How To Use Virtual Histology in Clinical Practice by Understanding Plaque Composition

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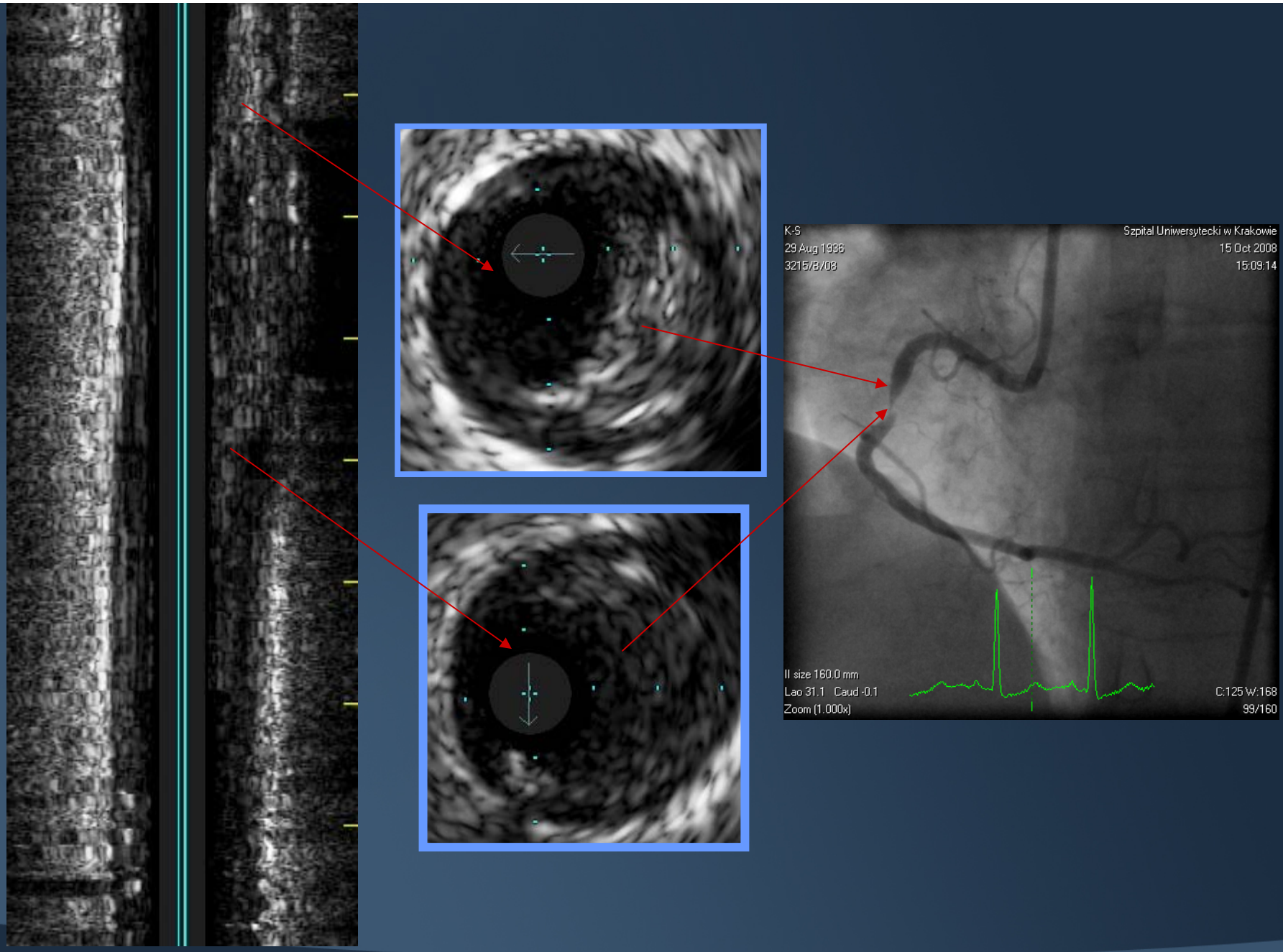
- PCI
  - Culprit of the culprit
  - Acute results
  - Complications
- Vulnerable plaque
- Limitations

- 72 year old female with diabetes and hypertension presented with 3 hours of chest and transient complete heart block
- Medication during transfer to hospital (40km) included aspirin 300mg, clopidogrel 600mg, heparin 400IU, abciximab (bolus).
- Chest pain resolved at the time of admission
- ECG showed ST elevation in II, III, and aVF and ST depression in I, aVL, and V2-V3



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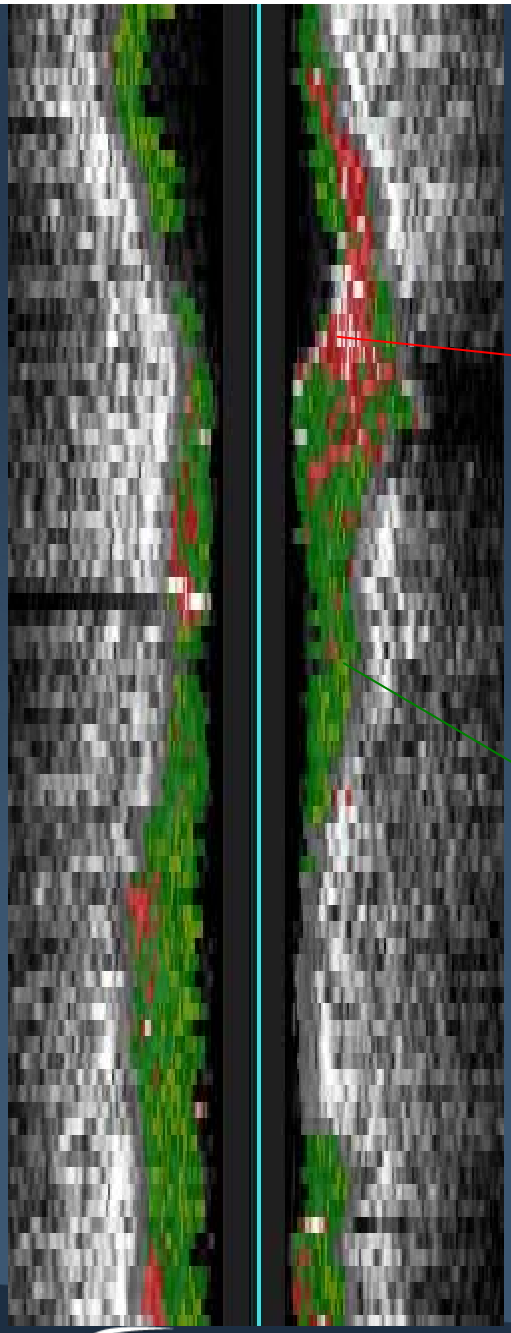
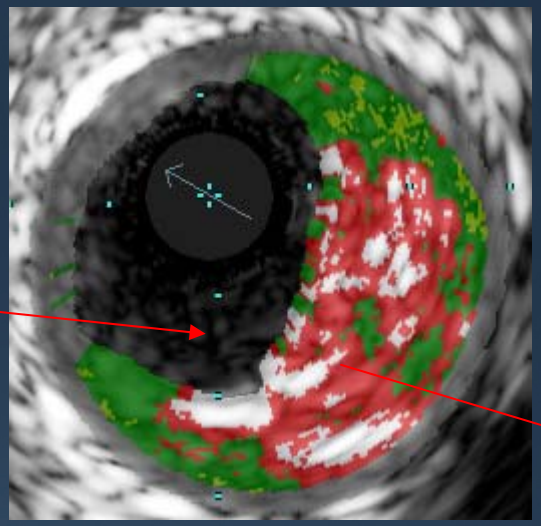
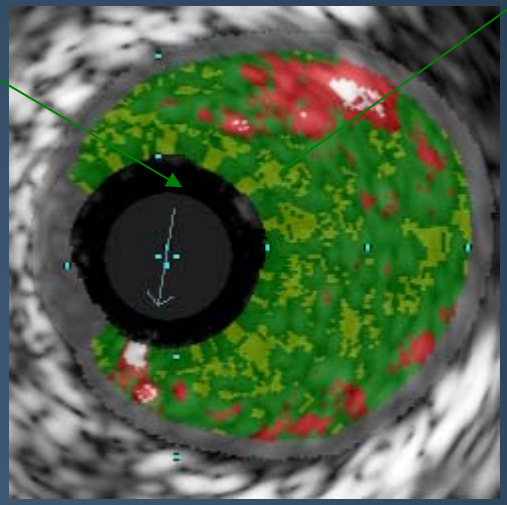
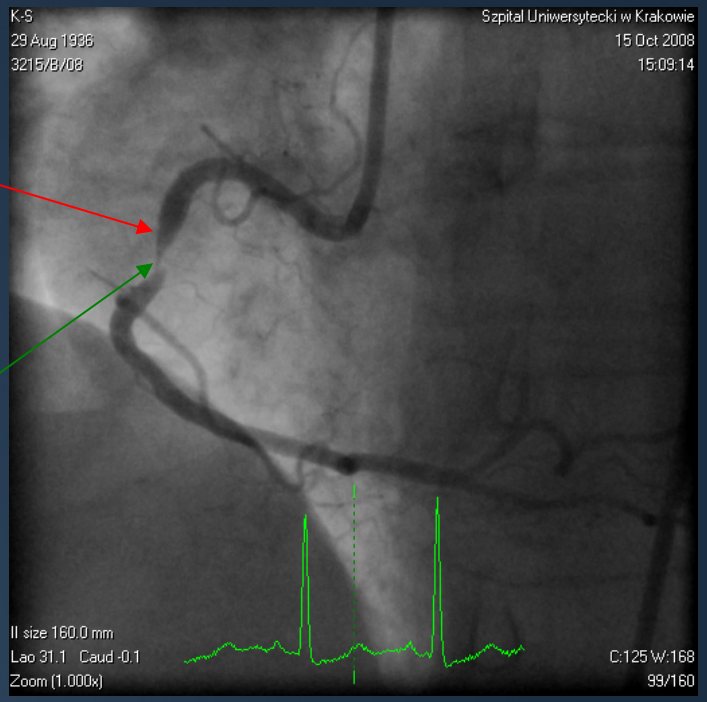




culprit of the culprit proximal to MLA



MLA



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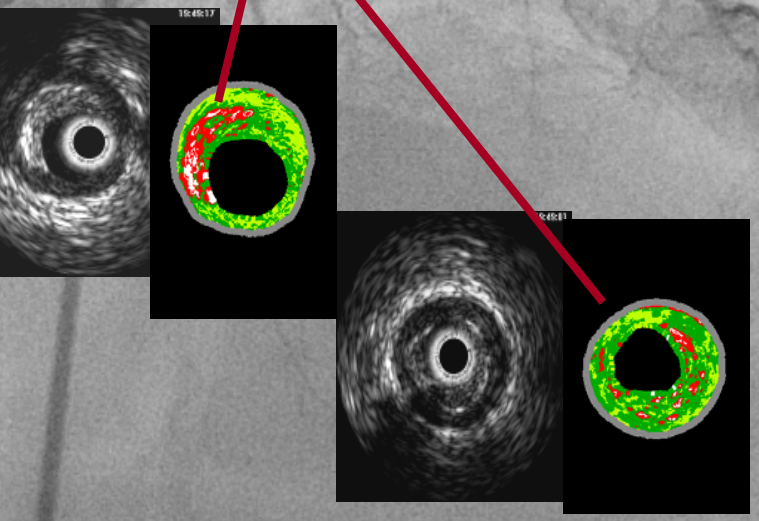
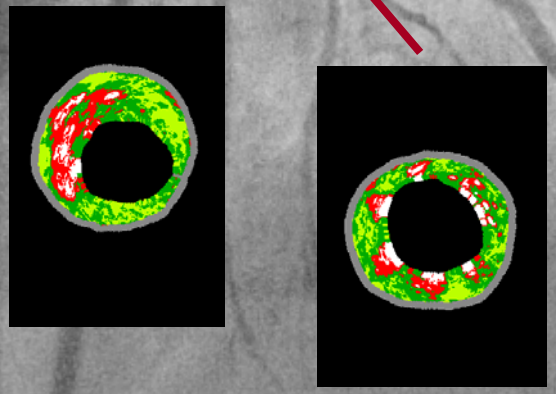
ACS; Baseline angiography pre thrombectomy

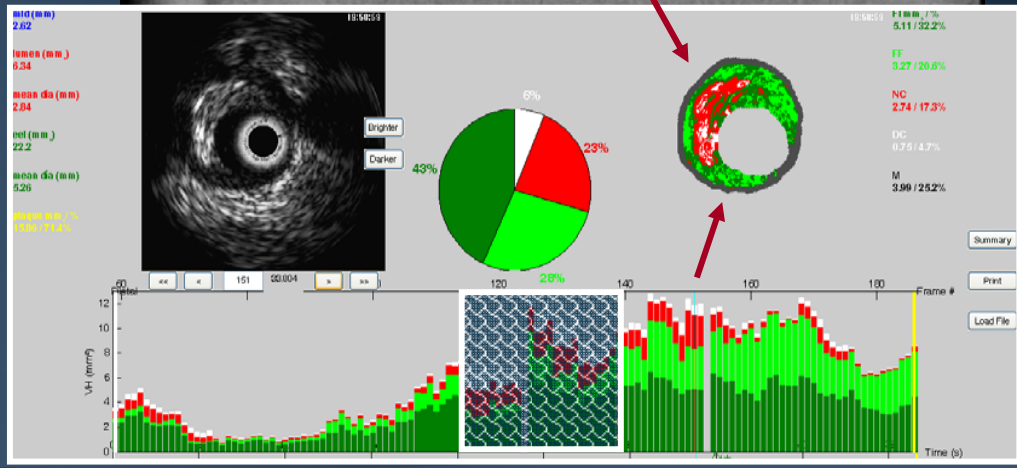


Post-thrombectomy
TIMI 3

Post stenting



Final result, the site of the plaque rupture, COC, was missed



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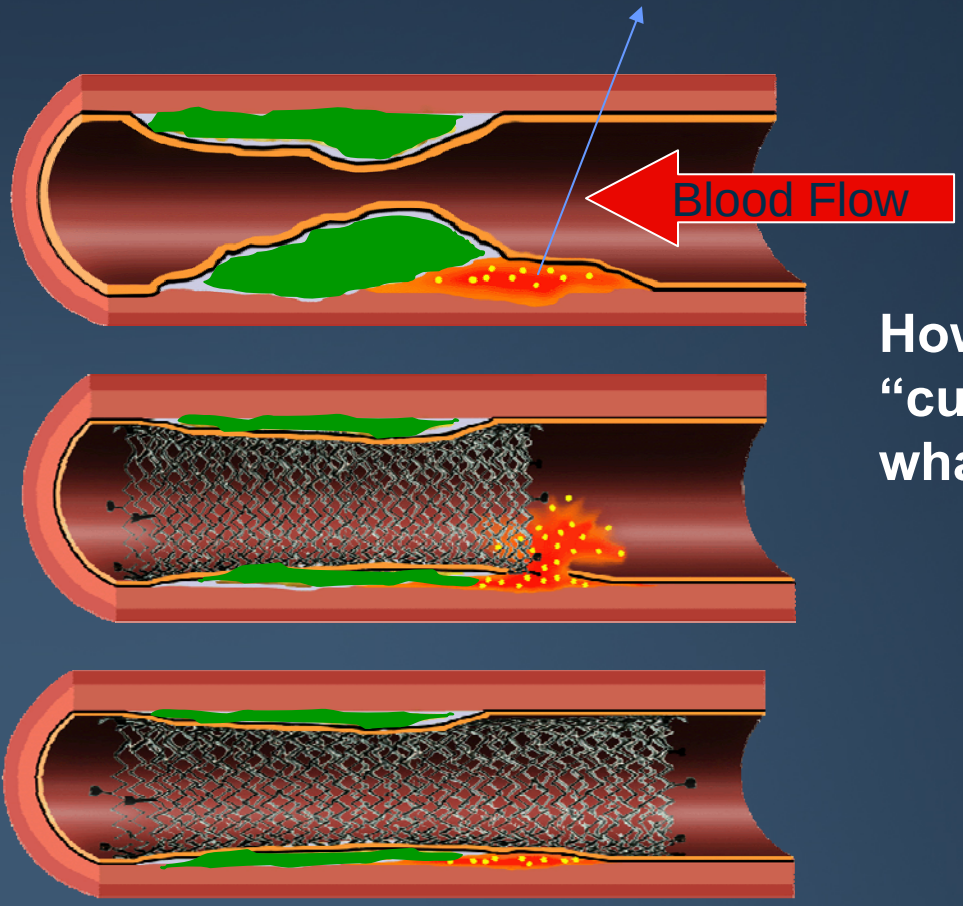
Possible Stent Positioning in Culprit Lesion PCI

NC, the “culprit of the culprit”



How often do we miss the “culprit of the culprit”? And what is the impact on

- Distal embolization
- Stent thrombosis
- Restenosis
- Plaque progression

444 ACS culprit lesions entirely imaged using post-stent VH-IVUS (The remaining patients were excluded because of incomplete imaging of stented lesion or unreliable pullback.)

TCFA behind stent (n=259)

No TCFA behind stent (n=185)

- No NC at all
- ThFA behind Stent
- Non-classifiable (Stent artifact)

TCFA behind stent with reference TCFA that was fully or partially uncovered (n=98)

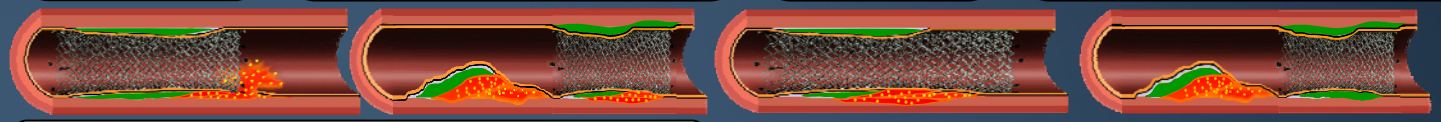
Edge TCFA partially uncovered (n=20)

TCFA behind stent with fully uncovered reference TCFA (n=78)

TCFA only behind stent (n=161)

No TCFA behind stent with fully uncovered reference TCFA (n=33)

No TCFA behind stent w/o reference TCFA (n=152)



NC protruding through stent (n=63)

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Tsujita et al, AHA 2008

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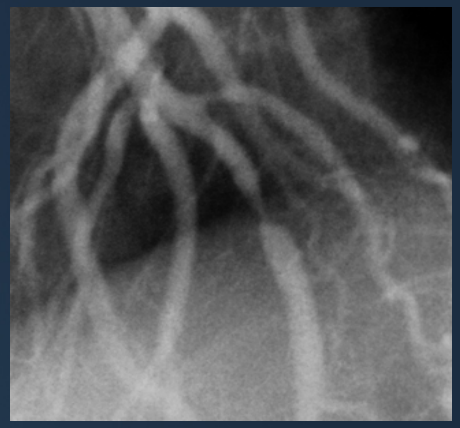
Predictors of DES Thrombosis & Restenosis

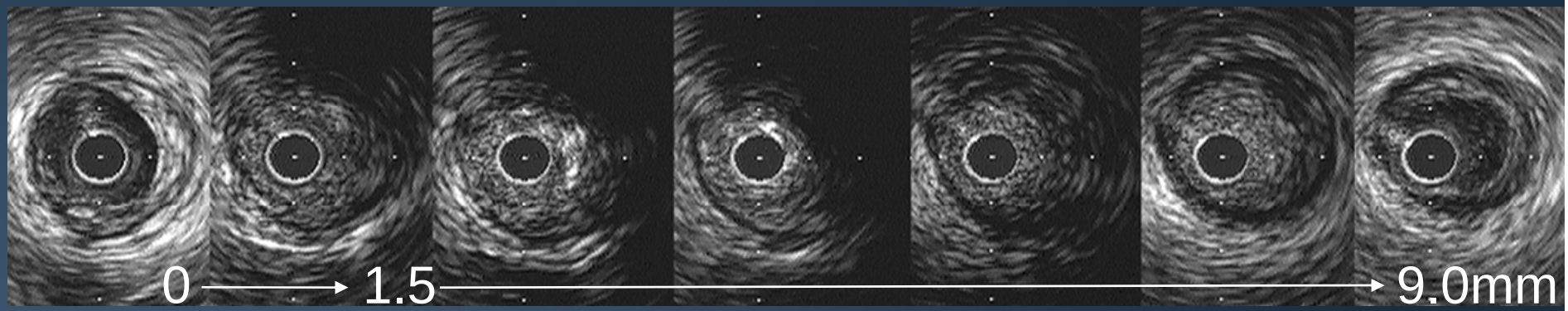
	DES Thrombosis	DES Restenosis
Underexpansion	•*Fujii et al. J Am Coll Cardiol 2005;45:995-8)* •*Okabe et al., Am J Cardiol. 2007;100:615-20* •*Liu et al. JACC Cardiovasc Interv. 2009;2:428-34* •*Choi et al. Circulation Cardiovascular Interventions (in press)*	•*Sonoda et al. J Am Coll Cardiol 2004;43:1959-63* •*Hong et al. Eur Heart J 2006;27:1305-10* •*Doi et al JACC Cardiovasc Interv. 2009;2:1269-75* •*Fujii et al. Circulation 2004;109:1085-1088*
Edge problems (geographic miss, secondary lesions, large plaque burden, etc)	•*Fujii et al. J Am Coll Cardiol 2005;45:995-8)* •*Okabe et al., Am J Cardiol. 2007;100:615-20* •*Liu et al. JACC Cardiovasc Interv. 2009;2:428-34* •*Choi et al. Circulation Cardiovascular Interventions (in press)*	•*Sakurai et al. Am J Cardiol 2005;96:1251-3* •*Liu et al.Am J Cardiol 2009;103:501-6* •*Costa et al, Am J Cardiol, 2008;101:1704-11*

VH-TCFAs were associated with a smaller MSA than non-VH-TCFAs: 5.8±1.8mm^2 vs 6.3mm^2

High Risk Plaque

Attenuated Plaque

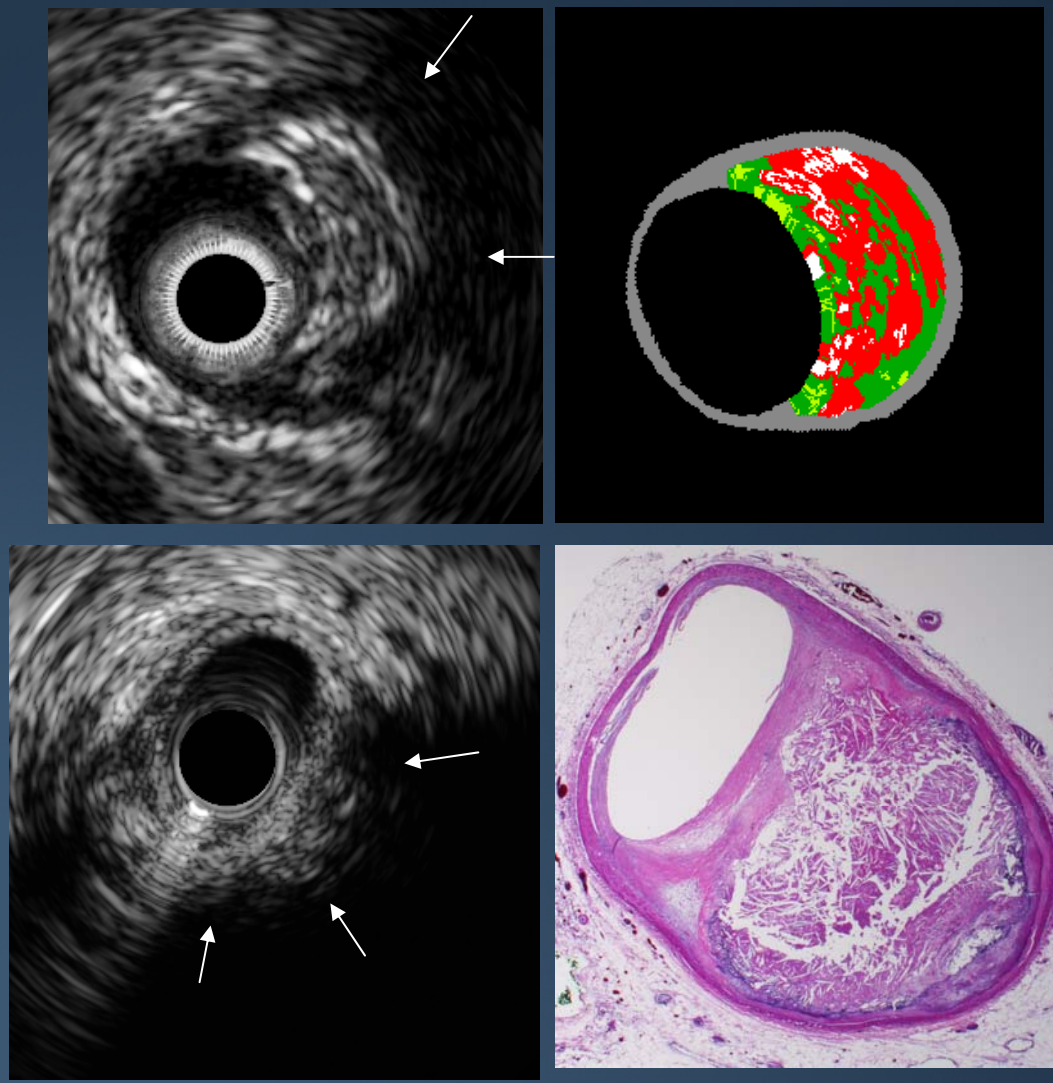




- Attenuated plaques were observed in 39.6% of STEMI, 17.6% of NSTEMI, and 0% of stable angina.
- Attenuate plaques were associated with more fibroatheromas and a larger necrotic core (on VH-IVUS).
- In ACS patients with attenuated plaques (1) the level of CRP was higher, (2) angiographic thrombus and initial coronary flow <TIMI 2 were more common, and (3) no-reflow or flow deterioration post-PCI were more common.

(Lee et al. JACC Cardiovasc Interv. 2009;2:65-72)
(Wu et al, Am J Cardiol 2010;105:48-53)

Attenuated Plaque & Necrotic Core



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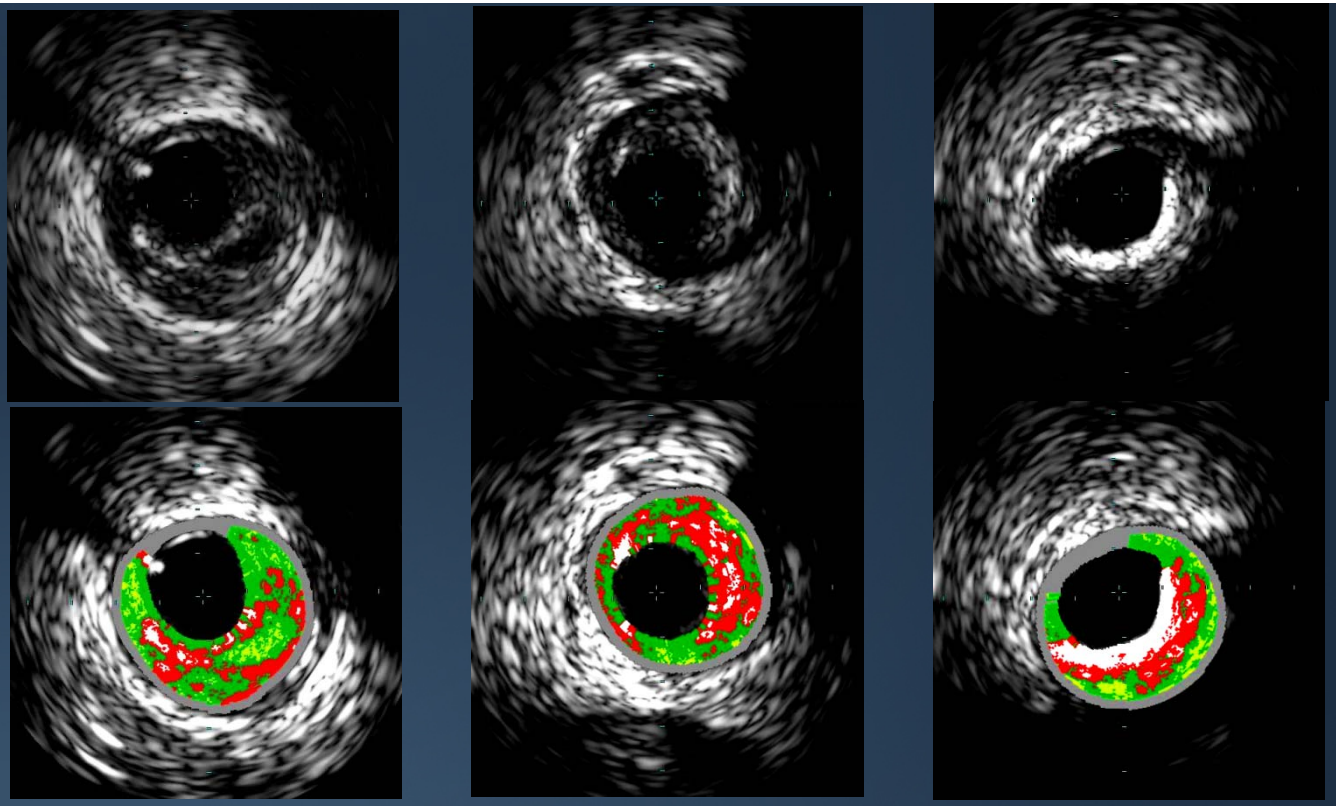

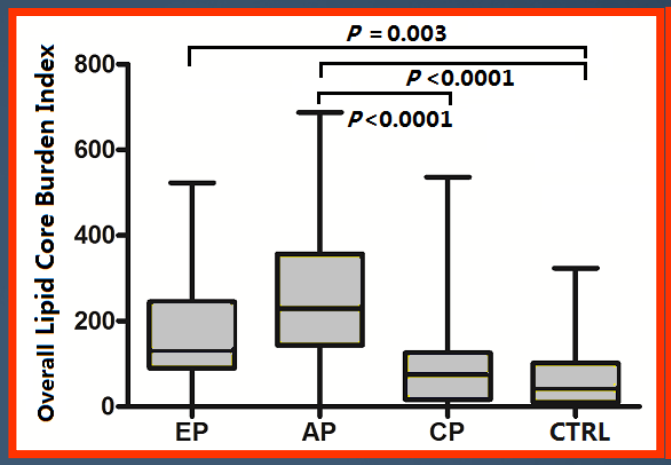

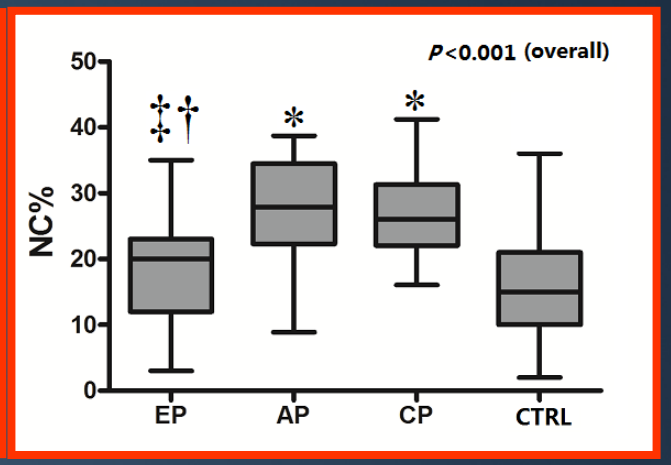

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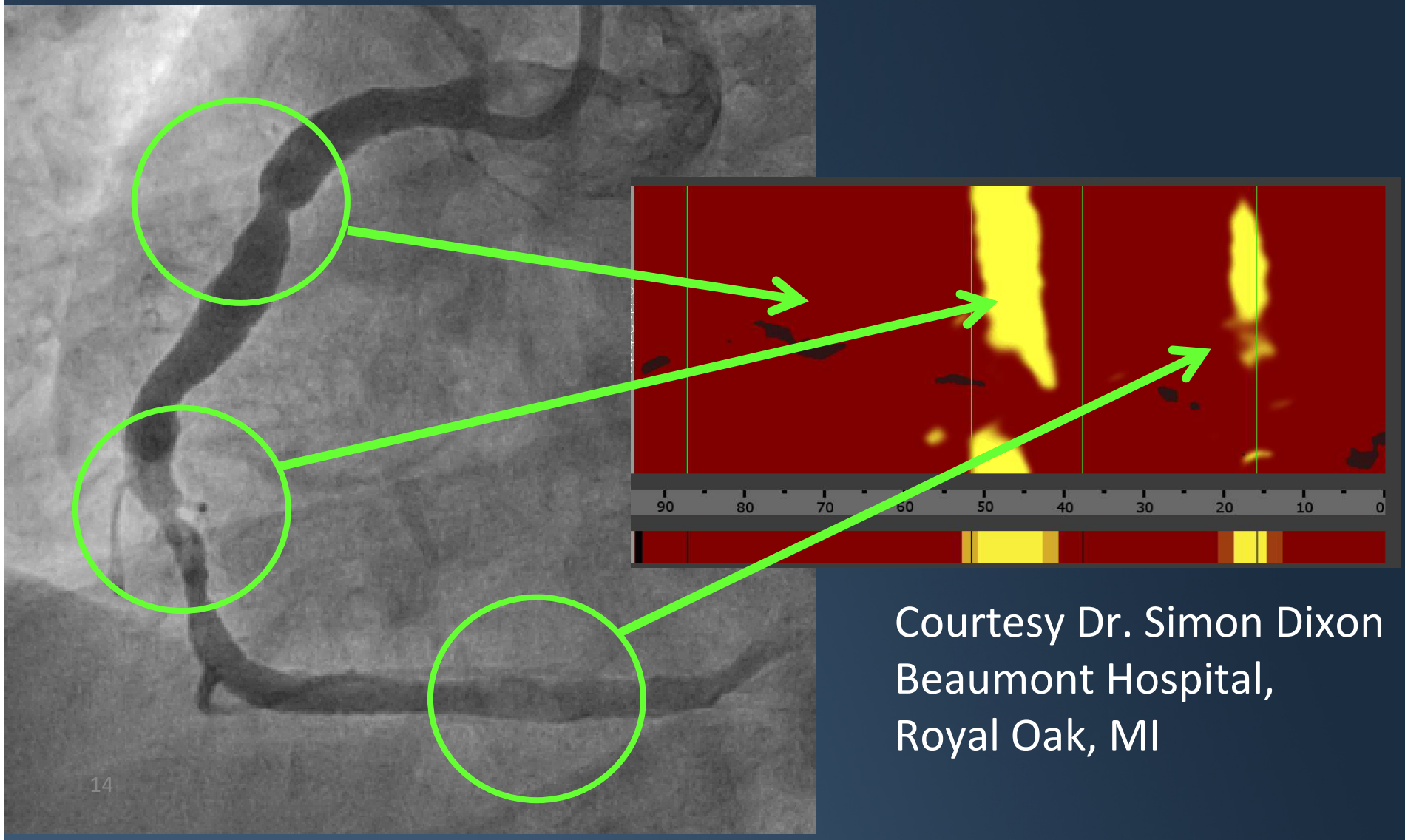
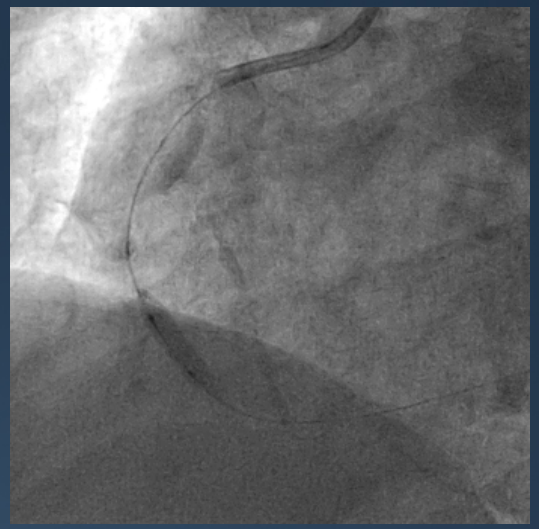
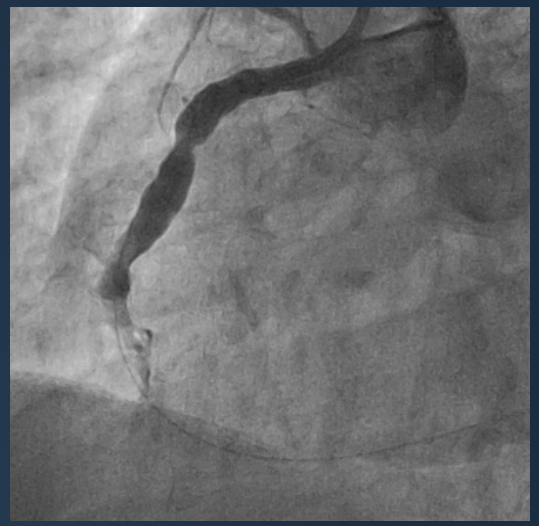


Courtesy Dr. Simon Dixon
Beaumont Hospital,
Royal Oak, MI

Goldstein et al, JACC Cardiovasc Imaging. 2009;2:1420-4





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Goldstein et al, JACC Cardiovasc Imaging. 2009;2:1420-4

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Numerous studies have shown a relationship between VH-IVUS plaque composition and post-PCI distal embolization

vs Nectoric Core

- Kawaguchi et al. J Am Coll Cardiol. 2007;50:1641-6
  - ST re-elevation in 71 pts with STEMI
- Kawamoto et al. J Am Coll Cardiol. 2007;50:1635-40
  - Doppler FloWire high intensity transit signals in 44 pts undergoing elective stenting resulting in poor recovery of CVFR
- Park et al. VH Summit 2007 (unpublished)
  - Largest NC independent predictor of CK-MB release (n=332)
- Hong et al. J Am Coll Cardiol Img, 2009;2:458-468
  - Troponin post elective stenting in 80 pts (29 stable and 51 unstable angina)
- Bose et al. Basic Res Cardiol 2008;103:587-97
  - CK and TnI in 55 pts undergoing direct stenting. Patients in the 4th quartile of NC volume had a particularly high increase in biomarkers.
- Higashikuni et al. Circ J 2008; 72: 1235-41
  - No reflow in 49 pts with ACS undergoing PCI
- Hong et al. Eur Heart J, in press
  - No reflow in 190 pts with ACS undergoing stenting

vs Fibrotic or Fibrofatty Plaque

- Bae et al. Heart. 2008;94:1559-64.
  - Multivariate analysis revealed that fibrofatty volume over the entire lesion length was the only independent predictor for slow flow during primary PCI in 57 pts with STEMI
- Nakamura et al. J Interv Cardiol. 2007;20:335-9
  - “Marble"-like image, mainly consisting of fibro-fatty and fibrous plaque was associated with angiographic no-reflow in 50 STEMI pts undergoing primary PCI

The PROSPECT Trial
3-vessel imaging post PCI

Culprit artery, followed by non-culprit arteries

Angiography (QCA of entire coronary tree)

IVUS

Virtual histology

Palpography (n=~350)

Proximal 6-8 cm of each coronary artery

Meds rec
Aspirin
Plavix 1yr
Statin
Repeat biomarkers
@ 30 days, 6 months

F/U: 1 mo, 6 mo, 1 yr, 2 yr, ±3-5 yrs

MSCT Substudy
N=50-100

Repeat imaging in pts with events

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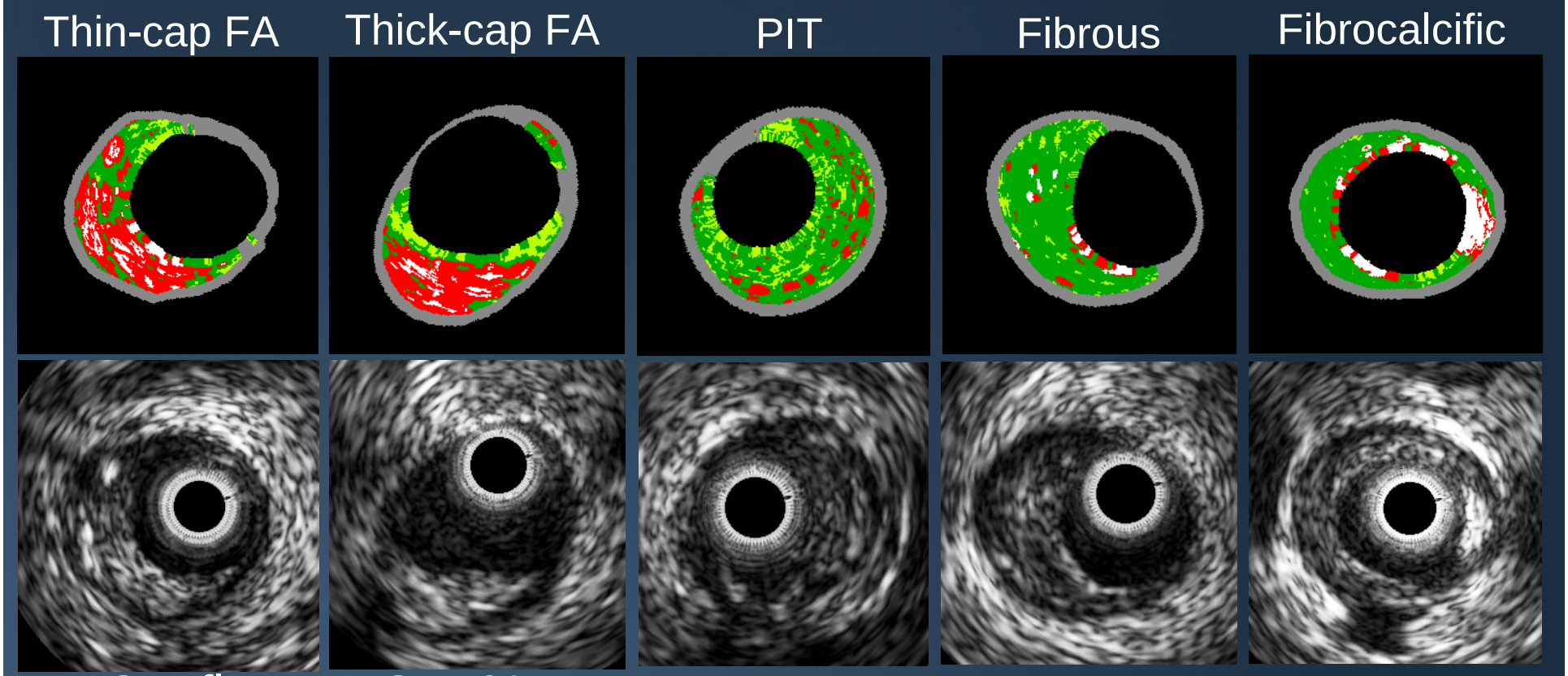
Pathological Atherosclerosis Classification

Terms for Atherosclerotic Lesions in Histological Classification		Other Terms for the Same Lesions Often Based on Appearance to the Unaided Eye	
Type I lesion	Initial lesion	Fatty dot or streak	Early lesion
Type II lesion			
IIa	Progression-prone type II lesion		
IIb	Progression-resistant type II lesion		
Type III lesion	Intermediate lesion (preatheroma)		
Type IV lesion	Atheroma	Atheromatous plaque, fibrolipid plaque, fibrousplaque, plaque	Advanced lesions, raised lesions
Va	Fibroatheroma (type V lesion)		
Vb	Calcific lesion (type VII lesion)	Calcified plaque	
Vc	Fibrotic lesion (type VIII)	Fibrous plaque	
Type VI lesion	Lesion with surface defect and/or hematoma/hemorrhage and/or thrombotic deposit	Complicated lesion, complicated plaque	

Virmani R et al. ATVB 2000;20:1262-75.

PROSPECT VH-IVUS Classification

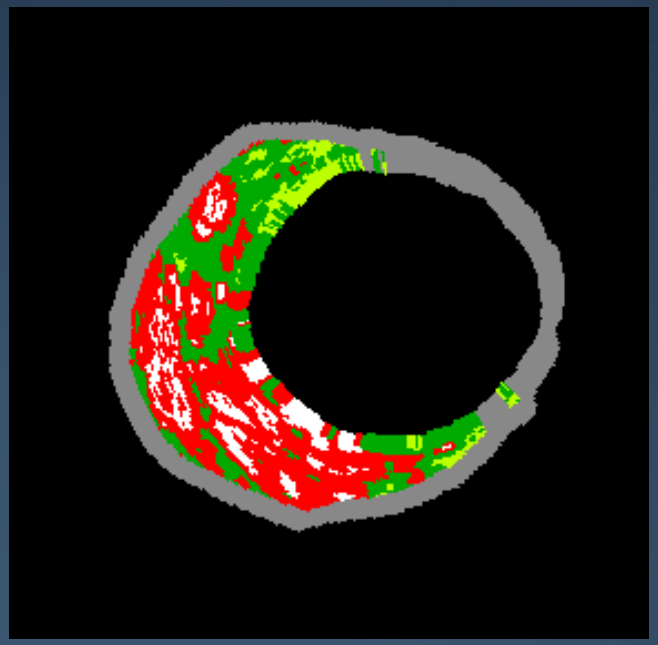


Confluent NC>10%

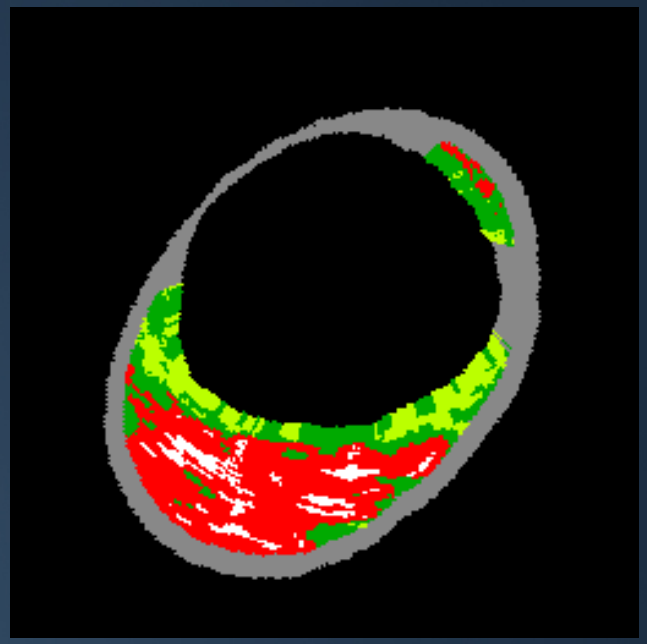
30° NC abutting the lumen in
3 consecutive frames
(=1.5mm in length)

Because of the resolution of IVUS, diagnosis of a thin fibrous cap is inferred by the contact of necrotic core with the lumen – regardless of the technology

Thin Cap



Thick Cap

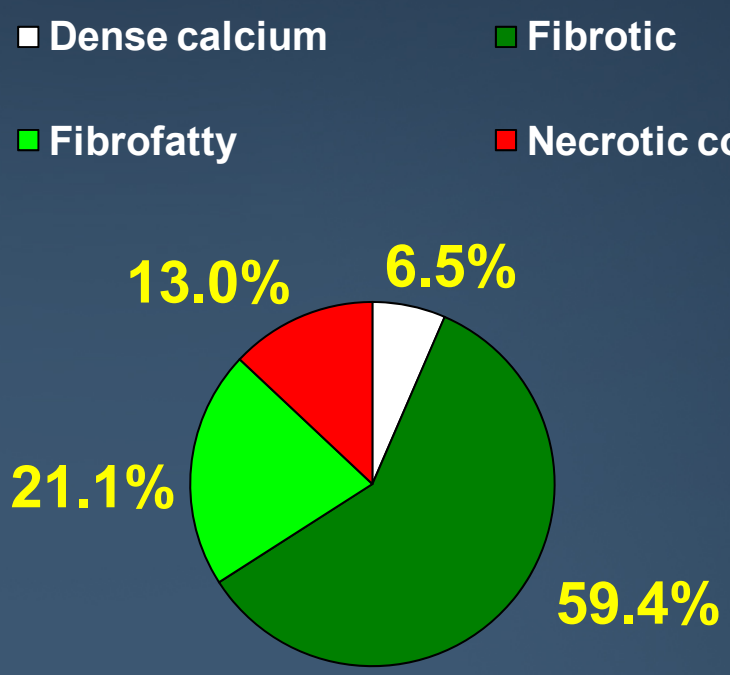


- Pathologic thin fibrous cap typical of TCFA is <65 μ
- However, all fibrous caps <200 μ will abut the lumen on VH-IVUS analysis

PROSPECT: Imaging Summary

Virtual histology (N=2811 lesions in 611 pts)

- Mean plaque composition-



Plaque subtype	N=2811
Fibrotic	2.5%
Fibrocalcific	1.2%
PIT	35.9%
Fibroatheroma	57.4%
- Thick cap	36.2%
- VH-TCFA	18.9%
- Single, - Ca	5.2%
- Single, + Ca	0.5%
- Multiple, - Ca	9.5%
- Multiple, + Ca	6.1%

Independent predictors of patient level events by Cox Proportional Hazards regression

Variable	HR [95% CI]	P value
Insulin dependent diabetes	3.32 [1.43, 7.72]	0.005
Prior PCI	2.03 [1.15, 3.59]	0.02

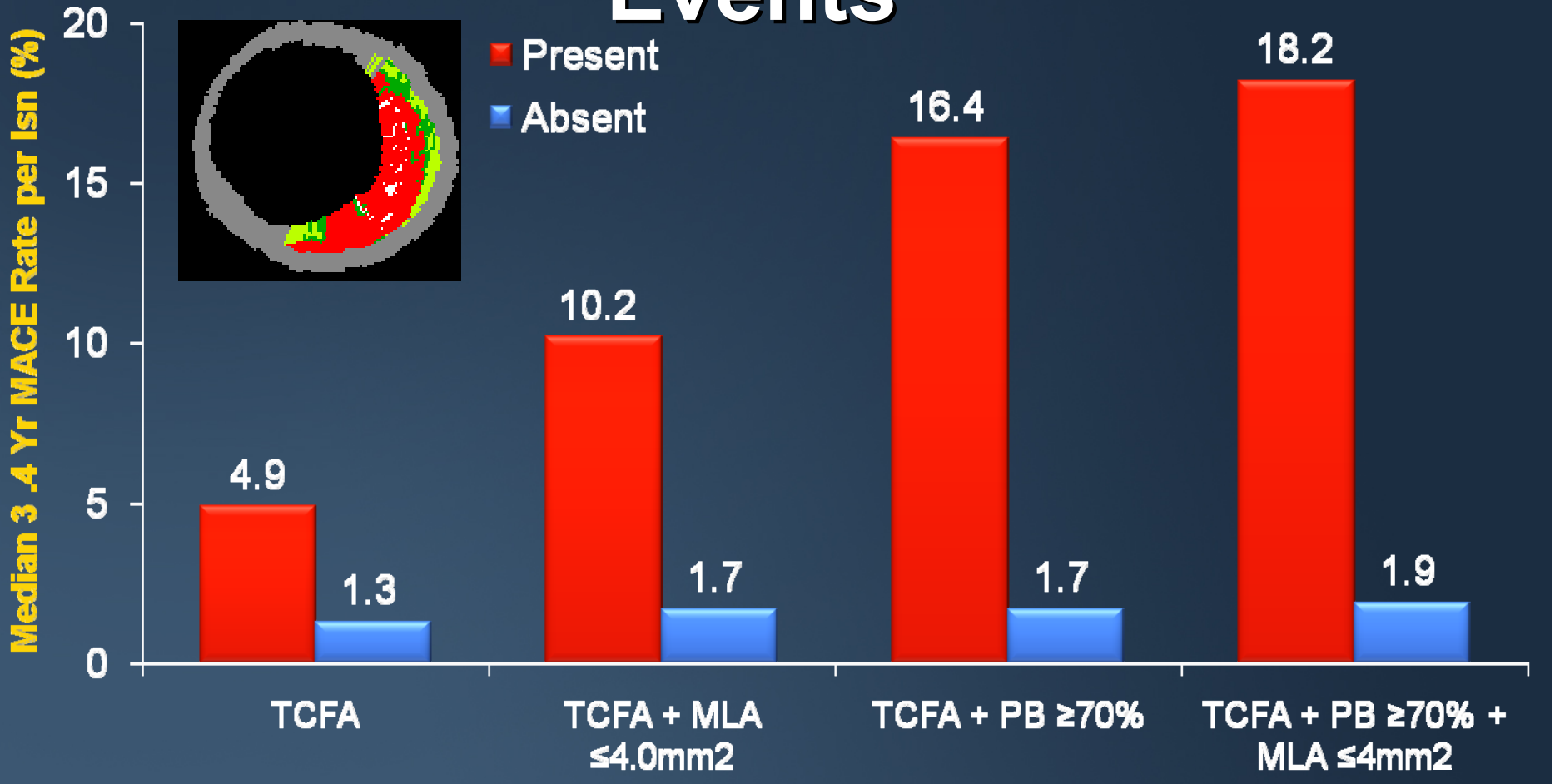
Variables entered into the model: age, gender, hypertension, insulin dependent diabetes, prior PCI, CRP at baseline, family history

Independent predictors of lesion level events by Cox Proportional Hazards regression

Variable	HR [95% CI]	P value
$PB_{MLA} \geq 70\%$	5.03 [2.51, 10.11]	<0.0001
VH-TCFA	3.35 [1.77, 6.36]	0.0002
MLA ≤ 4.0 mm^2	3.21 [1.61, 6.42]	0.001

Variables entered into the model: minimal luminal area (MLA) ≤ 4.0 mm^2; plaque burden at the MLA (PB_{MLA}) $\geq 70\%$; external elastic membrane at the MLA (EEM_{MLA}) <median (14.1 mm^2); lesion length $\geq$median (11.2 mm); distance from ostium to MLA $\geq$median (30.4 mm); remodeling index $\geq$median (0.94); VH-TCFA.

VH-TCFA and Non Culprit Lesion Events



	TCFA	TCFA + MLA ≤4.0mm2	TCFA + PB ≥70%	TCFA + PB ≥70% + MLA ≤4mm2
Lesion HR	3.90 (2.25, 6.76)	6.55 (3.43, 12.51)	10.83 (5.55, 21.10)	11.05 (4.39, 27.82)
P value	<0.0001	<0.0001	<0.0001	<0.0001
Prevalence*	46.7%	15.9%	10.1%	4.2%

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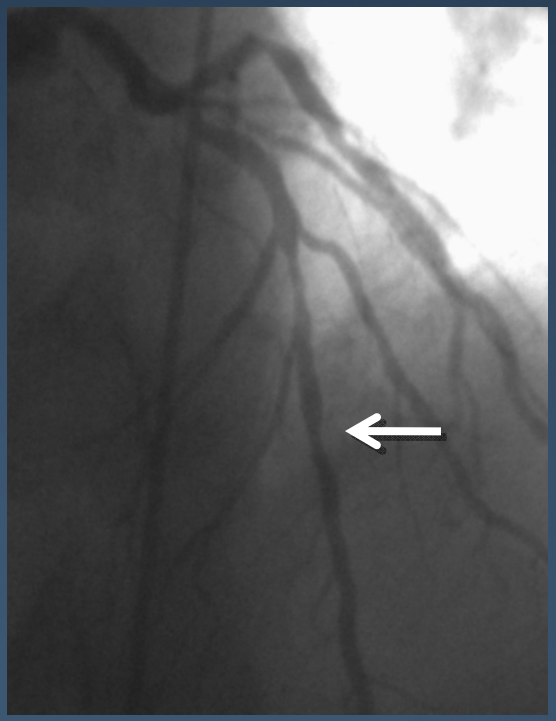
PROSPECT 27731-003: 58 yo♂

3/15/05: NSTEMI, PCI of MRCA

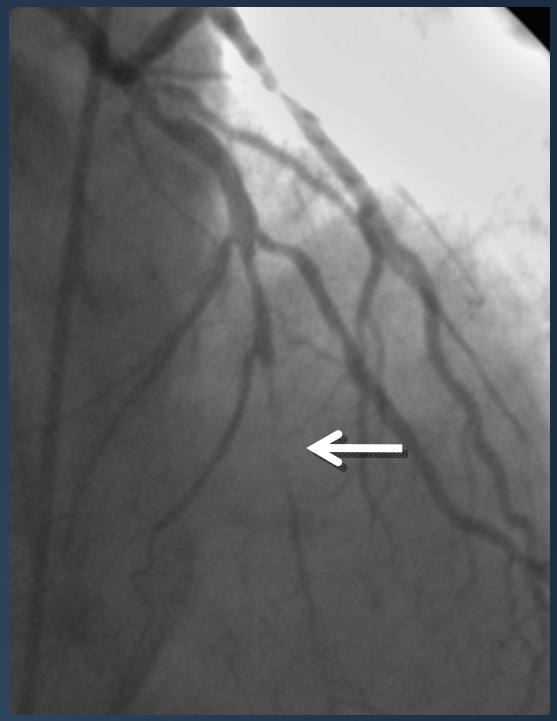
3/23/06 (1 year): Unstable angina attributed to LAD

Index 3/15/05



QCA MLAD DS 31.1%

Event 3/23/06



QCA MLAD DS 100%

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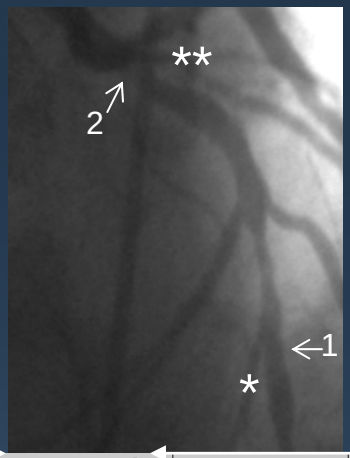
PROSPECT 27731-003: Index 3/15/05

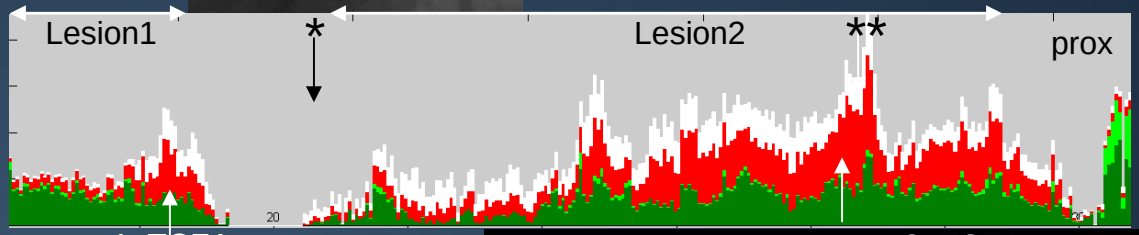


Baseline MLAD

QCA: DS 31.1%

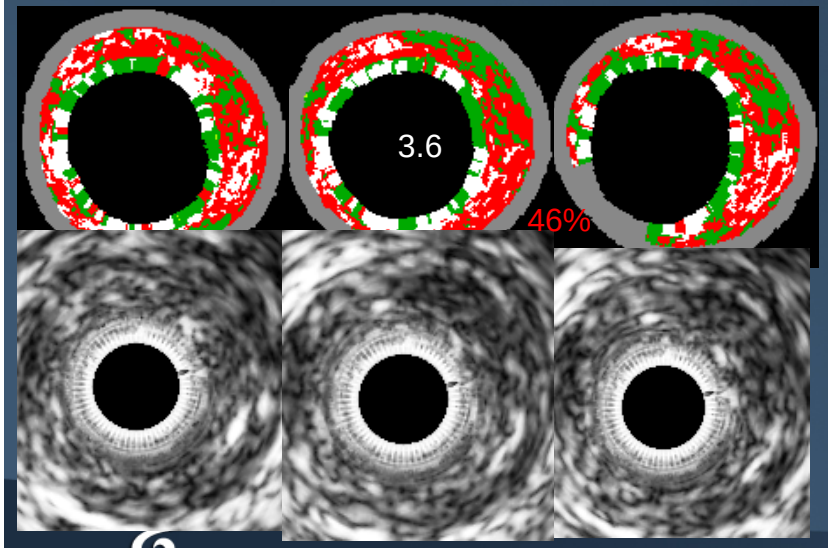
IVUS: MLA 3.6 mm^2

VH: TCFA



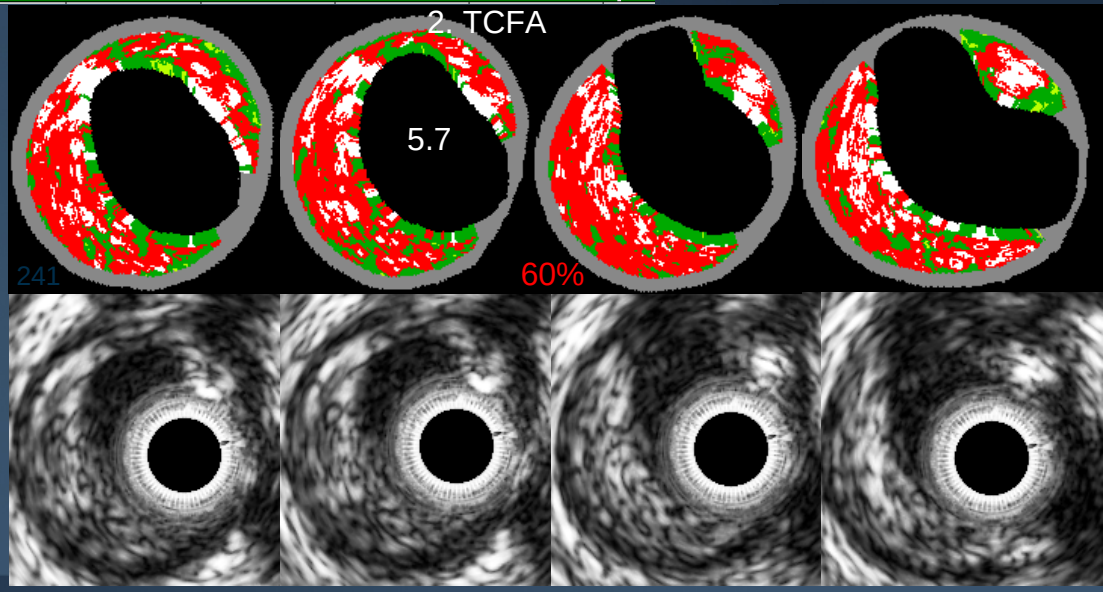
MLAD

1. TCFA



PLAD

2. TCFA



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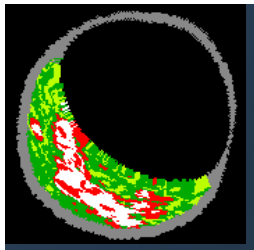


PROSPECT: Imaging Summary

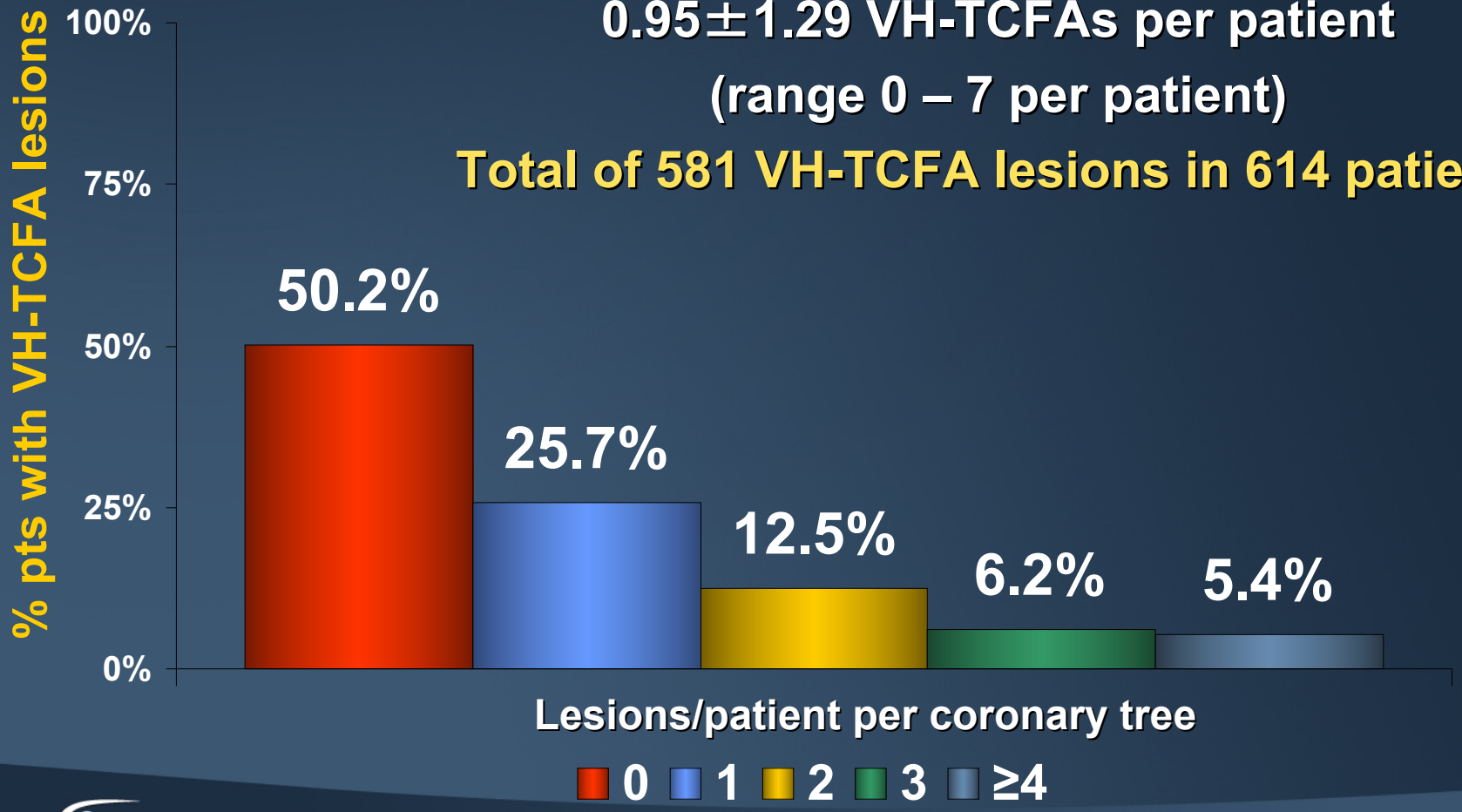
Per patient incidence of VH-TCFAs

49.8% of patients have ≥1 VH-TCFA

0.95±1.29 VH-TCFAs per patient

(range 0 – 7 per patient)

Total of 581 VH-TCFA lesions in 614 patients



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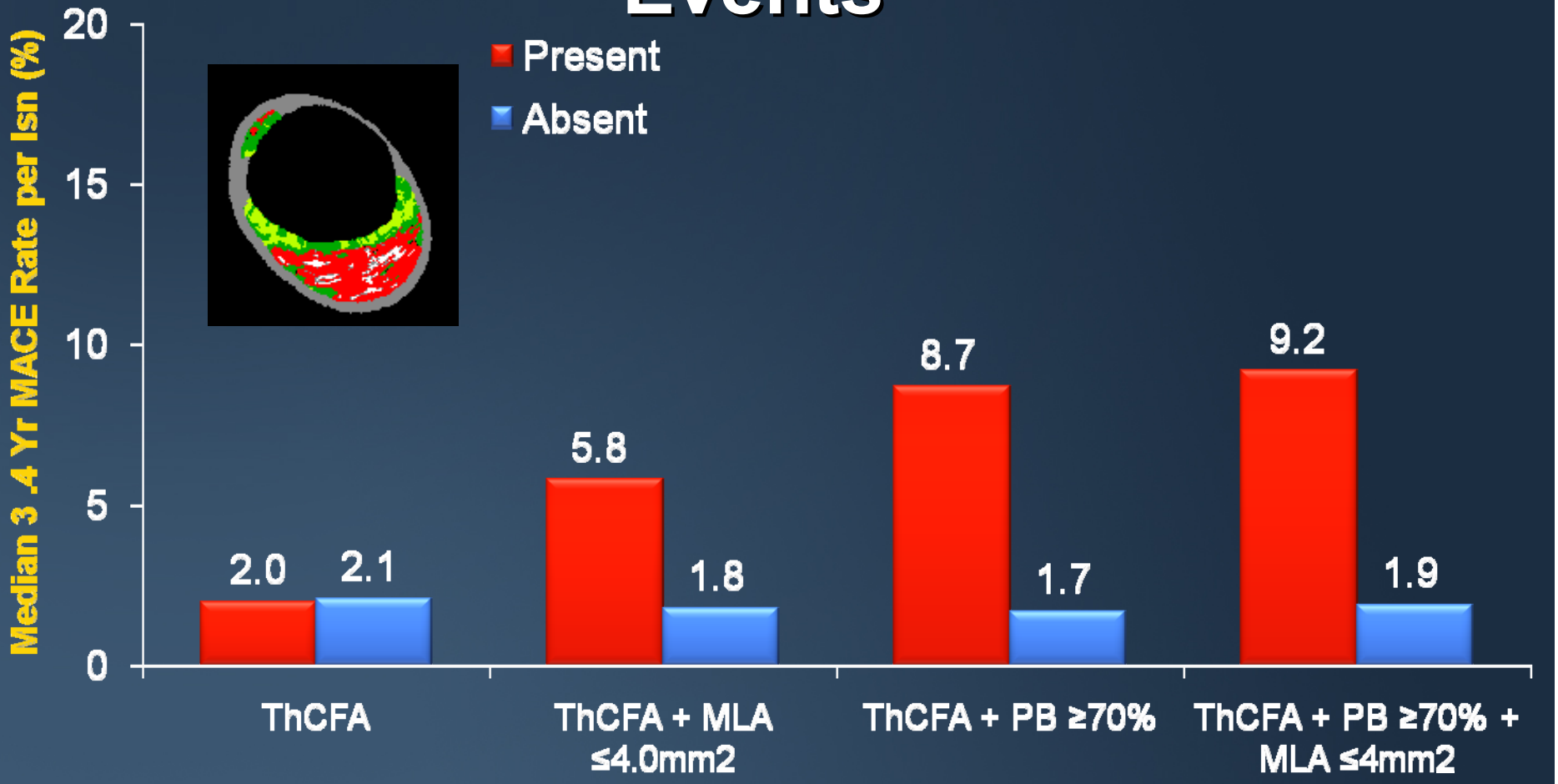
Thick-cap FA and Non Culprit Lesion Events



	ThCFA	ThCFA + MLA ≤4.0mm2	ThCFA + PB ≥70%	ThCFA + PB ≥70% + MLA ≤4mm2
Lesion HR	0.92 (0.52, 1.63)	3.41 (1.75, 6.65)	5.17 (2.59, 10.32)	5.02 (1.99, 12.63)
P value	0.77	0.0003	<0.0001	<0.0001
Prevalence*	67.6%	22.7%	15.6%	8.3%

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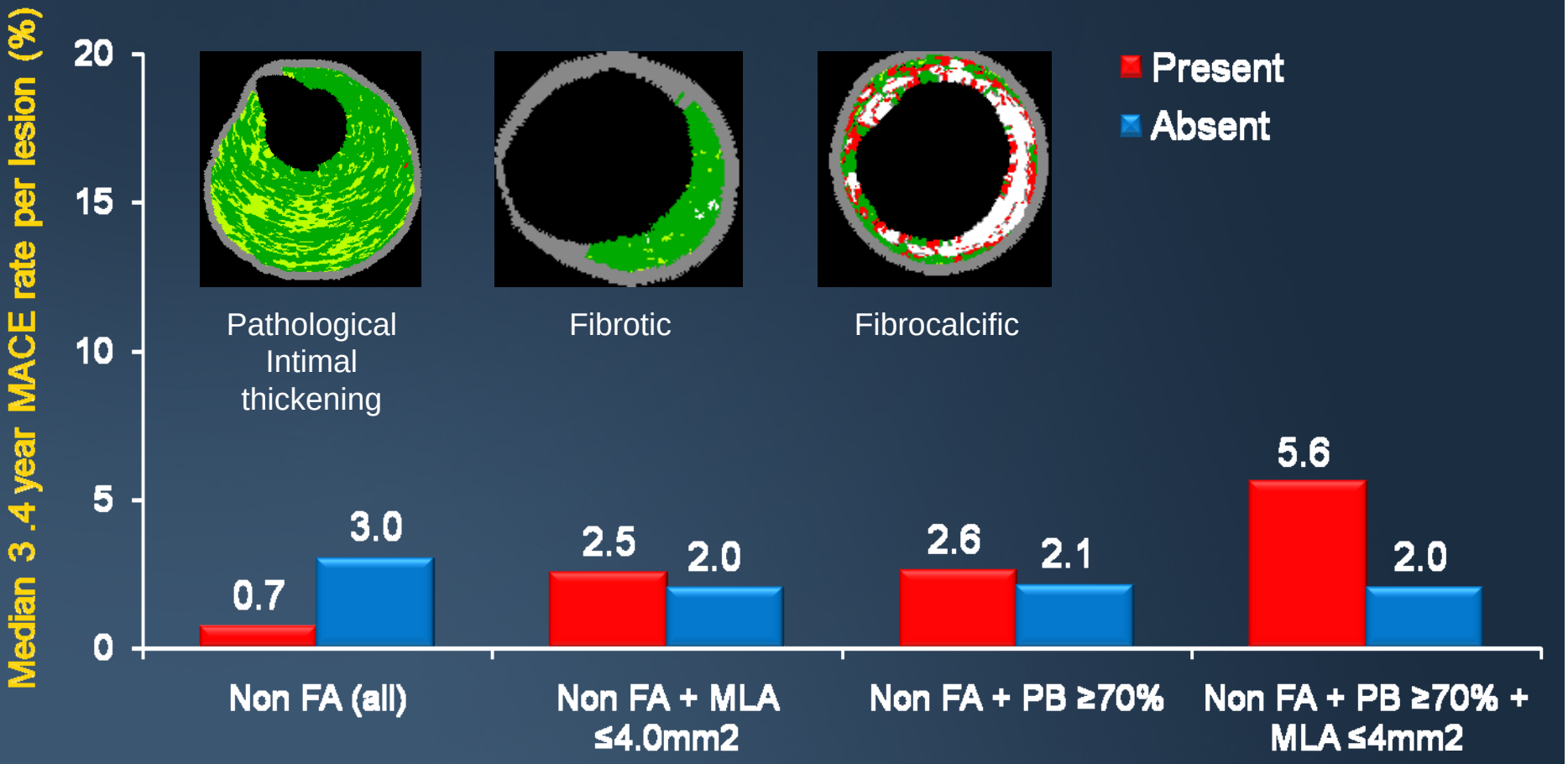
Non Fibroatheromas and Non Culprit Lesion Events



Lesion HR	0.22 (0.10, 0.49)	1.22 (0.44, 3.39)	1.25 (0.17, 9.01)	2.60 (0.36, 18.84)
P value	0.0002	0.70	0.83	0.34
Prevalence*	67.9%	19.7%	5.6%	2.7%

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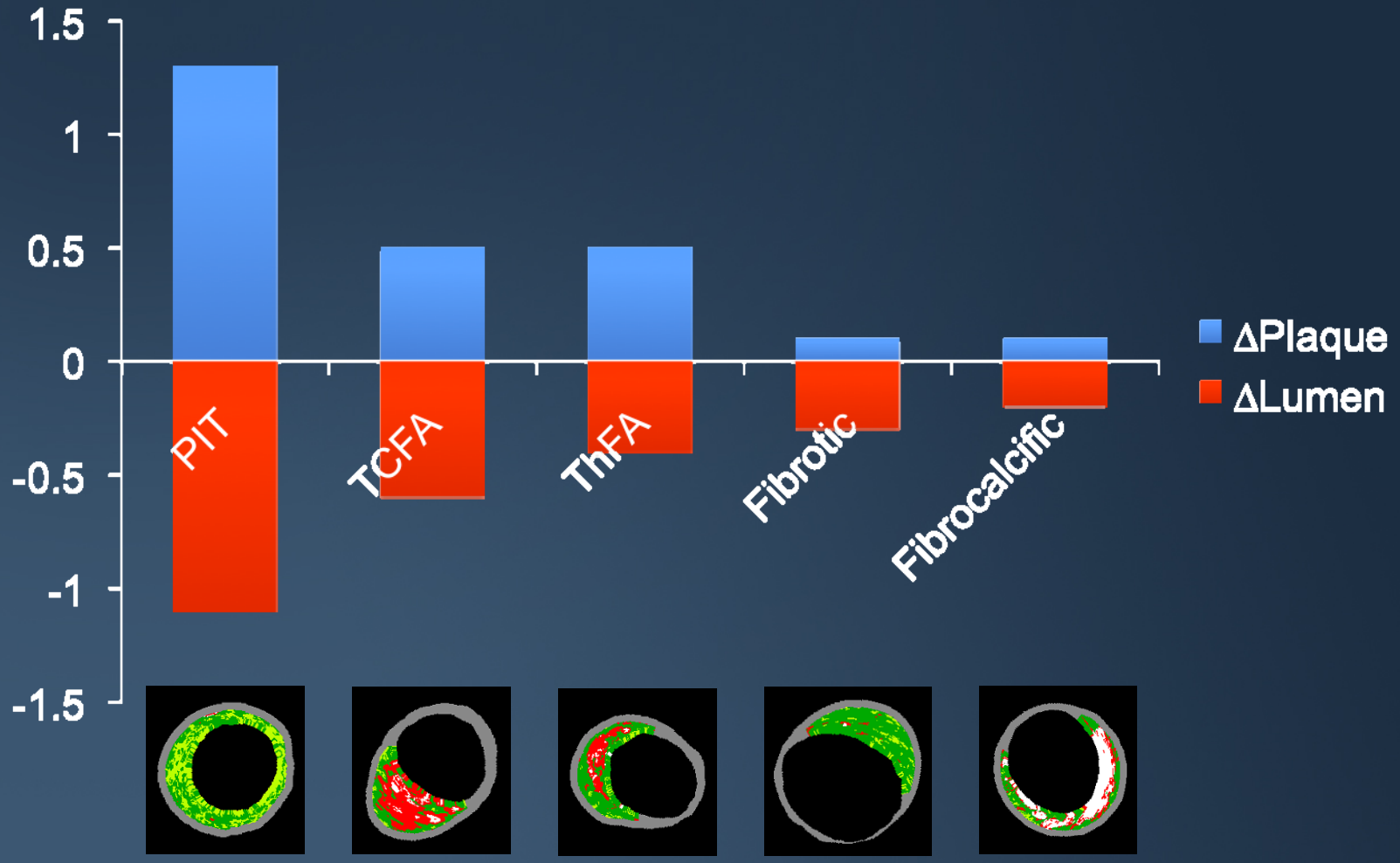

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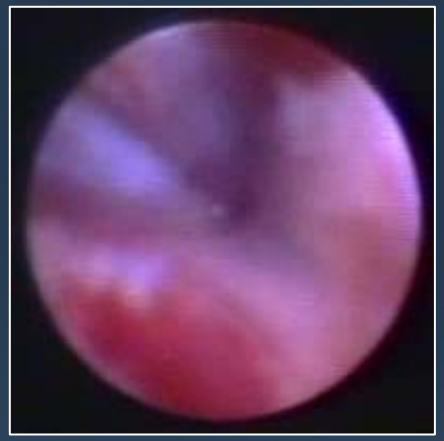
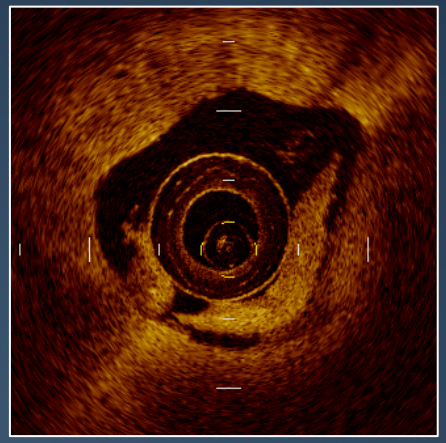
Limitations – I: Thrombus

- Thrombus was detected in 81 of 259 histology slices. Thrombus was colored as fibrous or fibro-fatty by VH-IVUS.
  - Nasu et al Am J Cardiol 2008;101:1079-83
- As a result. . .
  - Superficial thrombus will cause a TCFA to be classified as a ThFCA
  - A thrombus-containing lesion may be classified as PIT or fibrotic (stable) rather than unstable
- In all probability RF-IVUS detection of thrombus will not be possible by any technique since the IVUS signal changes with the "age" of the thrombus





Red Thrombus

Sensitivity = 95%
Specificity = 88%
Positive predictive value = 86%
Negative predictive value =95%

White Thrombus

- There were no significant differences in the peak intensity of the OCT signal between red and white thrombi.
- The OCT signal attenuation of red thrombus was significantly more rapid than that of white thrombus.

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(Kubo et al. Circulation 2006;114:II-645)

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Limitations – II: Plaque behind Calcium

- 80% of regions of interest behind calcium contained a distinct low-amplitude signal that had a coherent periodic pattern on adjacent scan lines and a signal increase in the region of the adventitia indicating that this signal contained reflected ultrasound information as well as noise
- 20% of the regions of interest behind calcium had only noise
- Nevertheless, the signal level observed behind calcium is often very close to the noise level. Spectral assessment at such low signal-to-noise ratio might be unreliable, and VH data should be masked when a strong signal is followed by a very low intensity one or the algorithm should report a lower confidence (ala iMAP).

VH-IVUS and Plaque Behind Calcium

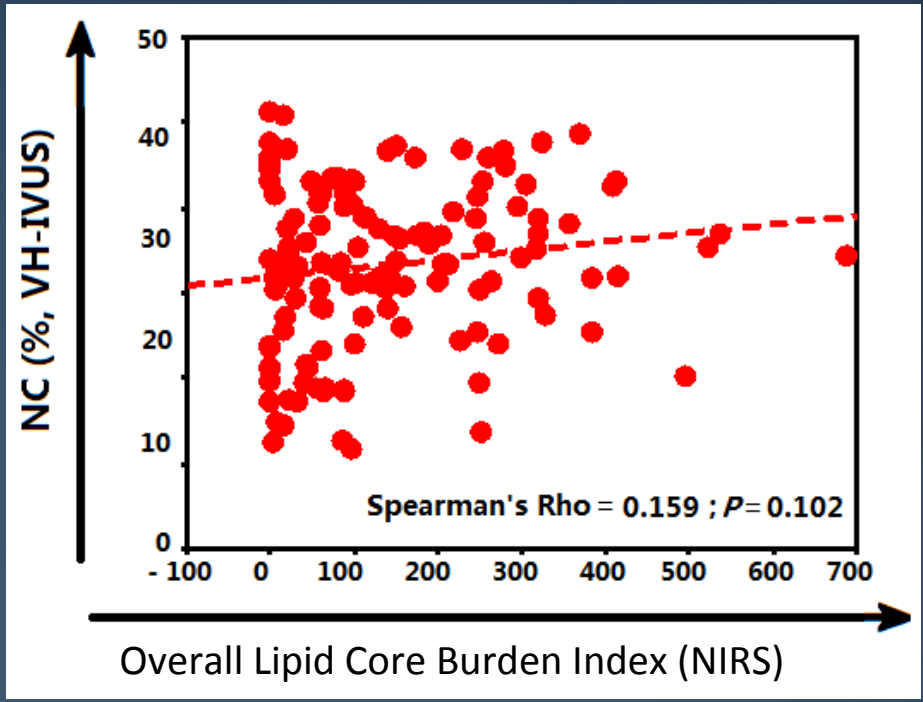
- **Using the 20MHz transducer, 80% of regions of interest behind calcium contained reflected ultrasound information as well as noise although the signal-to-noise ratio was low. 20% of the regions of interest behind calcium had only noise** *(Tanaka et al. J Am Coll Cardiol 2007;49:29B)*
- **When inaccurate, tissue is classified as NC 65% of the time, FT 18% of the time, and FF 14% of the time** *(Vince. Volcano Corp)*

		Correct	Incorrect	ROIs	Accuracy
Mild microcalcium	IVG	2	0	2	100%
	S5	1	1	2	50%
Heavy microcalcium	IVG	3	6	9	33.3%
	S5	18	9	27	66.7%
Dense calcium	IVG	27	10	37	73%
	S5	27	16	43	62.8%
Overall	IVG	32	16	48	66.7%
	S5	46	26	72	63.9%

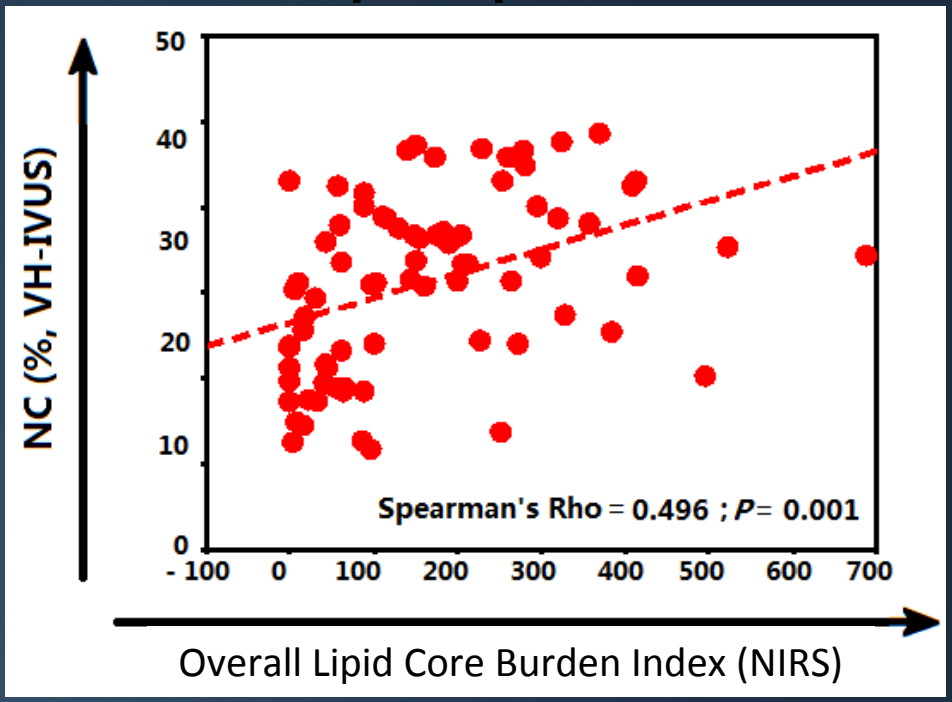
Overall Accuracy: 65.0 %

Correlation between VH-%NC and LCBI-NIRS

All Plaques



Non-calcified plaque

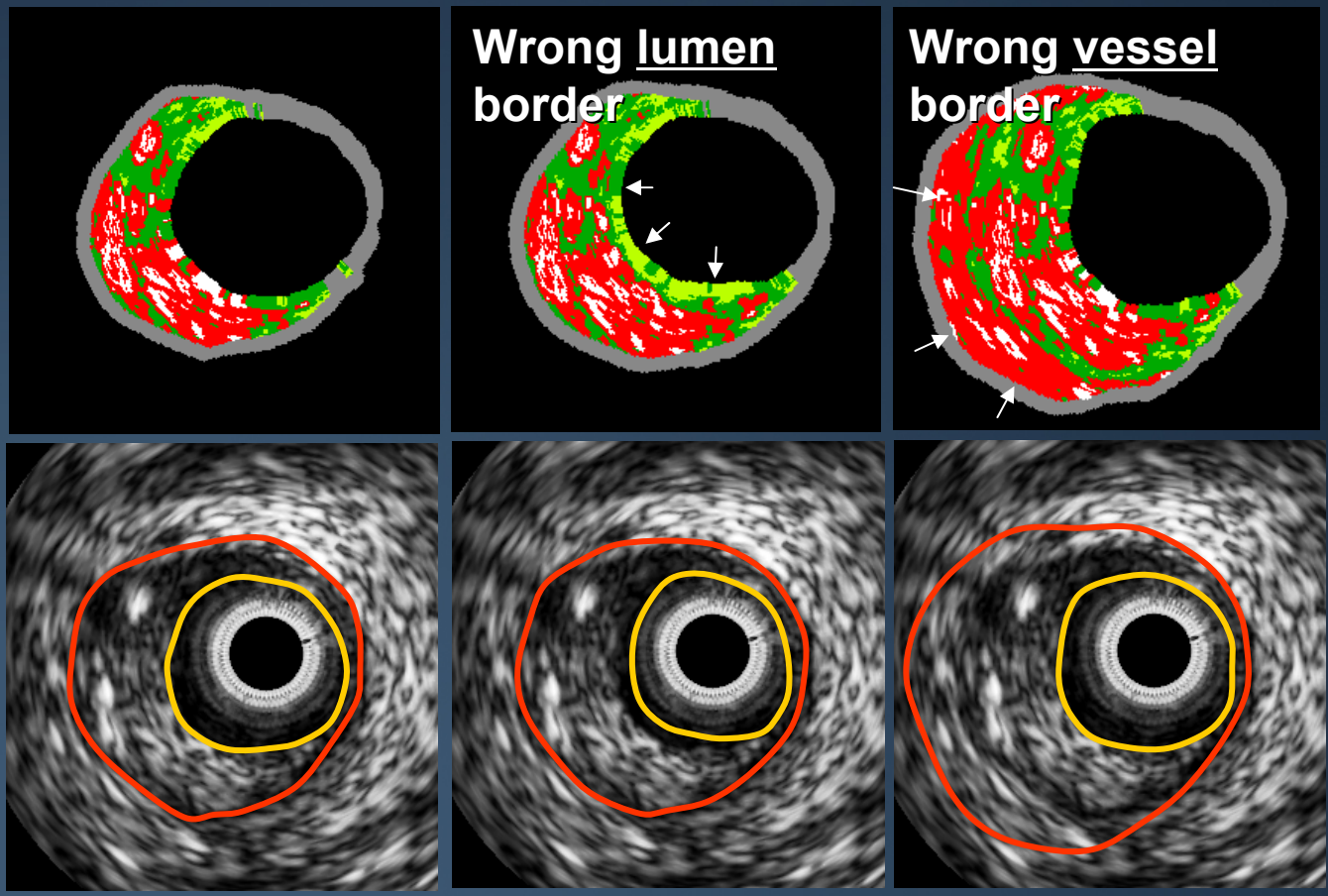


Limitations – III: Others

- All tissue between lumen and vessel borders must be classified as one of the four tissue types and VH analysis depends on accurate borders.
- Stent metal appears as calcium surrounded by necrotic core even when implanted acutely (Kim et al. Am J Cardiol 2008;102:1182-6). Should not be interpreted as inflammation.
- No validation for intimal hyperplasia

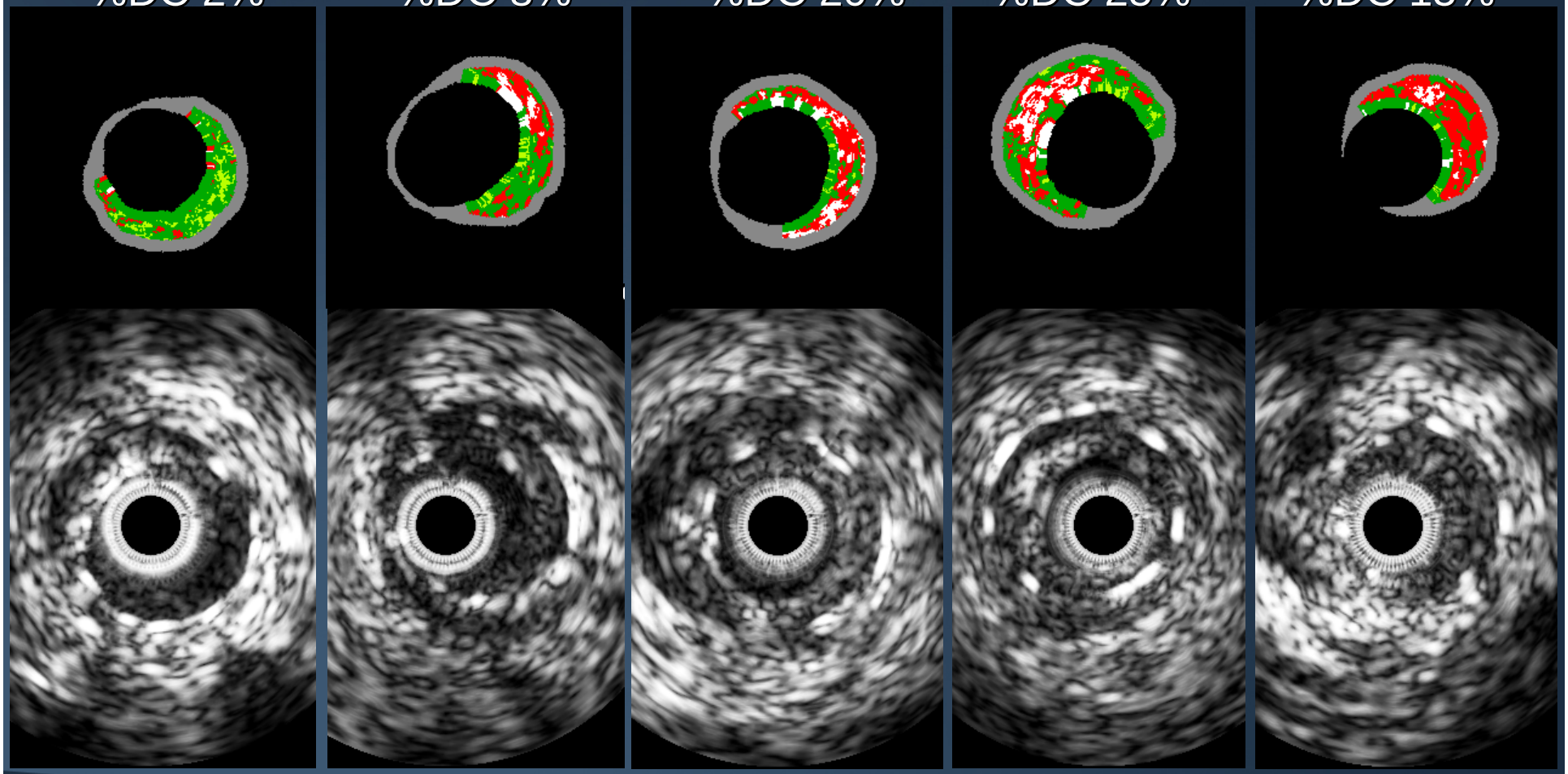
Border Definition

All tissue between lumen and vessel borders must be classified as one of the pre-defined tissue types



In-stent Neointimal VH-IVUS Composition at Maximal %IH Sites

6-mo Taxus	9-mo Taxus	22-mo Taxus	48-mo BMS	57-mo BMS
%NC 8%	%NC 28%	%NC 39%	%NC 40%	%NC 57%
%DC 2%	%DC 8%	%DC 20%	%DC 25%	%DC 15%



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Kang et al. Am J Cardiol, in press

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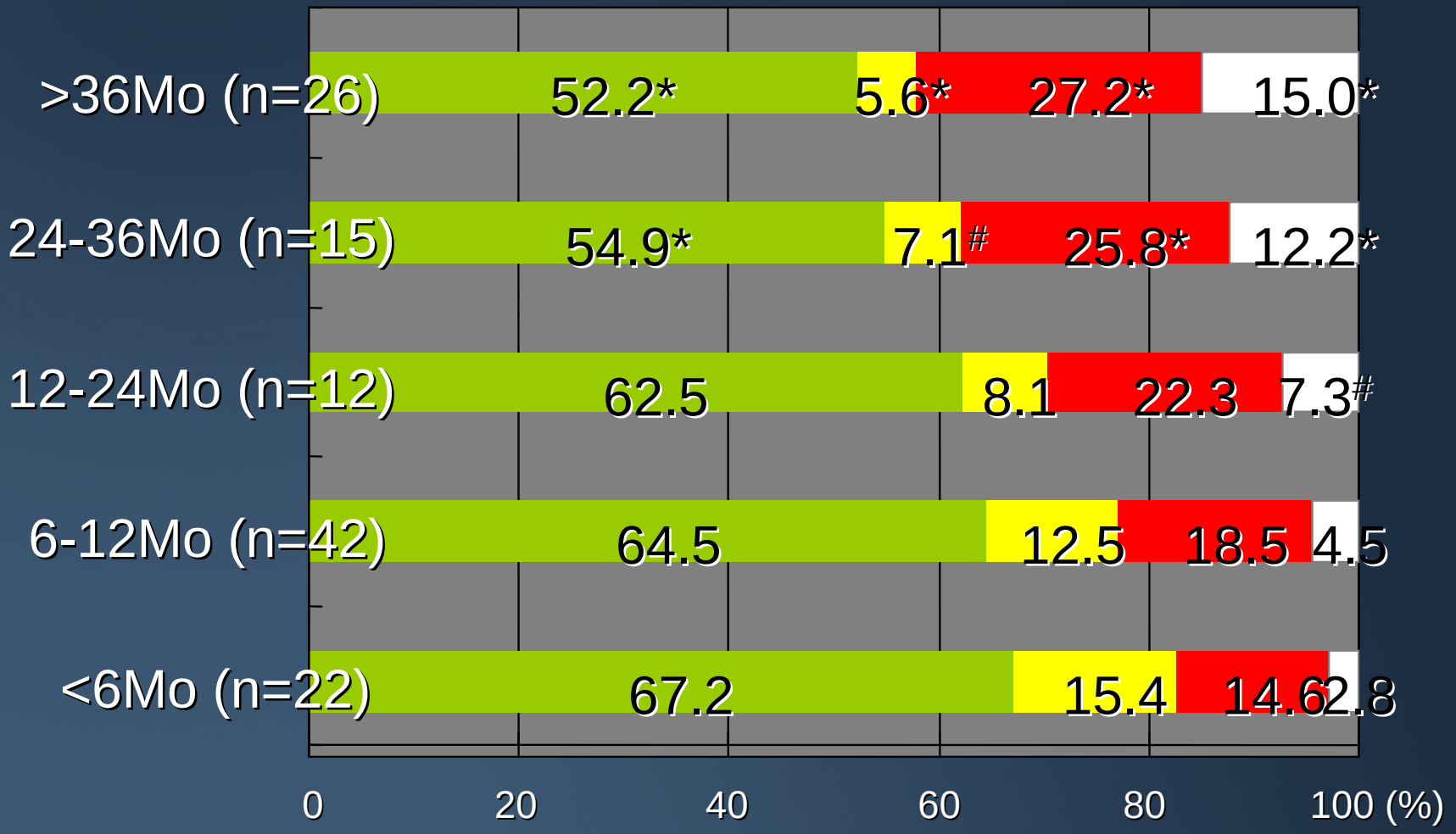
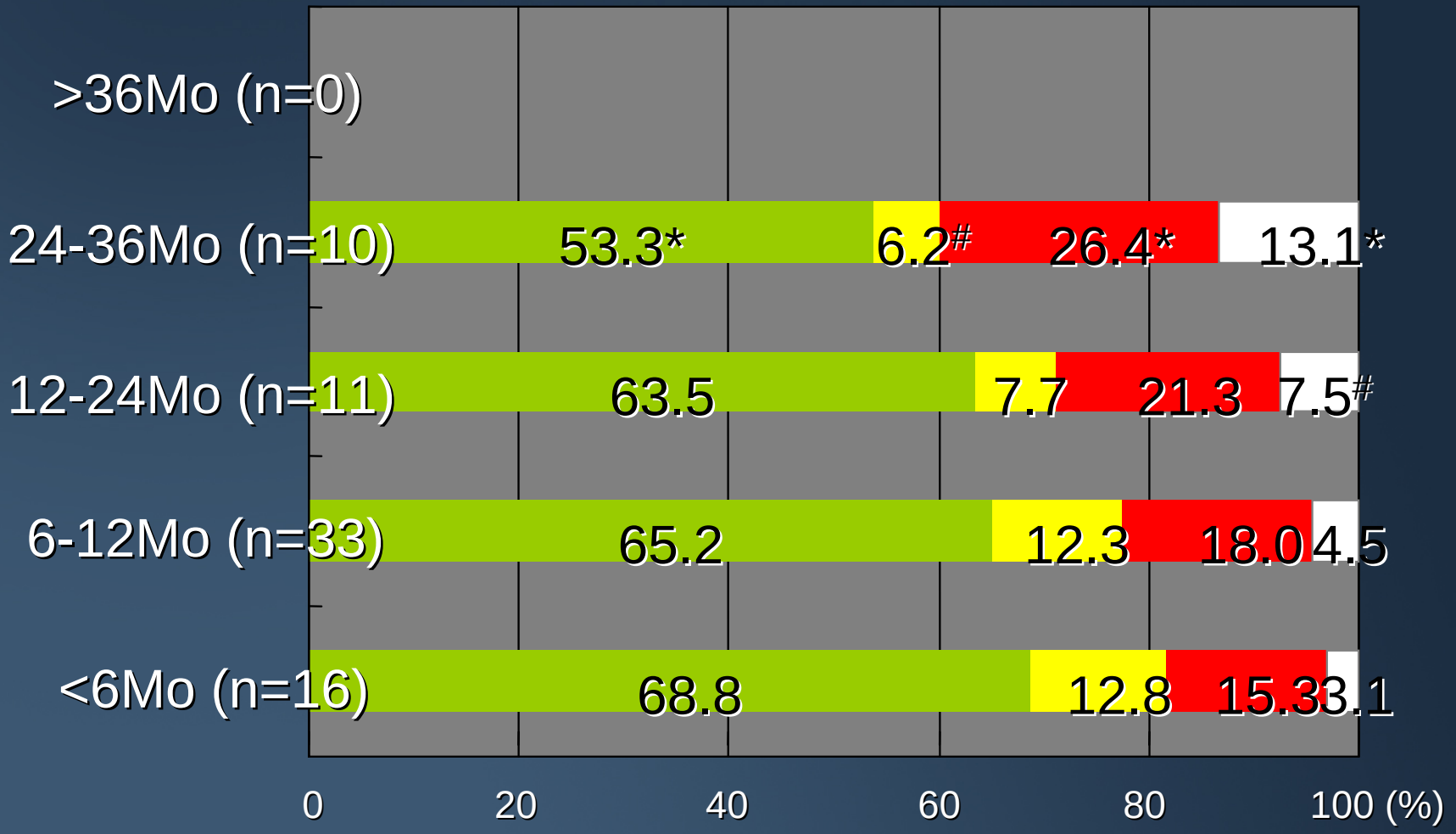
VH Composition of Neointima at Various Follow-Up Times in 117 ISR Lesions Combining BMS and DES



Kang et al. Am J Cardiol, in press

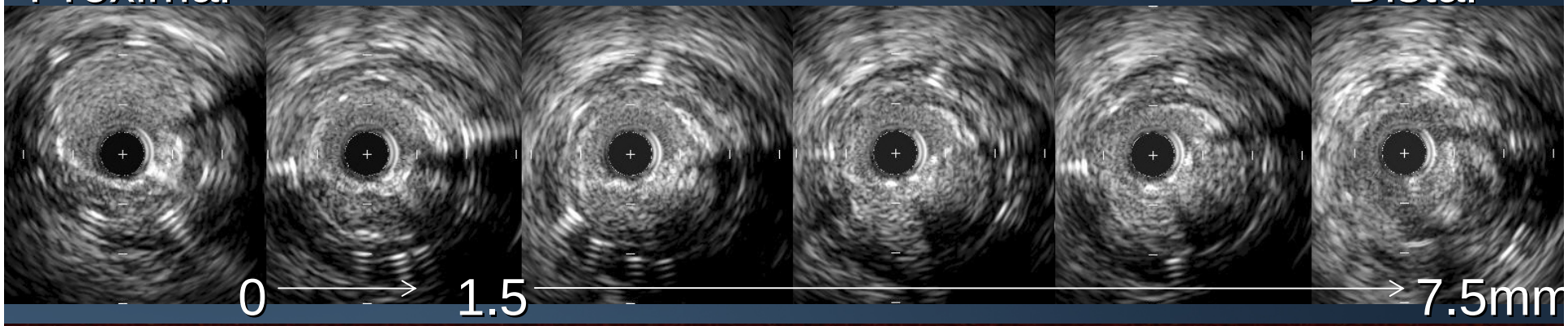
VH Composition of Neointima at Various Follow-Up Times in 70 DES Restenosis Lesions



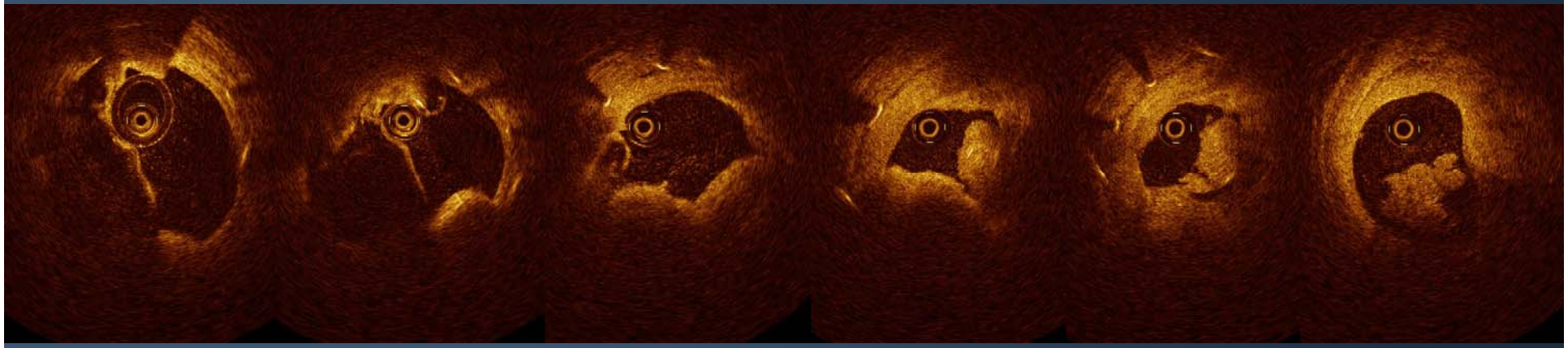
Kang et al. Am J Cardiol, in press

Proximal

Distal



0 → 1.5 → 7.5mm



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