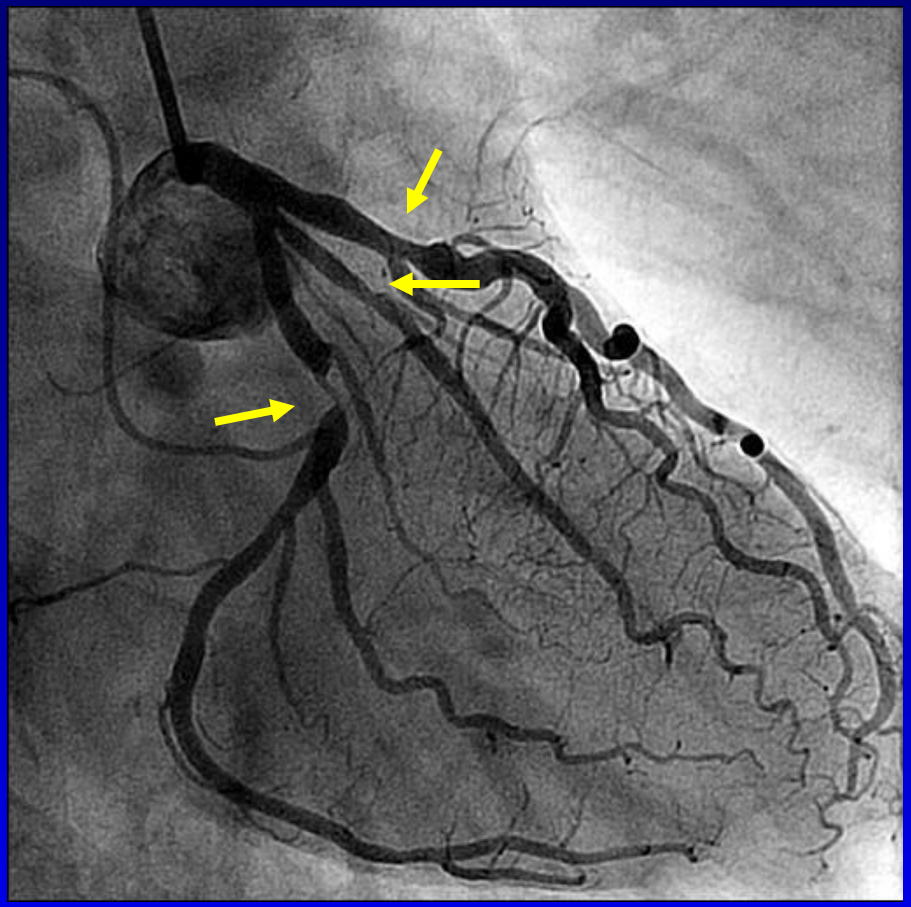
Pim A.L. Tonino, MD, PhD

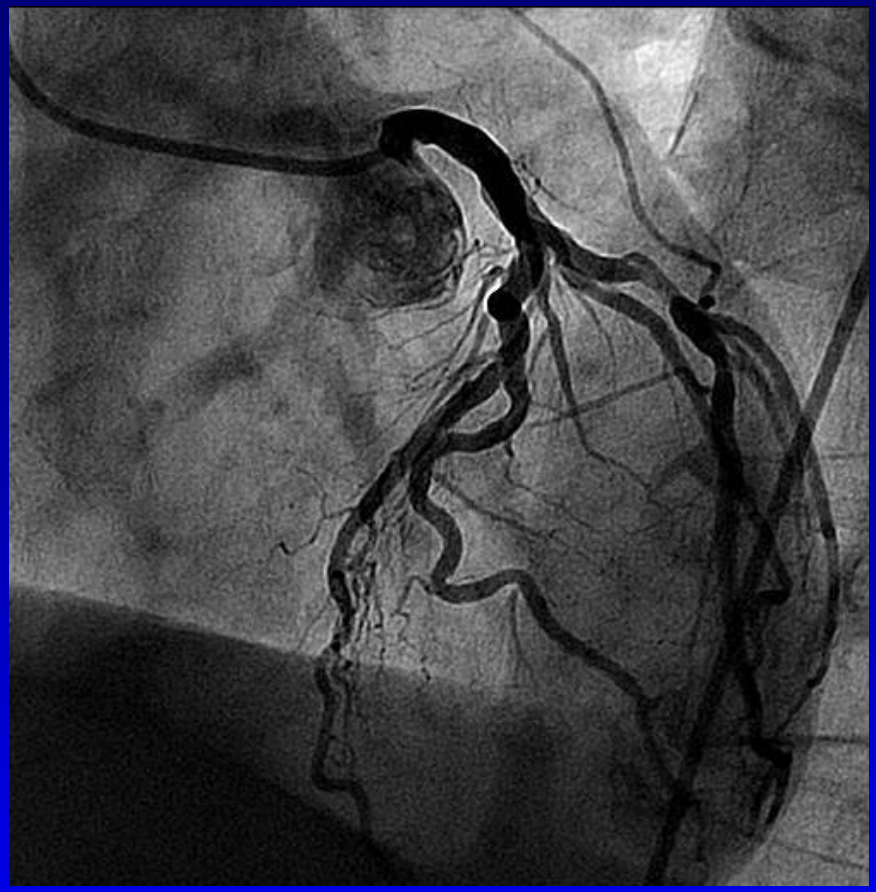
CATHARINA-ZIEKENHUIS

A rather common patient in our cath lab today…….

- 72-year-old male, stable angina class 3
- small non-STEMI 3 weeks earlier,
  no diagnostic Δ-ECG
- residual angina class 2-3
- positive exercise stress test

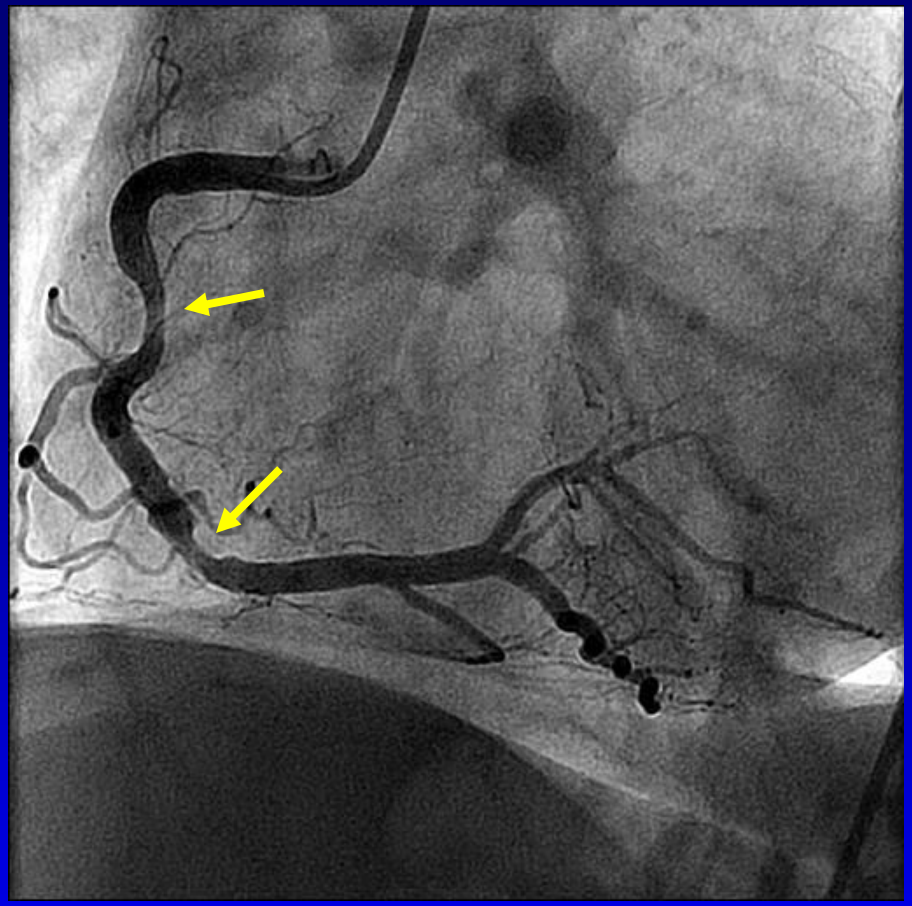
⟶ Coronary angiography

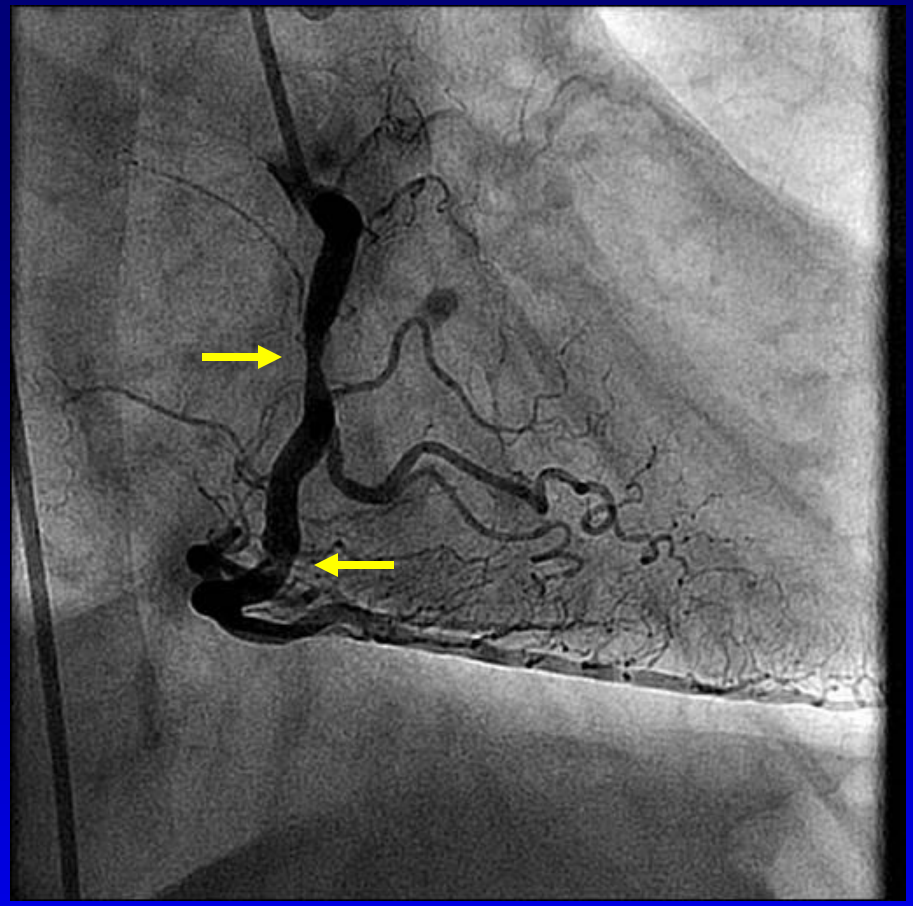




LCA

FAME STUDY patient # 1249
June 25th, 2007





RCA

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A rather common patient in our cath lab today…….

- 72-year-old male, stable angina class 3
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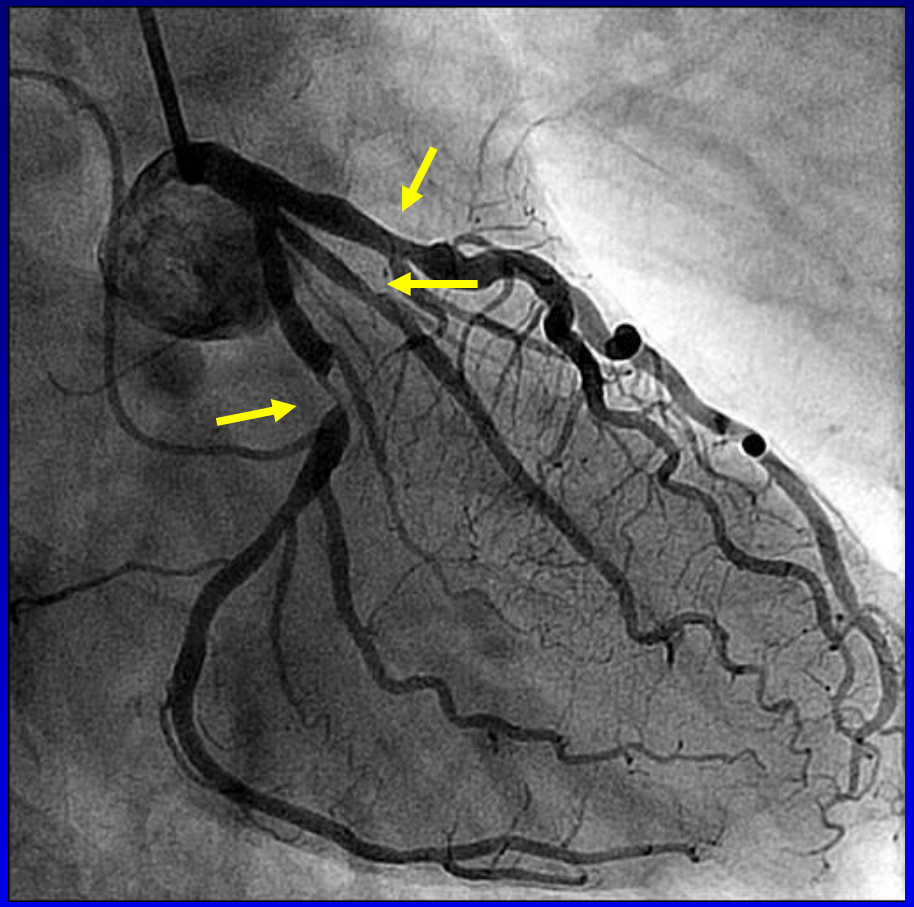
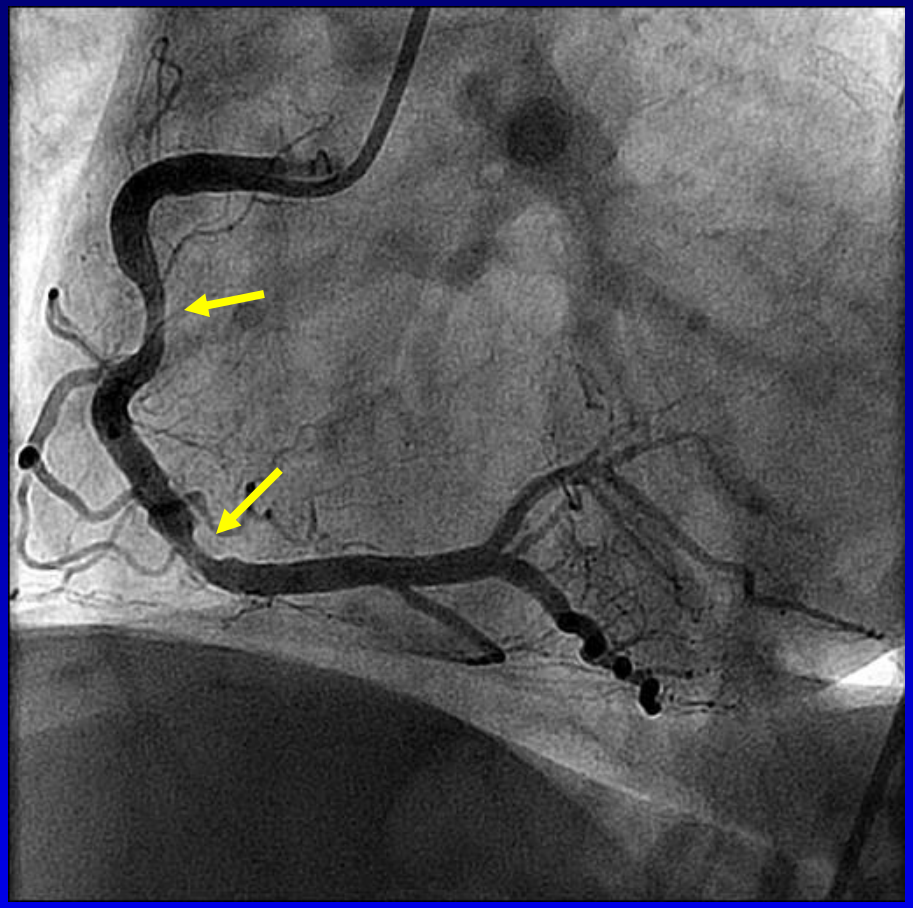
⟶ Coronary angiography

- 50% LAD artery
- 50% Intermediate branch
- 90% LCX artery
- 70 % RCA proximal
- 50% RCA mid

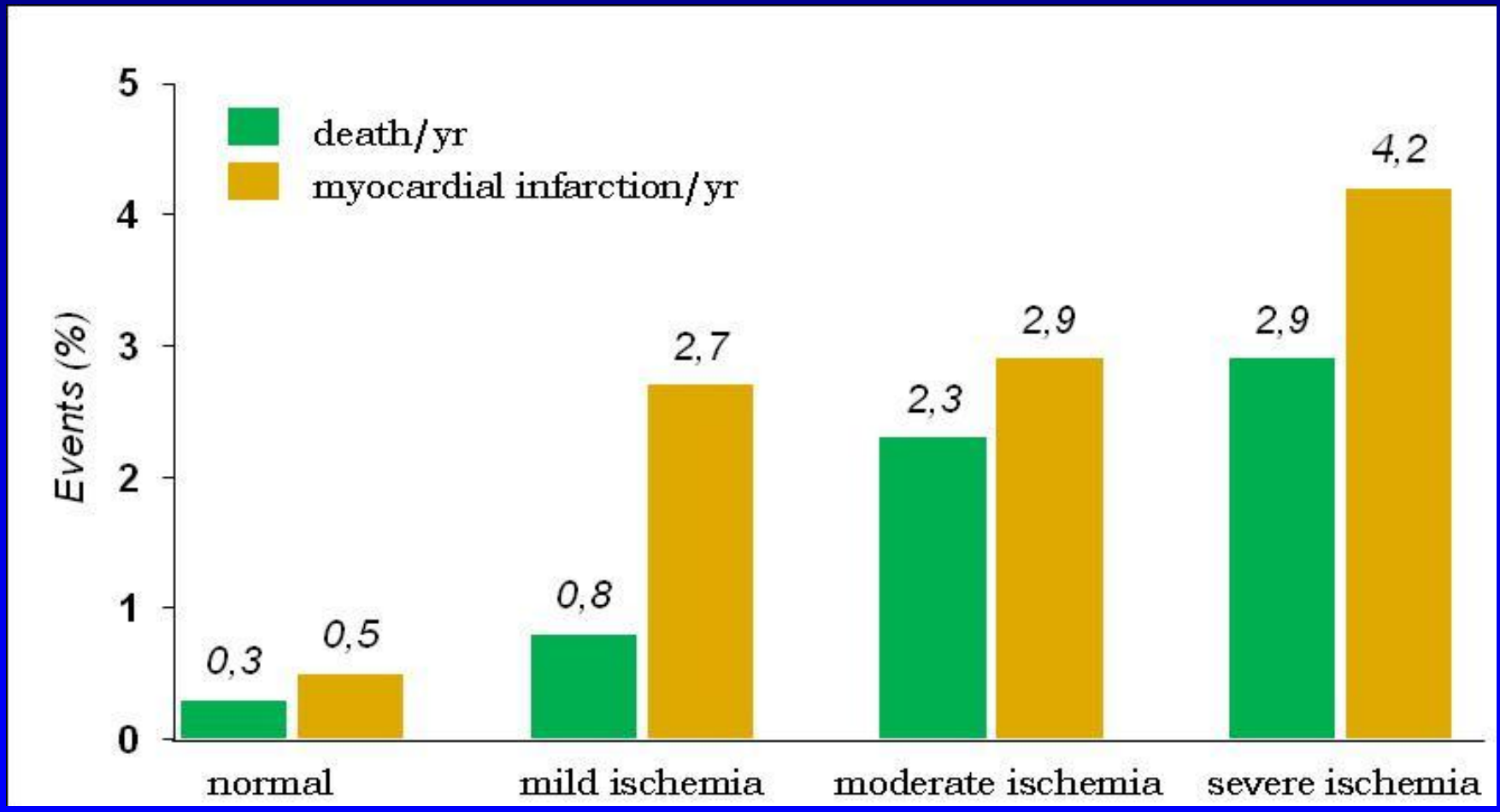




How to proceed?

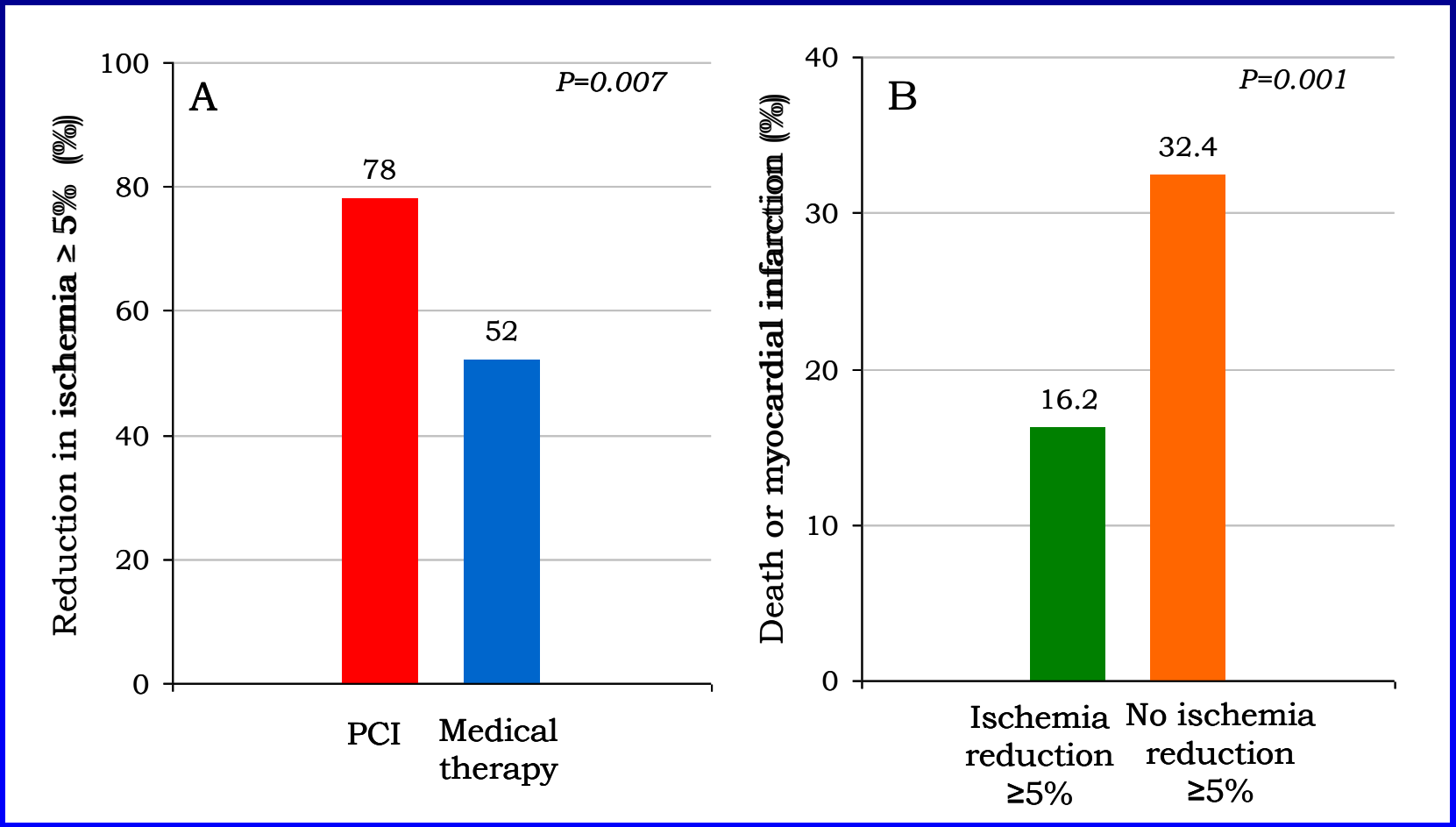
It is not the question *IF* stenting is indicated, but *WHERE* and *HOW MANY*

Ischemia-producing coronary lesions cause symptoms and cardiac events



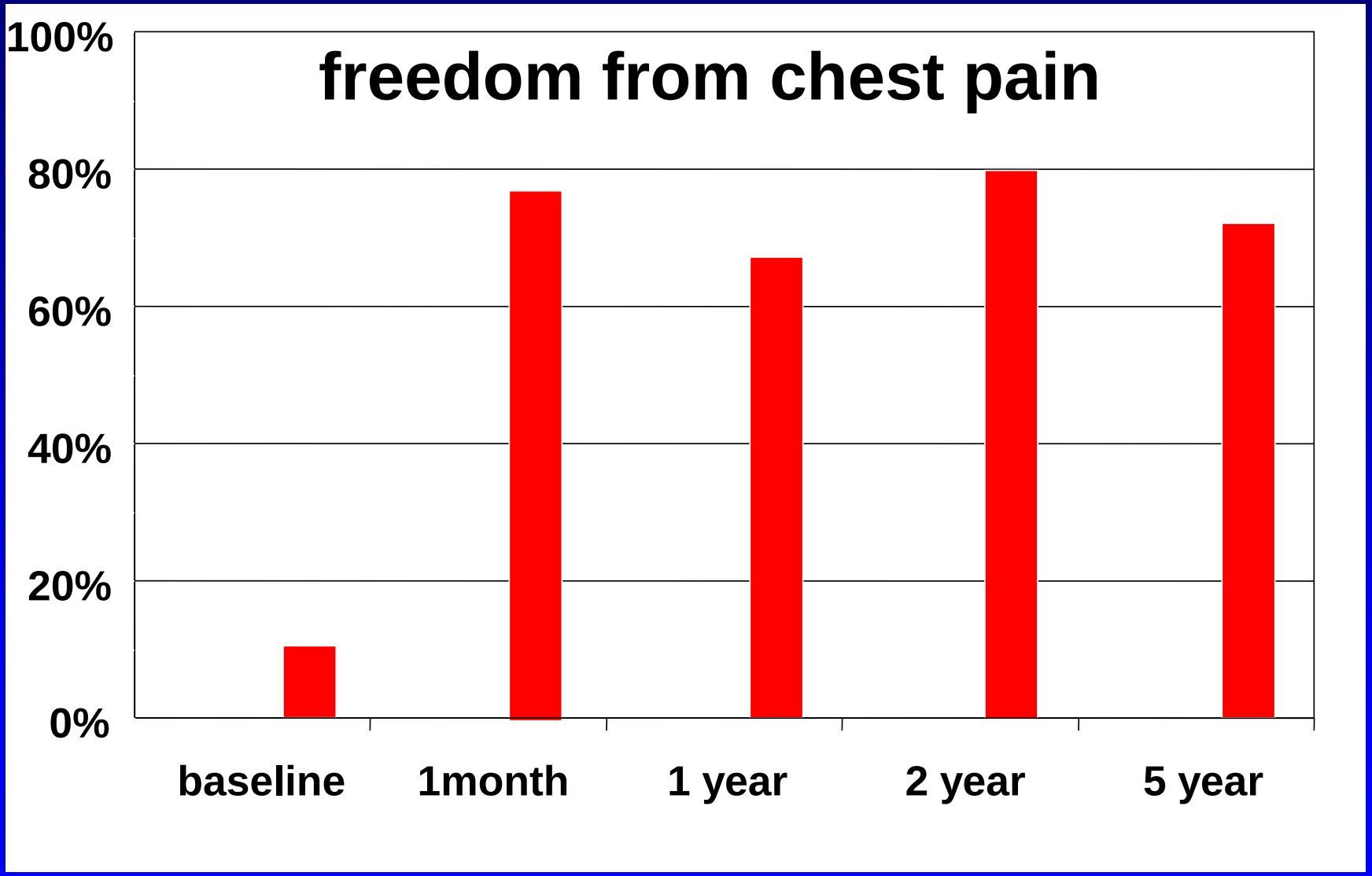
Hachamovitch et al., Circulation 1998

PCI of ischemic lesions → better outcome



Shaw et al. COURAGE trial nuclear substudy. Circulation 2008

Ischemic lesions (FFR < 0.75) treated by stenting



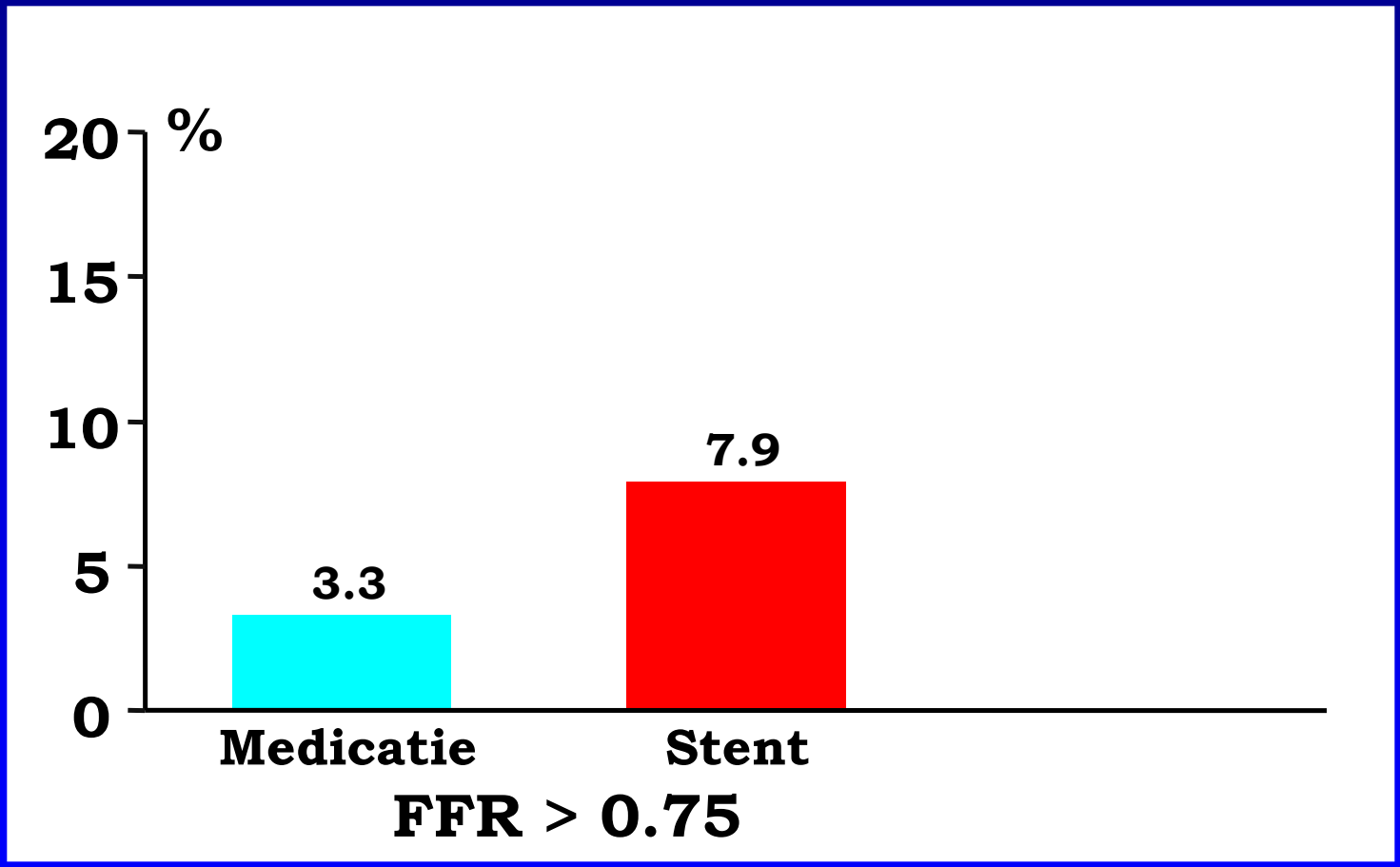
DEFER-study, JACC 2007; 49 : 2105-2111

Functionally NON-significant stenoses

a functionally non-significant stenosis ("non-ischemic stenosis") generally gives no complaints

So, from the symptomatic point of view there is no reason to stent such lesion

Cardiac Death And Acute MI After 5 Years: *functionally non-significant stenoses*

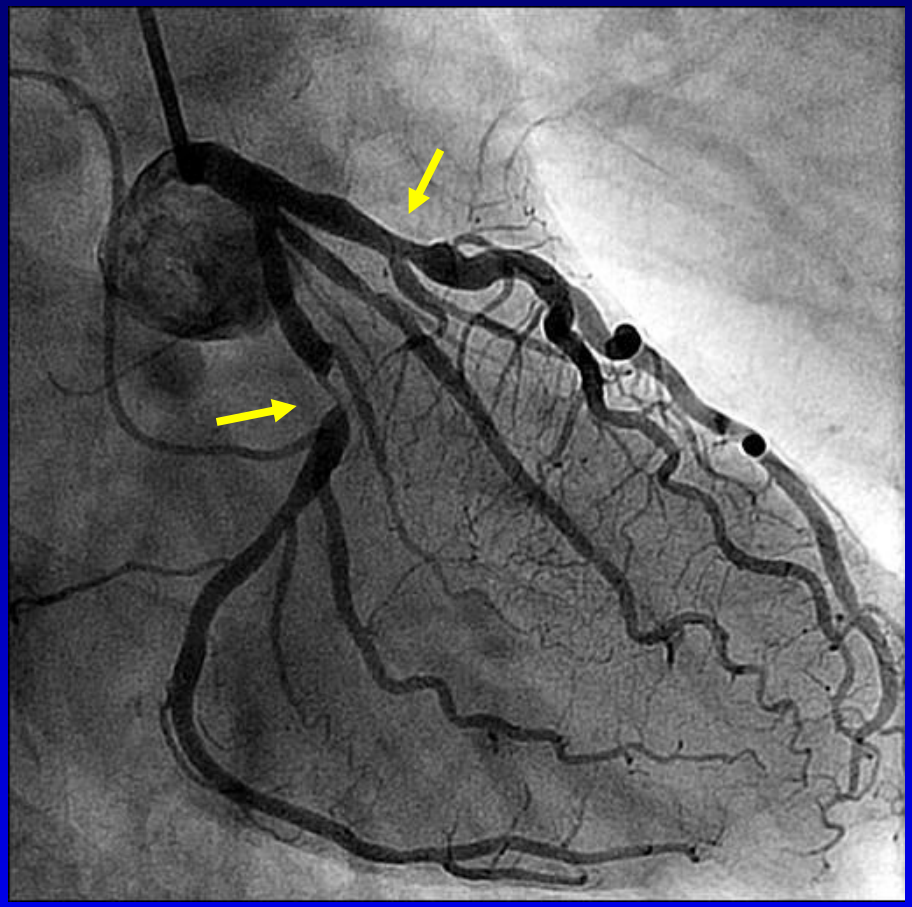


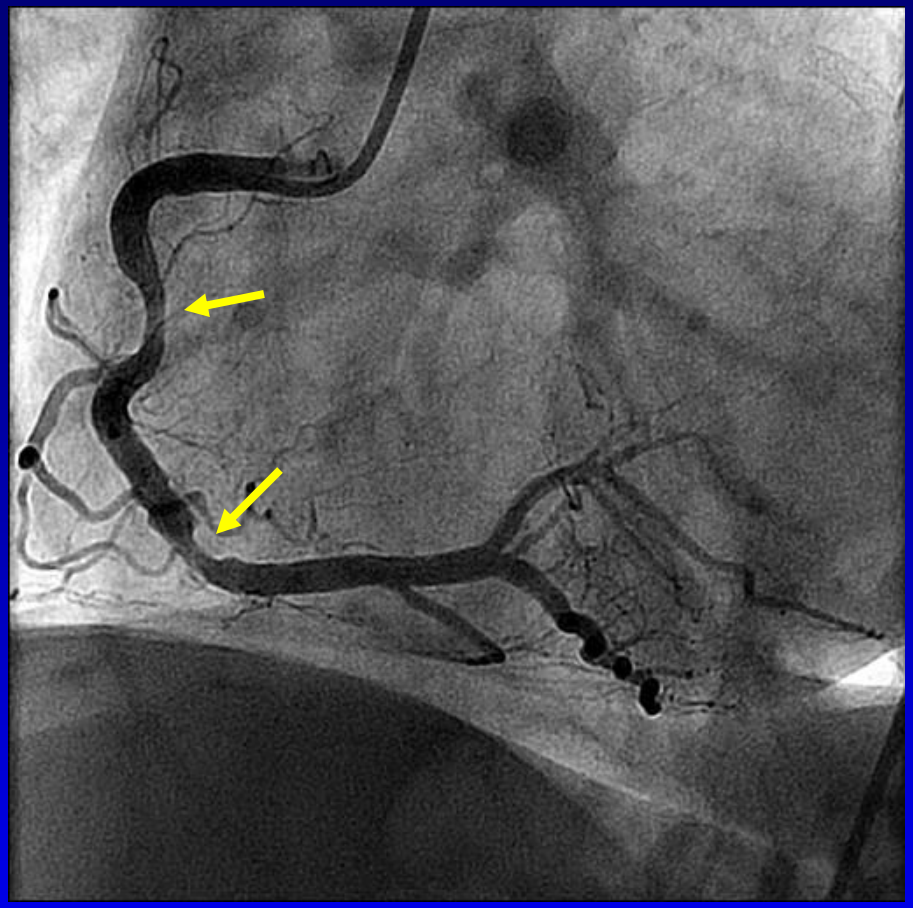
Defer, JACC, 2008

So, *functionally significant (= ischemic) lesions should be revascularized*, …..

……..…whereas it makes *no sense to stent non-ischemic lesions*

So, if we are able to accurately discriminate ischemic from non-ischemic lesions we can selectively treat the ischemic lesions by PCI and the non-ischemic lesions by medical treatment

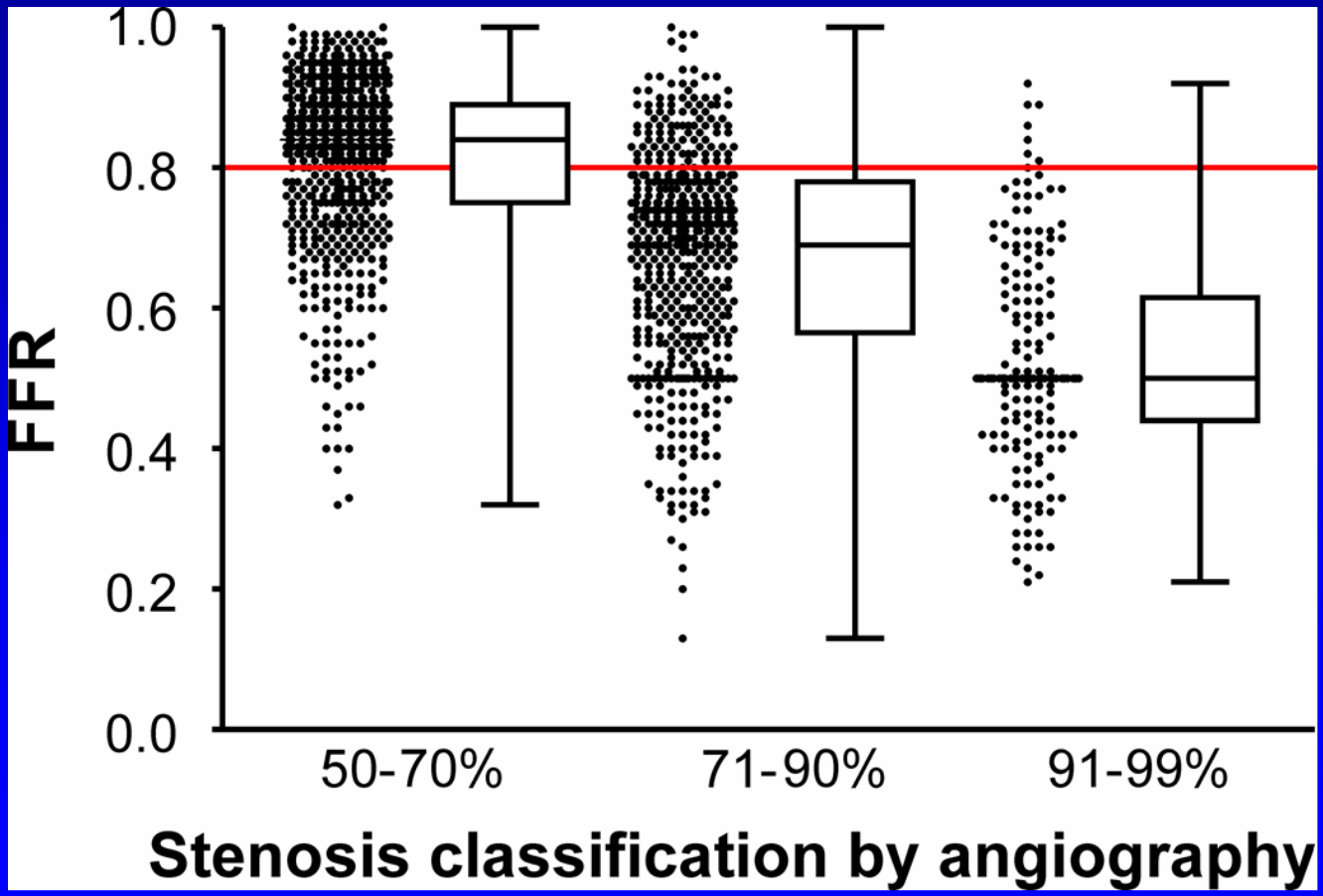




Particularly in multivessel disease we often have insufficient information about stenosis-related myocardial ischemia

Because …

The angiogram poorly predicts presence of myocardial ischemia related to a specific coronary stenosis

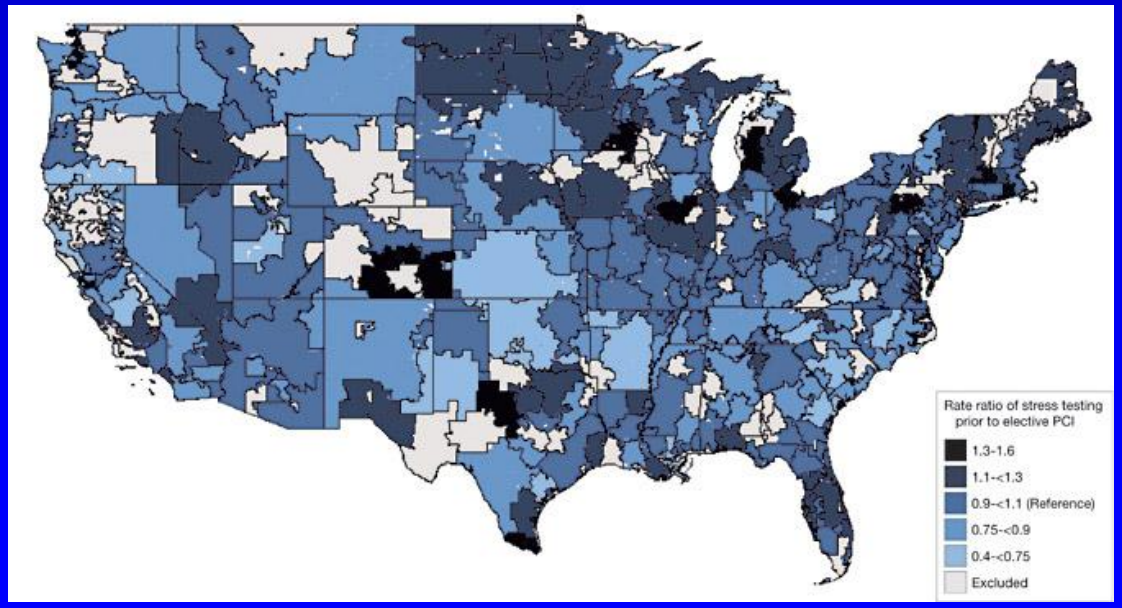


Tonino et al., JACC, June 2010

Because …

Non-invasive tests aren't always performed pre-PCI

Only 44.5% (20.1% - 70.6%) of Medicare patients undergoing elective PCI, underwent stress-testing < 90 days before PCI



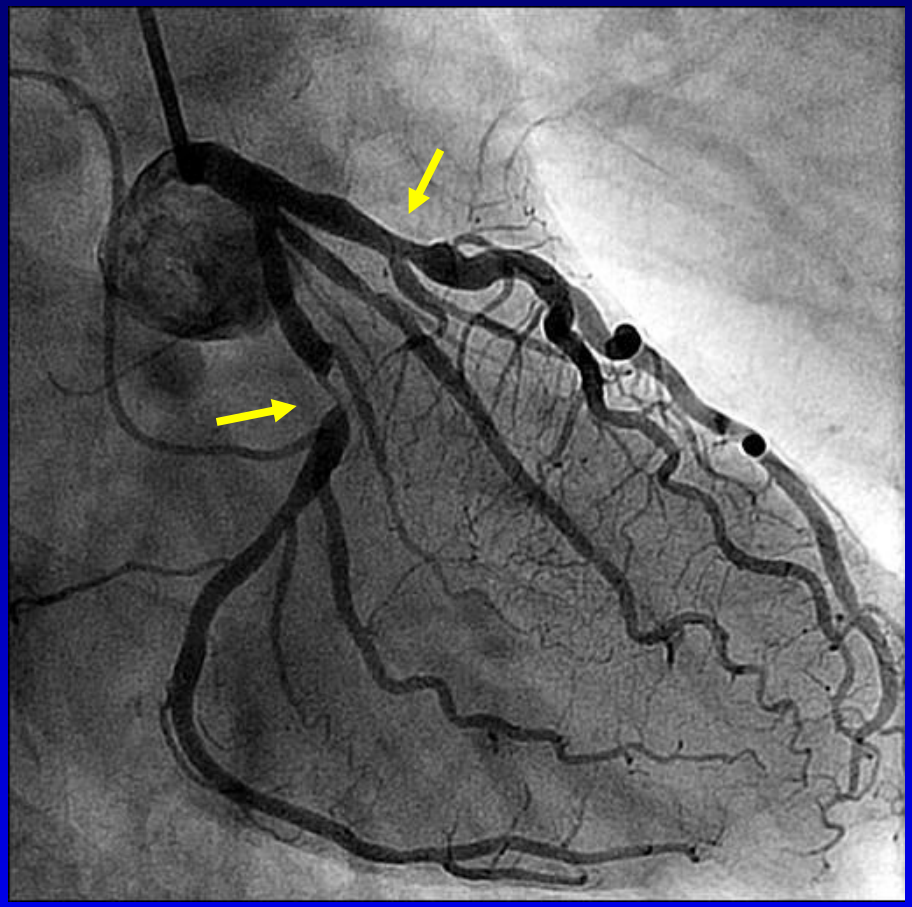
Lin et al. JAMA 2008

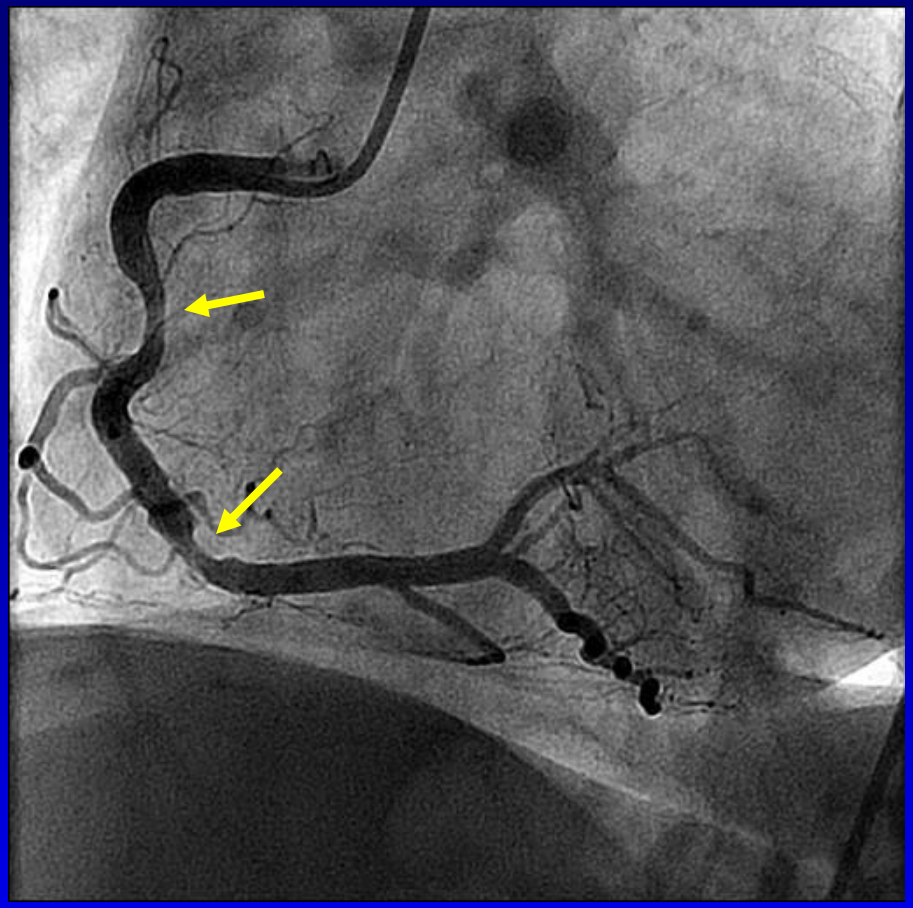
Because …

Non-invasive tests are frequently inaccurate in multivessel disease:

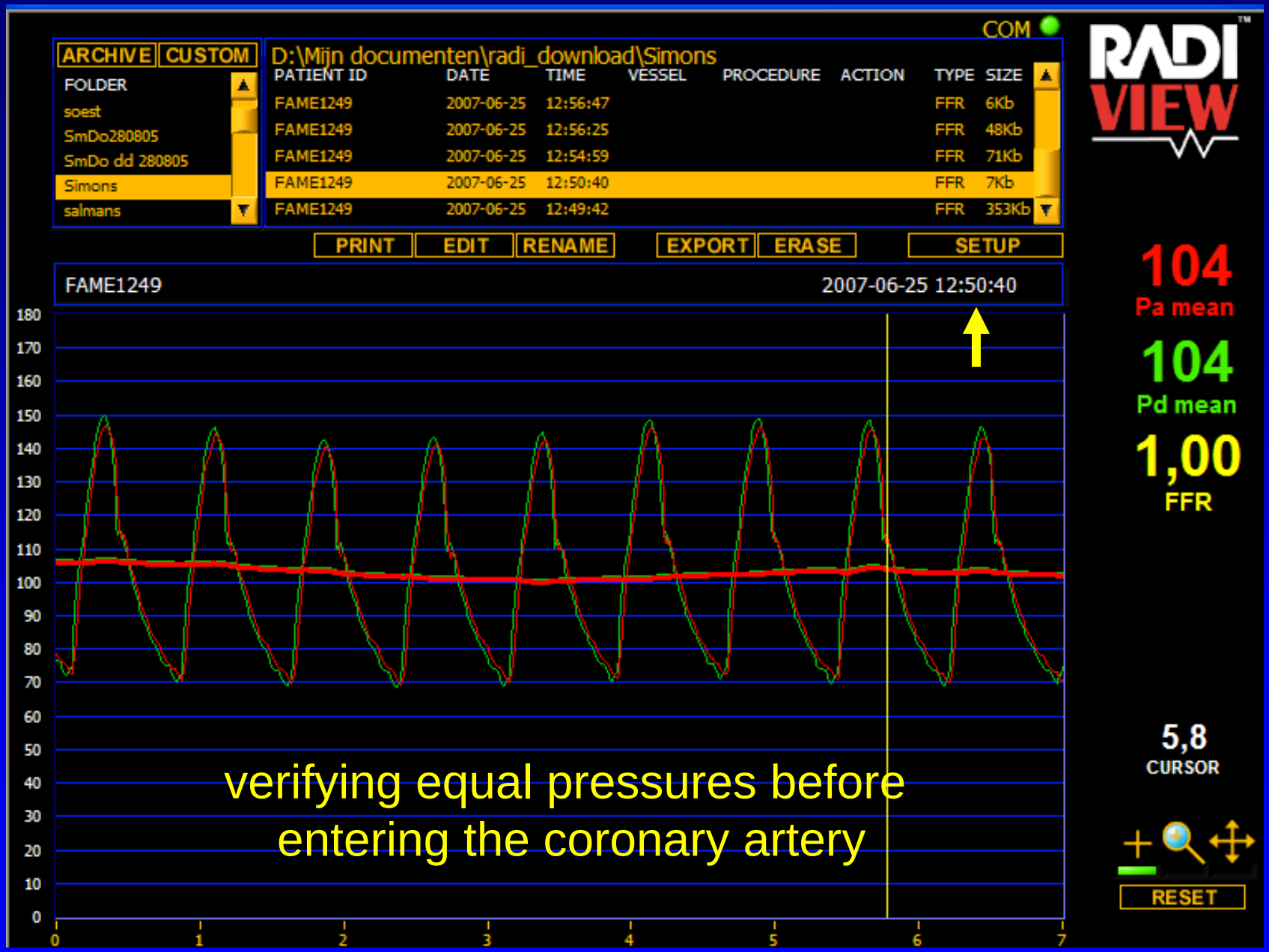
- ***Excercise test:*** *non-conclusive, information per patient*

- ***Nuclear scan:*** *inaccurate in MVD (balanced ischemia, serial stenosis)*





So ….. we need FFR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FAME1249 2007-06-25 12:50:40 FFR 7Kb
FAME1249 2007-06-25 12:49:42 FFR 353Kb
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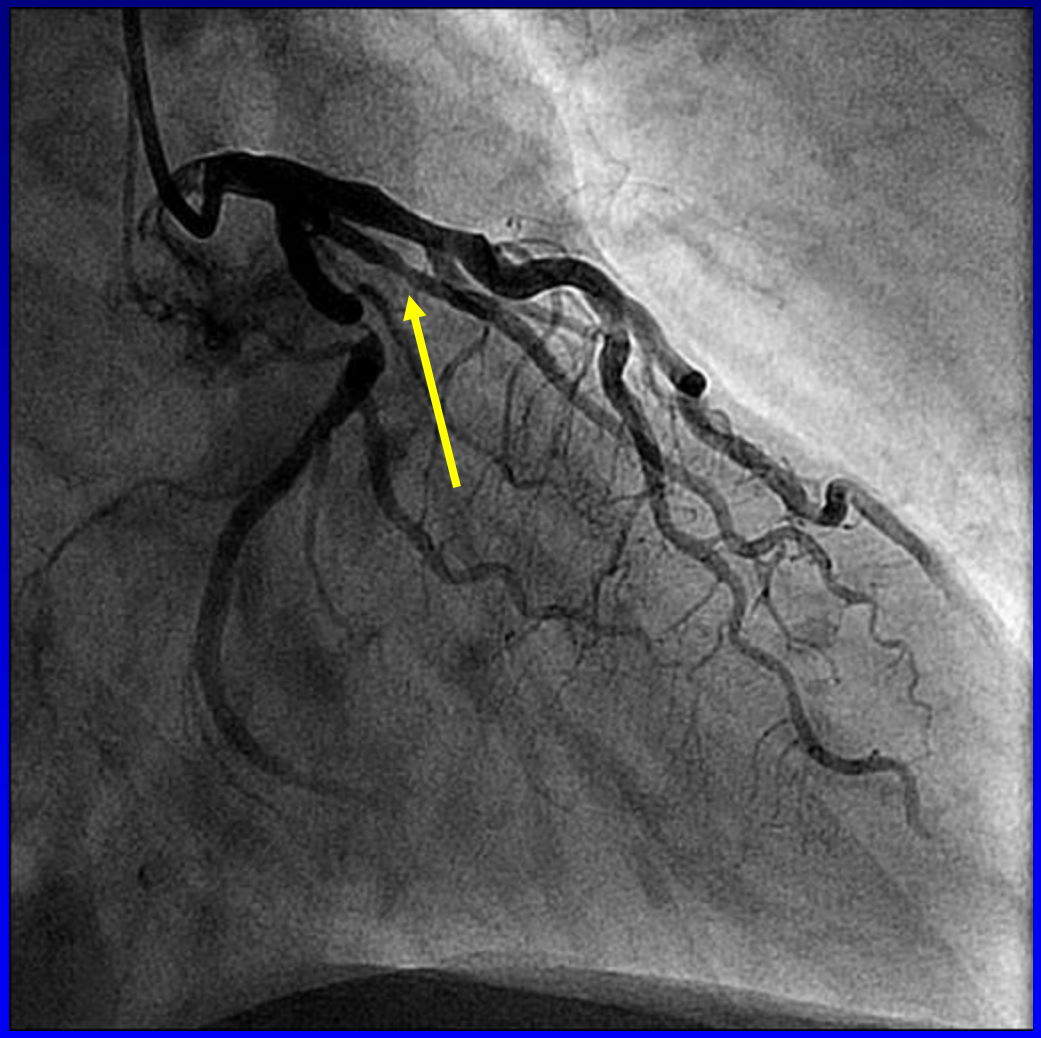
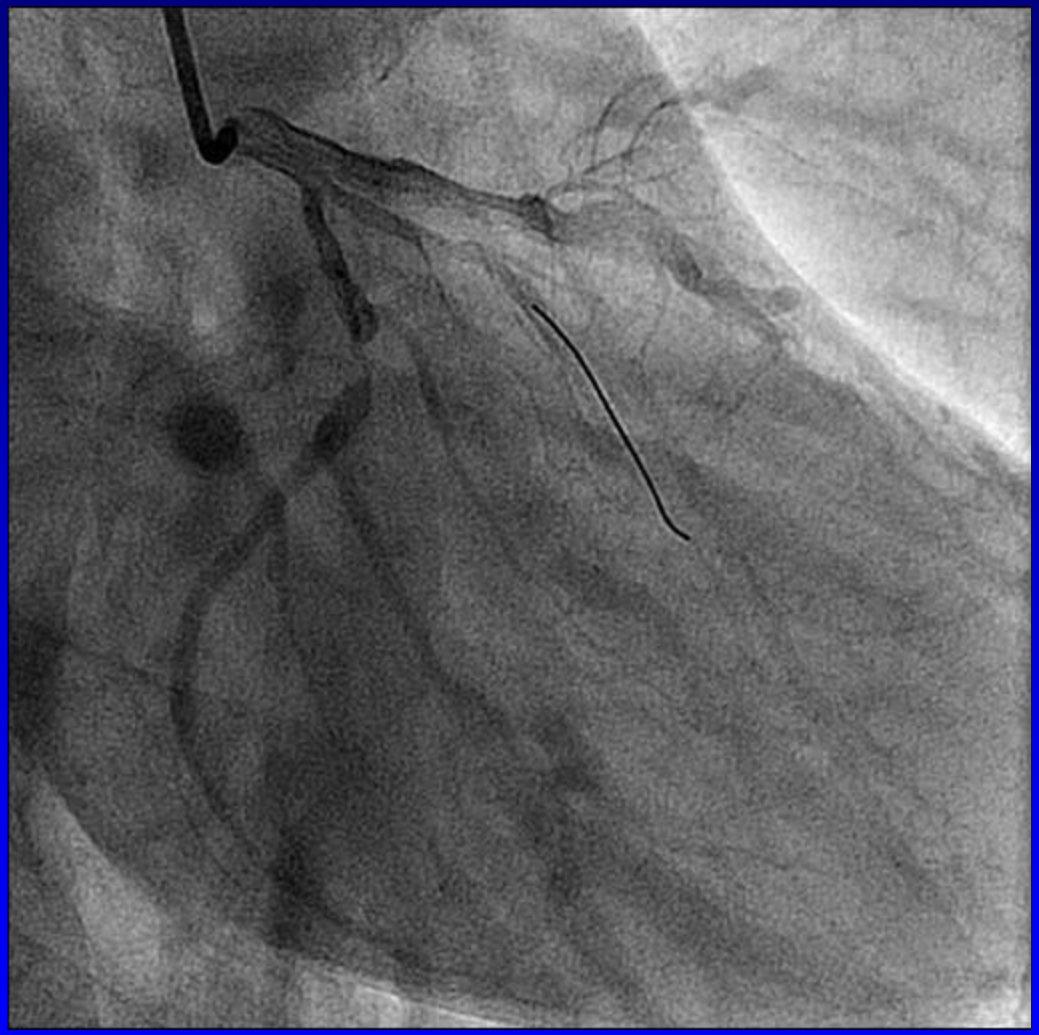
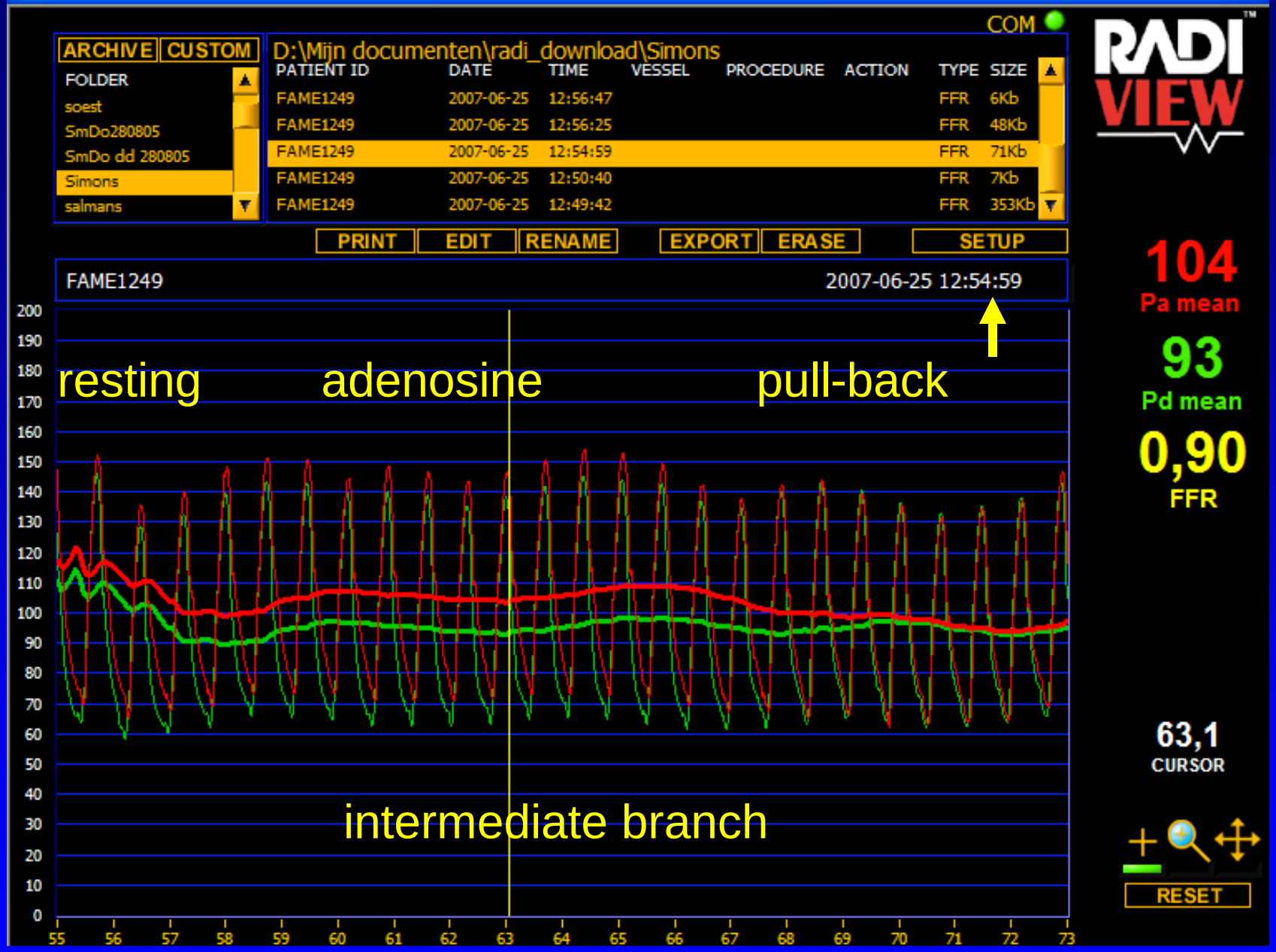
verifying equal pressures before entering the coronary artery



intermediate branch



PW (Certus wire) in intermediate branch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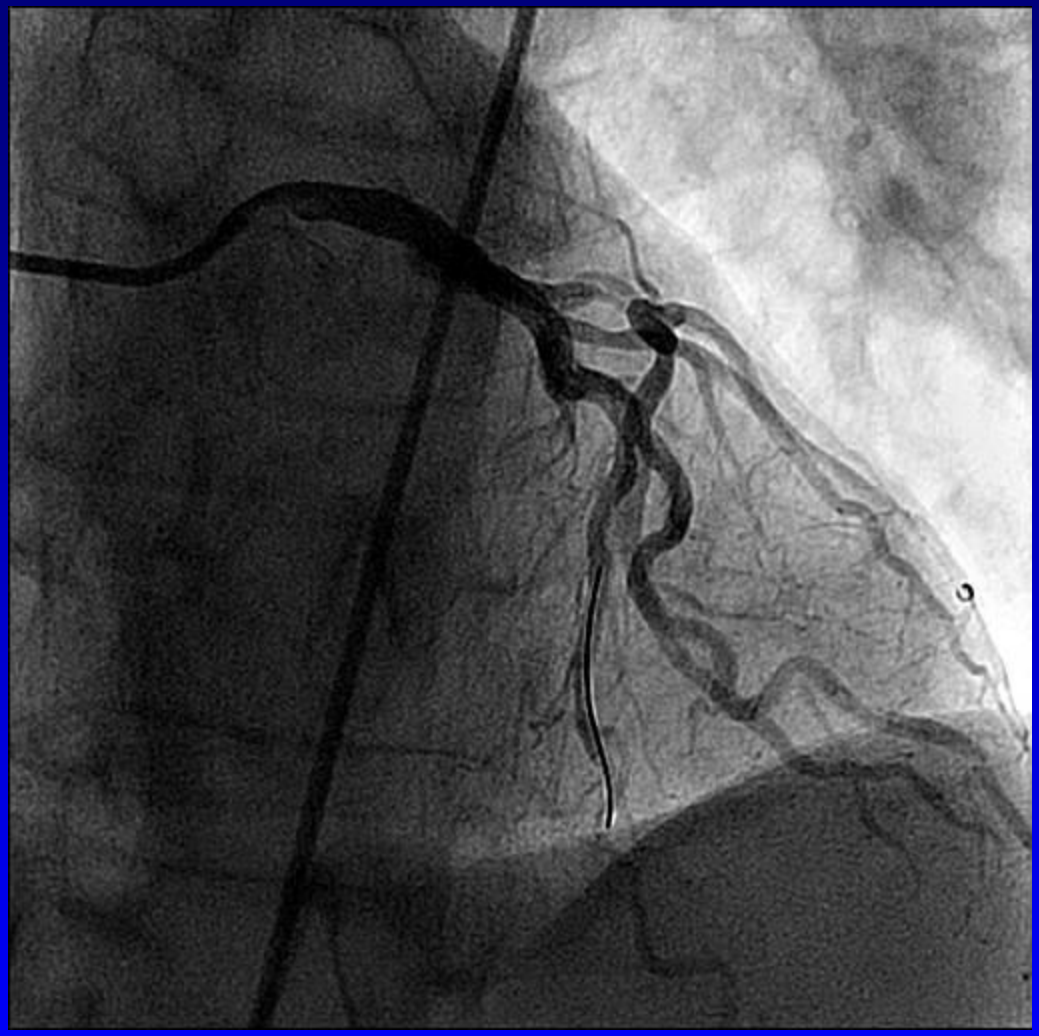
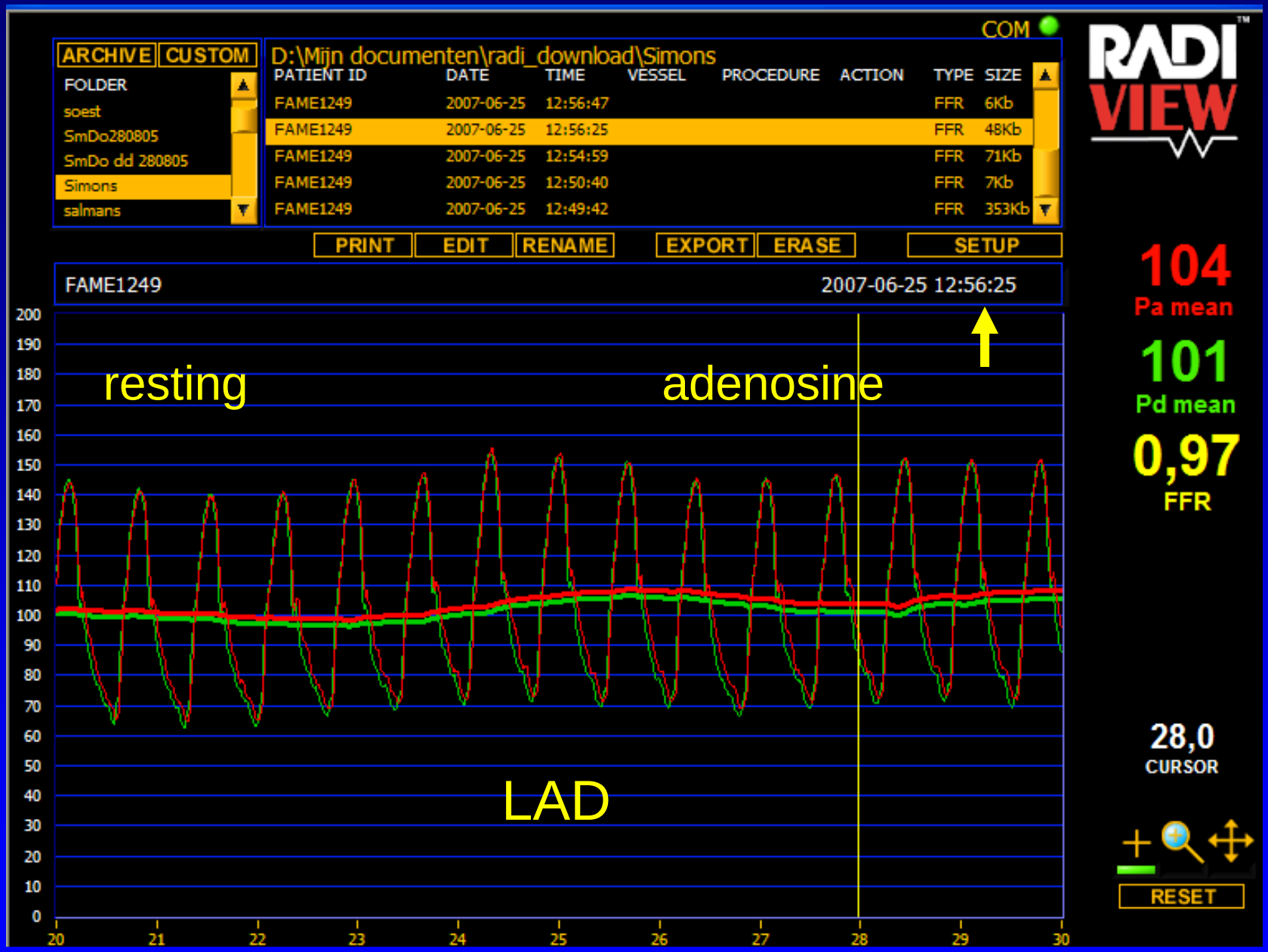


PW in LAD artery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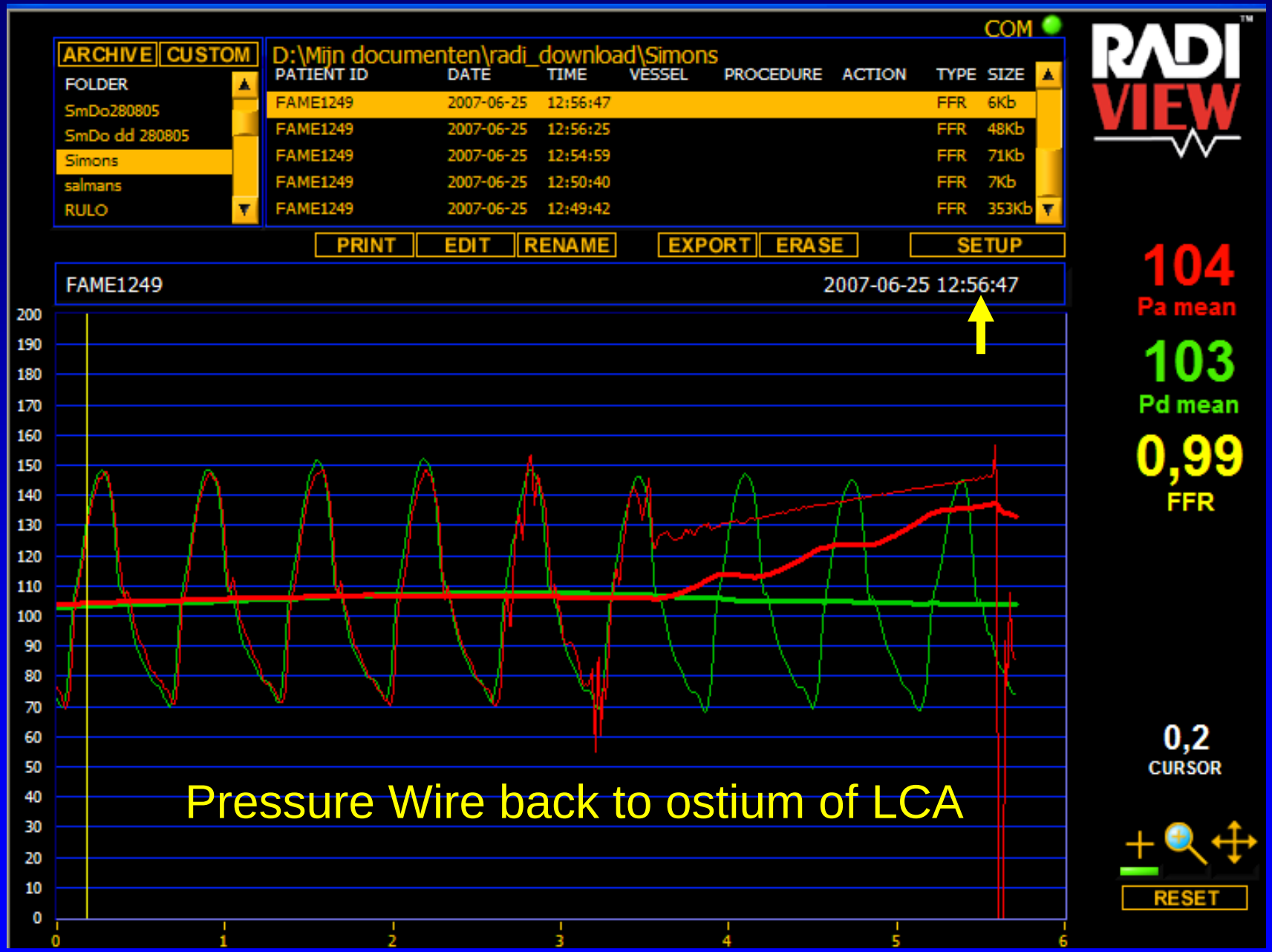
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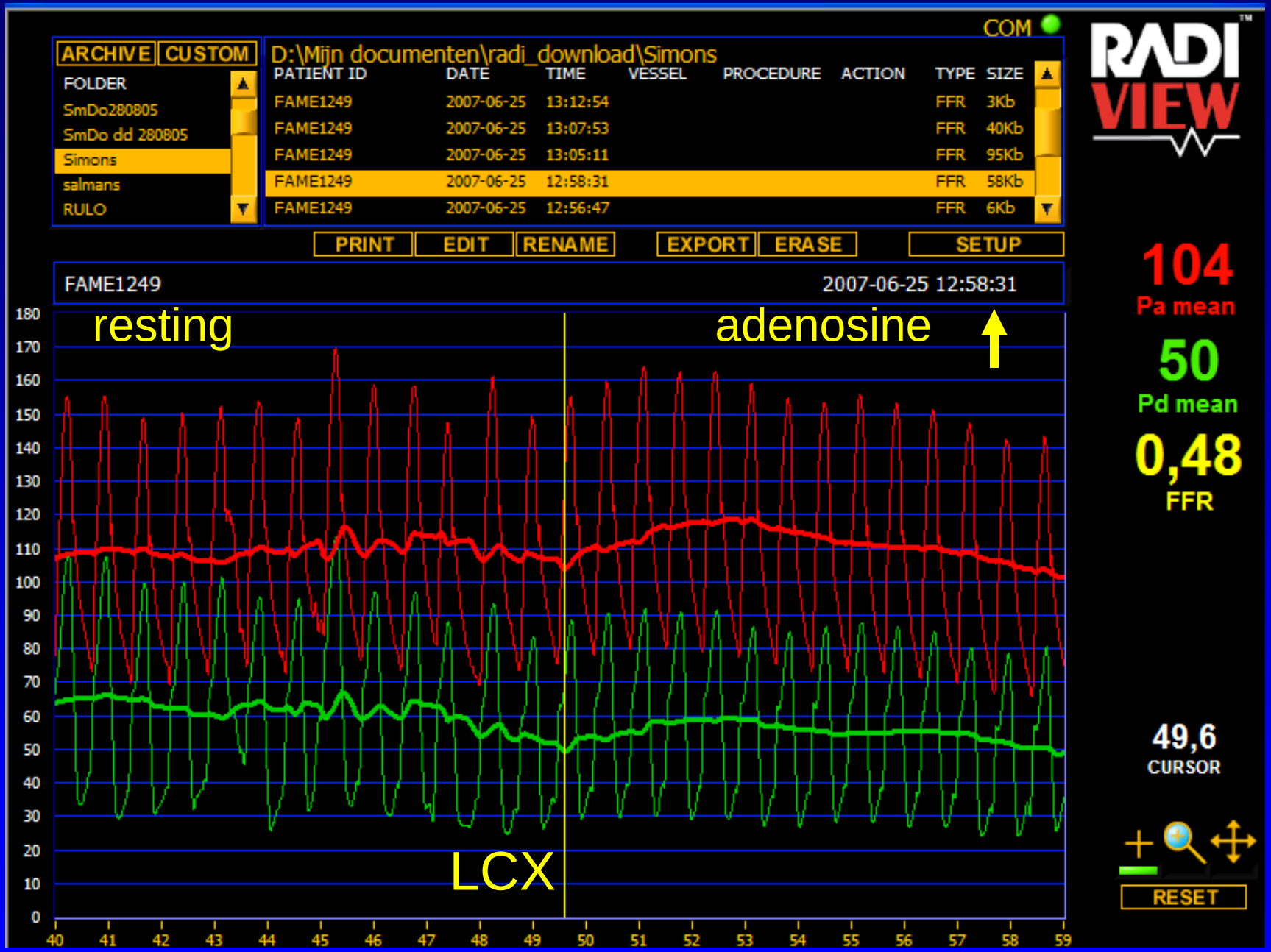
Pressure Wire back to ostium of LCA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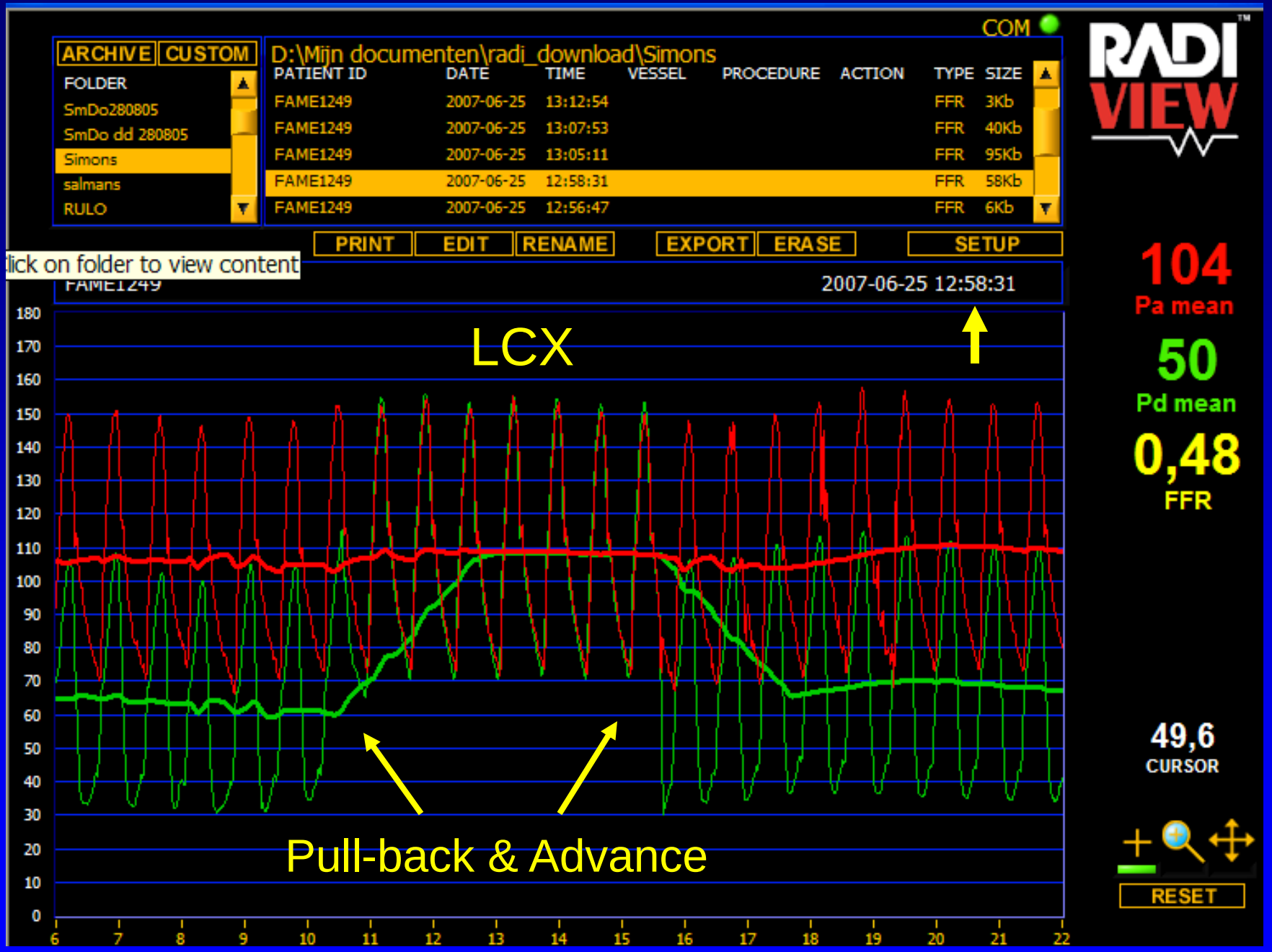
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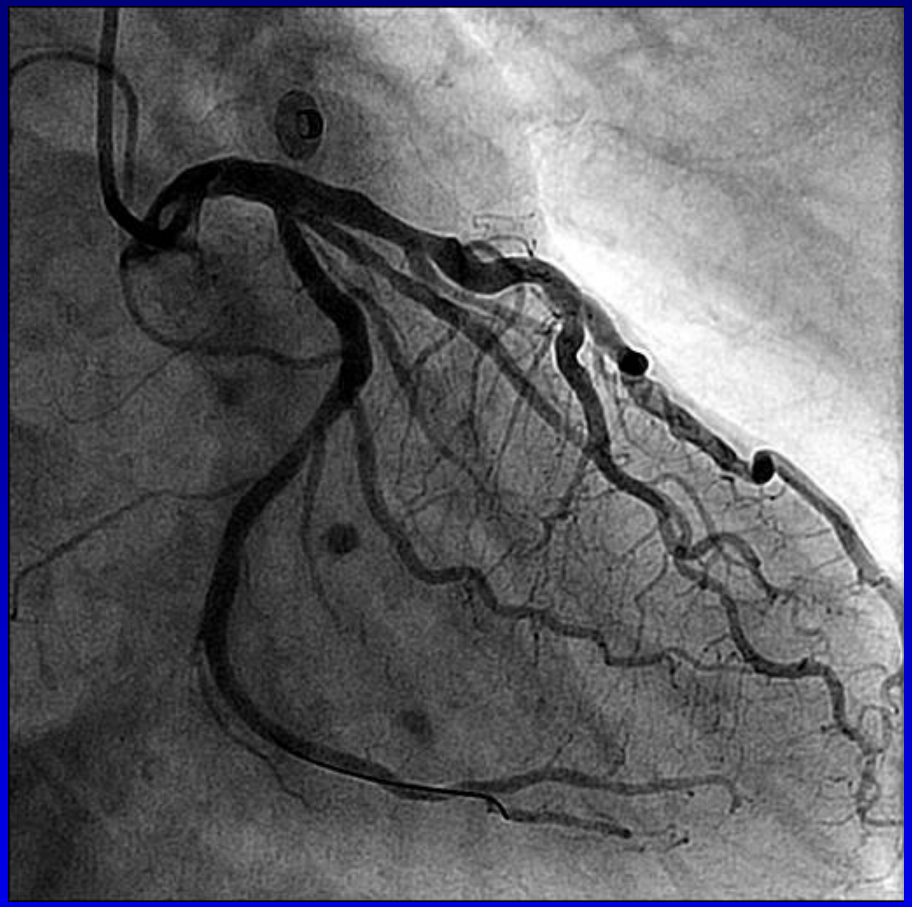
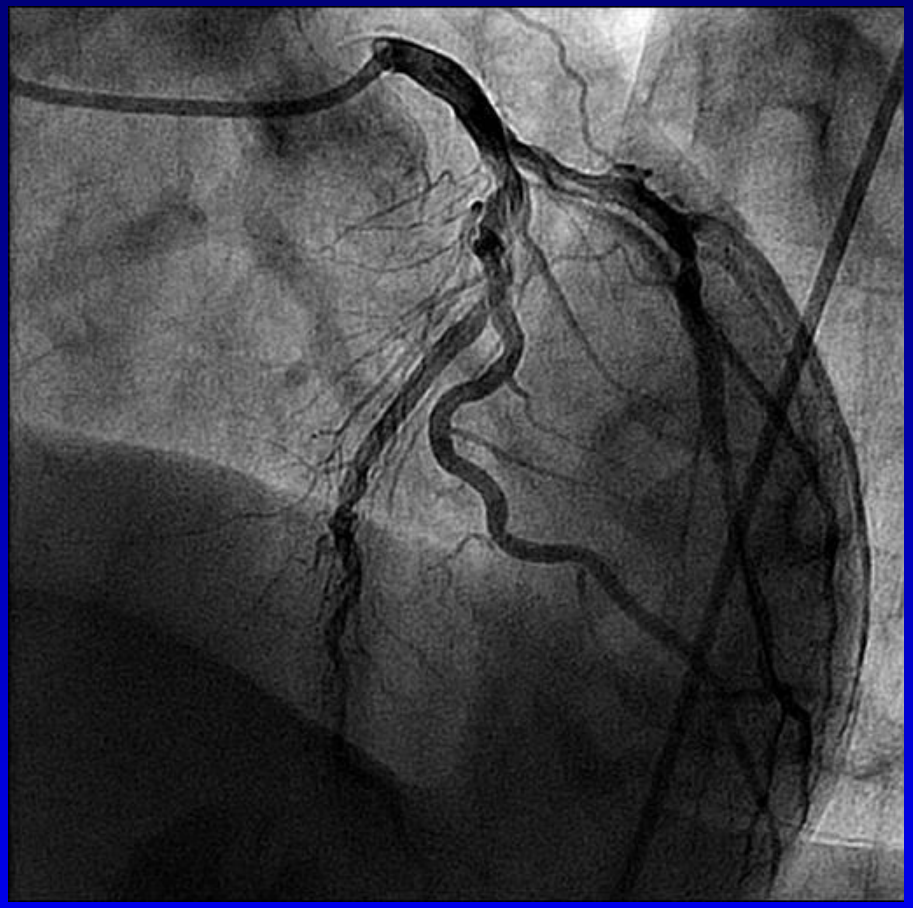
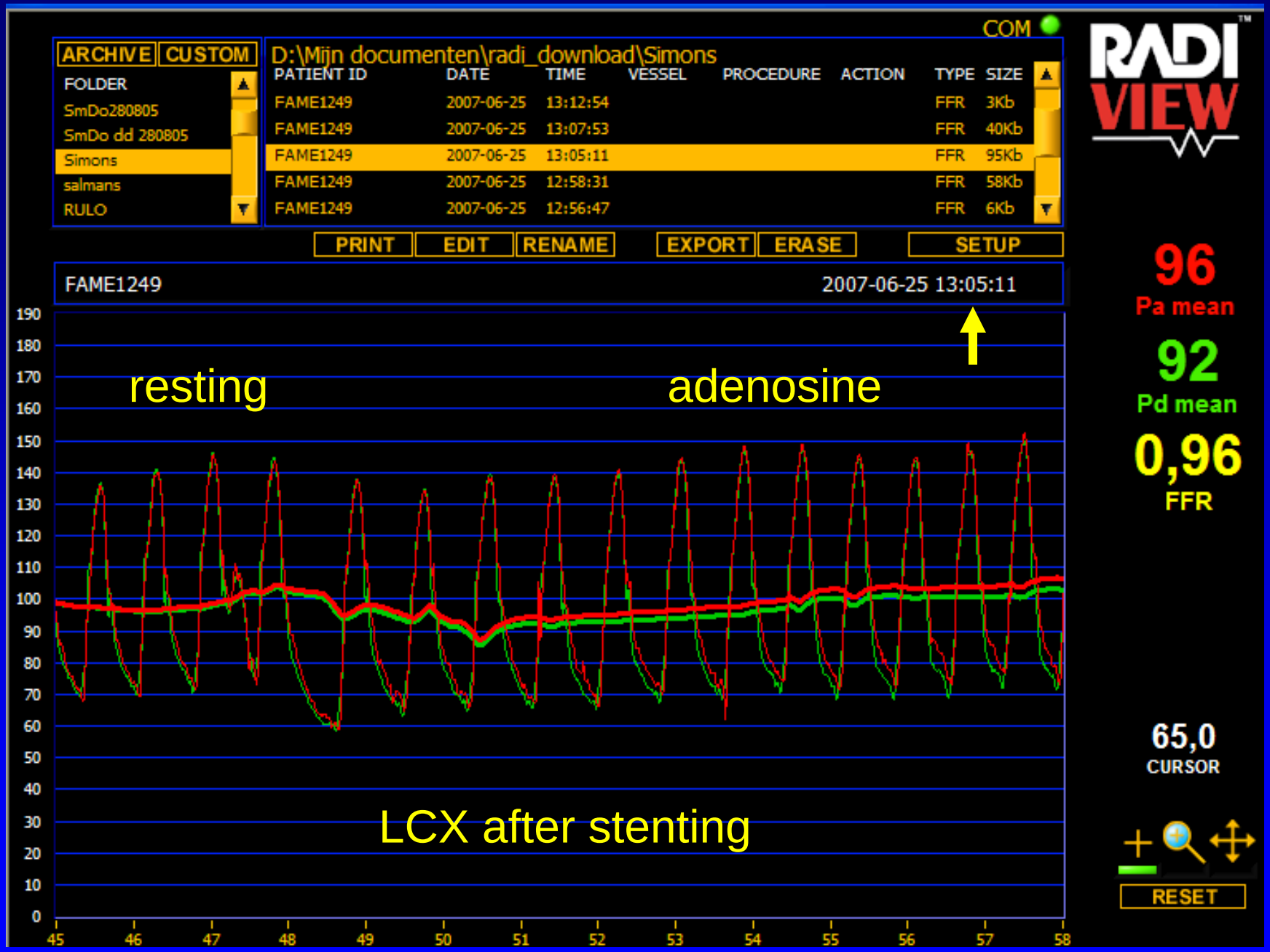




LCX after stenting (Endeavour 3.5 x 12)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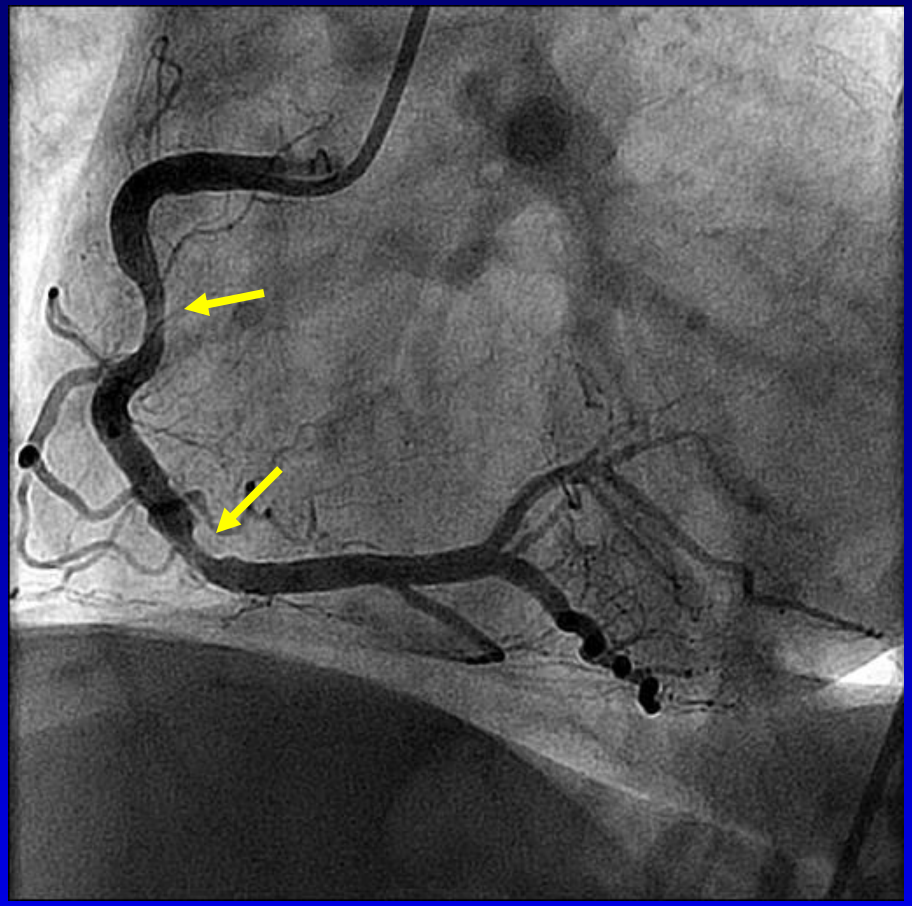

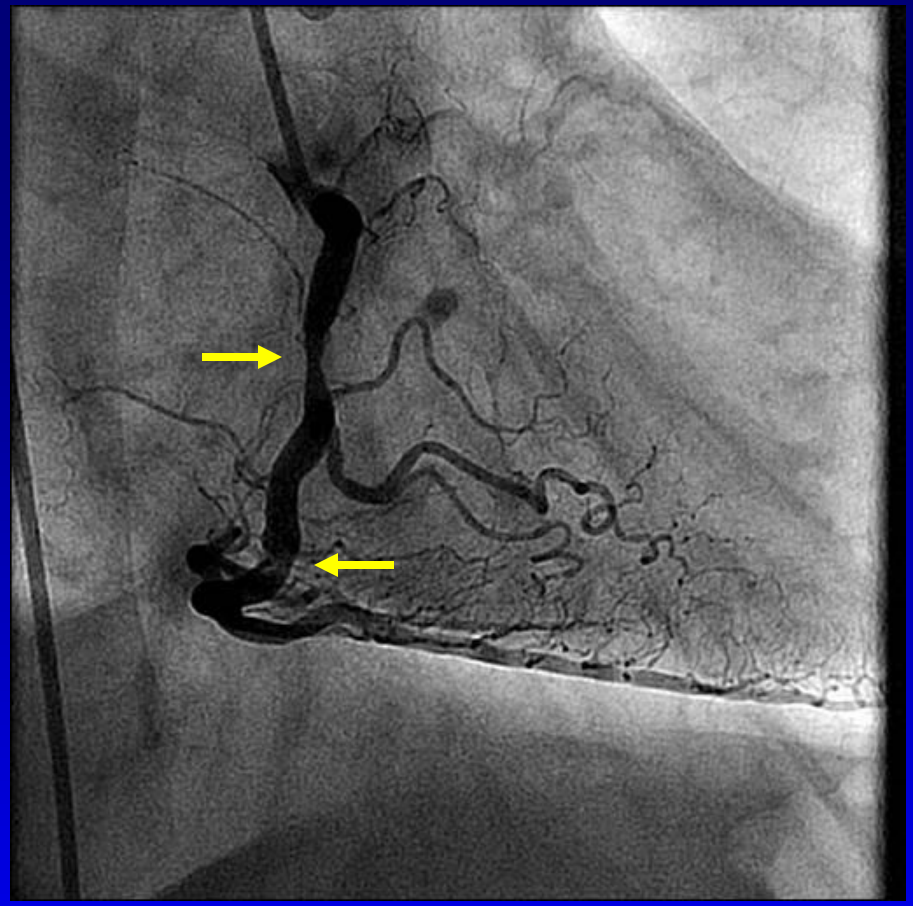

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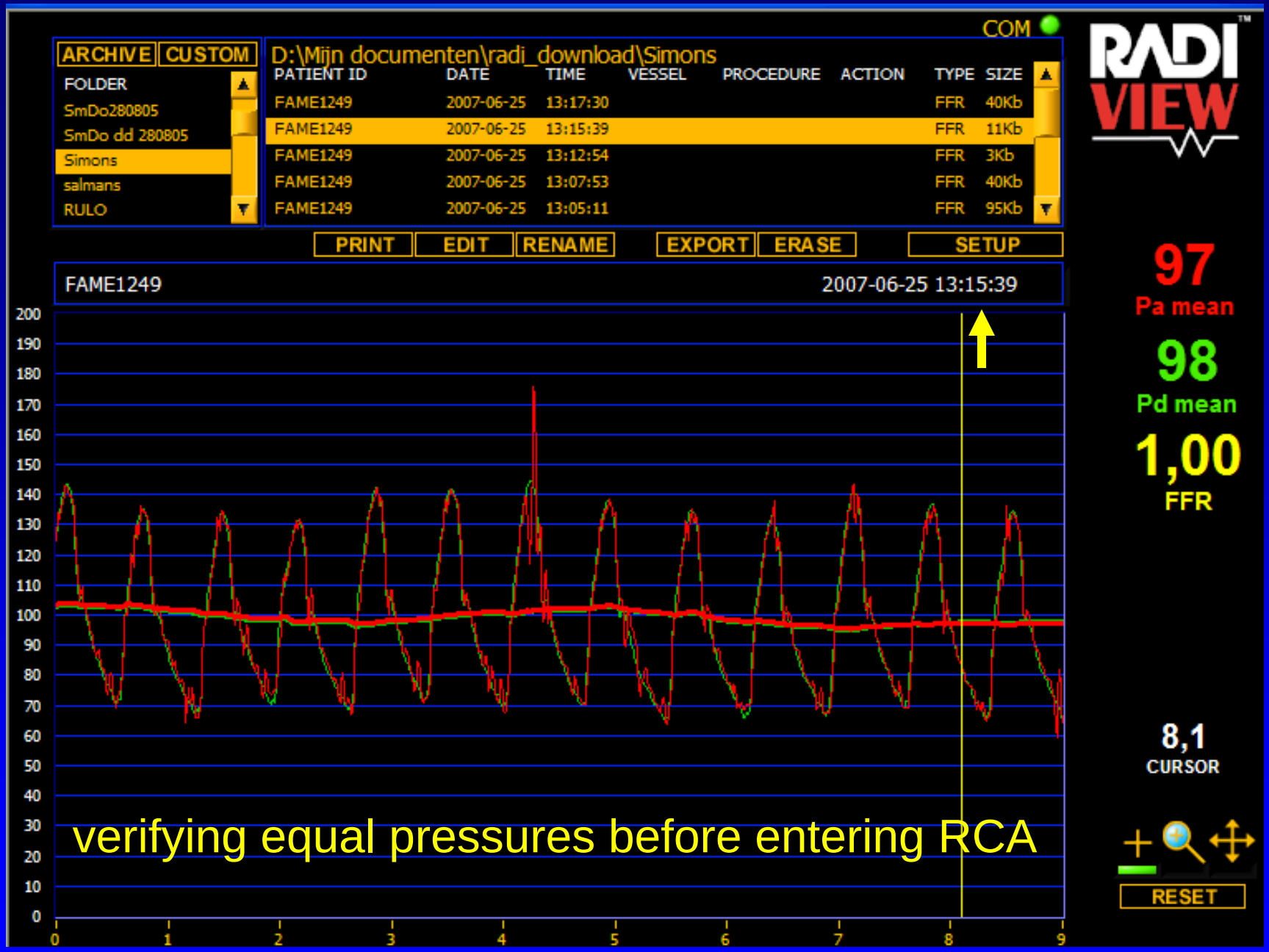
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FAME1249 2007-06-25 13:07:53 FFR 40Kb
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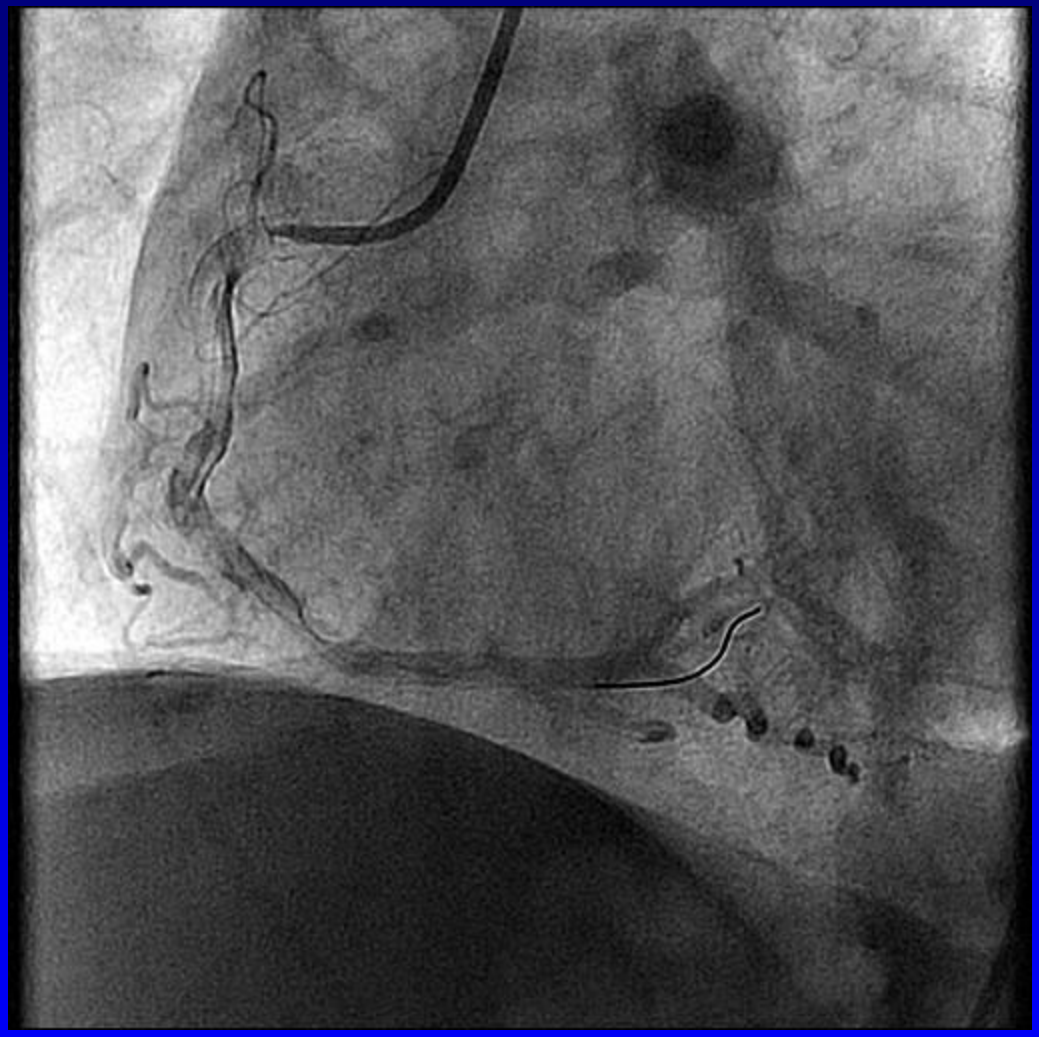
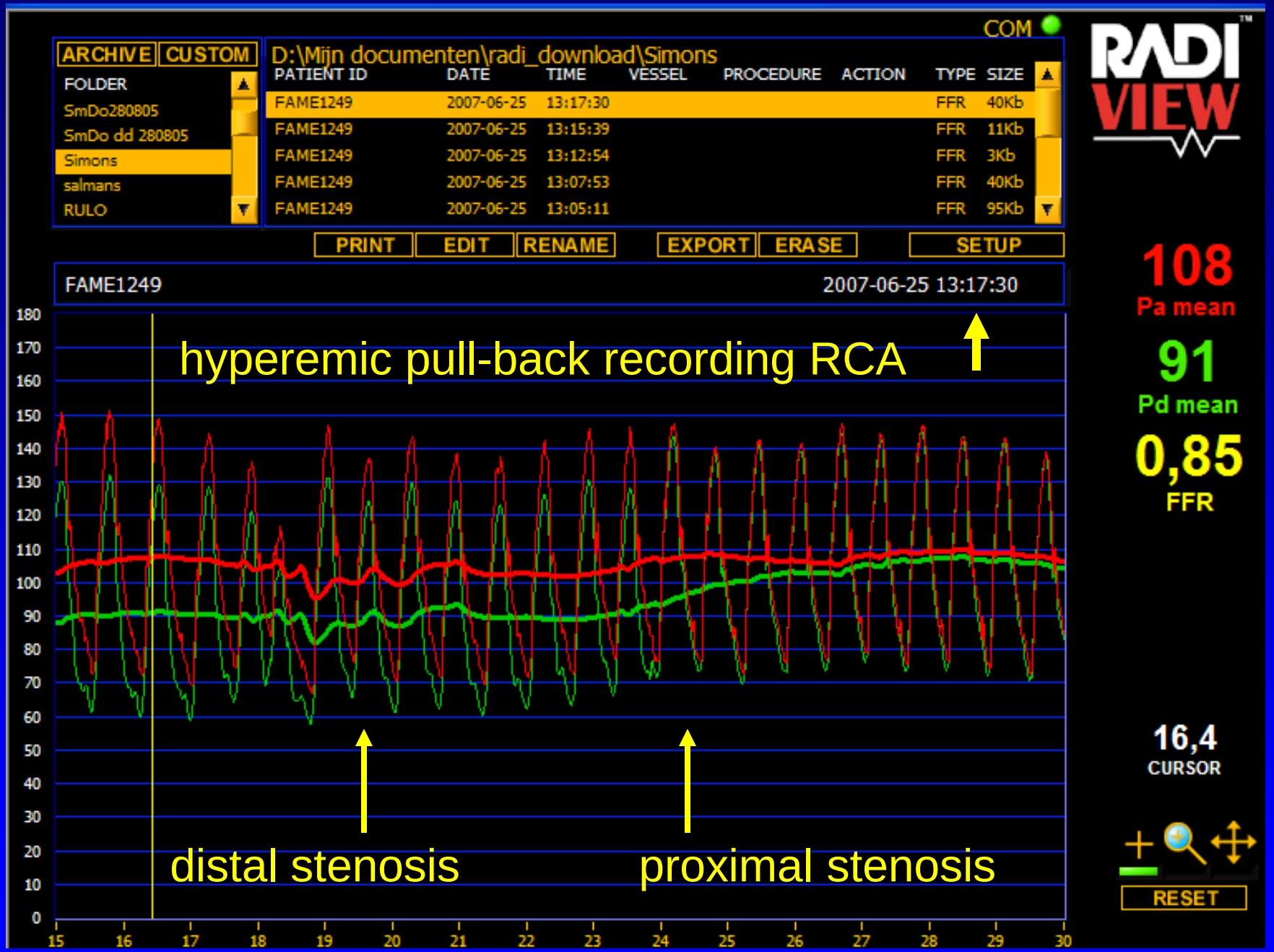
verifying equal pressures before entering RCA



Pressure Wire in RCA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hyperemic pull-back recording RCA
distal stenosis
proximal stenosis
108
Pa mean
91
Pd mean
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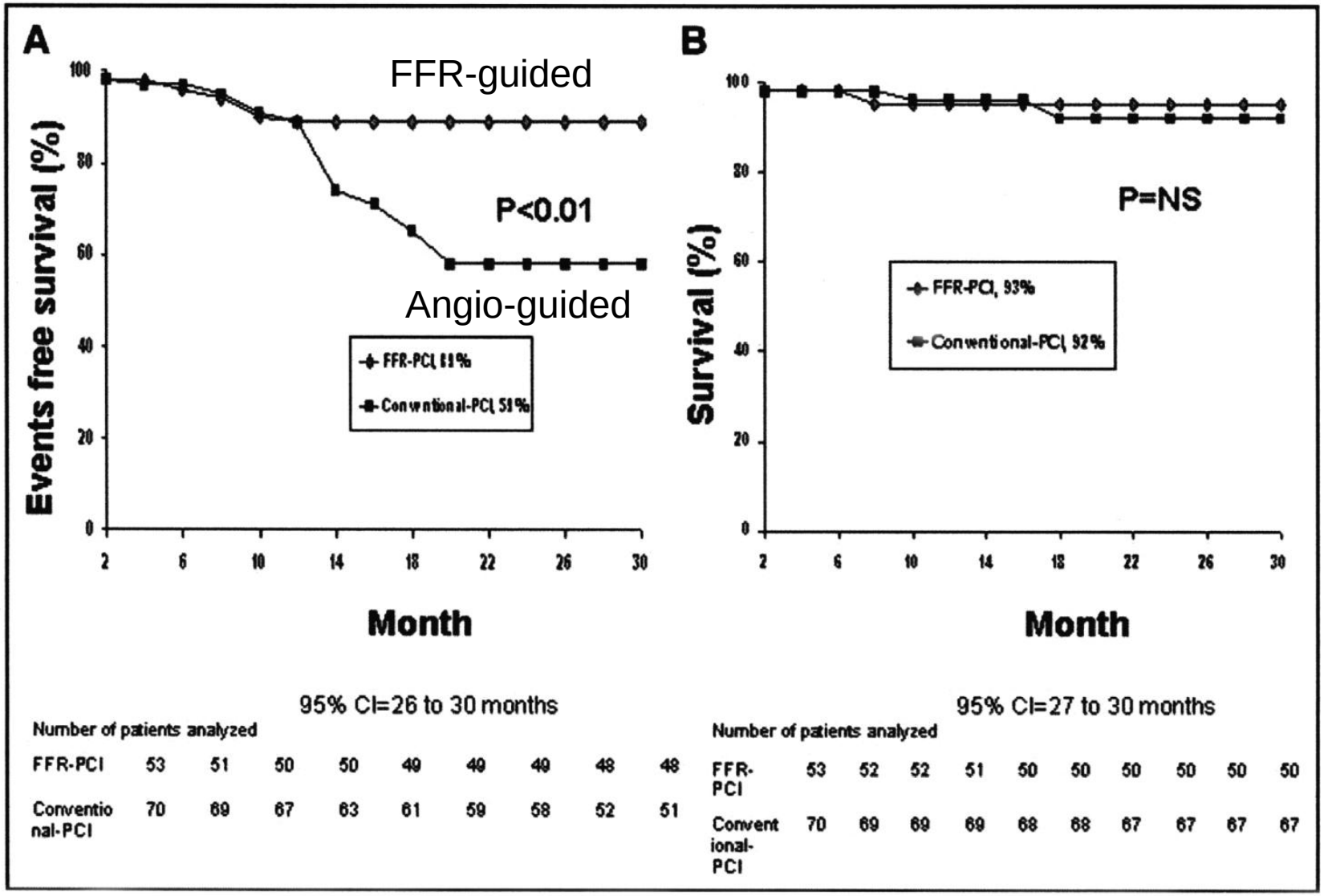
LESSONS FROM THIS PATIENT:

- only 1 stent necessary ; cost-savings!
- if treatment was based upon angio and performed by “more agresssive” interventionalist (or had been randomized to angio-guided arm of FAME study), at least 3 and maybe 4 or 5 stents would have been placed



FFR-guided vs. Angio-guided multivessel PCI (125 patients)
(event-free survival after 30 months)

Leesar et al, JACC 2005

But, ….. does it matter to selectively stent ischemic stenoses? Does routine use of FFR in MVD impact prognosis? What about functional class? Procedure time?

→ *The windtunnel for testing such an FFR-guided PCI strategy is a randomized trial*

FAME Study Flow Chart

Lesions warranting PCI identified

Randomized

FFR-Guided

PCI performed on indicated lesions only if FFR <0.80

Angio-Guided

PCI performed on indicated lesions

Primary Endpoint

Composite of death, MI and repeat revasc. (MACE) at 1 year

Key Secondary Endpoints

Individual rates of death, MI, and repeat revasc., MACE, and functional status at 2 years

Participating Centers

USA (6)

Stanford University
(William F. Fearon)

Northeast Cardiology, Bangor, Maine
(Peter N. Ver Lee)

University of Louisville
(Massoud Leesar)

St Louis University
(Michael Lim)

University Hospital Virginia
(Michael Ragosta)

University of South Carolina
(Eric Powers)

EUROPE (14)

King´s College Hospital, London)
(Ph.MacCarthy)

Cardiovascular Center Aalst *(B. De Bruyne)*

Catharina Hospital Eindhoven *(N.Pijls)*

Rigshospitalet, Copenhagen (*T.Engstrom*)

Klinikum der Universitat Munchen *(V.Klauss)*

Aarhus University Hospital *(Ole Frobert)*

University Hospital Bergmannsheil
(Waldemar Bojara)

Sodersjukhhuset, Stockholm *(I Herzfeld)*

Helsingborgs Lasarett *(F Schersten)*

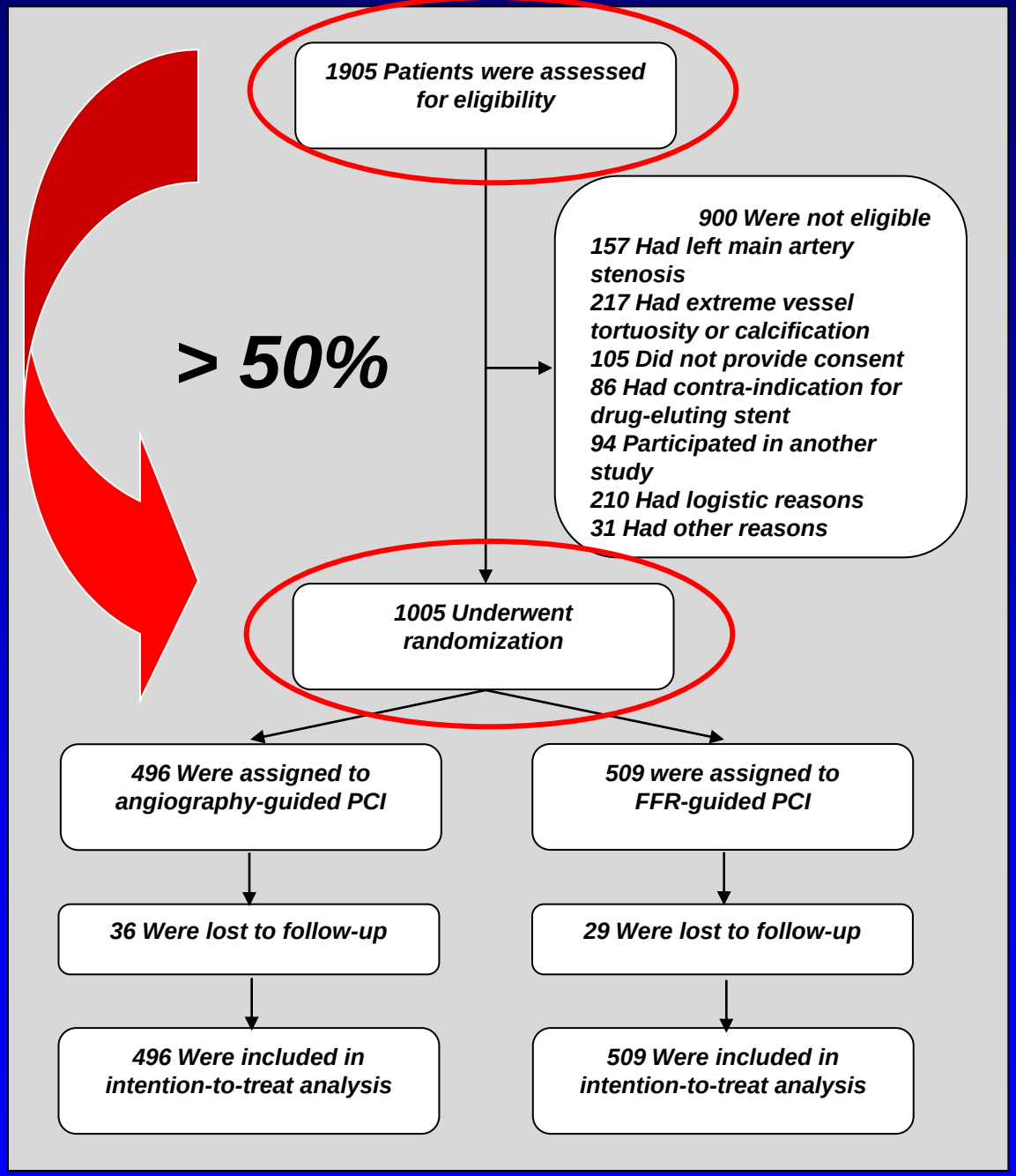
Klinikum Darmstadt *(Gerald Werner)*

Bristol Royal Infirmary *(A.Baumbach)*

Staedt. Krankenhaus, Bogenhausen
(G.Riess)

Glasgow Western Infirmary *(Keith Oldroyd)*

Royal Victoria Hospital, Belfast *(Ganesh Manoharan)*


1905 Patients were assessed for eligibility
900 Were not eligible
157 Had left main artery stenosis
217 Had extreme vessel tortuosity or calcification
105 Did not provide consent
86 Had contra-indication for drug-eluting stent
94 Participated in another study
210 Had logistic reasons
31 Had other reasons
> 50%
1005 Underwent randomization
496 Were assigned to angiography-guided PCI
509 were assigned to FFR-guided PCI
36 Were lost to follow-up
29 Were lost to follow-up
496 Were included in intention-to-treat analysis
509 Were included in intention-to-treat analysis

Baseline

	Angio-Guided n = 496	FFR-Guided n = 509	P Value
Age, mean ±SD	64±10	65±10	0.47
Male, %	73	75	0.30
Diabetes, %	25	24	0.65
Hypertension, %	66	61	0.10
Current smoker, %	32	27	0.12
Hyperlipidemia, %	73	72	0.62
Previous MI, %	36	37	0.84
NSTE ACS, %	36	29	0.11
Previous PCI , %	26	29	0.34
LVEF, mean ±SD	57±12	57±11	0.92
LVEF < 50% , %	27	29	0.47

Tonino et al. N Engl J Med. 2009

Baseline

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Previous PCI , %	**26**	**29**	**0.34**
LVEF, mean ±SD	57±12	57±11	0.92
LVEF < 50% , %	**27**	**29**	**0.47**

Tonino et al. N Engl J Med. 2009

Procedural data

	Angio-Guided n = 496	FFR-Guided n = 509	P Value
Indicated lesions / patient	**2.7±0.9**	**2.8±1.0**	**0.34**
Stents / patient	**2.7 ± 1.2**	**1.9 ± 1.3**	**<0.001**
Procedure time (min)	**70 ± 44**	**71 ± 43**	**0.51**
Contrast agent used (ml)	**302 ± 127**	**272 ± 133**	**<0.001**
Equipment cost (US $)	**6007**	**5332**	**<0.001**
Length of hospital stay (days)	**3.7 ± 3.5**	**3.4 ± 3.3**	**0.05**

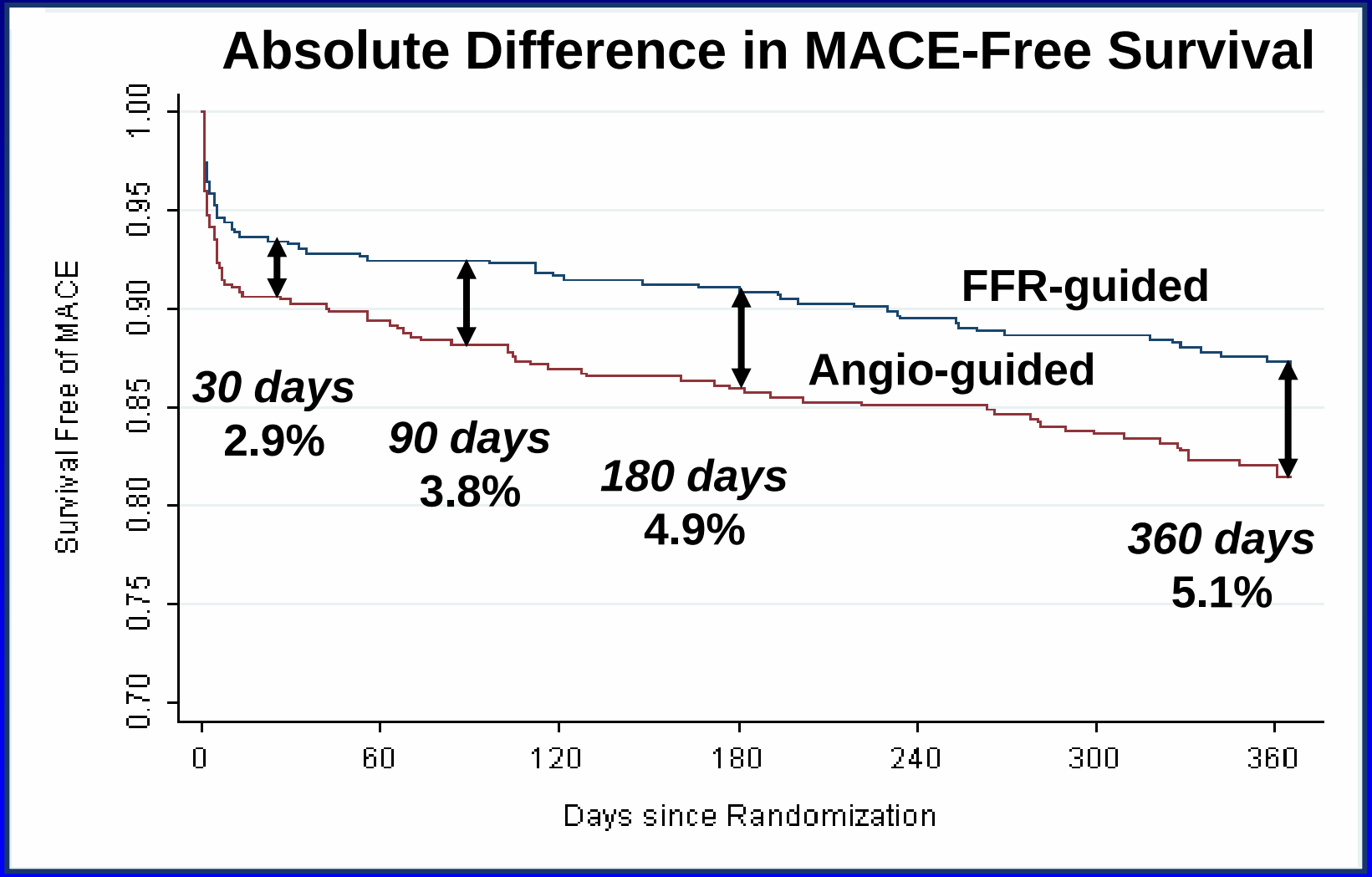
Tonino et al. N Engl J Med. 2009

Adverse events after 1 year

	Angio-Guided n = 496	FFR-Guided n = 509	P Value
Total no. of MACE	**113**	**76**	**0.02**
Death	**15 (3.0)**	**9 (1.8)**	**0.19**
Myocardial Infarction	**43 (8.7)**	**29 (5.7)**	**0.07**
CABG or repeat PCI	**47 (9.5)**	**33 (6.5)**	**0.08**
Death or Myocardial Infarction	**55 (11.1)**	**37 (7.3)**	**0.04**
Death, MI, CABG, or re-PCI	**91 (18.3)**	**67 (13.2)**	0.02

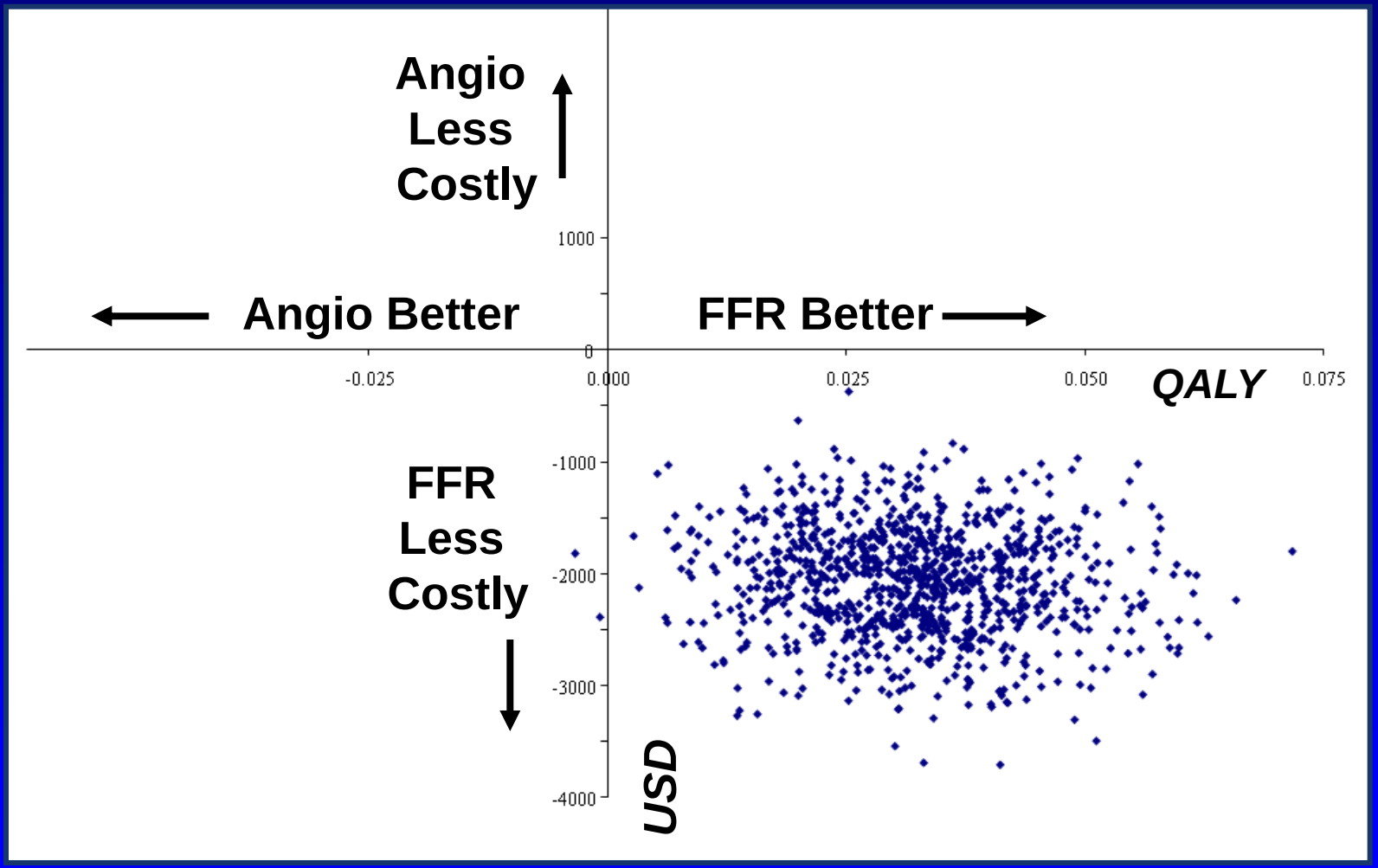
Tonino et al. N Engl J Med. 2009

1 year event-free survival



1 year economic evaluation

Bootstrap Simulation



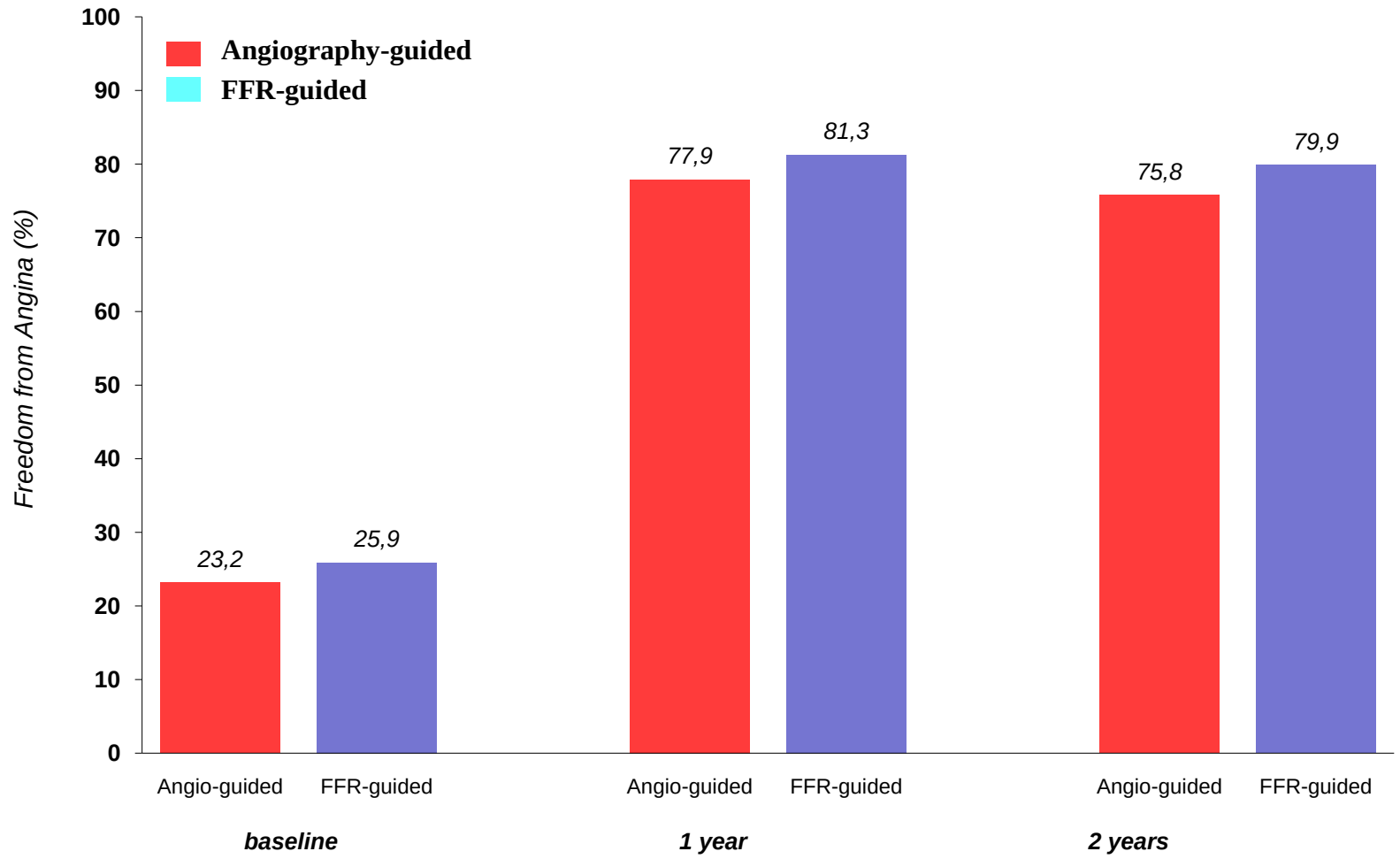
Fearon et al. Circulation, December, 2010

Adverse events after 2 years

	Angio-Guided n = 496	FFR-Guided n = 509	P Value
Total no. of MACE	**139**	**105**	**0.01**
Individual Endpoints			
Death	**19 (3.8)**	**13 (2.6)**	**0.25**
Myocardial Infarction	**48 (9.7)**	**31 (6.1)**	**0.03**
CABG or repeat PCI	**61 (12.3)**	**53 (10.4)**	**0.35**
Composite Endpoints			
Death or Myocardial Infarction	**63 (12.7)**	**43 (8.4)**	**0.03**
Death, MI, CABG, or re-PCI	**110 (22.2)**	**90 (17.7)**	**0.07**

Tonino et al. N Engl J Med. 2009

Freedom from angina



Does this mean we really have to measure
all lesions with FFR in MVD patients?

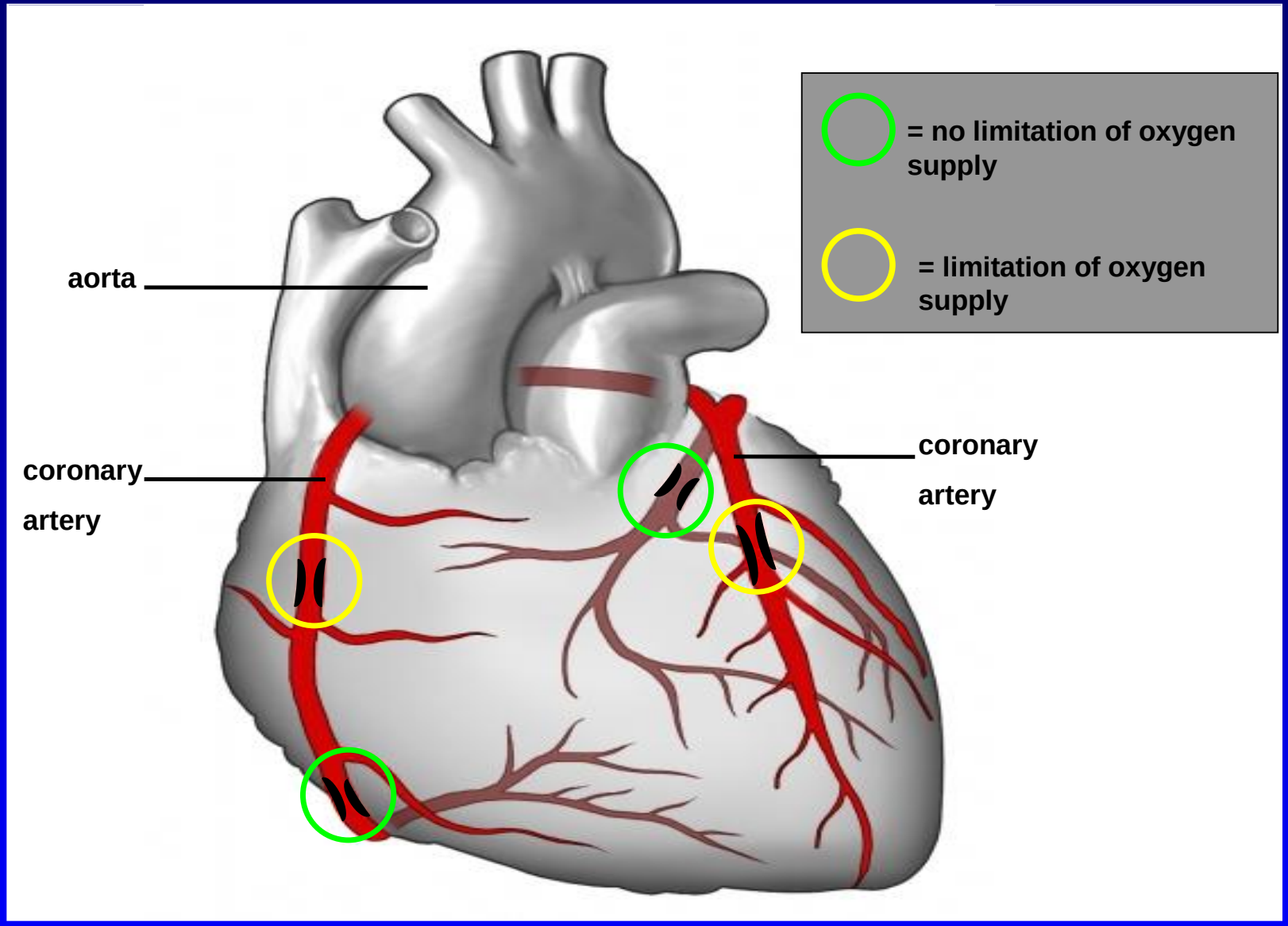
→

FAME angiographic substudy:
FFR mandatory in all MVD PCI, in all stenoses of 50-90%

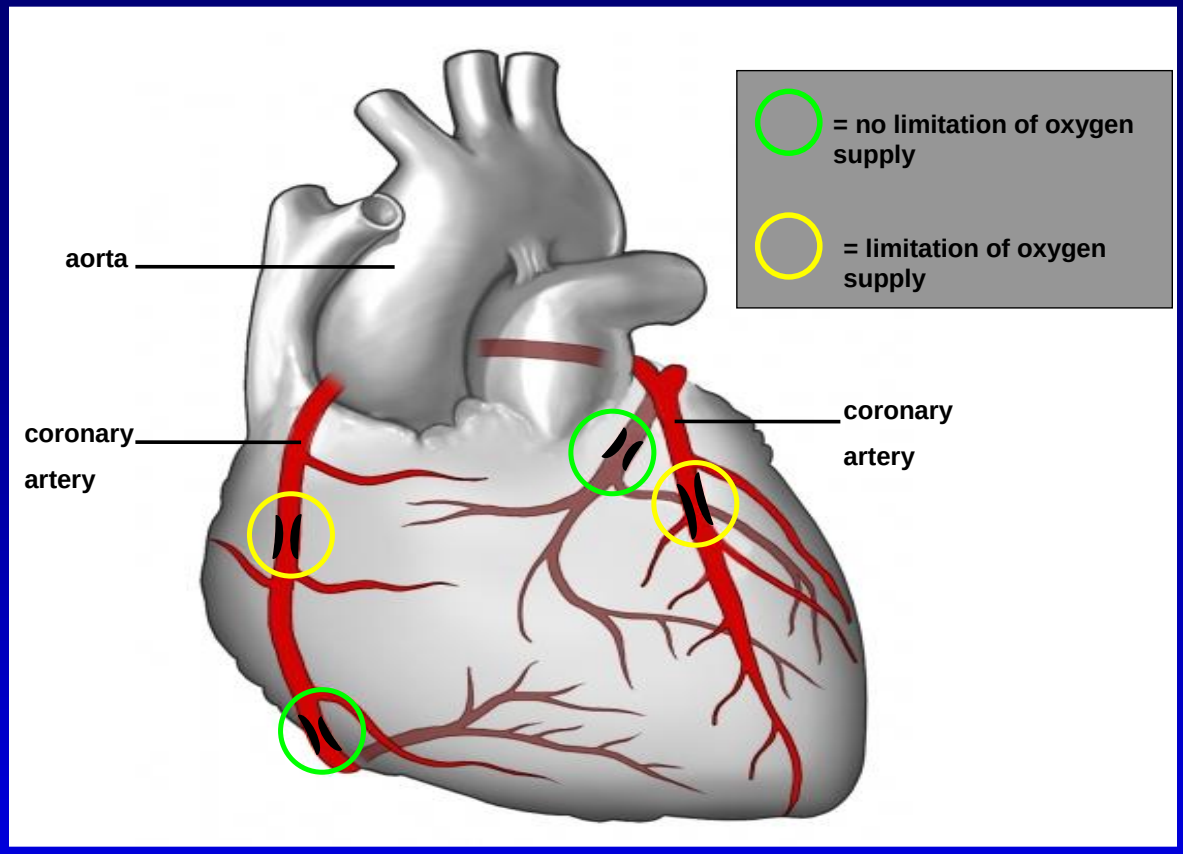
How does FAME fit with other recently performed RCT's to (DES) stenting in Multivessel Disease ?

→ Keynote lecture

Why is outcome of FFR guided procedures so good?



Intrinsic risk of death and myocardial infarction ?



Ischemic lesion → intrinsic risk 5 % per year
Non-ischemic lesion → intrinsic risk 1 % per year
Stented stenosis → intrinsic risk 3 % per year

"stent 'm all" → intrinsic risk 12% → 12%
"stent only the ischemic ones" → intrinsic risk 12 → 8 %
both strategies eliminate ischemia → similar functional class

FAME study: CONCLUSIONS (1)

Routine measurement of FFR during PCI with DES in patients with multivessel disease, when compared to current angiography guided strategy

- ***Reduces the rate of the composite endpoint of death, myocardial infarction, re-PCI and CABG at 1 year by ~ 30%***

- ***Reduces mortality and myocardial infarction at 1 year by ~ 35 %***

FAME study: CONCLUSIONS (2)

Routine measurement of FFR during PCI with DES in patients with multivessel disease, when compared to current angiography guided strategy

- ***Is cost-saving and does not prolong the procedure***
- ***Reduces the number of stents used***
- ***Decreases the amount of contrast agent used***
- ***Results in a similar, if not better, functional status***

FAME study: CONCLUSIONS (3)

Routine measurement of FFR during DES-stenting in patients with multivessel disease is superior to current angiography guided treatment.

It improves outcome of PCI significantly

It supports the evolving paradigm of

"Functionally Complete Revascularization", i.e. stenting of ischemic lesions and medical treatment of non-ischemic ones.

FAME study: CONCLUSIONS (3)

Routine measurement of FFR during DES-stenting in patients with multivessel disease is superior to current angiography guided treatment.

It improves outcome of PCI significantly

It supports the evolving paradigm of

"Functionally Complete Revascularization", i.e. stenting of ischemic lesions and medical treatment of non-ischemic ones.

FFR now Class I Level A in ESC guidelines!

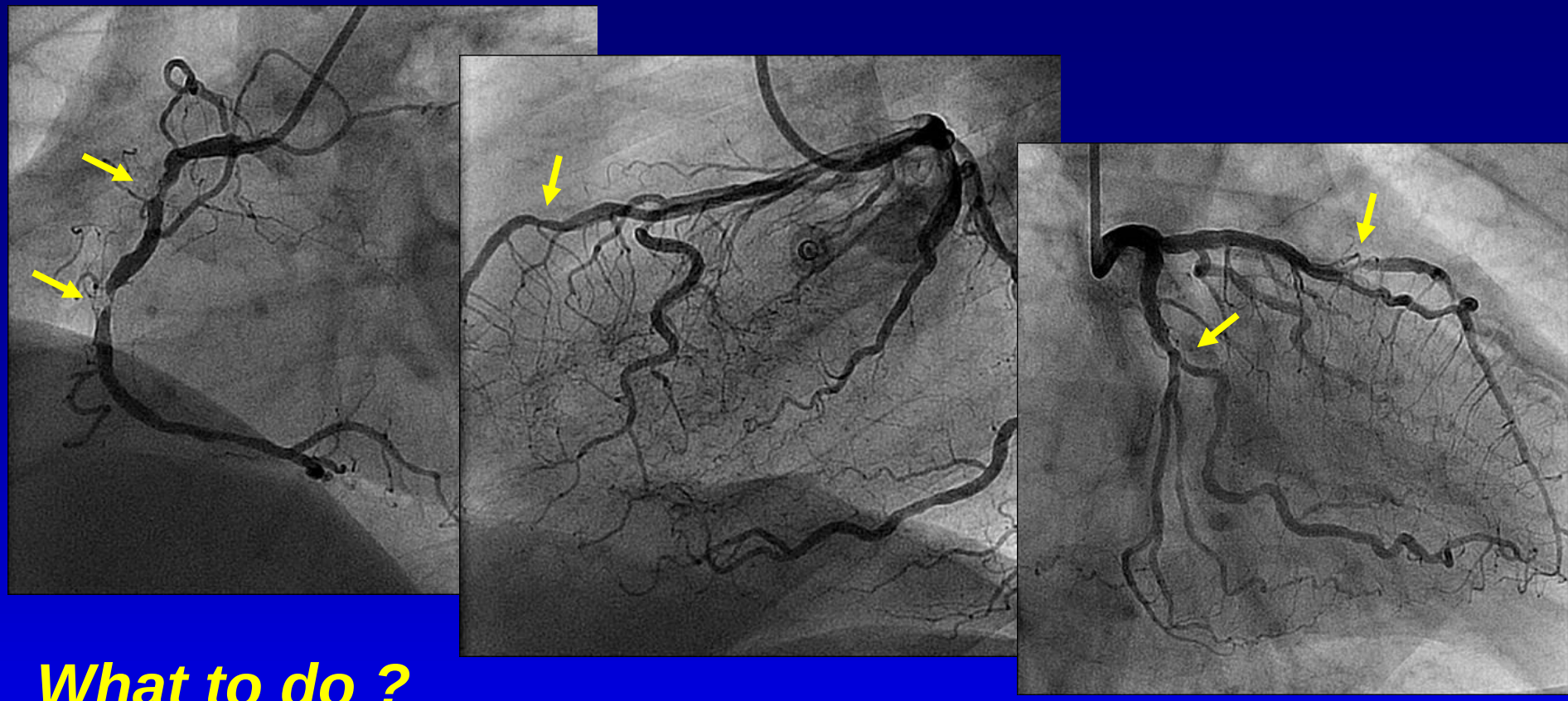
European Heart Journal
doi:10.1093/eurheartj/ehq277

ESC/EACTS GUIDELINES

Guidelines on myocardial revascularization

Table 33 Recommendations for specific percutaneous coronary intervention devices and pharmacotherapy

	Class[a]	Level[b]	Ref.[c]
FFR-guided PCI is recommended for detection of ischaemia-related lesion(s) when objective evidence of vessel-related ischaemia is not available.	I	A	15, 28
DES[d] are recommended for reduction of restenosis/re-occlusion if no contraindication to extended DAPT	I	A	45, 46,

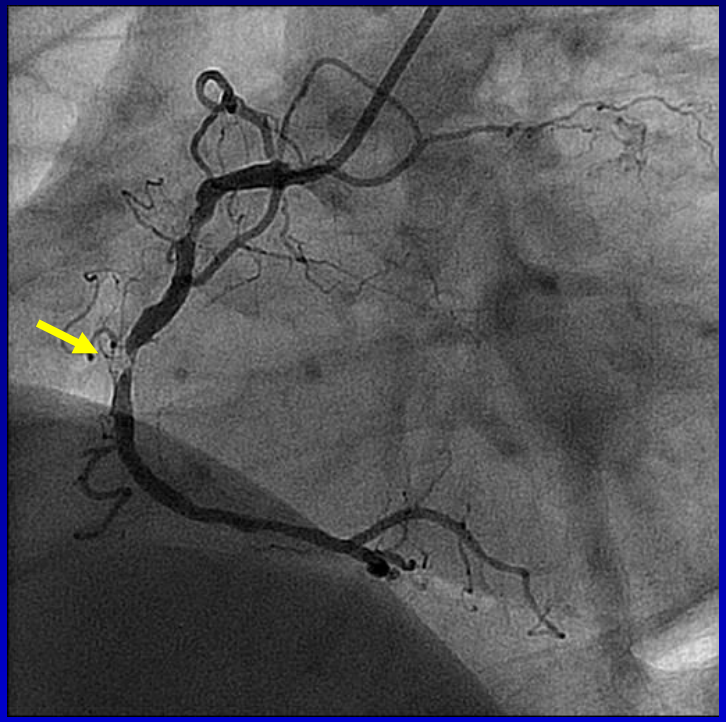


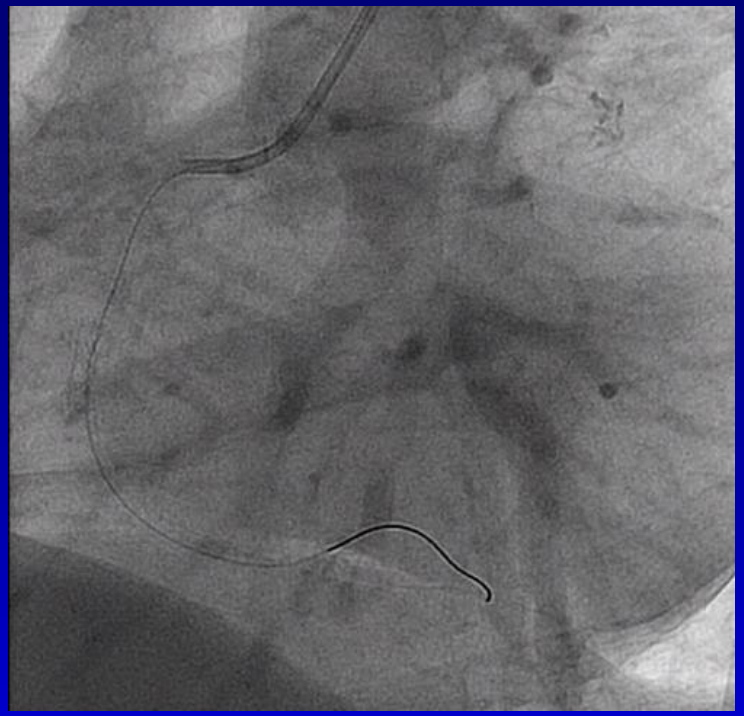
What to do ?

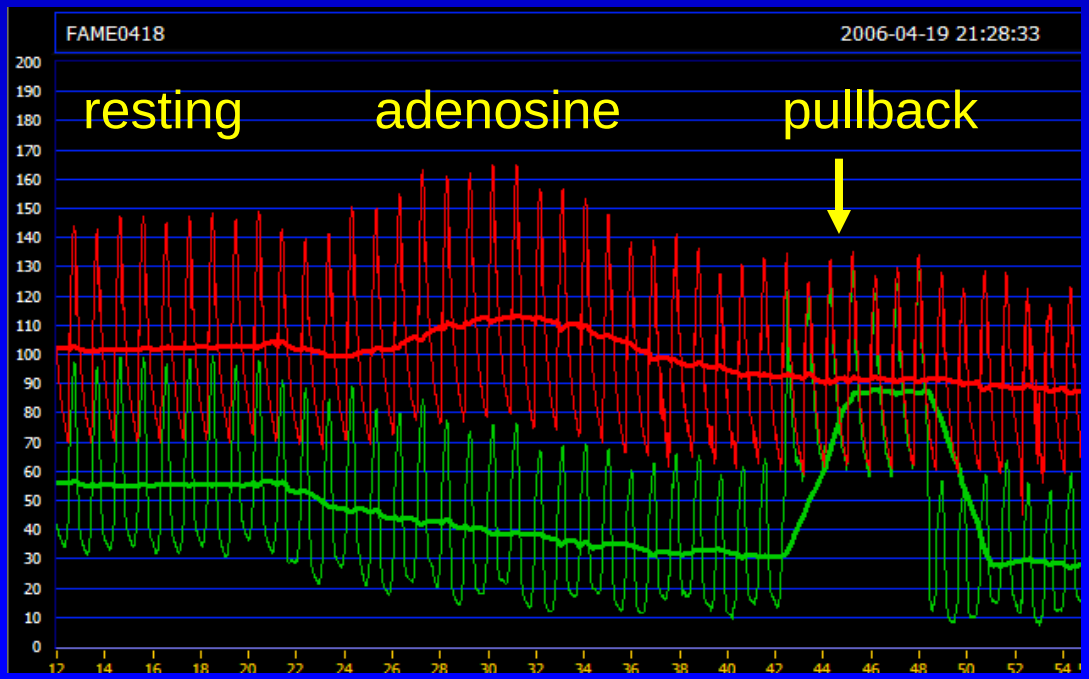
1. CABG anyway (3-vessel disease)
2. PCI of RCA lesions only
3. Nuclear test (MIBI Spect)
4. PCI of all lesions (5 stents)
5. further invasive diagnostic testing (FFR)

Start of procedure:

sensor close to tip of JR guiding catheter to verify equal pressures at that point

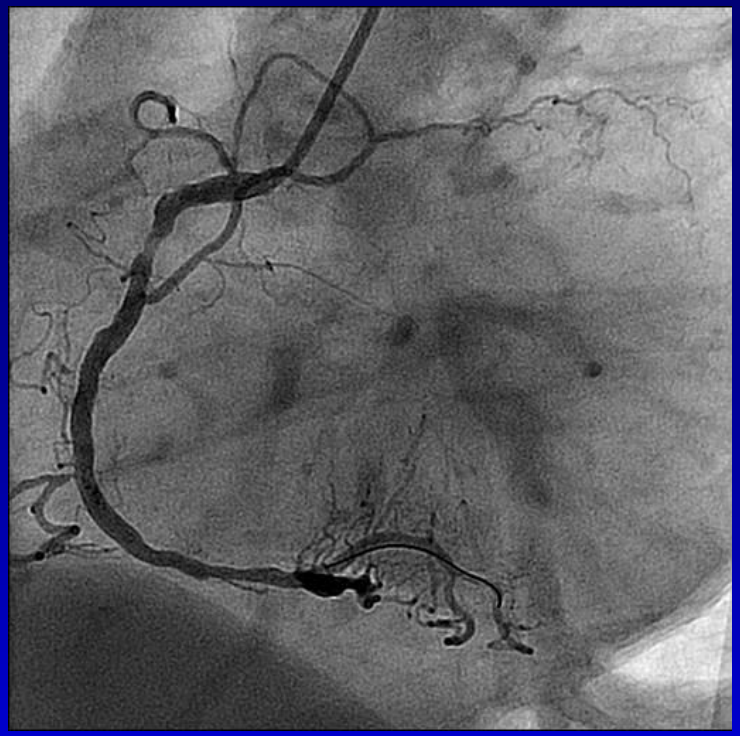


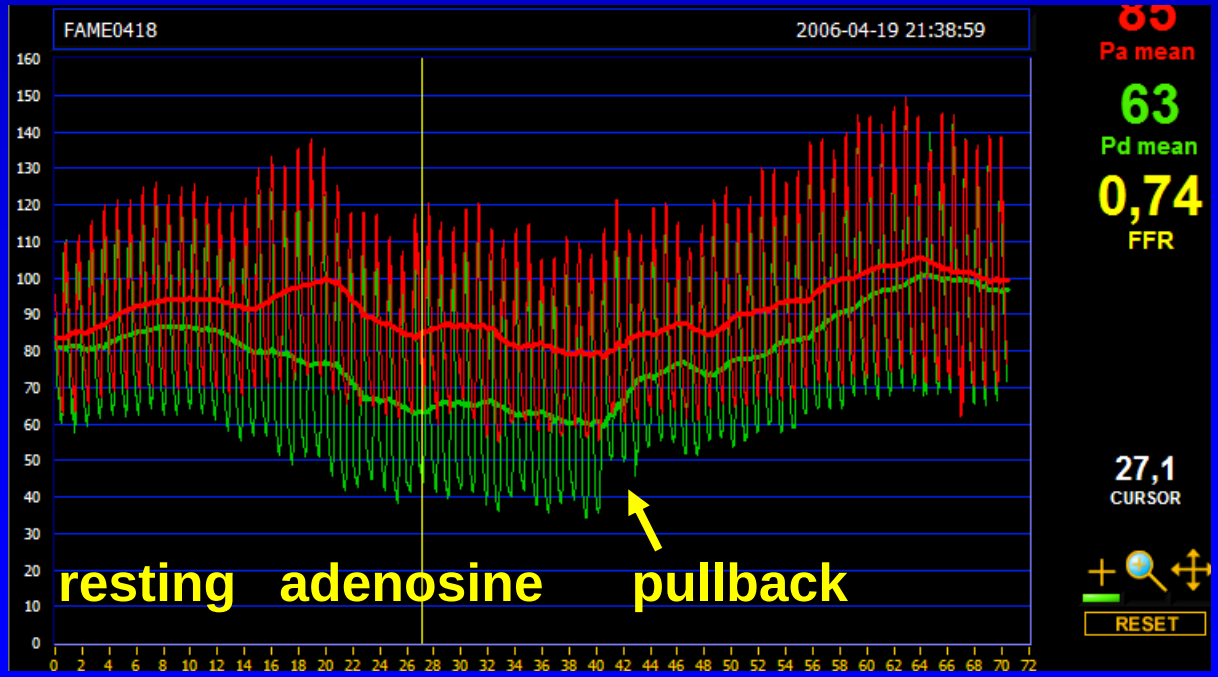



FAME0418
2006-04-19 21:28:33
resting
adenosine
pullback
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
46
48
50
52
54

RCA:

FFR = 0.34

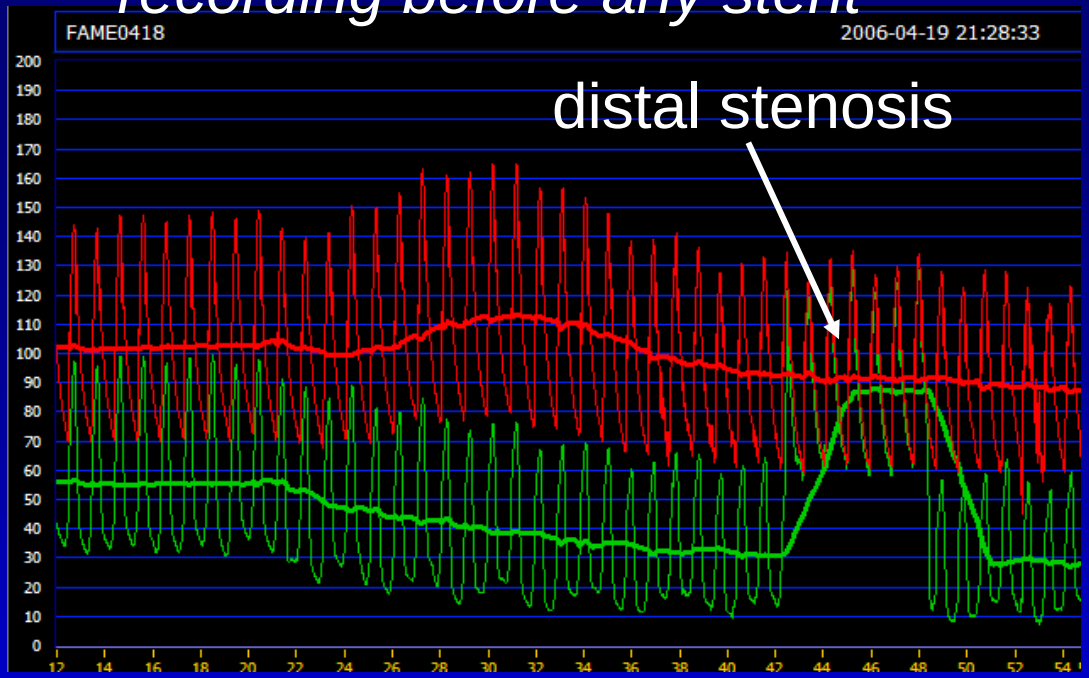




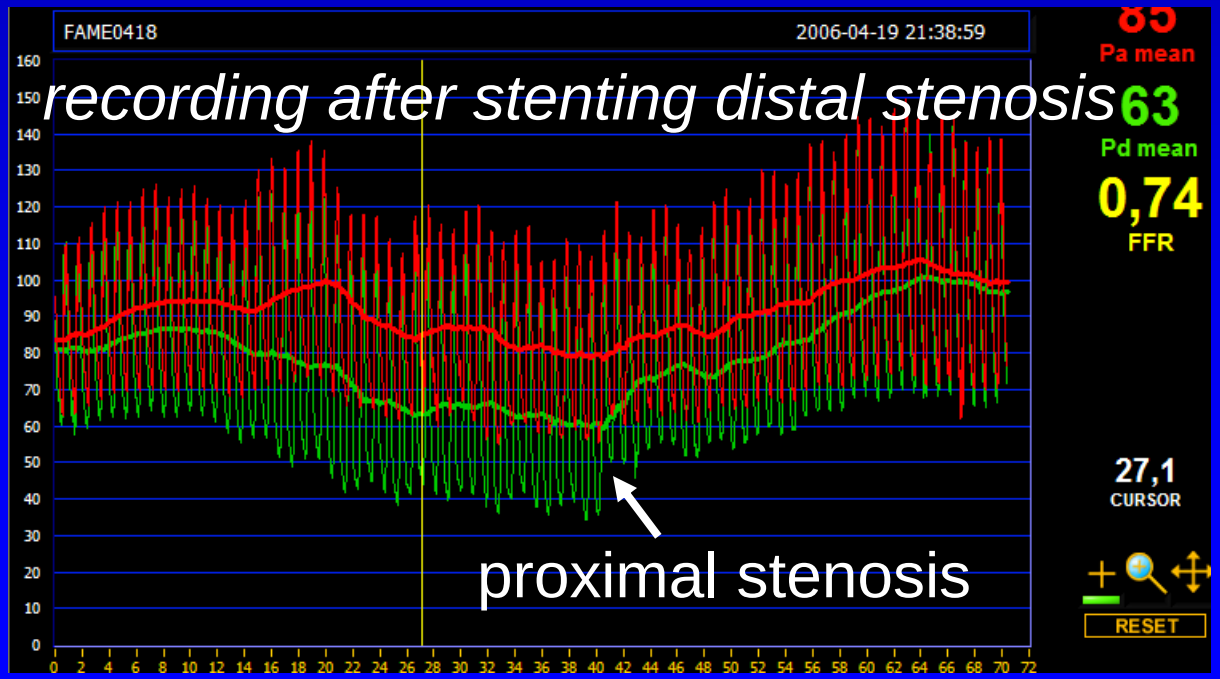
RCA after one stent:

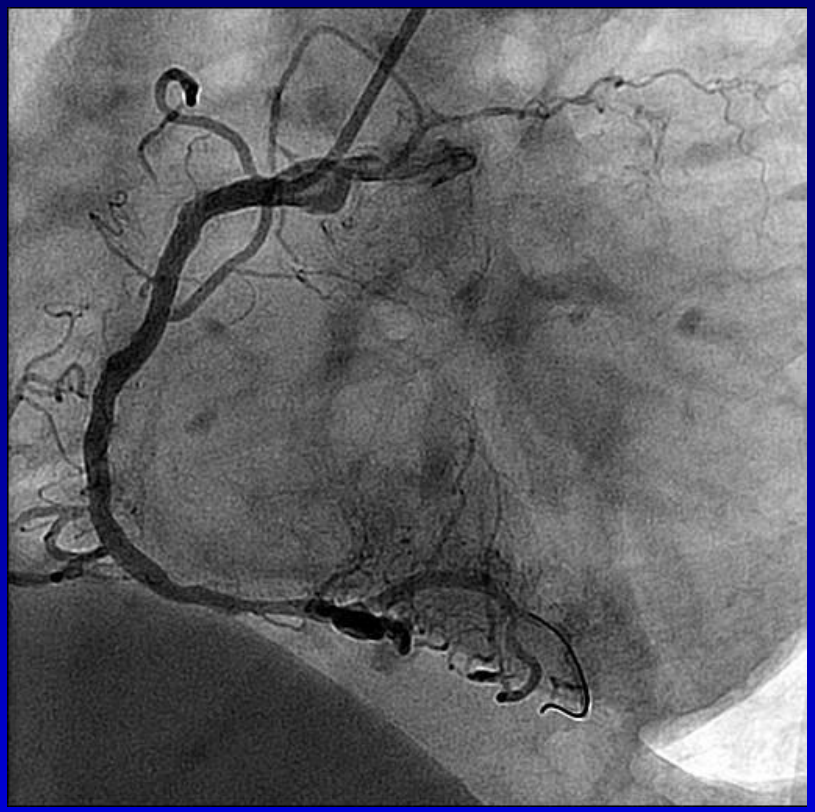
FFR = 0.74

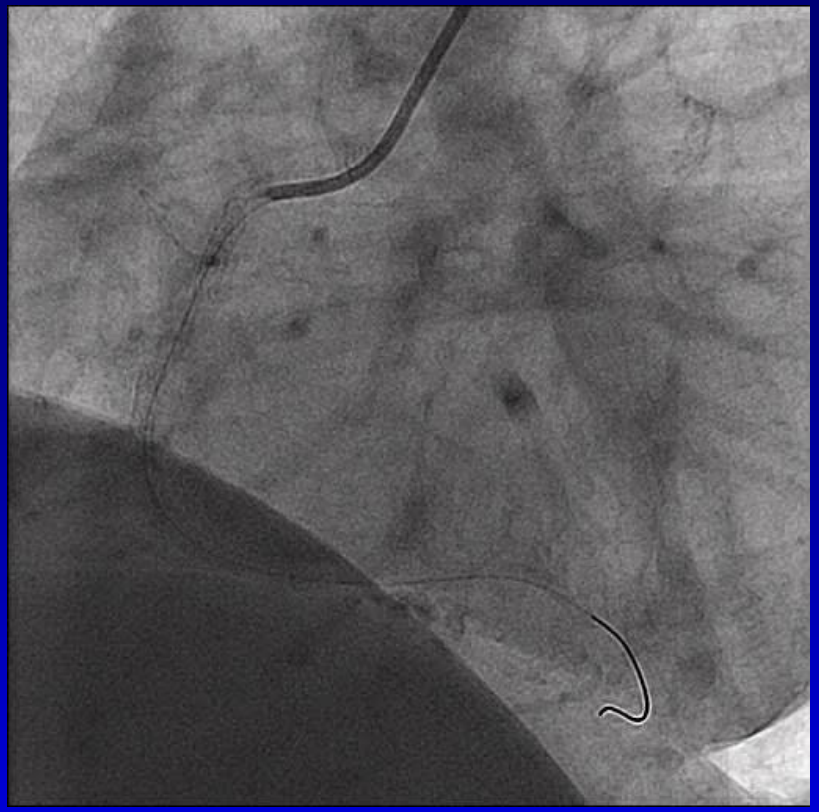
recording before any stent

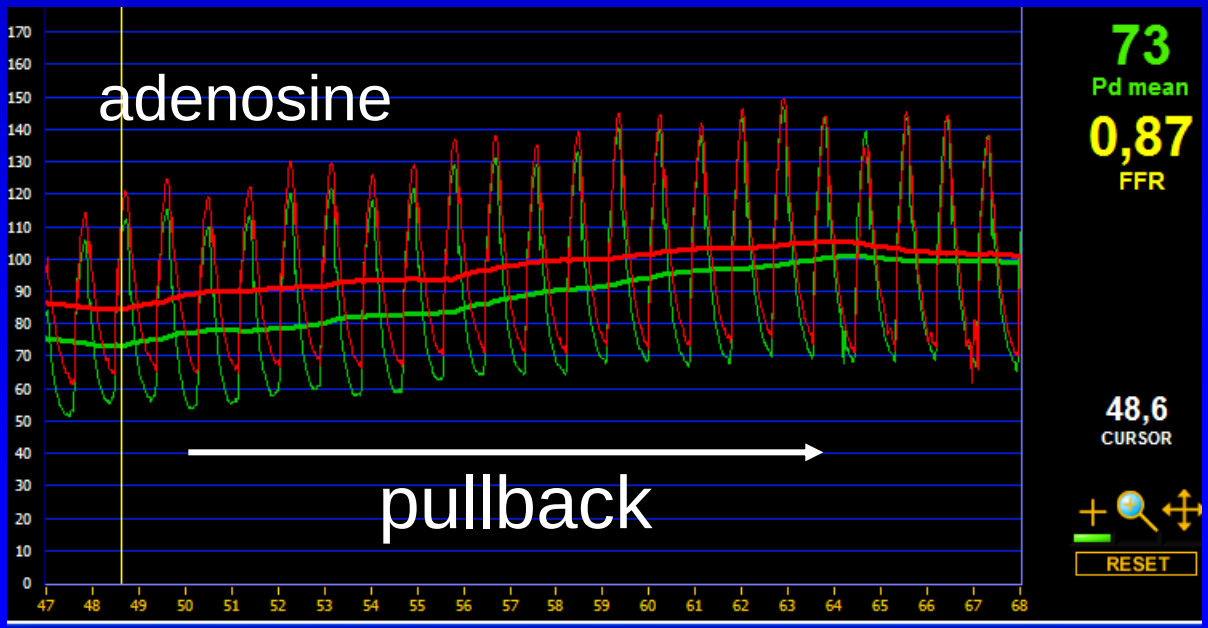


Why do we find gradient across proximal stenosis after having stented the distal one ?



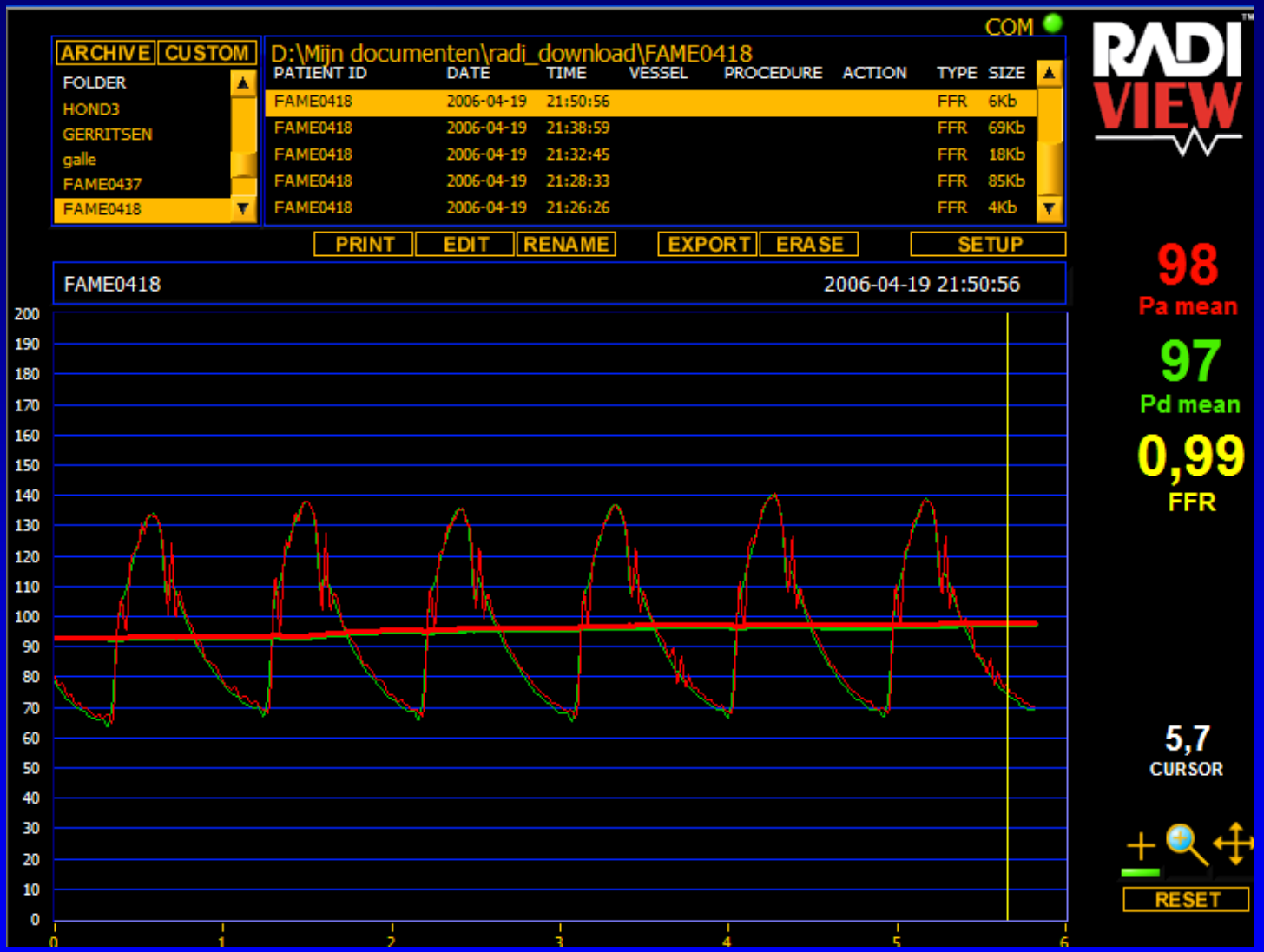






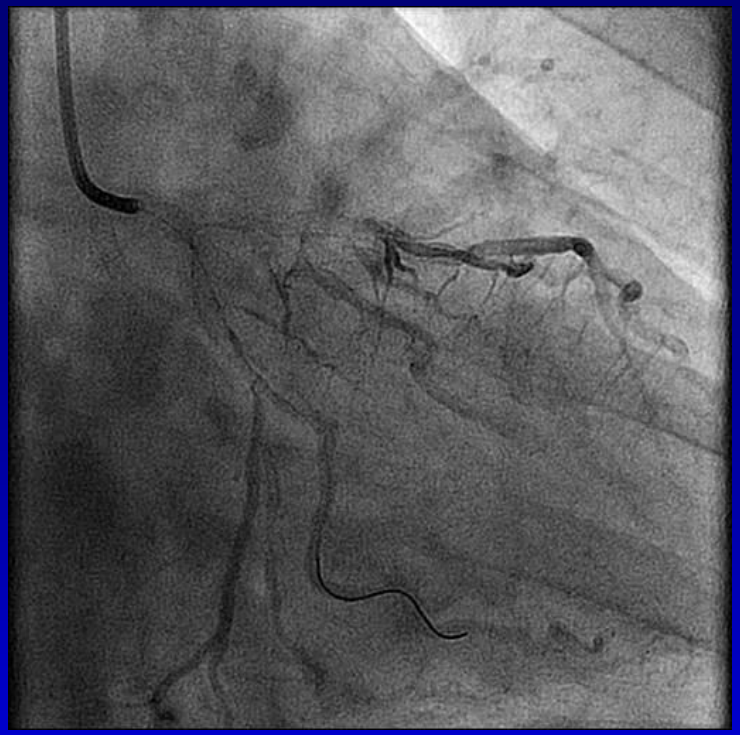
RCA
after 2 stents:

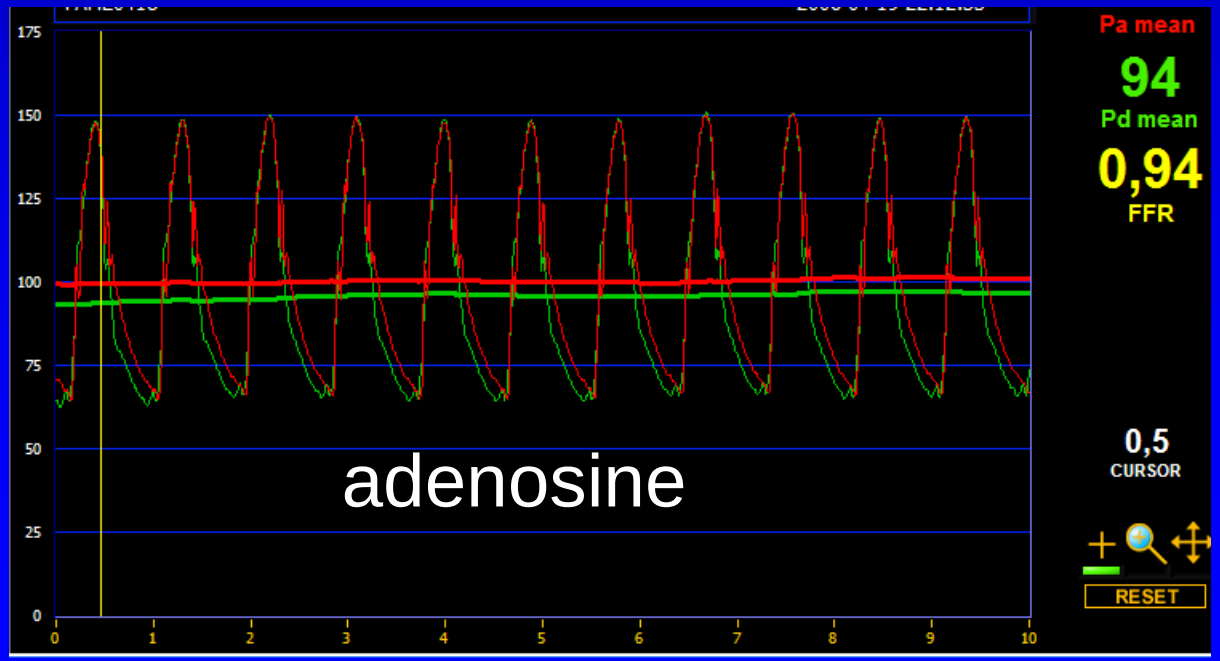
FFR = 0.87



Before entering into LCA:

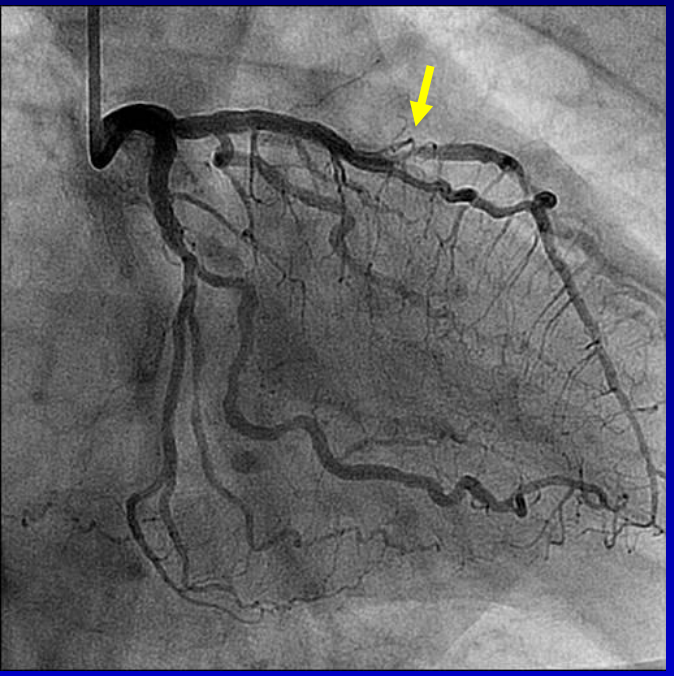
verify again equal pressures when sensor at tip of the guiding catheter

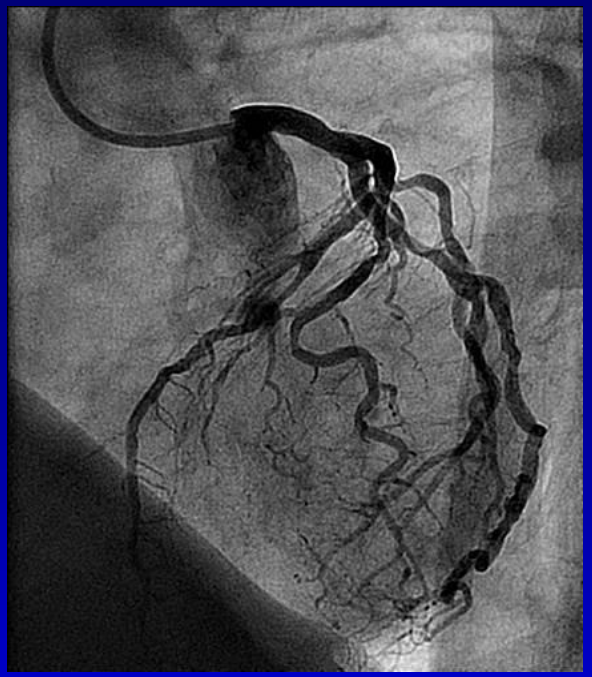


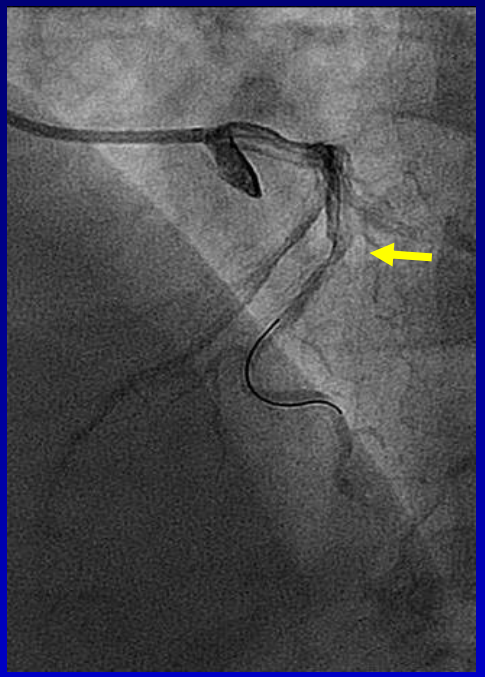

Pa mean
94
Pd mean
0,94
FFR
adenosine
0,5
CURSOR
RESET
175
150
125
100
75
50
25
0
0
1
2
3
4
5
6
7
8
9
10

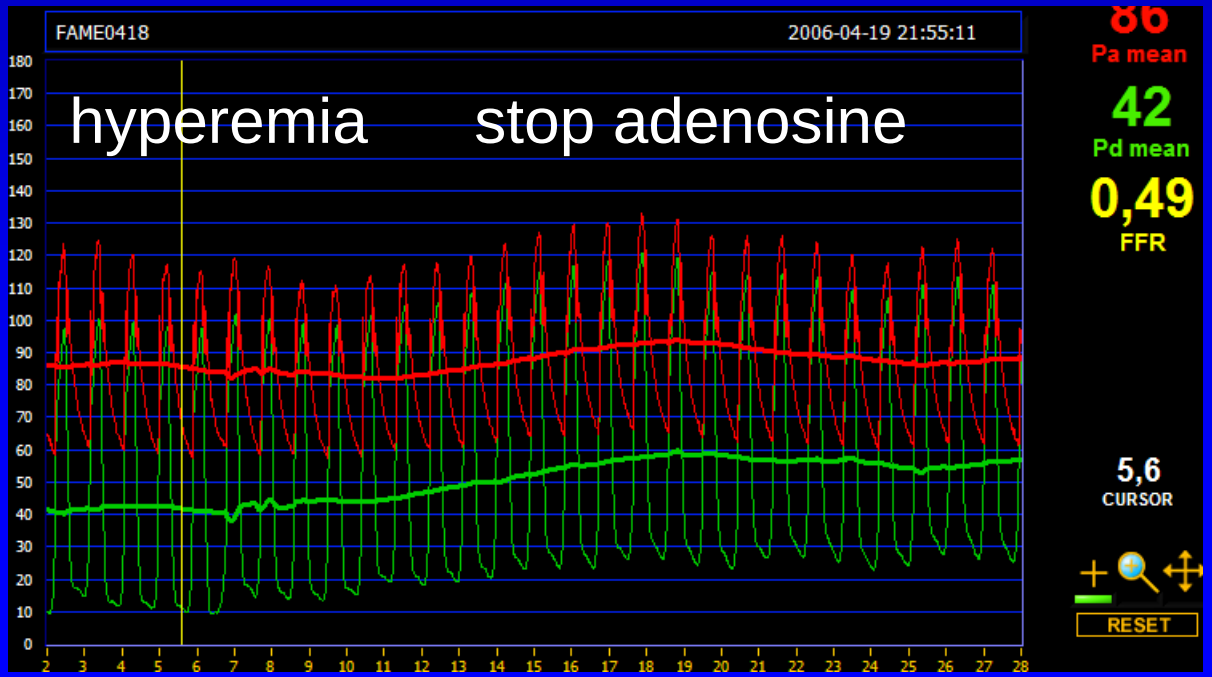
LCX:

FFR = 0.94



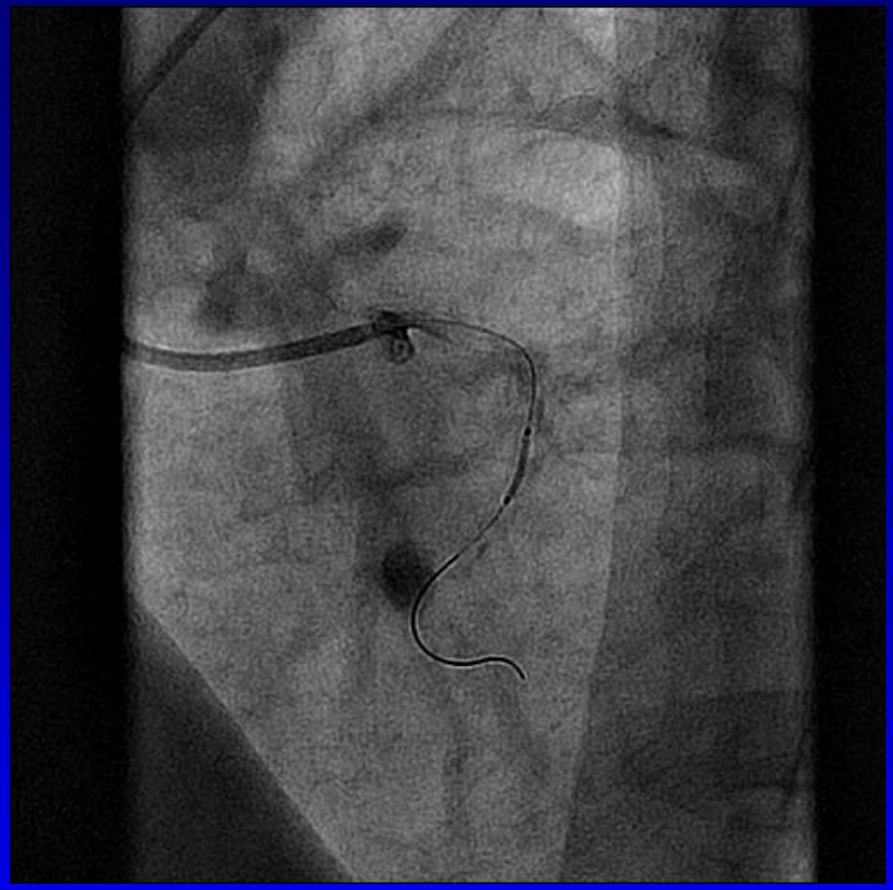


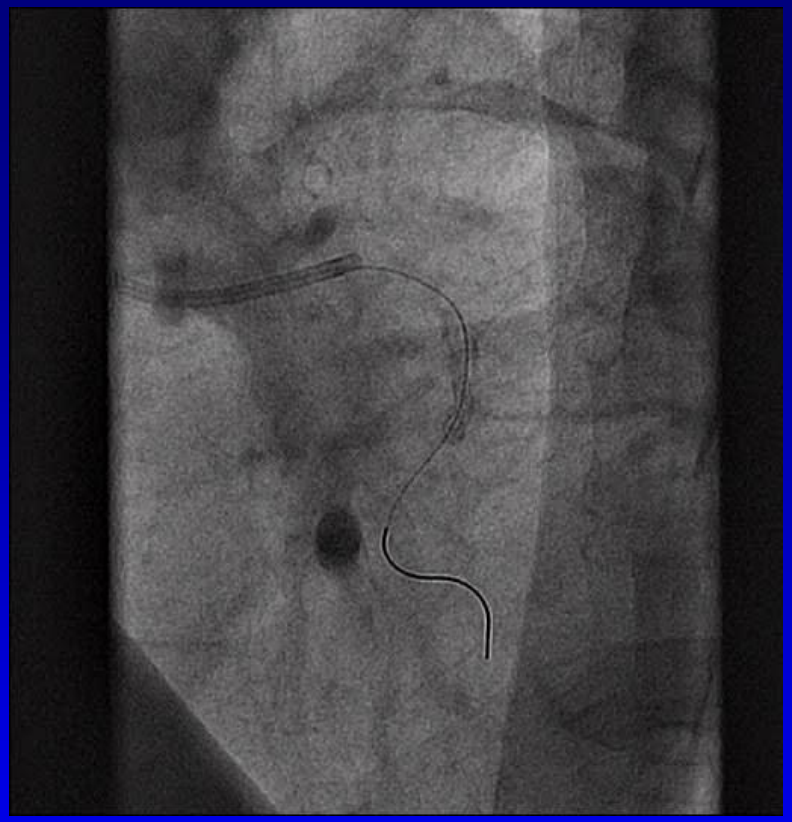




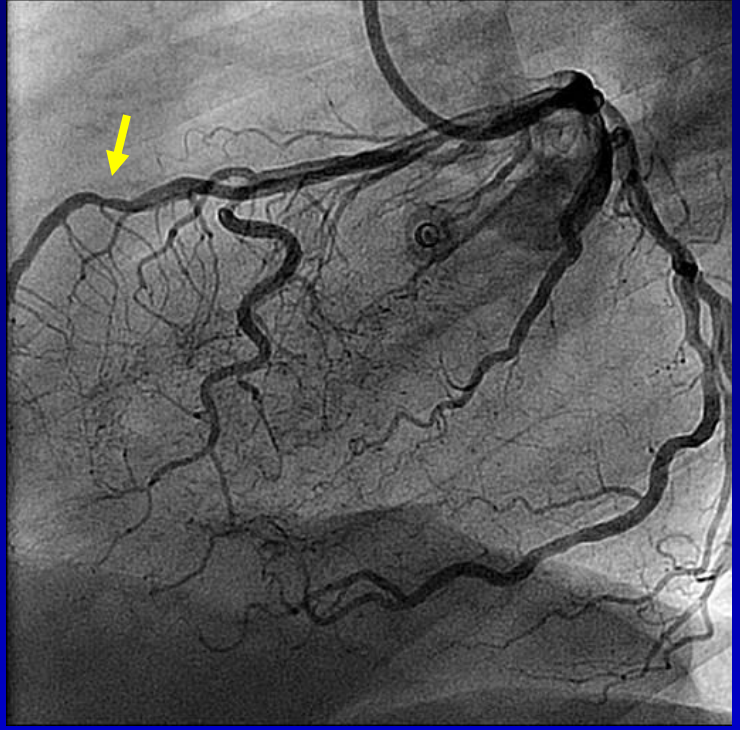
Diag branch:

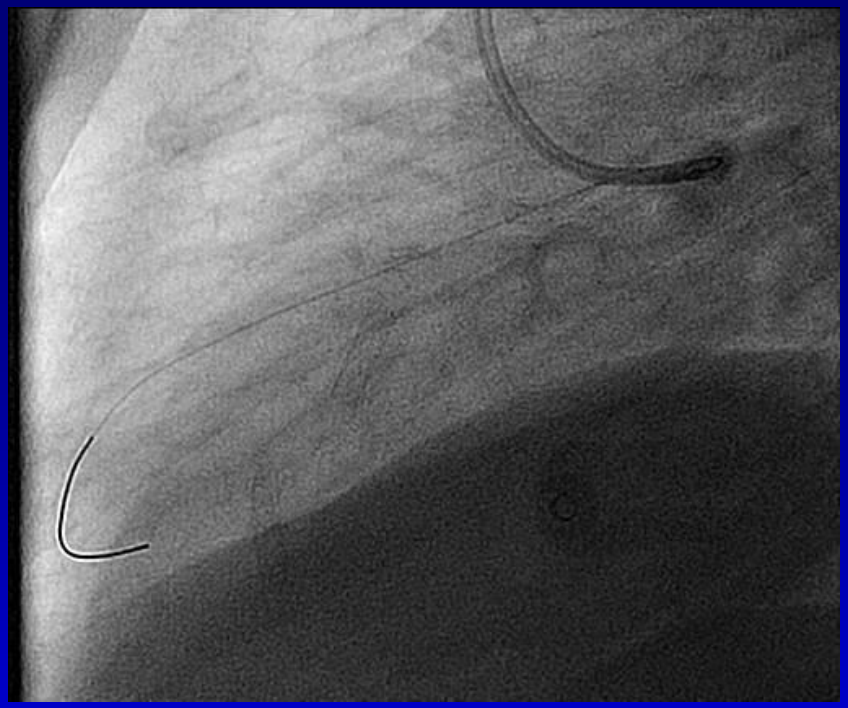
FFR = 0.49

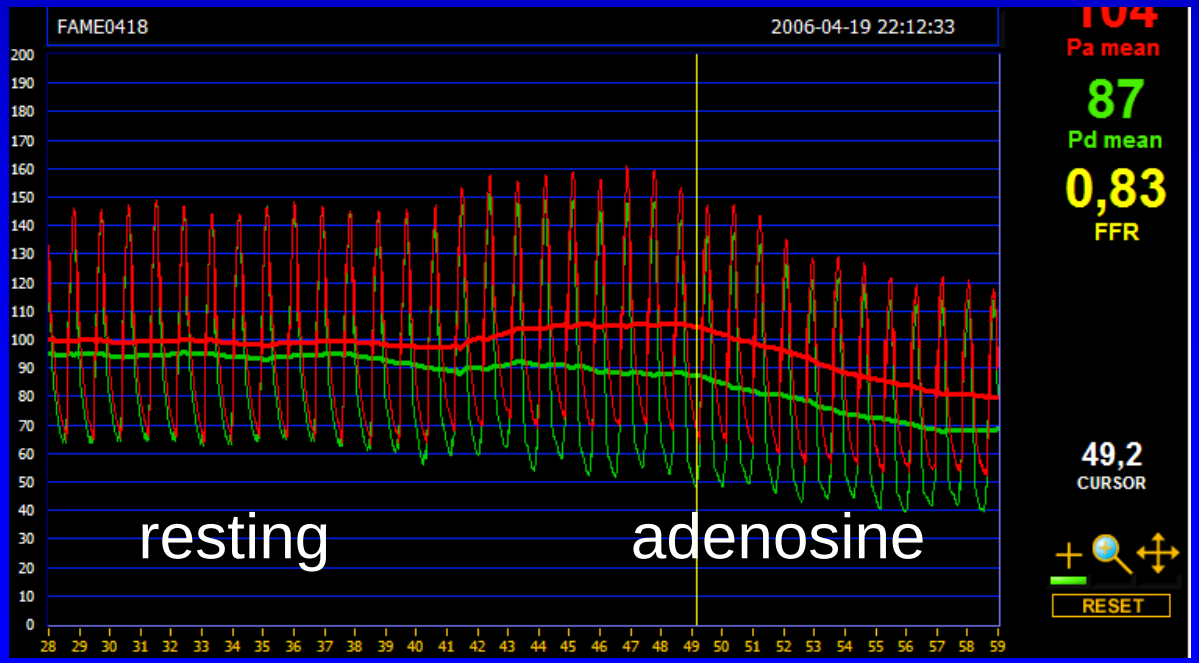




Diag branch after stenting: FFR = 0.81
(no recording found)






FAME0418
2006-04-19 22:12:33
Pa mean
87
Pd mean
0,83
FFR
49,2
CURSOR
RESET
resting
adenosine

LAD:

FFR = 0.83

In summary:

- RCA (2 stenoses) : FFR 0.34 → 0.74 → 0.84
  (2 stents)
- MOCX : FFR 0.94 → no stent
- Diag branch: FFR 0.49 → 0.81 (1 stent)
- LAD: FFR 0.83 → no stent

Total time of procedure: 21.26 h → 22.12 h = 46 min

Case performed by Guus Brueren

Patient participated in FAME study

What about ref diameter, vessel size?

***Reference diameter*:**

- **FAME 2.5mm**
- **Pivotal DES trials 2.6-2.8mm**

selection bias

single vessel disease

excluding lesions <2.5mm

less extensive disease

→ **Most studies on PCI in MVD: no QCA**

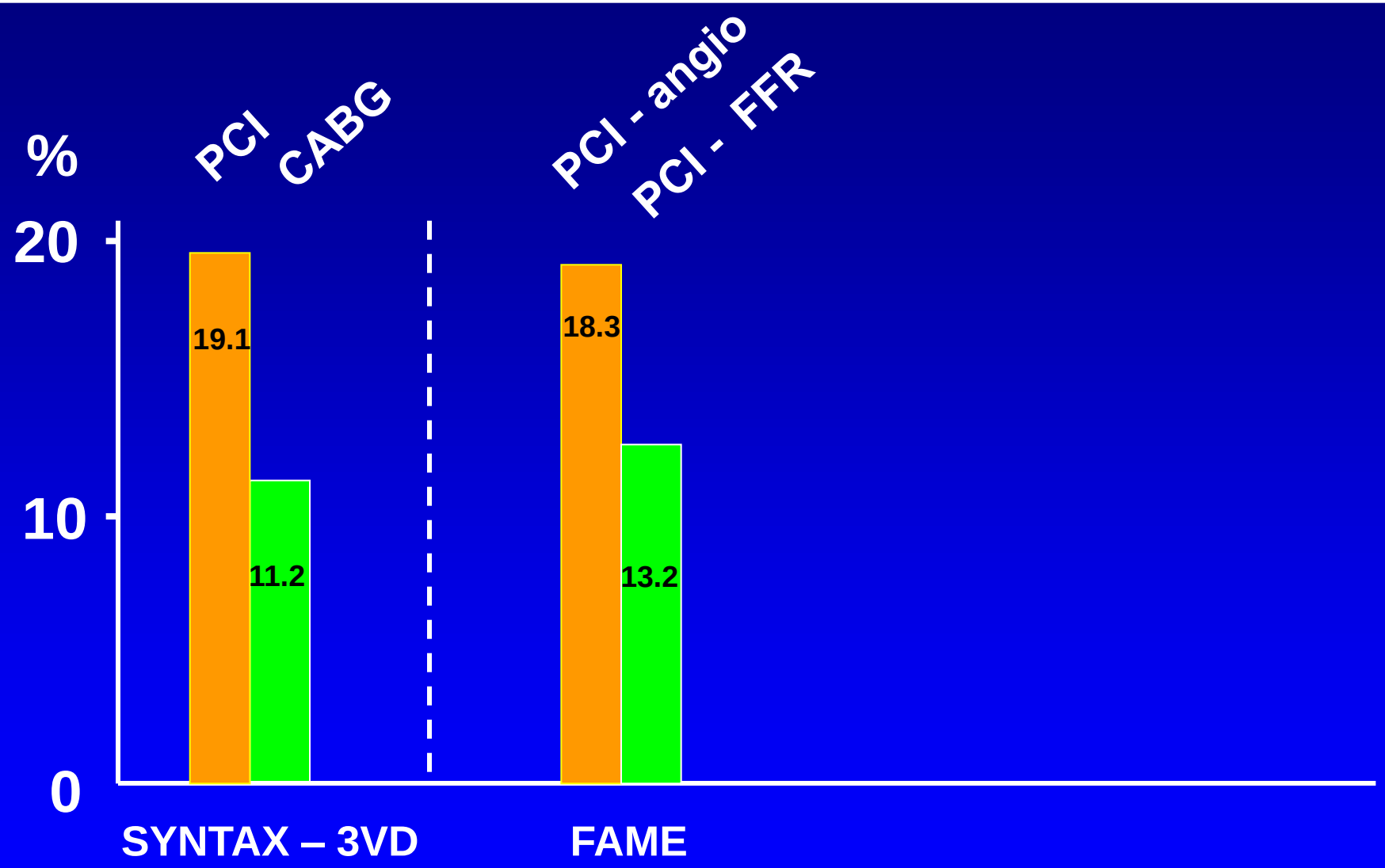
(MASII, ARTS, SYNTAX)

What about ref diameter, vessel size?

	Angio-guided group	FFR-guided group
% lesions proximal	29%	32%
% lesions prox or mid	71%	73%

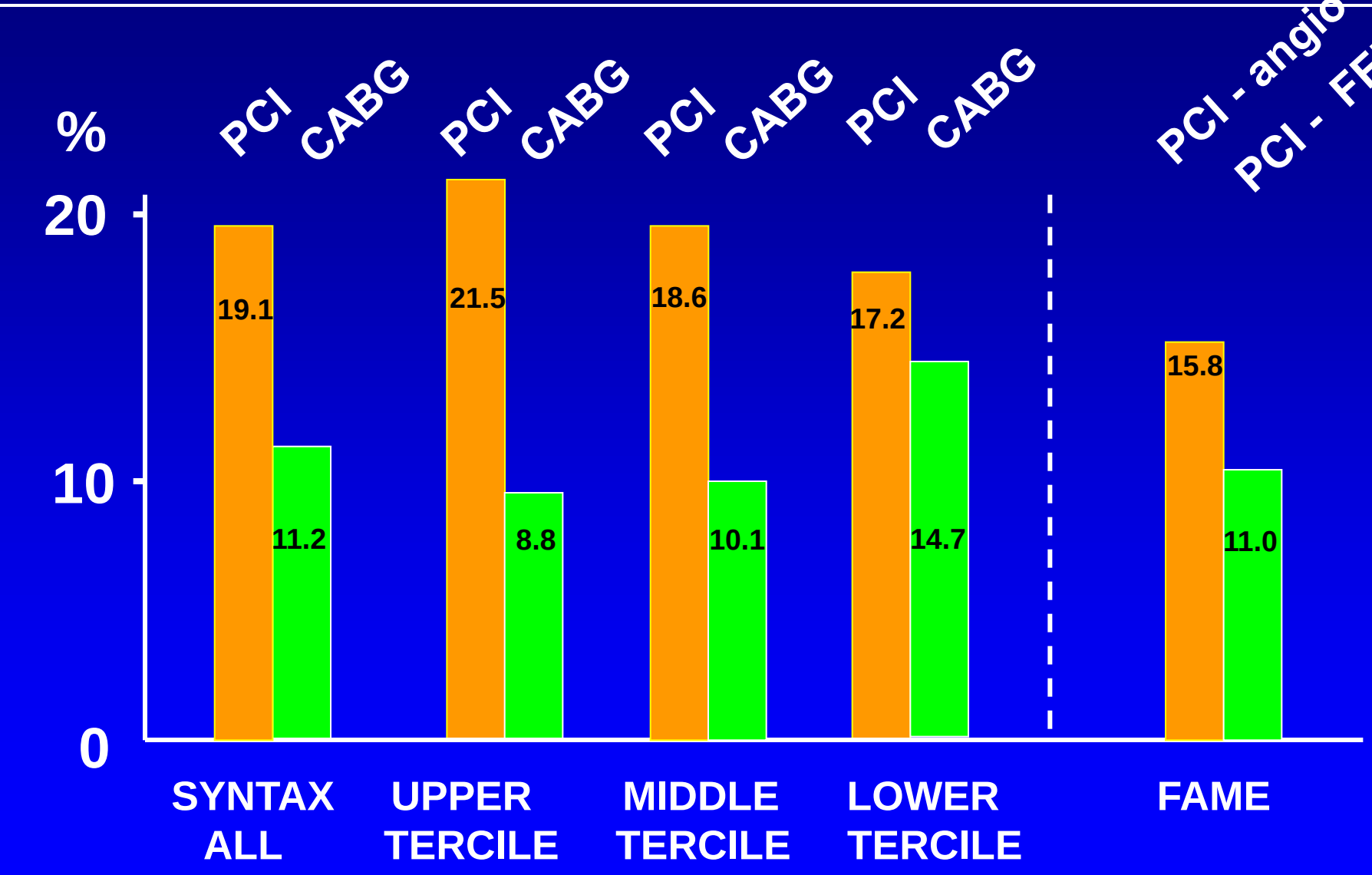
So, FAME does not represent 'smaller' vessels, but the early DES trials represent 'larger' vessels

MACE in SYNTAX – 3VD and FAME

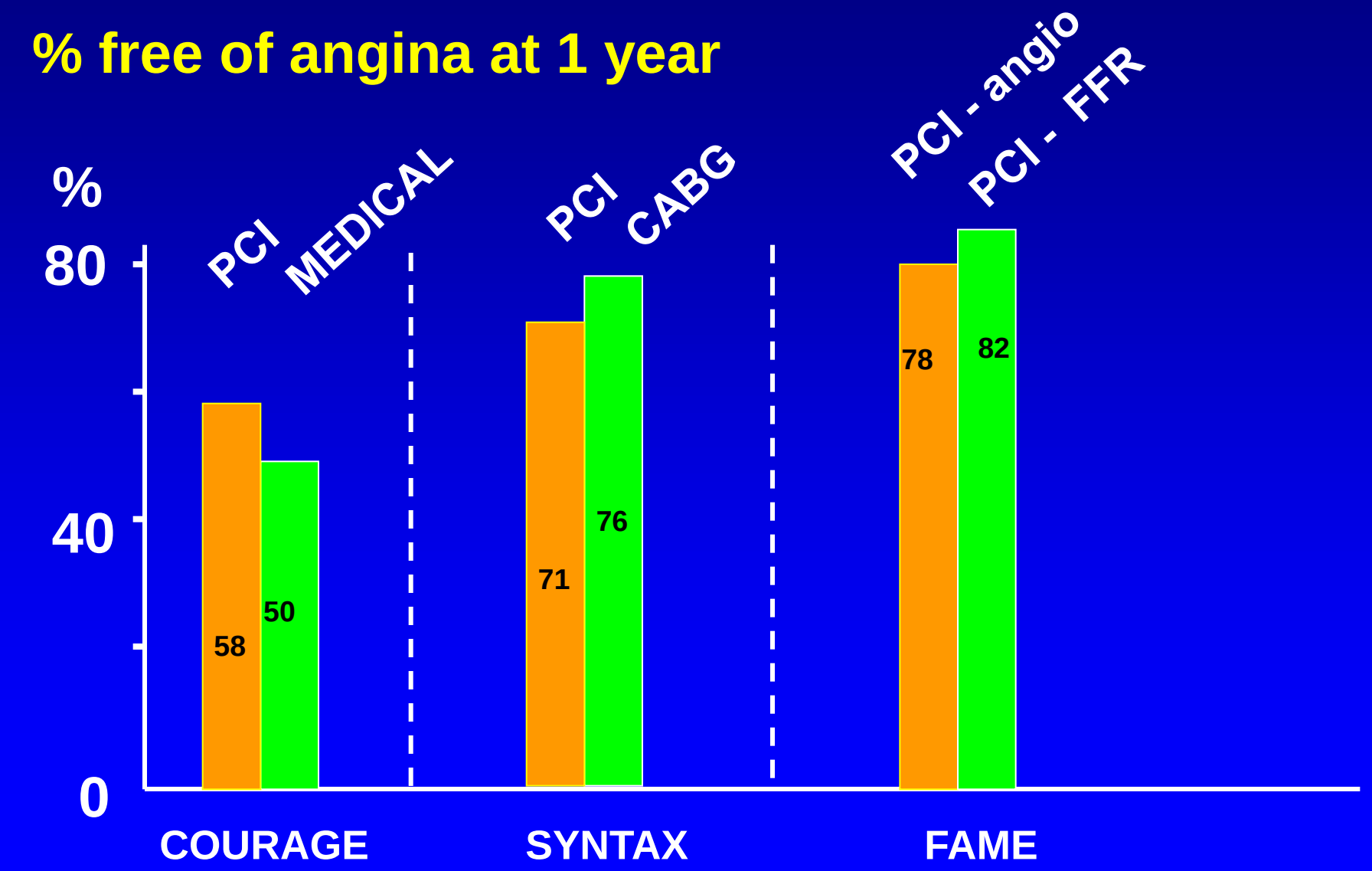


MACCE in SYNTAX – 3VD and FAME

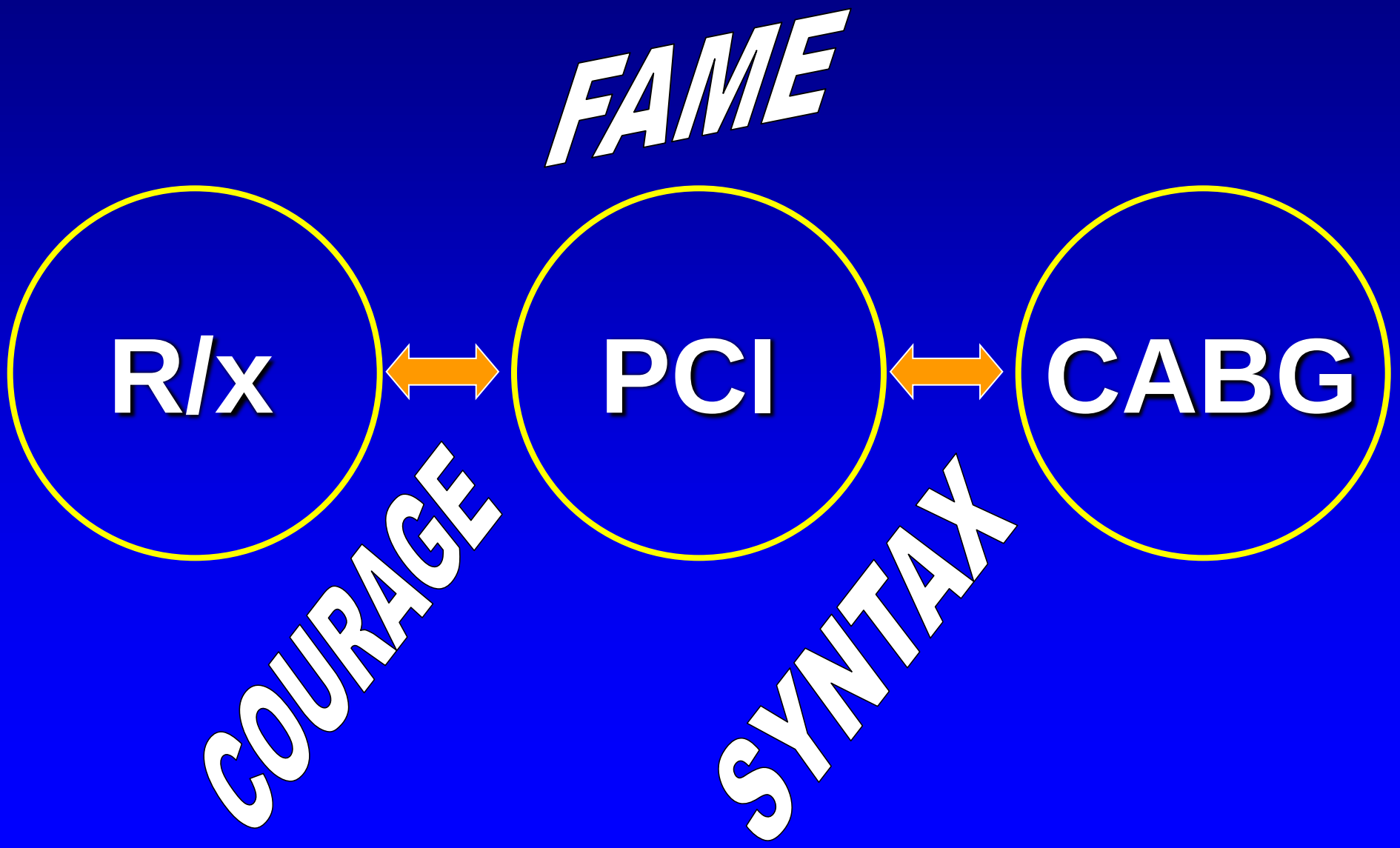
similar definition of MACCE, including CVA and excluding CKMB 3-5 x N



FUNCTIONAL CLASS in COURAGE - SYNTAX – 3VD and FAME



TREATMENT OPTIONS FOR MVD



TREATMENT OPTIONS FOR MVD

FAME

R/x → PCI ← CABG