Virtual Histology: An Update and How It Might Be Used in Clinical Practice

Gary S. Mintz, MD

Cardiovascular Research Foundation
New York, NY

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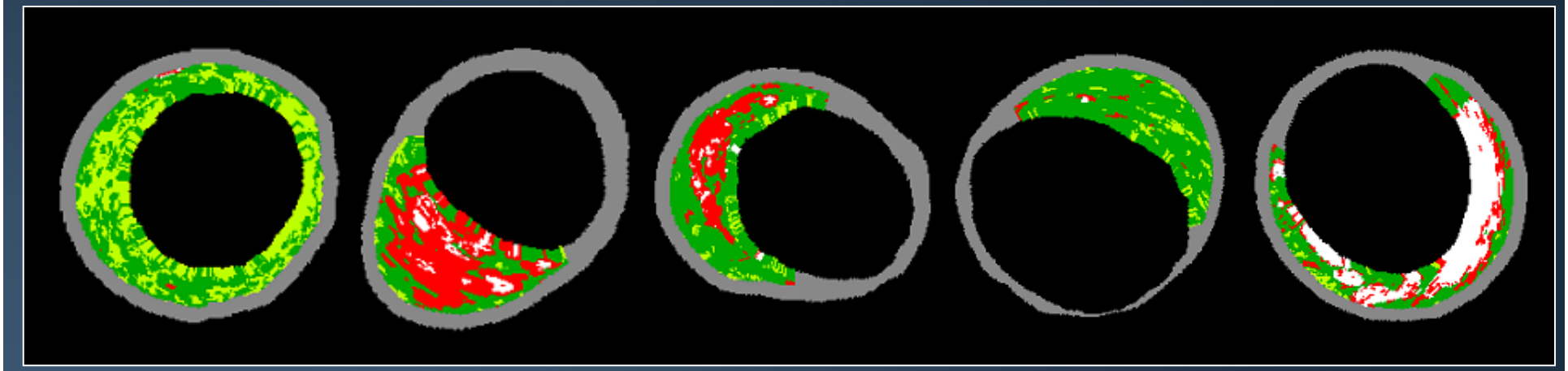
Eagle Eye (20MHz Electronic Array Transducer)

VH IVUS vs histopathology from fresh 51 fresh, post mortem LADs (115 sections and 407 regions of interest)

	Sensitivity	Specificity	Predictive Accuracy
Fibrous tissue (n=162)	84.0%	98.8%	92.8%
Fibrofatty (n=84)	86.9%	95.1%	93.4%
Necrotic core (n=69)	97.1%	93.8%	94.4%
Dense calcium (n=92)	97.8%	99.7%	99.3%

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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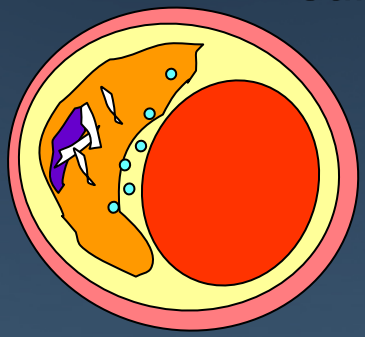
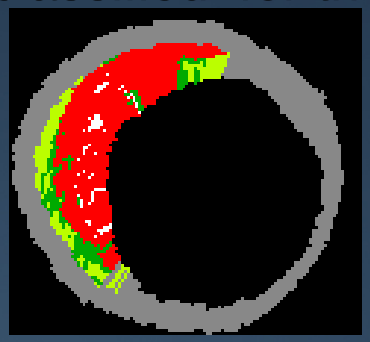
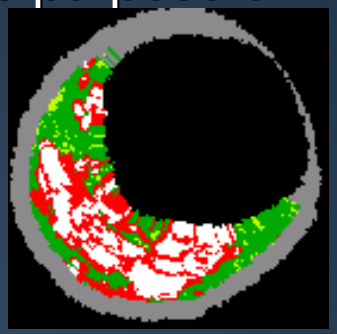
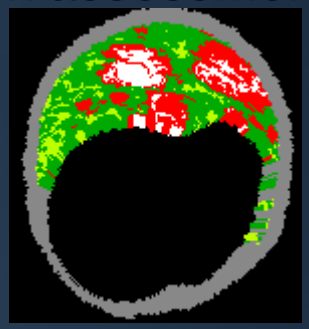
Thin Cap Fibroatheroma (TCFA)

"Thin Cap Fibro-Atheroma (TCFA)" or "Vulnerable Plaque" – Confluent necrotic core >10% of total plaque and located at the lumen in 3 consecutive frames. Based on the presence or absence of Ca, the length of the NC, or signs of previous ruptures, TCFA can be further sub-classified for the purpose of risk assessment



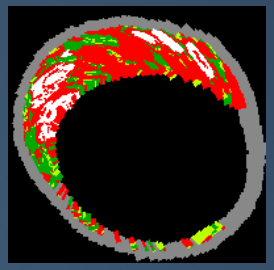


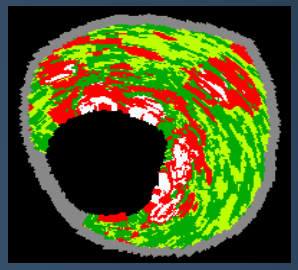




Still further sub-classification can be based on presence of luminal narrowing.

"TICFA without significant narrowing" - plaque burden <50% on IVUS and/or less than 25% narrowing on angiogram. (Pathologic data suggests that TCFA without significant plaque burden are less "vulnerable")





"Highest Risk TCFA"

a. Confluent NC>20%
b. No evidence of fibrotic cap
c. Calcium >5%
d. Remodeling index >1.05
e. >50% plaque burden by IVUS

(Pathologic data suggests that TCFA with significant plaque burden are the most vulnerable)

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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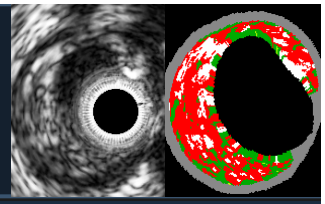
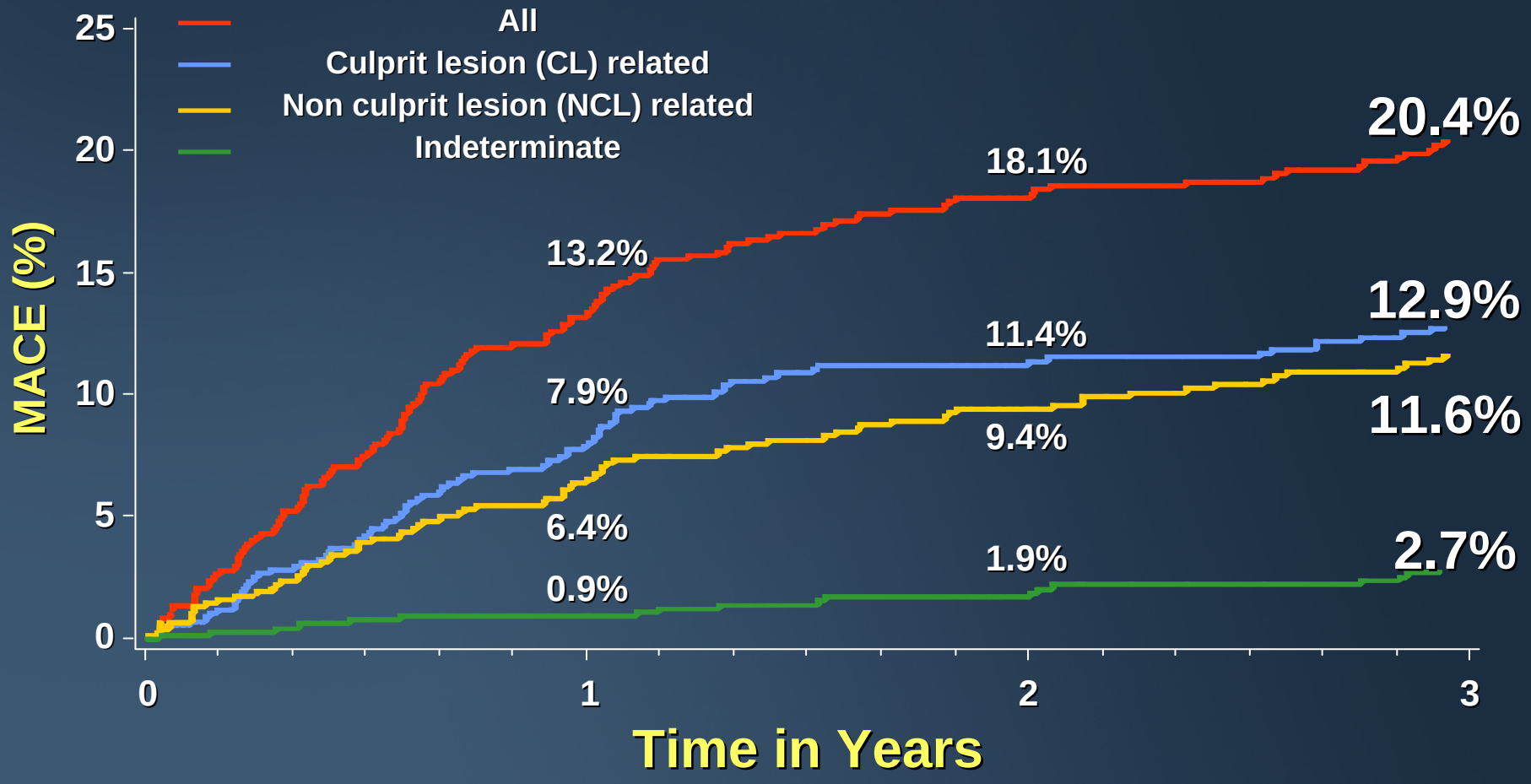
PROSPECT: MACE





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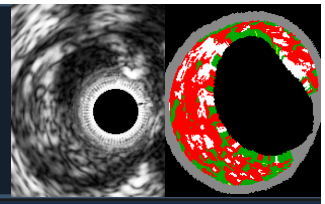
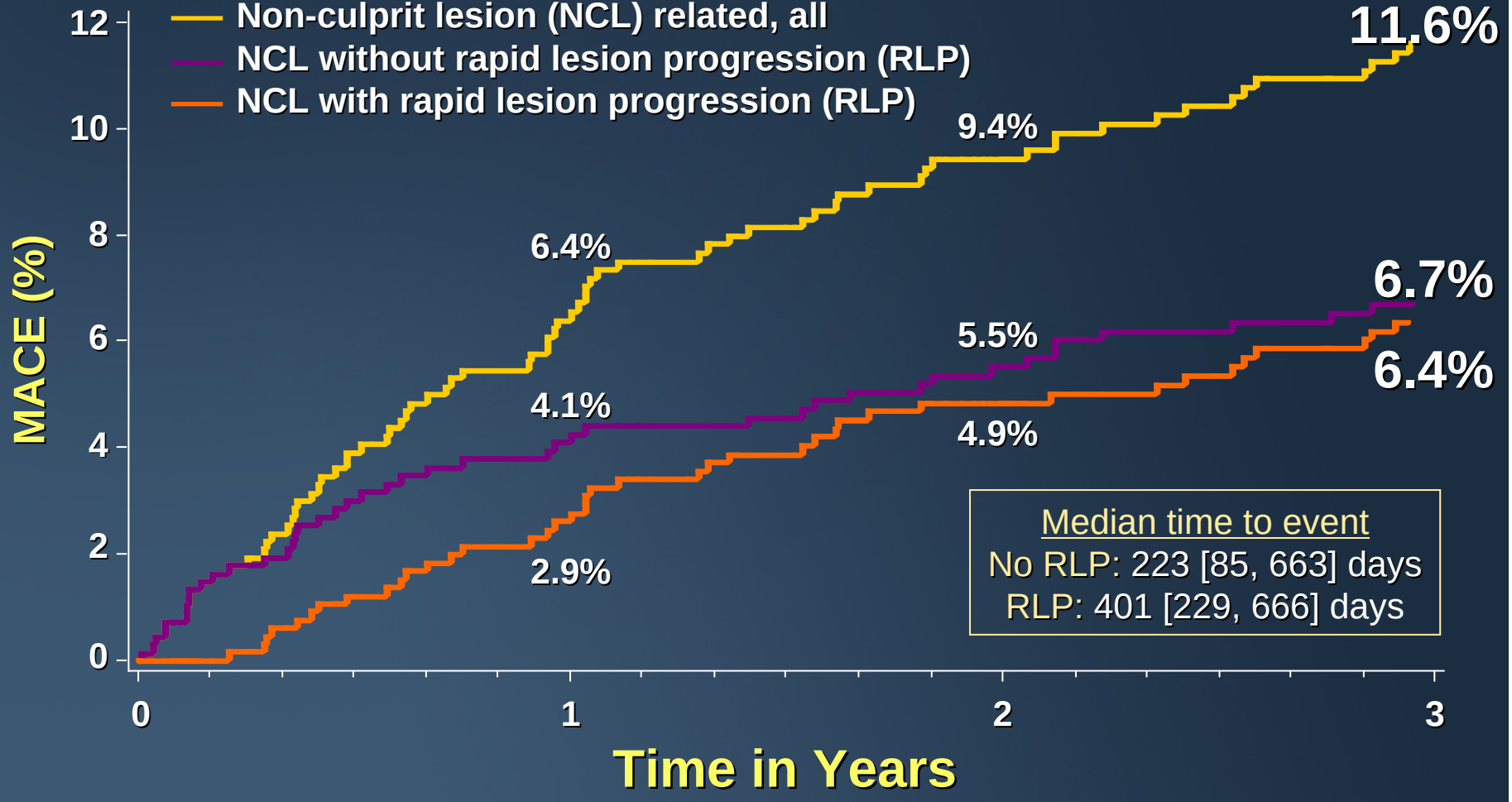
PROSPECT: NCL MACE





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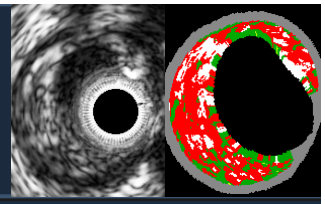
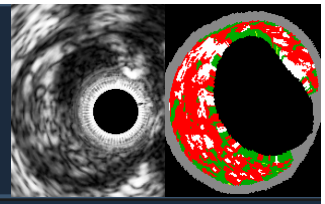
3-year follow-up MACE

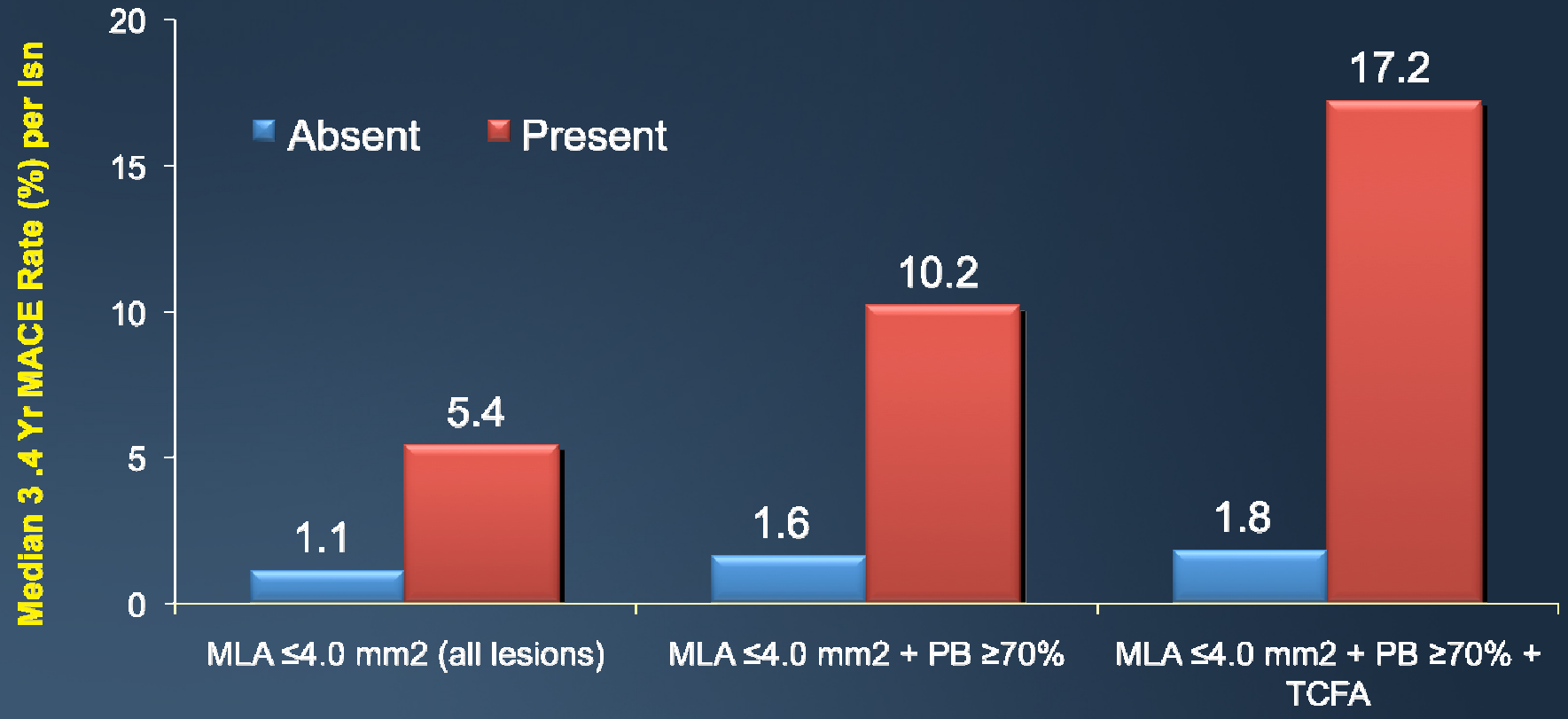


	All	Culprit lesion related	Non culprit lesion related	Indeter-minate
Cardiac death	1.9% (12)	0.2% (1)	0% (0)	1.8% (11)
Cardiac arrest	0.5% (3)	0.3% (2)	0% (0)	0.2% (1)
MI (STEMI or NSTEMI)	3.3% (21)	2.0% (13)	1.0% (6)	0.3% (2)
Unstable angina	8.0% (51)	4.5% (29)	3.3% (21)	0.5% (3)
Increasing angina	14.5% (93)	9.2% (59)	8.5% (54)	0.3% (2)
Composite MACE	20.4% (132)	12.9% (83)	11.6% (74)	2.7% (17)
Cardiac death, arrest or MI	4.9% (31)	2.2% (14)	1.0% (6)	1.9% (12)

Rates are 3-yr Kaplan-Meier estimates (n of events)

Correlates of Non Culprit Lesion Related Events





Lesion HR	5.0 (2.9, 8.7)	6.7 (3.4, 13.0)	10.8 (4.3, 2712)
P-value	<0.0001	<0.0001	<0.0001
Prevalence*	49.1%	15.4%	4.6%

*Likelihood of one or more such lesions being present per patient. PB = plaque burden at the MLA

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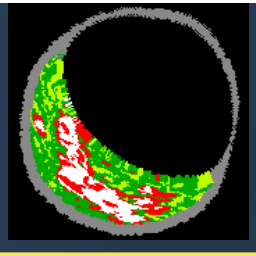
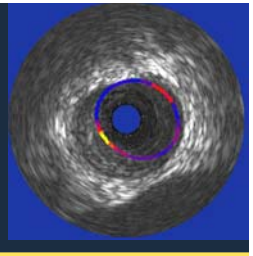


Imaging Summary



In 615/697 pts with a mean of 2.6 (19.3cm) epicardial arteries imaged

≈2700 NC IVUS lesions w/ plaque burden >40% (4.5/pt)

≈60% Fibroatheromas

≈38% VH-ThCFAs

≈22% VH-TCFAs

≈4.6% MLA <4.0mm² and plaque burden >70% per pt

≈5% MLA <4.0mm²

≈17% MLA ≥4.0mm²

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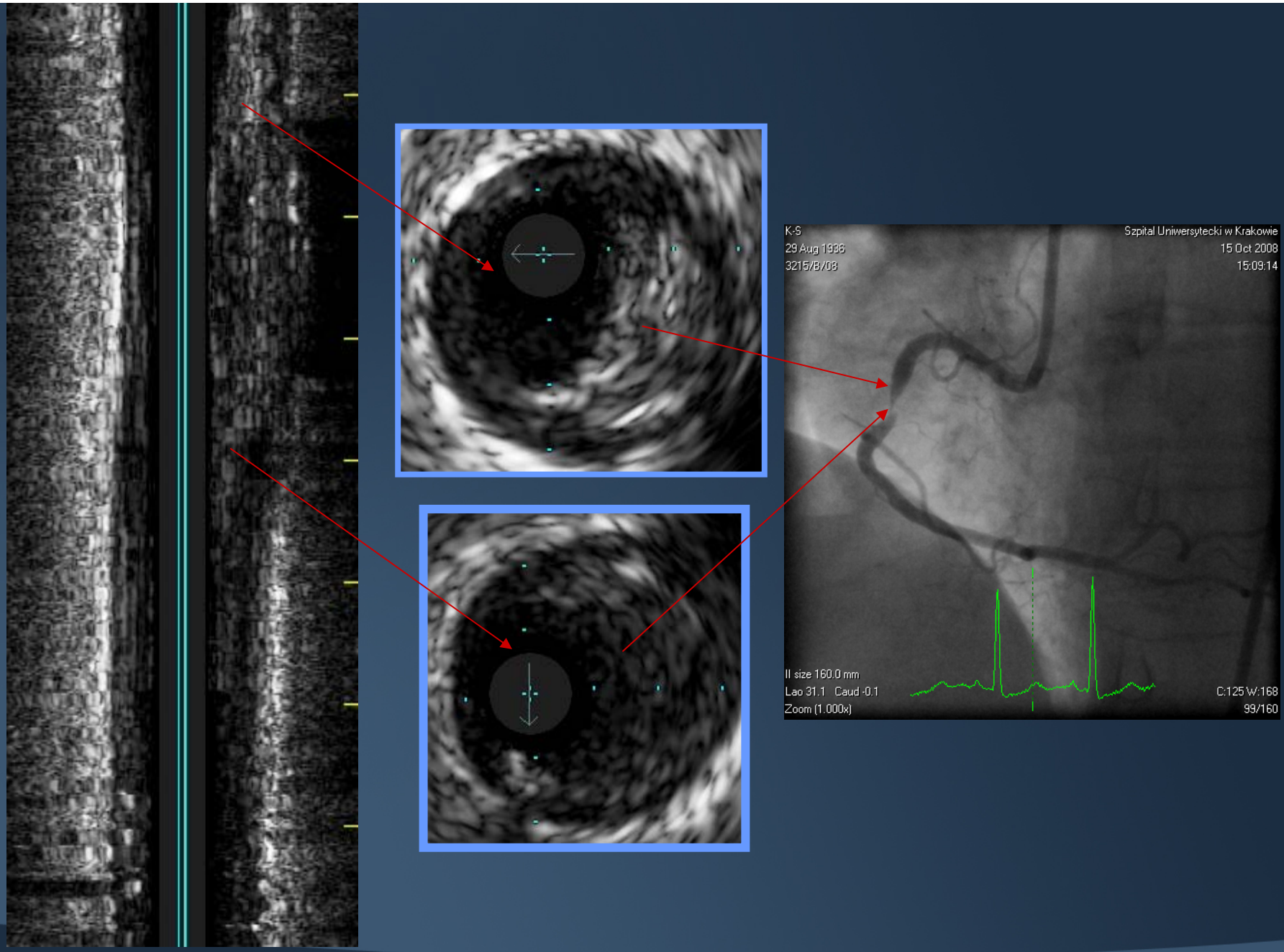

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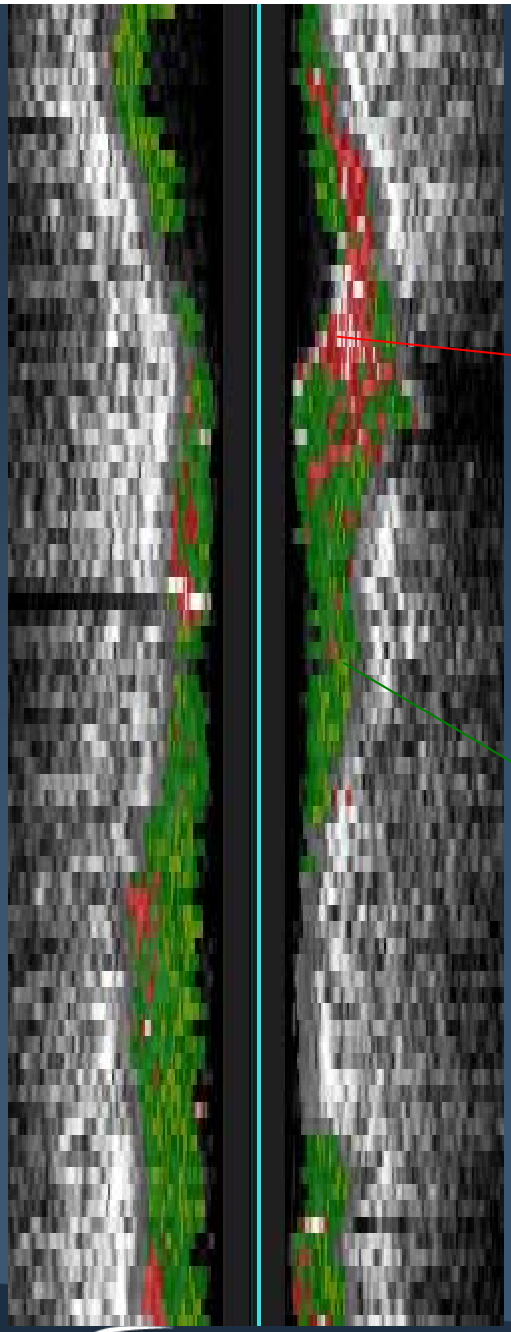
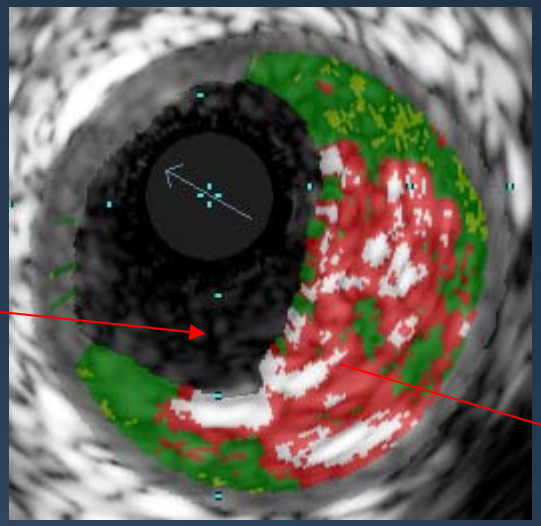
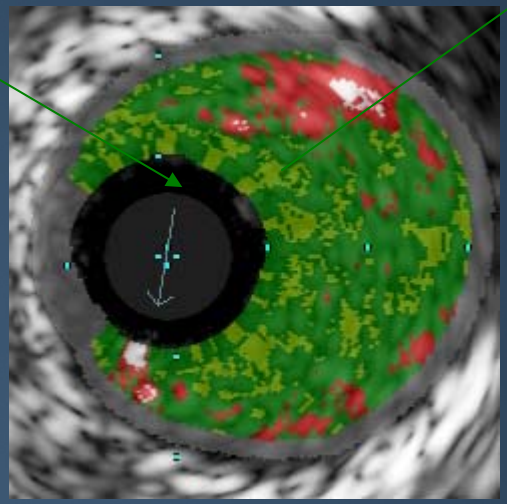
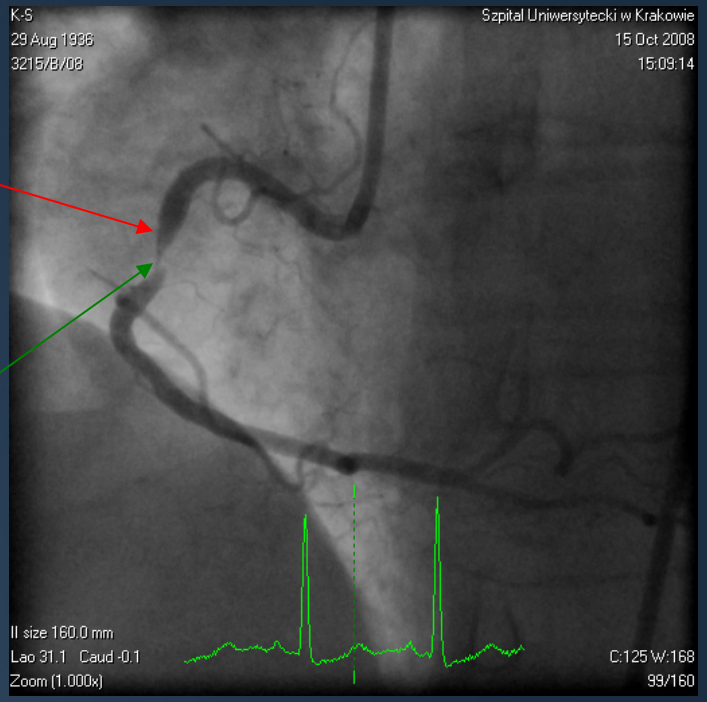




culprit of the culprit proximal to MLA



MLA



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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.
  - 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

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

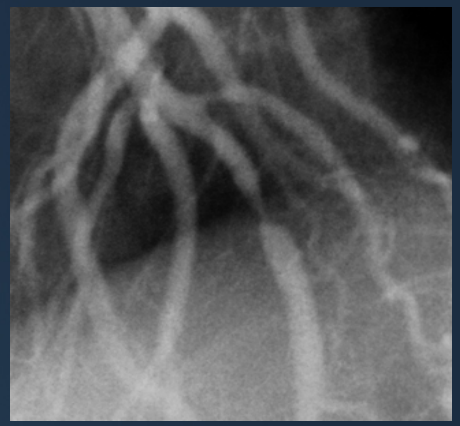
vs Nectoric Core

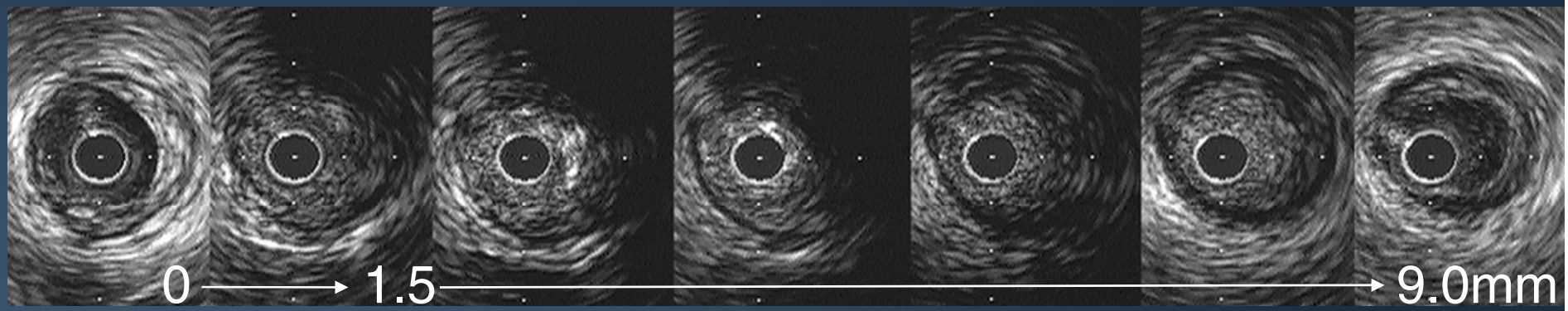
- Kawaguchi et al. J Am Coll Cardiol. 2007;50:1641-6
  - ST re-elevation in 71 pts with STEMI
- Kawamoto et al. J Am Coll Cardiol. 2007;50:1635-40
  - Doppler FloWire high intensity transit signals in 44 pts undergoing elective stenting resulting in poor recovery of CVFR
- Park et al. VH Summit 2007 (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

Attenuated Plaque

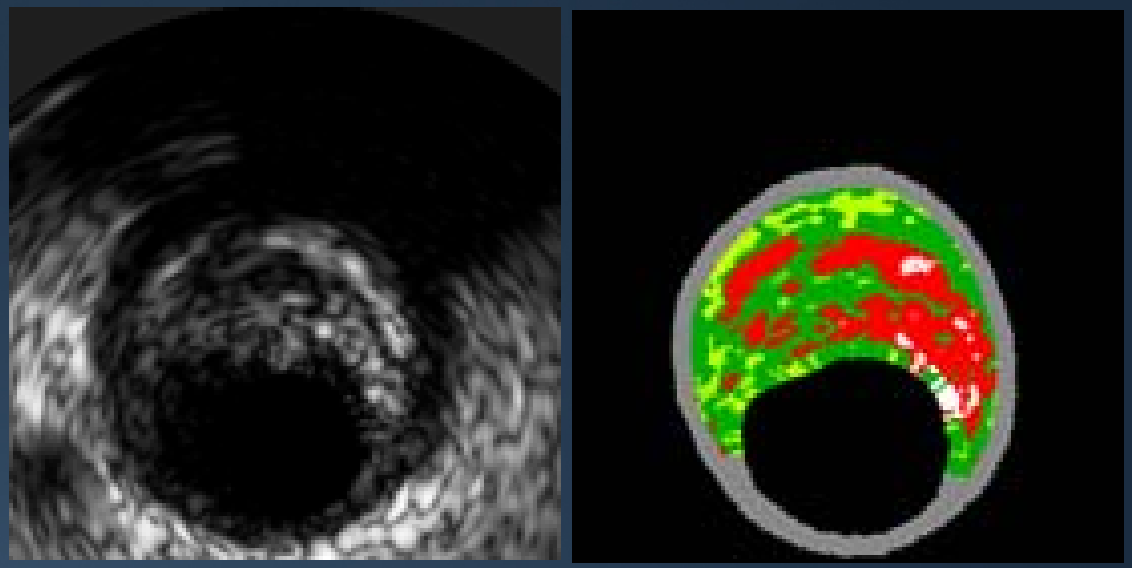




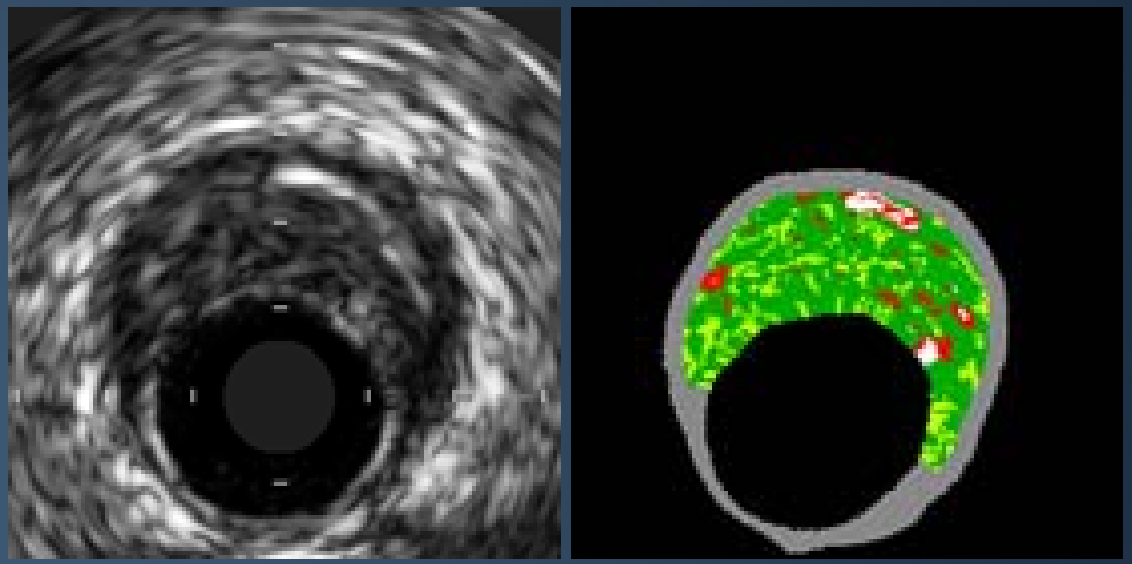
- Attenuated plaques were observed in 39.6% of STEMI, 17.6% of NSTEMI, and 0% of stable angina.
- Attenuate plaques were associated with more fibroatheromas and a larger necrotic core (on VH-IVUS).
- In ACS patients with attenuated plaques (1) the level of CRP was higher, (2) angiographic thrombus and 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, unpublished)

Attenuated Plaque



Non-attenuated plaque



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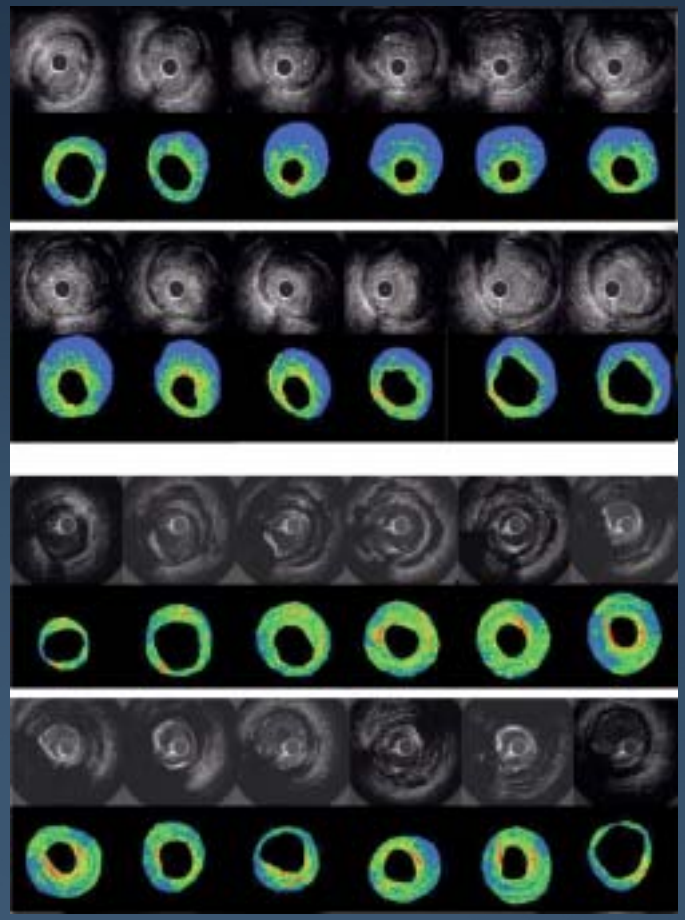
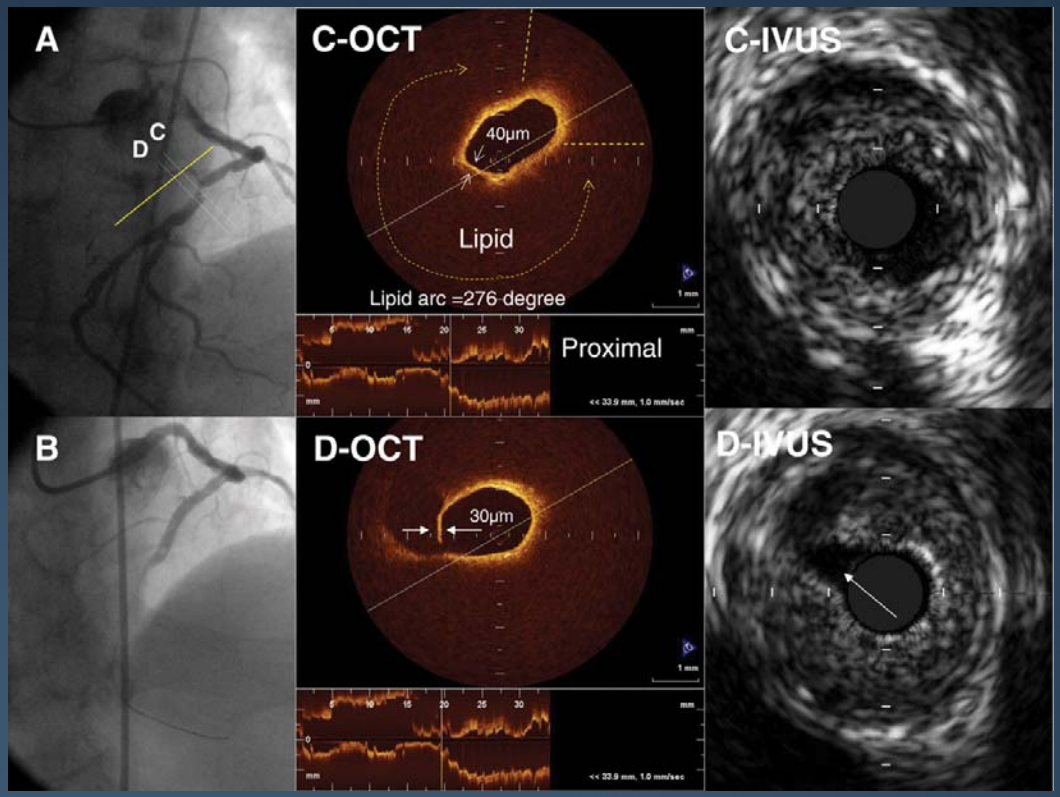


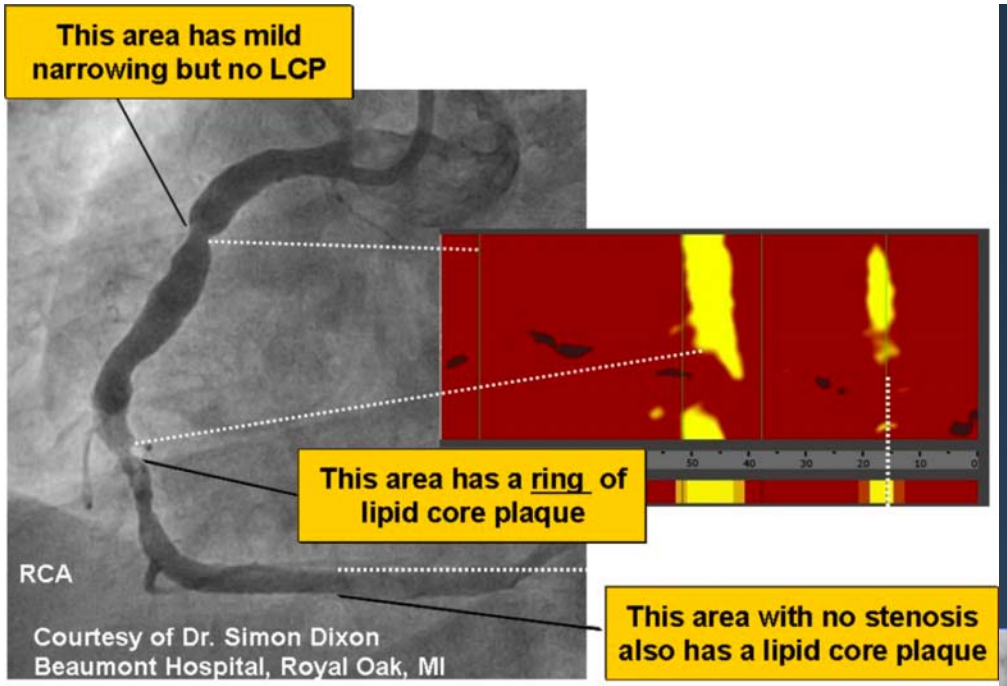
- 114 consecutive patients who received elective stent implantations following IB-IVUS analysis were enrolled.
- The volume of each plaque component (lipid, fibrous, and calcified) was calculated for the target lesion.
- Creatine kinase-MB (CK-MB) and troponin-T (TnT) were evaluated 18 h after procedure.
- Post-procedural TnT level higher than three times the normal limit defined post-procedural myocardial injury.
- Lipid volume fraction (lipid volume/total plaque volume) correlated with post-procedural TnT and CK-MB.

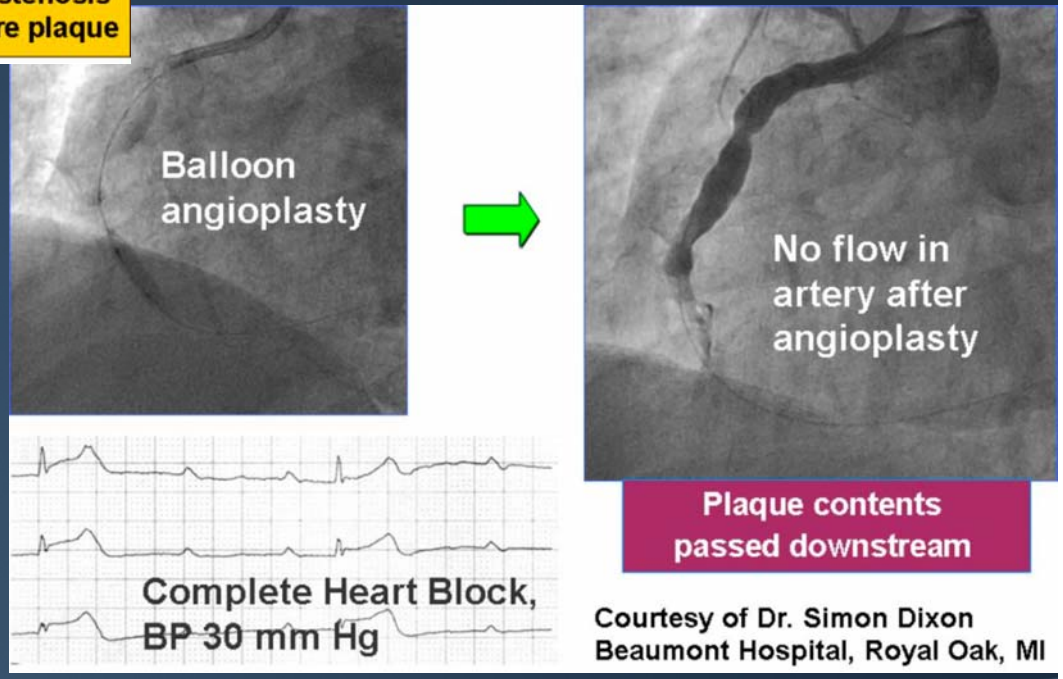
Uetani et al. Eur Heart J 2008;29:1714-20



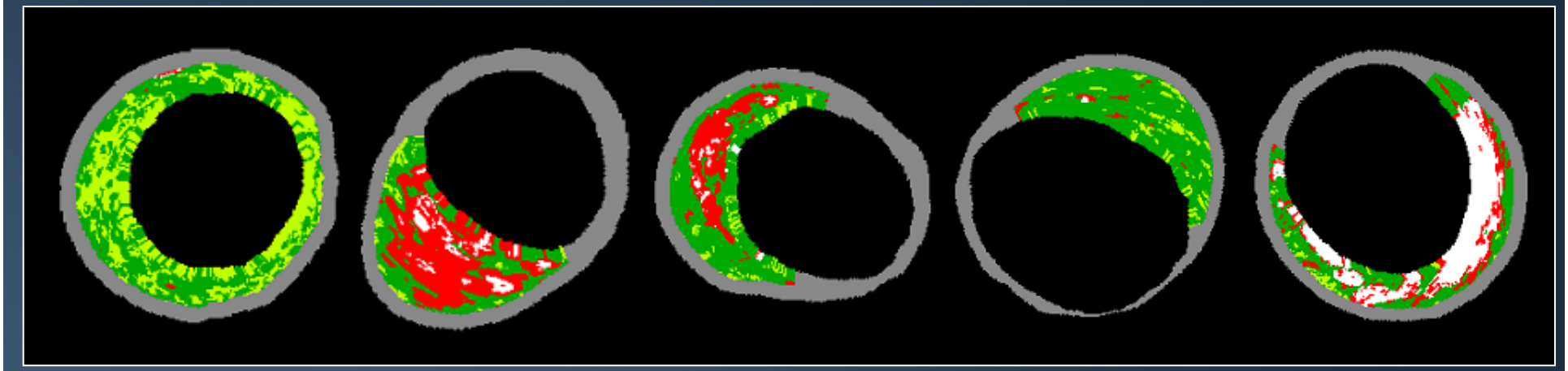
- Patients with NSTE ACS who underwent OCT and successful emergent primary stenting were divided into two groups on the basis of post-stent TIMI flow: no-reflow group (n = 14) and reflow group (n = 69).
- Thin-cap fibroatheroma were more frequently observed in the no-reflow group than in the reflow group (50% vs. 16%, P = 0.005)
- The frequency of the no-reflow phenomenon increased according to the size of the lipid arc in the culprit plaque.
- Final TIMI blush grade also deteriorated according to the increase in the lipid arc.

Tanaka, A. et al. Eur Heart J 2009;30:1348-1355


This area has mild narrowing but no LCP
This area has a ring of lipid core plaque
RCA
Courtesy of Dr. Simon Dixon
Beaumont Hospital, Royal Oak, MI
This area with no stenosis also has a lipid core plaque


Balloon angioplasty
No flow in artery after angioplasty
Complete Heart Block, BP 30 mm Hg
Plaque contents passed downstream
Courtesy of Dr. Simon Dixon
Beaumont Hospital, Royal Oak, MI

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. J Am Coll Cardiol, in press

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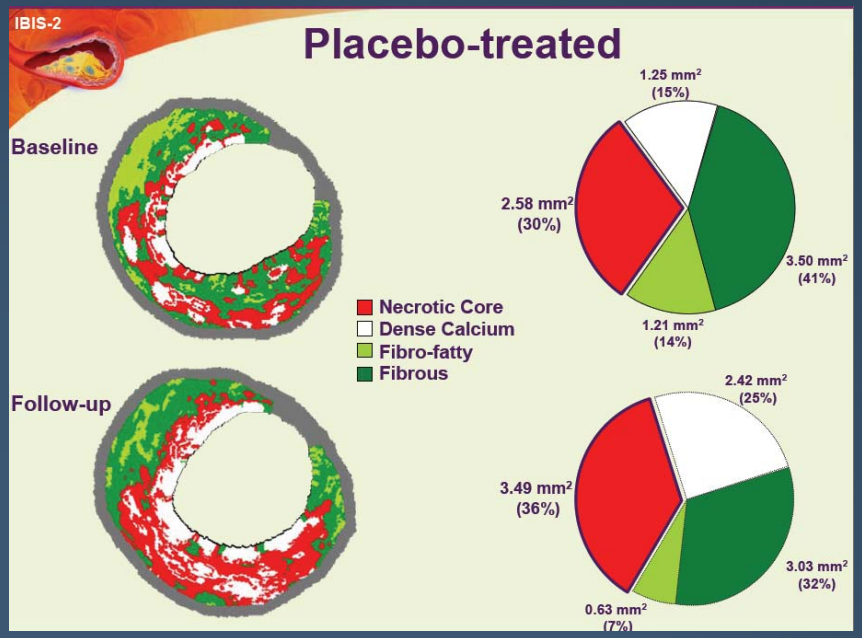
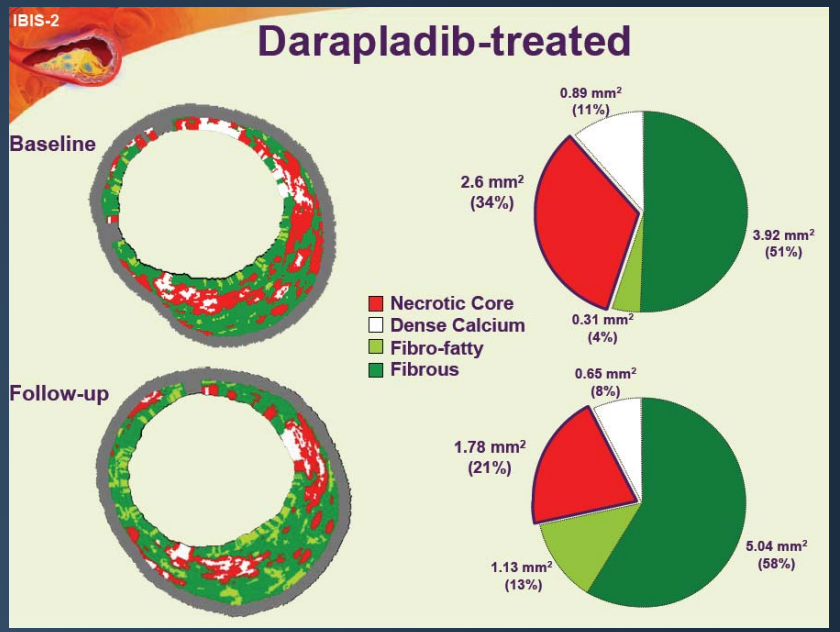
IBIS-2: Effects of the direct Lp-PLA$_2$ inhibitor darapladib vs placebo on human coronary atherosclerotic plaque.

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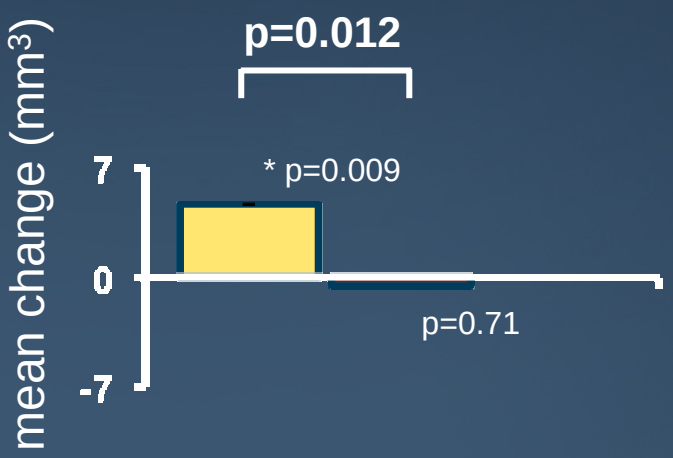
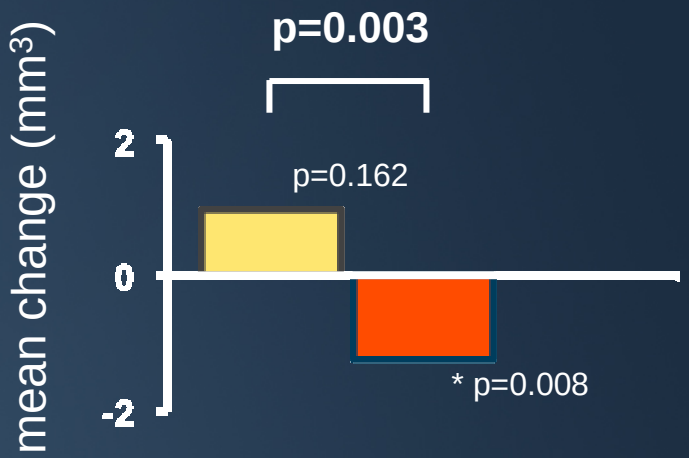
Plaque Composition
by IVUS - VH
change from baseline in necrotic core volume

Entire region of interest
[mean 48 mm]



The worst 10 mm subsegment

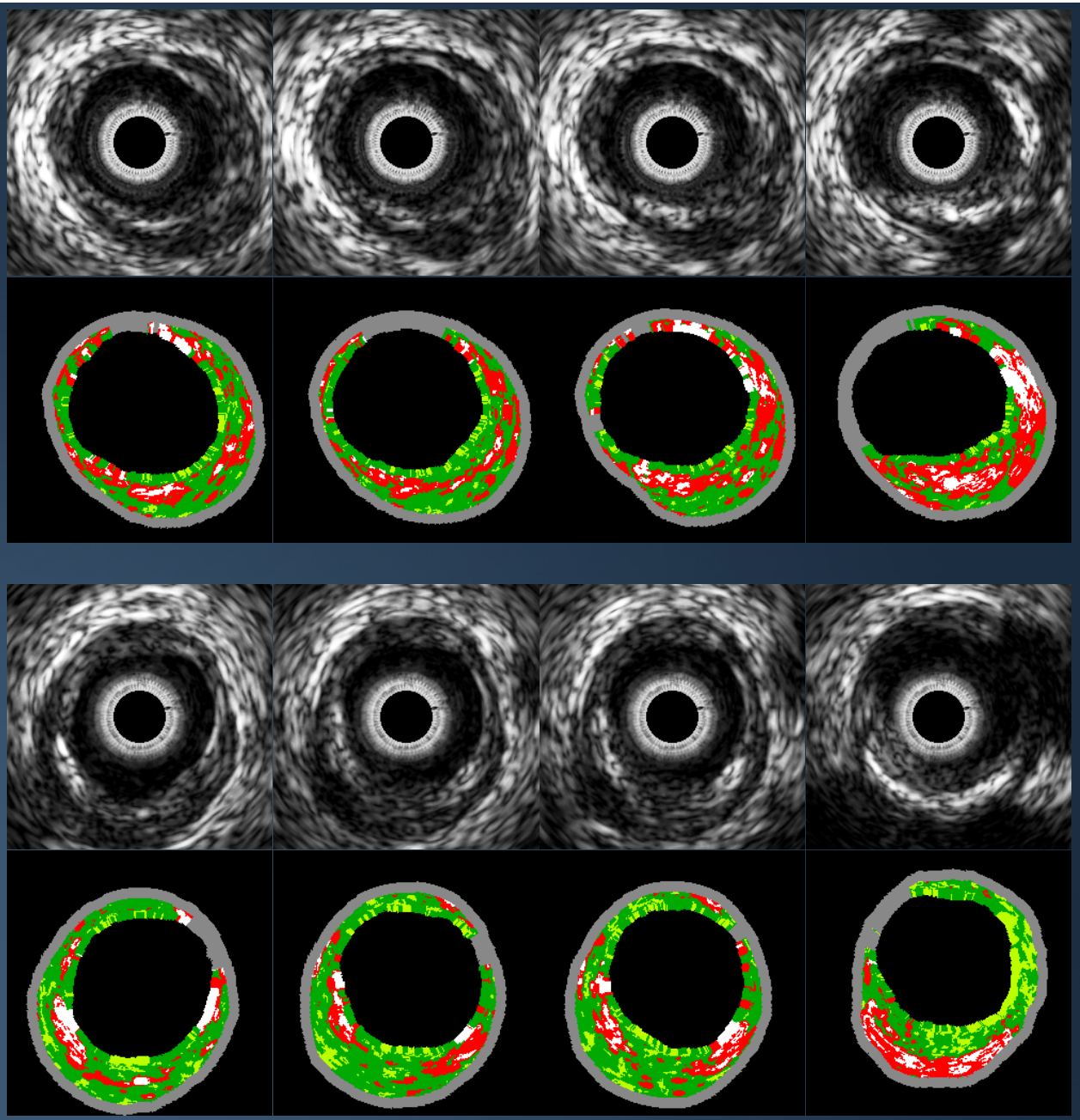


placebo (plus standard of care) n=110
darapladib 160 mg (plus standard of care) n=129

Darapladib

Baseline

Follow-up



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Plaque behind Calcium

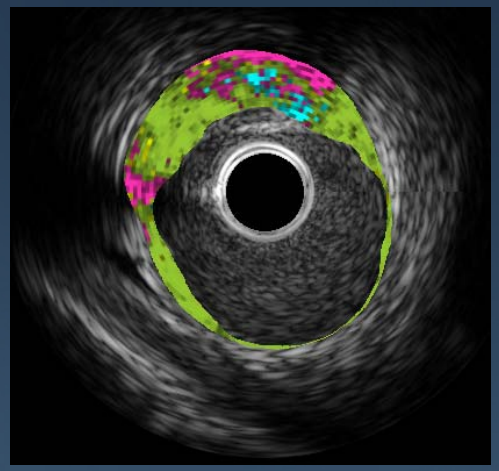
- 80% of regions of interest behind calcium contained a distinct low-amplitude signal that had a coherent periodic pattern on adjacent scan lines and a signal increase in the region of the adventitia indicating that this signal contained reflected ultrasound information as well as noise
- 20% of the 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).

		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%

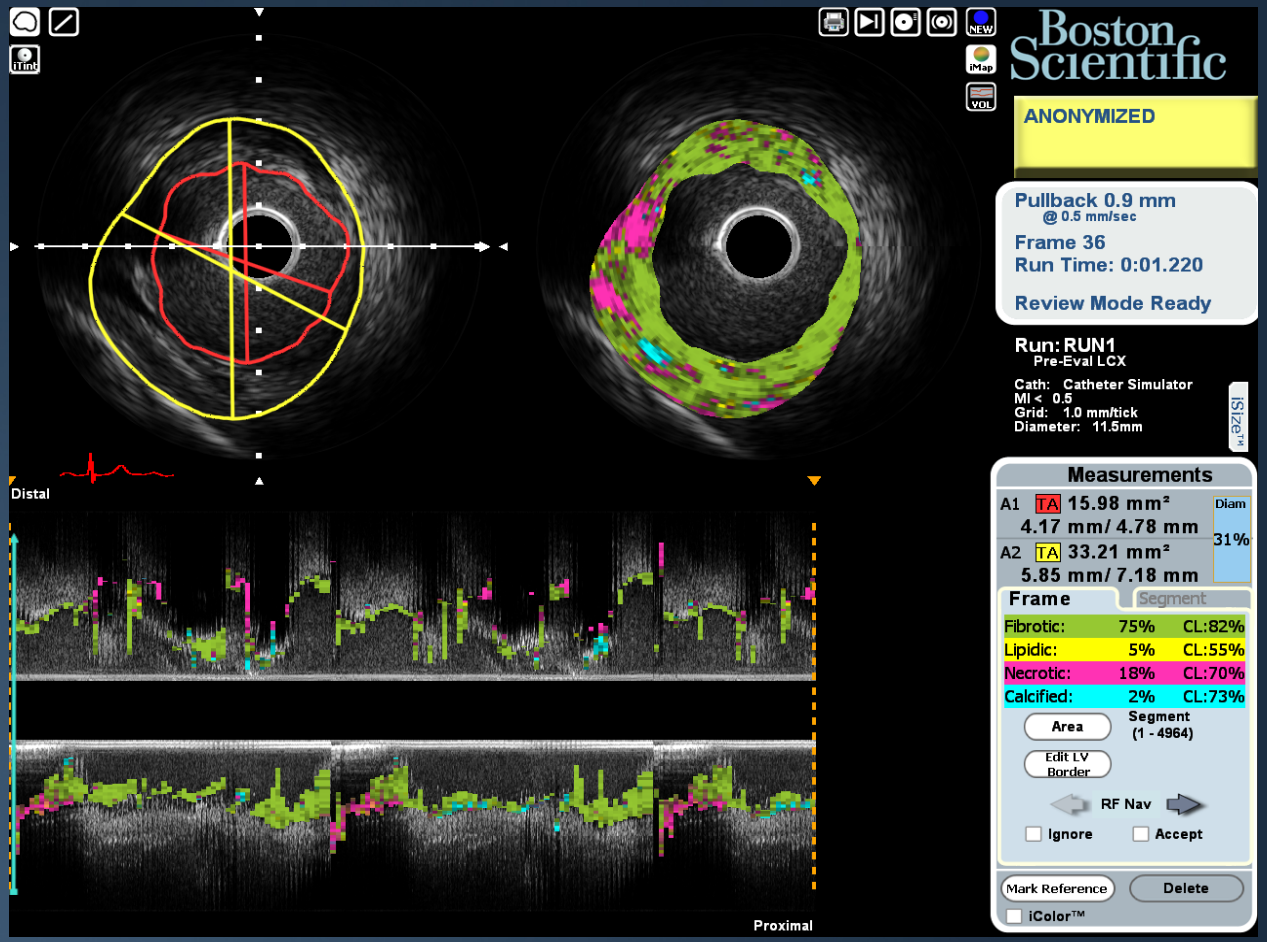
Overall Accuracy: 65.0 %

When inaccurate, tissue is classified as NC (65% of the time), as FT (18% of the time), as FF (14% of the time)

iMAP



- Fibrotic
- Lipidic
- Necrotic
- Calcified



iMAP

- 40MHz temporal and spatial resolution
- Not ECG-gated. Instead, 2 frames/mm are captured
- Output includes confidence limits - overall and regionally (i.e., behind calcium)
- 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.