EUROPEAN HEART HOUSE
Coronary Physiology in the Catheterization Laboratory (9th Edition)
Thursday, April 23 – Saturday, April 25, 2015

Course Directors:
B. De Bruyne (BE), W.F. Fearon (US), N.H.J. Pijls (NL)

Coronary Pathophysiology & Microcirculation
ESC Working Group

Resting measures, Pd/Pa and iFR

Flavio Ribichini
Università di Verona,
Italy

Flavio Ribichini,

I have no conflict of interest related to this talk

I was ESC Research Fellow in Aalst 1997-1998

I use of FFR since 1999 in Italy.

I am an FFR believer

Sixth Panafrican Course On Interventional Cardiology

September 29th to October 1st, 2005. Monastir Tunisia

Under the High Patronage of his Excellency the President of The Republic of Tunisia Zine El Abidine Ben Ali

and the Auspices of the Tunisian Society of Cardiology and Cardio-Vascular Surgery

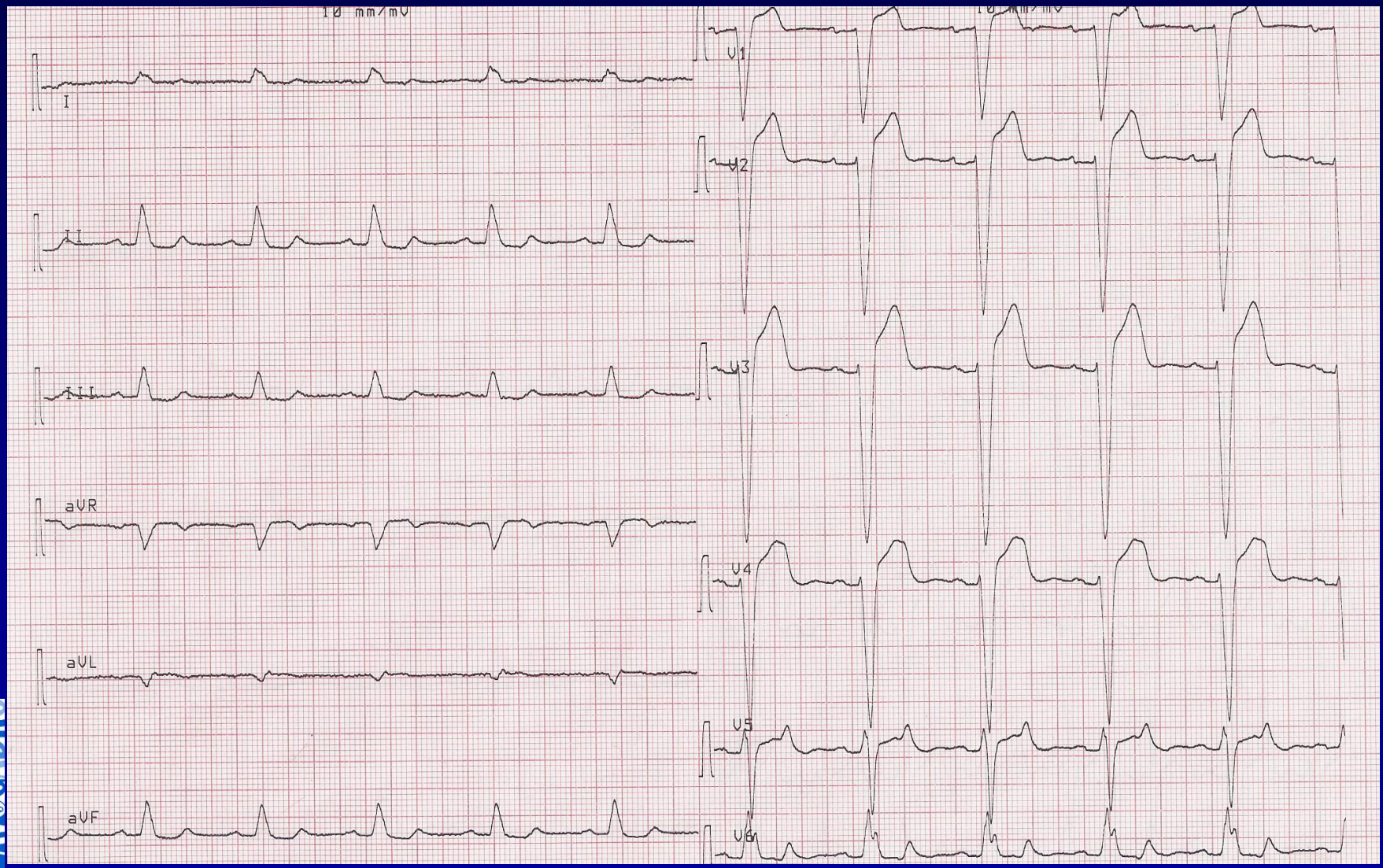
Sixth Panafrican Course on Interventional Cardiology

September 29th, to October 1st, 2005

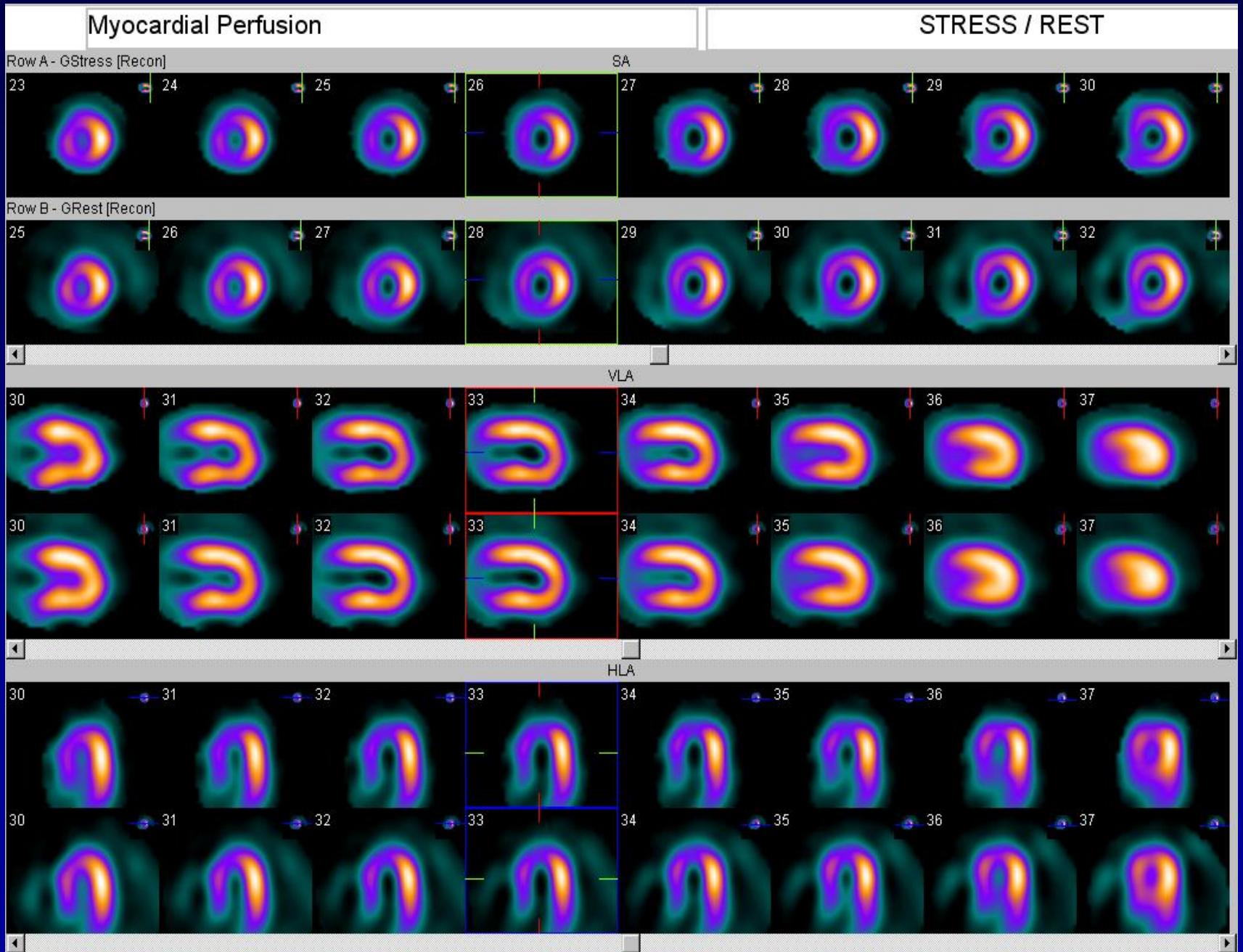
Monastir-Tunisia

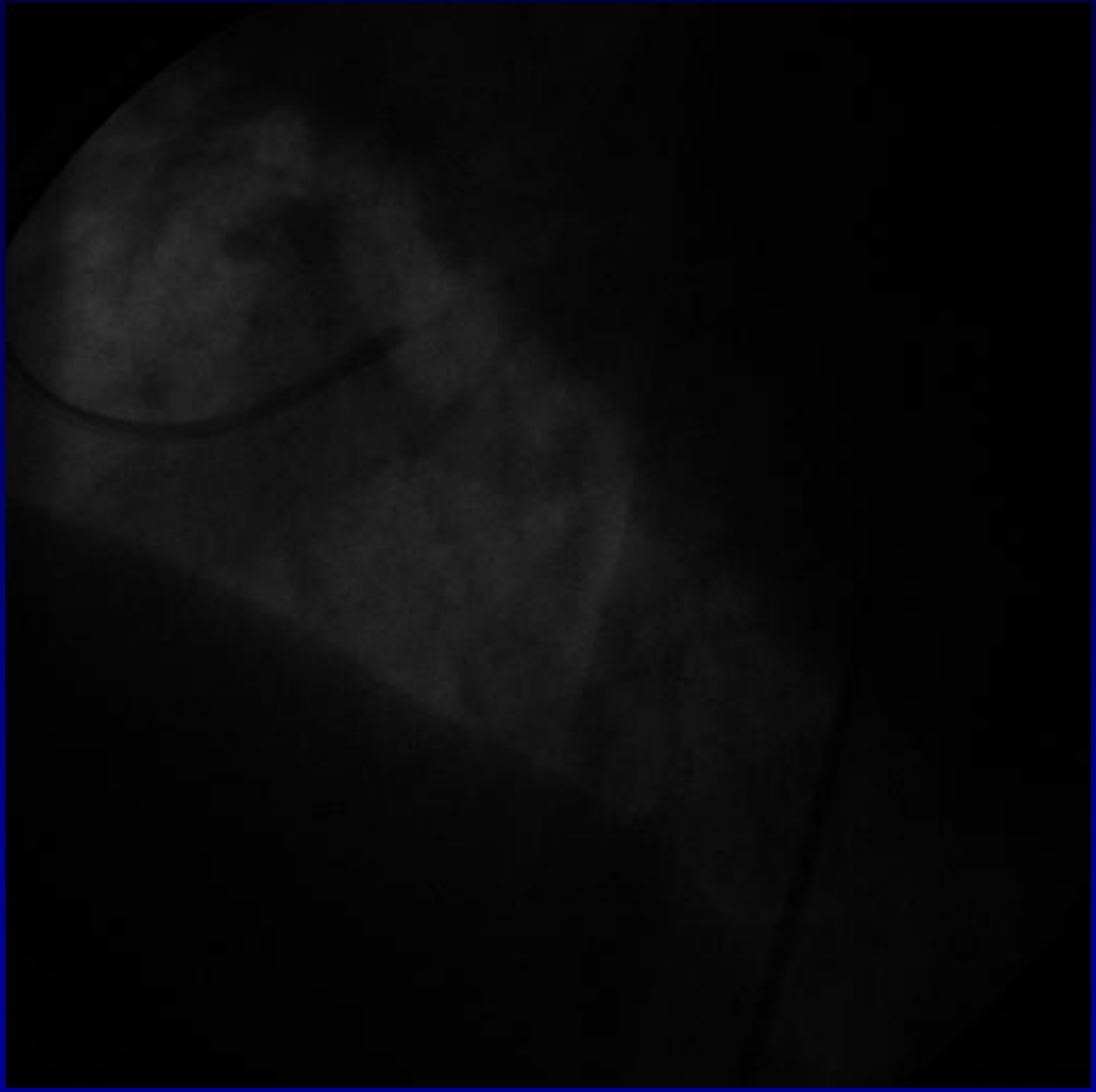
Live cases from Novara, Italy

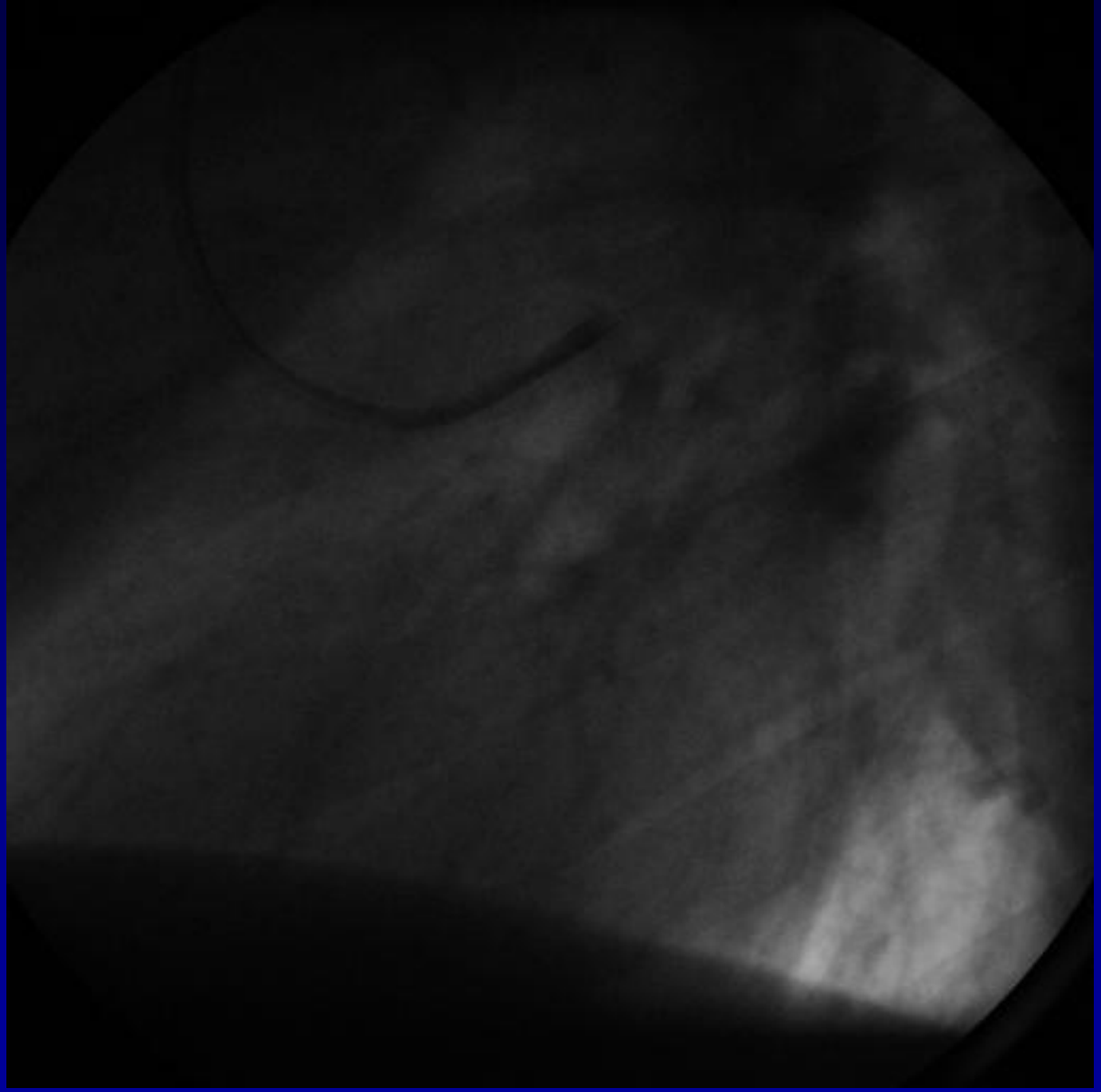
65 yo male, effort chest pain



Myocardial perfusion scintigraphy with adenosine 99mTc SPECT

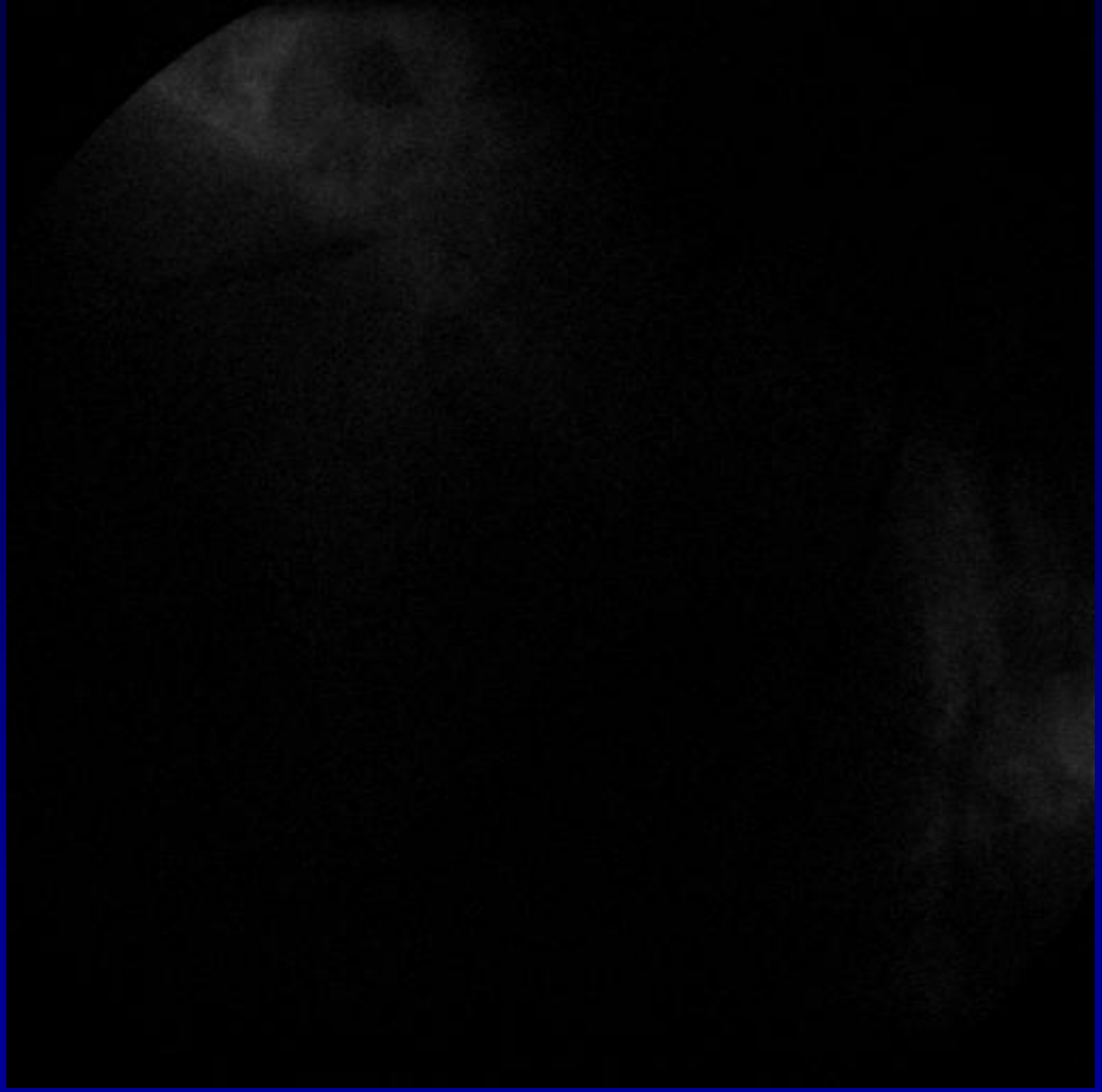






PAFCIC
2005

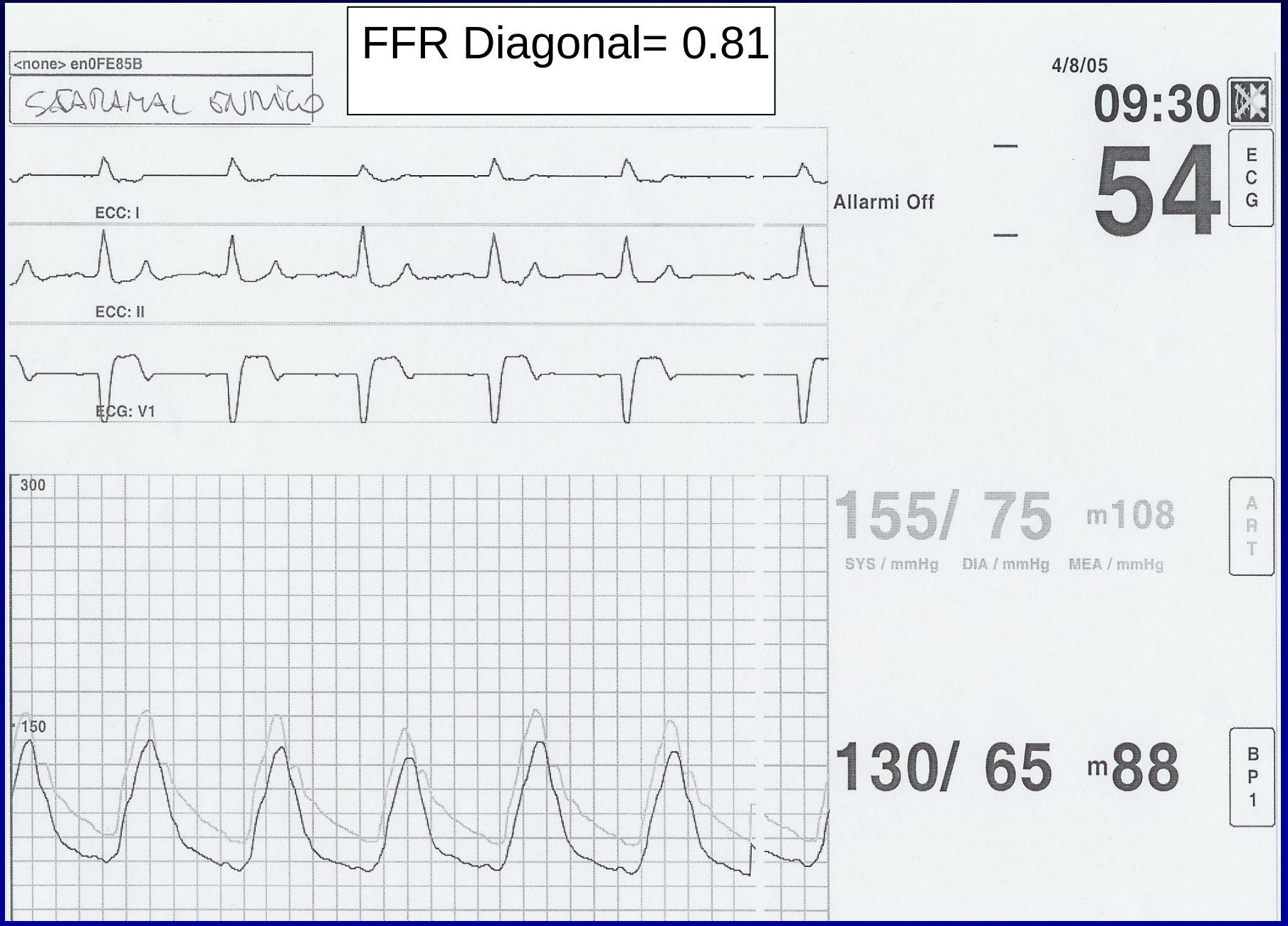
AMEDEO AVOGADRO
università degli studi del piemonte orientale

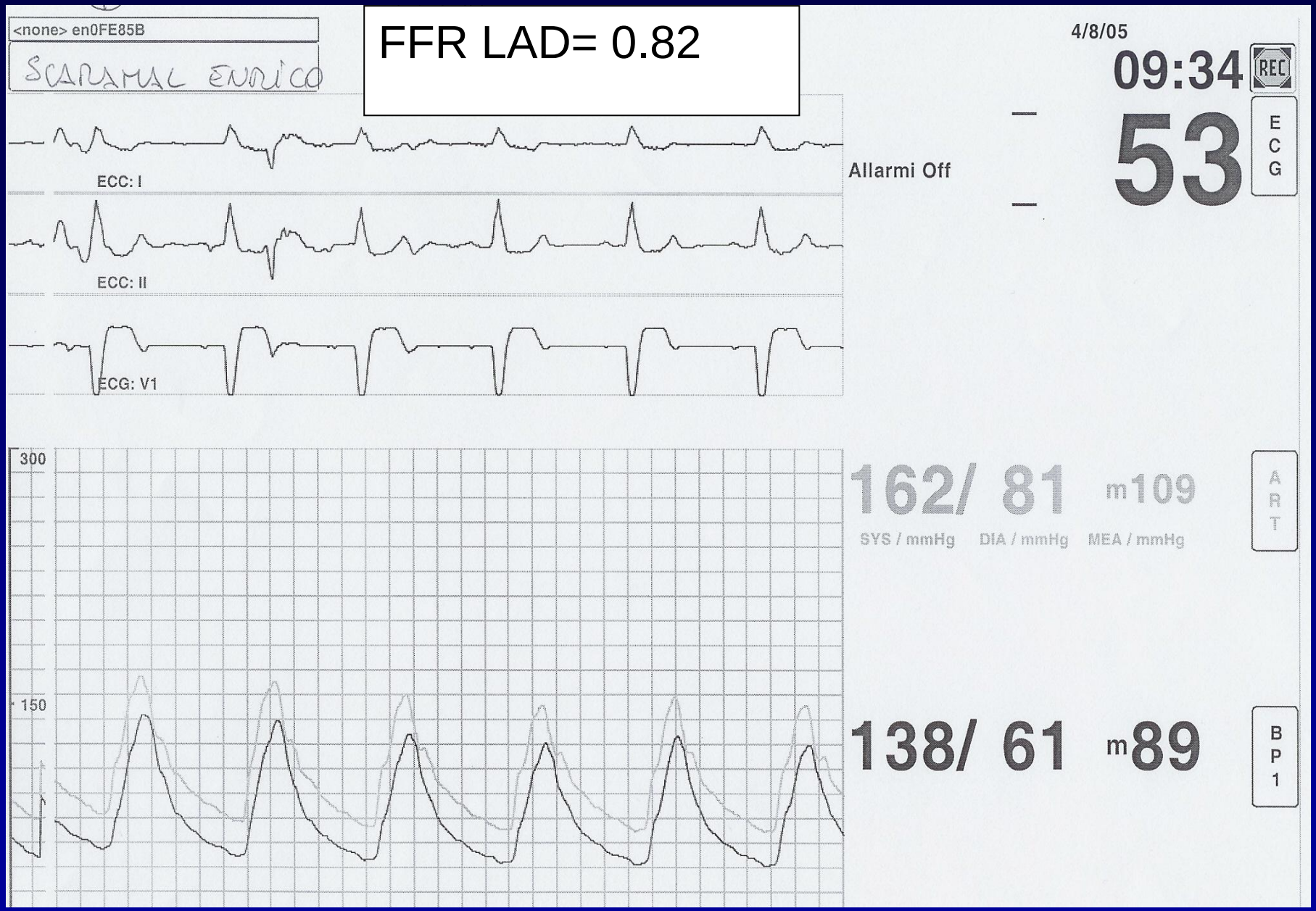


PAFCIC
2005

AMEDEO AVOGADRO
università degli studi del piemonte orientale

FFR Diagonal= 0.81




FFR LAD= 0.82
<none> en0FE85B
SCARAMAL ENRICO
4/8/05
09:34
REC
53
ECG
Allarmi Off
ECC: I
ECC: II
ECG: V1
300
150
162/ 81
m109
SYS / mmHg
DIA / mmHg
MEA / mmHg
ART
138/ 61
m89
BP 1

I got news of this patient for more than 5 years (2010) and He had no recurrences of ischemia.

Then, He lost me at follow-up.

At TCT 2011 formal presentation of the iFR concept.

In 2012 pubblication of the ADVISE Study.

instant wave-Free Ratio

Using Pressure to Get Flow

- Coronary pressure is simple to measure
- Flow velocity is more challenging

Fundamental Equation for relating Pressure and Flow:

$$P = Q \times R$$

Pressure = Flow x Resistance

or

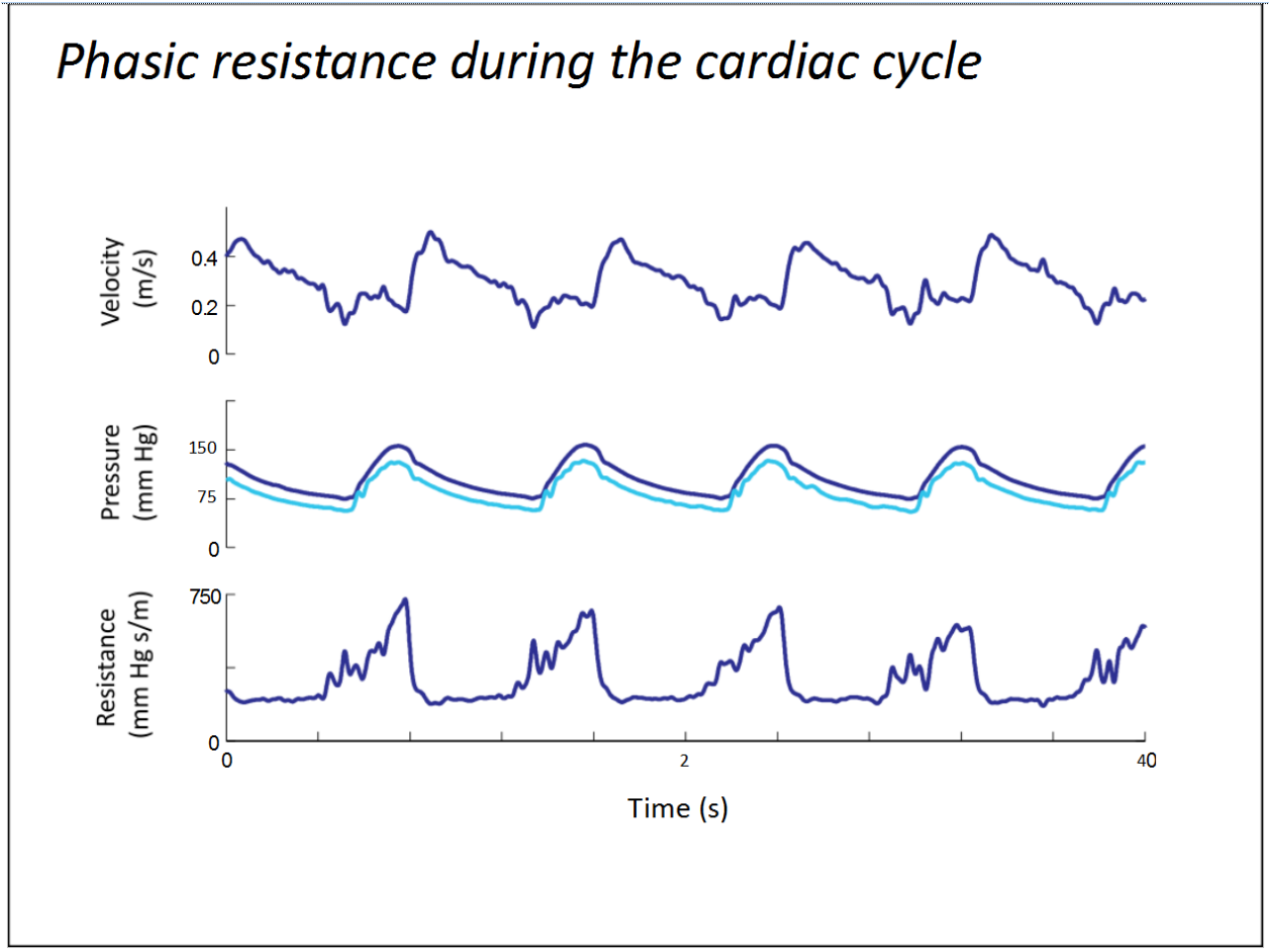
$$\Delta P \approx \Delta Q \times R$$

Change in Pressure = Change in Flow x Constant Resistance

When ***Resistance is Constant***, changes in Pressure are proportional to changes in Flow

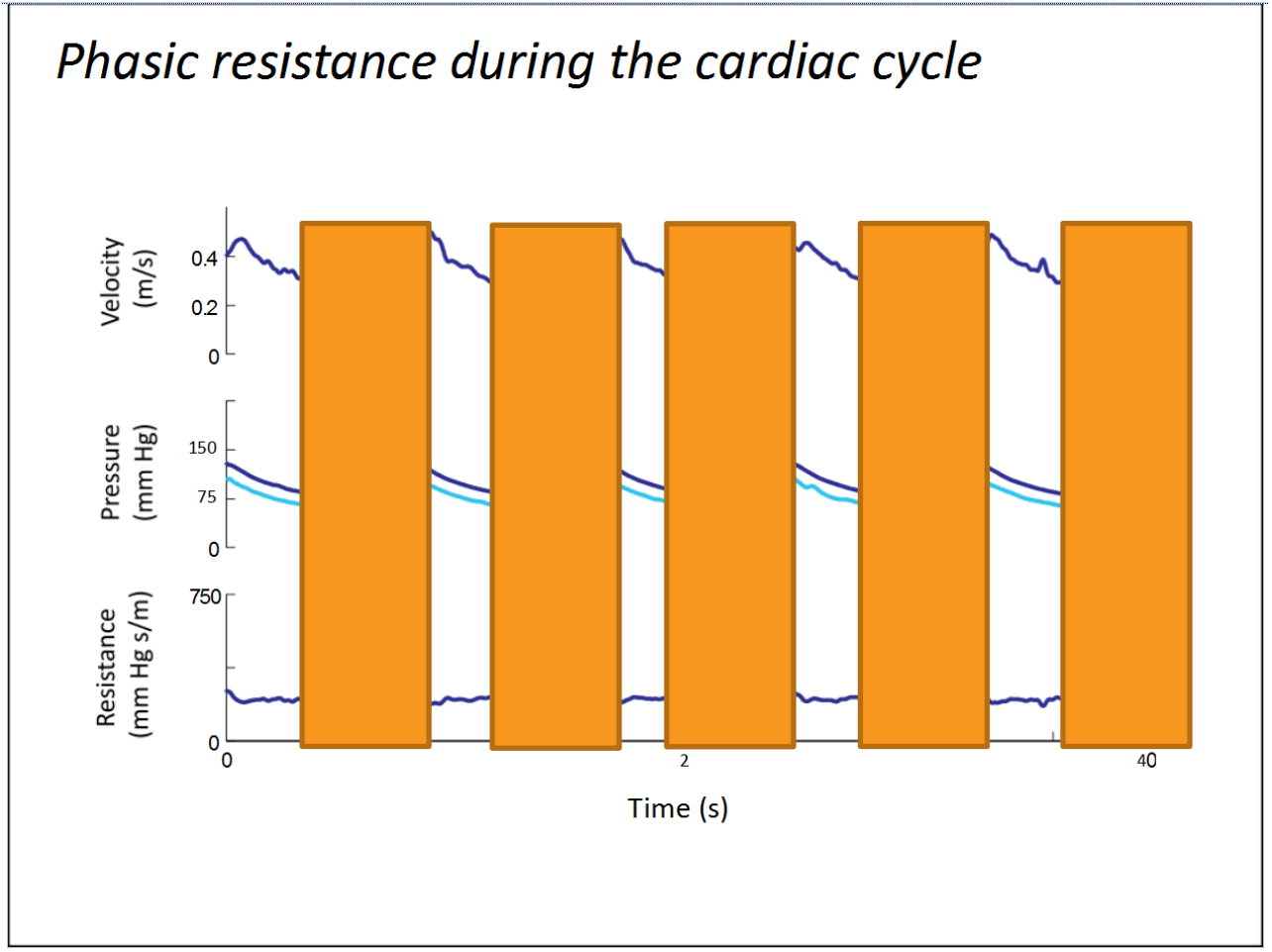
Derived from Poiseuille's Law for Fluid Dynamics

Resistance is Constant in the Wave-Free Period



Davies J. PRIMARY Results of ADVISE. TCT 2011.

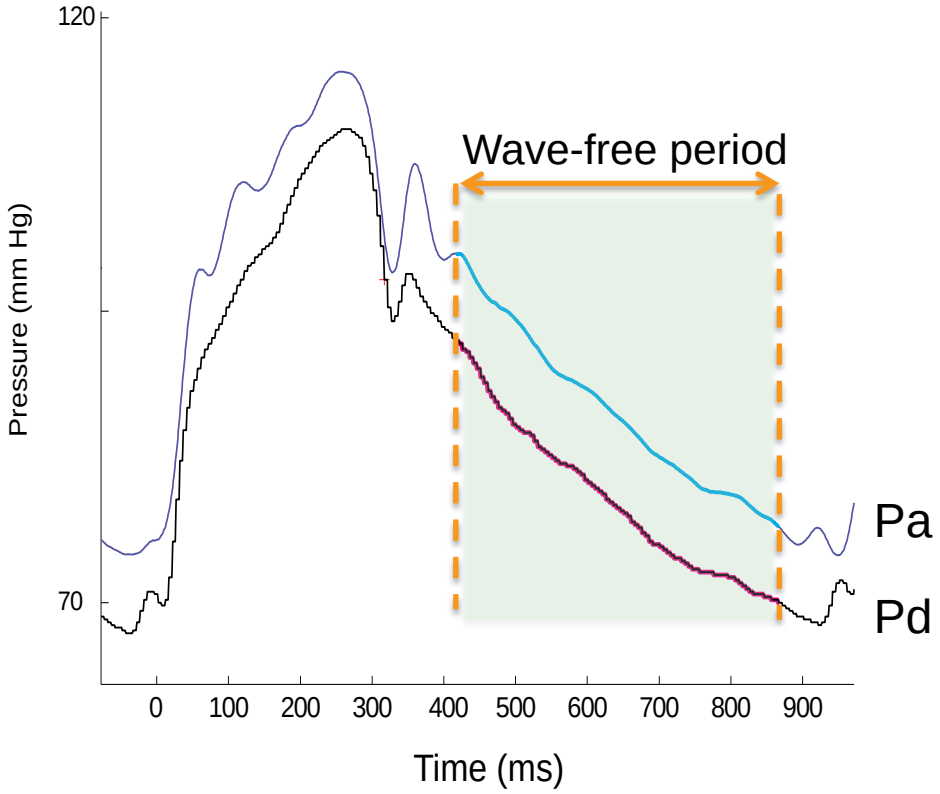
Resistance is Constant in the Wave-Free Period



Davies J. PRIMARY Results of ADVISE. TCT 2011.

Introduction of the iFR Modality

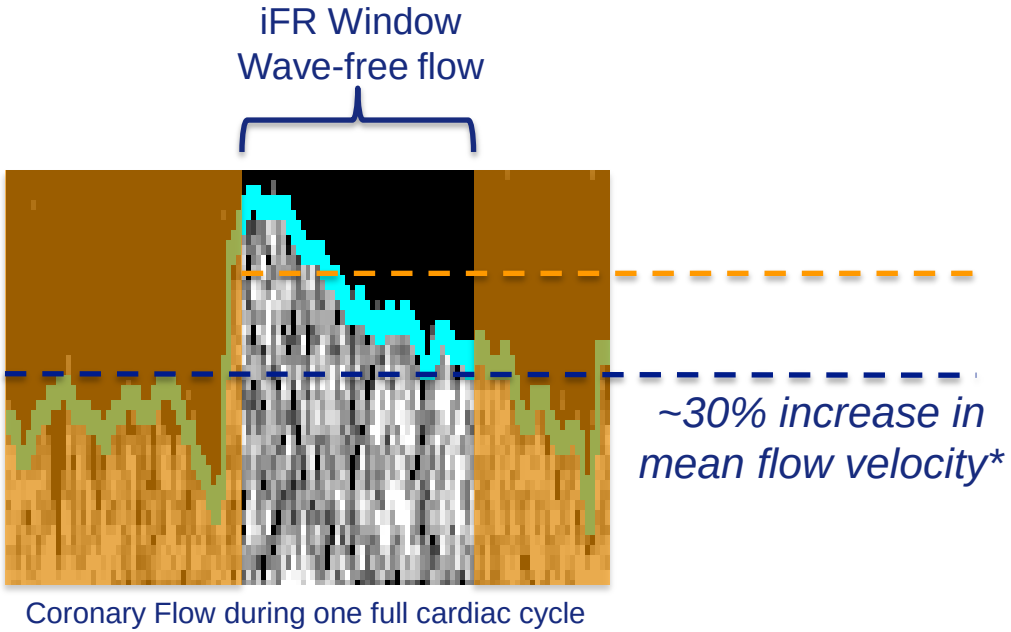
Definition: Instantaneous pressure ratio, across a stenosis during the wave-free period, when ***resistance is more constant*** and minimized in the cardiac cycle

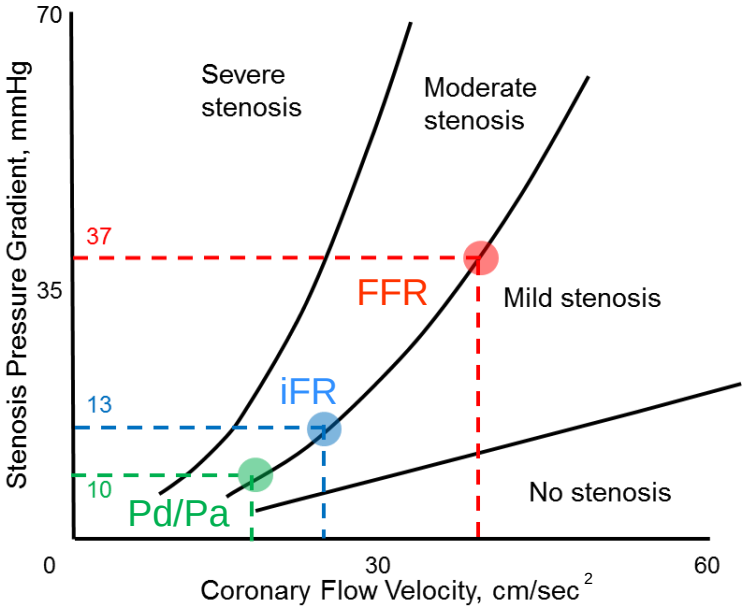


Escaned J. ADVISE II: A Prospective, Registry Evaluation of iFR vs. FFR. TCT 2013.

iFR Window Maximizes Flow Velocity

- iFR Flow is ~30% higher which amplifies the signal vs. Pd/Pa alone





- Increasing Flow Velocity exaggerates the pressure drop across a stenosis
- Bigger pressure drop allows for better classification of stenosis severity

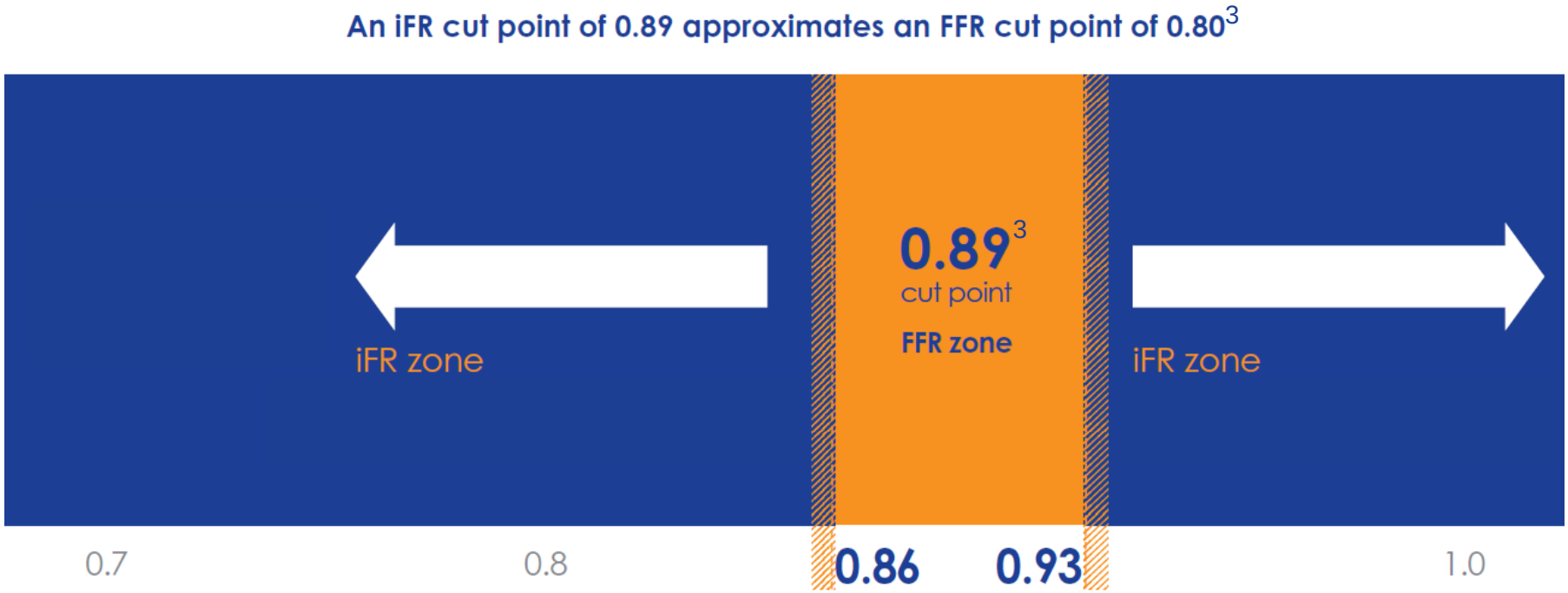
Consistent iFR Cutt Off

Best iFR cut off compared with FFR≤ 0.80

ADVISE-Registry(n=339)	0.89
South Korean Study(n=238)	0.90
RESOLVE(n=1593)	0.90
ADVISE-*in Practice*(n=392)	0.90
ADVISE 2 (n=689)	0.89

The Hybrid iFR/FFR Approach

- 94.0% match to FFR[1]
- 65.1% of patients were free from hyperemic agents[2]



1. Using the iFR cut points of 0.85 and 0.94 matches best with an FFR ischemic cut-point of 0.80 with a specificity of 90.7% and sensitivity of 96.2%.

2. The ADVISE II study illustrated a 5.8%, i.e. (17+23)/690, classification discordance between the iFR Hybrid Approach and FFR. Among 477 lesions that would be assessed without hyperemia by the iFR Hybrid Approach, 40 (17+23) were due to classification discordance.

3. An iFR cut-point of 0.89 matches best with an FFR ischemic cut-point of 0.80 with a specificity of 87.8% and sensitivity of 73.0%. (iFR Operator's Manual 505-0101.23)

Providing Choice

An iFR of 0.89 aproximates an FFR of 0.80[1]

Fractional Flow Reserve

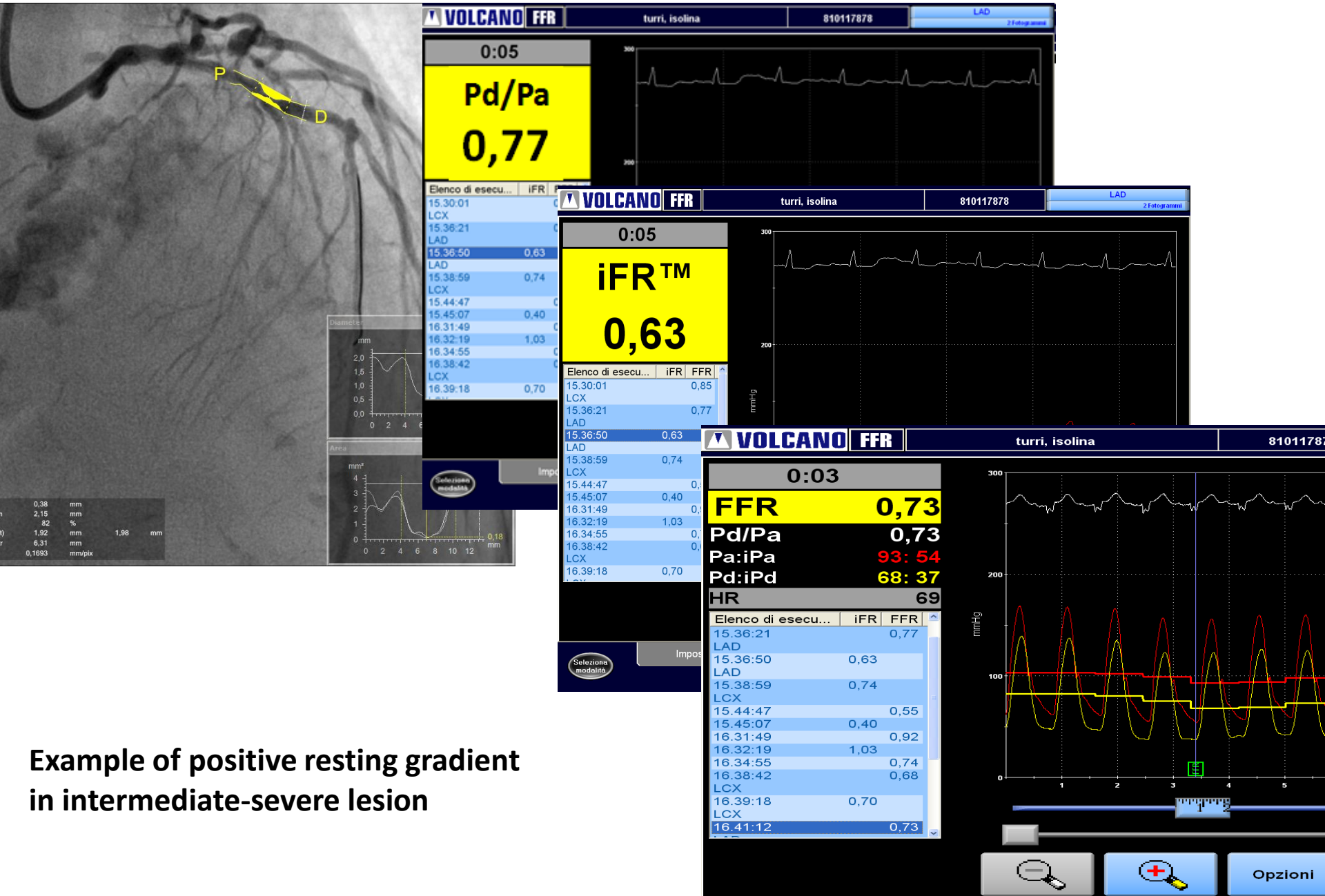
- Clinically proven for ischemia detection[2]
- Supported by guidelines worldwide
- However, use of FFR is still very low

The iFR Modality

- Volcano's proprietary instantaneous, trans-lesional pressure ratio measured during the wave-free period
- Prospectively tested in the ADVISE II Study and in the ongoing RCT FLAIR

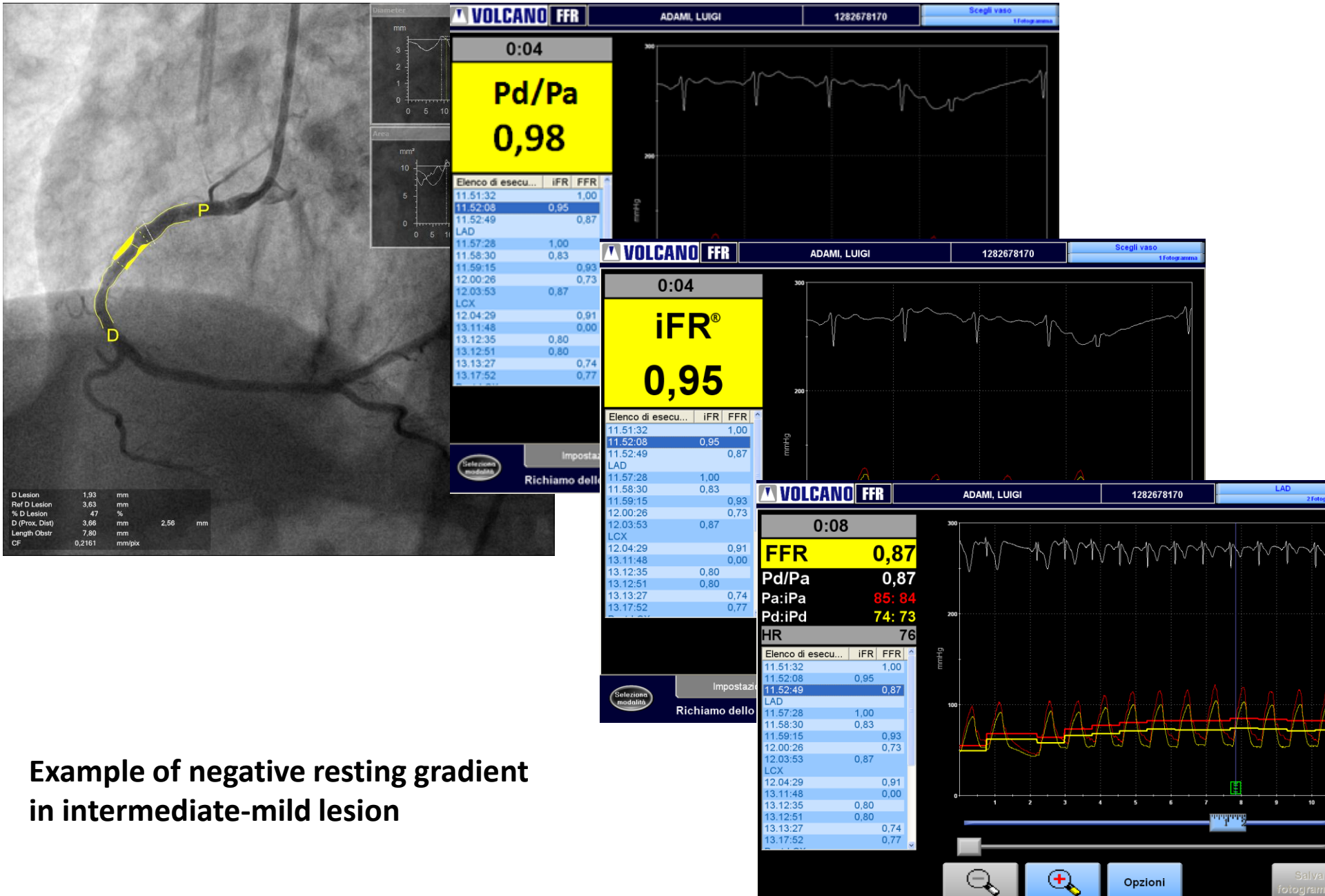
1. An iFR cut-point of 0.89 matches best with an FFR ischemic cut-point of 0.80 with a specificity of 87.8% and sensitivity of 73.0%. (iFR Operator's Manual 505-0101.23)
2. Tonino et al. Fractional Flow Reserve Versus Angiography for Guiding Percutaneous Coronary Intervention. NEJM 2009; 360, 3:213-224.

Measurement of any gradient is better than no proof of ischemia before PCI



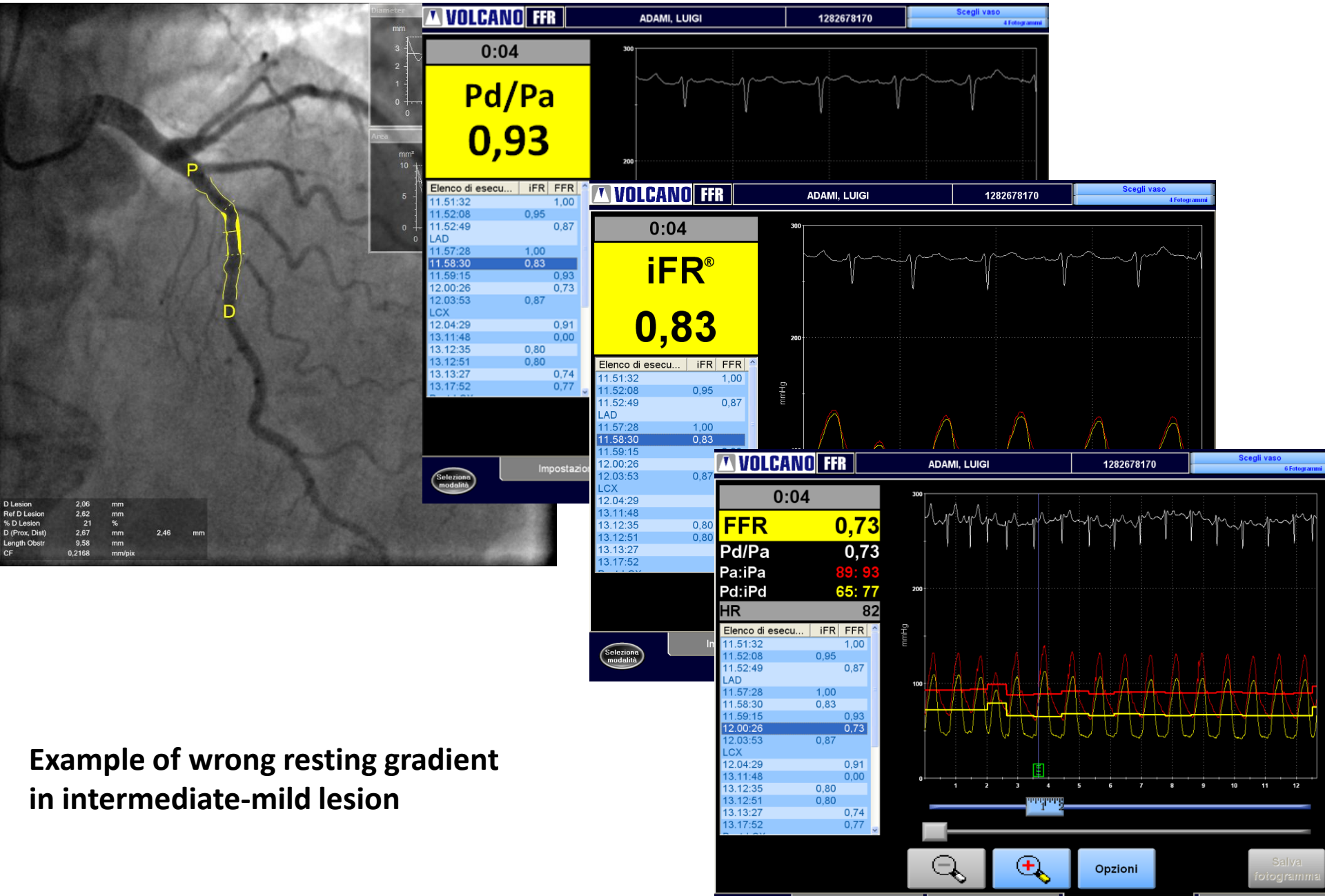
Example of positive resting gradient in intermediate-severe lesion

Measurement of any gradient is better than no proof of ischemia before PCI



Example of negative resting gradient in intermediate-mild lesion

Measurement of any gradient is better than no proof of ischemia before PCI, but….



Example of wrong resting gradient in intermediate-mild lesion

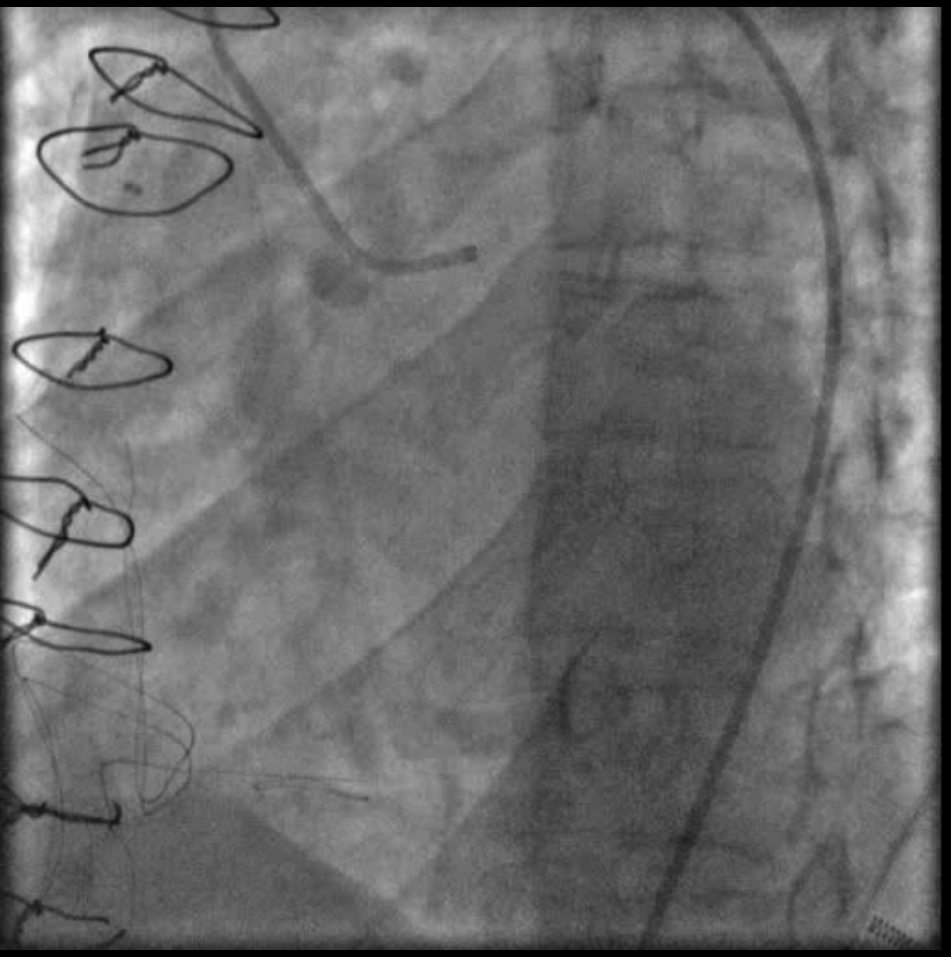
Case presentation to remind the “good physiologic Practice”

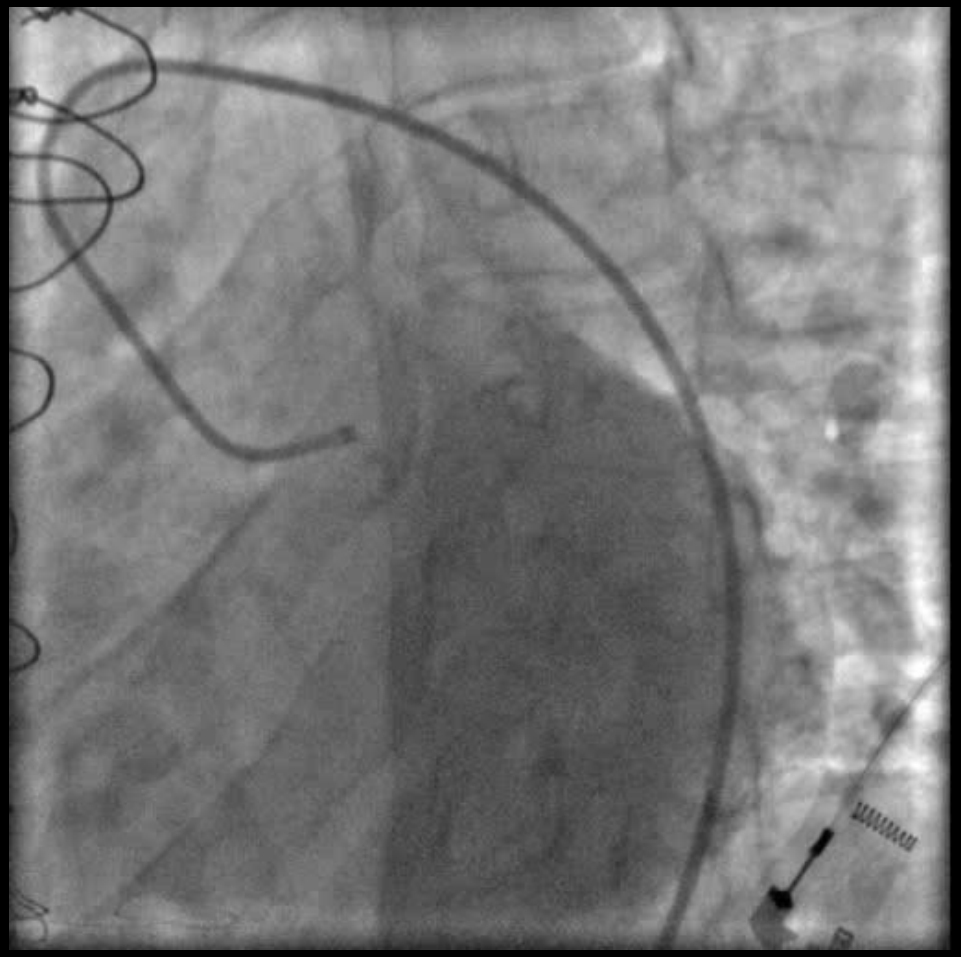
35 years old male

Heart transplant at the age of 28

Intensive life with regular exercise

Routine coronary angiogram in October 2014 for CAV stratification





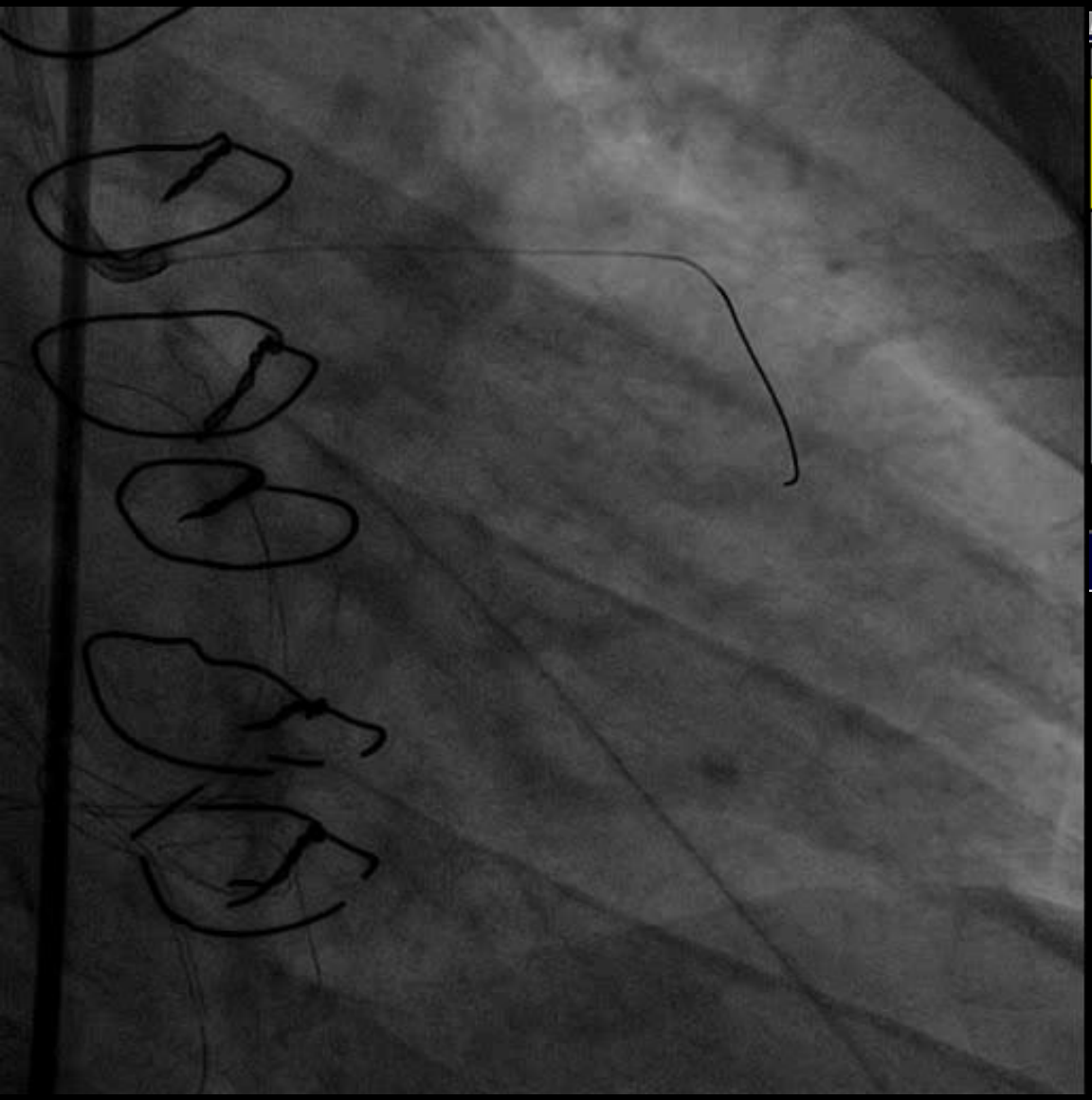
Advanced CAV with severe LM stenosis.

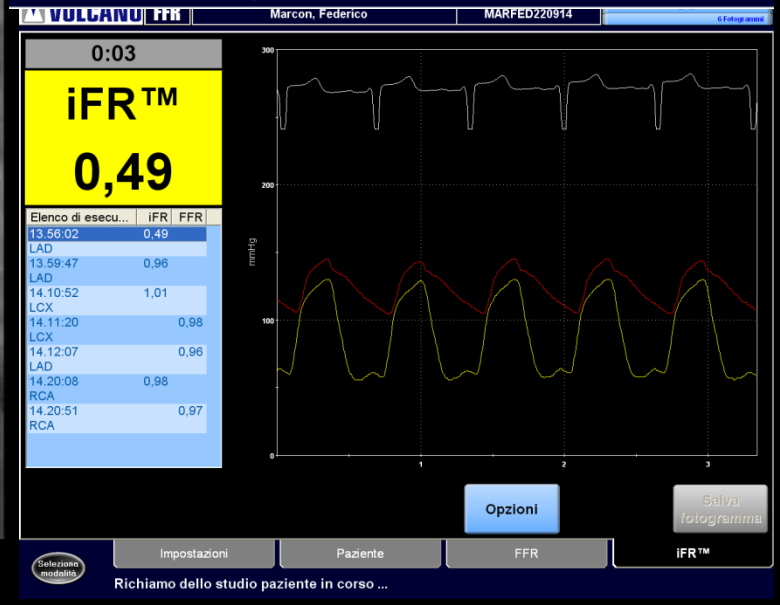
Scheduled for elective PCI of the LM after Heart Team discussion.

No symptoms or signs of ischemia…

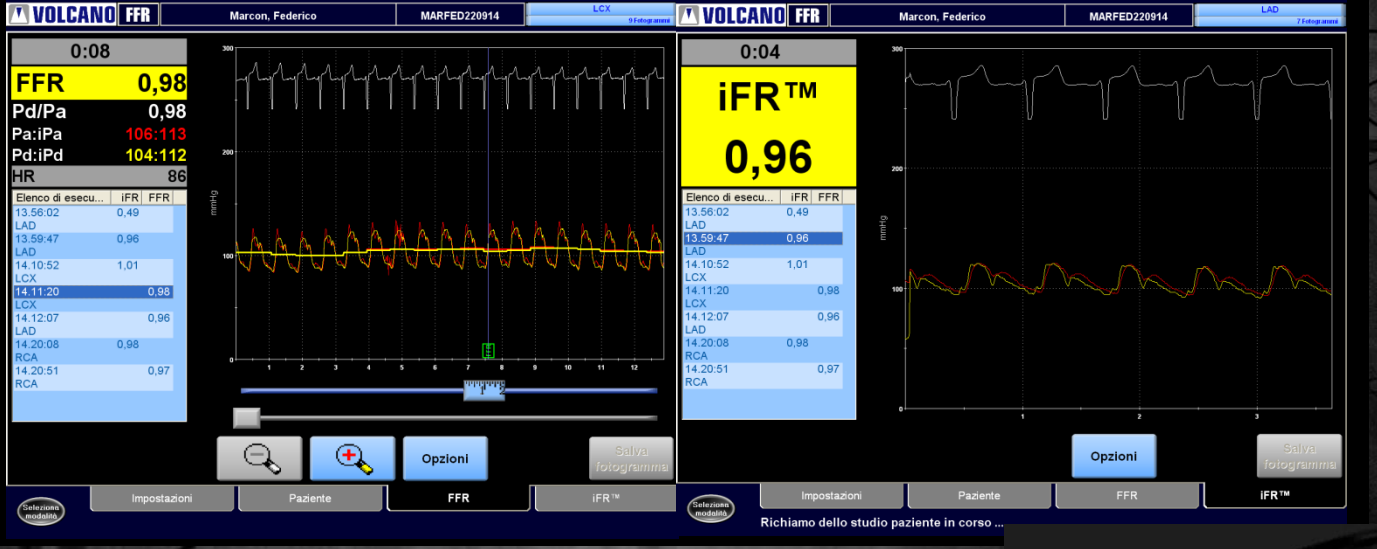
Pre-PCI angiogram confirms the LM stenosis in advanced CAV

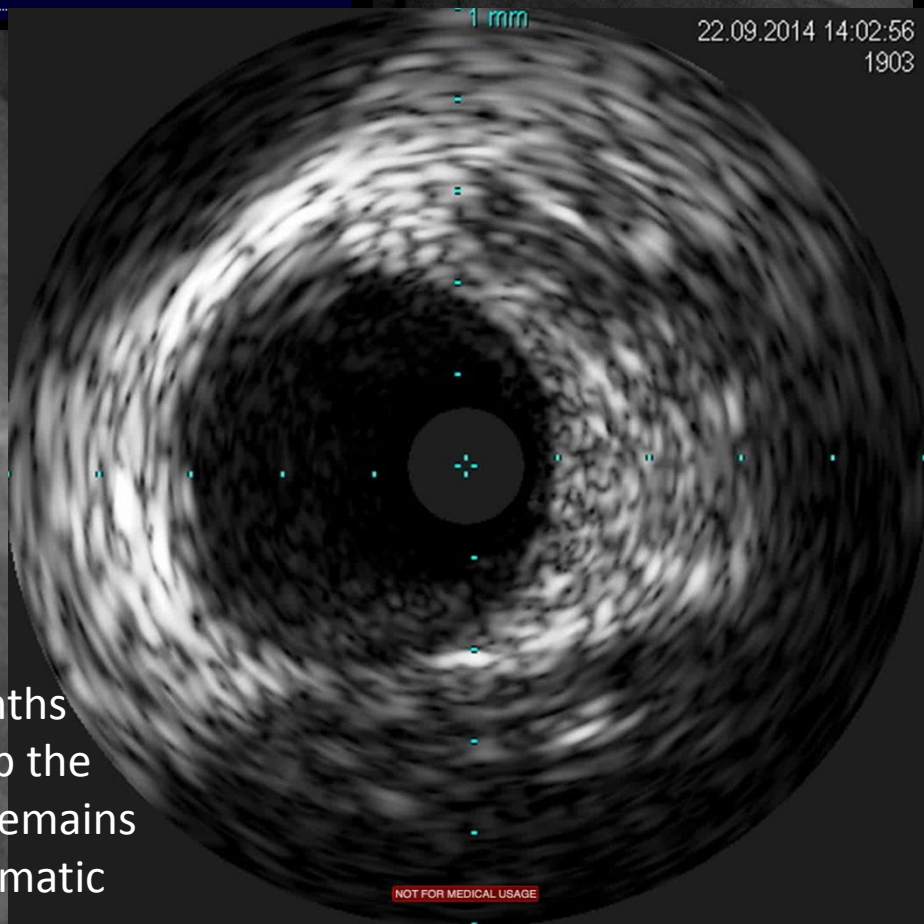
Resting gradients confirm the stenosis severity





But, after infusion of nitrates and ADN…





At 8 months follow-up the patient remains asymptomatic

But there are opinions against the reliabiity of iFR

Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. xx, No. x, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.09.065

VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice)

A Multicenter Study in Consecutive Patients

Colin Berry, MBChB, PhD,*† Marcel van 't Veer, MSc, PhD,‡ Nils Witt, MD, PhD,§ Petr Kala, MD,‖ Otakar Bocek, MD,‖ Stylianos A. Pyxaras, MD,¶ John D. McClure, MSc, PhD,* William F. Fearon, MD,# Emanuele Barbato, MD, PhD,¶ Pim A. L. Tonino, MD, PhD‡ Bernard De Bruyne, MD, PhD,¶ Nico H. Pijls, MD, PhD,‡ Keith G. Oldroyd, MBChB, MD,†

Glasgow, United Kingdom; Eindhoven, the Netherlands; Stockholm, Sweden; Brno, Czech Republic; Aalst, Belgium; and Stanford, California

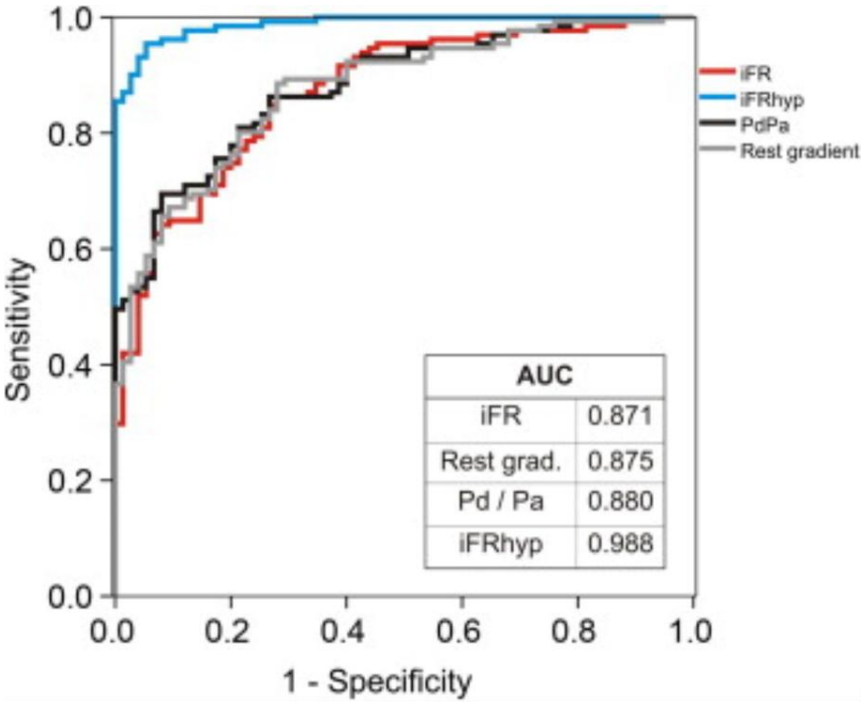
Objectives This study sought to compare fractional flow reserve (FFR) with the instantaneous wave-free ratio (iFR) in patients with coronary artery disease and also to determine whether the iFR is independent of hyperemia.

Background FFR is a validated index of coronary stenosis severity. FFR-guided percutaneous coronary intervention (PCI) improves clinical outcomes compared to angiographic guidance alone. iFR has been proposed as a new index of stenosis severity that can be measured without adenosine.

Methods We conducted a prospective, multicenter, international study of 206 consecutive patients referred for PCI and a retrospective analysis of 500 archived pressure recordings. Aortic and distal coronary pressures were measured in duplicate in patients under resting conditions and during intravenous adenosine infusion at 140 μg/kg/min.

Results Compared to the FFR cut-off value of ≤0.80, the diagnostic accuracy of the iFR value of ≤0.80 was 60% (95% confidence interval [CI]: 53% to 67%) for all vessels studied and 51% (95% CI: 43% to 59%) for those patients with FFR in the range of 0.60 to 0.90. iFR was significantly influenced by the induction of hyperemia: mean ± SD iFR at rest was 0.82 ± 0.16 versus 0.64 ± 0.18 with hyperemia ($p < 0.001$). Receiver operating characteristics confirmed that the diagnostic accuracy of iFR was similar to resting Pd/Pa and trans-stenotic pressure gradient and significantly inferior to hyperemic iFR. Analysis of our retrospectively acquired dataset showed similar results.

Conclusions iFR correlates weakly with FFR and is not independent of hyperemia. (Comparison of Fractional Flow Reserve Versus Instant Wave-Free Ratio for Assessment of Coronary Artery Stenosis Severity in Routine Practice; NCT01559493). (J Am Coll Cardiol 2013;xx:xxx) © 2013 by the American College of Cardiology Foundation



- iFR correlates weakly with FFR and is not independent of hyperemia
- iFR cannot be raccomanded for clinical decision making in patients with coronary heart disease

Berry C, *et al.* VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice): A Multicenter Study in Consecutive Patients**.** J Am Coll Cardiol. 2013 Apr 2;61(13):1421-7.

Objections of the iFR authors to VERIFY

VERIFY paper's primary conclusion was based on the ***assumption that an iFR of 0.80 is equivalent to an FFR 0.80***, which is incorrect. The proper cut-point in the FDA labeling is iFR of 0.89 equivalent to an FFR of 0.80.

"The best cut-off value was not published in this paper."

VERIFY Investigators pointed out that the iFR window is not 'independent' of hyperemia."

iFR does not intend to show independence from adenosine, but rather that adenosine may not be needed to measure lesion severity.

Results

The clinical characteristics of the patients in the prospective study are shown in Table 1. The relationships between FFR and iFR are shown in Figure 2. Compared to the commonly used FFR cut-off value of ≤0.80, the diagnostic performance of iFR of ≤0.80 is shown in Table 2. Overall accuracy was 60% (95% CI: 53% to 67%) for all vessels studied and 51% (95% CI: 43% to 59%) for those with FFR in the range of 0.60 to 0.90. Sen et al. (14) proposed that iFR of ≤0.83 has diagnostic performance equivalent to an FFR of ≤0.80. The diagnostic performance of iFR at ≤0.83 in our prospectively acquired dataset is shown in Table 3. Overall accuracy was 68% (95% CI: 61% to 75%) for all

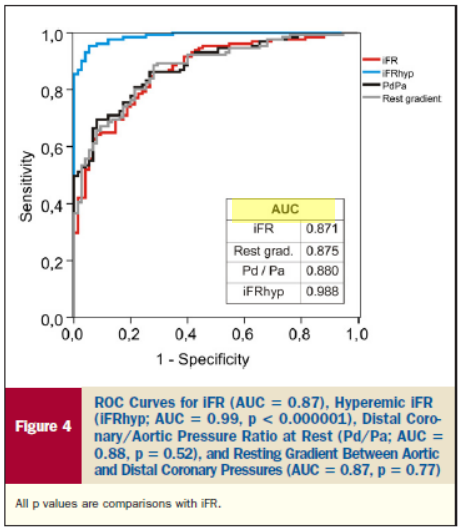


Figure 4 ROC Curves for iFR (AUC = 0.87), Hyperemic iFR (iFRhyp; AUC = 0.99, p < 0.000001), Distal Coronary/Aortic Pressure Ratio at Rest (Pd/Pa; AUC = 0.88, p = 0.52), and Resting Gradient Between Aortic and Distal Coronary Pressures (AUC = 0.87, p = 0.77)

All p values are comparisons with iFR.

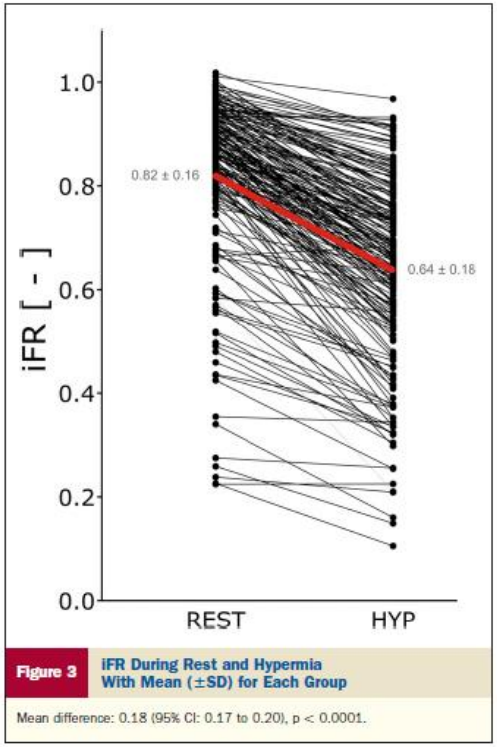


Figure 3 iFR During Rest and Hypermia With Mean (±SD) for Each Group

Mean difference: 0.18 (95% CI: 0.17 to 0.20), p < 0.0001.

Hyperaemic and baseline physiological pressure indices have an equivalent diagnostic classification agreement in comparison to myocardial blood flow quantified by [^{15}O]H_2O PET

Guus A de Waard[1]; Ibrahim Danad[1]; Ricardo Petraco[2]; Paul FA Teunissen[1] ; Alexander Nap[1]; Maarten AH van Leeuwen[1]; Koen M Marques[1]; Hendrik J Harms[3]; Pieter G Raijmakers[3]; Adriaan A Lammertsma[3]; Justin E Davies[2]; Paul Knaapen[1]; Niels van Royen[1]

1 Department of Cardiology, VUMC, Amsterdam, The Netherlands 2 International Center for Circulatory Health, Imperial College London, UK
3 Department of Nuclear Medicine and PET, VUMC, Amsterdam, The Netherlands

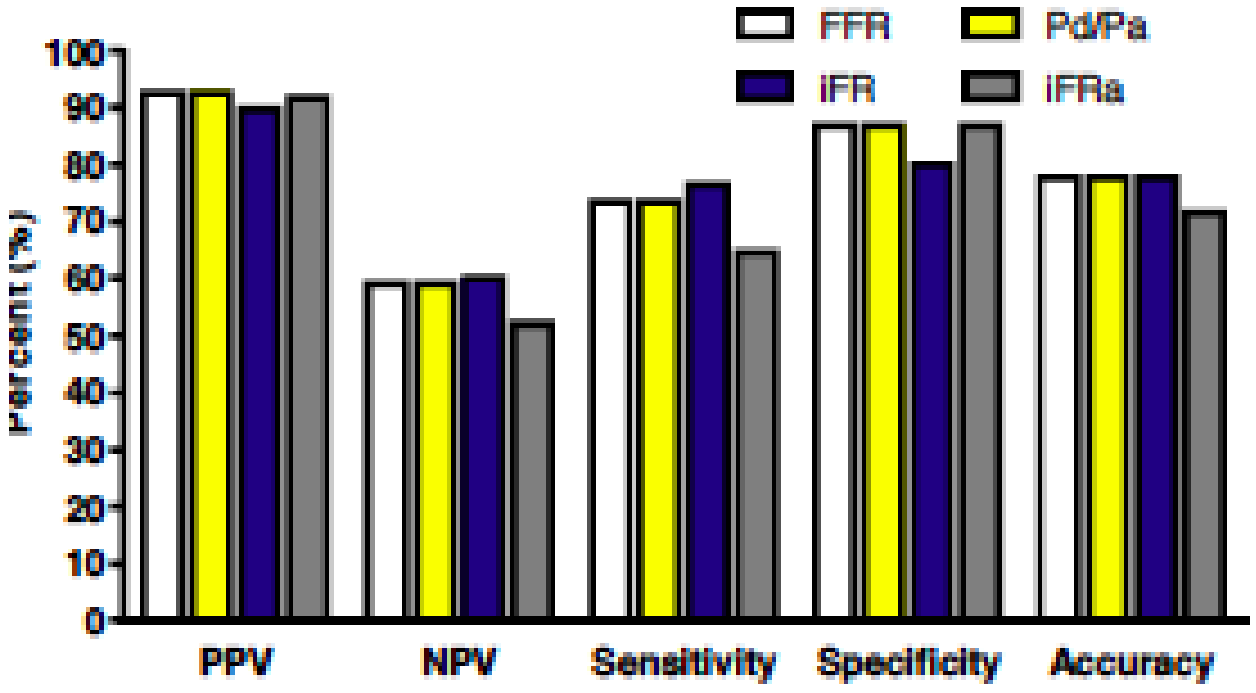


Fig. 3: Test characteristics of pressure indices for the prediction of impaired PET MBF

Conclusions

Hyperaemic and non-hyperaemic intracoronary indeces have an equivalent diagnostic performance in comparison to PET MBF for the assessment of intermediate coronary artery stenoses.

ACC 2014 A1692
JACC April 1, 2014
Volume 63, Issue 12

I am an FFR believer,

I am a clinician and a researcher

I work in a University Hospital

When we introduce a new technology we **VERIFY** it…

because "I trust what I see"
and "I do what I trust"

Let's do an independent validation study of iFR versus FFR…

FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

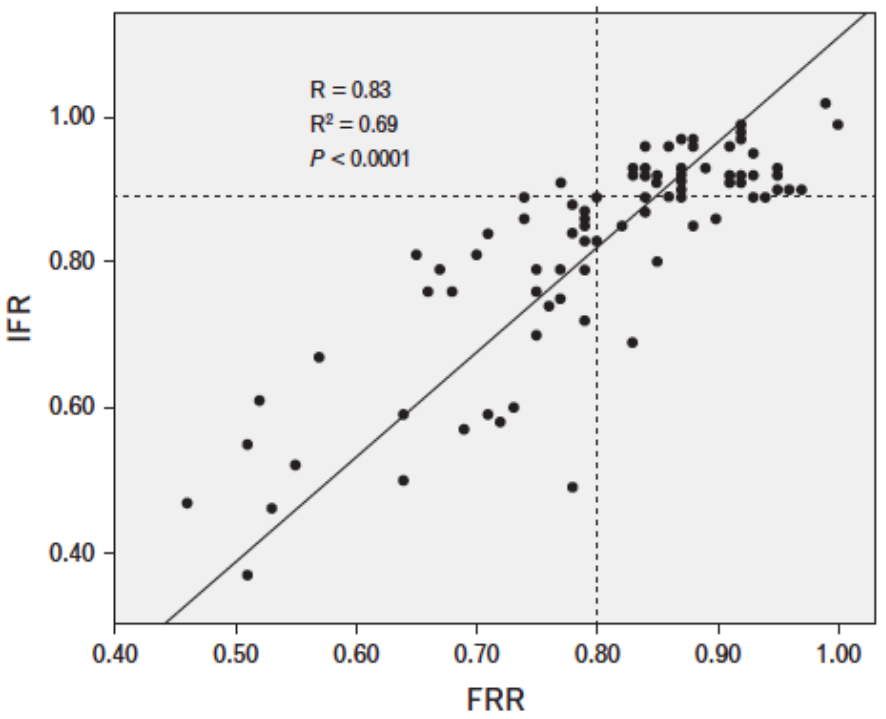
iFR-FFR comparison in daily practice: a single-center, prospective, online assessment

Table 1 Clinical and angiographic characteristics of the entire population

Patient demographic data (54 patients)	
Male sex	41 (76%)
Age (years)	67 ± 11
Diabetes	14 (26%)
Hypertension	44 (81%)
Dyslipidemia	49 (91%)
Stable angina (CCS I-II-III)	36 (66%)
Unstable angina	9 (17%)
NSTEMI	9 (17%)
NYHA class I–II	50 (93%)
Angiographic characteristics	
Number of assessed stenosis	89
Left anterior descending	52 (58%)
Left circumflex	20 (23%)
Right coronary artery	17 (19%)
Mean % diameter stenosis	59 ± 9%
Mean lesion length	17.54 ± 5.38 mm
Mean reference vessel diameter	2.63 ± 0.65 mm
Mean minimum lumen diameter	1.21 ± 0.73 mm
Mean iFR ratio	0.82 ± 0.14
Mean FFR ratio	0.81 ± 0.12

CCS, Canadian Cardiac Society; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; NSTEMI, non-ST-segment elevation myocardial infarction; NYHA, New York Heart Association.

Fig. 1



Correlation between iFR and FFR values of the 68 lesions analyzed, with the respective cut-off values indicated, which, apart from a correlation value of 0.83, highlight the low number of false-positive and false-negative values when the two methods are compared. FFR, fractional flow reserve; iFR, instantaneous wave-free ratio.

iFR-FFR comparison in daily practice: a single-center, prospective, online assessment

iFR FFR 100% agreement in 45% of cases (ADN not needed)

Gray zone (iFR 0.86-0.93) 55%, of these, 70% were both negative

iFR identified positive values in 15% of FFR >0.80.

In conclusion, in our experience, iFR identified correctly all FFR negative lesions and would induce 15% more PCI in lesions with an FFR value >0.80 <0.85.

I am an FFR believer,

I am a clinician and a researcher

I work in a University Hospital

When we introduce a new technology we VERIFY it…

Let’s do a validation study of iFR versus FFR…

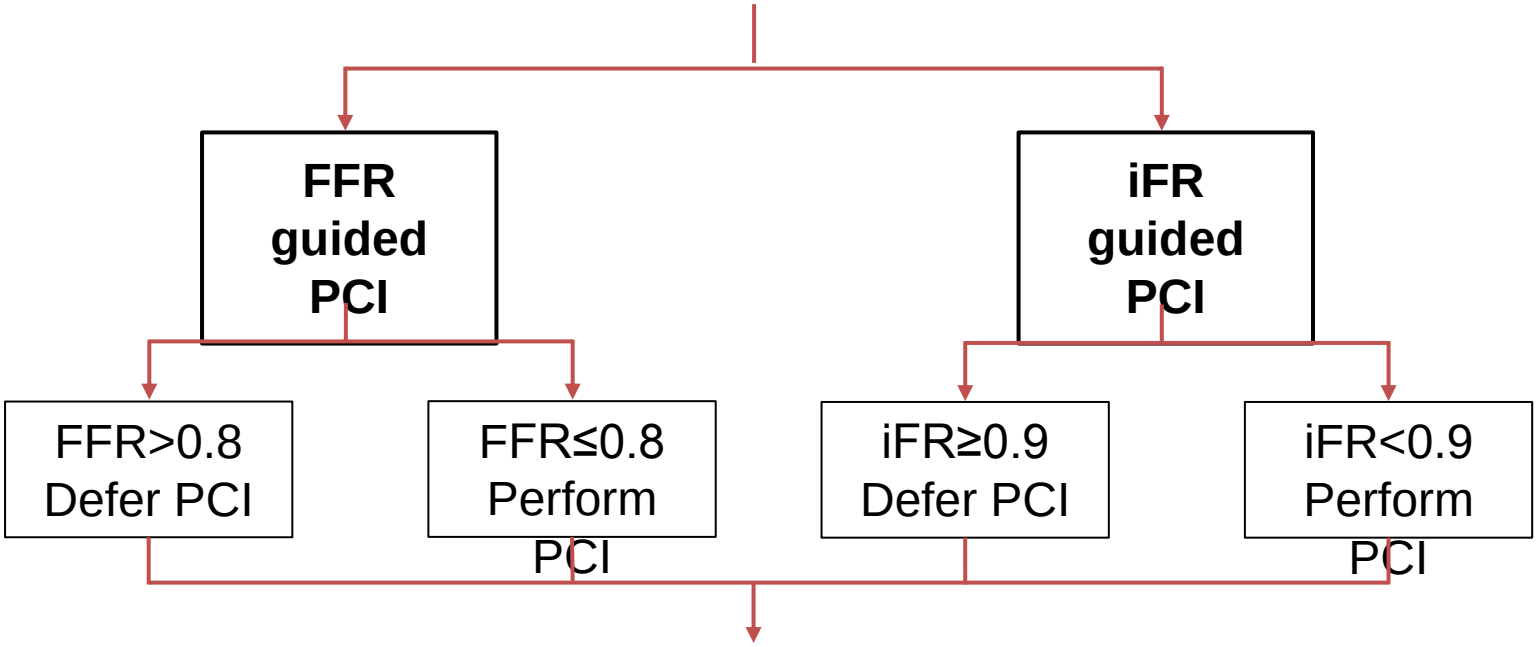
Following our validation study, we were invited to participate in DEFINE FLAIR

DEFINE FLAIR

Functional Lesion Assessment of Intermediate stenosis to guide Revascularisation

Intermediate lesion requiring physiological assessment
In ACS : intermediate *non-culprit* lesion

N=2500, 1:1 Randomisation



30 day, 1, 2 and 5yr follow-up

Example of a DEFINE FLAIR PATIENT RANDOMIZED IN VERONA.

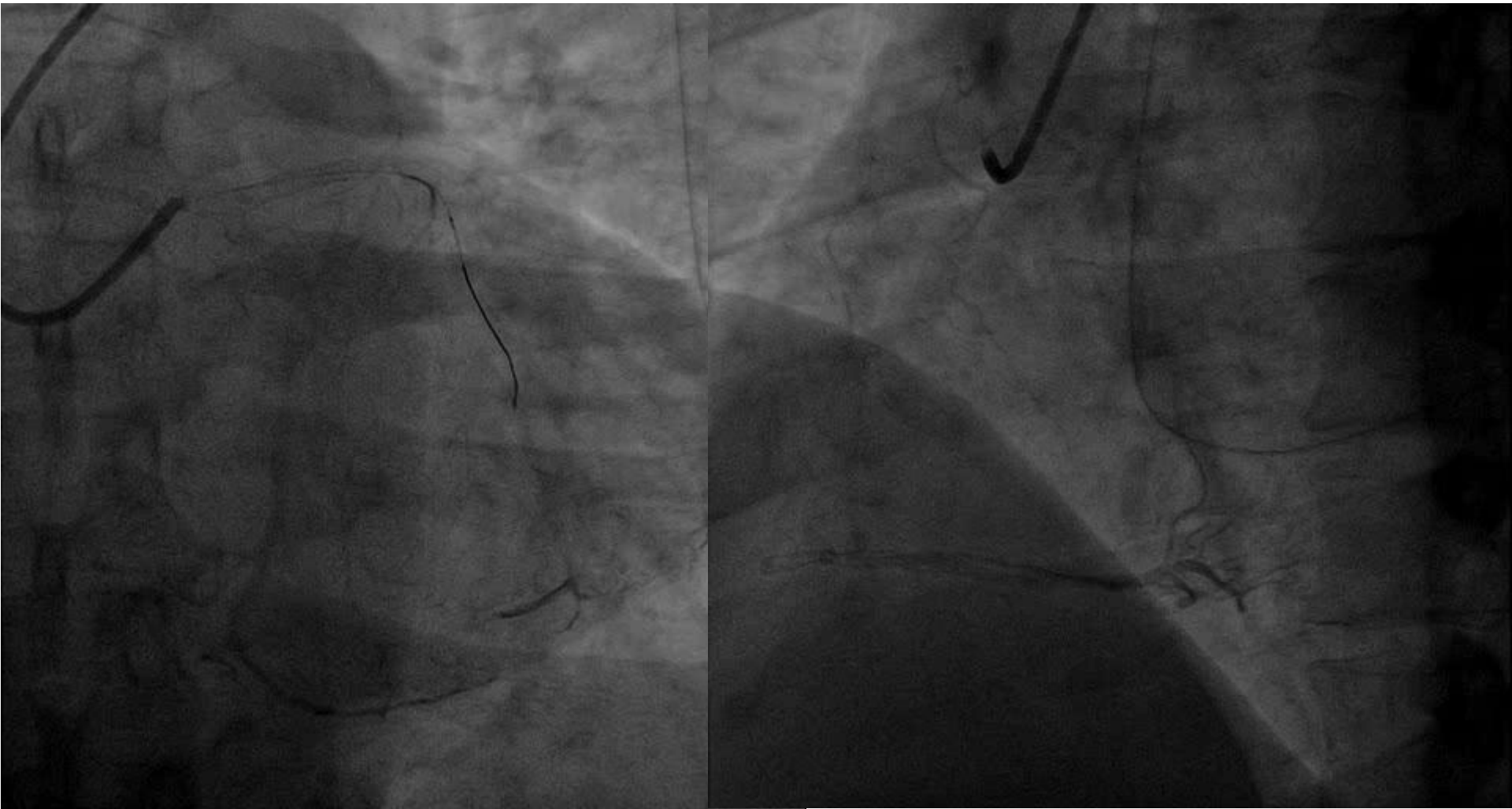
54 y.o male
ACS presentation
Proximal LAD culprit
Distal LAD significant

PCI on LAD

Significant lesions on ostial RI and LCx

PCI on LAD

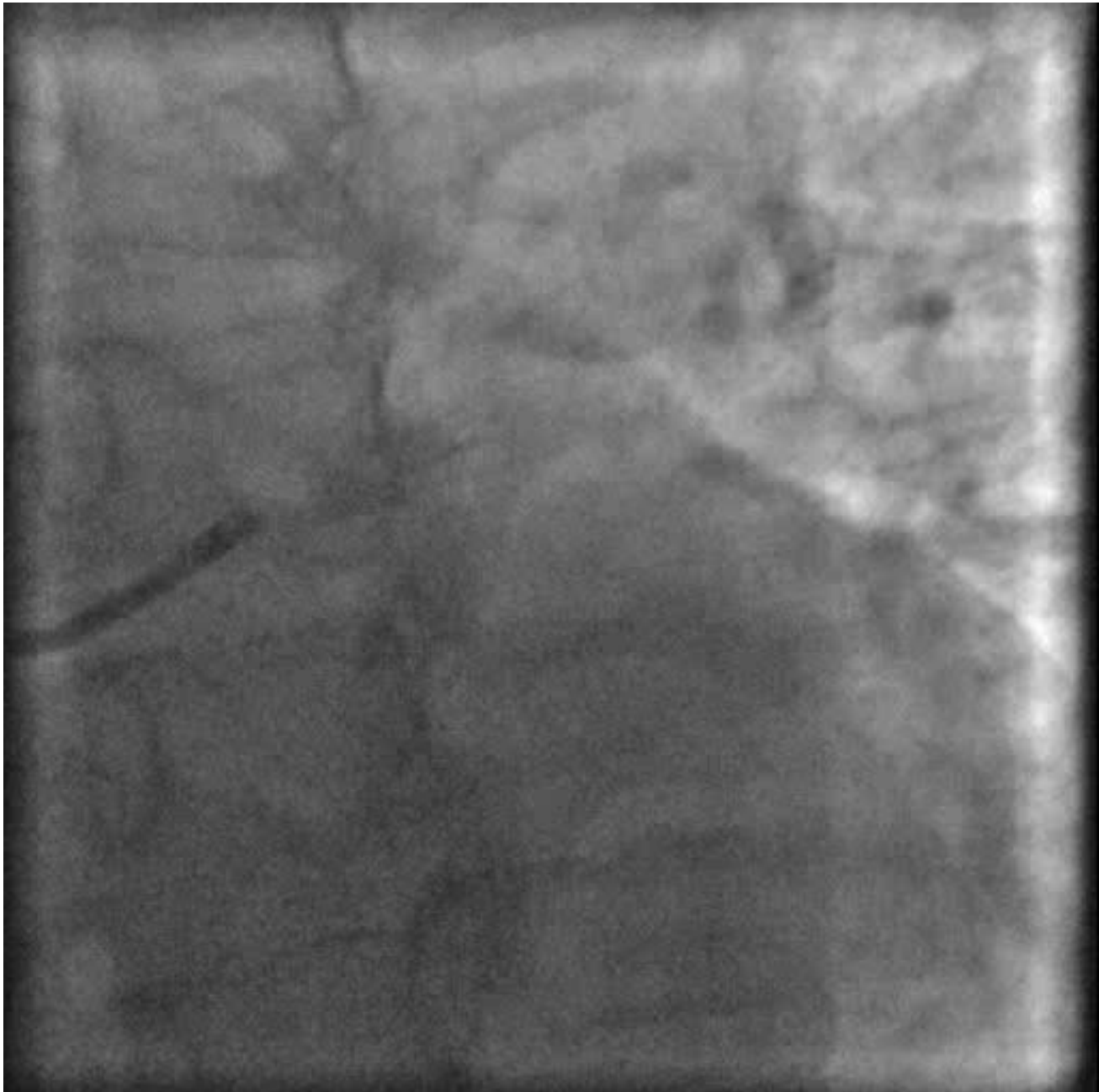
Significant lesions on ostial RI and LCx and the RCA



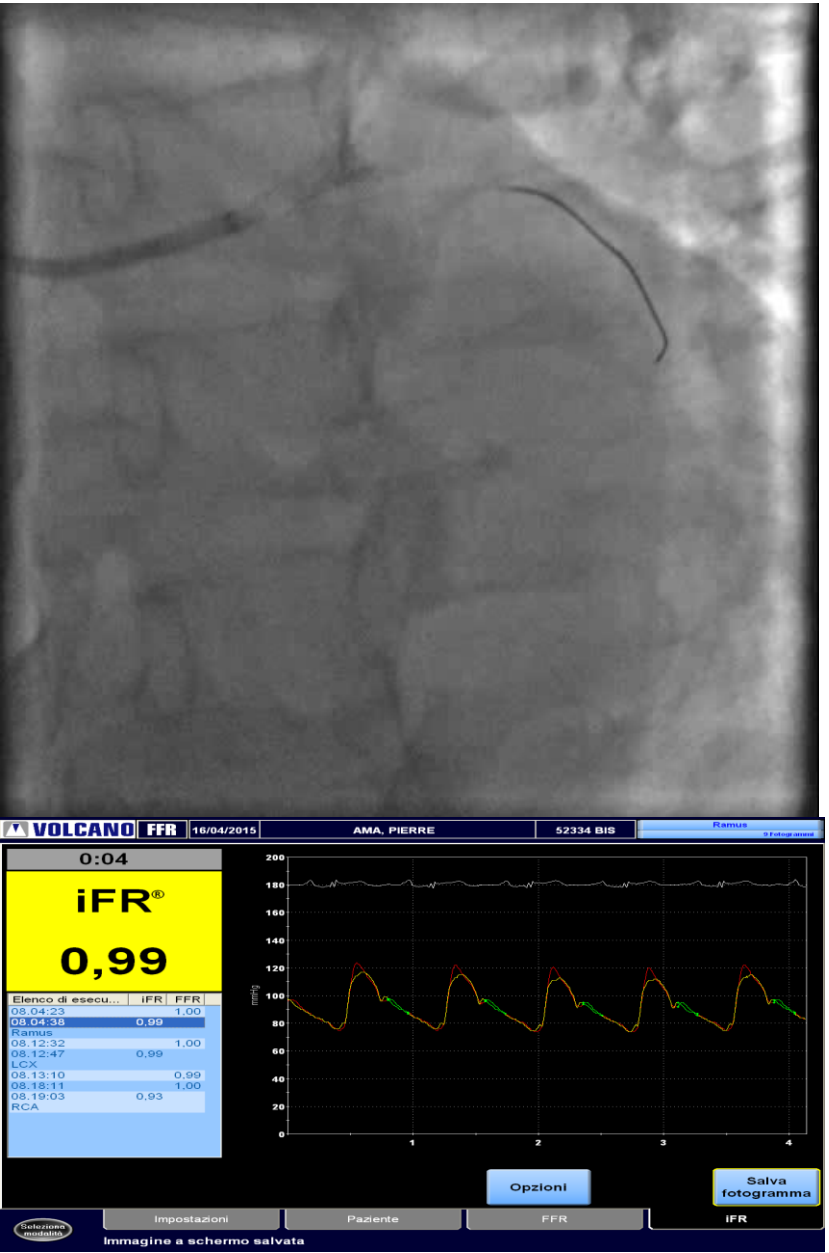
Pre-discharge functional assessment of the RI and LCx

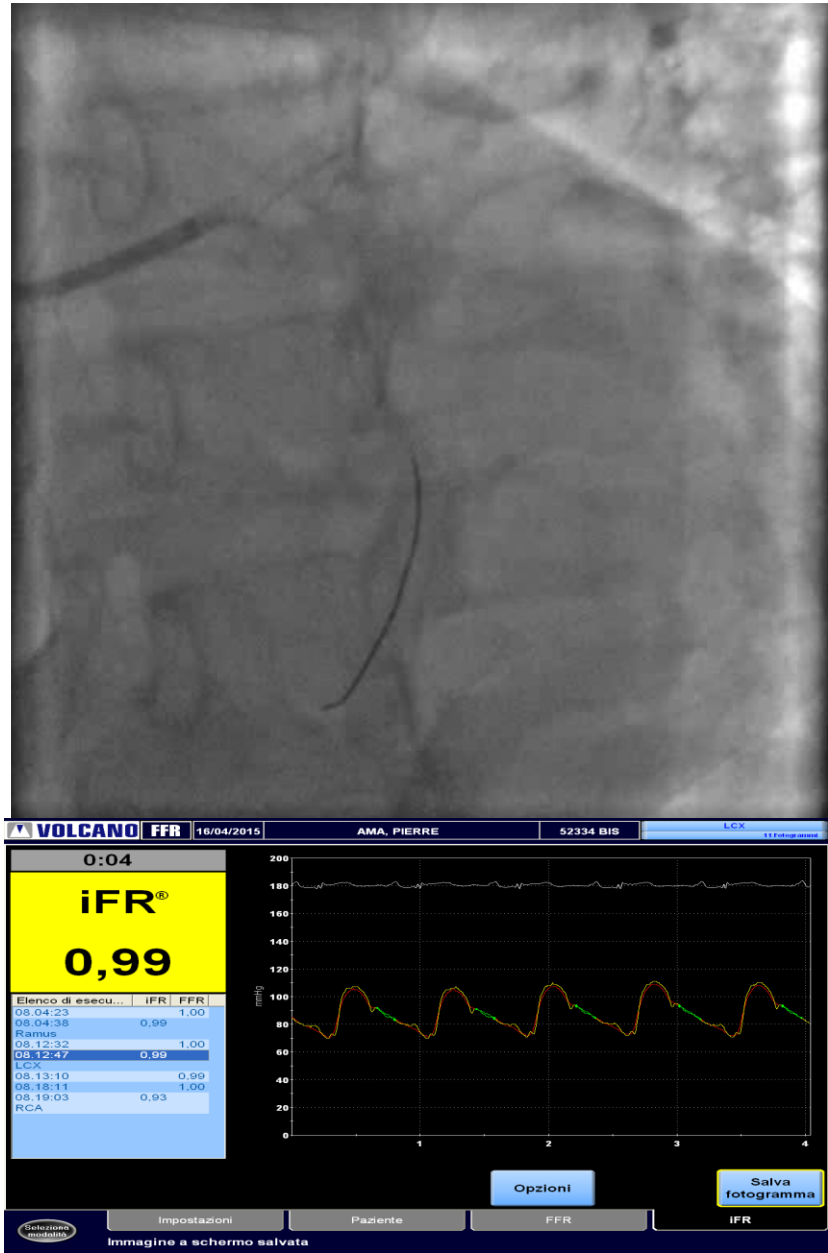
Enrolled
DEFINE
FLAIR
TRIAL

April 4
2014



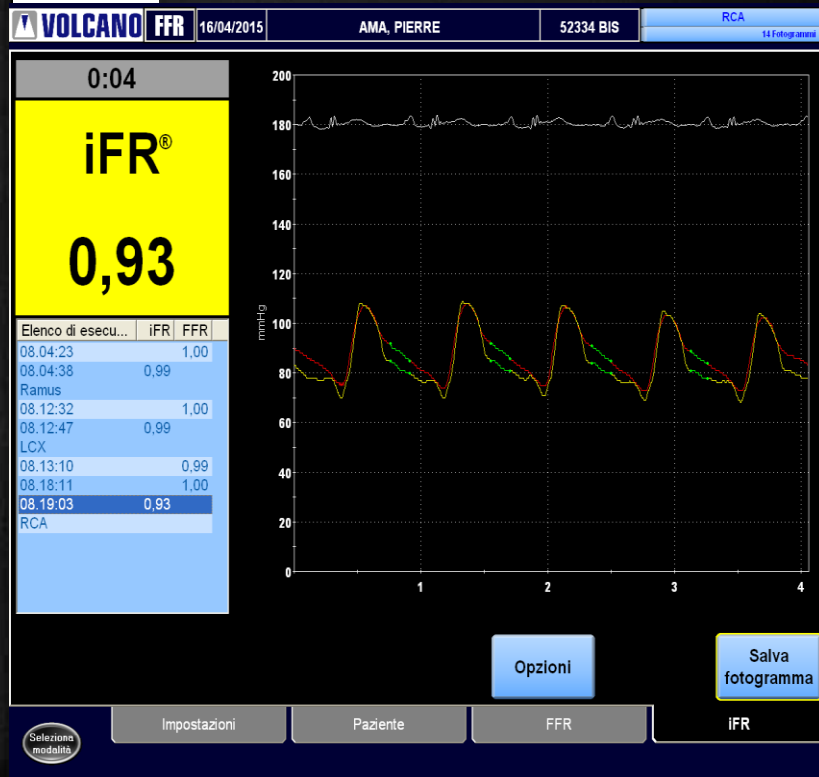
Pre-discharge functional assessment of the RI and LCx





Pre-discharge functional assessment of the RCA

Enrolled DEFINE FLAIR TRIAL April 4 2014



DEFINE FLAIR

This patient has completed one-year follow-up

- No clinical events
- No angina

- So far 36 patients enrolled (21 to FFR and 15 to iFR)
- Of 51 lesions, 13 treated and 38 lesions deferred
- None has been re-admitted for recurrence of ischemia.

I am an FFR believer,

I am a clinician and a researcher

I work in a University Hospital

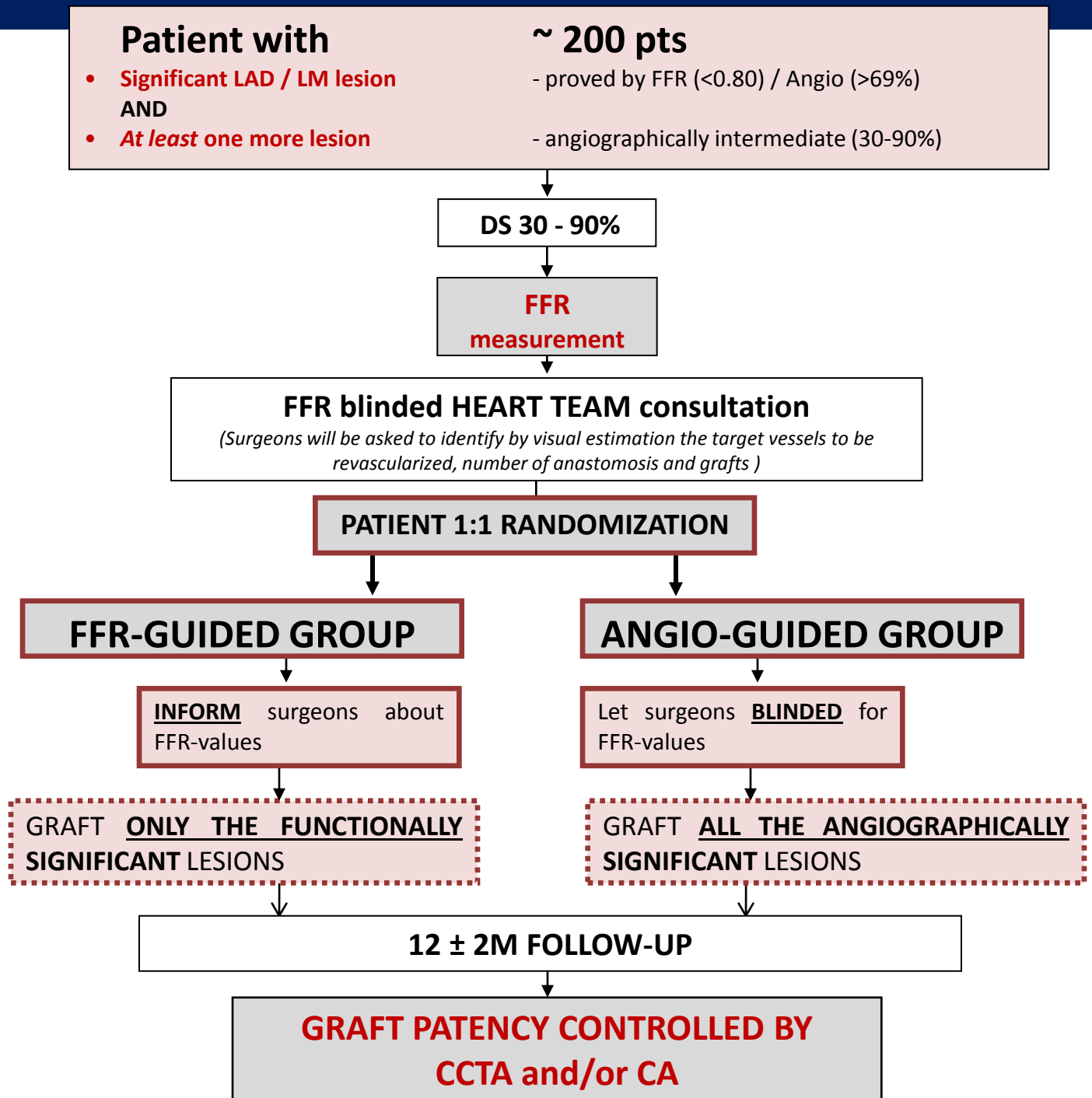
When we introduce a new technology we VERIFY it…

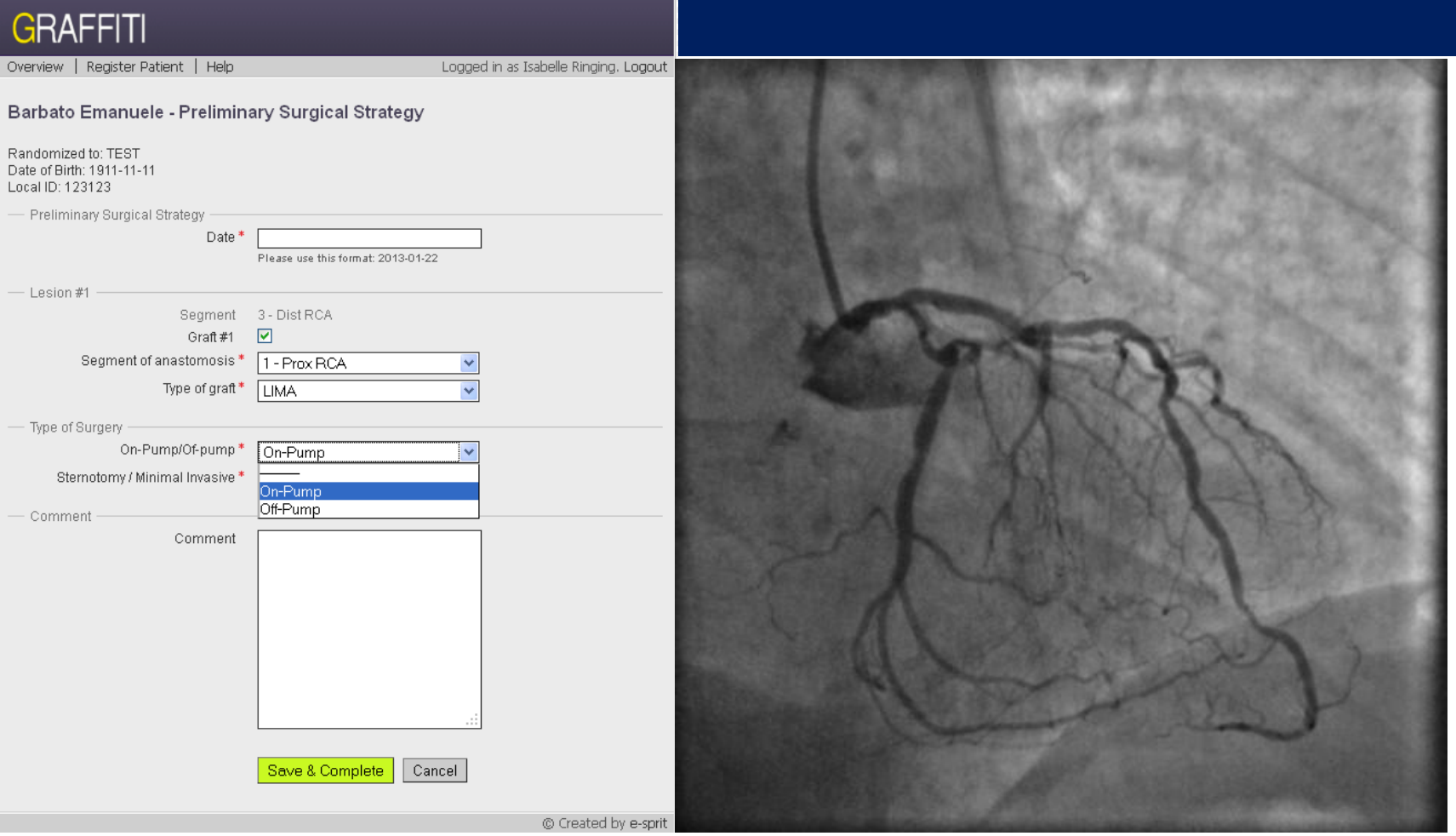
Let's do a validation study of iFR versus FFR…

Following our validation study, we were invited to participate In DEFINE FLAIR.

… and my friend Emanuele Barbato from Aalst got very jealous and asked us to participate in GRAFFITI

GRaft Patency **A**fter **FF**R-guided versus Ang**i**o-guided CABG: a randomized clinical **T**r**i**al (**GRAFFITI**)





CARDIOVASCULAR CENTER AALST

www.cardio-aalst.be

- First case enrolled February 24° 2014
- Total cases enrolled in Verona: 20
- Complete follow-up obtained in the first 5 cases

I am an FFR believer,

I am a clinician and a researcher

I work in a University Hospital

When we introduce a new technology we VERIFY it…

Let's do a validation study of iFR versus FFR…

Following our validation study, we were invited to participate In DEFINE FLAIR

… and my friend Emanuele Barbato got very jealous and asked us to participate in GRAFFITI

… and we still like doing new clinical studies…

CART STUDY

Cardiac Allograft Reparative Therapy

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"

Search for studies: [ ] Search

Advanced Search | Help | Studies by Topic | Glossary

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Search Results Text Size

1 study found for: CART Verona

Modify this search | How to Use Search Results

List | By Topic | On a Map | Search Details

+ Show Display Options

Download | Subscribe to RSS

[ ] Include only open studies [ ] Exclude studies with unknown status

Rank	Status	Study
1	Recruiting	Safety and Efficacy of Everolimus - Eluting Bioresorbable Vascular Scaffold for Cardiac Allograft Vasculopathy **Condition:** Cardiac Allograft Vasculopathy **Intervention:** Device: Everolimus-Eluting Bioresorbable Vascular Scaffold (ABSORB)

CART STUDY

Cardiac Allograft Reparative Therapy

MULTI-MODALITY DIAGNOSIS IN CAV, INCLUDING FFR IN TRANSPLANTED HEART.

RESTENOSIS AFTER BVS IMPLANTATION IN CAV

CLINCALTRIAL.GOV IDENTIFIER.

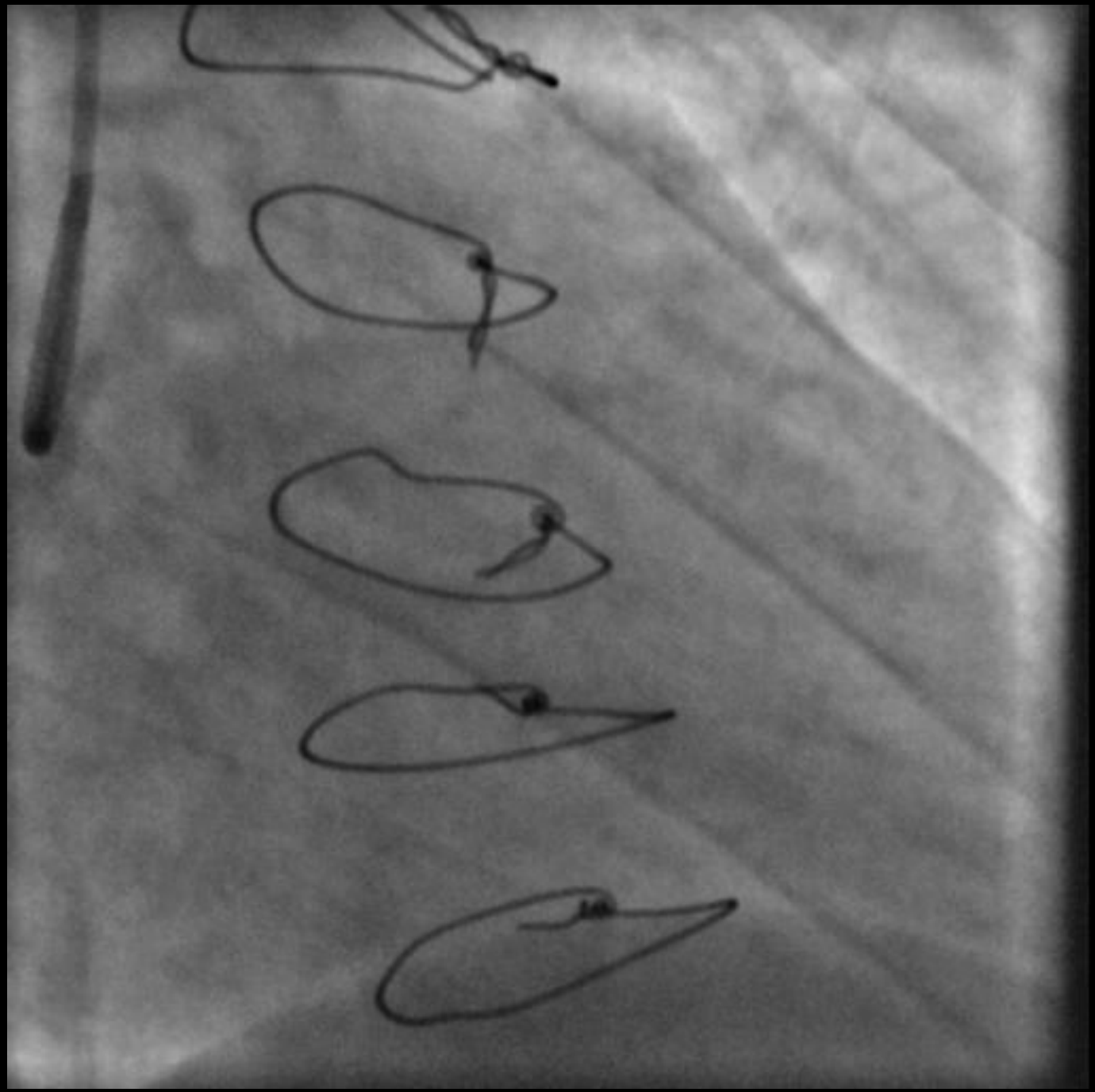
PARTICIPATING CENTERS: VERONA, ROME, MILANO, PADOVA, PAVIA

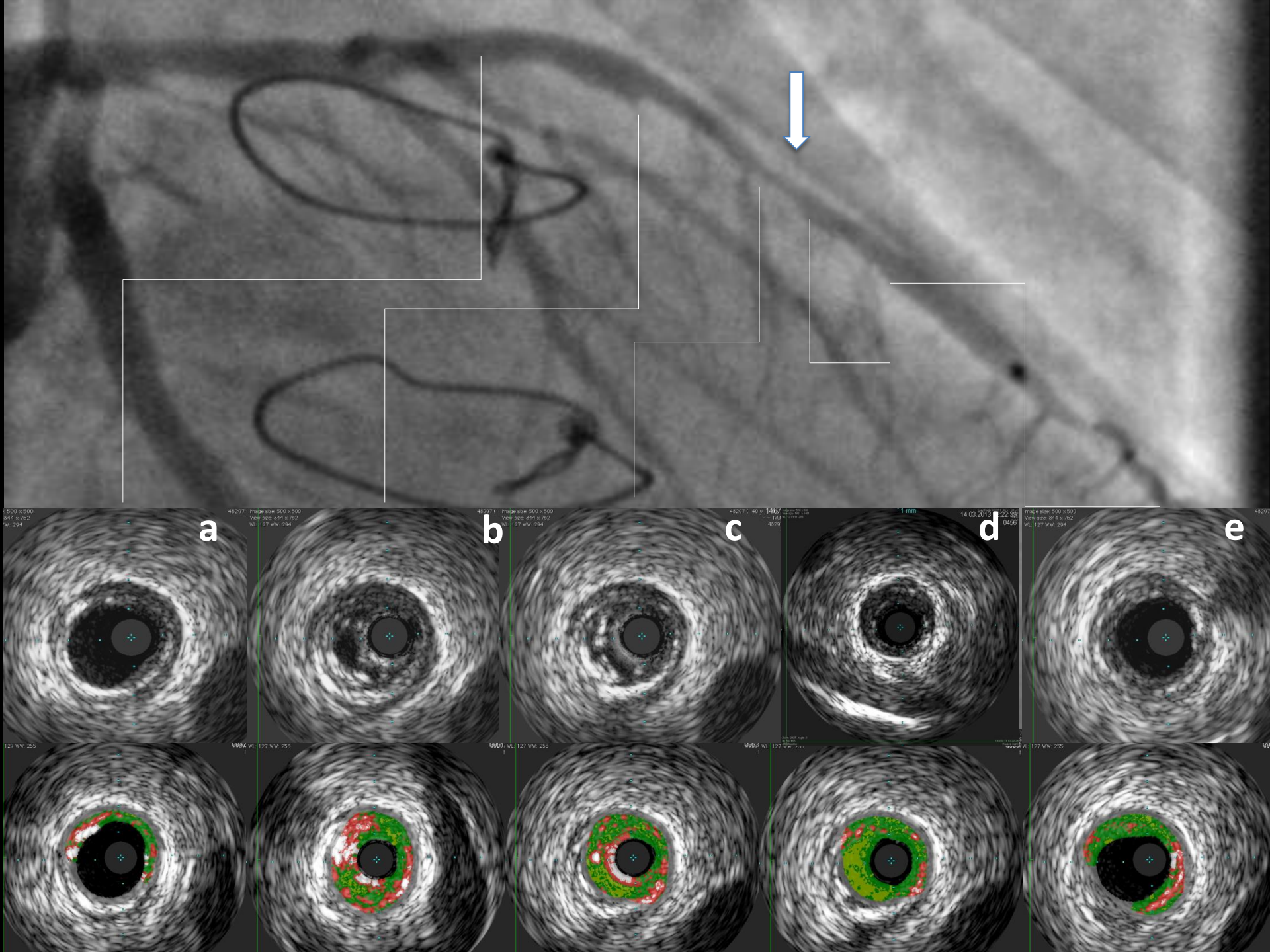
SO FAR 8 PATIENTS ENROLLED

Case Presentation

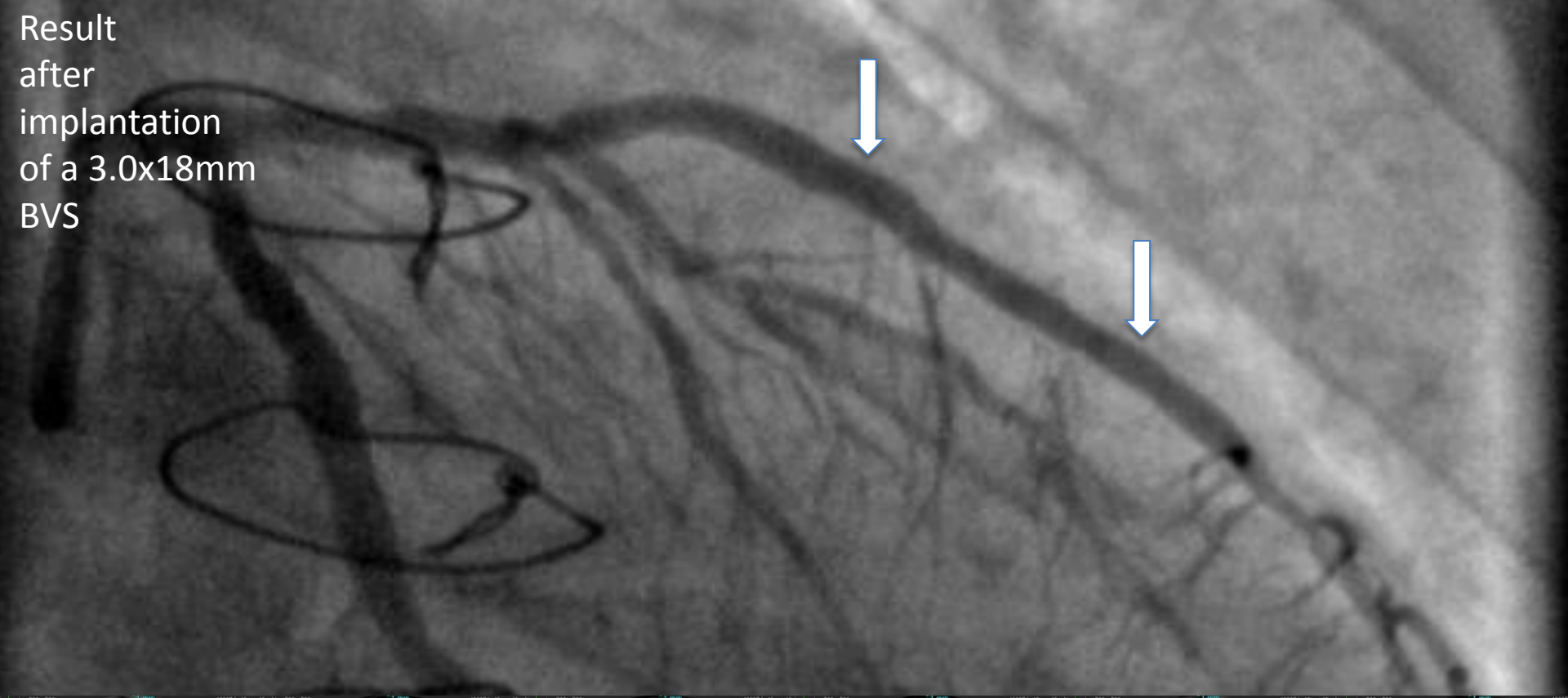
40 years old male

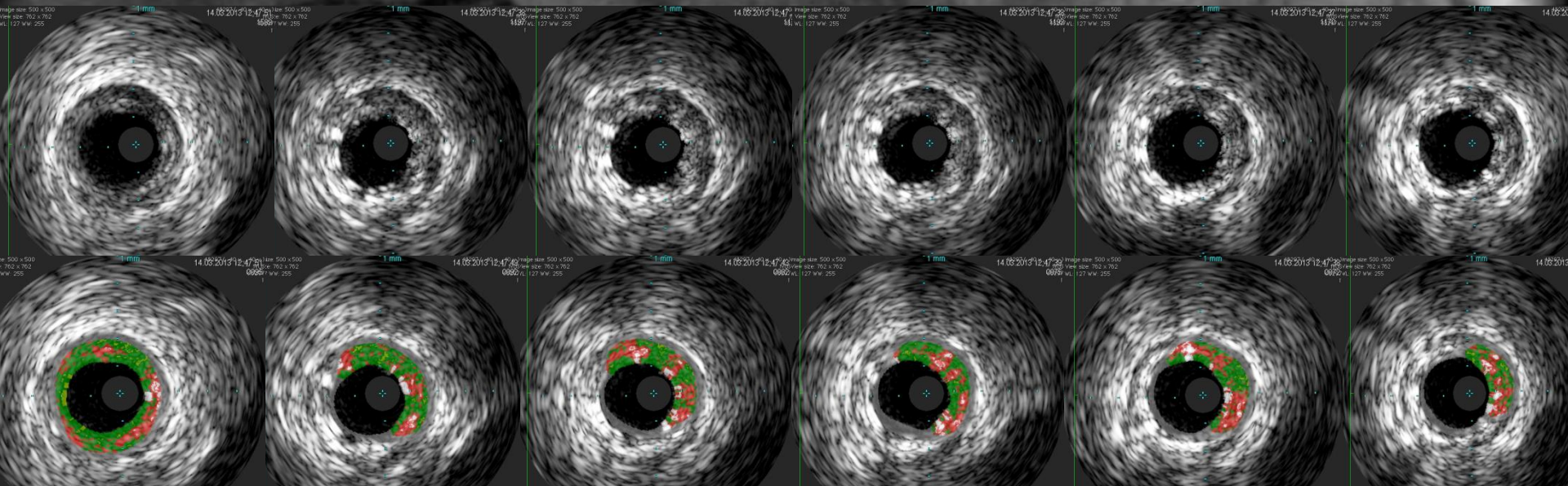
Heart transplant at the age of 30
Intensive life with regular exercise
Since November 2012, typical effort angina
Admitted for coronary angiogram in March 2013



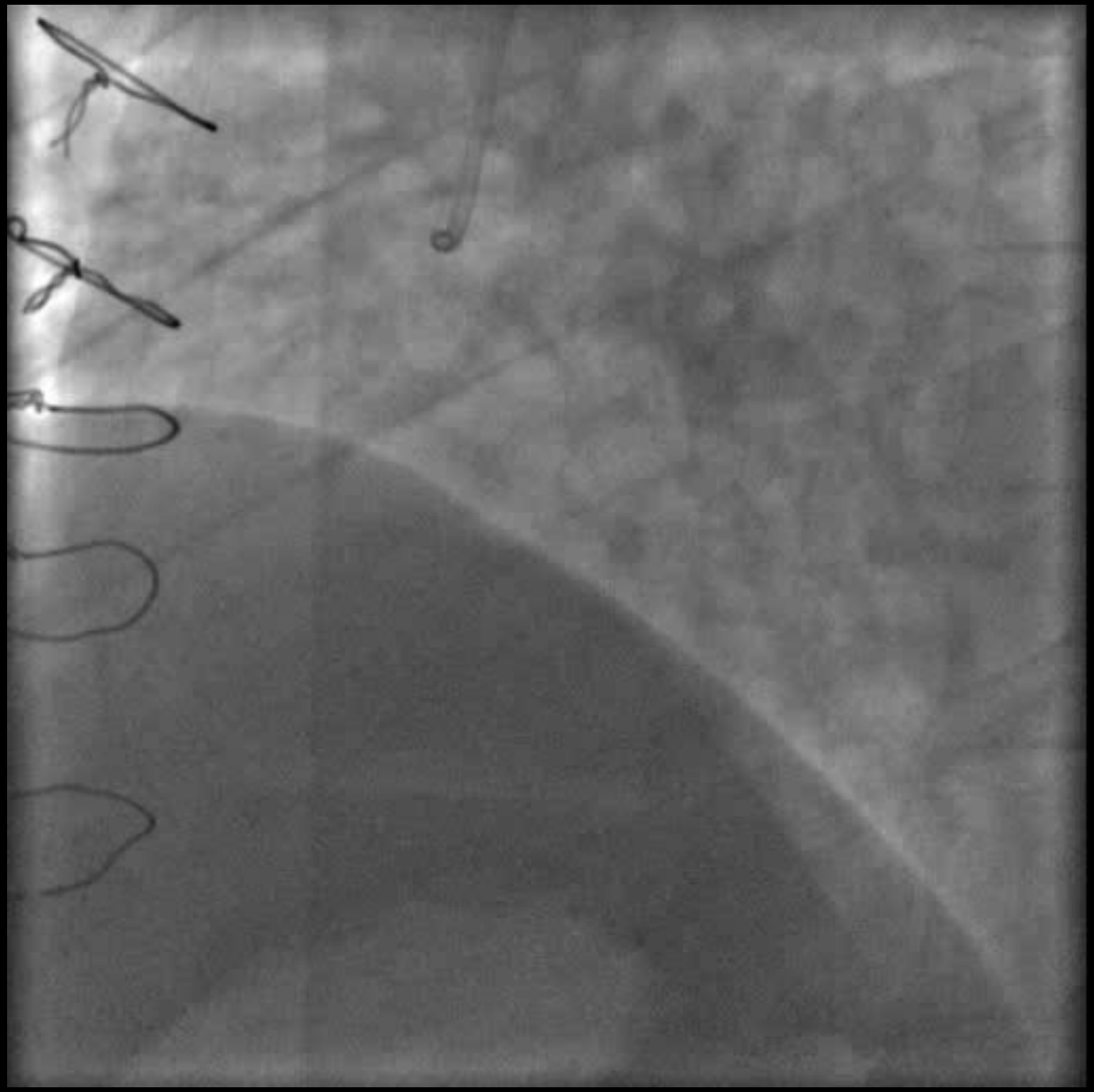

a
b
c
d
e

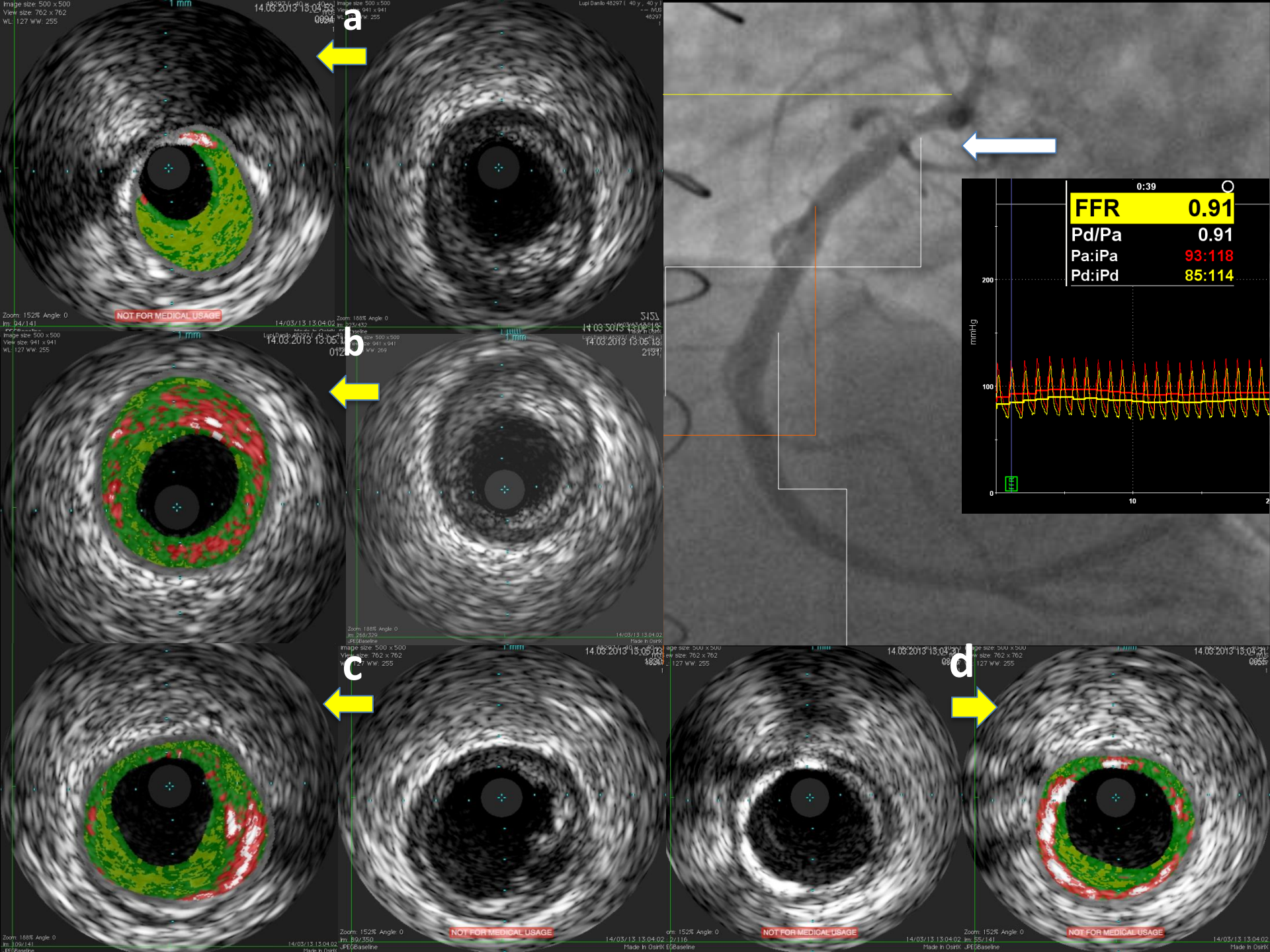
Result after implantation of a 3.0x18mm BVS





RCA: mild proximal stenosis




a
b
c
d
FFR 0.91
Pd/Pa 0.91
Pa:iPa 93:118
Pd:iPd 85:114
0:39
mmHg
200
100
0
10
NOT FOR MEDICAL USAGE

Uneventful hospital course
Discharged 48 hours later

Medical therapy:
DAPT x 12m
Atorvastatin 80mg
Nitrates
Beta bloker
Prednisione 5mg and Everolimus 10mg day

Bioresorbable Vascular Scaffolds (BVS) in Cardiac Allograft Vasculopathy: A New Therapeutic Option.

Prof. Flavio Ribichini
flavio.ribichini@univr.it

The American Journal of Medicine
AJM12180
S0002-9343(13)00724-9
10.1016/j.amjmed.2013.05.025

THE AMERICAN JOURNAL of MEDICINE®

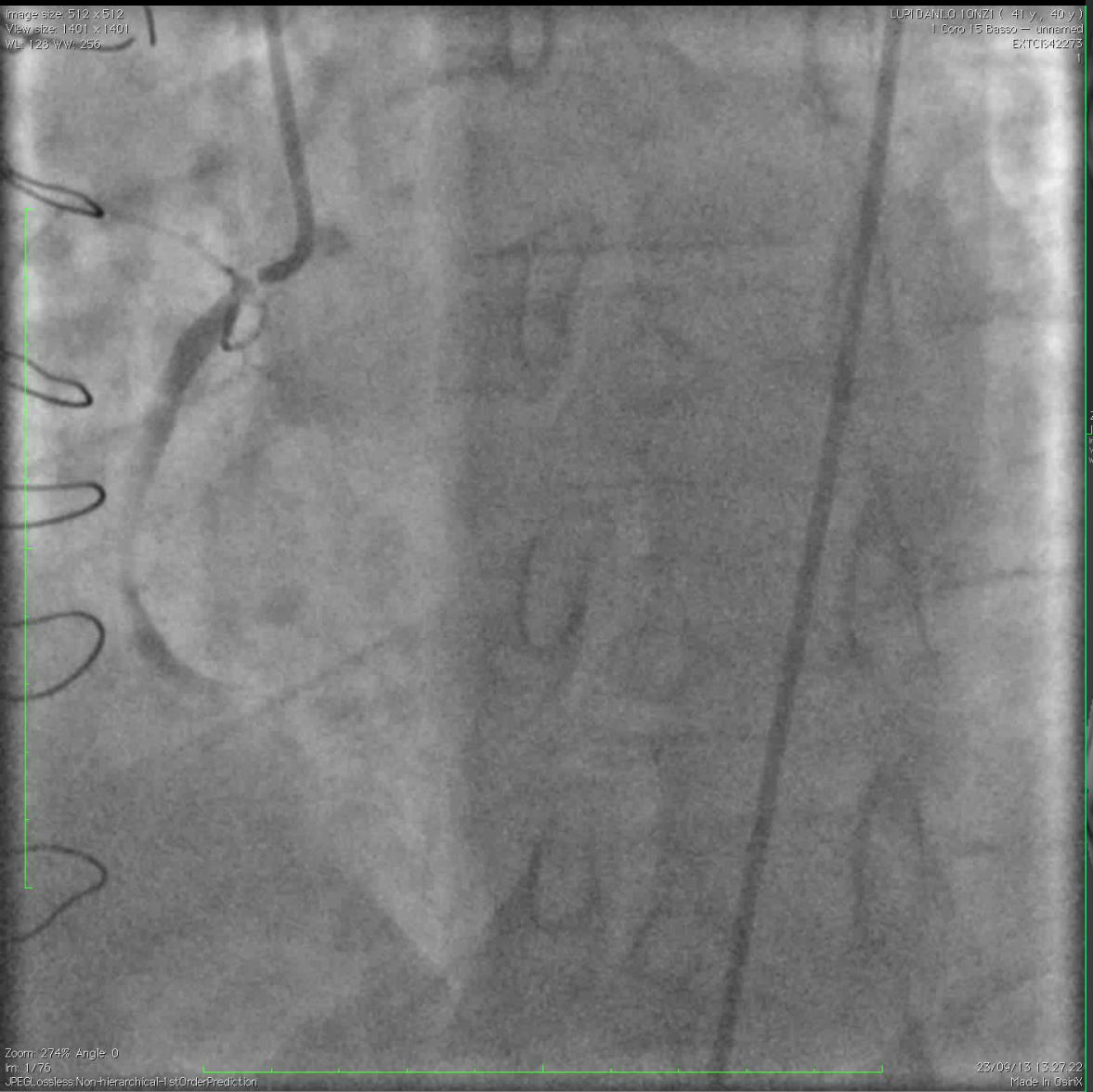
Case follow-up

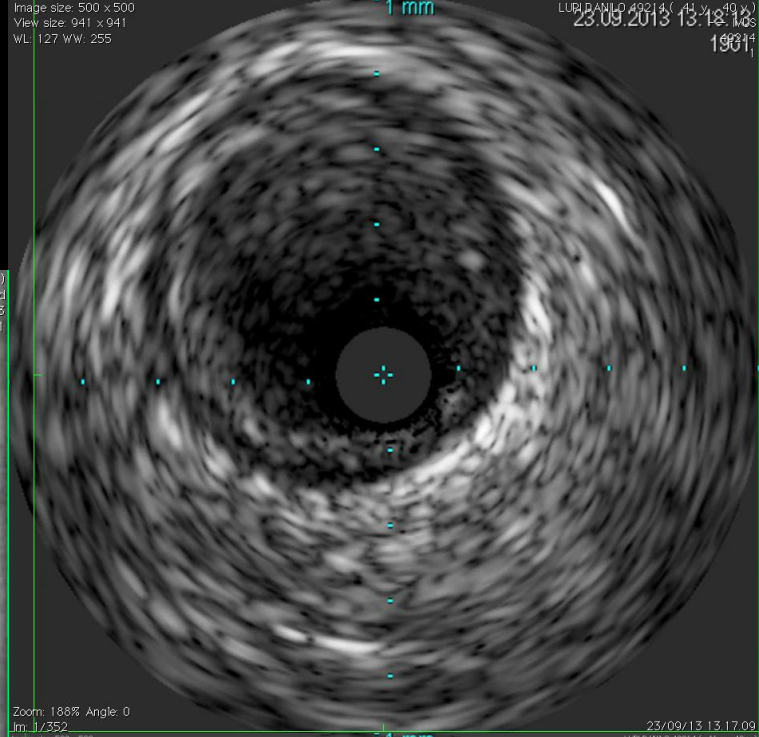
After 6 months of total well being, the patient complains rapidly worsening effort angina from CCS class I to III in a few weeks.

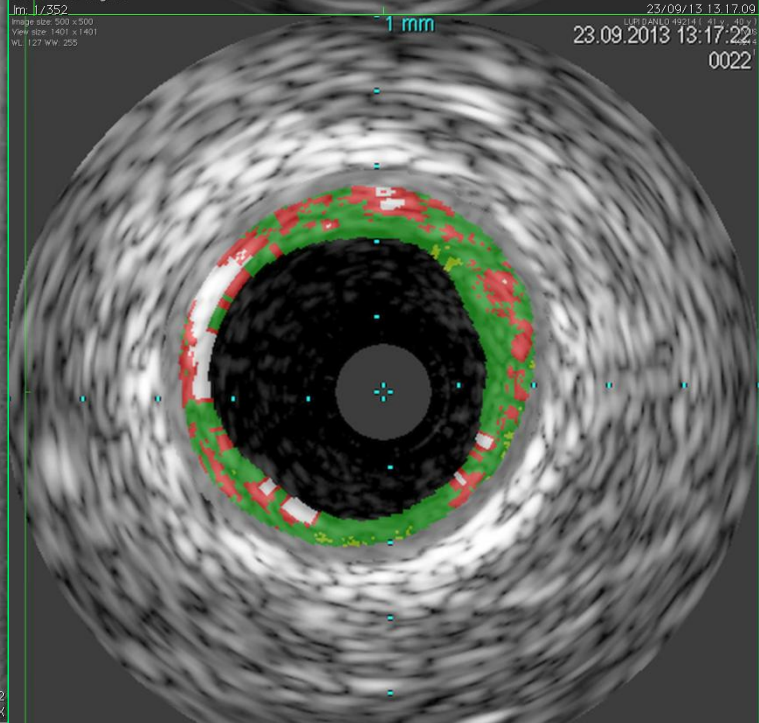
He came back to our Center for a control angio.

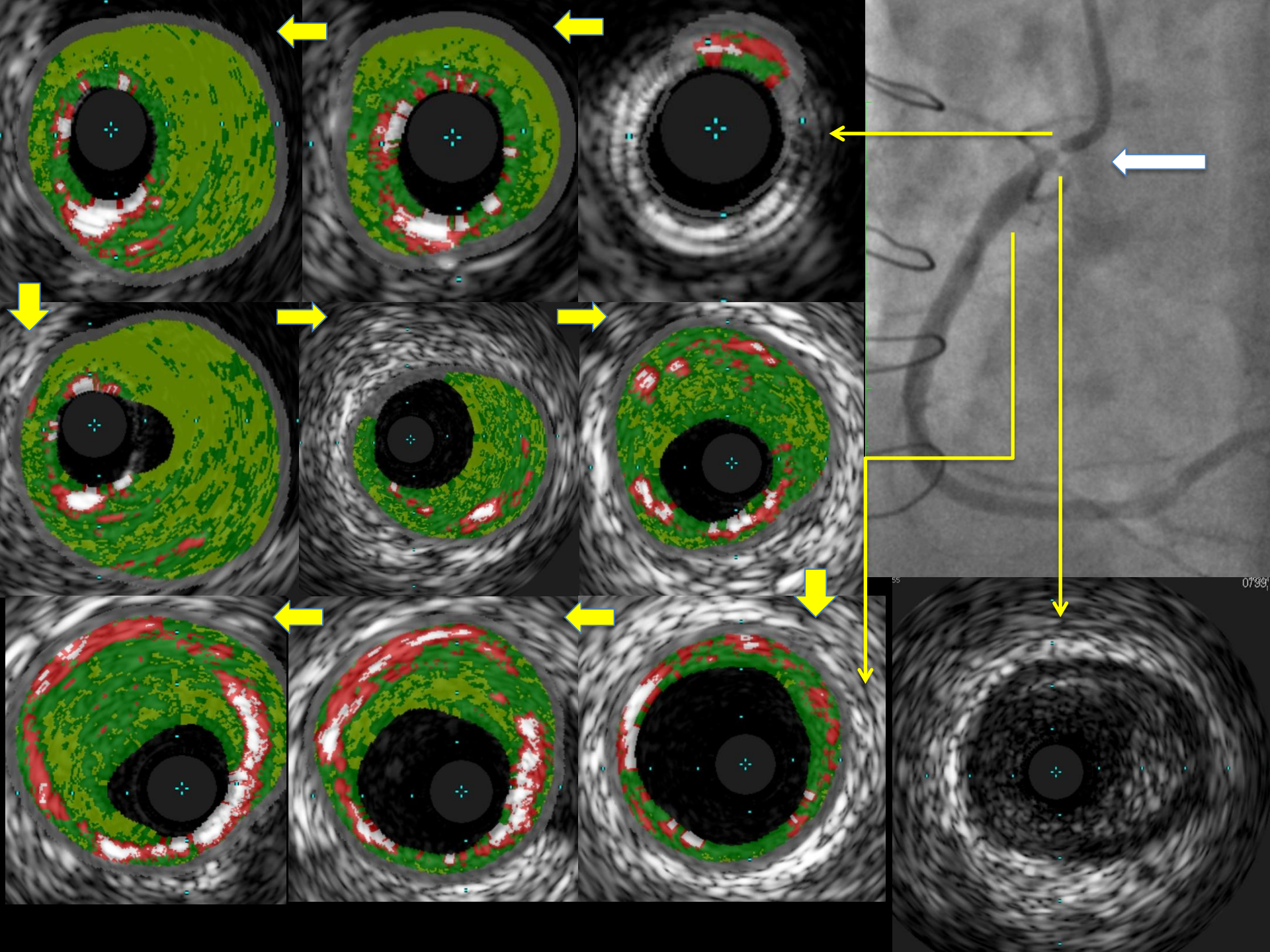
Follow-up angiogram of the left coronary artery

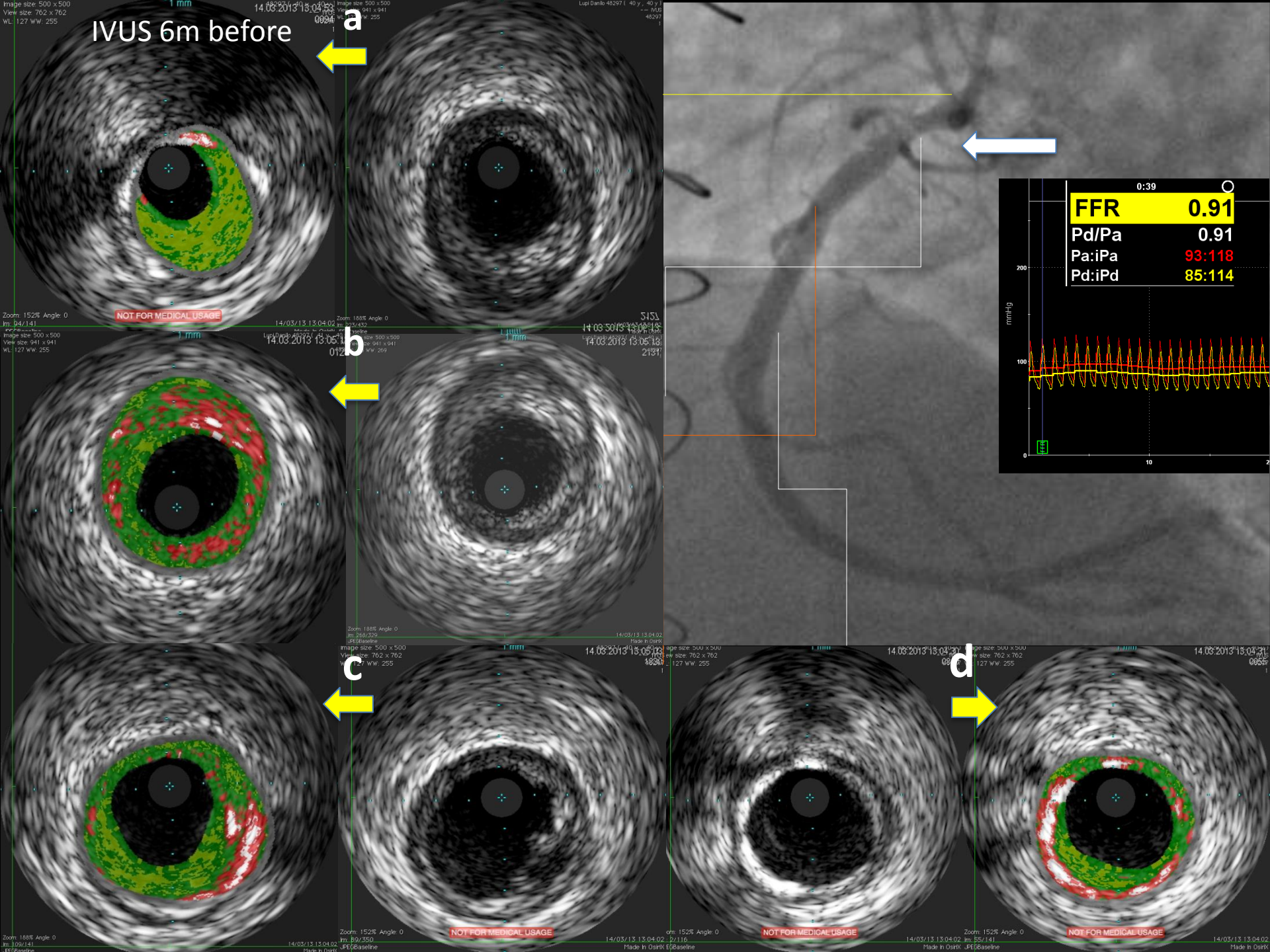
Right coronary artery at follow-up with IVUS and VH of the proximal segment (September 2013)










IVUS 6m before
a
b
c
d
FFR 0.91
Pd/Pa 0.91
Pa:iPa 93:118
Pd:iPd 85:114
mmHg
NOT FOR MEDICAL USAGE

Follow-up at 2 years is OK.

CAV represents a very aggressive form of ATH.

In this case, a non-significant lesion (FFR -) became sub-occlusive in less than 6 months.

The value of FFR in CAV needs validation.

My personal opinion on the hyperaemia-free method:

- Will facilitate penetration of physiology in the cath lab.
- Speeds the procedures and reduces cost of adenosine.
- May cause a slight increment (10%) in the number of treated lesions compared to FFR.
- May yield similar clinical outcomes compared to FFR.

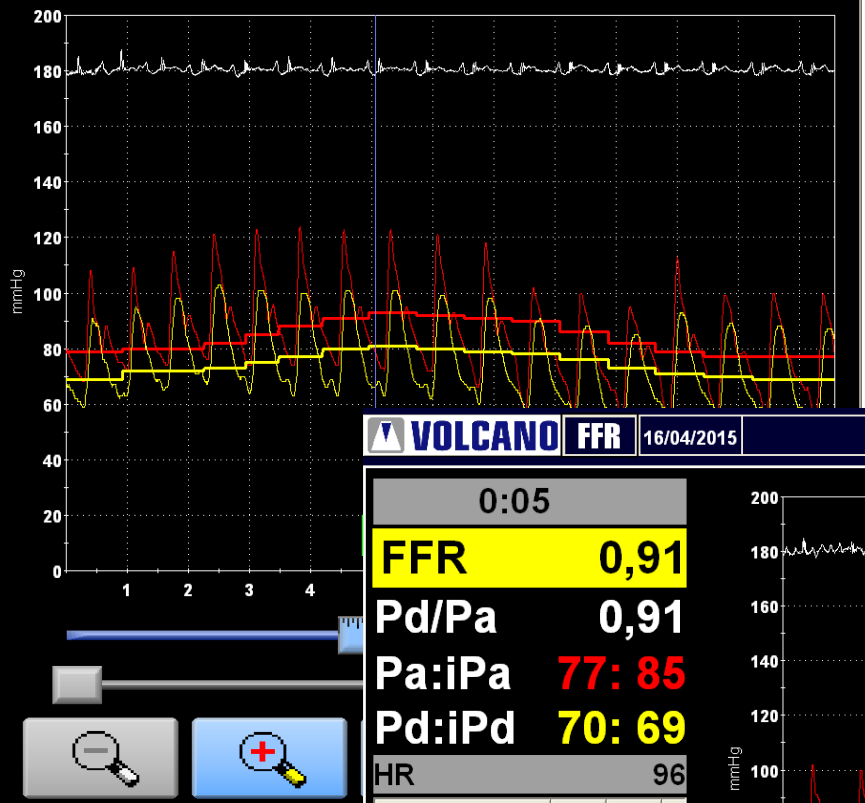
Thank you

VOLCANO | FFR | 16/04/2015 | AMA, PIERRE | 52334 TER | RCA | 4 Fotogrammi

0:05

FFR	0,87
Pd/Pa	0,87
Pa:iPa	93: 79
Pd:iPd	81: 66
HR	81

Elenco di esecu...	iFR	FFR
08.22:16		0,00
08.22:48		0,87
RCA		
08.23:33		0,91
RCA		



VOLCANO | FFR | 16/04/2015 | AMA, PIERRE | 52334 TER | RCA | 5 Fotogrammi

0:05

FFR	0,91
Pd/Pa	0,91
Pa:iPa	77: 85
Pd:iPd	70: 69
HR	96

Elenco di esecu...	iFR	FFR
08.22:16		0,00
08.22:48		0,87
RCA		
08.23:33		0,91
RCA		

Opzioni

Salva fotogramma

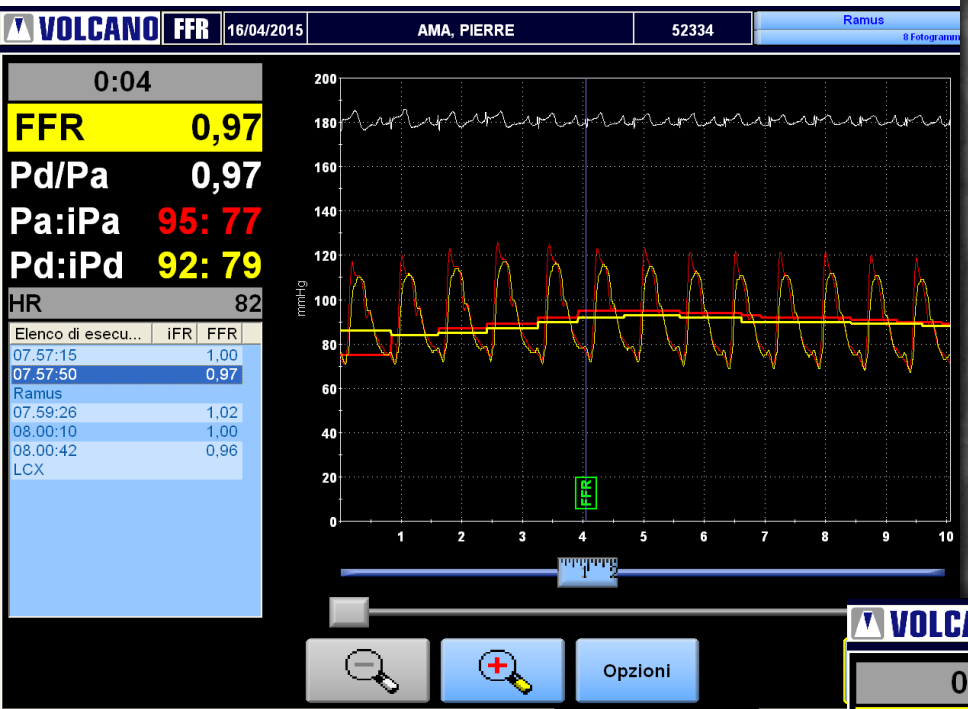
Seleziona modalità

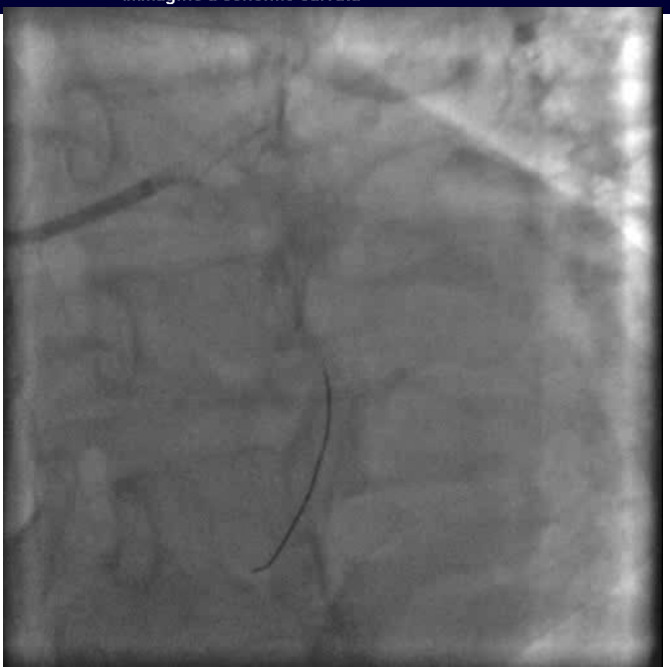
Impostazioni | Paziente | FFR | iFR

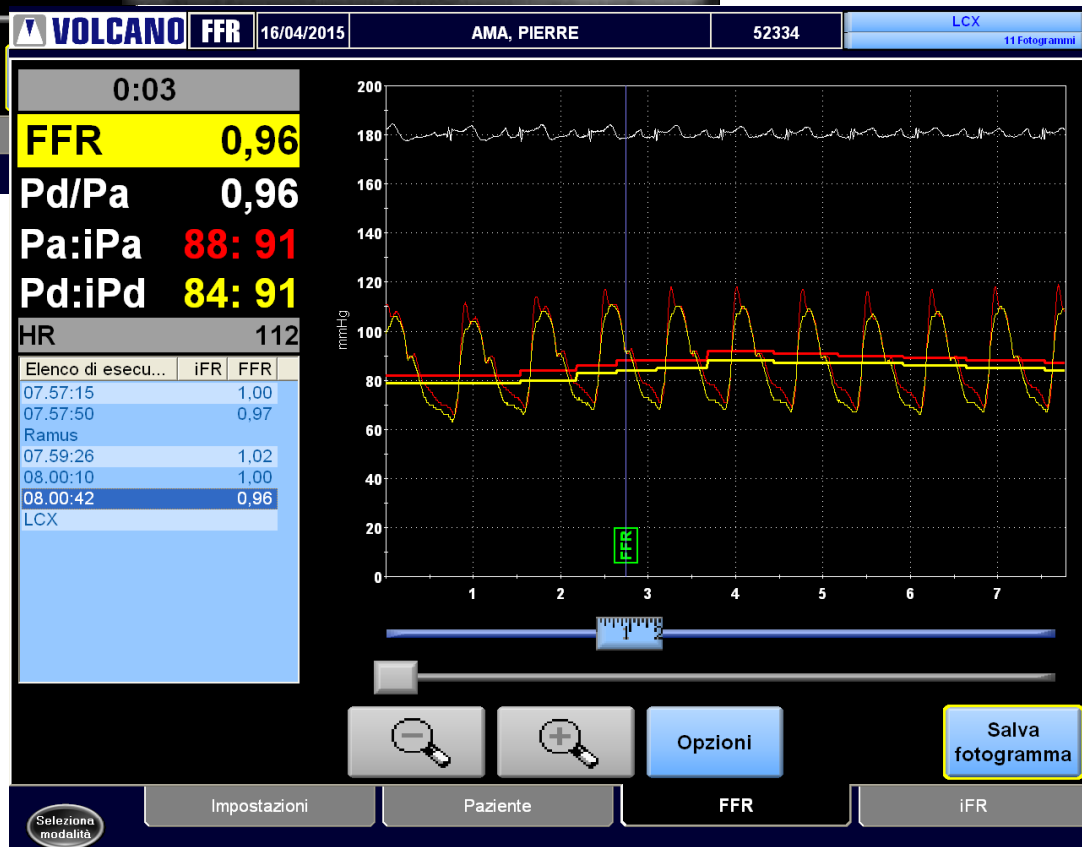
Seleziona modalità

Impostazioni | Paziente

Immagine a schermo salvata

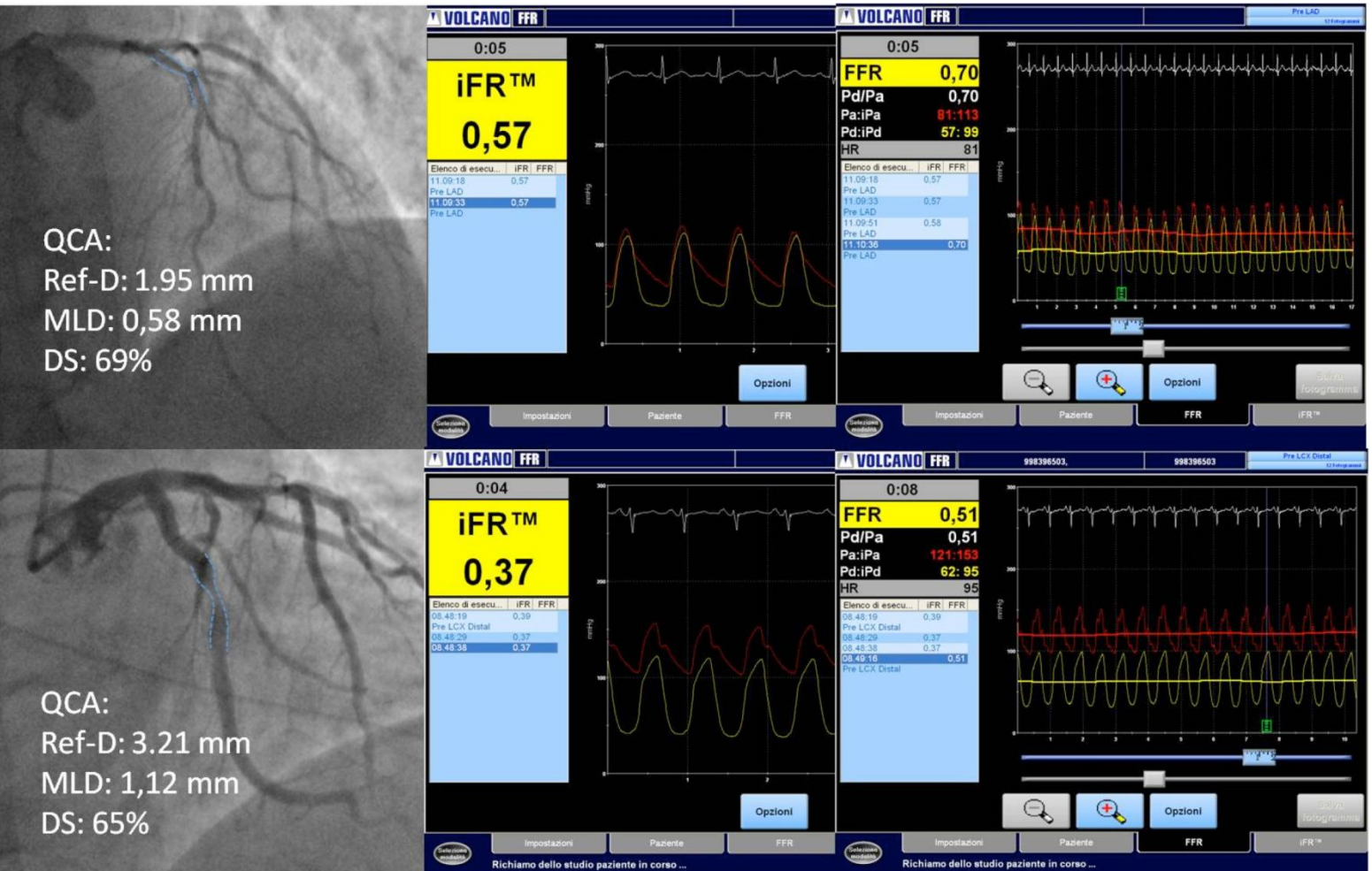

VOLCANO
FFR
16/04/2015
AMA, PIERRE
52334
Ramus
8 Fotogrammi
0:04
FFR 0,97
Pd/Pa 0,97
Pa:iPa 95: 77
Pd:iPd 92: 79
HR 82
Elenco di esecu... iFR FFR
07.57:15 1,00
07.57:50 0,97
Ramus
07.59:26 1,02
08.00:10 1,00
08.00:42 0,96
LCX
mmHg
FFR
Opzioni
Seleziona modalità
Impostazioni
Paziente
FFR
Immagine a schermo salvata




VOLCANO
FFR
16/04/2015
AMA, PIERRE
52334
LCX
11 Fotogrammi
0:03
FFR 0,96
Pd/Pa 0,96
Pa:iPa 88: 91
Pd:iPd 84: 91
HR 112
Elenco di esecu... iFR FFR
07.57:15 1,00
07.57:50 0,97
Ramus
07.59:26 1,02
08.00:10 1,00
08.00:42 0,96
LCX
mmHg
FFR
Opzioni
Salva fotogramma
Seleziona modalità
Impostazioni
Paziente
FFR
iFR

FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

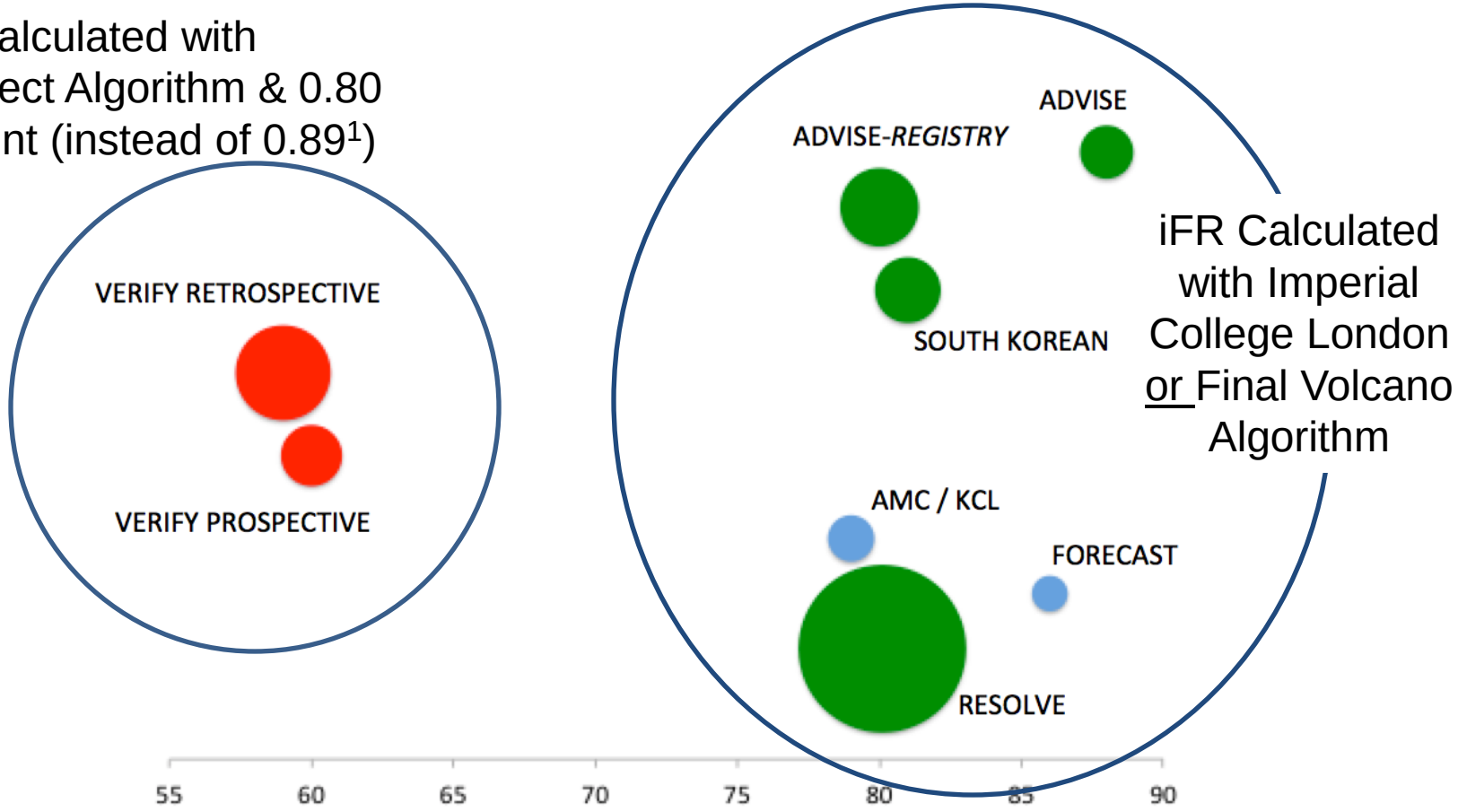
iFR-FFR comparison in daily practice: a single-center, prospective, online assessment



Impact on the numerical correlation of different values with the same meaning.

Algorithm is Critical for Accurate iFR® Calculation

iFR Calculated with Incorrect Algorithm & 0.80 cutpoint (instead of 0.89[1])



iFR Calculated with Imperial College London or Final Volcano Algorithm

iFR - FFR Classification Match[2]

1. An iFR cut-point of 0.89 matches best with an FFR ischemic cut-point of 0.80 with a specificity of 87.8% and sensitivity of 73.0%. (iFR Operator's Manual 505-0101.23)
2. Adapted from Sen S., et al. Reply: Is the instantaneous wave-free ratio equivalent to fractional flow reserve? J Am Coll Cardiol. 2013 Sep 3;62(10):943-5.

Objections of the iFR authors to VERIFY

VERIFY used an offline analysis tool that did not have the ECG trigger that iFR uses, and had a window that does not seem constant with the iFR window. In the published diagram the two waveforms are out of phase, and the wave-free window seems to creep into the upswing of the systolic portion of the next heartbeat. The possible consequences of this disagreement are unknown."

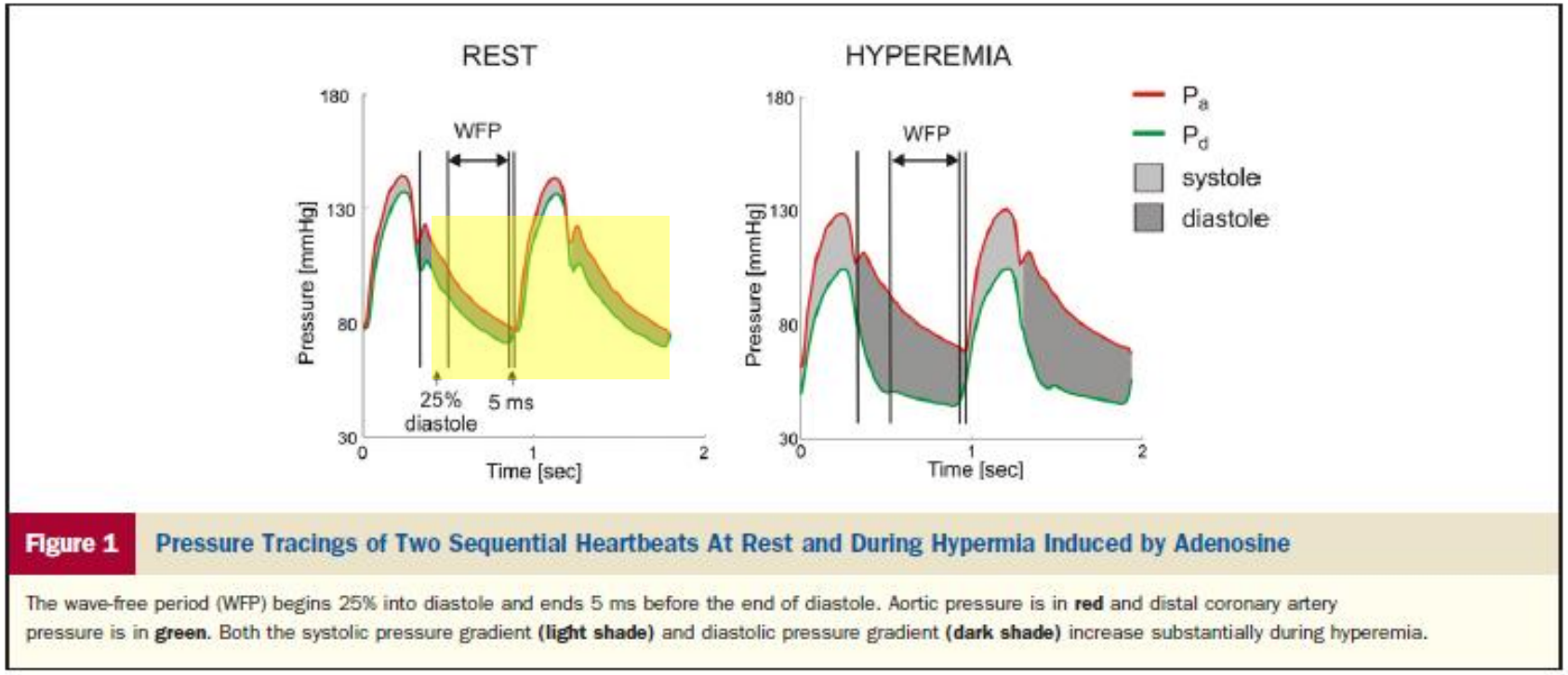


Figure 1 **Pressure Tracings of Two Sequential Heartbeats At Rest and During Hyperemia Induced by Adenosine**

The wave-free period (WFP) begins 25% into diastole and ends 5 ms before the end of diastole. Aortic pressure is in **red** and distal coronary artery pressure is in **green**. Both the systolic pressure gradient **(light shade)** and diastolic pressure gradient **(dark shade)** increase substantially during hyperemia.

Berry C, *et al.* VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice): A Multicenter Study in Consecutive Patients. J Am Coll Cardiol. 2013 Apr 2;61(13):1421-7.