Put It Altogether: What and Why Do We Need More?

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Cardiovascular Research Foundation

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Disclosure Statement of Financial Interest

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

Affiliation/Financial Relationship	Company
• *Grant/Research Support*	• *Volcano, Boston Scientific, InfraReDx, St Jude*
• *Consulting Fees/Honoraria*	• *Volcano, Boston Scientific, ACIST, Abbott, St Jude*

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Modalities

- FFR
- IVUS
- RF-IVUS (VH-IVUS, iMAP, or IB-IVUS)
- OCT
- Spectroscopy
- Some combination of the above

Clinical questions

- Is this lesion flow-limiting?
  - Non-LMCA
  - LMCA
- Pre-intervention lesion assessment (ie., what is the culprit?)
- Is this “other” lesion a vulnerable plaque that is at risk for future events?
- What is the likelihood of embolization during stent implantation?
- How do I optimize acute stent results (size, length, expansion, edge coverage)?
  - Is this jailed sidebranch significant?
- Why did this stent thrombose or restenose?

Randomized FFR Trials in Non-LMCA Lesions

- **DEFER showed that it was safe to defer PCI in lesions with an FFR >0.75**
  - *Bech et al. Circulation 2001;103:2928-34*
  - *Pijls et al. J am Coll Cardiol 2007;49:2105-11*
- **FAME-I showed that treating lesions with an FFR >0.80 with first generation DES was harmful and that a deferred PCI strategy was safer and cost-saving**
  - *Tonino et al. N Engl J Med. 2009;360:213-24*
  - *Pijls et al. J am Coll Cardiol 2010;56:177-84*
  - *Fearon et al. Circulation 2010;122:2545-50*
- **FAME-II showed that deferring PCI in lesions with an FFR <0.80 was harmful compared to optimal medical therapy. While more expensive at the beginning, the cost of this strategy decreased by 50% at 1 year. In addition, FAME-II confirmed the findings of DEFER**
  - *De Bruyne et al. N Engl J Med 2012;367:991-1001*
  - *Fearon et al. Circulation 2013;17:1335-40*
  - *De Bruyne et al. N Engl J Med 2014;371:1208-17*

Effect of Intravascular Ultrasound-Guided vs. Angiography-Guided Everolimus-Eluting Stent Implantation: the IVUS-XPL Randomized Clinical Trial

Myeong-Ki Hong, MD. PhD
on behalf of the IVUS-XPL trial investigators

Severance Cardiovascular Hospital and Cardiovascular Research Institute, Yonsei University College of Medicine, Seoul, Korea

Hong et al. JAMA 2015, in press

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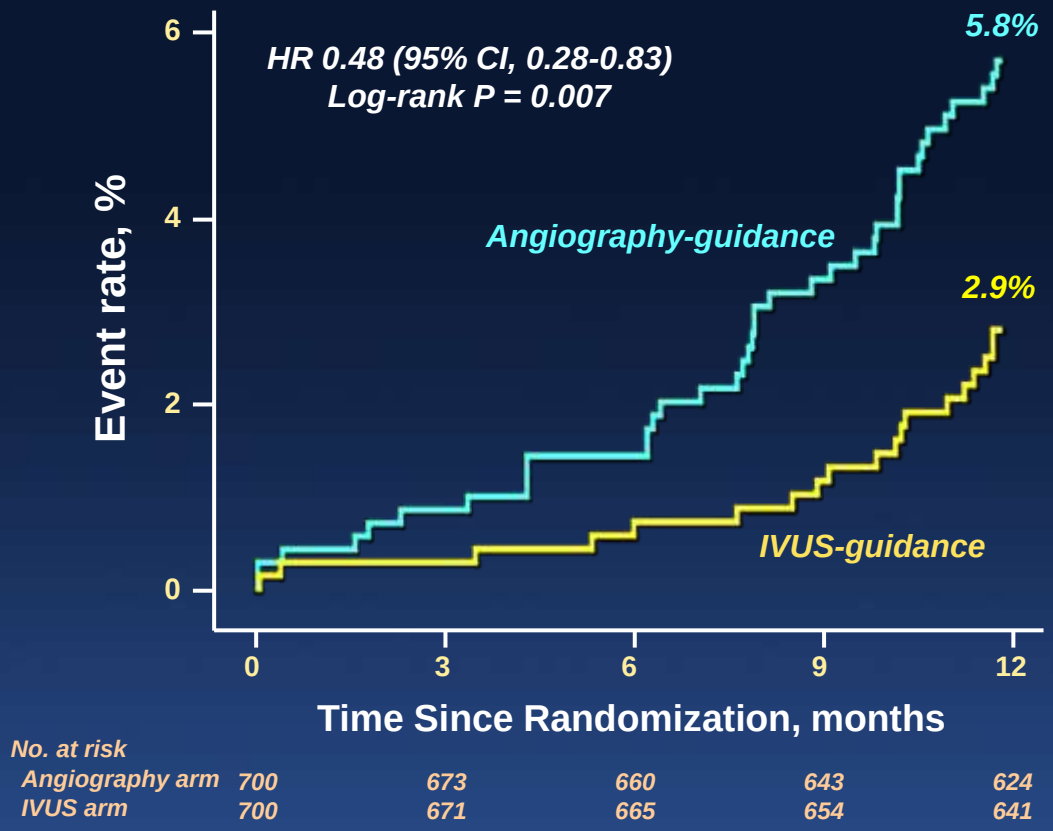
Primary End Point – Intention to Treat Analysis



	IVUS-guidance (n=700)	Angio-guidance (n=700)	Log-Rank *P* value
X-over	22 (3.1%)	30 (4.3%)	
MACE	19 (2.9%)	39 (5.8%)	.007
Cardiac death	3 (0.4%)	5 (0.7%)	.48
MI	0	1 (0.1%)	.32
TLR	17 (2.5%)	33 (5.0%)	.02
ST	2 (0.3%)	2 (0.3%)	1.00

Hong et al. JAMA 2015, in press

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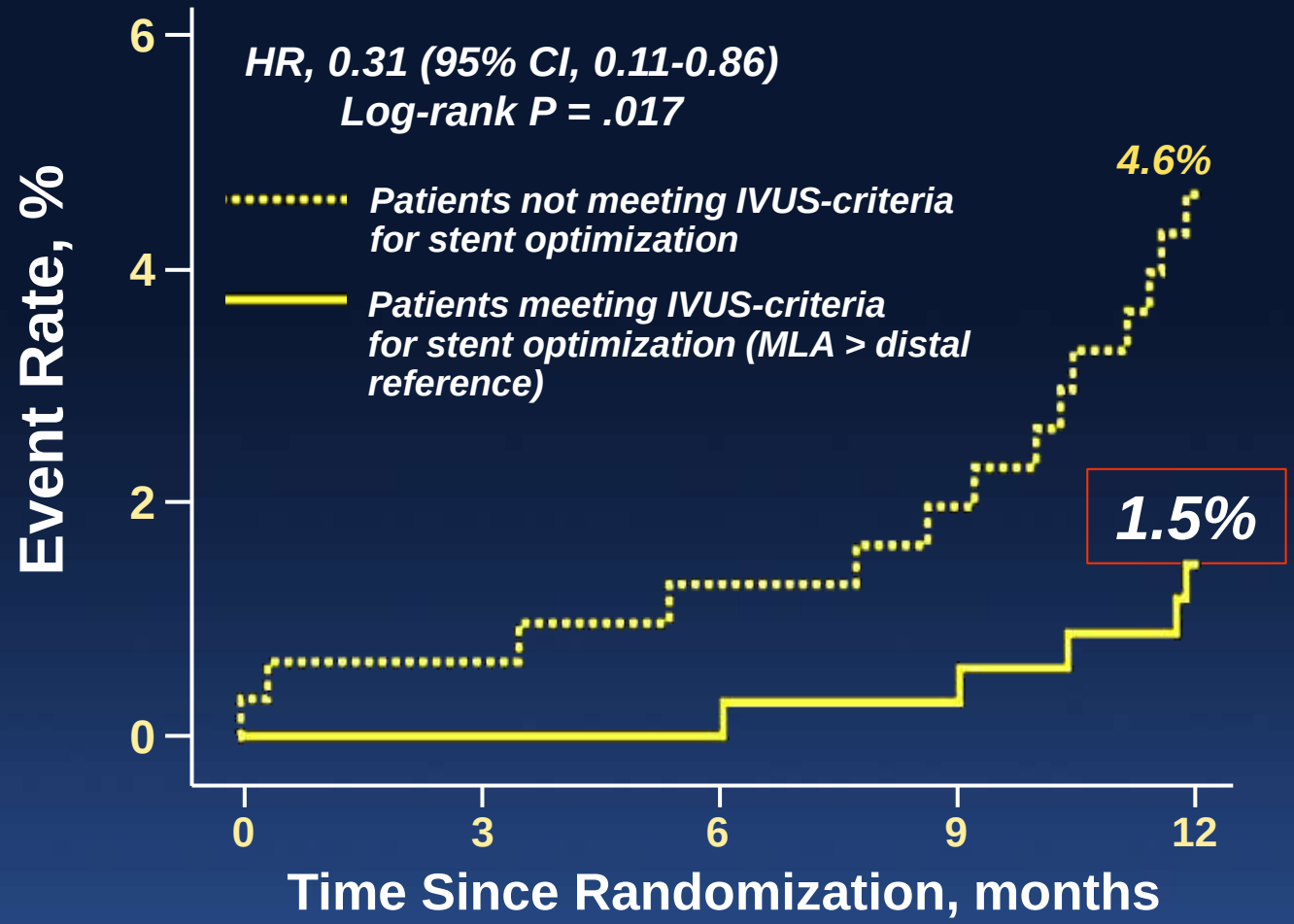
Primary End Point in IVUS Guidance



No. at risk					
Not meeting criteria	315	299	297	394	285
Meeting criteria	363	362	345	338	334

Hong et al. JAMA 2015, in press

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- Is this lesion flow-limiting?
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Modalities

- FFR
- IVUS
- RF-IVUS (VH-IVUS, iMAP, or IB-IVUS)
- OCT
- Spectroscopy
- Some combination of the above

Clinical questions

- Is this lesion flow-limiting?
  - Non-LMCA
  - LMCA
- Pre-intervention lesion assessment (ie., what is the culprit?)
- **The common denominator is a fibroatheroma, in particular a TCFA**
- How do I optimize acute stent results (size, length, expansion, edge coverage)?
  - Is this jailed sidebranch significant?
- Why did this stent thrombose or restenose?

“Validation” of intravascular imaging detection of TCFAs or Plaque Ruptures

	Grayscale IVUS	Grayscale + VH-IVUS	Grayscale + IB-IVUS	OCT	NIRS - IVUS	Angioscopy
Consistent with histology	+	+	+	+	+	+
Direct comparison with histology	+	+	+	+	+	+
Findings in ACS vs stable pts	+	+	+	+	+	+
Predictive of events						
Patient level	+	+			+	+
Lesion level	Retrospective	**Prospective**		Retrospective		

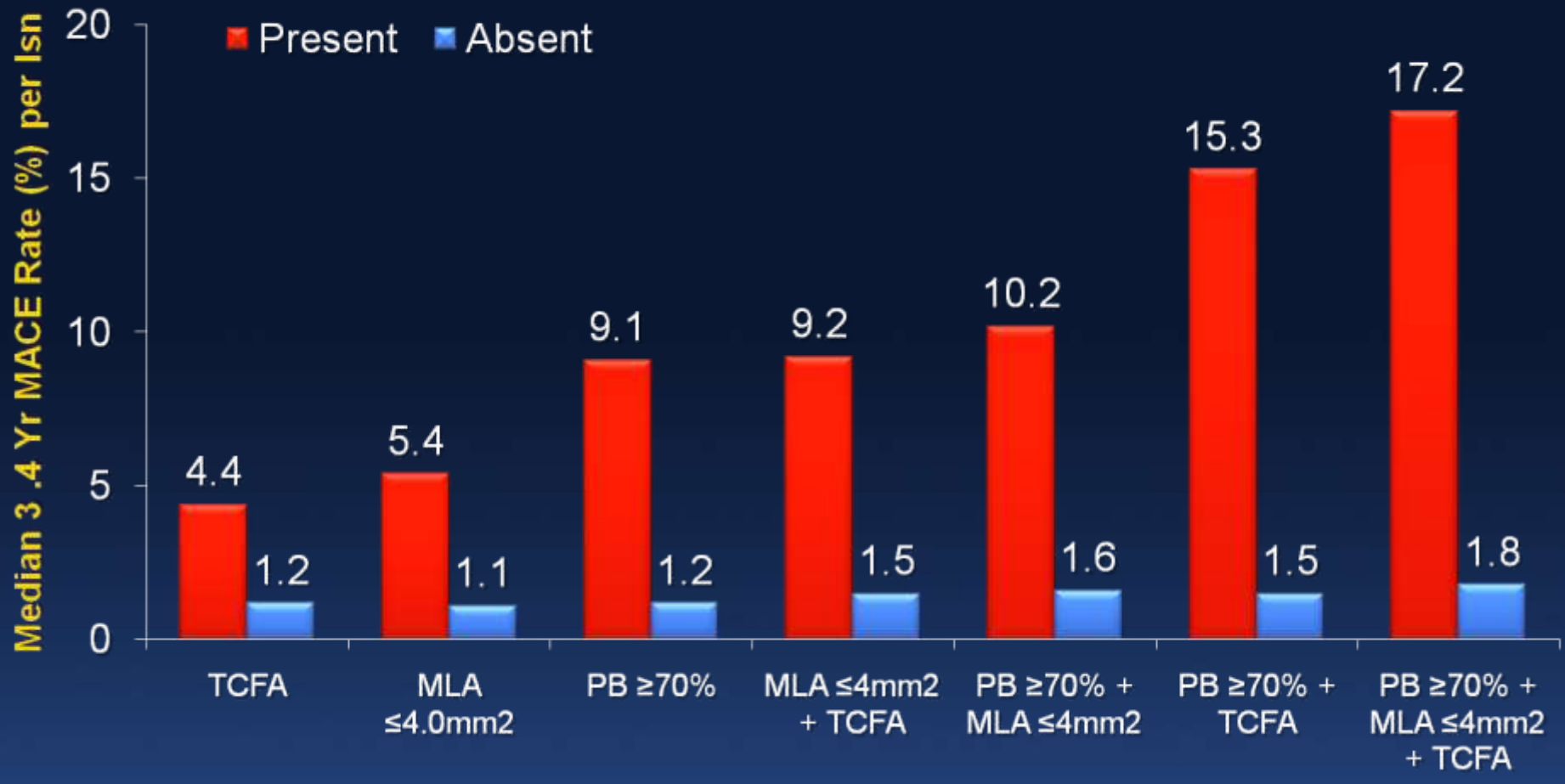
“Validation” of intravascular imaging detection of Plaque Erosions

	Grayscale IVUS	Grayscale + VH-IVUS*	Grayscale + IB-IVUS	OCT	NIRS - IVUS	Angioscopy
Consistent with histology				+		
Direct comparison with histology						
Findings in ACS vs stable pts				+		+
Predictive of events						
Patient level						
Lesion level						

PROSPECT: Multivariable Correlates of Non Culprit Lesion Related Events

Variable	HR [95% CI]	p
Plaque burden$_{MLA}$ ≥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

Stone et al. N Engl J Med 2011;361:226-35



Lesion HR	*3.8 (2.2, 6.6)*	*5.0 (2.9, 8.7)*	*7.9 (4.6, 13.8)*	*6.4 (3.4, 12.2)*	*6.7 (3.4, 13.0)*	*10.8 (5.5, 21.0)*	*10.8 (4.3, 27.2)*
P value	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*
Prevalence*	***51.2%***	***49.1%***	***30.7%***	***17.4%***	***15.4%***	***11.0%***	***4.6%***

Stone et al. N Engl J Med 2011;361:226-35

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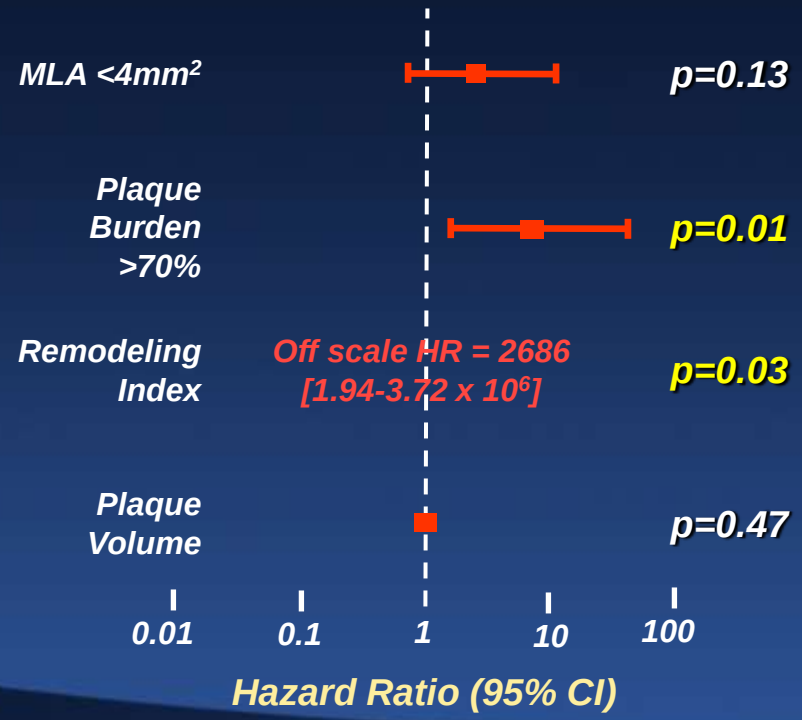
VIVA: VH-IVUS in Vulnerable Atherosclerosis

167 pts with stable CAD or ACS underwent 3-vessel VH-IVUS imaging; 1,096 plaques were classified; median follow-up 625 days

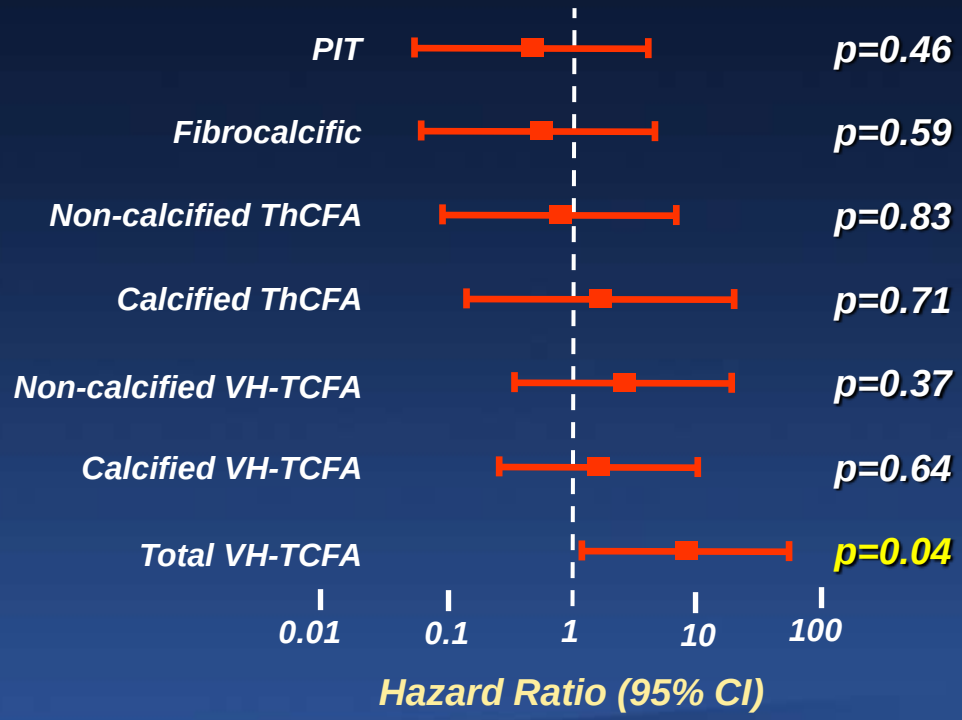
18 MACE (death [2], MI [2] or revasc [14]) occurred in 16 pts from 19 lesions (13 nonculprit lesions and 6 culprit lesions)

Univariate predictors of non-culprit MACE

Grayscale IVUS characteristics



VH-IVUS lesion classification



Calvert et al. JACC Cardiovasc Imaging 2011;4:894-901

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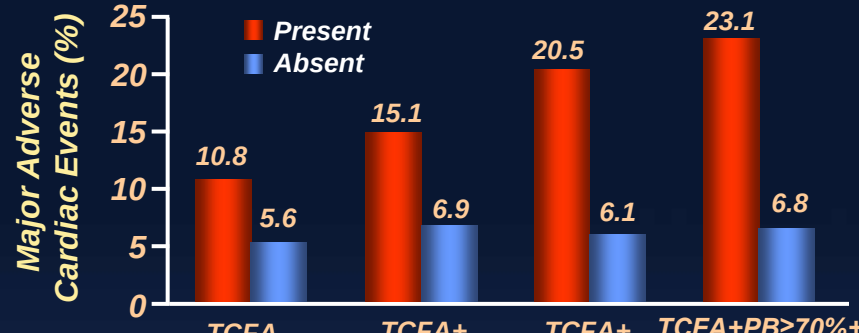
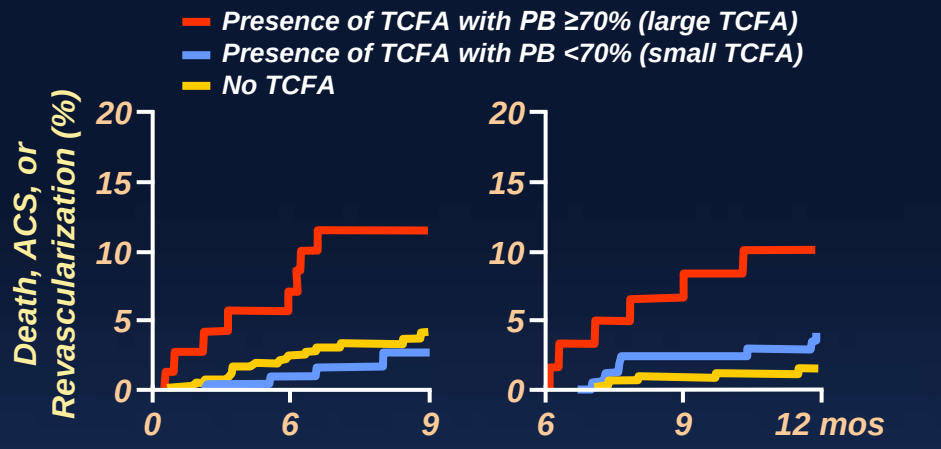
ATHEROREMO-IVUS

1 non-culprit artery imaged in 581 pts (stable CAD or ACS)
LAD>RCA>LCX



	TCFA		TCFA+ MLA≤4mm²		TCFA+ PB≥70%		TCFA+PB≥70%+ MLA≤4mm²	
Prevalence (%)	41.7	58.3	10.5	89.5	11.9	88.1	6.0	94.0
No. at risk at 1 yr (n)	211	312	50	473	52	471	52	471
HR	1.96		2.26		3.47		3.70	
P value	0.024		0.025		<0.001		<0.001	



- *VH-TCFAs with a plaque burden ≥70% were associated with a higher MACE rate both in the first 6 months (P=0.011) and after 6 months (P<0.001)*
- *VH-TCFAs with a plaque burden <70% were only associated with a higher MACE rate after 6 months (P=0.033)*

Cheng et al. Eur Heart J 2014;35:639-47

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Limitations

- Resolution: approximately 200μ for 20MHz synthetic aperture array
- Requires accurate contours of lumen and adventitia (EEM)
- Wire artifact and masking
- No validation for stent metal that appears as “calcium” surrounded by “necrotic core” even when implanted acutely
- No validation for intimal hyperplasia
- No validation for thrombus that appears as fibrous or fibrofatty. As a result. .
  - A thrombus-containing lesion may be classified as PIT or fibrotic plaque – stable - rather than unstable
  - Superficial thrombus may cause a VH-TCFA to be classified as a ThFCA
  - In all probability an algorithm for thrombus will not be possible since the IVUS signal changes with the “age” of the thrombus
- Accuracy behind calcium where the grayscale IVUS image shows shadowing

Interobserver variability in VH-IVUS phenotype diagnosis

		Observer #1					
		PIT	Fibrocalcific	ThCFA	TCFA	Total	Histology
Observer #2	PIT	62	0	1	0	63	60
	Fibrocalcific	1	13	0	0	14	32
	ThCFA	2	4	15	1	22	45
	TCFA	2	9	5	42	58	22
	Total	67	26	21	43	212	
	Histology	60	32	45	22		

The greatest difficulty was to differentiate between a fibroatheroma that is was a VH-TCFA vs a ThFCA

Brown et al. Circ Cardiovasc Imaging. 2015;8:e002518

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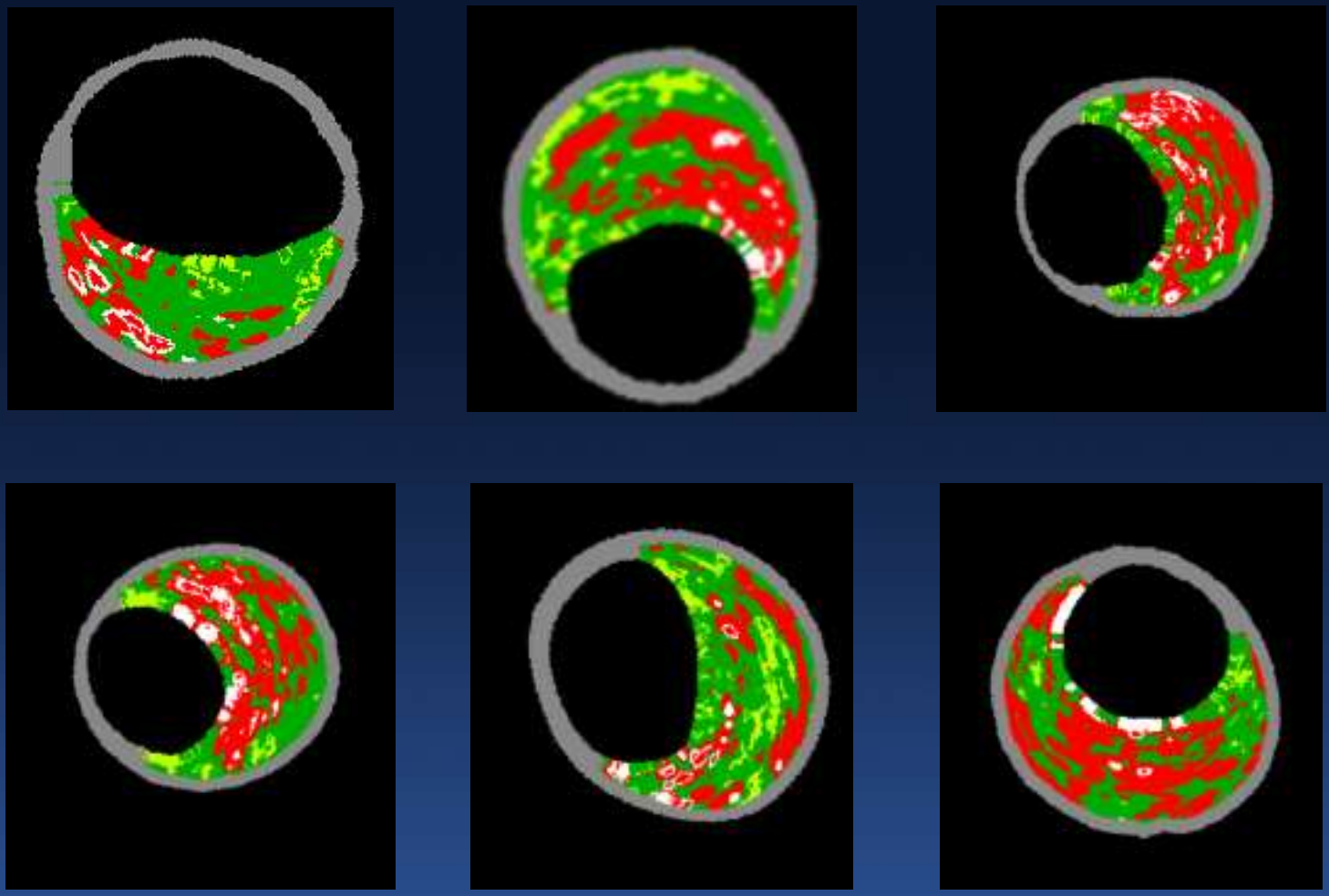
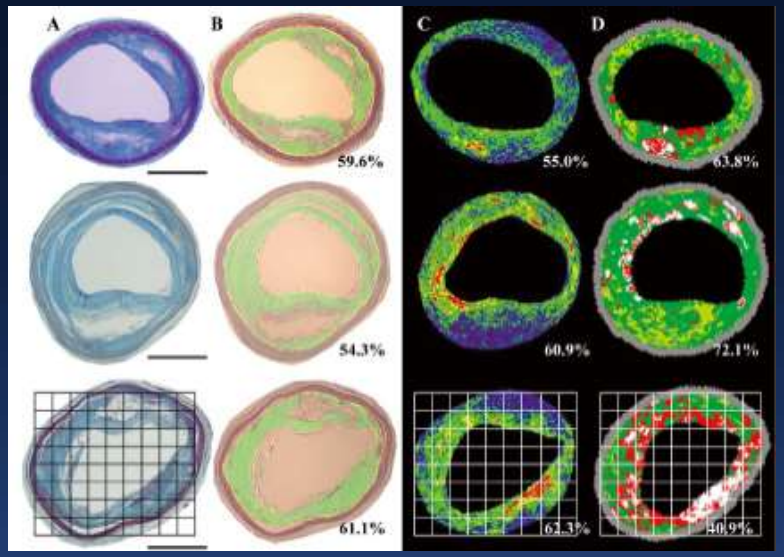
VH-TCFA vs ThFCA



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



The agreement between histology and IB-IVUS was higher (kappa=0.81) than between the histology and IVUS-VH (kappa=0.66)

Okubo et al. Circulation J 2008;72:1631-9

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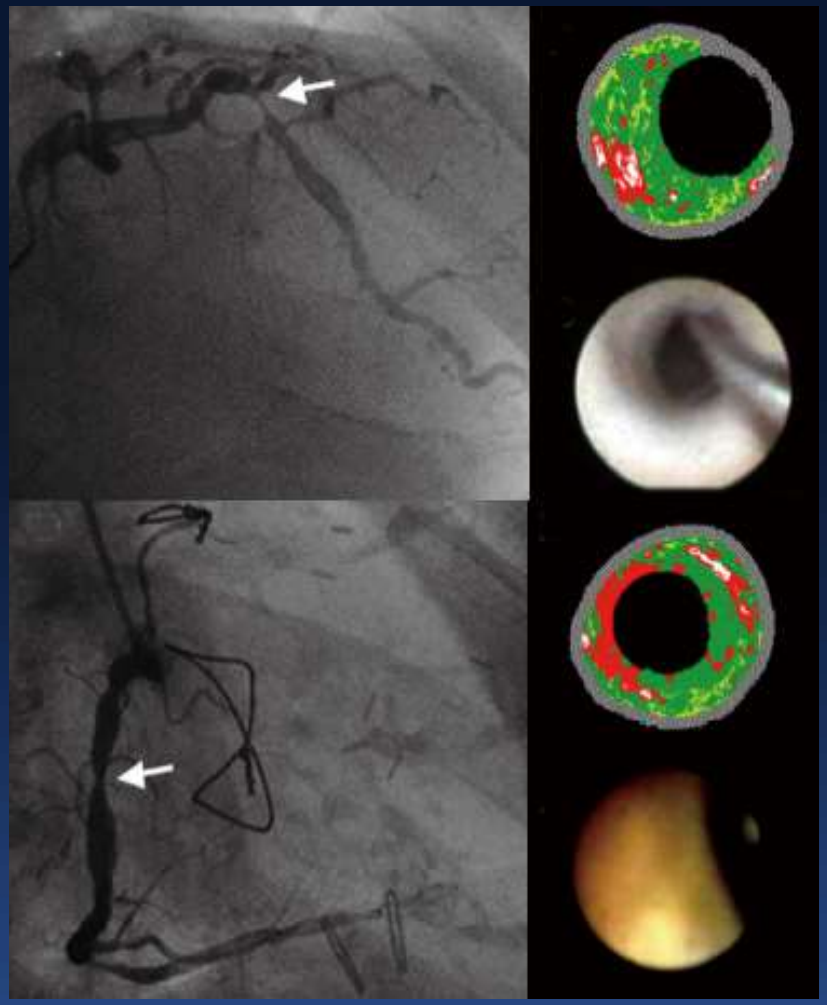

Angioscopy vs VH-IVUS TCFA in 57 culprit lesions in 57 pts

VH - IVUS	Angioscopy	
	+	-
+	17 (30%)	8 (14%)
-	6 (11%)	26 (46%)

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

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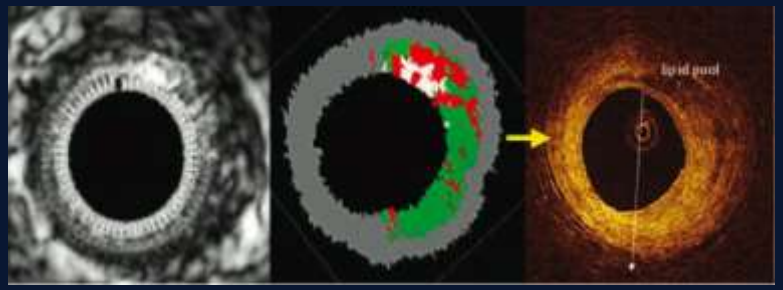
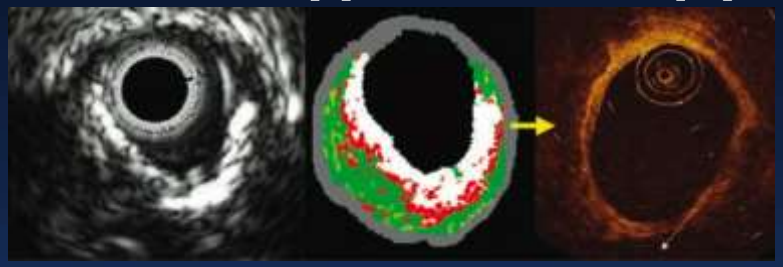
OCT vs VH-IVUS TCFA in 126 lesions in 56 pts

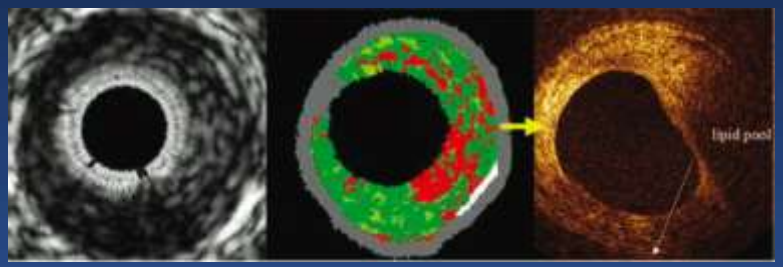
VH-IVUS (+) and OCT (-)



VH-IVUS (-) and OCT (+)



VH-IVUS (+) and OCT (+)



VH - IVUS	OCT	
	+	-
+	28 (22%)	33 (26%)
-	8 (6%)	57 (45%)

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

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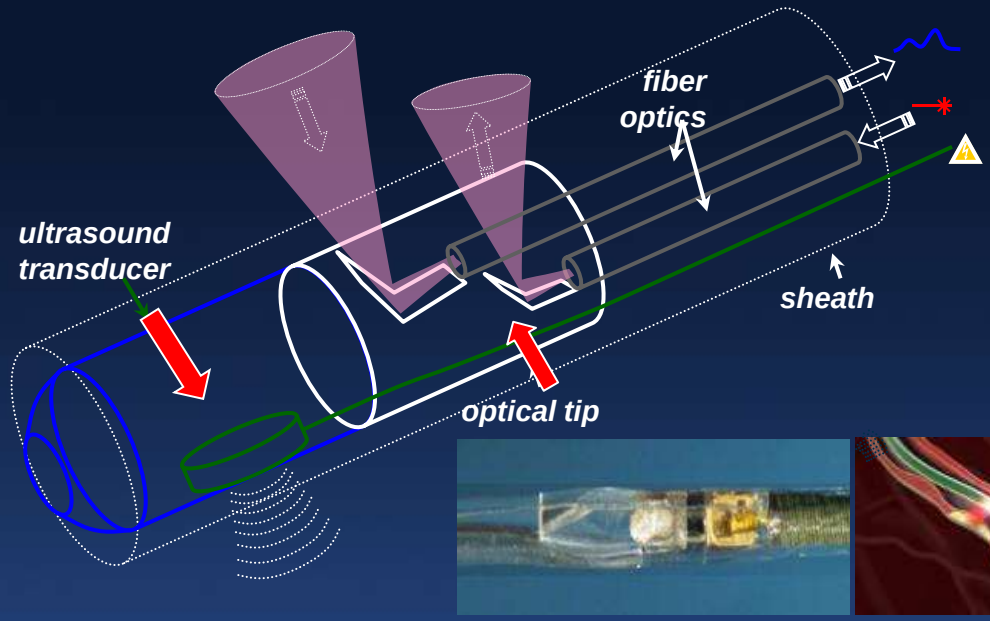
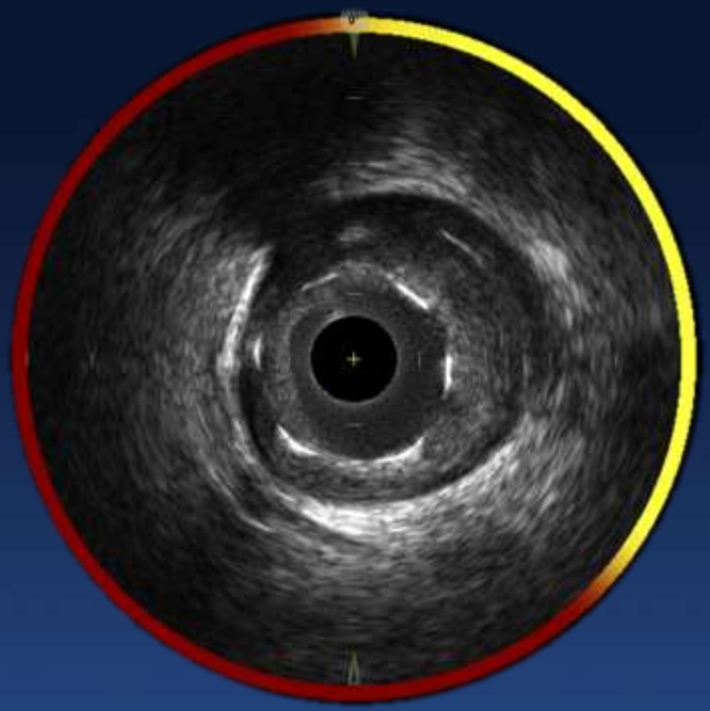
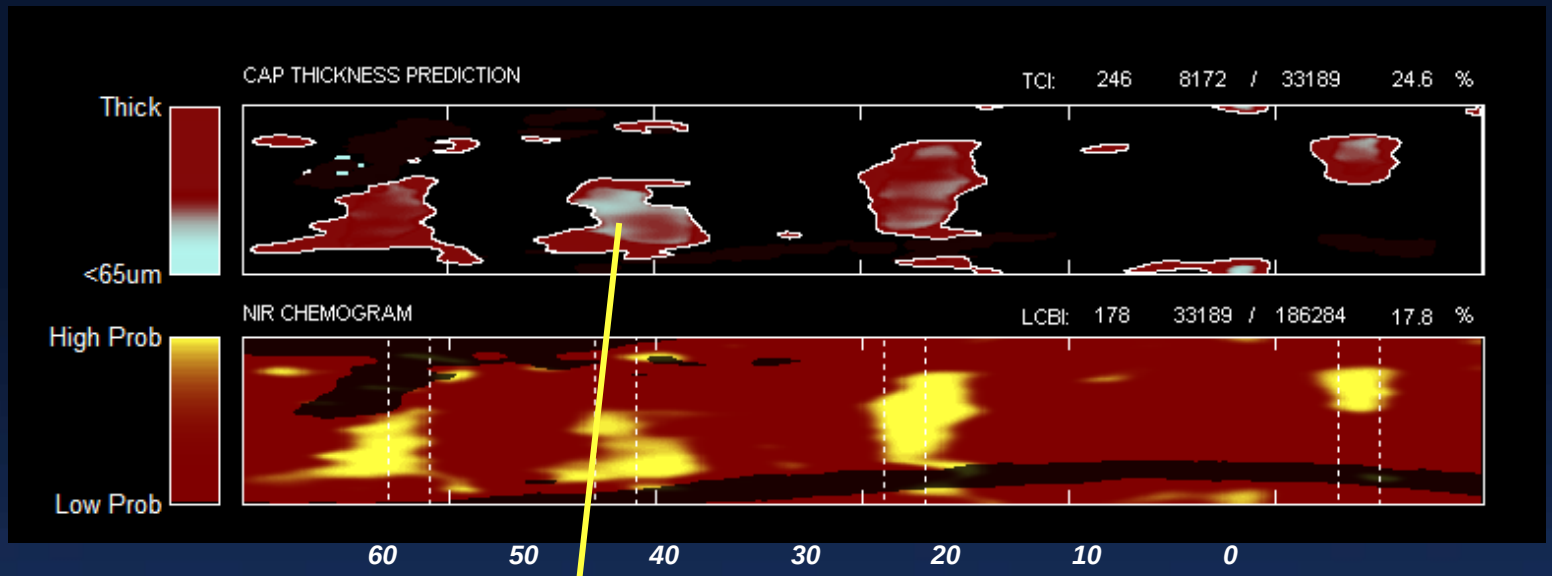
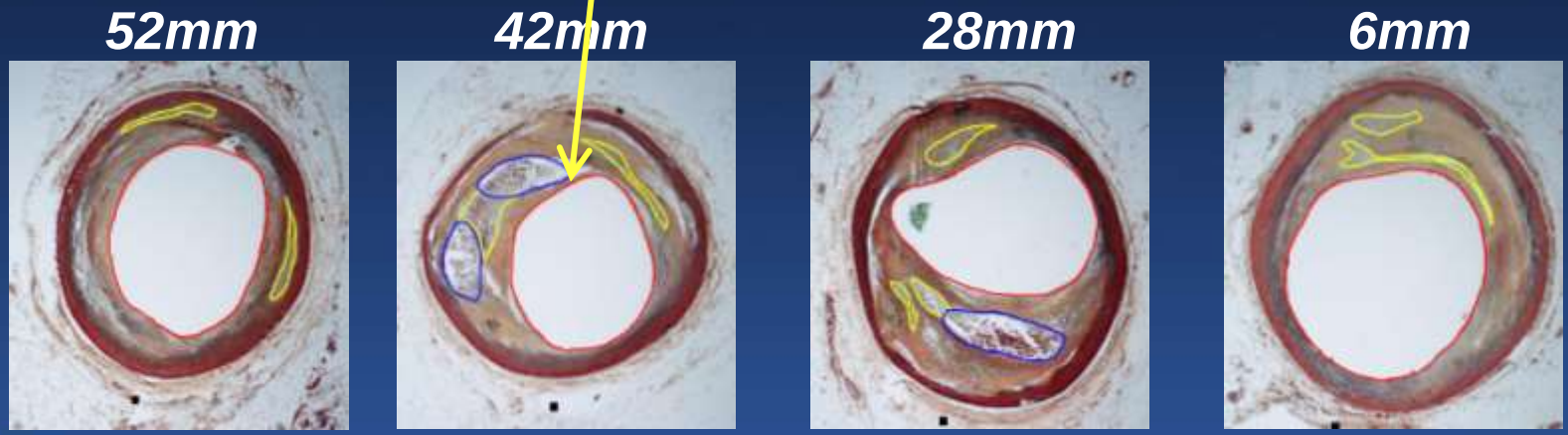
Infraredx: Combined NIRS - Next Generation IVUS





Spectral differences can be used to distinguish LCP with thin fibrous cap (less collagen) from LCP with thicker fibrous cap (more collagen)





Madden et al. J Am Coll Cardiol 2012;59:E308

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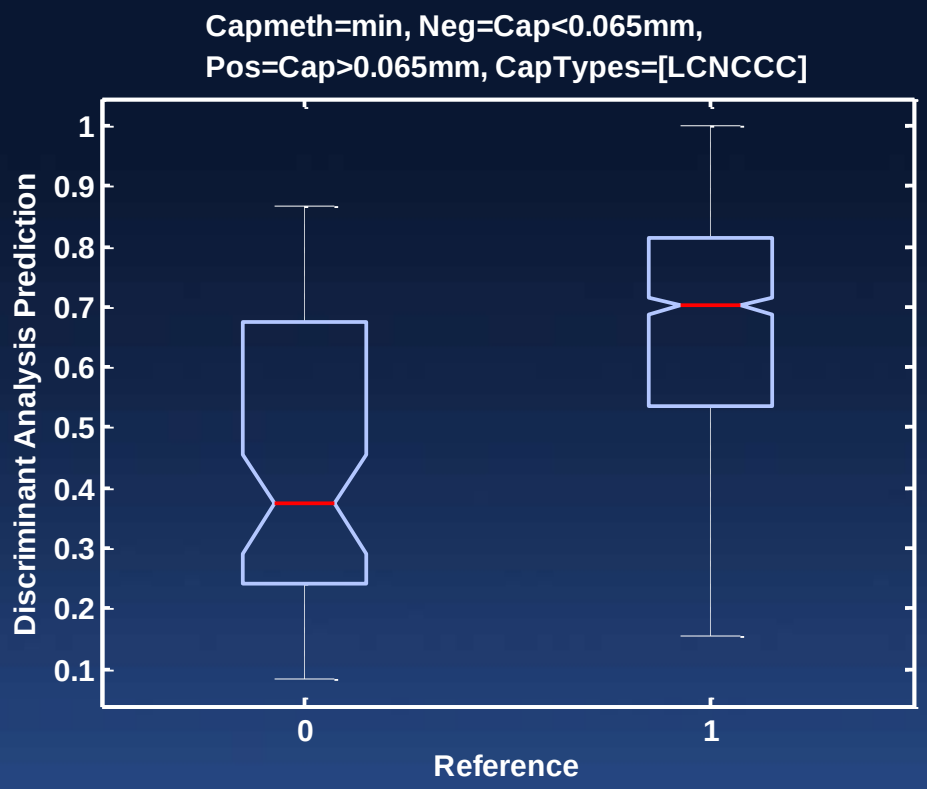
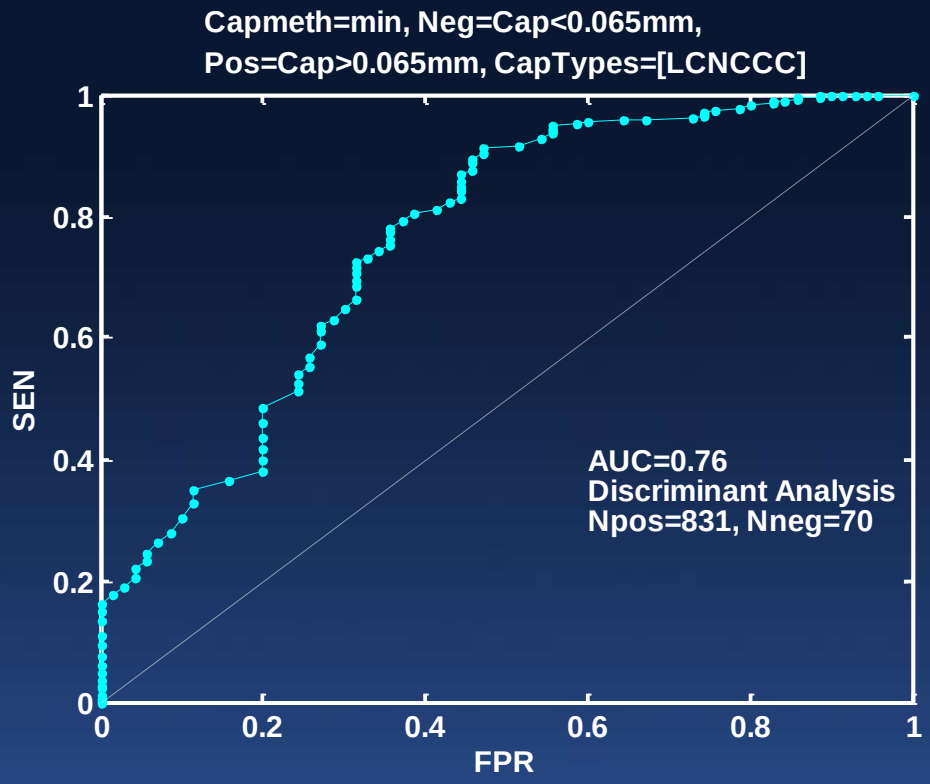
Ability to Predict Thin Cap (<0.065mm)





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OCT has been proposed as the gold standard to detect a TCFA, but. . .

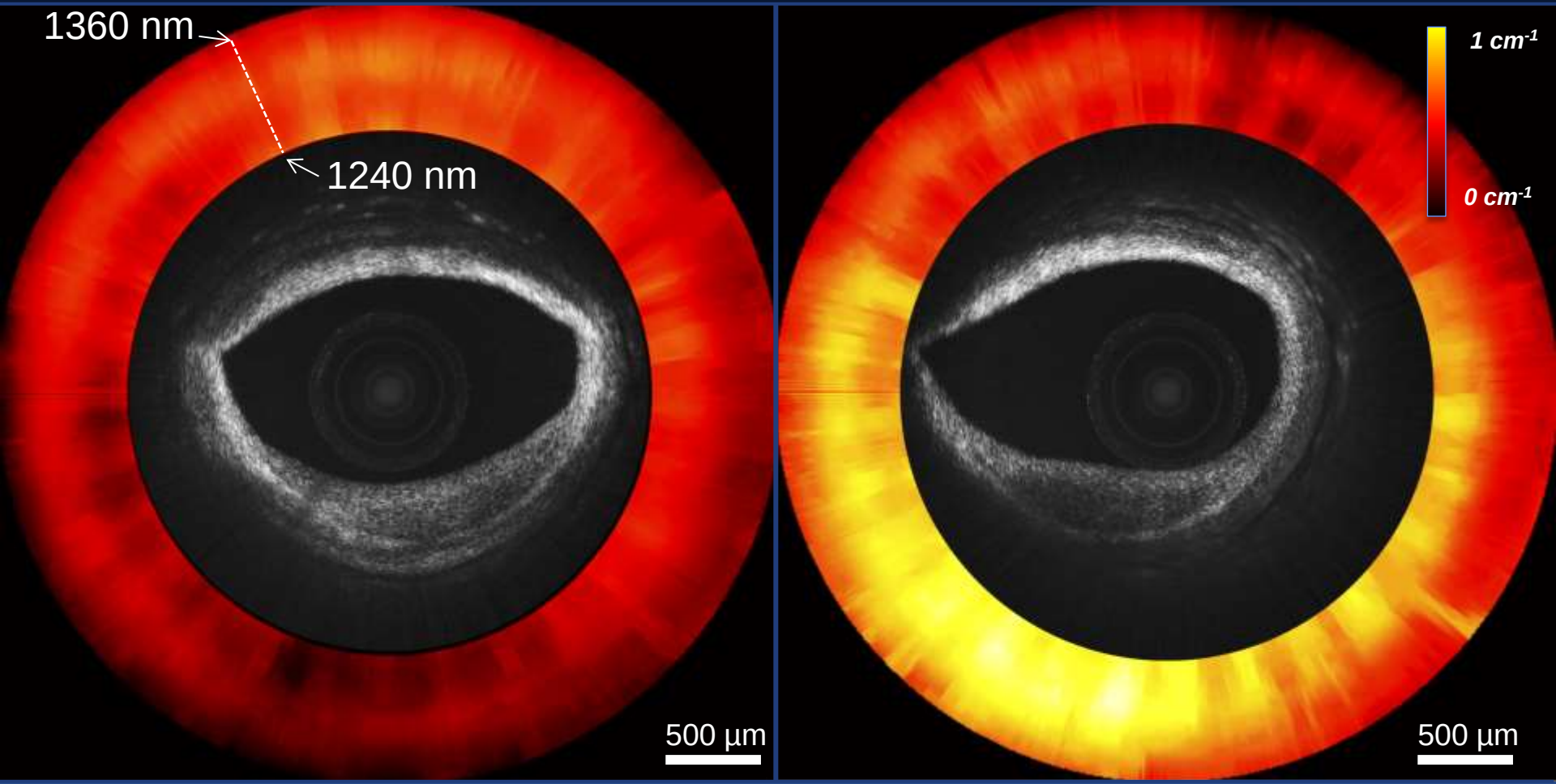
	Positive Predictive Value				
	Histology (#)	OCT	IVUS	RF-IVUS	OCT+IVUS
Brown et al. Circ Cardiovasc Imaging, in press	22	31%		26%	50%
Nakano et al. JACC Cardiovasc Imaging, in press	18	31%		14%	100%
Fujii et al. JACC Cardiovasc Imaging 2015;8:451-60	12	41%	19%		69%

	Interobserver correlation coefficient			
		FC thickness	Mean lipid arc	Max lipid arc
Kim et al. JACC Cardiovasc Imaging 2012;5:1072-4	25	0.49	0.71	0.77

Feldman. TCT2015	Of 21 IVOCT TCFAs identified by two independent IVOCT Core Labs (fibrous cap <65 μm, lipid arc >1 quadrant), only 8 were true histologic TCFA. False positive diagnoses foam cell infiltration (62%), SMC-rich fibrous tissue (15%), loose connective tissue (8)

OCT-NIRS

Cadaver Coronary Plaques



Tearney. TCT2013

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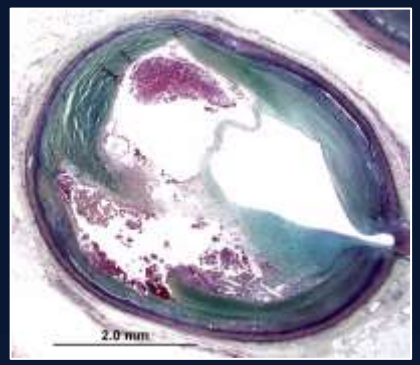
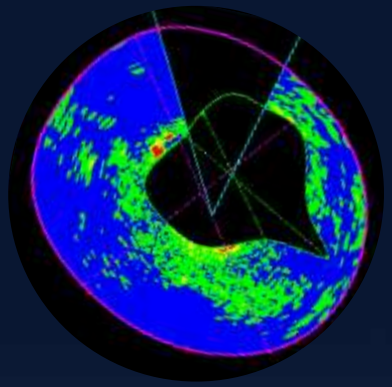
TCFA detection by IB-IVUS





	TCFA detection
PPV	50.0%
NPV	98.2%
Sensitivity	66.7%
Specificity	96.5%

TCFA detection by OCT + IB-IVUS

	# of sections	# TCFA	Probability (PPV)
Definite TCFA (by OCT and IB-IVUS)	10	10	100%
Probable TCFA (either by OCT or IB-IVUS)	27	6	22%
Neither by OCT and IB-IVUS	323	2	1%

Nakano et al. JACC Cardiovasc Imaging, in press

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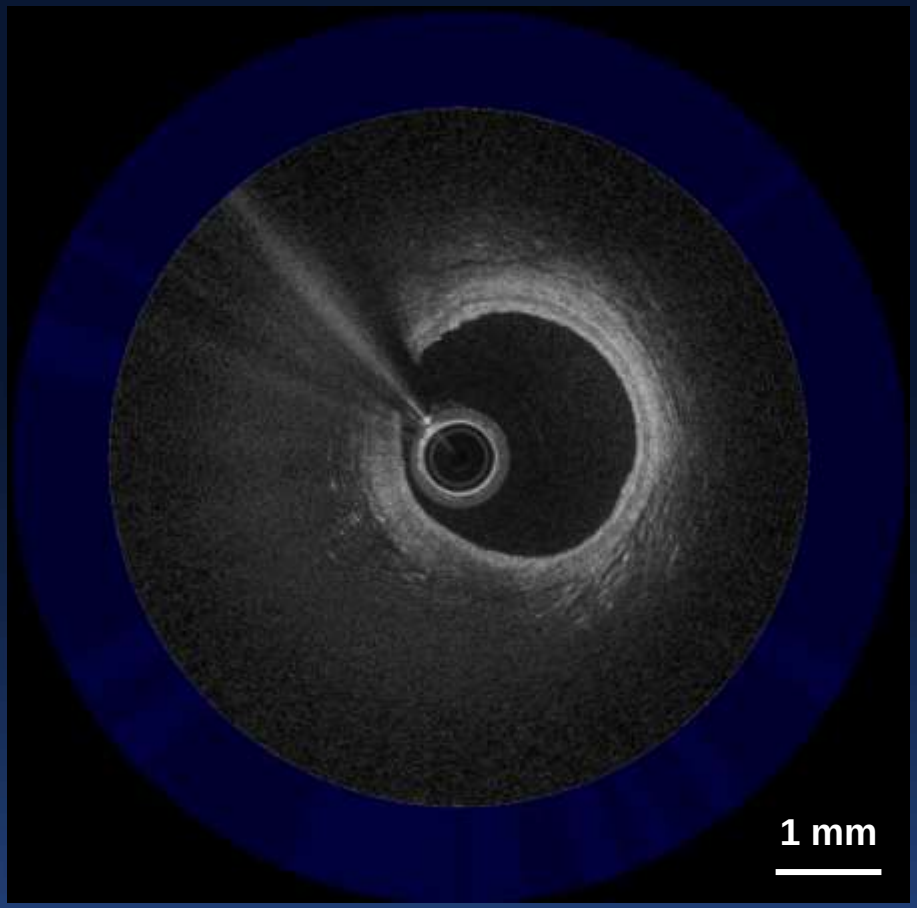
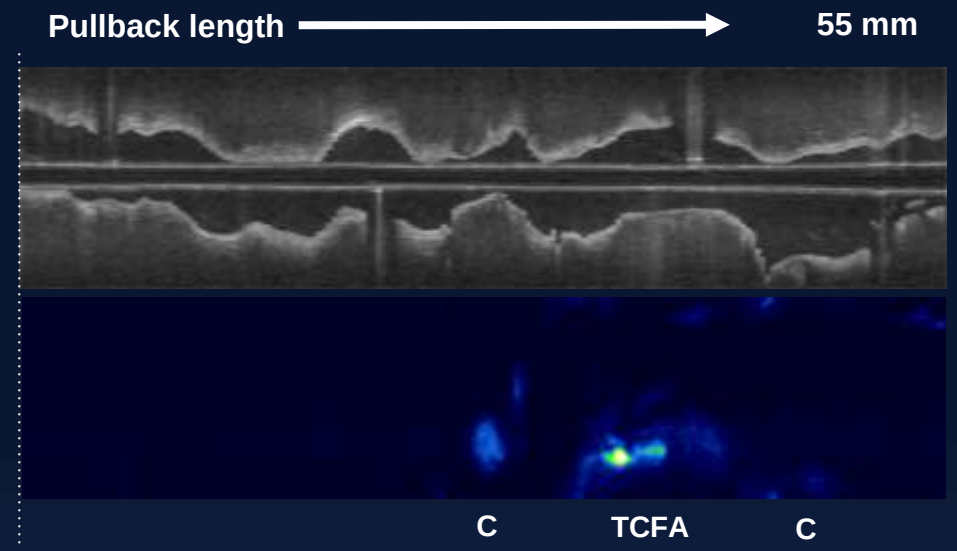
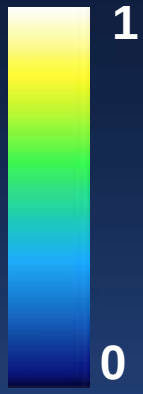
Structure and "Composition/Function" OCT combined with . . .

- Short wave length infrared (SWIR) to detect lipid
  - Shimokado et al. ESC2015

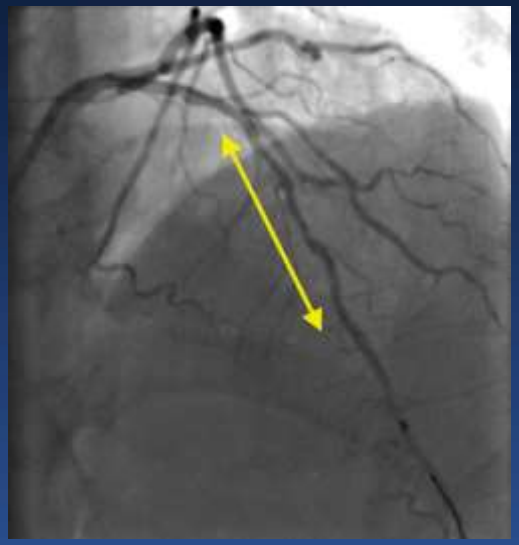
- Near infrared fluorescence molecular imaging (NIRF) to detect inflammatory plaque cathepsin protease activity and fibrin deposition post-stenting
  - Jaffer and Tearney. TCT2015
- Two photon luminescence (TPL) determine lipid, collagen, elastin and calcium due to auto-fluorescence
  - Feldman. TCT2015







Normalized NIRAF intensity



Tearney. TCT2015

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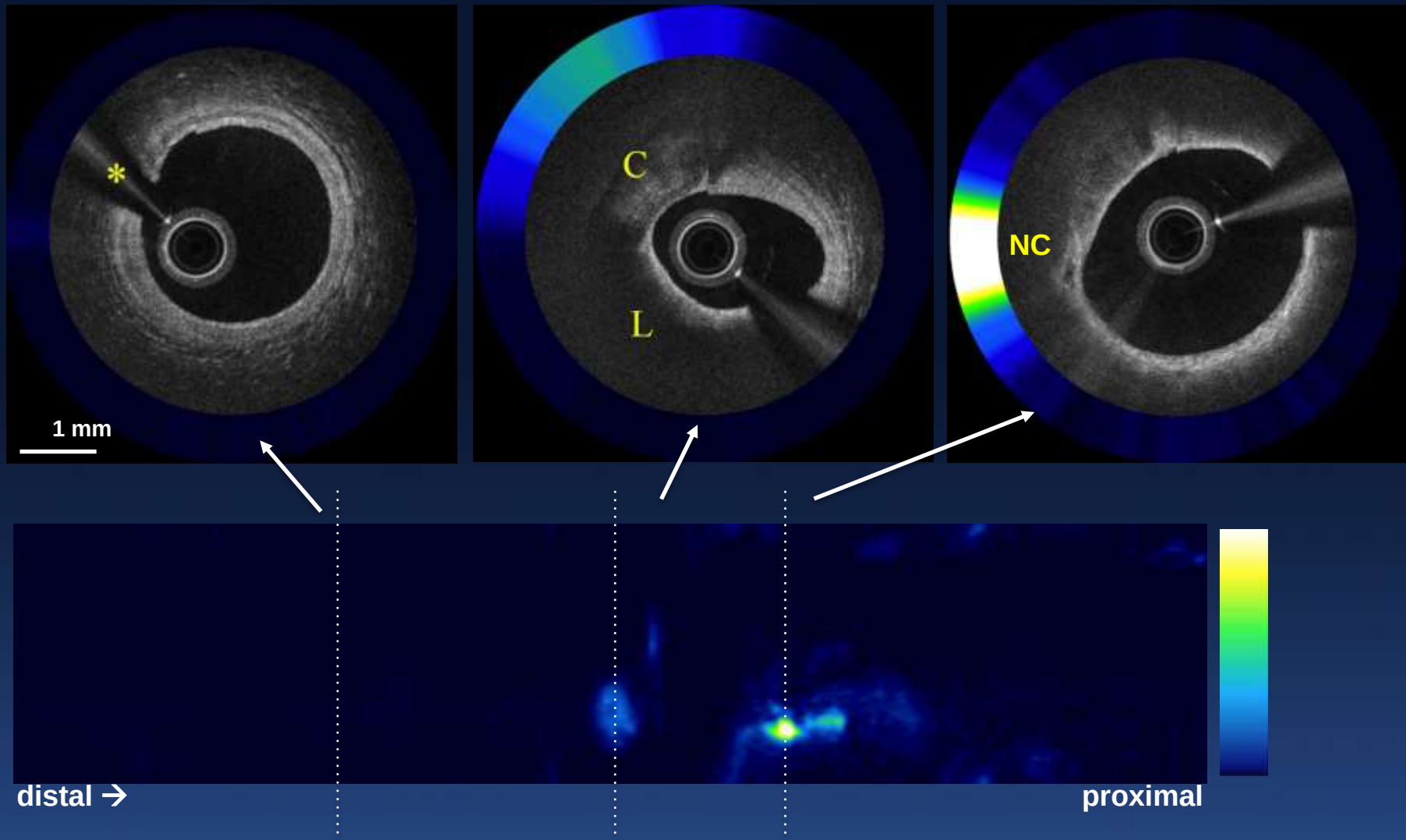

Tearney. TCT2015

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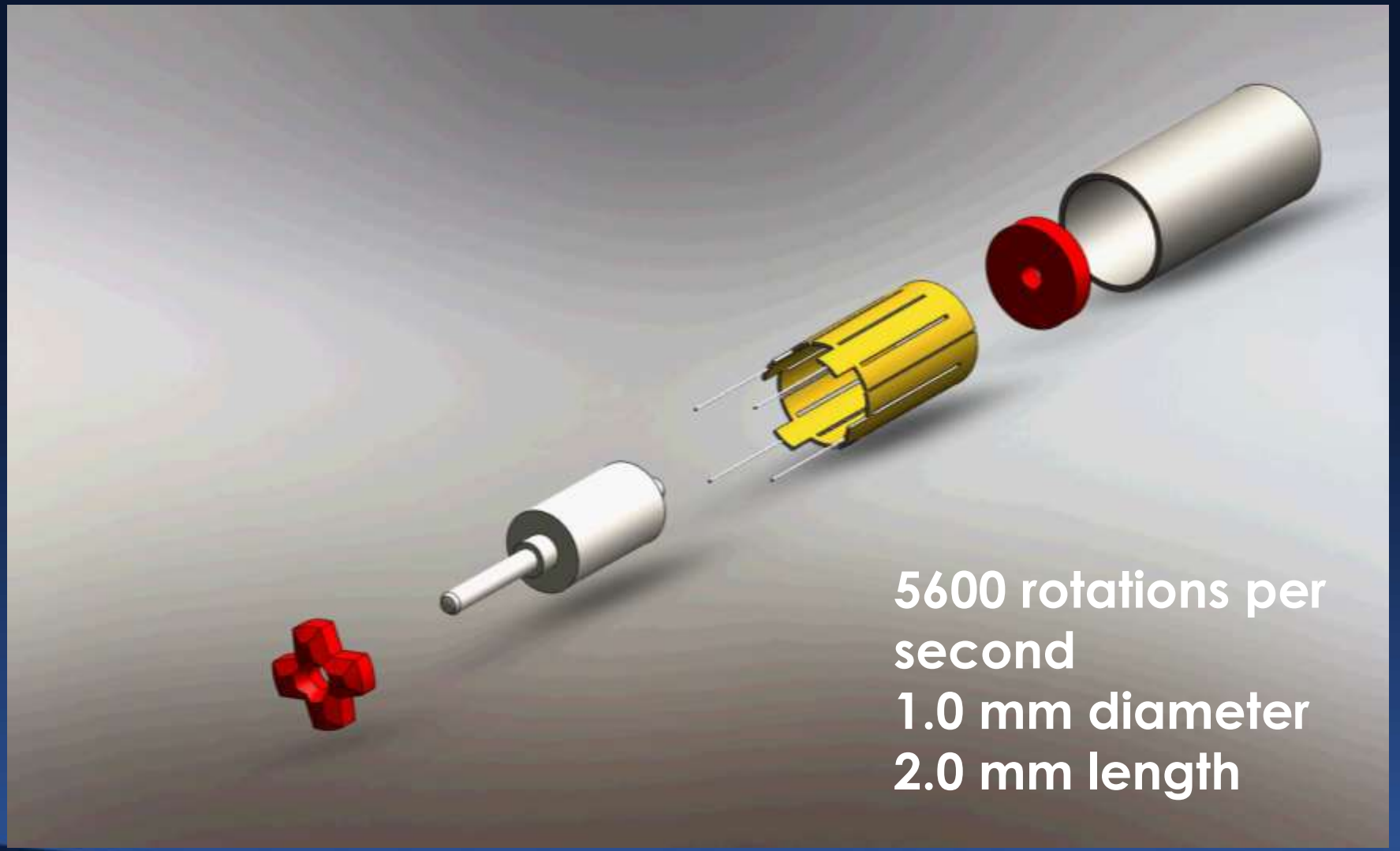
Heartbeat (micromotor) OCT



van der Steen. TCT2015

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1.2 mm outer diameter
1.7 mm length

van der Steen. TCT2015

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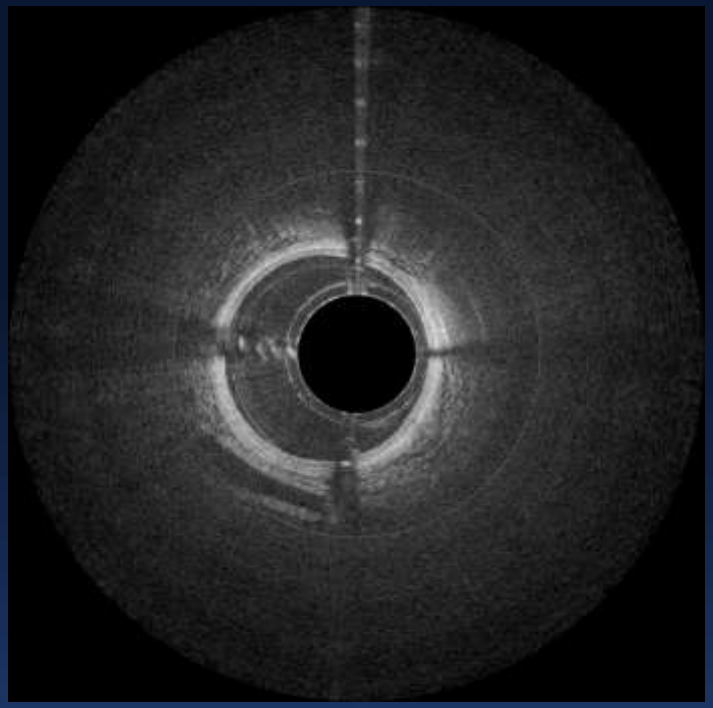
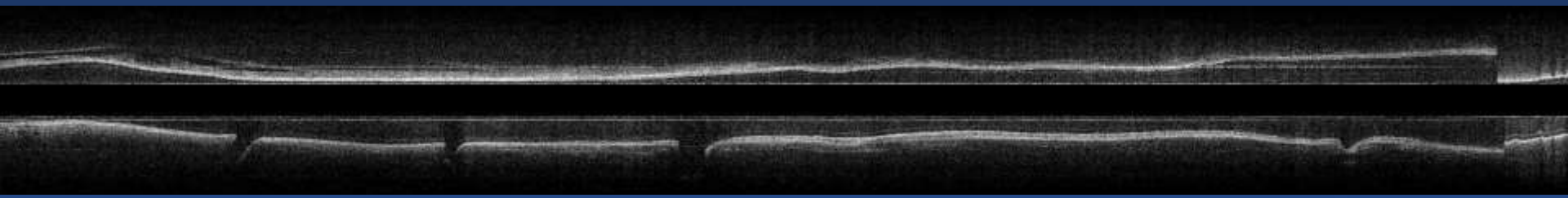
In vivo imaging of LAD





2000 frames, 50 mm

van der Steen. TCT2015

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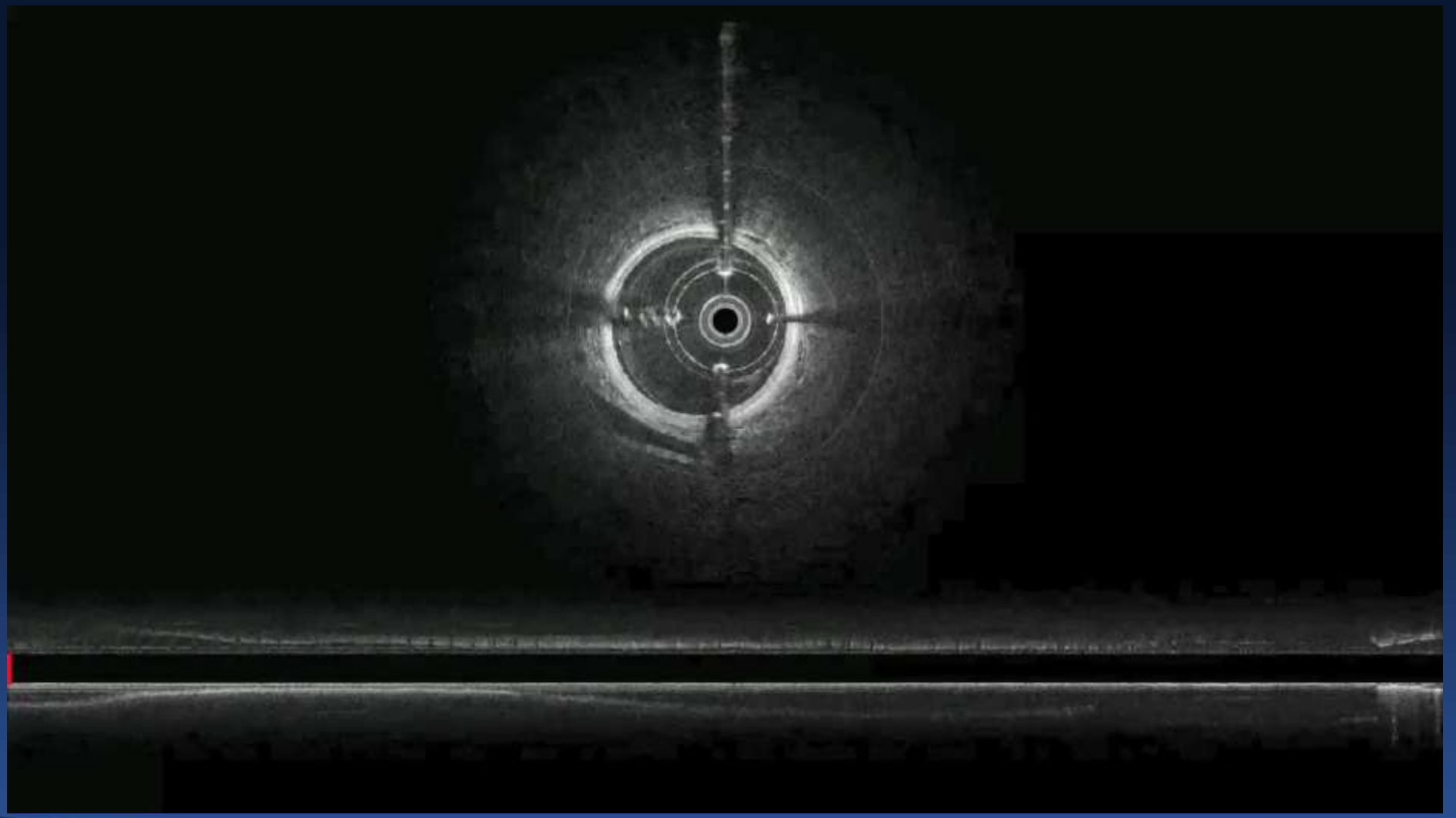
160 times slower



van der Steen. TCT2015

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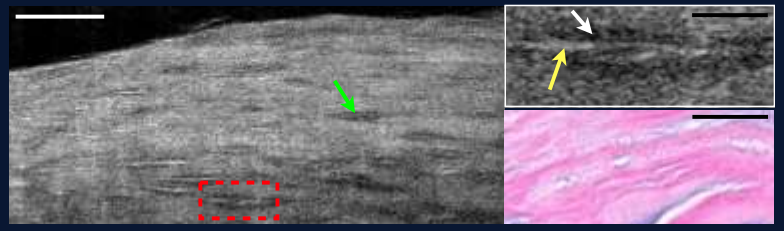
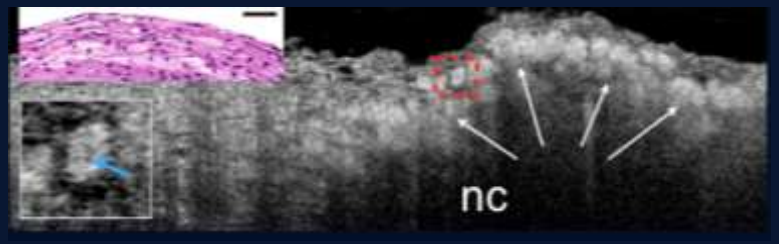
Micro OCT with 1-2 micron resolution

Smooth Muscle Cells



Macrophages



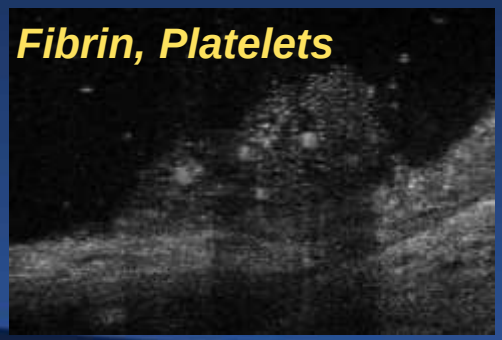
Endothelium

Necrotic Core Cholesterol Crystals

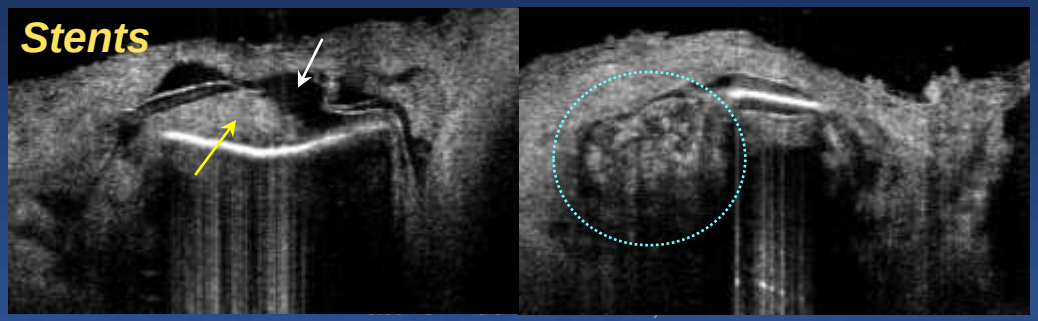
"The short update is that we have finally figured out how to make a µOCT catheter and it works. In the next few months, we will be demonstrating the catheter ex vivo. Hopefully by next year's TCT we will have conducted a first-in-human study and will have our first in vivo images."

-Gary Tearney MD, PhD, October 20, 2015

Fibrin, Platelets



Stents



Tearney. TCT2013

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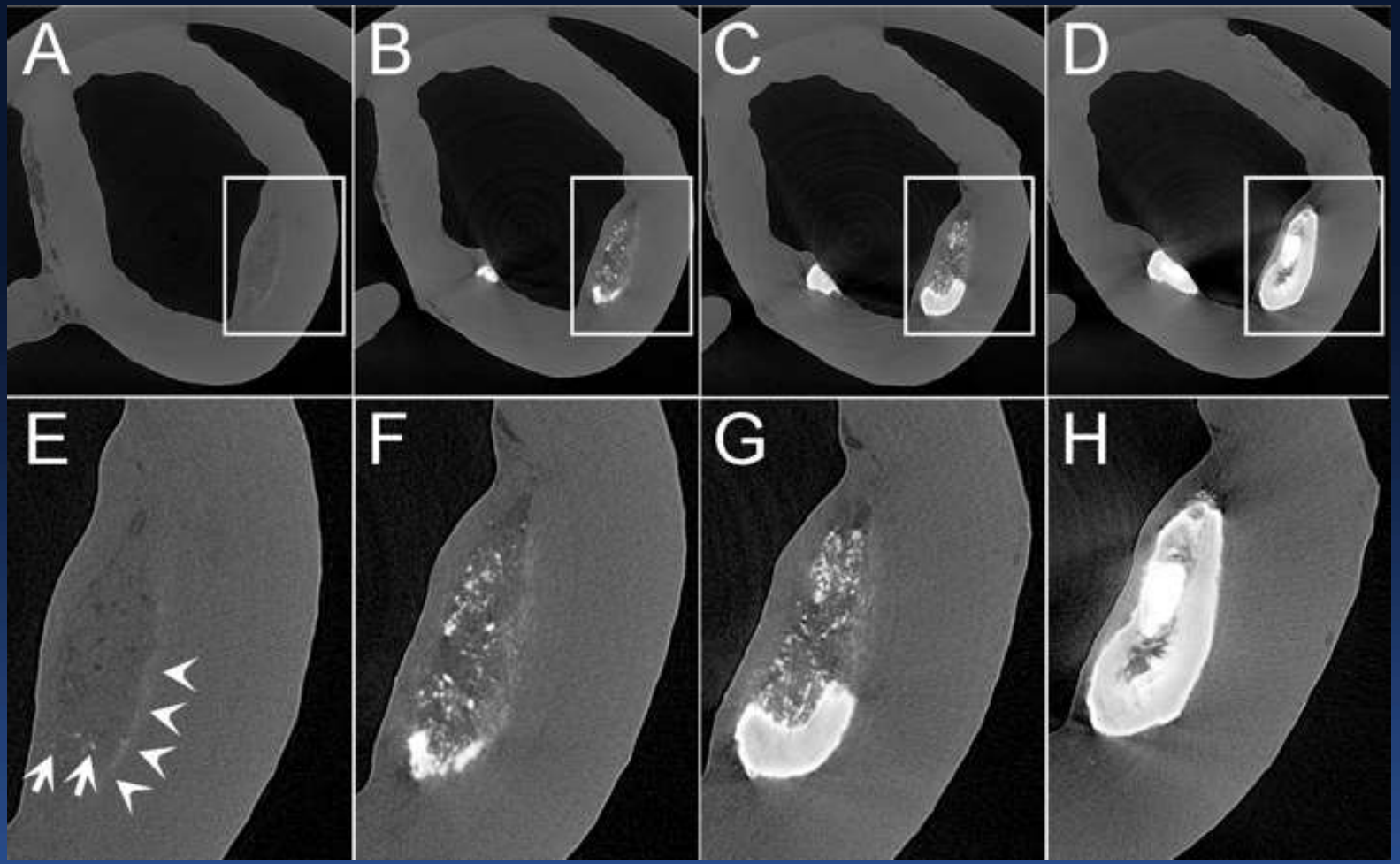
High Resolution (*2.1μ*) Micro-CT



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Effect of tissue properties, shape and orientation of microcalcifications on vulnerable cap stability using different hyperelastic constitutive models

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Abstract

Approximately half of all cardiovascular deaths associated with acute coronary syndrome occur when the thin fibrous cap tissue overlying the necrotic core in a coronary vessel is torn, ripped or fissured under the action of high blood pressure. From a biomechanics point of view, the rupture of an atheroma is due to increased mechanical stresses in the lesion, in which the ultimate stress (i.e. peak circumferential stress (PCS) at failure) of the tissue is exceeded. Several factors including the cap thickness, morphology, residual stresses and tissue composition of the atheroma have been shown to affect the PCS. Also important, we recently demonstrated that microcalcifications (μCalcs) > 5 μm are a common feature in human atheroma caps, which behave as local stress concentrators, increasing the local tissue stress by at least a factor of two surpassing the ultimate stress threshold for cap tissue rupture. In the present study, we used both idealized μCalcs with spherical shape and actual μCalcs from human coronary atherosclerotic caps, to determine their effect on increasing the circumferential stress in the fibroatheroma cap using different hyperelastic constitutive models. We have found that the stress concentration factor (SCF) produced by μCalcs in the fibroatheroma cap is affected by the material tissue properties, μCalcs spacing, aspect ratio and their alignment relative to the tensile axis of the cap.

Keywords

micro computed tomography; vulnerable plaque; microcalcifications; fibrous cap rupture

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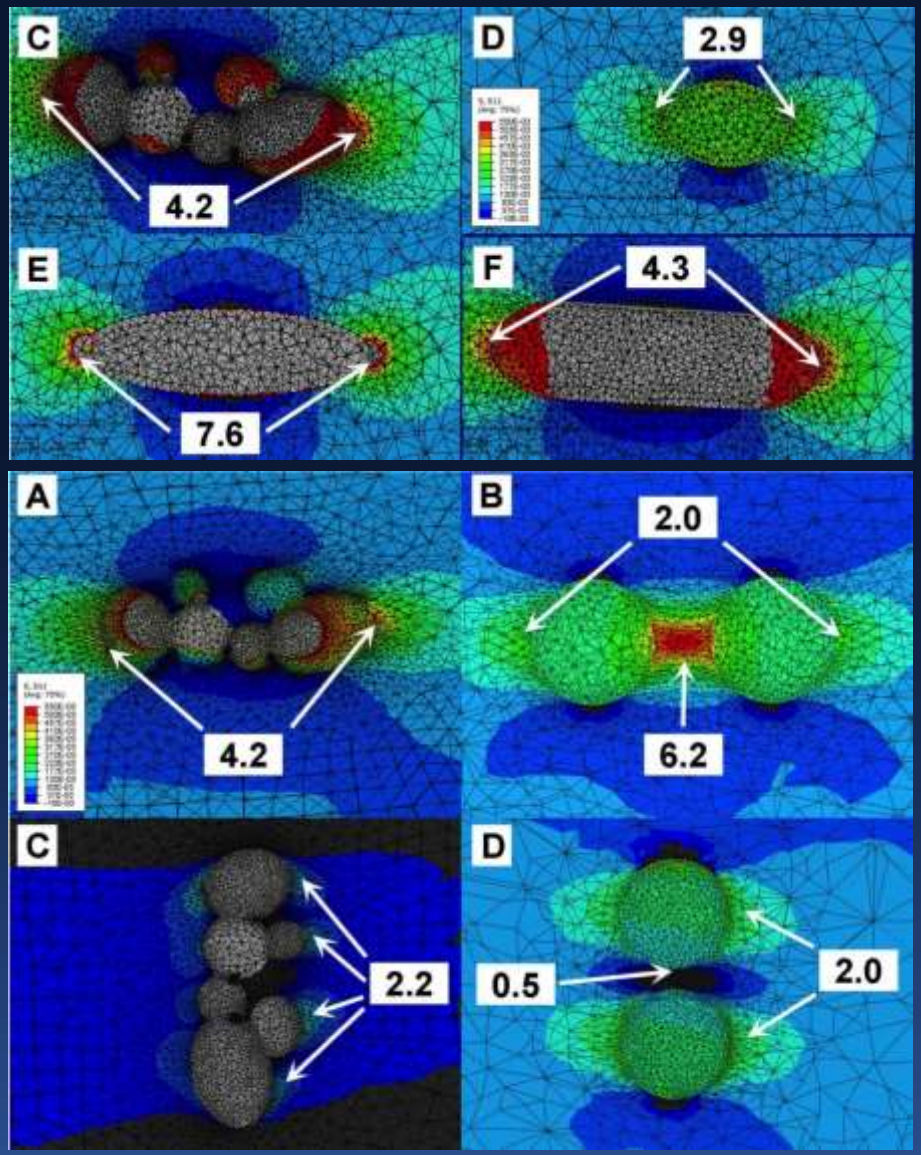
Conflict of interest
The authors have no conflict of interest.



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Kelly-Arnold et al. Proc Natl Acad Sci USA. 2013;110:10741-6

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Sharper Image Catalogue. Holiday 2015.

- **Outside of Japan and Korea and only isolated centers in the US and Europe, interventionalists look for any excuse not to perform FFR - IVUS (or OCT) even though there is undeniable data that these techniques improve PCI outcomes**
- **Technologic advancements may be good, but . .**
  - **There must be a clinical need**
  - **Images must be easy to interpret – and not just by experts or in a core lab setting or at IPS**
  - **Patient outcomes must be improved (without a major increase in cost)**