

# VH: Current Status and Future Perspectives

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CARDIOVASCULAR RESEARCH  
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COLUMBIA UNIVERSITY  
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# Disclosure Statement of Financial Interest

Within the past 12 months, I have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<u>Affiliation/Financial Relationship</u>	<u>Company</u>
Grant/Research Support	BostonScientific, Volcano
Consulting Fees/Honoraria	BostonScientific, Volcano, LightLab, Terumo
Major Stock Shareholder/Equity	Volcano
Royalty Income	
Ownership/Founder	
Intellectual Property Rights	
Other Financial Benefit	



# What does greyscale IVUS do poorly?

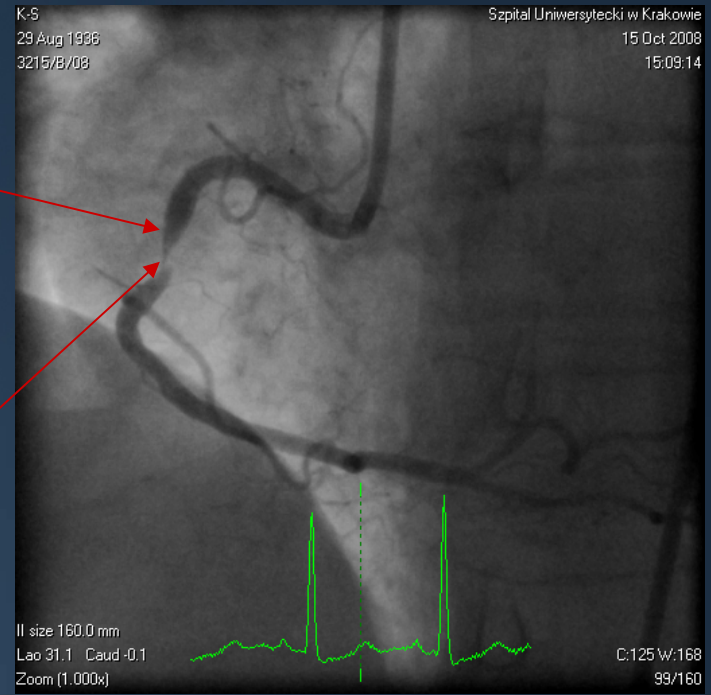
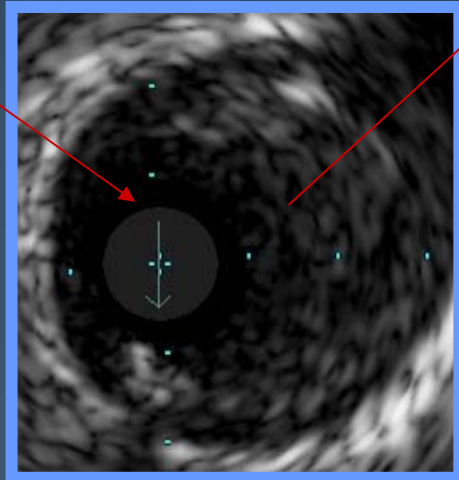
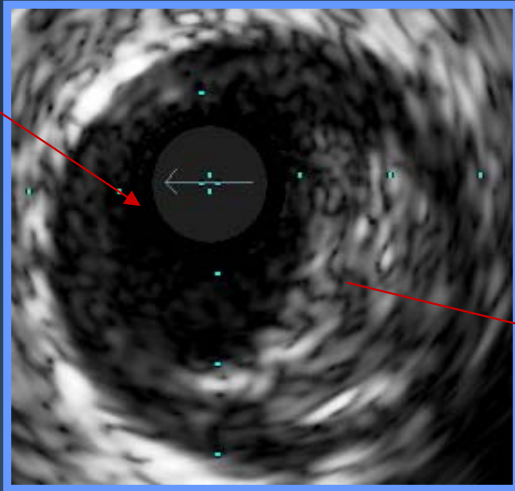
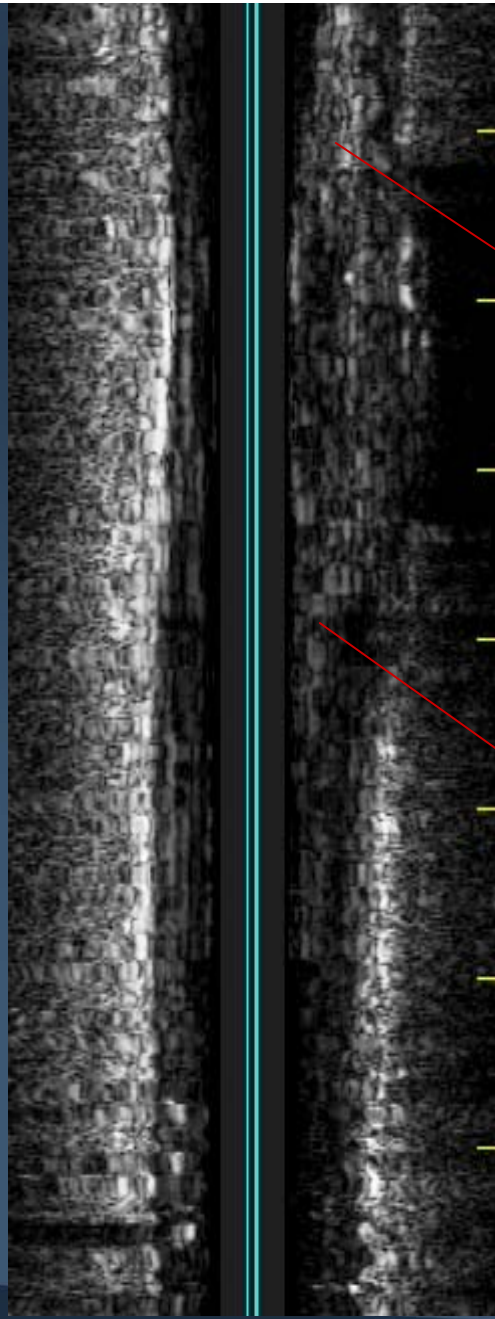
- Pre-intervention lesion assessment
  - 3-D orientation and spatial relationships
  - **Plaque composition (except calcium)**
  - **Vulnerable plaque and other lesion phenotypes**
  - High risk PCI lesions
  - Thrombus
- Post-intervention lesion assessment
  - Subtle dissections, stent malapposition, plaque prolapse, etc.
  - Thrombus
- Follow-up
  - Subtle malapposition
  - Small amounts of intimal hyperplasia
  - Predicting late events (especially very late stent thrombosis)
- Progression/regression
  - **Changes in individual plaque components**

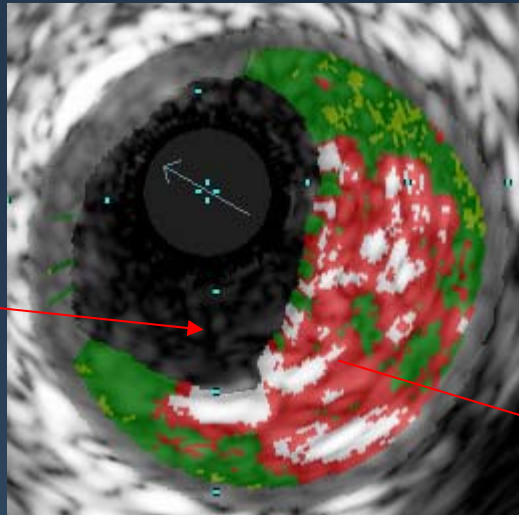
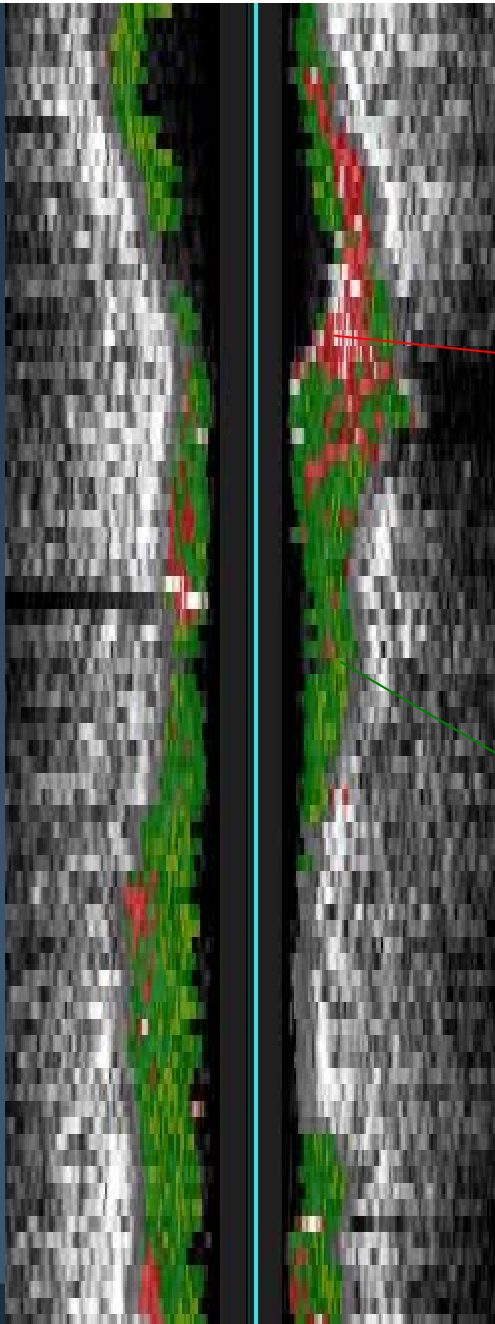


- **Culprit of the culprit**
- **PCI complications**
- **Serial analysis**
- **Limitations**

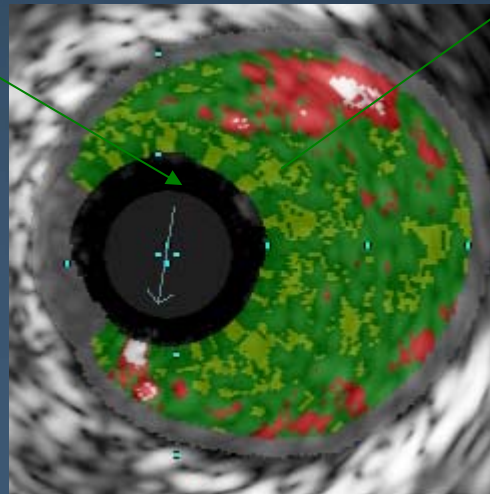


- 72 year old female with diabetes and hypertension presented with 3 hours of chest and transient complete heart block
- Medication during transfer to hospital (40km) included aspirin 300mg, clopidogrel 600mg, heparin 400IU, abciximab (bolus).
- Chest pain resolved at the time of admission
- ECG showed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

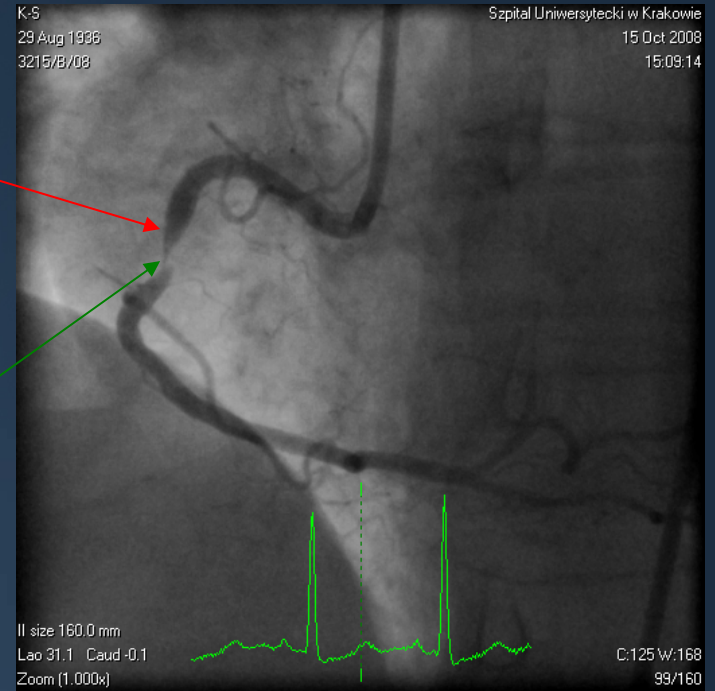


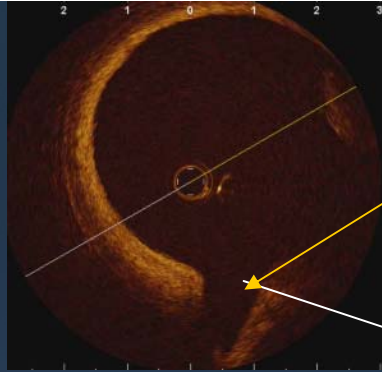
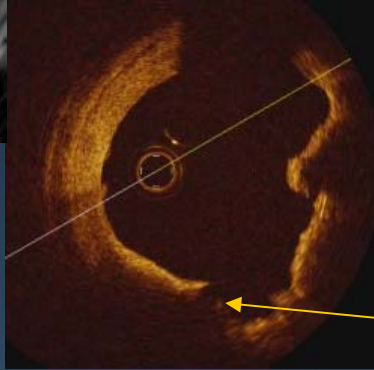
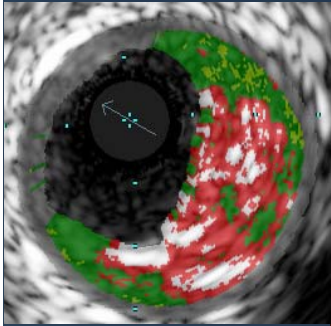


culprit of the culprit proximal to MLA

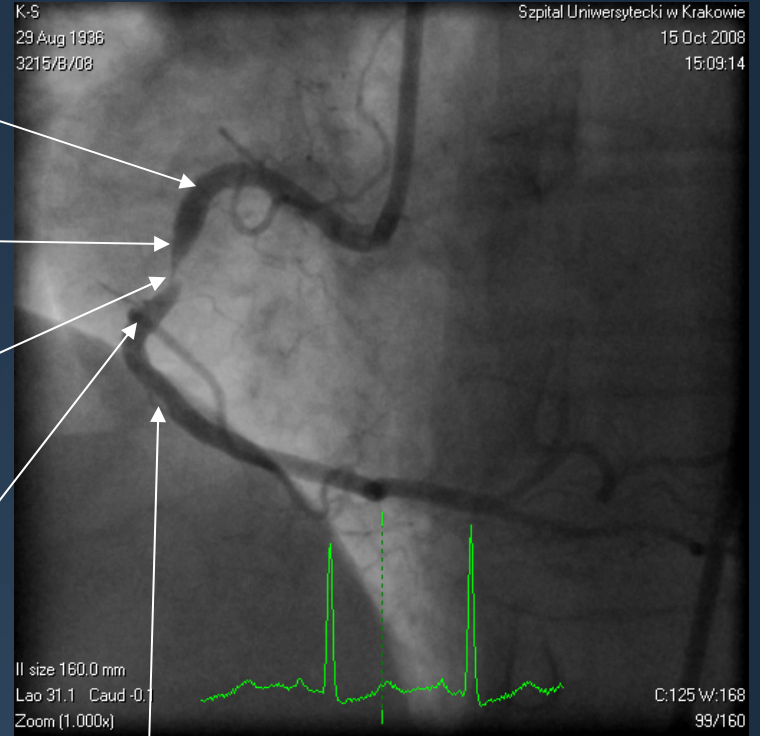


MLA

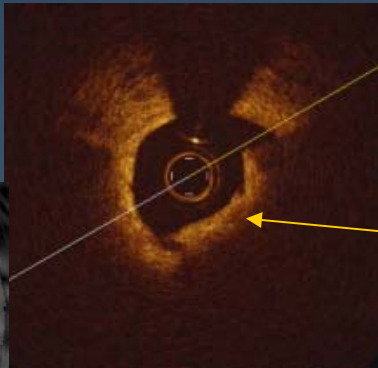
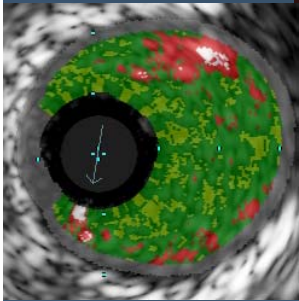




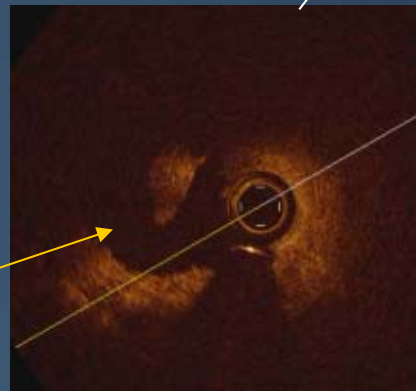
Side branch



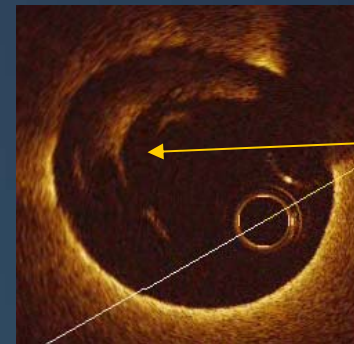
Plaque rupture



Thrombus



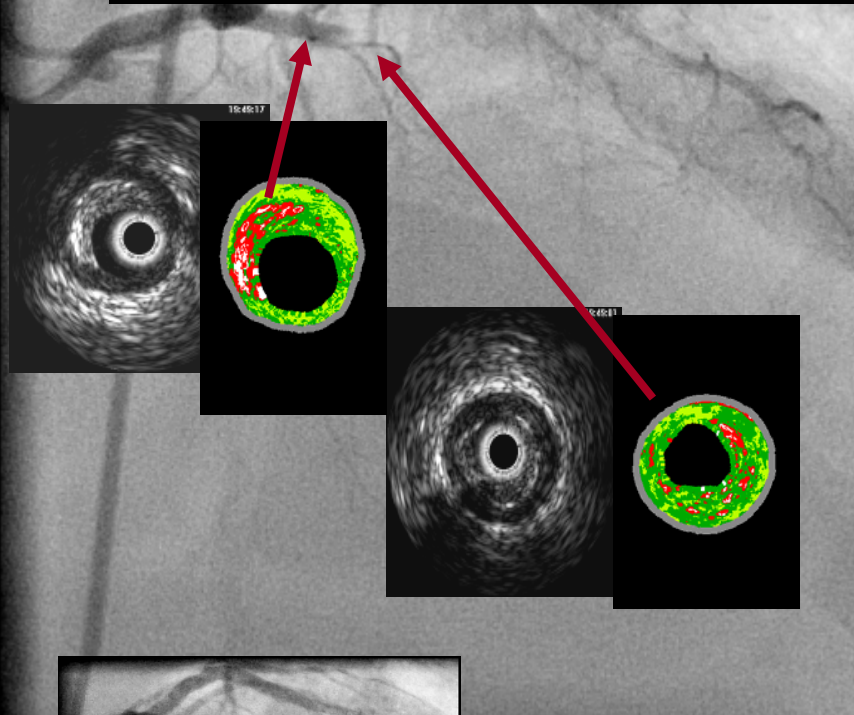
Side branch



Thrombus

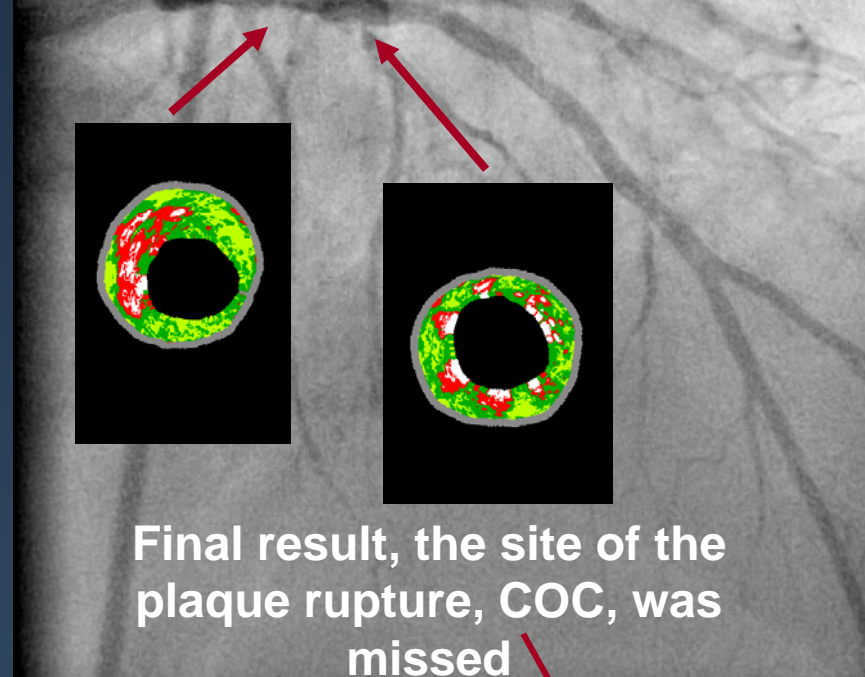


# ACS; Baseline angiography pre thrombectomy

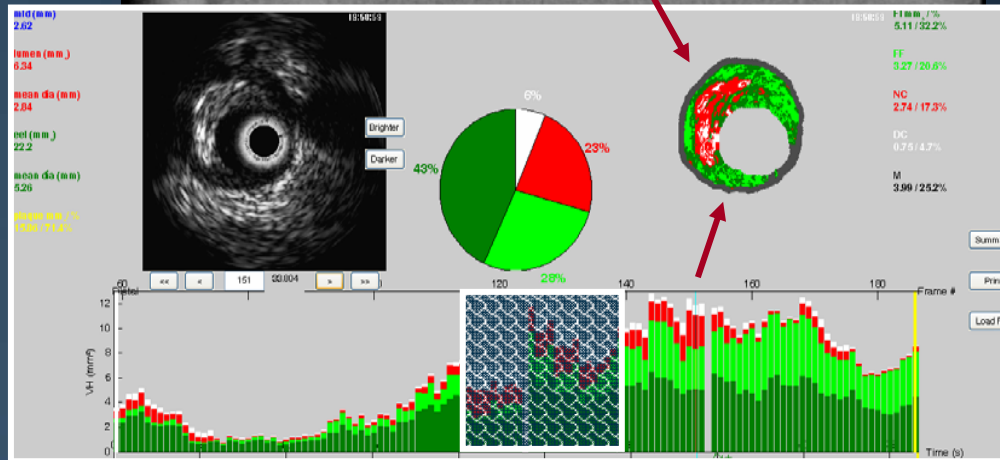


Post-thrombectomy  
TIMI 3

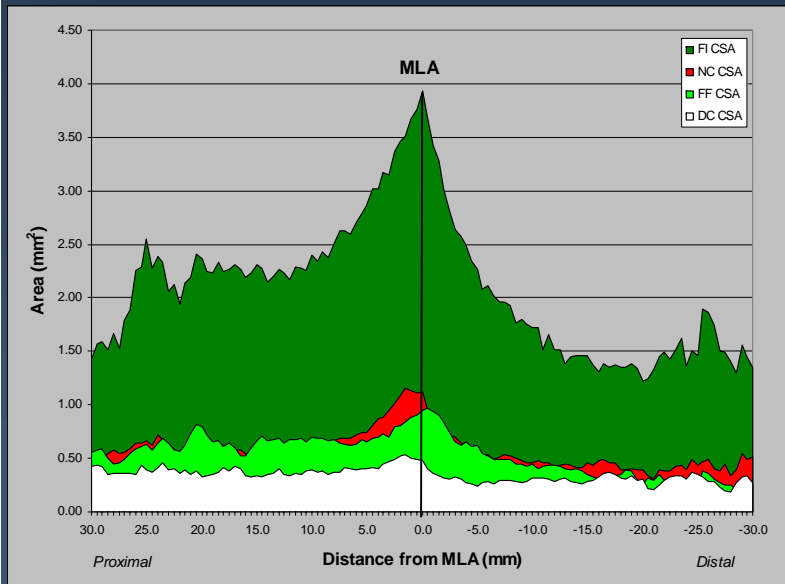
# Post stenting



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



# 90 lesions in 81 patients (47% ACS) from the Global VH Registry



Maximum NC at MLA in 3%

Maximum NC proximal to the MLA in 61%  
(mean=4.1mm)

Maximum NC distal to the MLA in 36%  
(mean=3.6mm)

## Max Necrotic Core

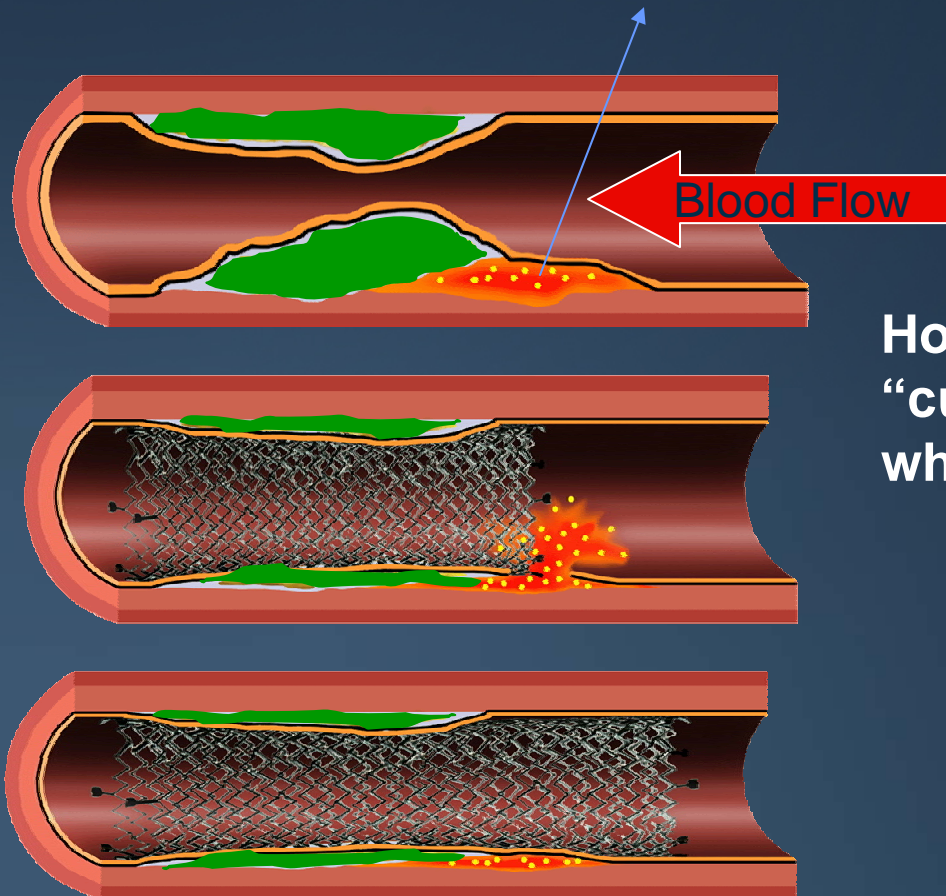
- ↑Vessel Area
- ↑Lumen Area
- ↑Plaque Area
- ↑Necrotic Core %
- ↑Dense Calcium %
- ↑Fibroatheroma #
- ↑Remodeling index
- ↑Positive remodeling #

## Minimum Lumen Area

- ↑Fibrotic Tissue %
- ↑Fibrofatty Tissue %

# 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

700 pts with ACS

UA (with ECG  $\Delta$ ) or NSTEMI or STEMI  $>24^{\circ}$

1-2 vessel CAD undergoing PCI  
at up to 40 sites in U.S., Europe

## Metabolic S.

- Waist circum
- Fast lipids
- Fast glu
- HgbA1C
- Fast insulin
- Creatinine

## Biomarkers

- Hs CRP
- IL-6
- sCD40L
- MPO
- TNF  $\alpha$
- MMP9
- Lp-PLA2
- others

PCI of culprit lesion(s)

Successful and uncomplicated

Formally enrolled

# 3-vessel imaging post PCI

Culprit artery, followed by non-culprit arteries

Angiography (QCA of entire coronary tree)

IVUS

Virtual histology

Palpography (n= $\sim$ 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,  
 $\pm$  3-5 yrs

MSCT

Substudy

N=50-100

Repeat imaging  
in pts with events



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)

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

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

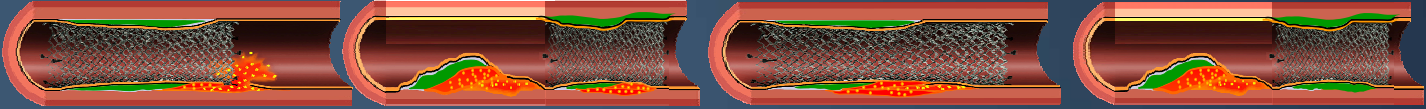
Edge TCFA partially uncovered (n=20)

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)

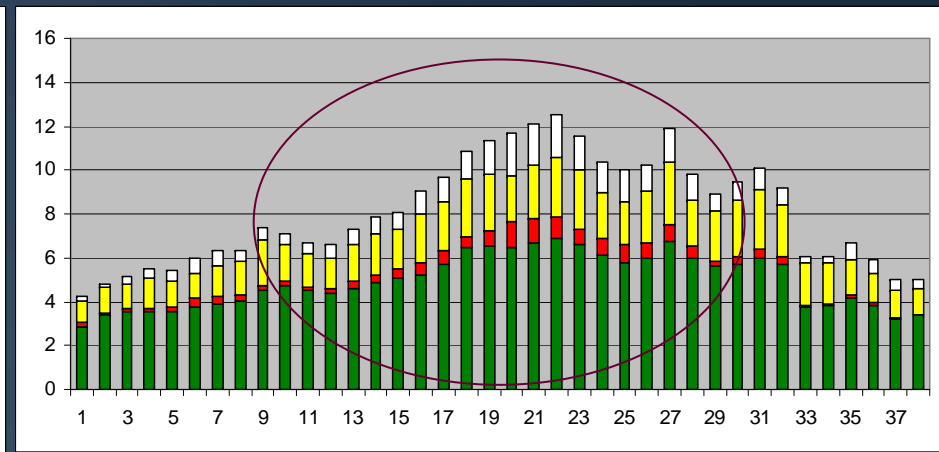
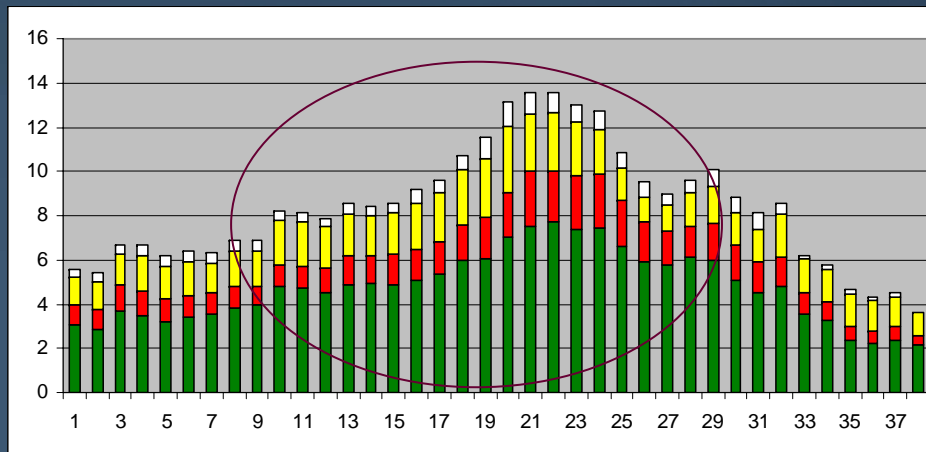
No TCFA behind stent w/o reference TCFA (n=152)



NC protruding through stent (n=63)

# Plaque Shift and Loss of Necrotic Core After Balloon Angioplasty in 20 pts with ACS

	Before BA	After BA	P value
Fibrous (mm <sup>3</sup> )	184 ± 26 (61%)	185 ± 29 (66%)	0.91
Fibro-fatty (mm <sup>3</sup> )	50 ± 12 (16%)	46 ± 10 (16%)	0.31
<b>Necrotic (mm<sup>3</sup>)</b>	<b>45 ± 10 (15%)</b>	<b>30 ± 11 (11%)</b>	<b>0.002</b>
Dense Calcium (mm <sup>3</sup> )	21 ± 9 (7%)	17 ± 7 (6%)	0.12



← Prox ref    Balloon segment    Dist ref →

← Prox ref    Balloon segment    Dist ref →

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

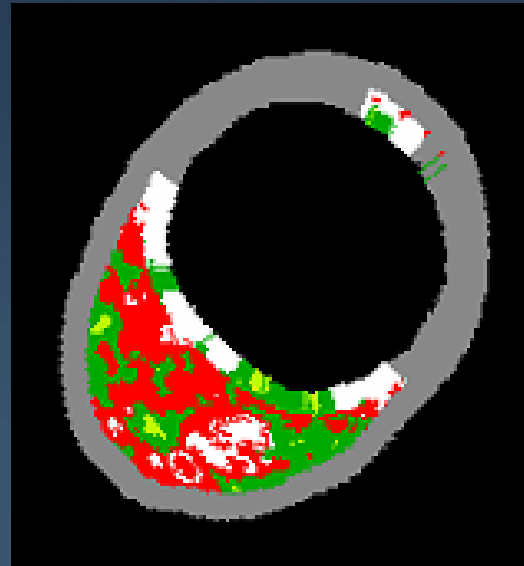
- Kawaguchi et al. J Am Coll Cardiol. 2007;50:1641-6
  - ST re-elevation in 71 pts with STEMI
- Kawamoto et al. J Am Coll Cardiol. 2007;50:1635-40
  - Doppler FloWire high intensity transit signals in 44 pts undergoing elective stenting resulting in poor recovery of CVFR
- Park et al. VH Summit 2007 (unpublished)
  - Largest NC independent predictor of CK-MB release (n=332)
- Erbel et al. unpublished
  - Troponin and CK-MB release in 36 pts undergoing elective stenting
- Washington Hospital Center. Unpublished
  - Troponin post elective stenting
- Bose et al. Basic Res Cardiol 2008;103:587-97
  - CK and Tnl 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



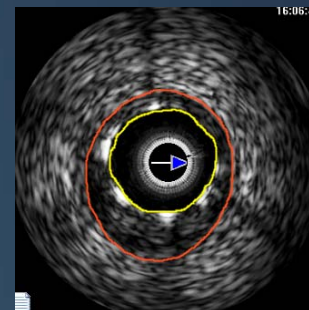
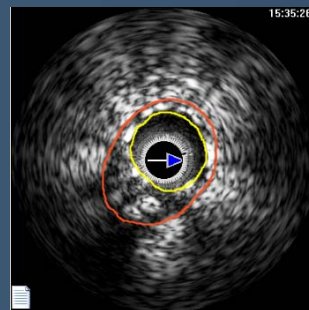
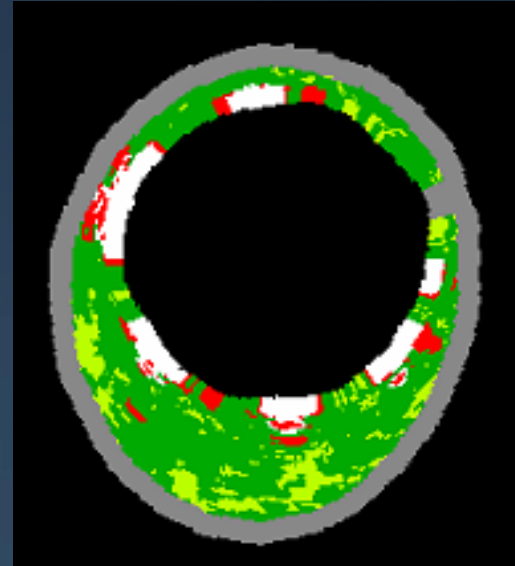


# Serial (baseline and follow-up) VH-IVUS assessment of plaque characteristics after stent deployment.

Fibroatheroma

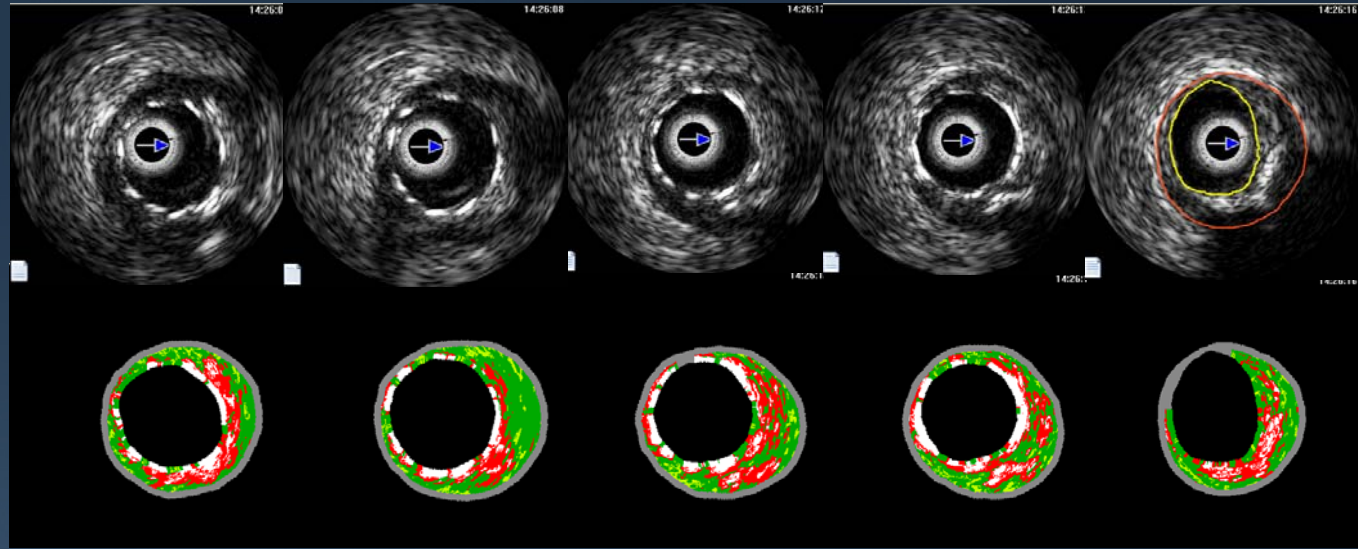


Non-fibroatheroma

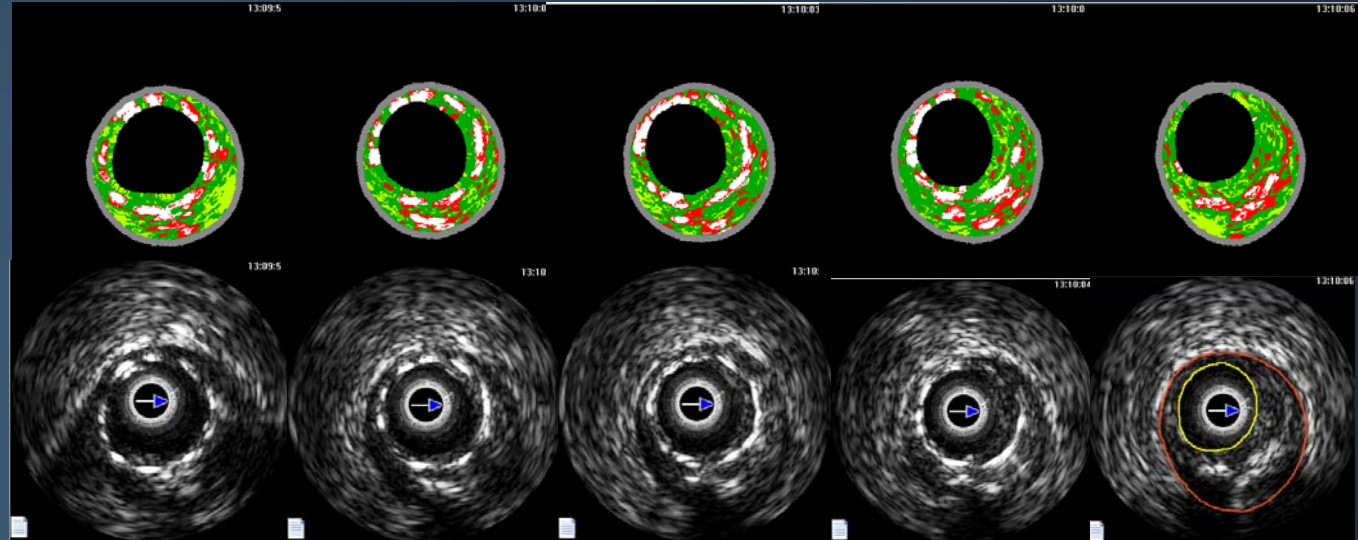


# BMS

Baseline

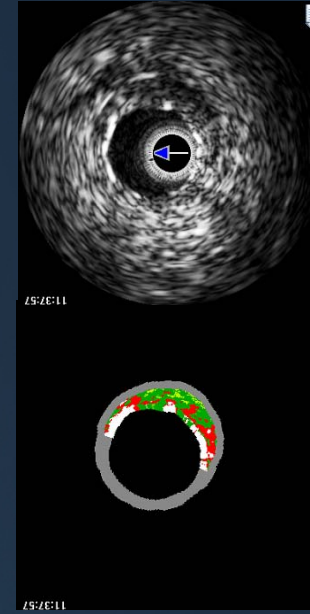
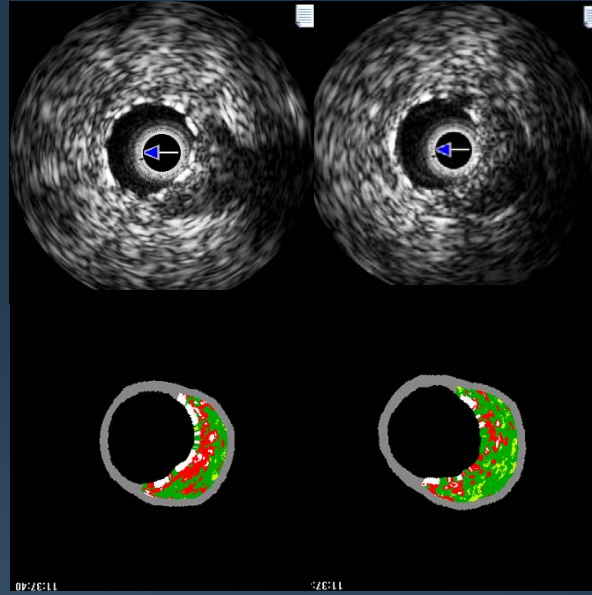


Follow-up

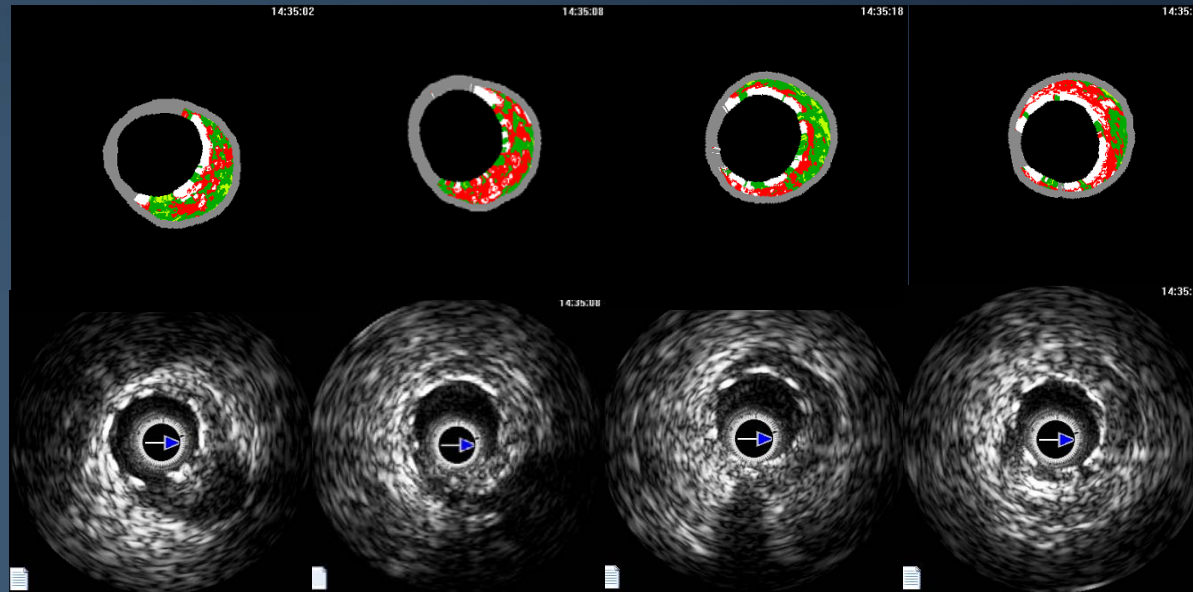


# DES

Baseline

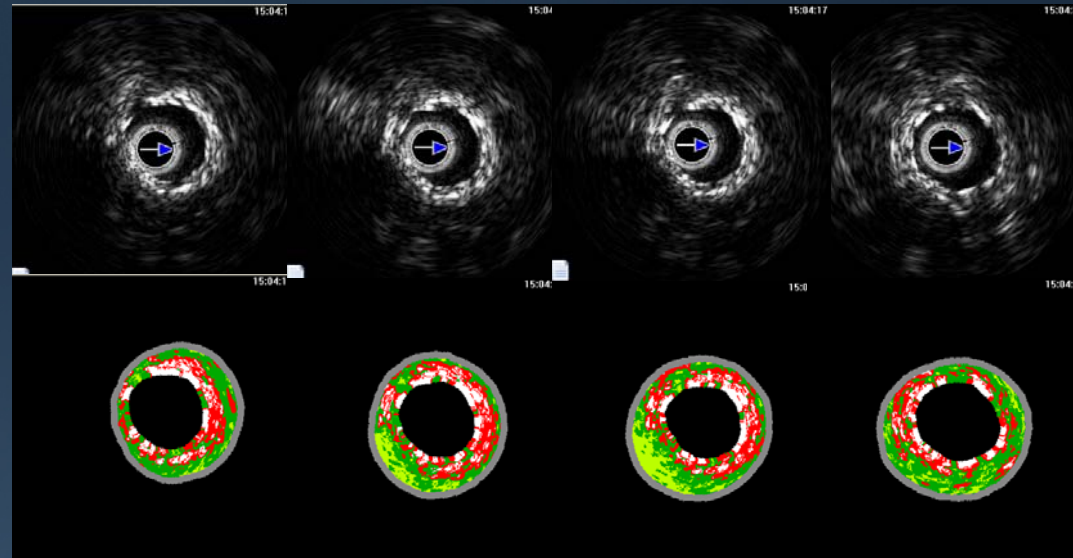


Follow-up

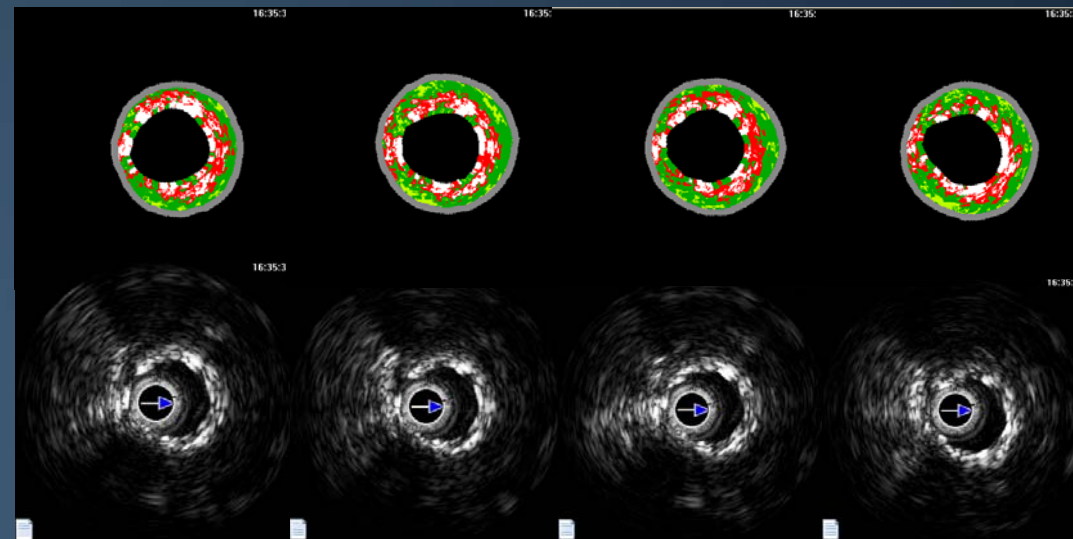


# DES

Baseline



Follow-up



# %Culprit lesion VH-TCFA post-stent and at follow-up from the Global VH Registry

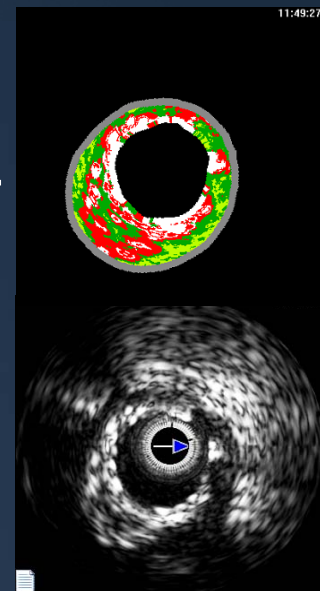
	DES (n=76)	BMS (n=32)
Stent		
Post-intervention	44%	38%
Follow-up	42%	14%
Stent Edge/Reference		
Post-intervention	25%	27%
Follow-up	22%	4%

**DES**

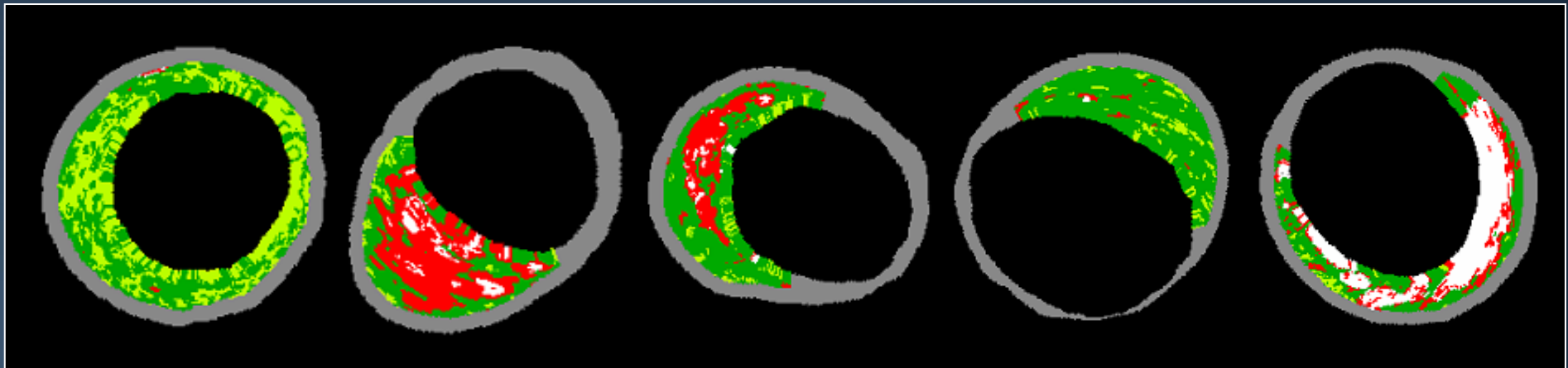
Baseline



Follow-up



# 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)

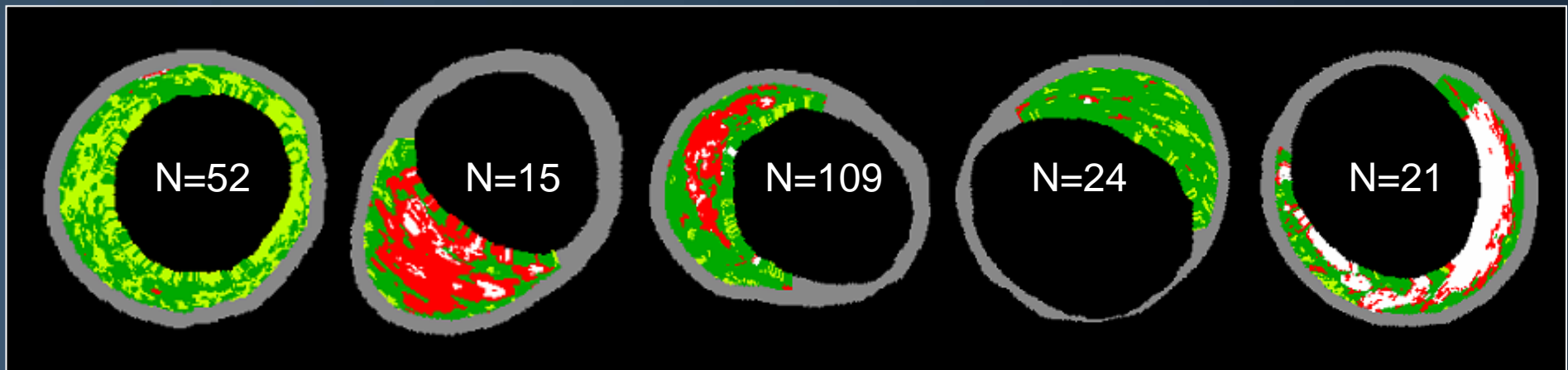
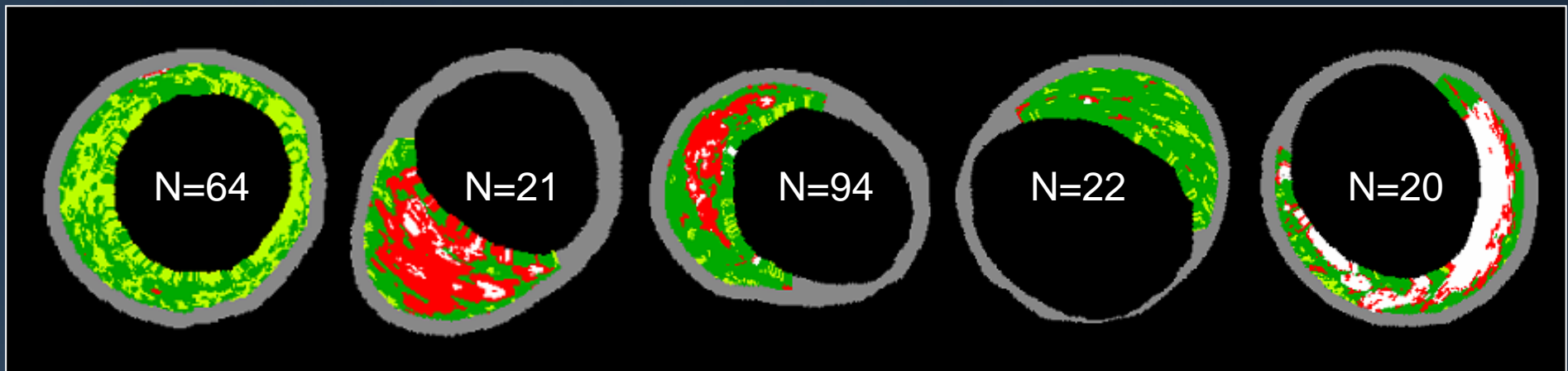
Thick-cap  
fibroatheroma  
(ThFA)

Fibrotic

Fibrocalcific

Baseline (n=201)	Follow-up (n=201)				
	PIT (n=52)	TCFA (n=15)	ThFA (n=109)	Fibrotic (n=24)	Fibrocalcific (n=21)
PIT (n=64)	48	6	10	0	0
TCFA (n=21)	0	5	14	2	0
ThFA (n=94)	0	4	85	4	1
Fibrotic (n=22)	4	0	0	18	0
Fibrocalcific (n=20)	0	0	0	0	20

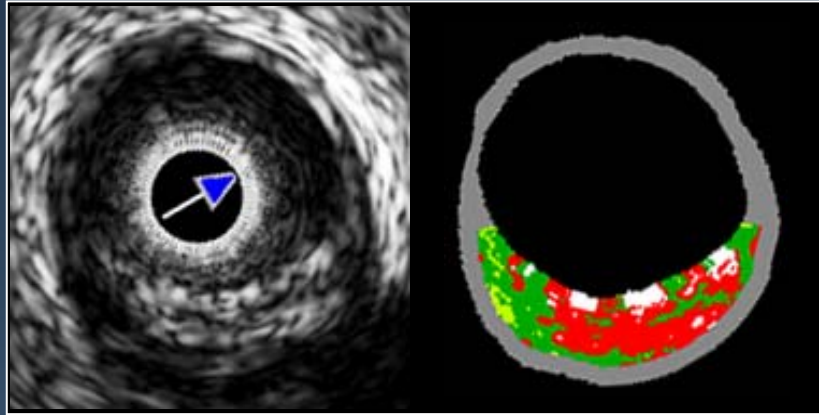




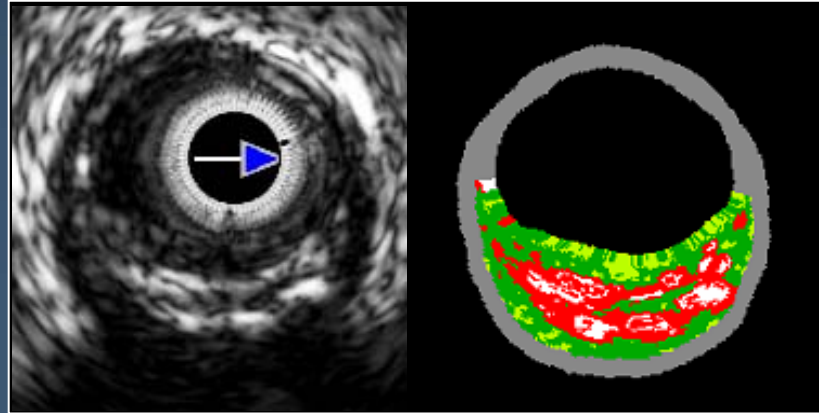
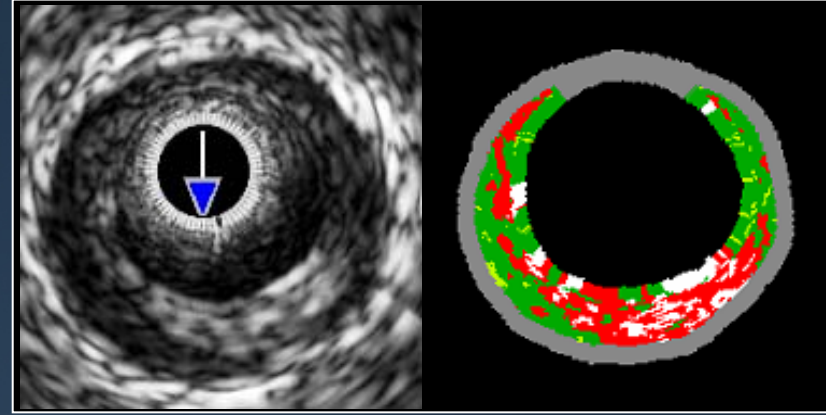


- **During follow-up. . .**
  - **76% of TCFAs healed and 24% remained unchanged although the location of the necrotic core in contact with the lumen shifted axially.**
- **Compared to TCFAs that healed, TCFAs that did not change were more proximal in location and had larger lumen area, vessel area, plaque area, calcium area, and necrotic core area.**
- **10 new TCFAs were noted**
  - **6 late-developing TCFAs were PIT and 4 were ThFA at baseline.**
- **No fibrotic or fibrocalcific plaques evolved into a TCFA.**

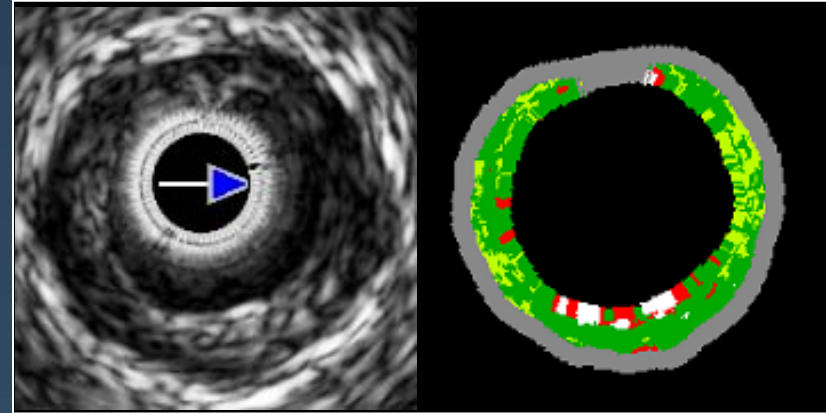


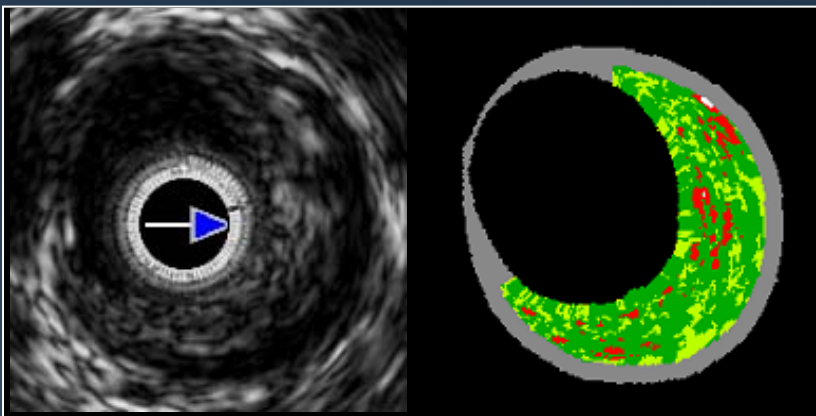


Baseline

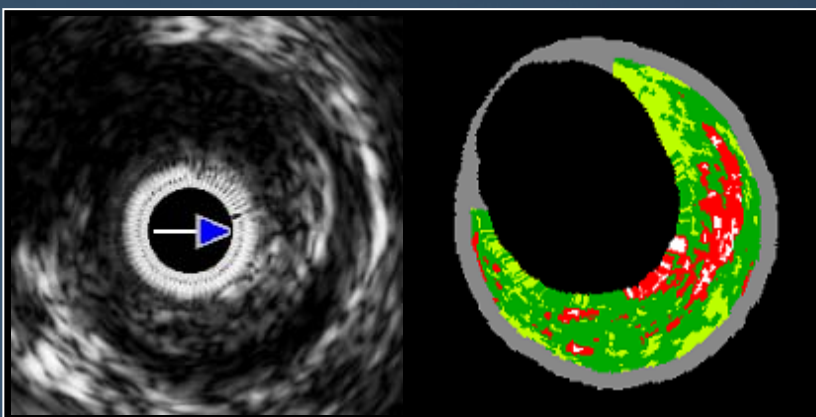
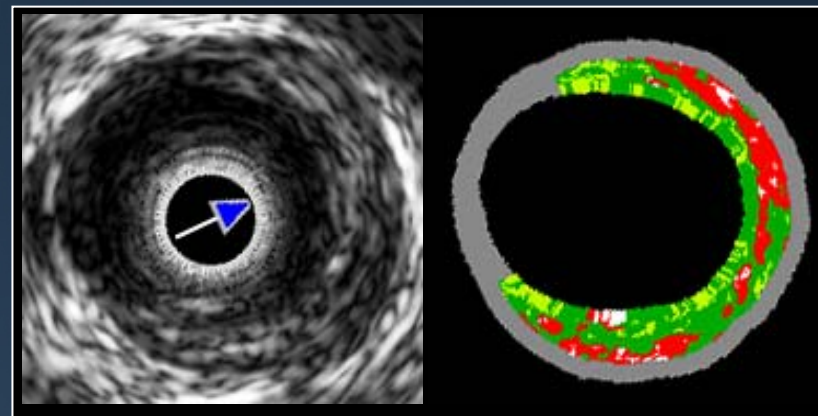


Follow-up

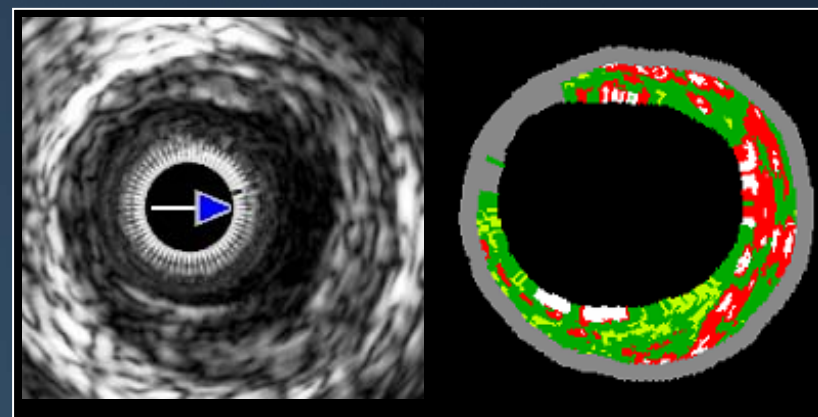




Baseline

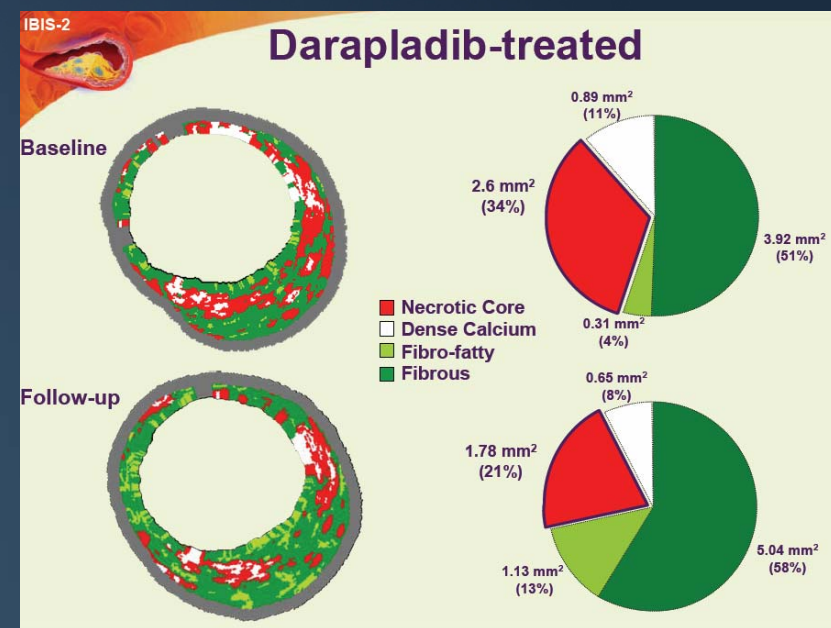
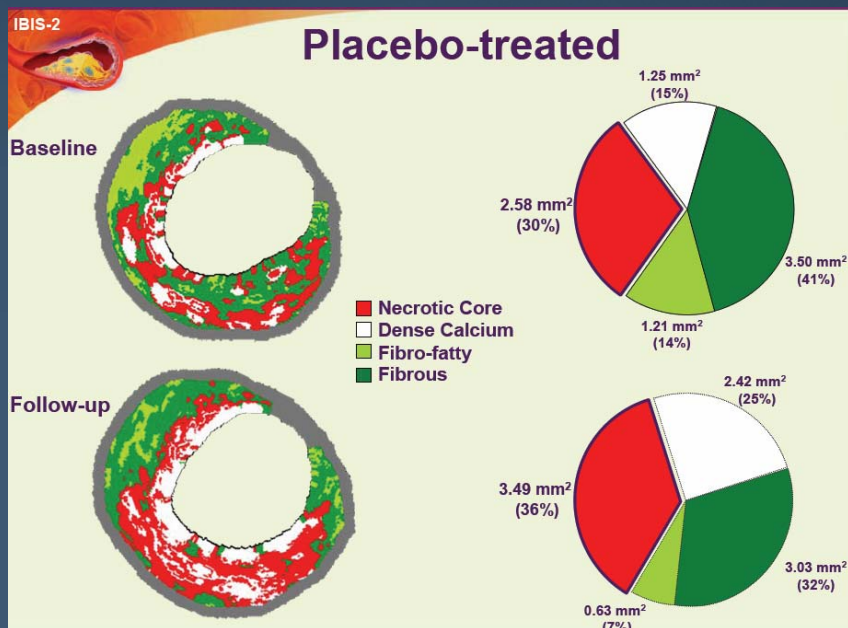


Follow-up



# IBIS-2: Effects of the direct Lp-PLA<sub>2</sub> inhibitor darapladib vs placebo on human coronary atherosclerotic plaque.

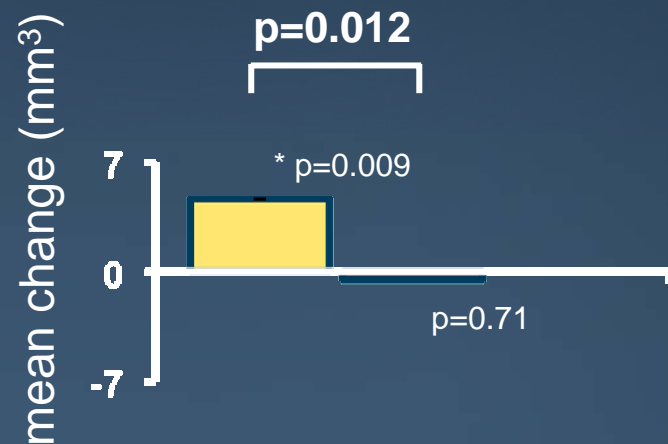
After 12 months, in the placebo-treated group NC volume increased significantly ( $\Delta\text{NC}=4.5\pm 17.9\text{mm}^3$ ,  $p=0.009$ ), whereas darapladib halted this increase ( $\Delta\text{NC}=-0.5\pm 13.9\text{mm}^3$ ,  $p=0.71$ ), resulting in a significant treatment difference of  $-5.2\text{mm}^3$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



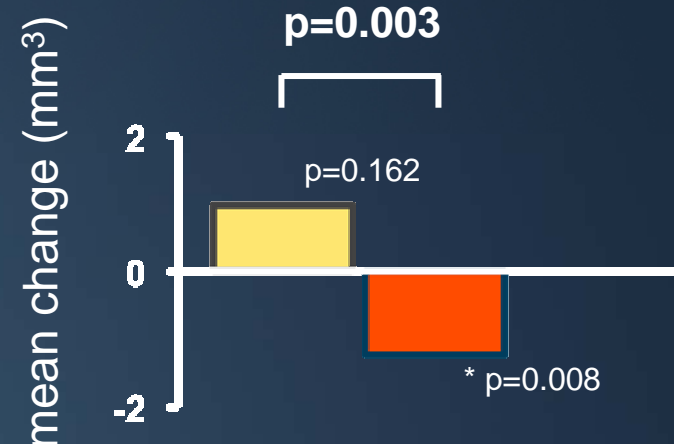
# Plaque Composition by IVUS - VH

## change from baseline in necrotic core volume

Entire region of interest  
[mean 48 mm]



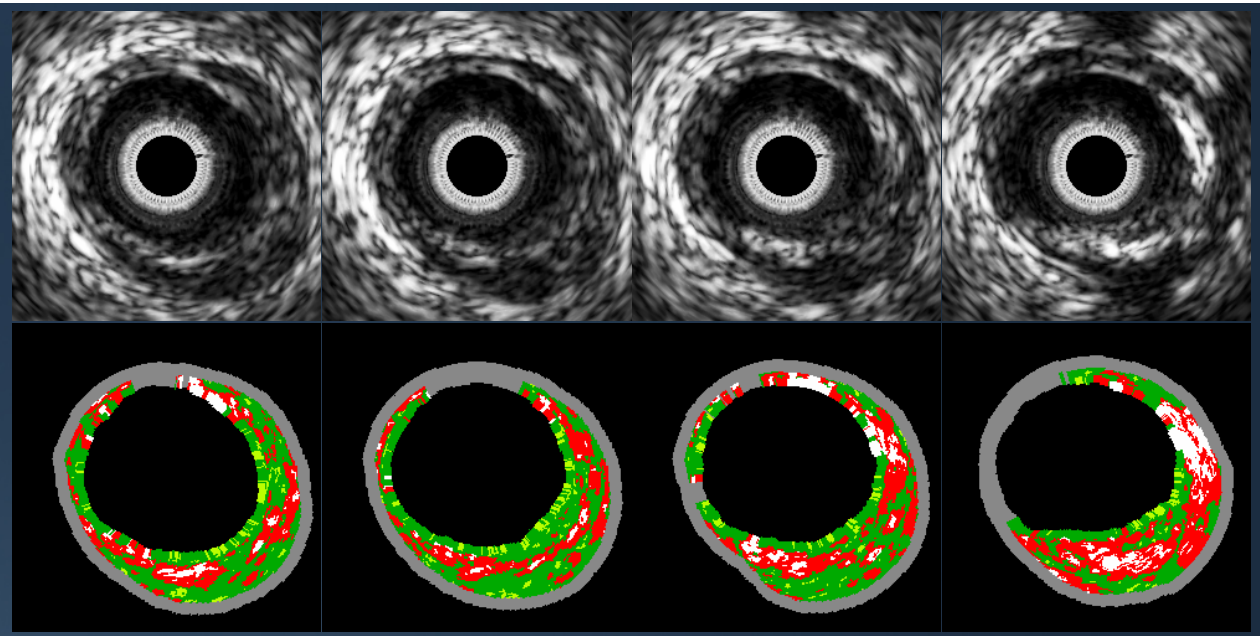
The worst 10 mm  
subsegment



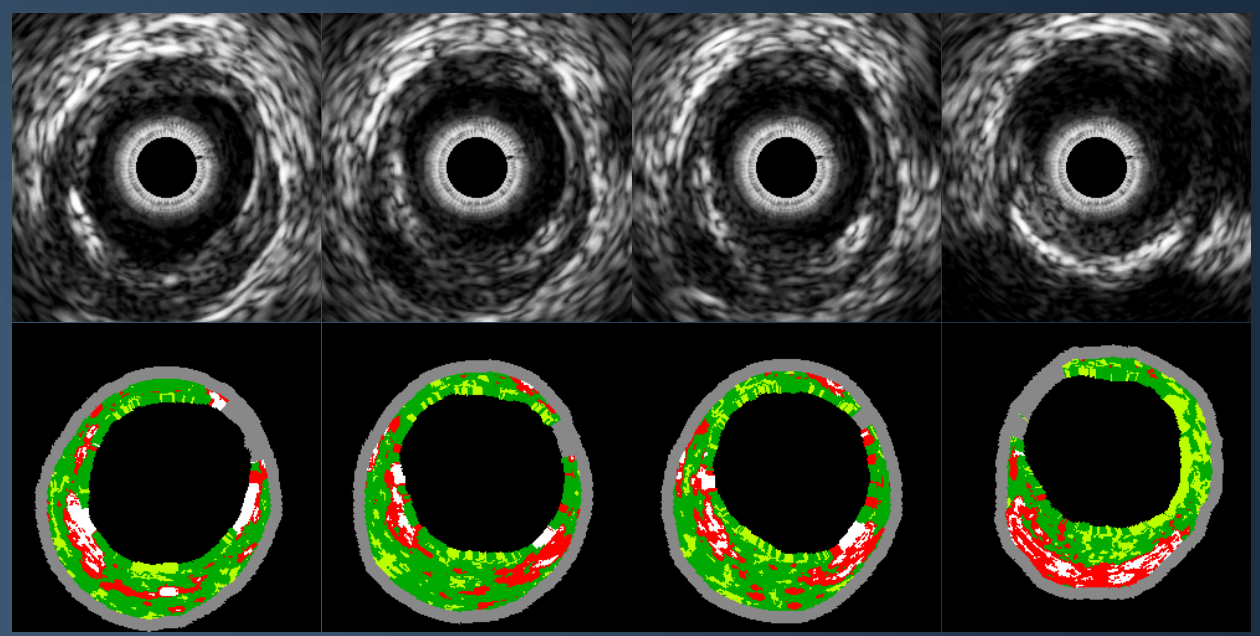
- placebo (plus standard of care) n=110
- darapladib 160 mg (plus standard of care) n=129

# Darapladib

Baseline



Follow-up



# 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 thrombus
  - However, specificities for fibrotic and fibrofatty plaque were lower in thrombus slices vs non-thrombus containing 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.

# 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.



**And, of course, we are all  
waiting for the results of  
PROSPECT**



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