Virtual Histology: Wrapping Up Current Clinical Trials and Future Perspectives

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- Culprit of the culprit
- PCI complications
- Serial analysis
- Comparative studies and competitive technologies
- Limitations

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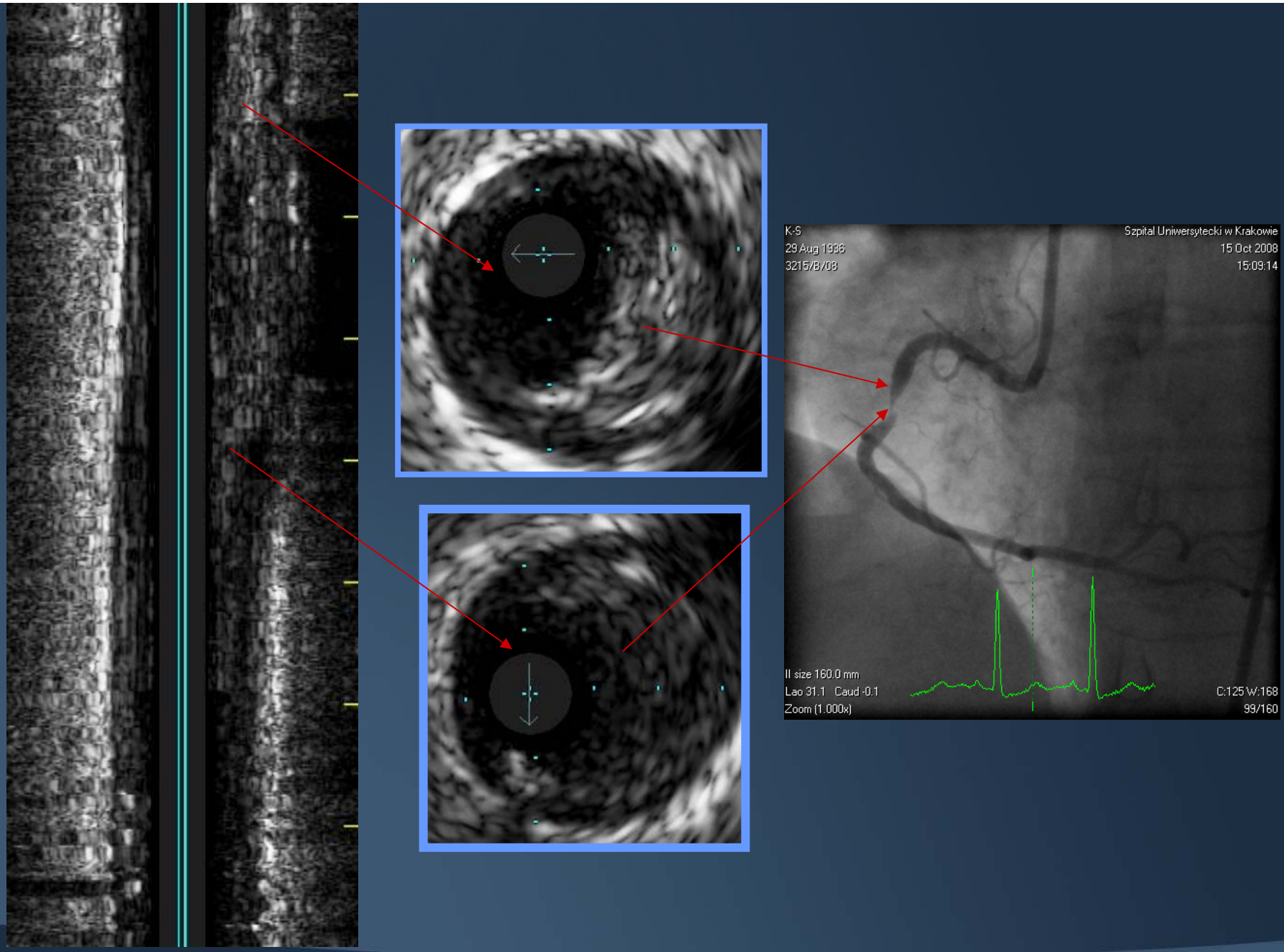
- 72 year old female with diabetes and hypertension presented with 3 hours of chest and transient complete heart block
- Medication during transfer to hospital (40km) included aspirin 300mg, clopidogrel 600mg, heparin 400IU, abciximab (bolus).
- Chest pain resolved at the time of admission
- ECG showed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



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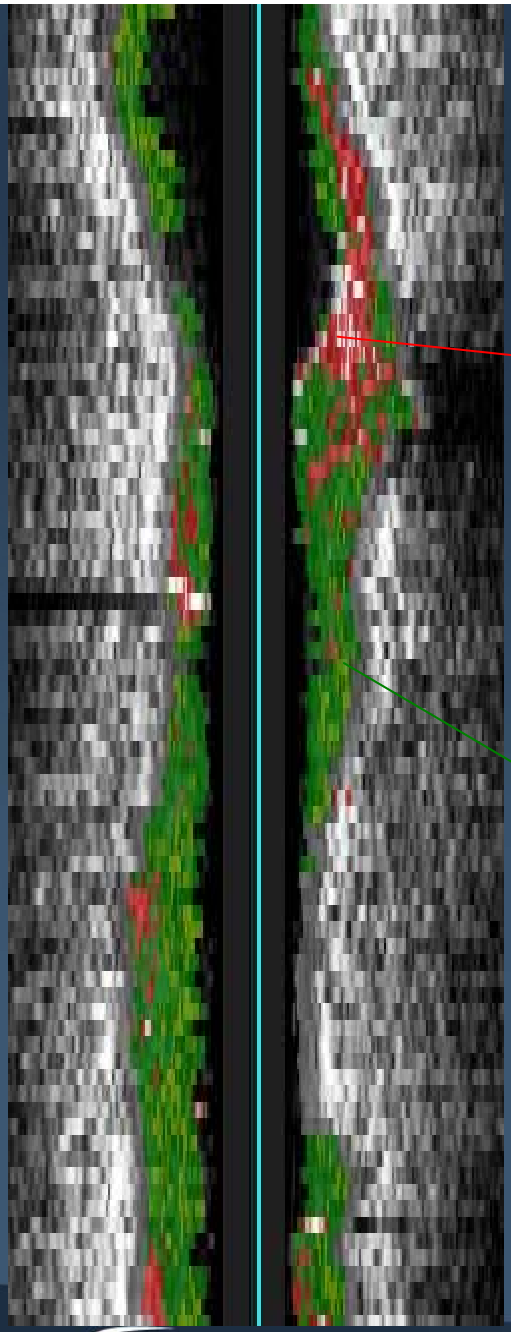
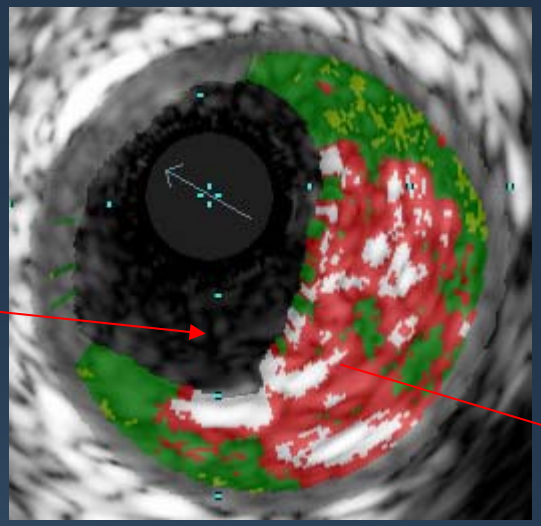
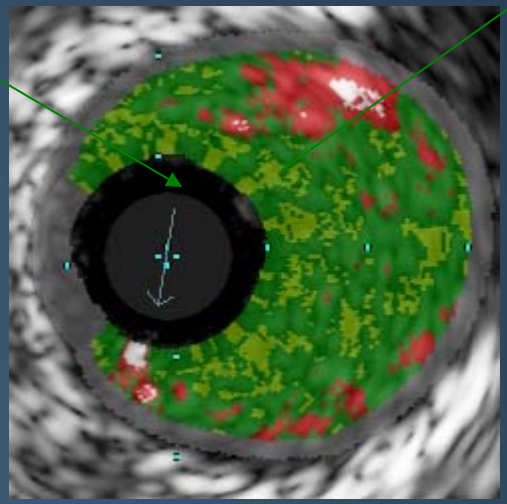
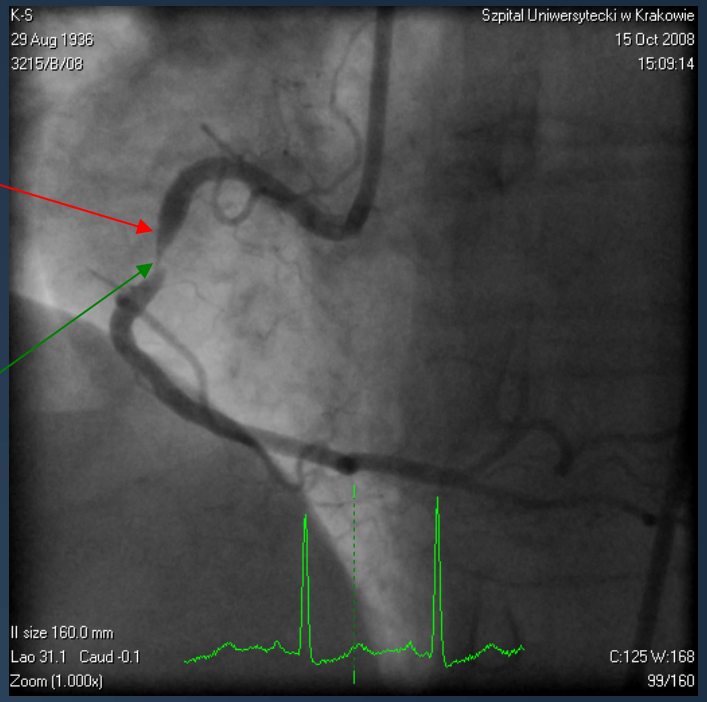




culprit of the culprit proximal to MLA



MLA



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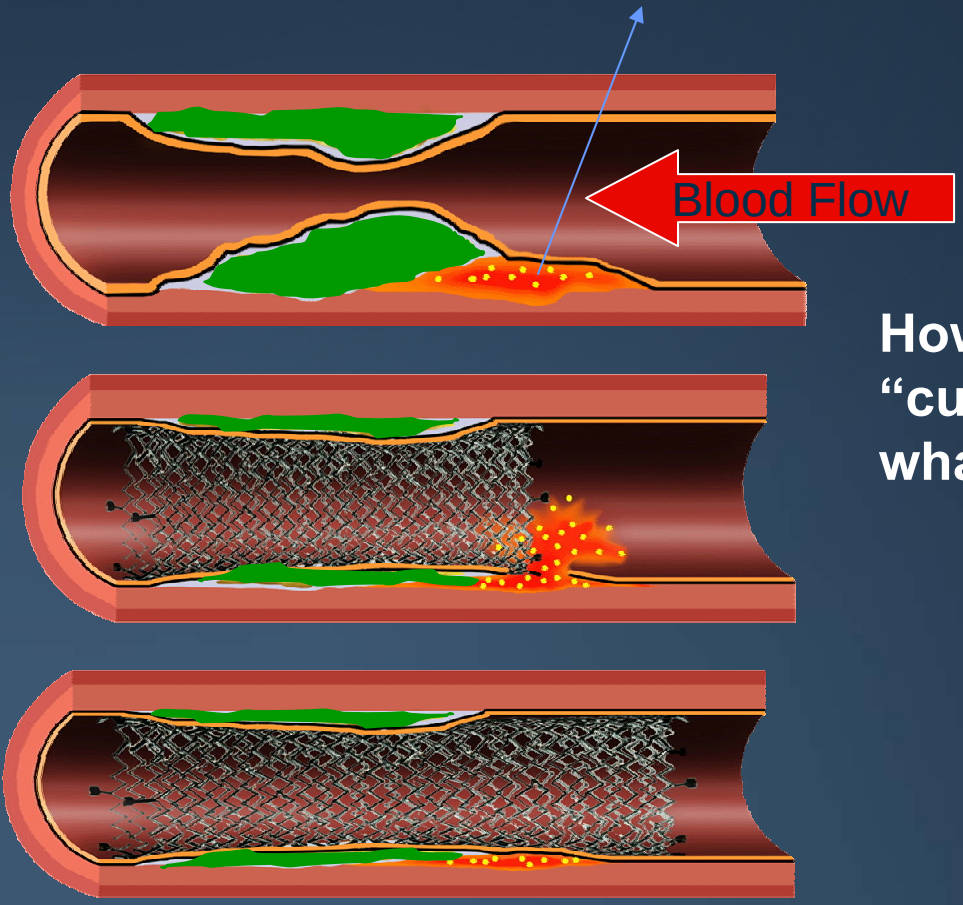
Possible Stent Positioning in Culprit Lesion PCI

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

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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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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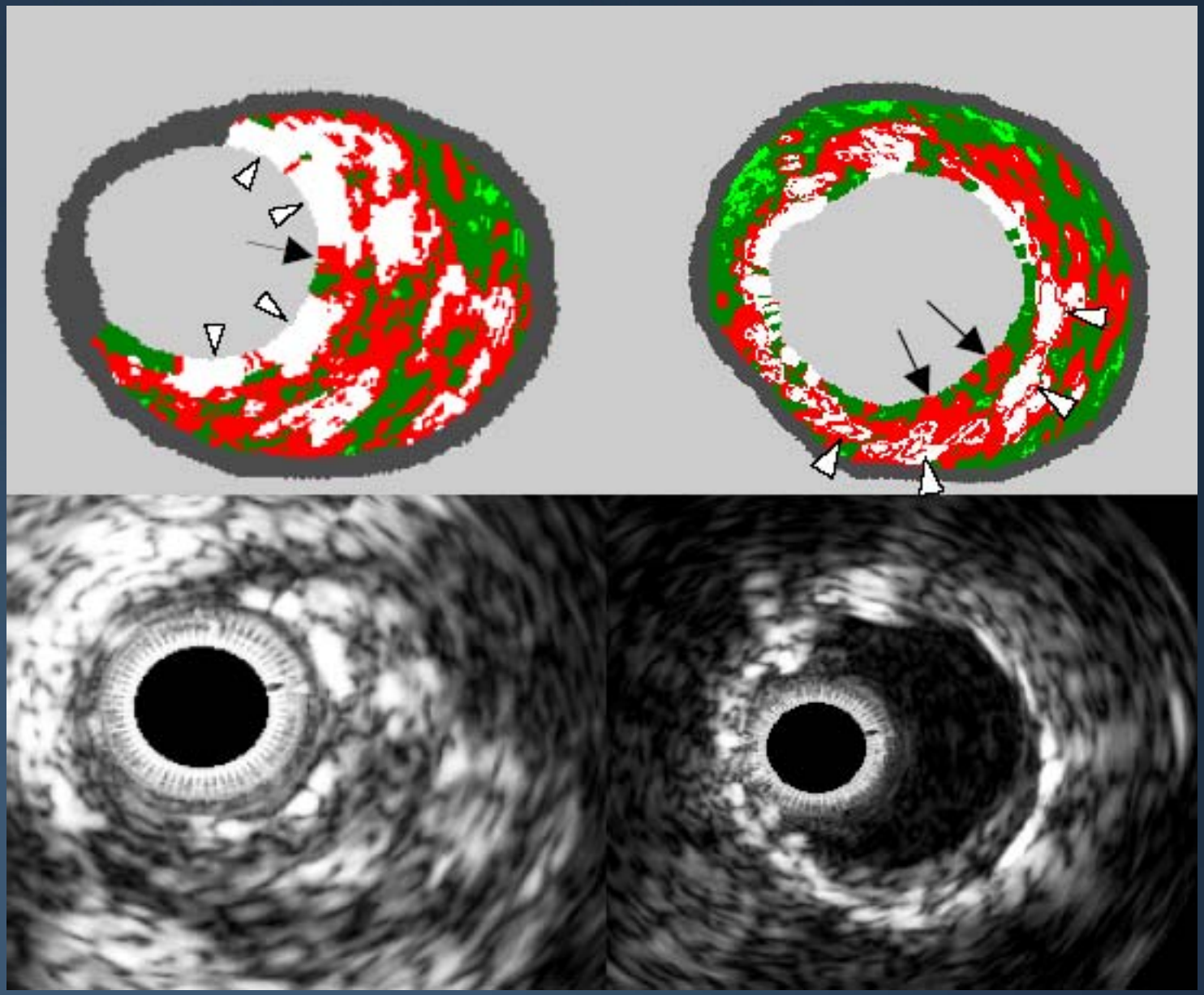

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VH-TCFAs were associated with a smaller MSA than non-VH-TCFAs: $5.8 \pm 1.8 mm^2$ vs $6.3 mm^2$

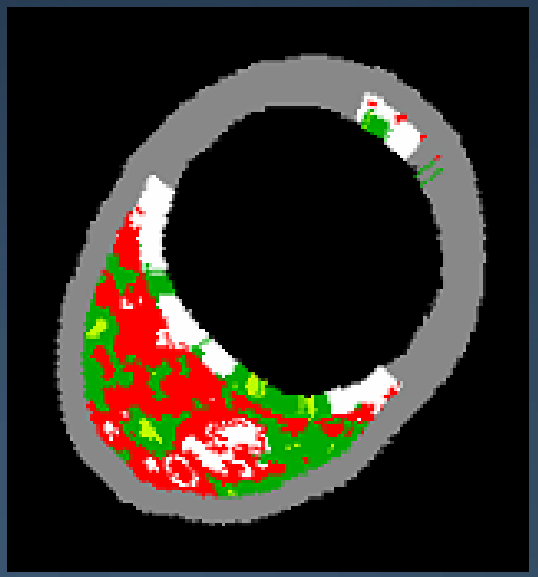
Numerous studies have shown a relationship between the maximum necrotic core and post-PCI distal embolization

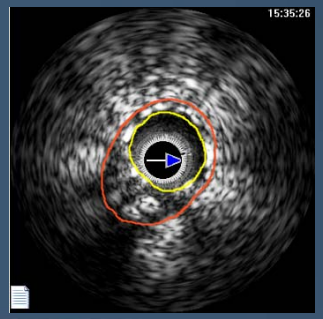
- Kawaguchi et al. J Am Coll Cardiol. 2007;50:1641-6
  - ST re-elevation in 71 pts with STEMI
- Kawamoto et al. J Am Coll Cardiol. 2007;50:1635-40
  - Doppler FloWire high intensity transit signals in 44 pts undergoing elective stenting resulting in poor recovery of CVFR
- Park et al. VH Summit 2007 (unpublished)
  - Largest NC independent predictor of CK-MB release (n=332)
- Washington Hospital Center. Unpublished
  - Troponin post elective stenting
- 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

- Culprit of the culprit
- PCI complications
- **Serial analysis**
- Comparative studies and competitive technologies
- Limitations

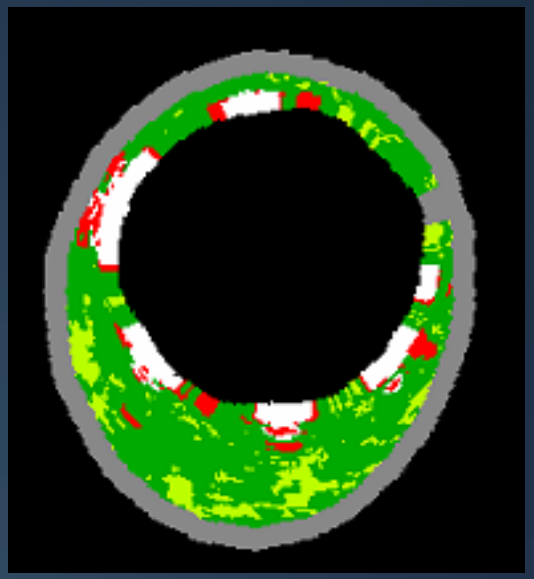
Serial (baseline and follow-up) VH-IVUS assessment of plaque characteristics after stent deployment.

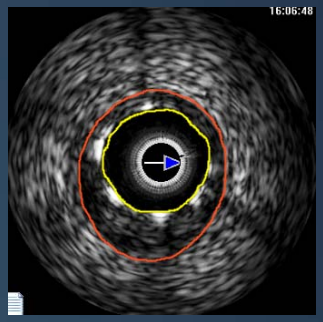
Fibroatheroma





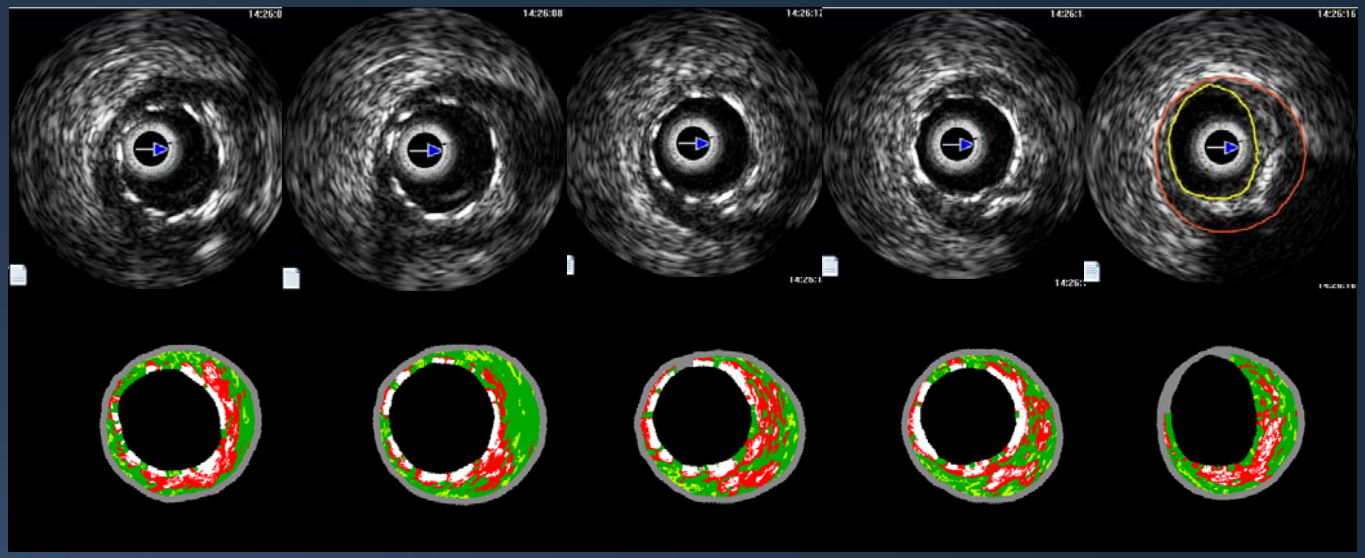
Non-fibroatheroma



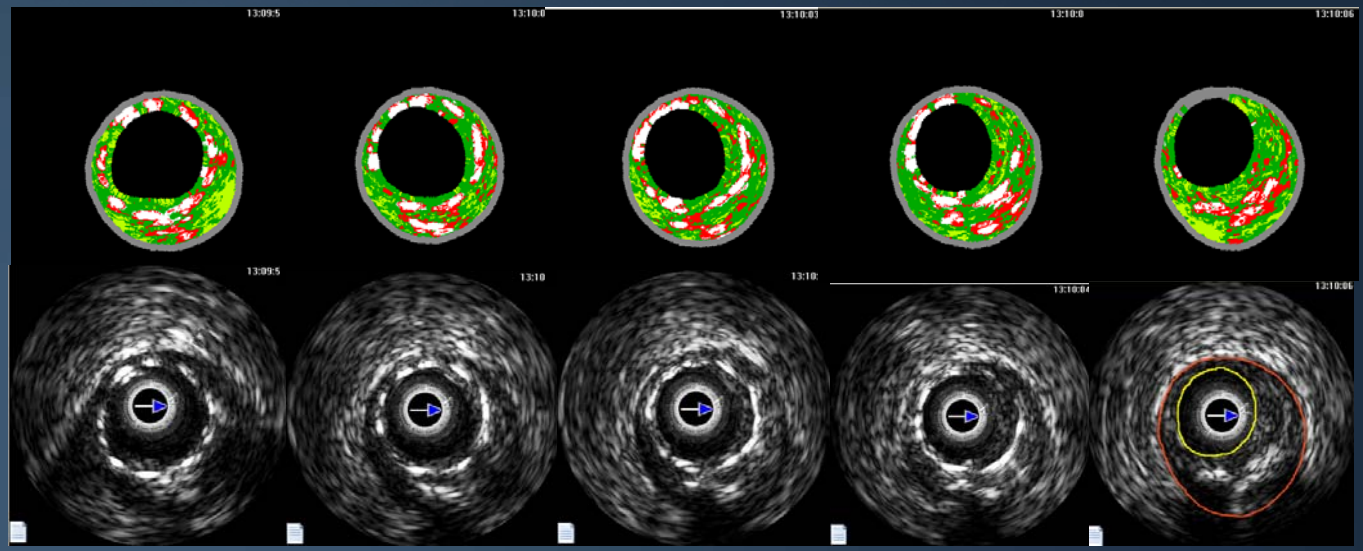


BMS

Baseline



Follow-up



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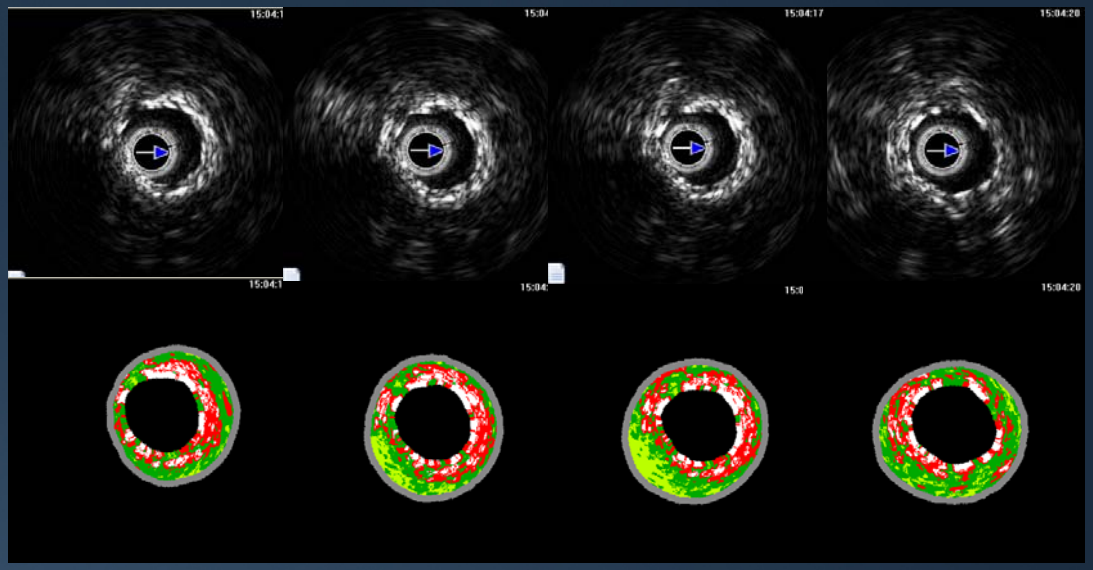
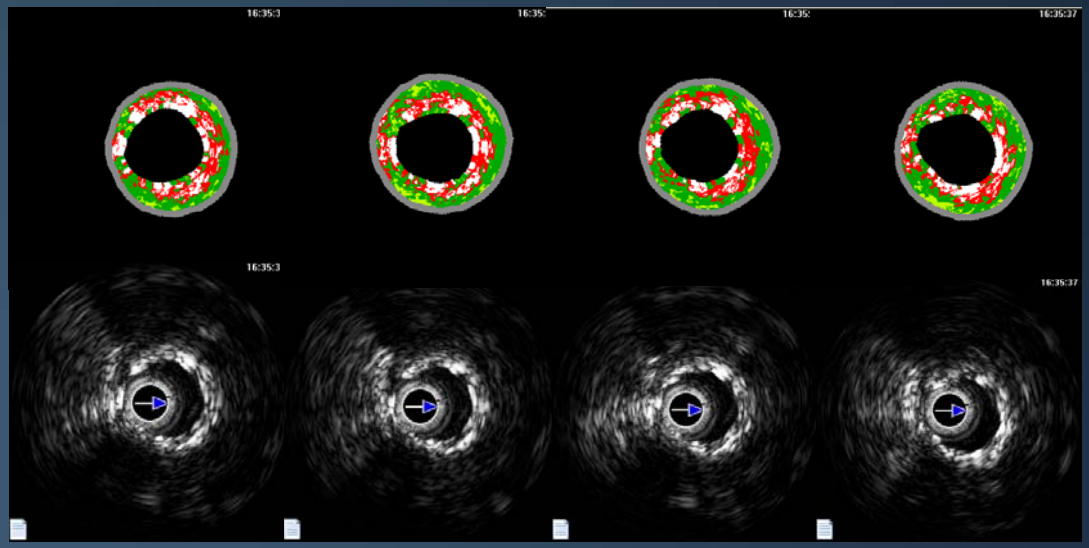
DES

Baseline



Follow-up



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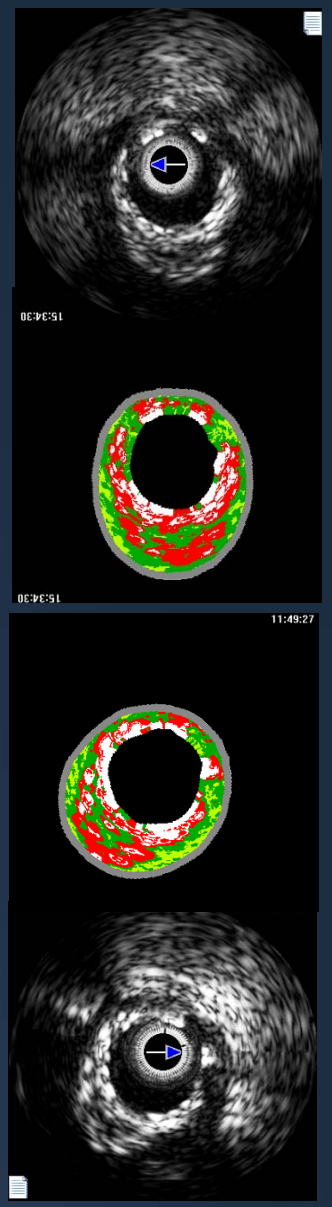
%Culprit lesion VH-TCFA (necrotic core abutting lumen) post-stent and at follow-up

	DES (n=76)	BMS (n=32)
Stent		
Post-intervention	76%	75%
Follow-up	61%	19%
Stent Edge/Reference		
Post-intervention	22% (prox)	23% (prox)
	23% (dist)	20% (dist)
Follow-up	17% (prox)	0% (prox)
	21% (dist)	0% (dist)

DES

Baseline

Follow-up



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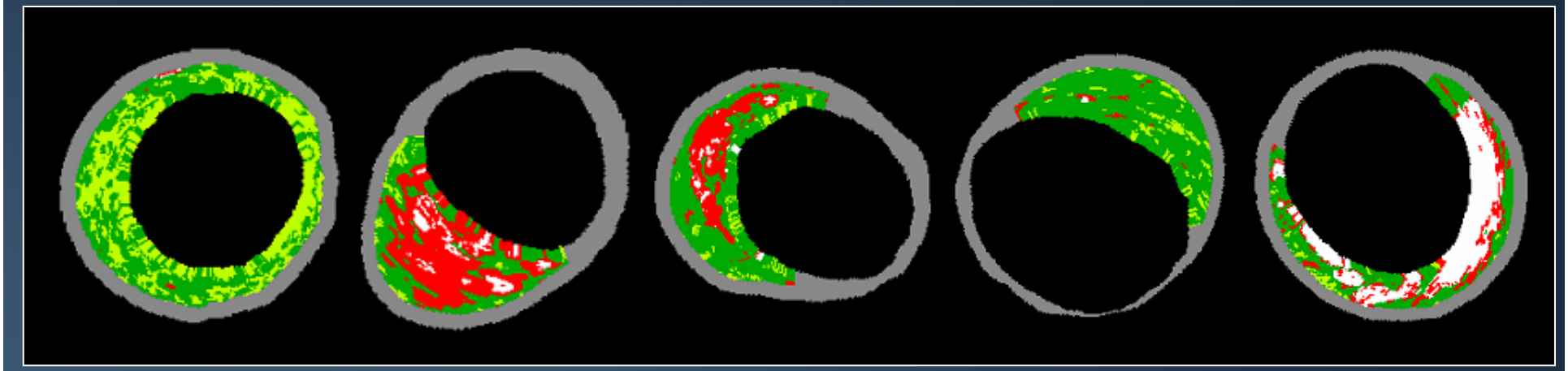
Change in non-culprit lesion phenotype in 106 patients (201 lesions) with plaque burden >40%) from the Global VH Registry with baseline and 8-month follow-up VH analysis



Pathological intimal thickening (PIT)	Thin-cap fibroatheroma (TCFA)	Thick-cap fibroatheroma (ThFA)	Fibrotic	Fibrocalcific

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Kubo et al. AHA 2008

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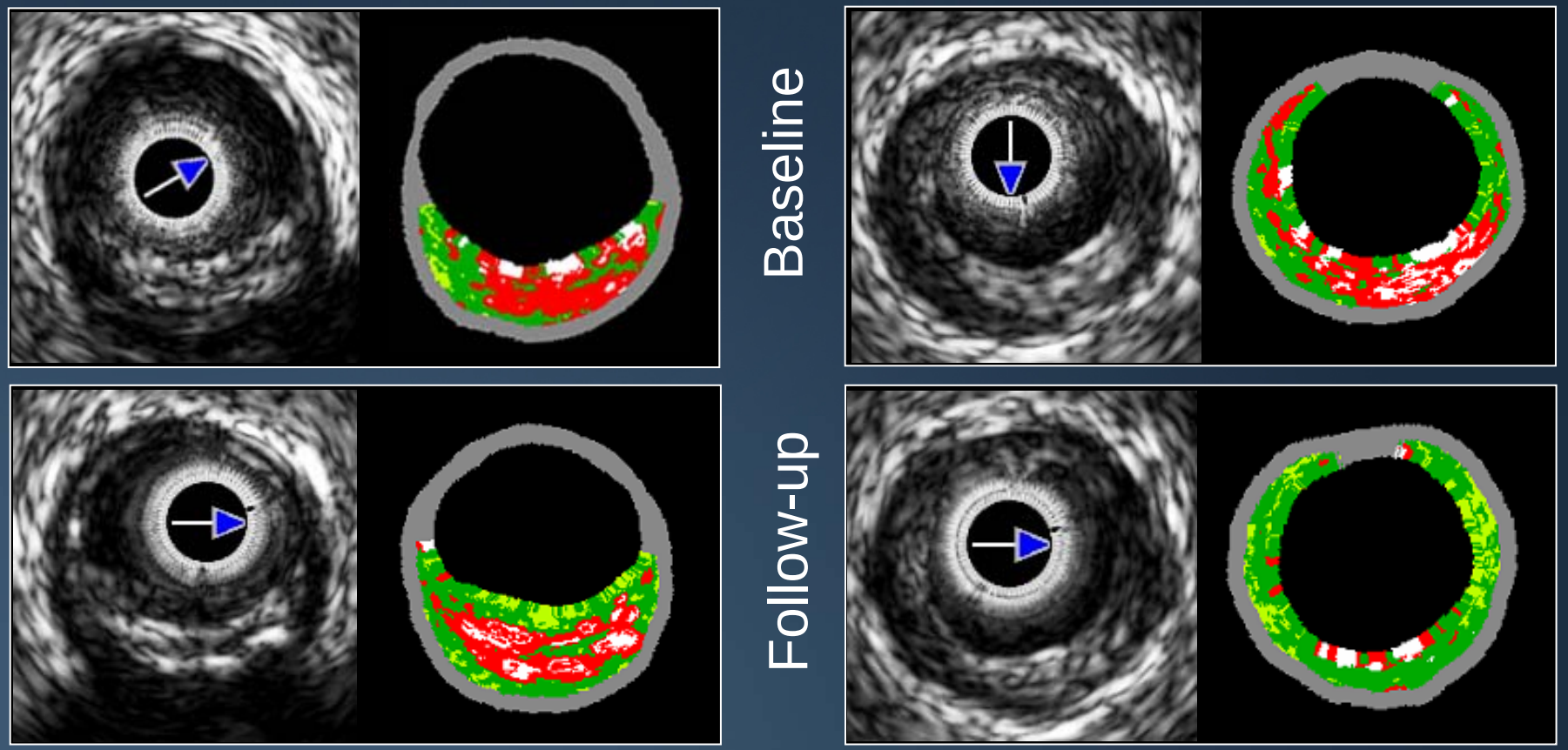
Baseline (n=216)	Follow-up (n=216)					
		PIT (n=48)	TCFA (n=17)	ThFA (n=109)	Fibrotic (n=23)	Fibrcalcific (n=19)
	PIT (n=62)	44	6	12	0	0
	TCFA (n=20)	0	5	13	2	0
	ThFA (n=93)	0	6	84	3	0
	Fibrotic (n=22)	4	0	0	18	0
	Fibrocalcific (n=19)	0	0	0	0	19

- During follow-up. . .
  - 75% of TCFAs healed and 25% remained unchanged although the location of the necrotic core in contact with the lumen shifted axially.
- Compared to TCFAs that healed, TCFAs that did not change were more proximal in location and had larger lumen area, vessel area, plaque area, calcium area, and necrotic core area.
- 12 new TCFAs were noted
  - 6 late-developing TCFAs were PIT and 6 were ThFA at baseline.
- No fibrotic or fibrocalcific plaques evolved into a TCFA.



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Baseline

Follow-up

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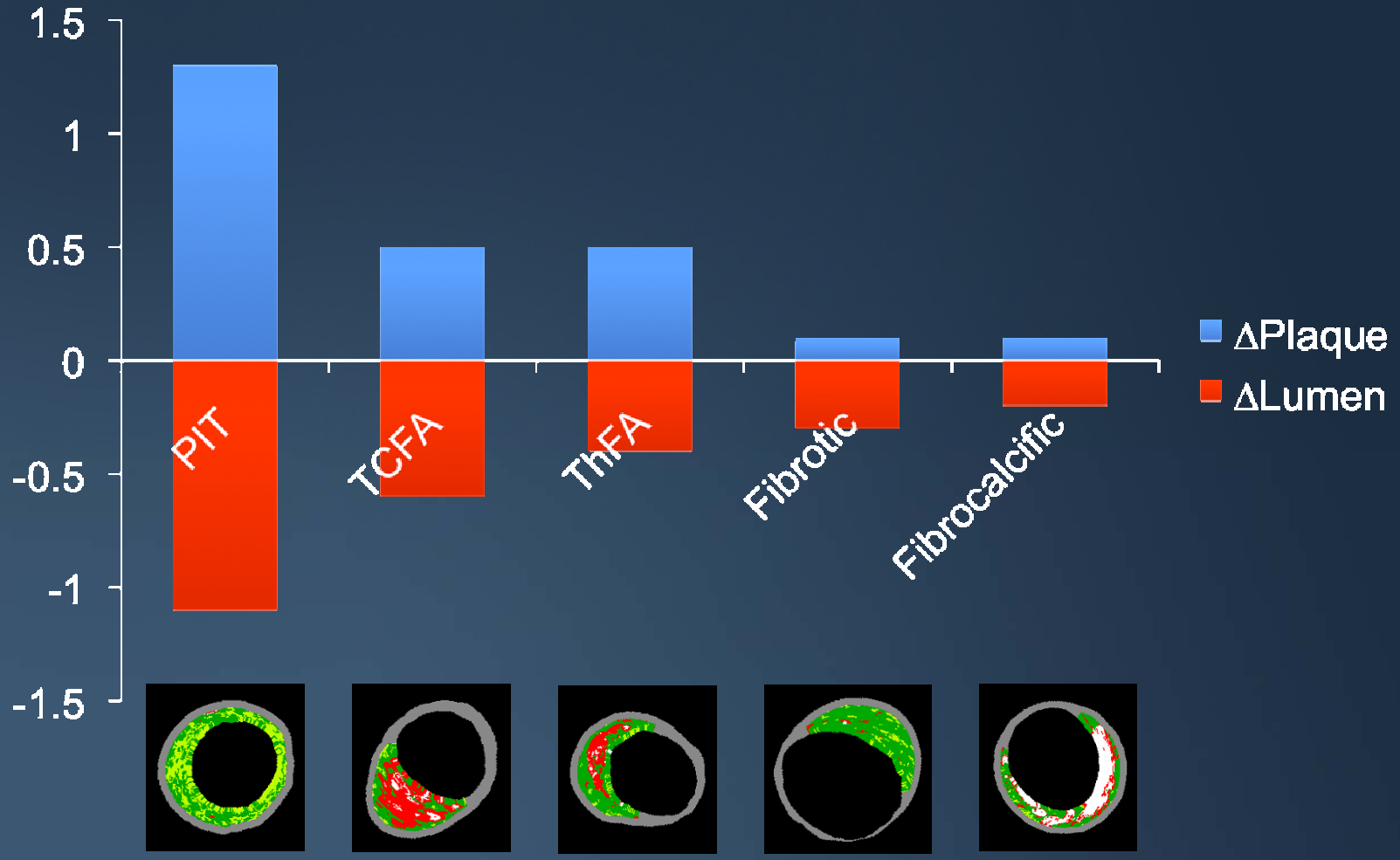

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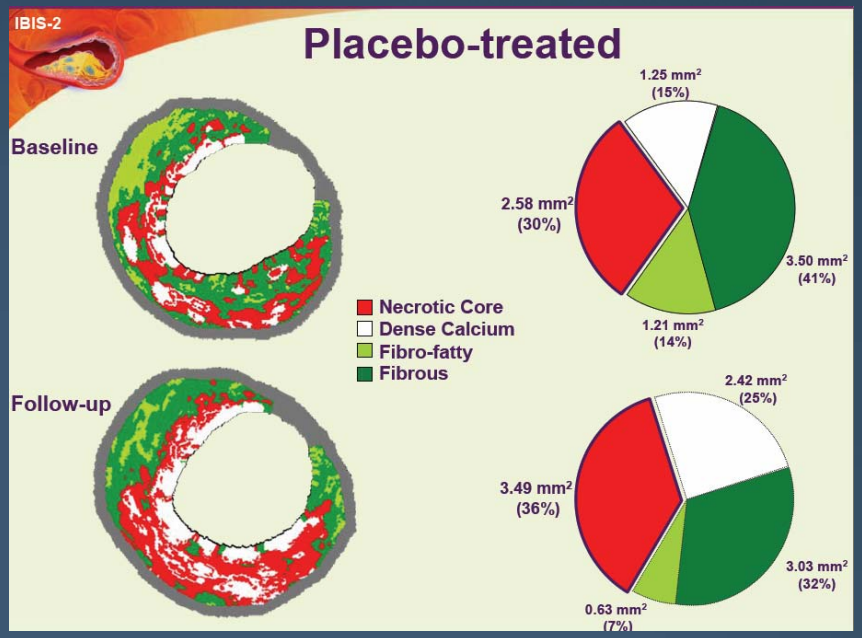
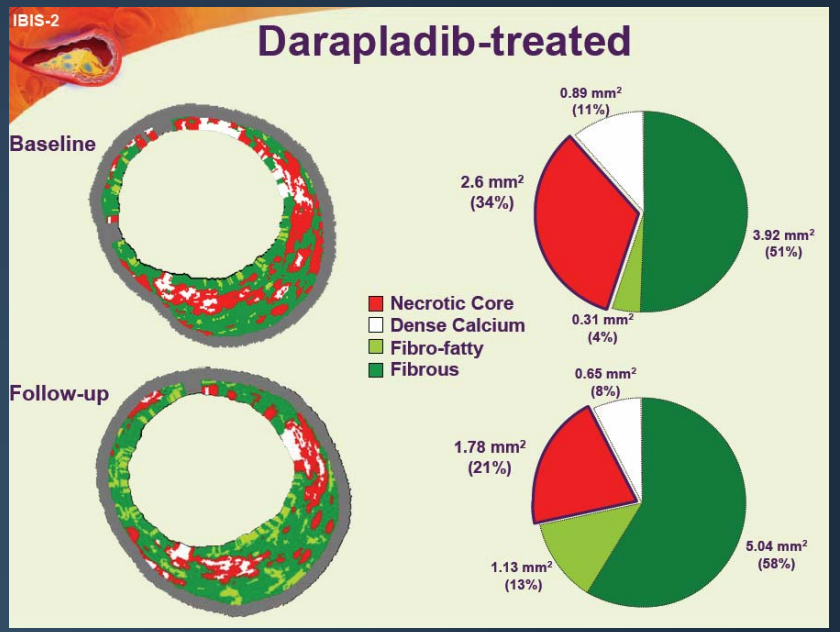
IBIS-2: Effects of the direct Lp-PLA$_2$ inhibitor darapladib vs placebo on human coronary atherosclerotic plaque.

After 12 months, in the placebo-treated group NC volume increased significantly (△NC=4.5±17.9mm^3, p=0.009), whereas darapladib halted this increase (△NC=-0.5±13.9mm^3, p=0.71), resulting in a significant treatment difference of -5.2mm^3 (p=0.012) without a significant treatment difference in total atheroma volume or plaque deformability..





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Serruys et al. Circulation. 2008 Sep 9;118:1172-82

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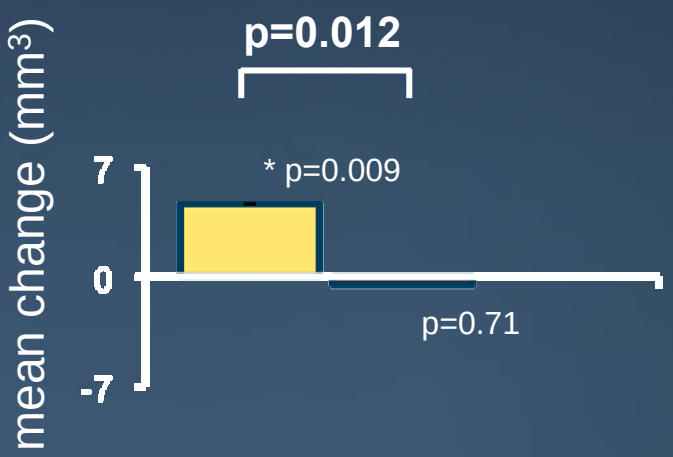
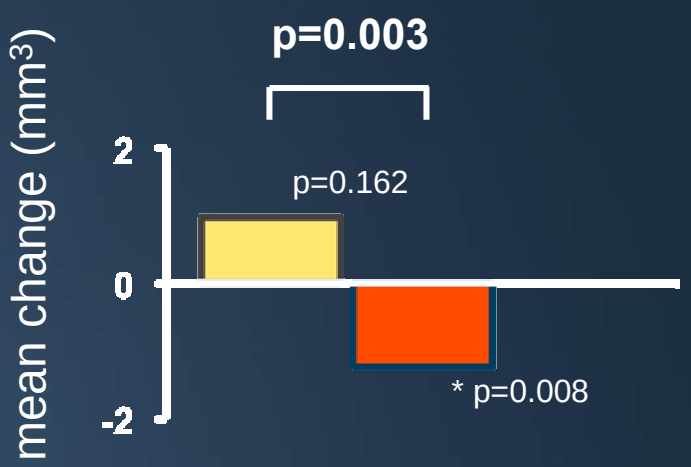
Plaque Composition
by IVUS - VH
change from baseline in necrotic core volume

Entire region of interest
[mean 48 mm]



The worst 10 mm subsegment



placebo (plus standard of care) n=110
darapladib 160 mg (plus standard of care) n=129

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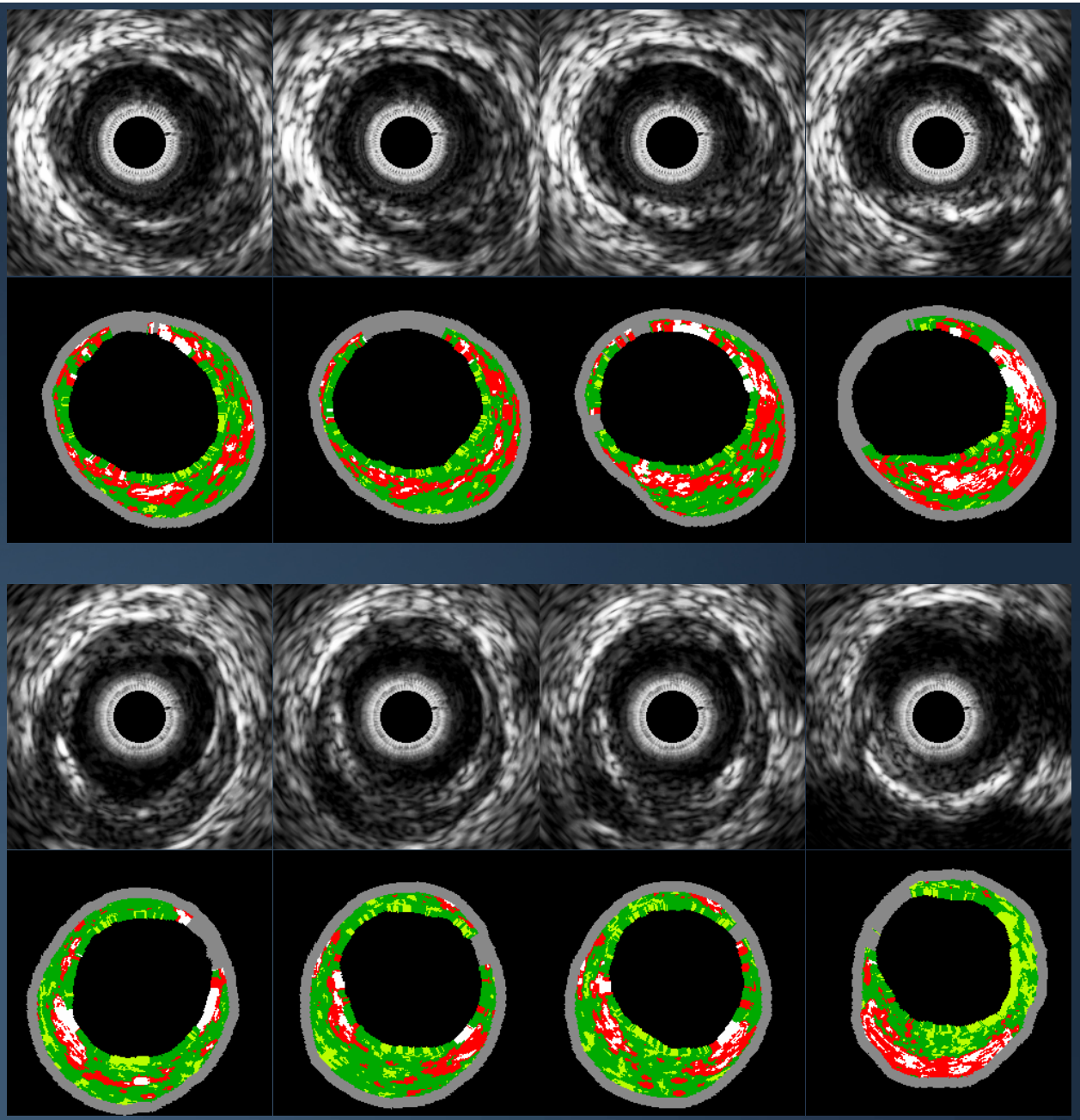
Darapladib

Baseline

Follow-up



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Prospective, randomized comparison of pioglitazone vs control in 54 patients (86 lesions) with type 2 diabetes and stable angina

	Pioglitazone (n=42)	Control (n=44)	P-value
Δ plaque burden	1.7±6.6%	-0.2±5.8%	0.14
Δ fibrous tissue	3.8±7.4%	-1.3±10.8%	0.014
Δ fibrofatty tissue	3.4±6.2%	-0.1±8.6%	0.039
Δ dense calcium	-2.3±5.1%	0.0±4.0%	0.017
Δ necrotic core	-4.6±5.9%	1.1±9.3%	0.001

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(Ogasawara et al. Circulation J 2009;73:343-51)

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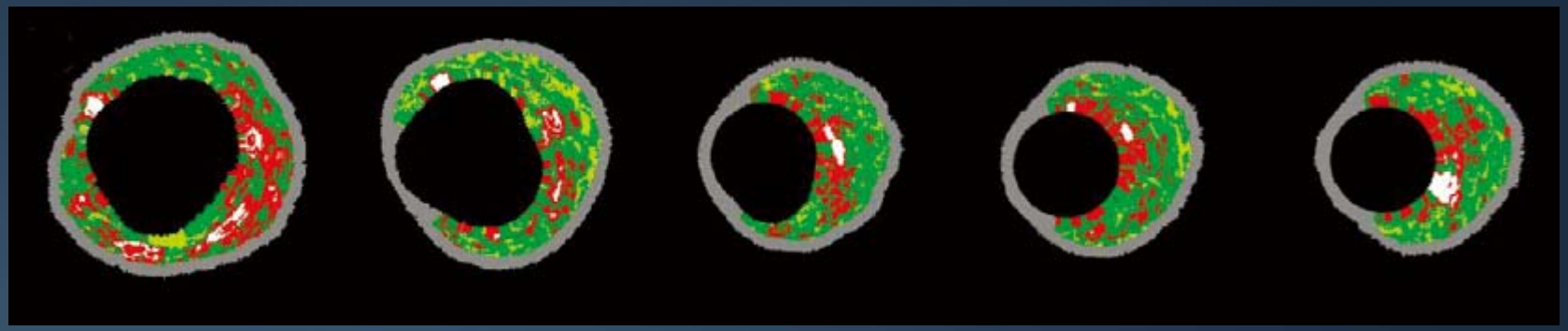
Representative image from patient treated with pioglitazone

Baseline NC volume = 28%



Follow-up NC volume = 18%

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- Culprit of the culprit
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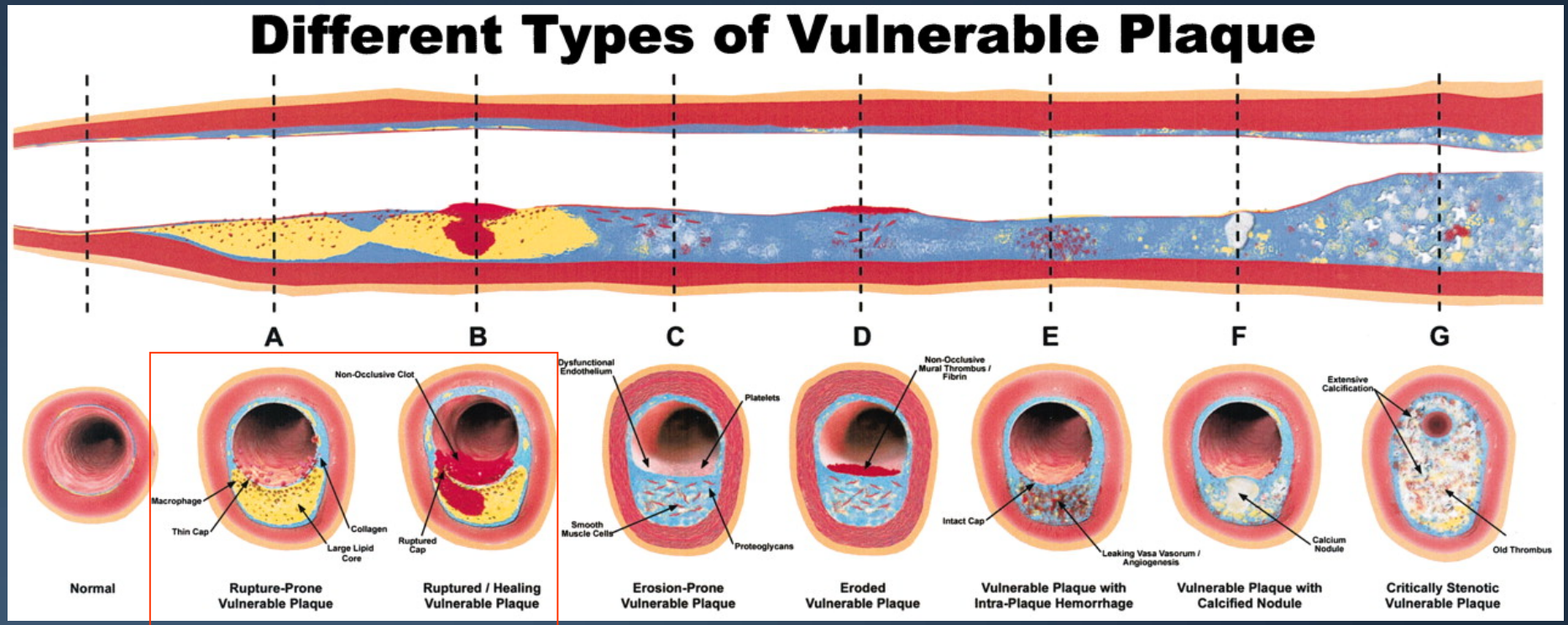
- Serial analysis
- **Comparative studies and competitive technologies**
- Limitations



70% of ACS culprit lesions

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(Naghavi et al. Circulation 2003;108:1664-72)

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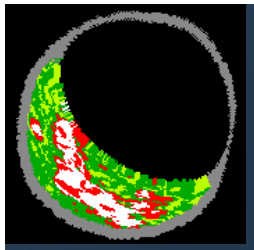


PROSPECT: Imaging Summary

Per patient incidence of VH-TCFAs/ThCFAs

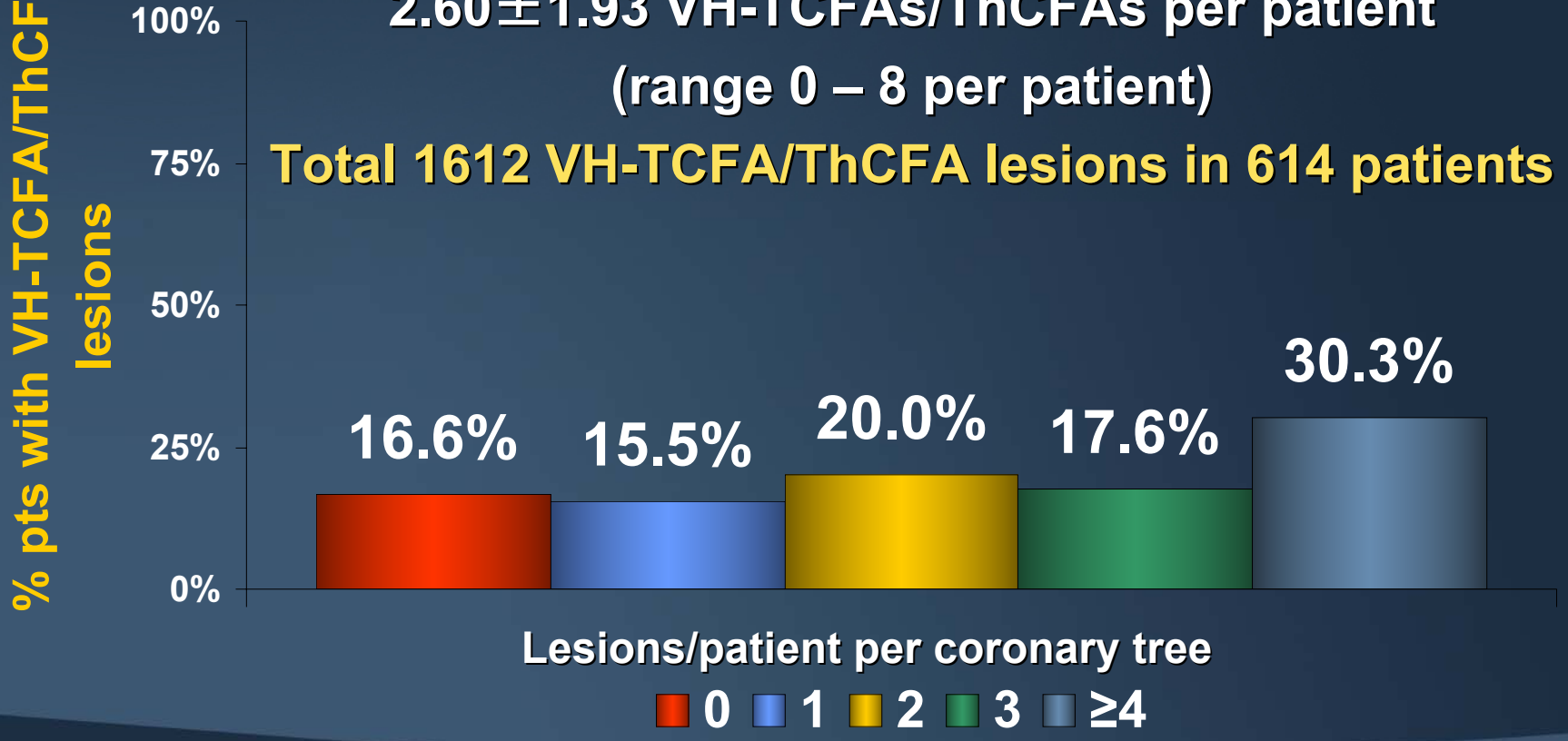
49.8% of patients have ≥1 VH-TCFA

71.8% of patients have ≥1 VH-ThCFA

2.60±1.93 VH-TCFAs/ThCFAs per patient

(range 0 – 8 per patient)

Total 1612 VH-TCFA/ThCFA lesions in 614 patients



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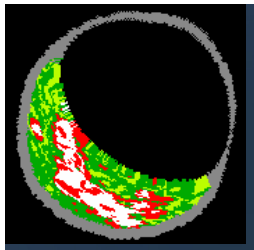


PROSPECT: Imaging Summary

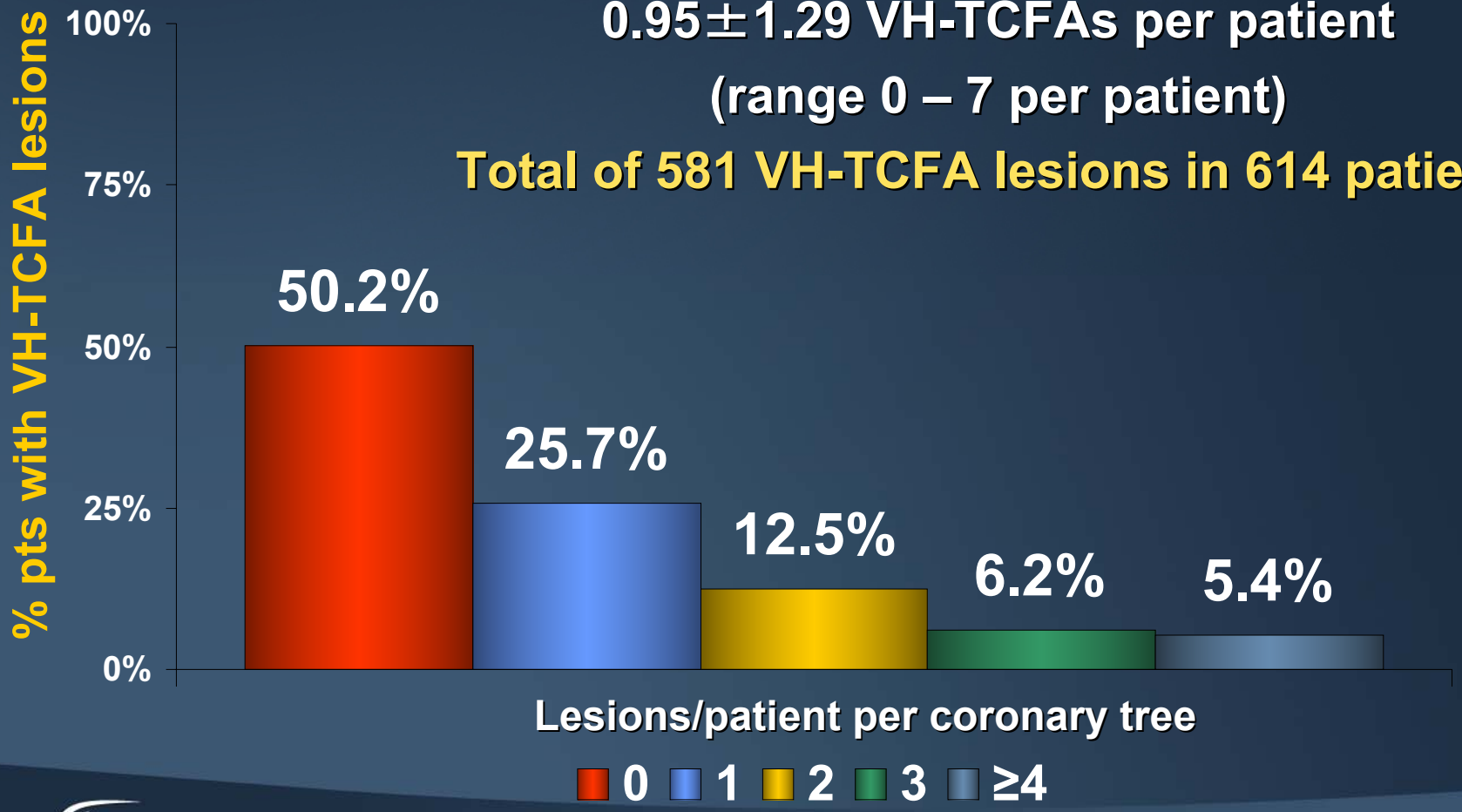
Per patient incidence of VH-TCFAs

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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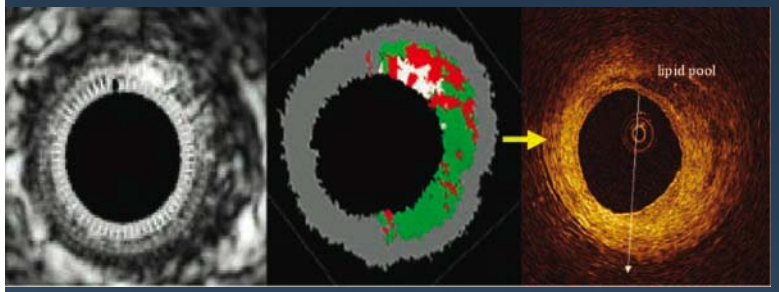
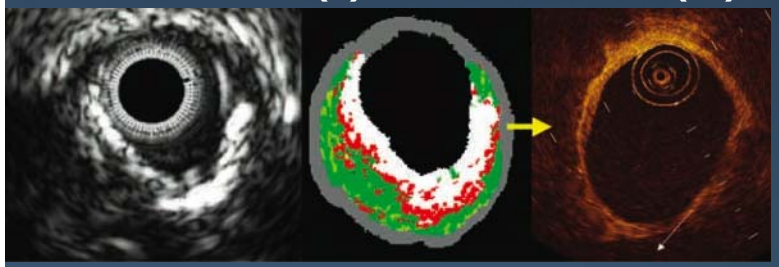
OCT vs VH-IVUS TCFA diagnosis in 126 lesions in 56 pts

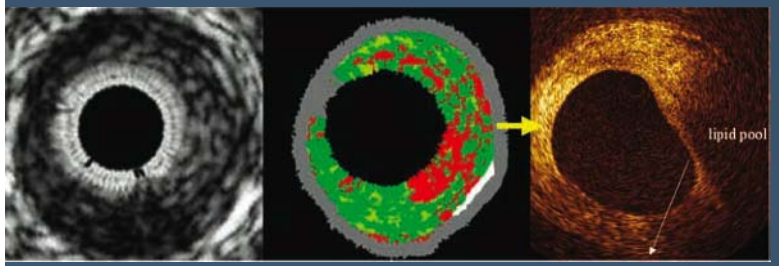
VH-IVUS (+) and OCT (-)



VH-IVUS (-) and OCT (+)



VH-IVUS (+) and OCT (+)



VH-IVUS	OCT +	OCT -
+	28 (22%)	33 (26%)
-	8 (6.3%)	

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(Sawada et al. Eur Heart J 2008;29:1136-46*)*

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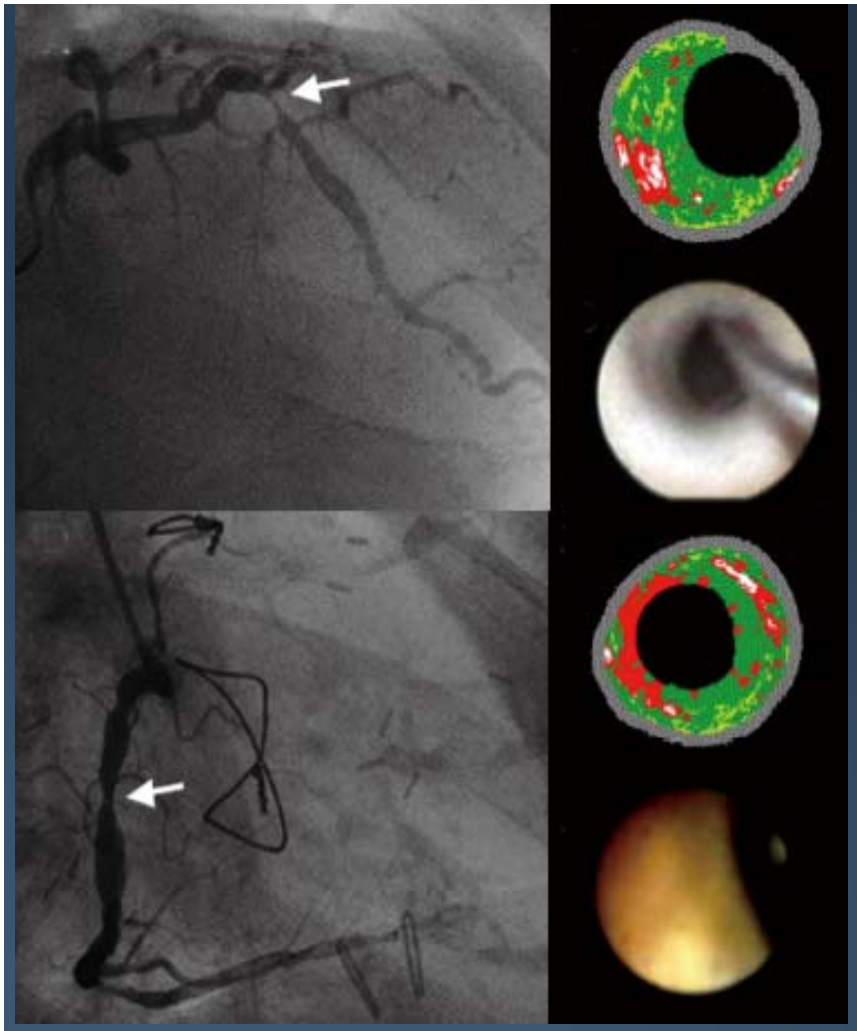

Angioscopy vs VH-IVUS TCFA diagnosis in 57 culprit lesions in 57 pts

VH-IVUS	OCT +	OCT -
+	17	8
-	6	26

When angioscopic-TCFA was used as the gold standard, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for VH-TCFA was 68%, 81%, 74%, 76%, and 75%, respectively.

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(Yamamoto et al. Circulation J 2009;73:497-502)

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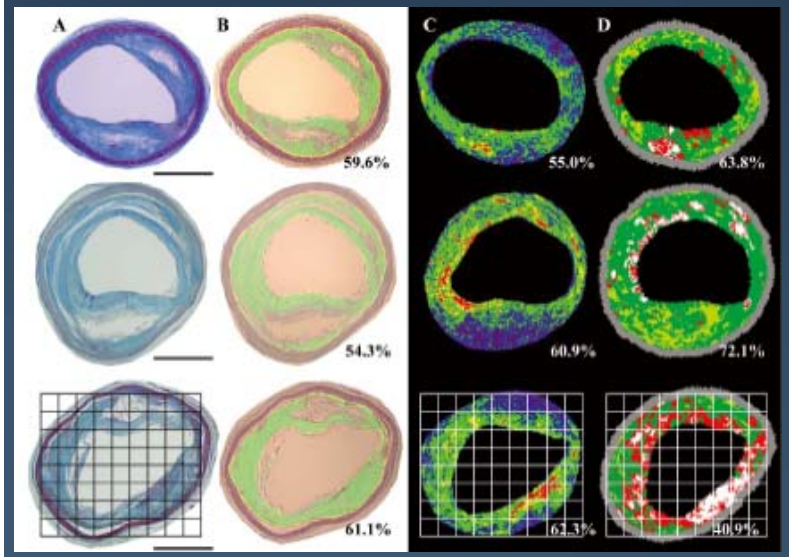
In vitro comparison of IB-IVUS With VH-IVUS in 392 histologic sections from 46 coronary arteries



- In the direct qualitative comparison, the overall agreement between the histological and IB-IVUS diagnoses was higher (Cohen's κ =0.81, 95% CI: 0.72–0.89) than between the histological and IVUS-VH diagnoses (Cohen's κ =0.30, 95%CI: 0.14–0.41) (Table 2).
- Although the location of each tissue component depicted by IVUS-VH did not always accurately reflect the histological location, the overall agreement of IVUS-VH in the "quantitative" comparison (0.73) was better than that in the "qualitative" comparison (0.66), whereas the IB-IVUS values were similar (0.83 and 0.81).

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(Okubo et al. Circulation J 2008;72:1631-1639)

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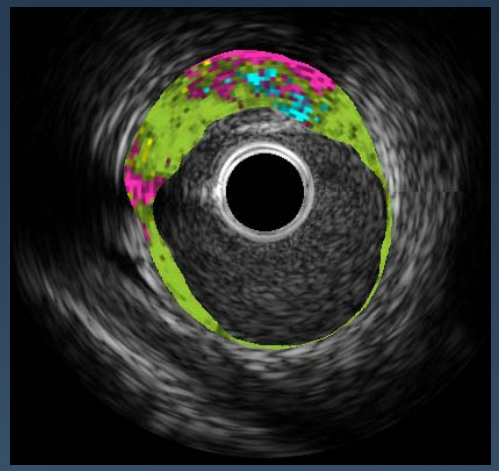
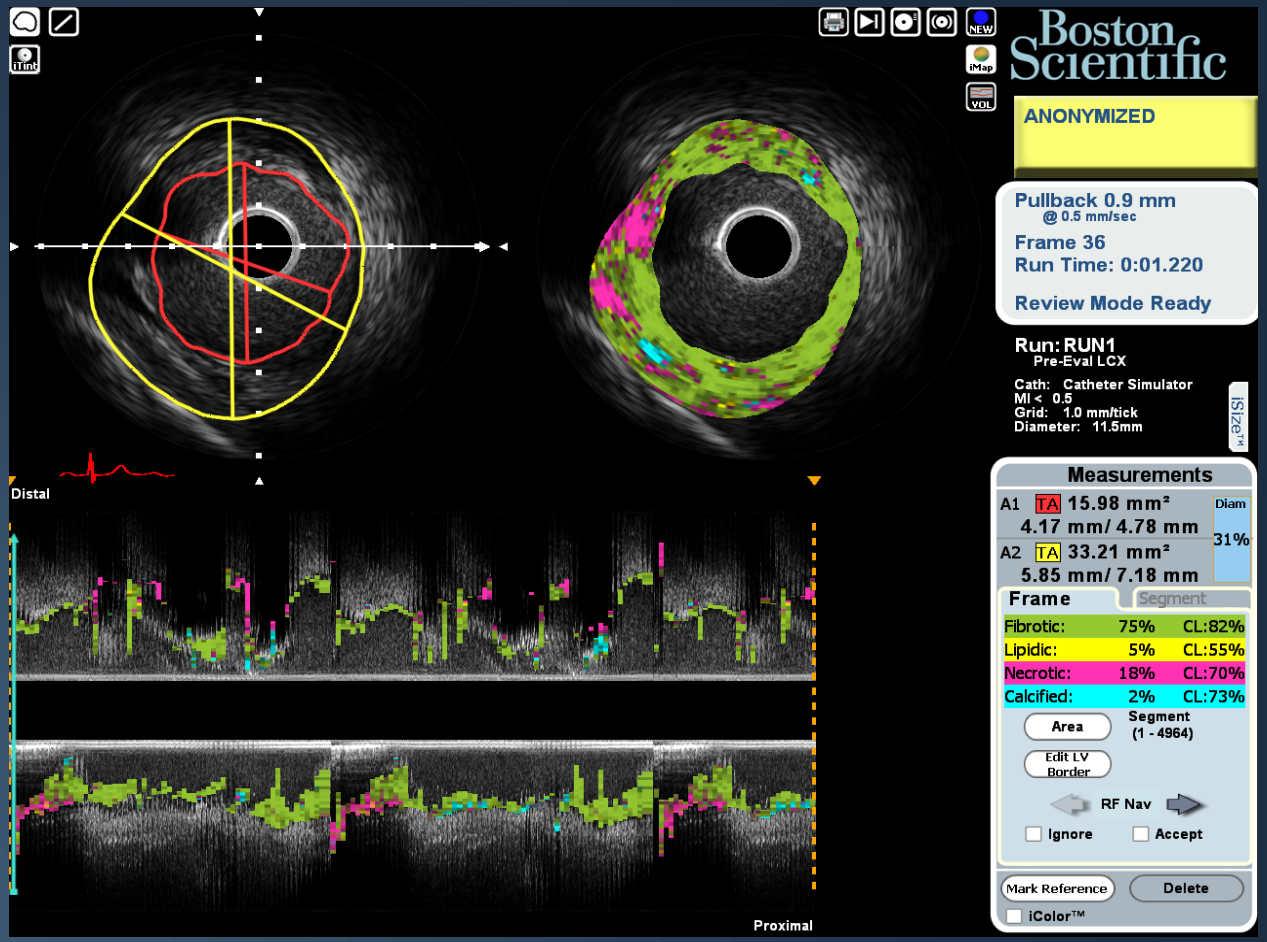
iMAP



- Fibrotic
- Lipidic
- Necrotic
- Calcified



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iMAP

- 40MHz temporal and spatial resolution
- Not ECG-gated. Instead, 2 frames/mm are captured
- Overall and regional limits (i.e., behind calcium)
- Real-time automatic border tracing and tissue characterization. When borders are manually corrected, entire volume is updated, also in real time.
- Longitudinal view.
- Can analyze specific regions of interest, rather than just entire atheroma.
- RF data always acquired, even if just saved in the background for “posterity.” Can be “resurrected” and viewed at any time in the future.

- Culprit of the culprit
- PCI complications
- Serial analysis
- Comparative studies and competitive technologies
- Limitations

Limitations – I: Thrombus

- A total of 259 in vitro histology slices were obtained and pathological thrombus was detected in 81 slices
- Intramural thrombus was colored as fibrous or fibro-fatty by VH-IVUS, reducing the VH accuracy in these kinds of lesions.
  - Correlation was favorable with high sensitivity for all plaque components, even in the presence of thormbus
  - However, specificities for fibrotic and fibrofatty plaque were lower in thrombus slices vs non-thrombus containig slices: 36.4% vs. 93.8%) for fibrotic plaque and 8.7% vs. 60% for fibro-fatty plaque thereby reducing the predictive accuracies from 98.6% to 78.1% for fibrotic plaque and from 82.7% to 67.7% for fibrofatty plaques.

Nasu et al Am J Cardiol 2008;101:1079-83

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).

Tanaka et al. J Am Coll Cardiol 2007;49:29B

Limitations – III: Others

- 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
- Guidewire artifact appears as necrotic core (iMAP)
- All tissue between lumen and vessel borders must be classified as one of the four tissue types