The Reality of Vulnerable Plaque Detection and Clinical Implications

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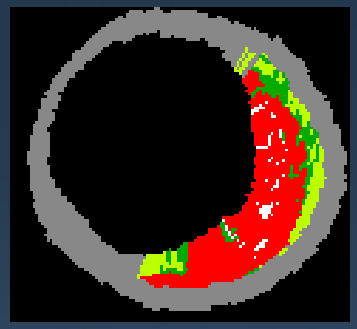
Currently, the only technique that has prospectively linked lesion phenotype to late events is VH-IVUS

VH-TCFA and Non Culprit Lesion Events in PROSPECT



	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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Stone et al. N Engl J Med 2011;364:226-35

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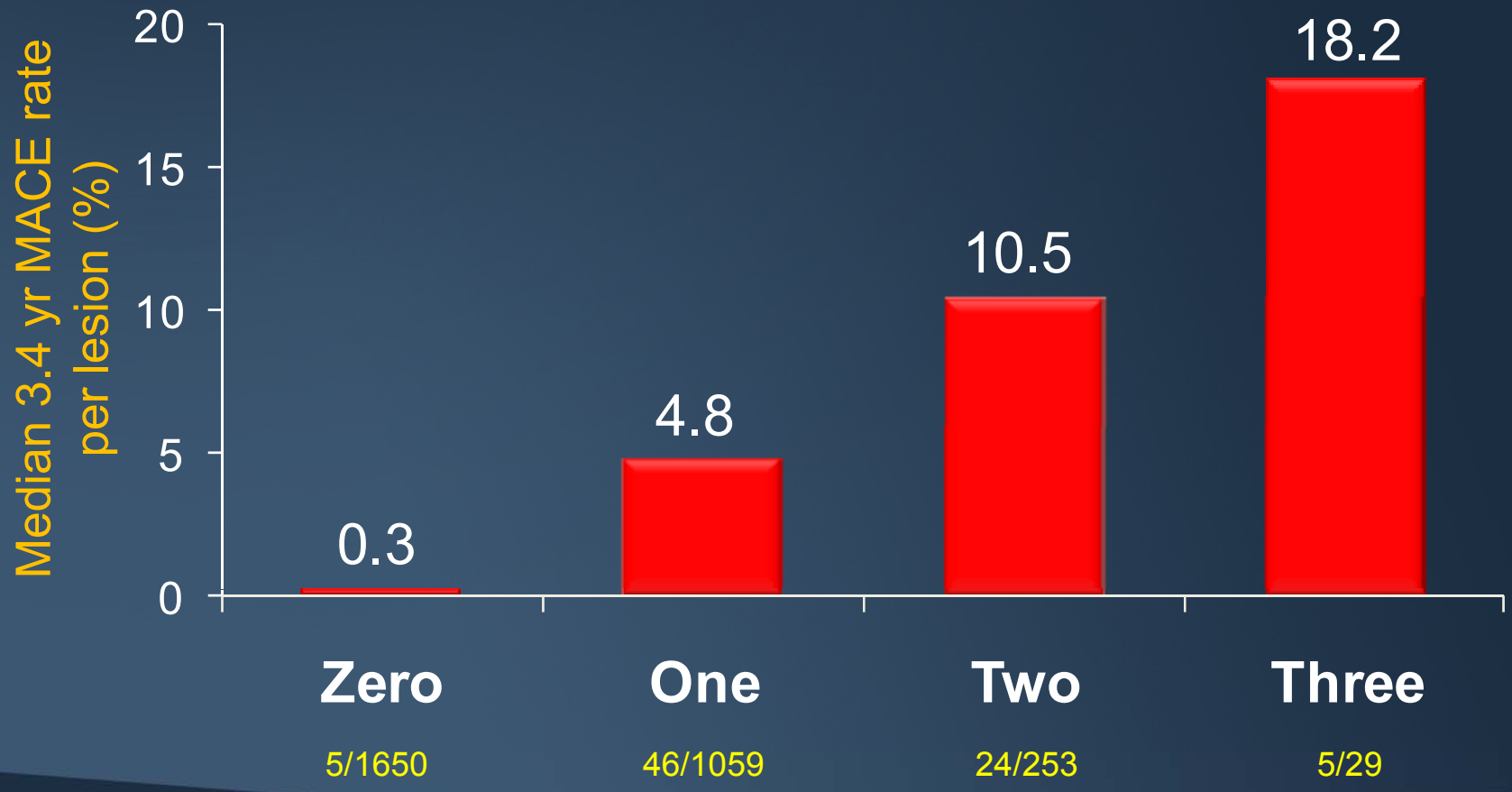
Events versus number of factors

PB_{MLA} ≥70%, MLA ≤4.0mm^2, and/or VH-TCFA



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VIVA: Virtual Histology in Vulnerable Atherosclerosis

- 932 non-culprit lesions in 170 pts were identified with 3-vessel IVUS imaging
- At a median follow-up of 625 days, there were 18 culprit and non-culprit MACE in 16 pts
  - 14 revascularizations, 2 MIs, and 2 deaths
- Univariate predictors of non-culprit MACE
  - Non-calcified VH-TCFA (p=0.025)
  - MLA <4mm^2 (p=0.021)
  - Plaque burden >70% (p<0.001)
  - Remodeling index (p=0.014)

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

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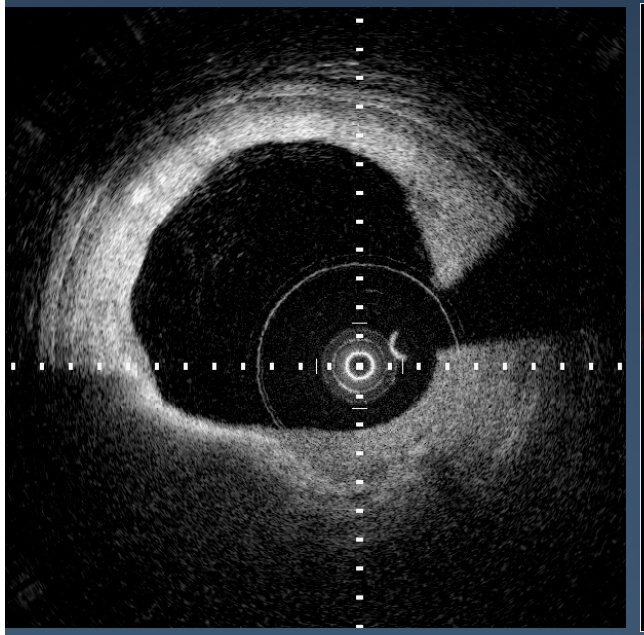
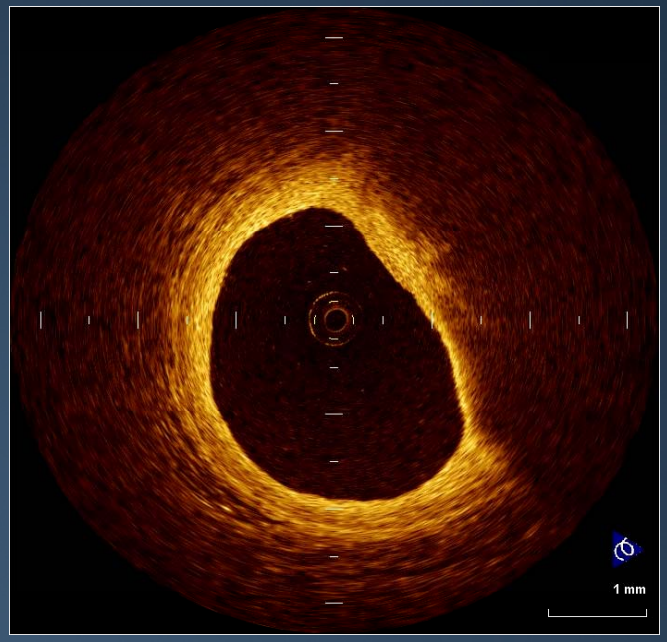
Optical Coherence Tomography

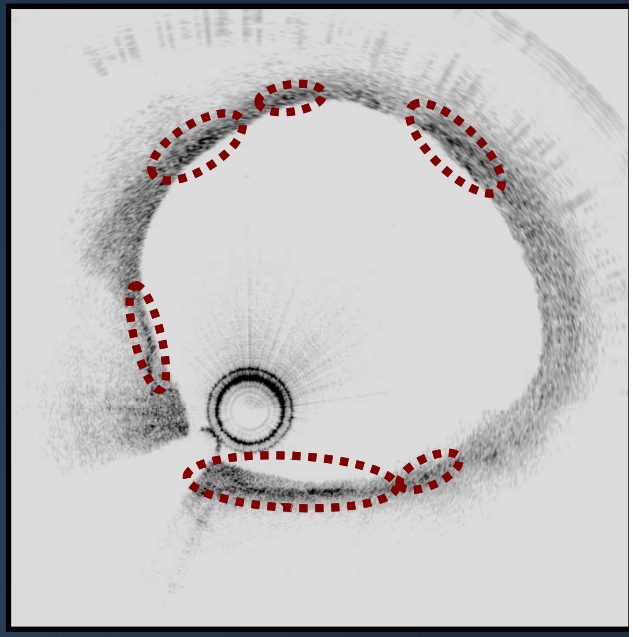
Fibroatheroma

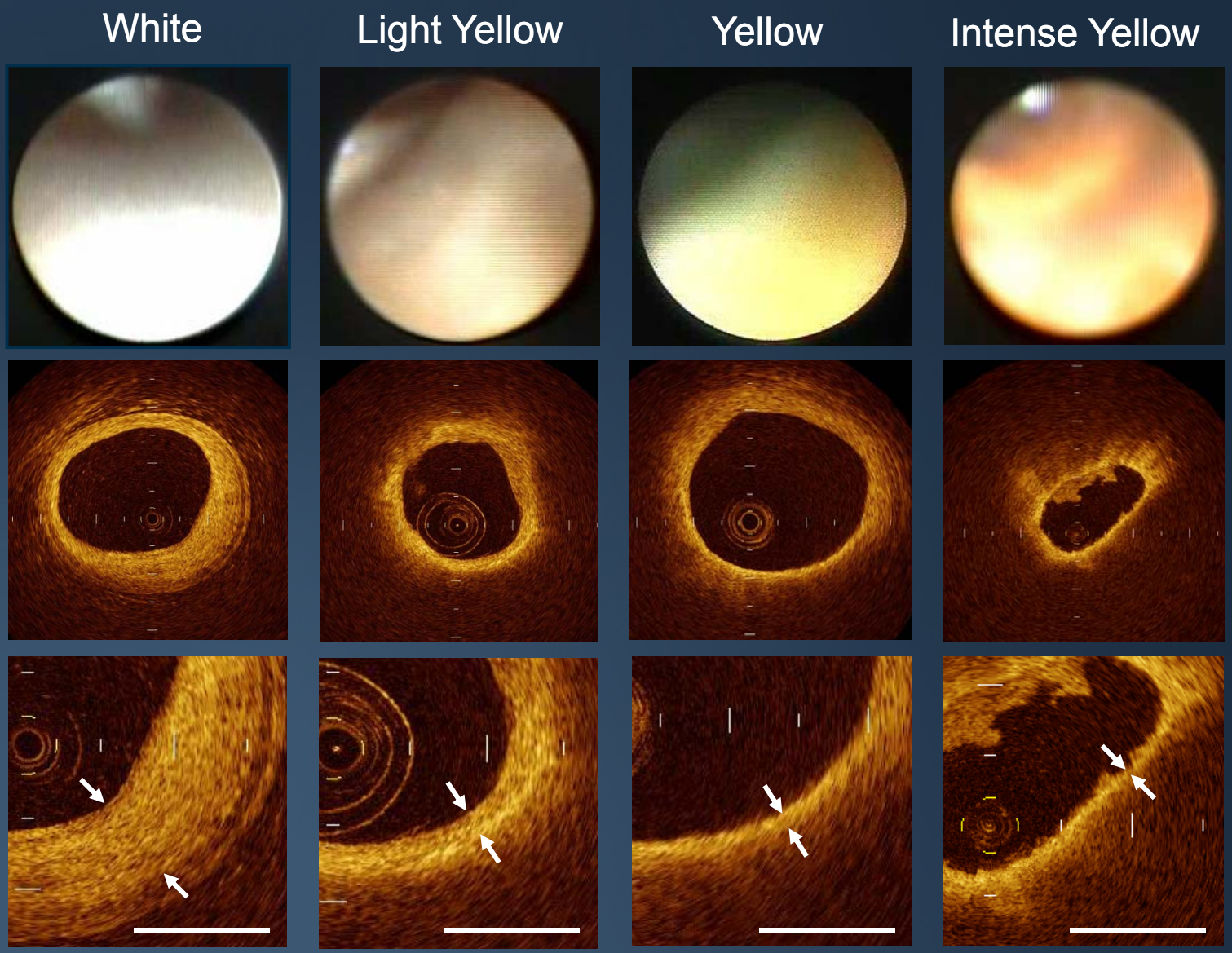


TCFA

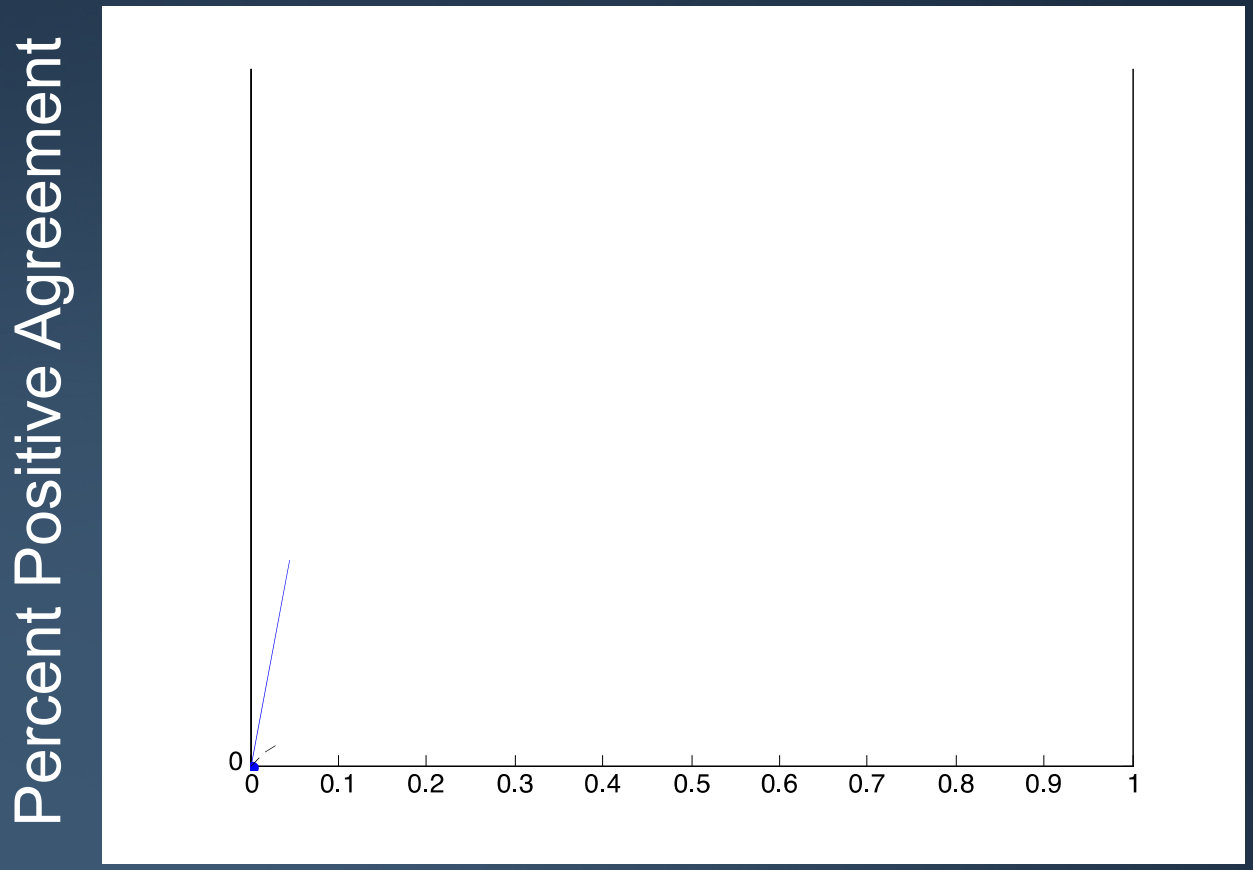


Macrophage Accumulations




White
Light Yellow
Yellow
Intense Yellow

ROC Analysis of Validation of NIR Spectroscopy in 51 Autopsy Hearts (algorithm for detection of confluent [>0.2mm thick and >60°] and relatively superficial necrotic core [overlying mean fibrous cap thickness <0.45mm])



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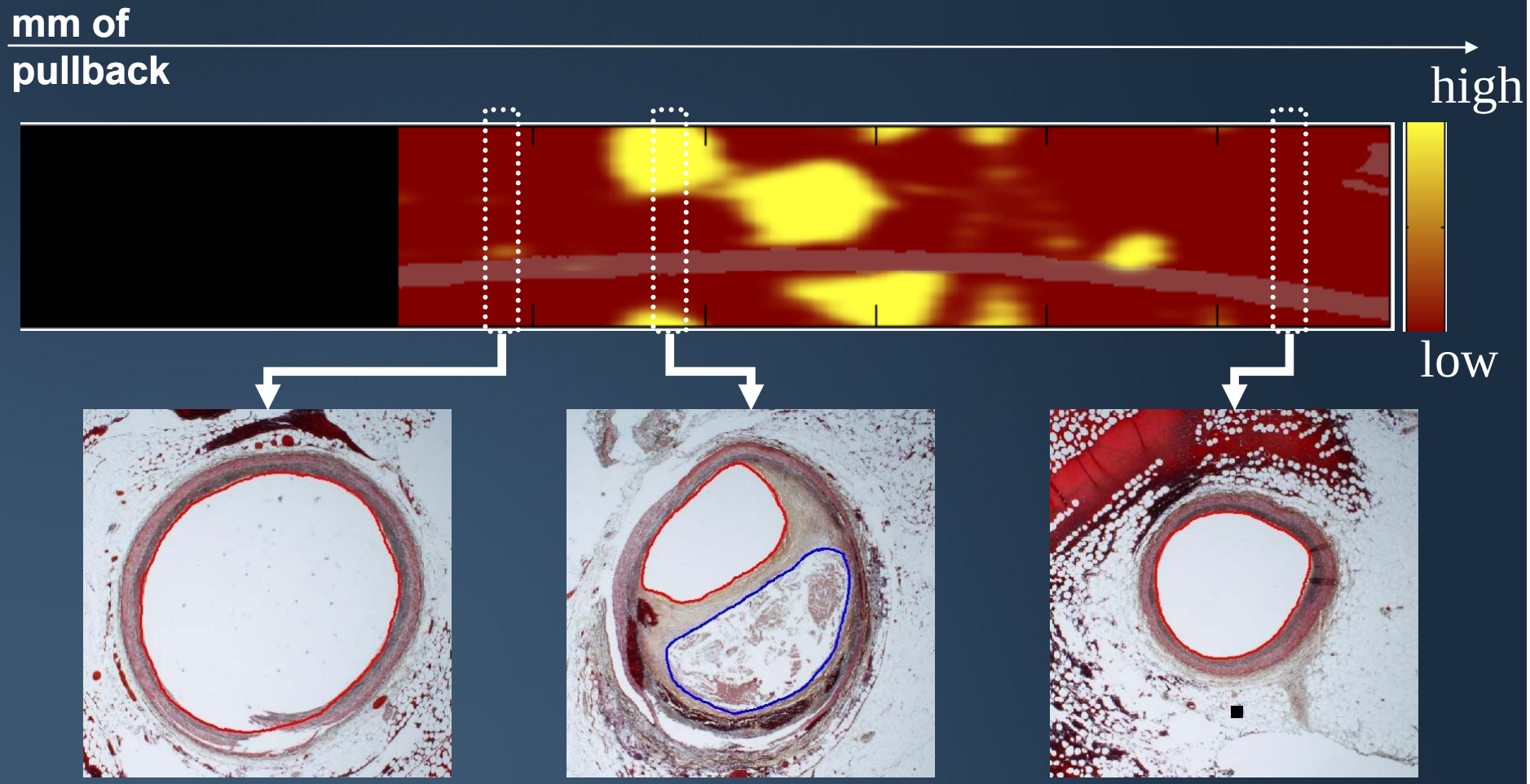
NIRS vs Histology



314 calcified nodules in PROSPECT

- The prevalence of at least one calcified nodule was 16% per artery (250 of 1573) and 30% per patient (185 of 623).
- Two or more calcified nodules were detected in 48 coronary arteries (3%) in 76 patients (12%).
- The angiographic appearance was severe calcium in 3, moderate calcium in 35, hazy in 19, and normal in 257
- The VH-IVUS appearance was a fibroatheroma in 42% (116 of 276) , but only a VH-TCFA in 5.

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Lee et al. Am J Cardiol 2011;108:1547-51
Xu et al. Circulation, in press

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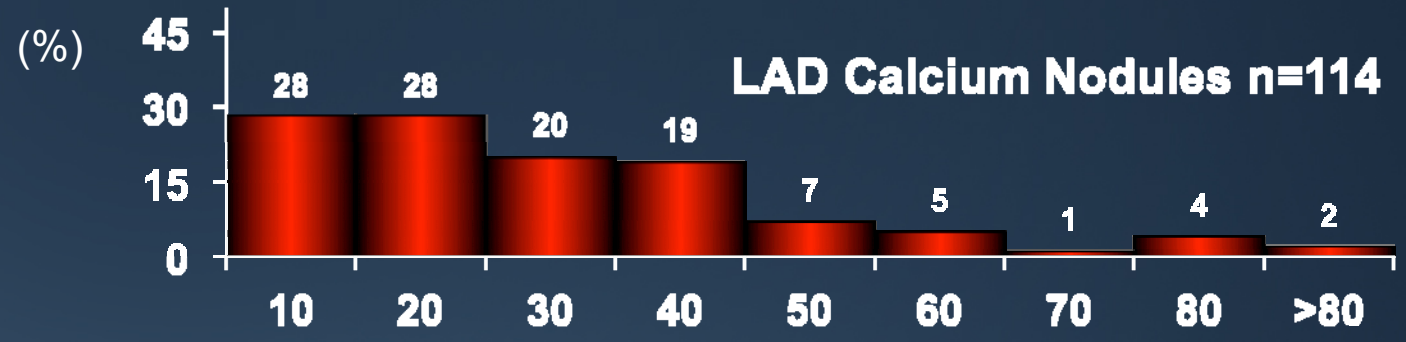
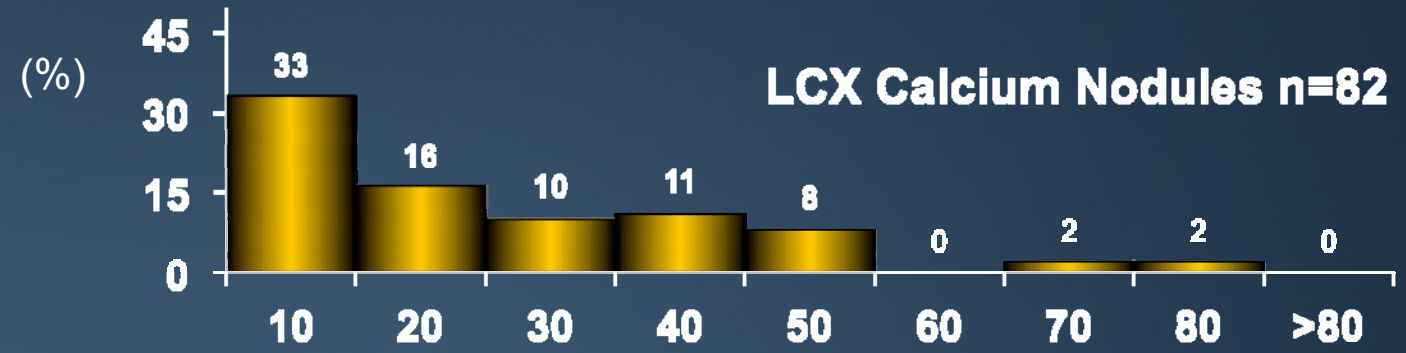
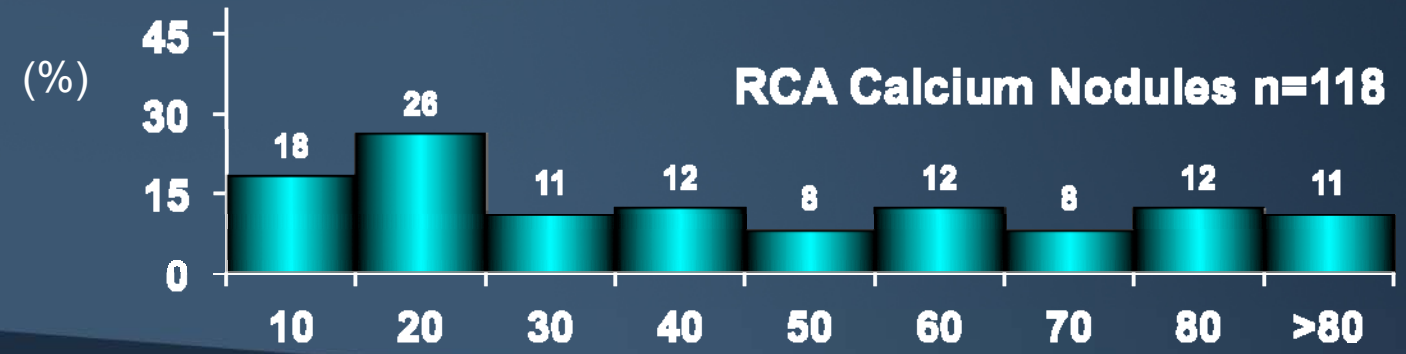
Longitudinal distribution of 314 calcified nodules



Distance from the ostium (mm)



Distance from the ostium (mm)



Distance from the ostium (mm)

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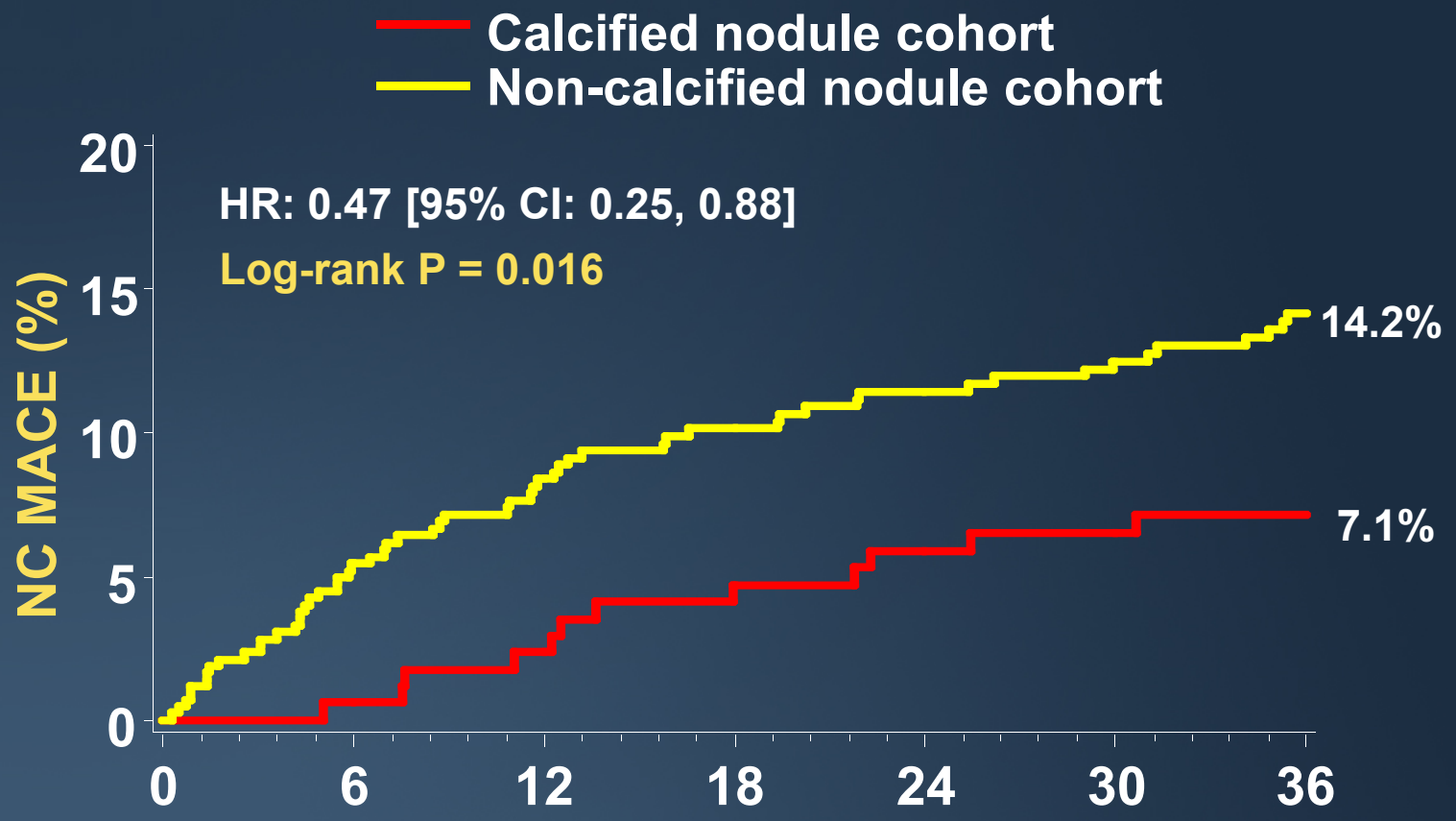

Number at risk

CN cohort	185	170	166	162	156	150	90
Non-CN cohort	438	389	370	352	338	324	190

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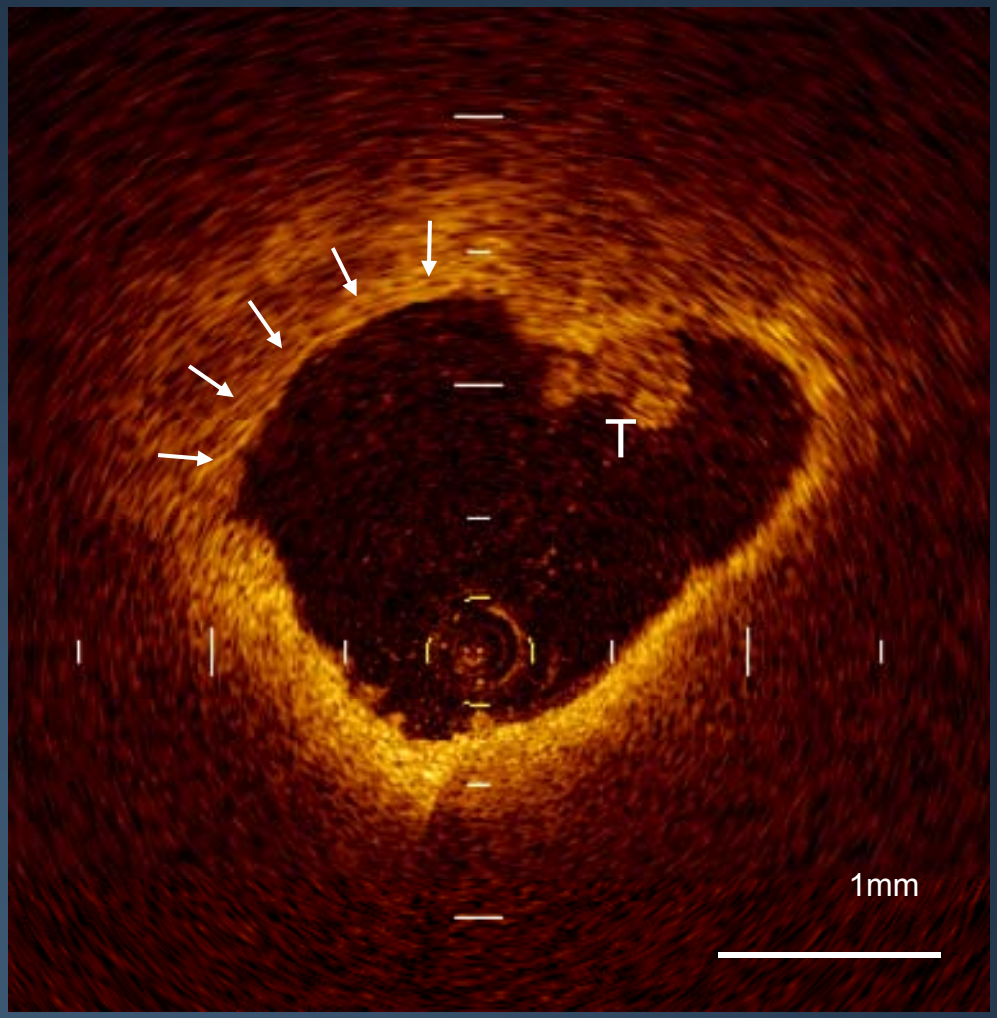
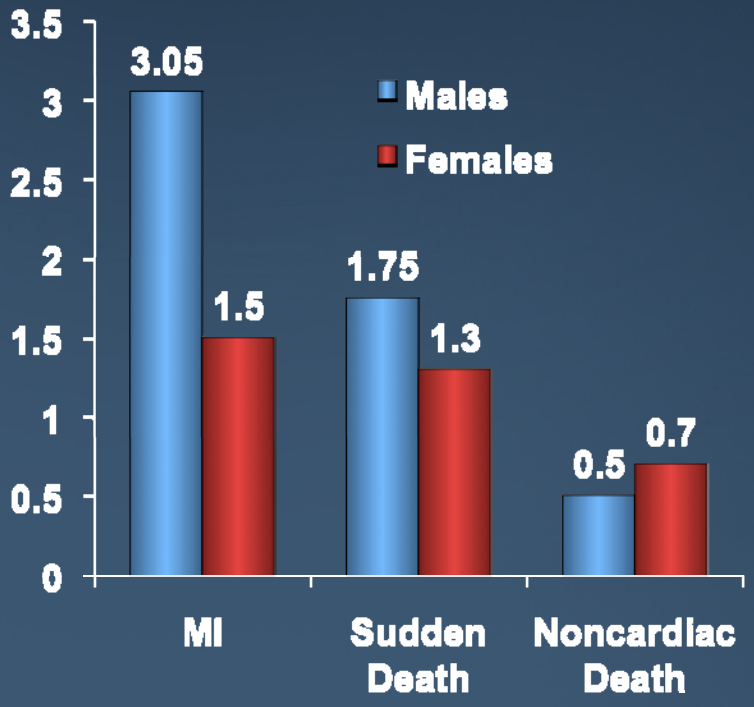
OCT Erosion



How common are vulnerable plaques?

Number of thin-cap fibroatheromas in patients dying with MI, sudden death, or noncardiac causes and studied at necropsy

Cross-sectional analysis



Longitudinal analysis

	All pts	Pts with ≥1 ruptured plaque	Pts with ≥1 TCFA or ruptured plaque	Pts with CV death
# of patients	50	14	20	33
# of ruptured plaques	19 (0.38/pt)		19 (0.95/pt)	15 (0.45/pt)
# fibroatheromas	193			
# TCFAs	23 (0.46/pt)	15 (1.21/pt)	23 (1.15/pt)	18 (0.55/pt)

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(Burke et al. J Am Coll Cardiol 2003;41:1874-86)
(Cheruvu et al. J Am Coll Cardiol 2007;50:940-9)

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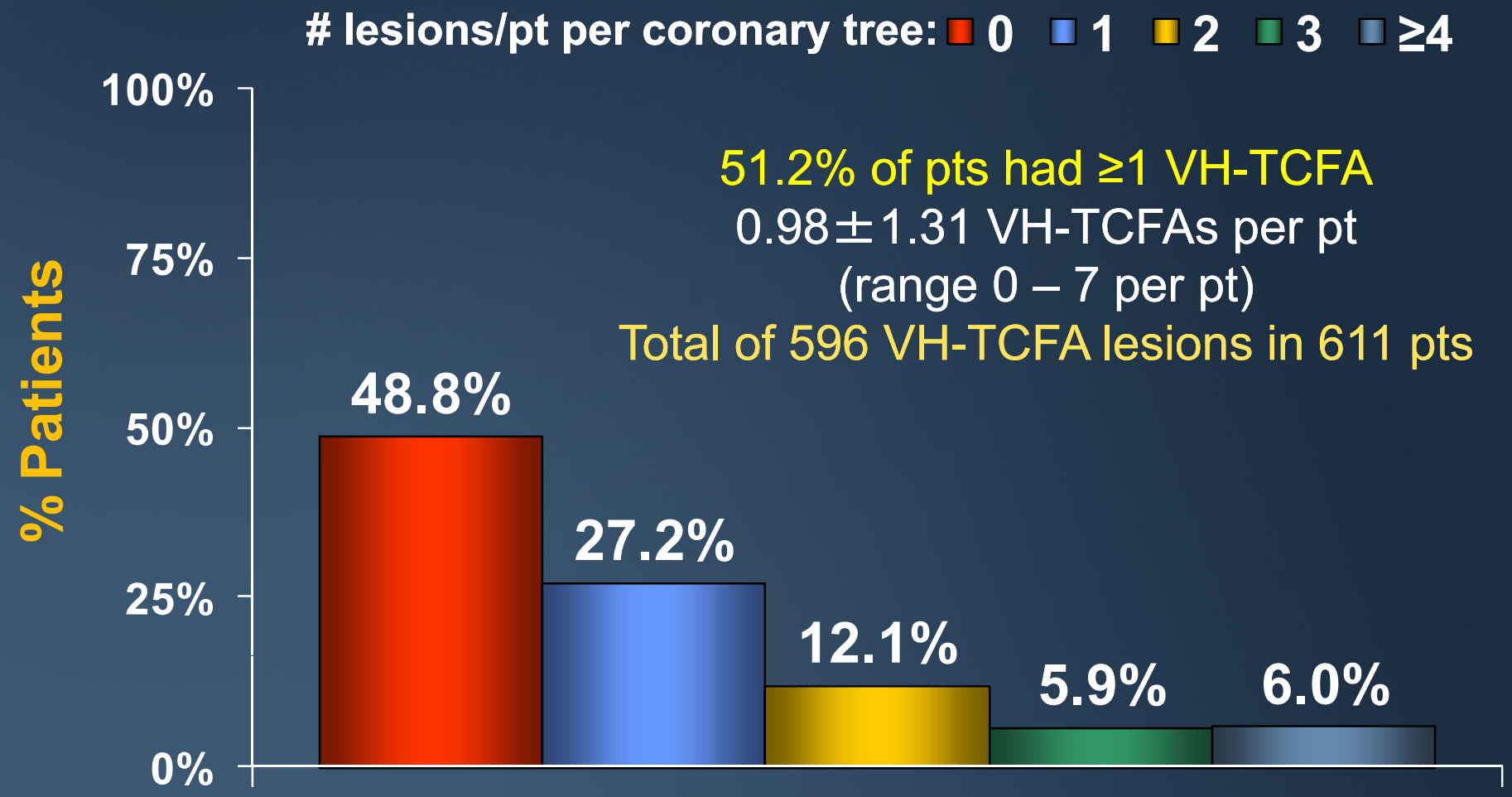
PROSPECT: Per patient incidence of VH-TCFAs



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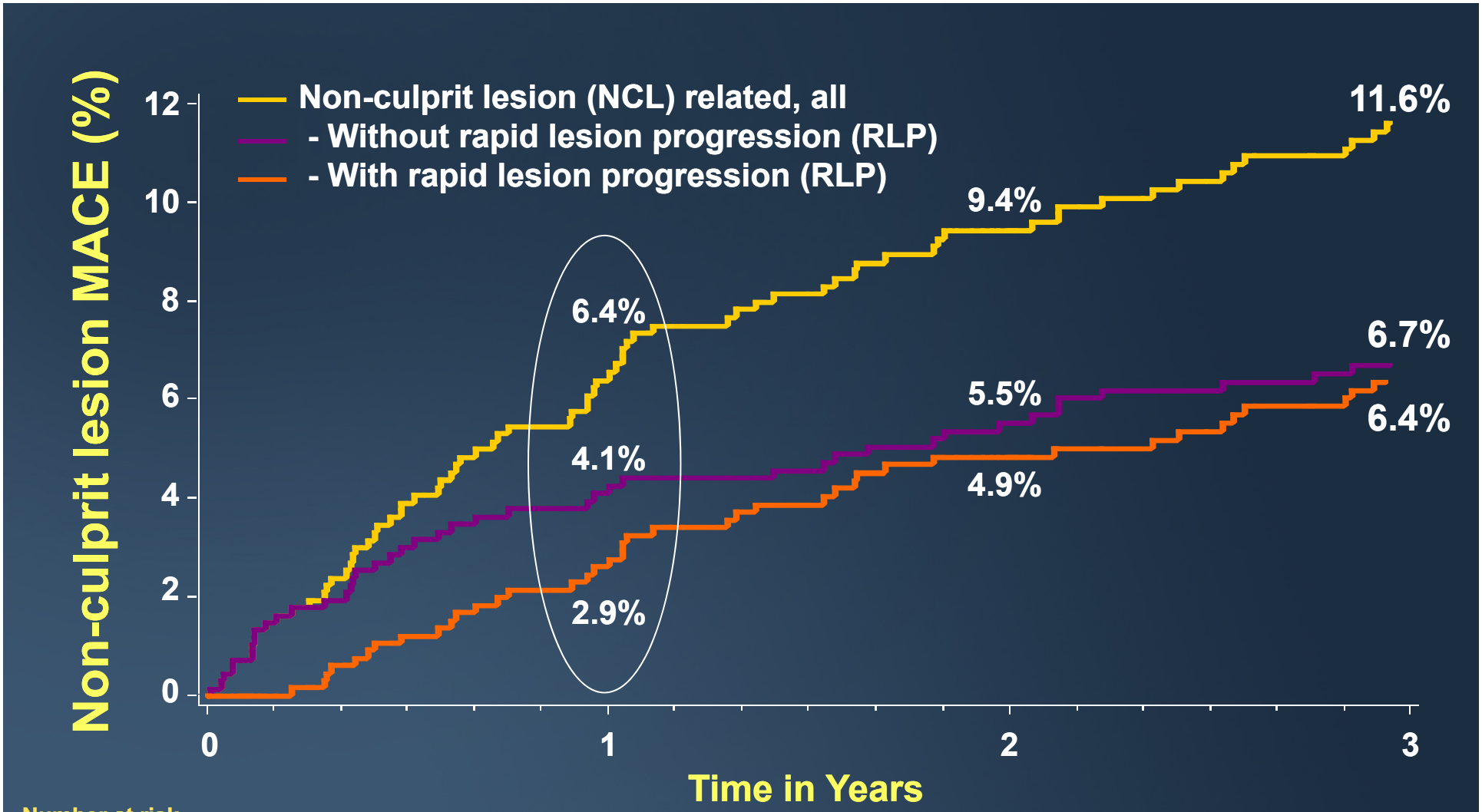
Are all non-culprit events in the first year post-PCI related to vulnerable plaques? Or are some related to incomplete revascularization at the time of initial PCI?



Number at risk

NCL related, all	697	595	553	521
- without RLP	697	610	577	551
- with RLP	697	620	579	550

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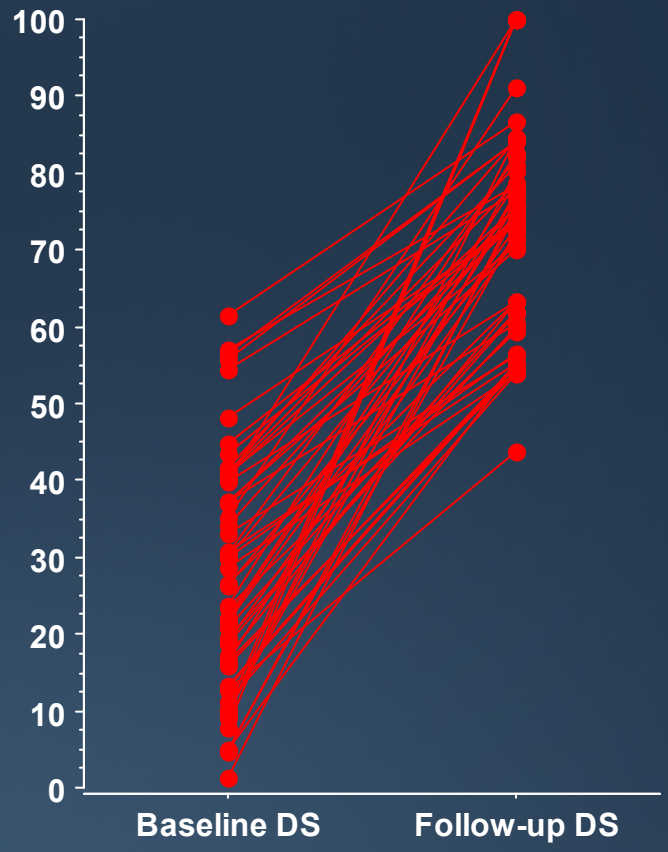

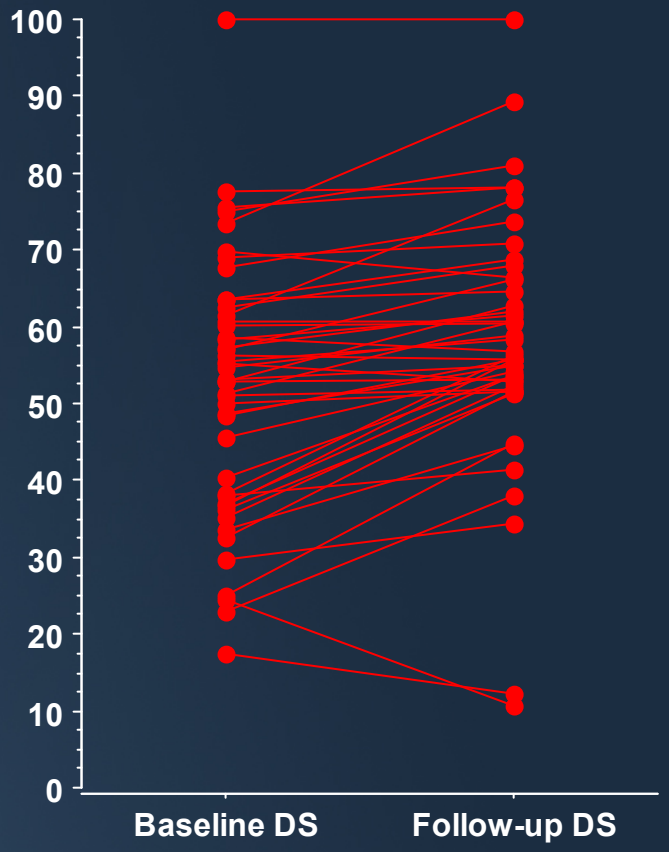

	Significant Progression	p	No Significant Progression
Time to events (median)	401	0.07	223
Baseline DS	27±16%	<0.0001	49±19%
Follow-up DS	72±14%	0.0001	59±16%
DS progression	44±18%	<0.0001	5±8%

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Sanidas et al. JACC Cardiovasc Imaging, in press

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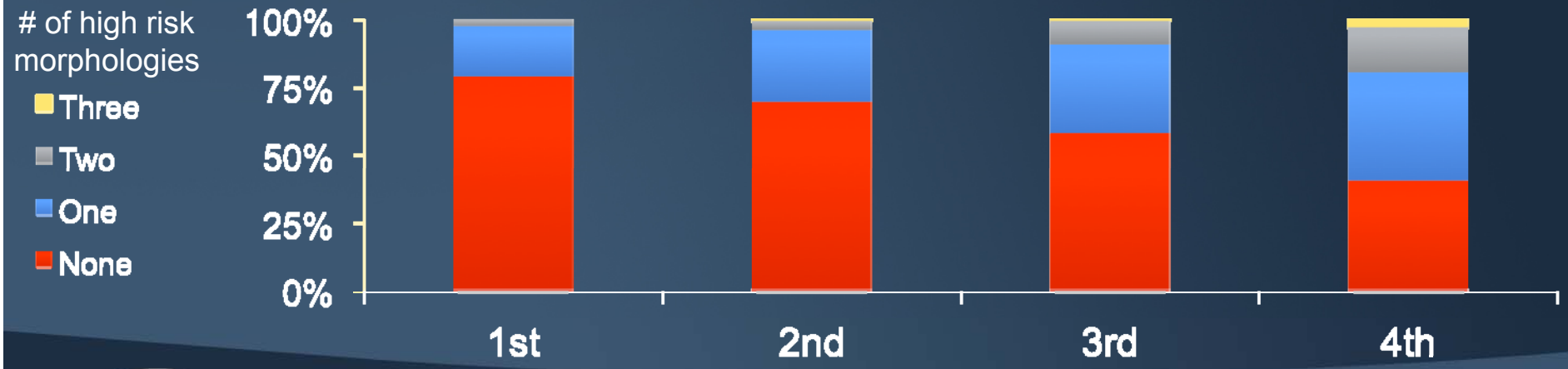
PROSPECT: Angiographic severity vs high risk morphology (n=3115)

	Quartile			
	1st	2nd	3rd	4th
QCA DS (%)	2.82 (2.56, 3.08)	9.95 (9.82, 10.08)	17.67 (17.47, 17.88)	33.52 (32.90, 34.14)
NC volume, %	12.3 (11.6, 13.0)	12.5 (11.8, 13.2)	13.0 (12.3, 13.7)	14.0 (13.3, 14.7)
VH-TCFA	13.4%	22.0%	24.4%	30.3%
FA	48.6%	56.2%	62.3%	72.3%



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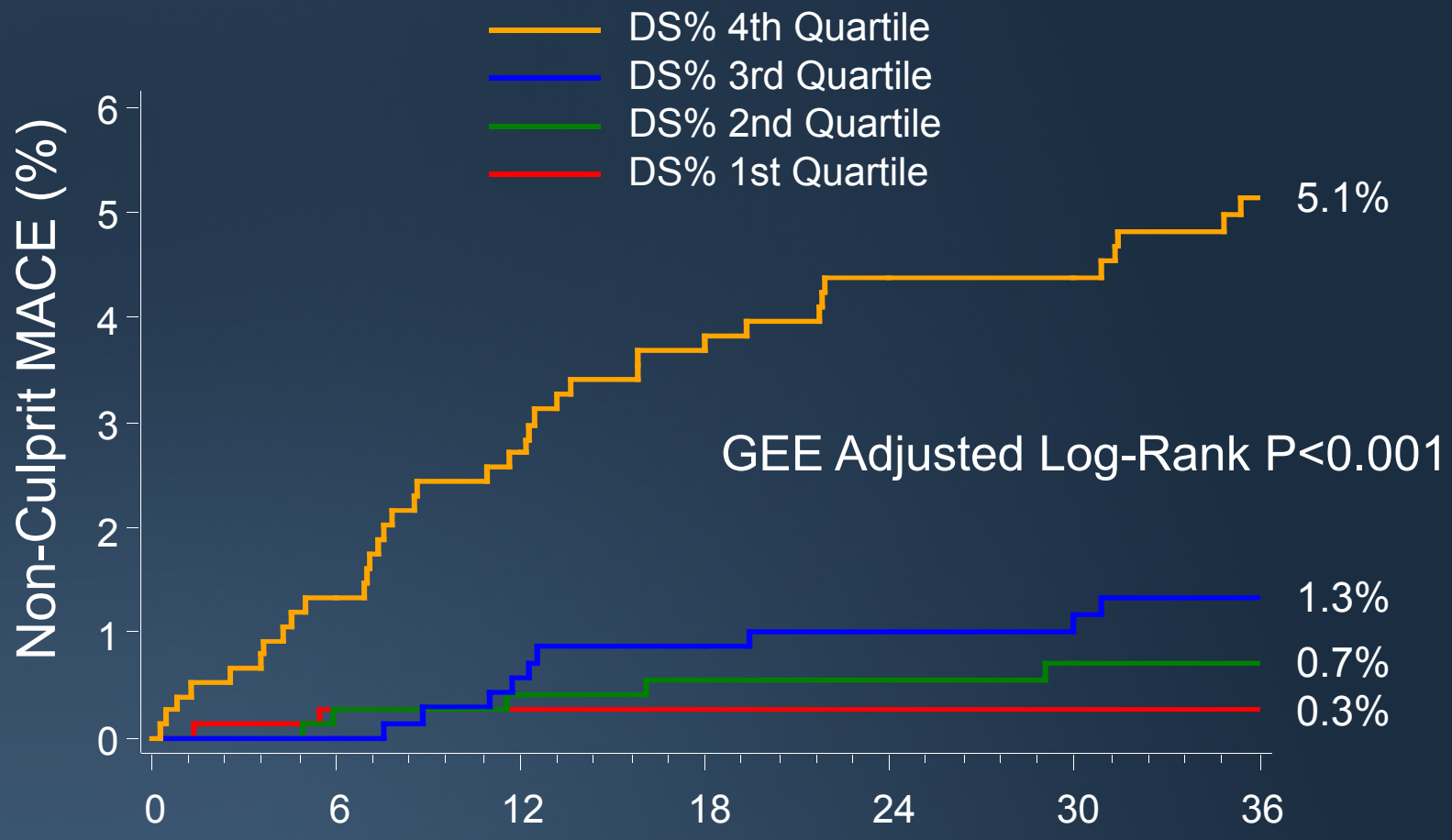

Number at risk

1st quartile	778	726	717	693	680	655	416
2nd quartile	779	721	711	692	679	659	411
3rd quartile	779	707	693	675	652	630	379
4th quartile	779	722	706	684	668	654	430

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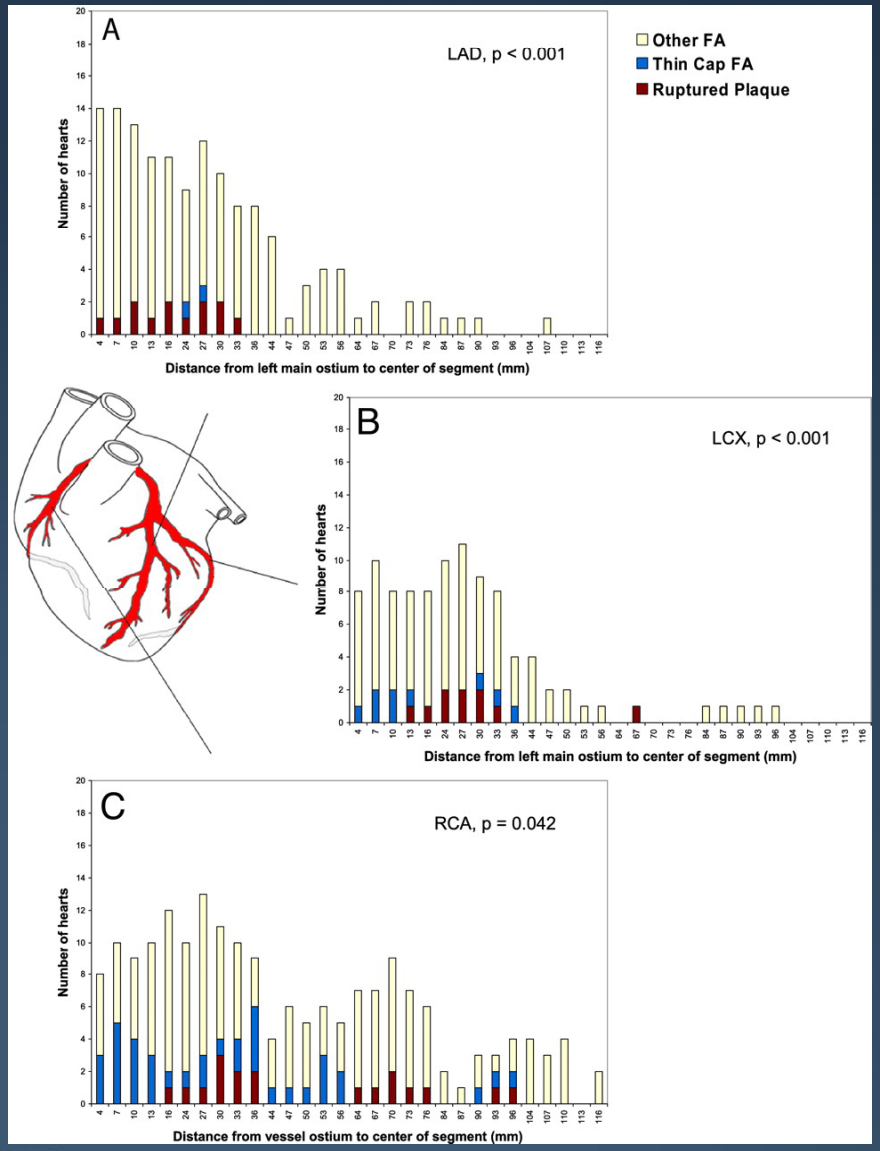
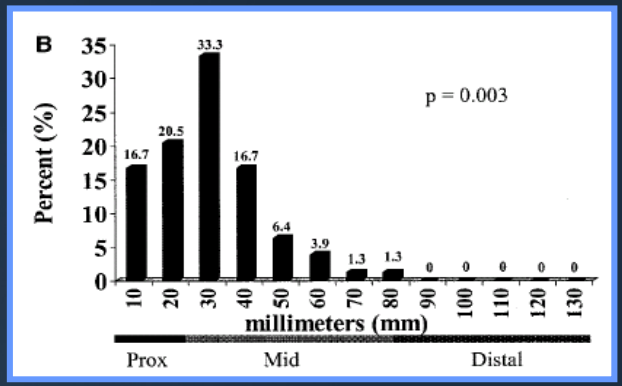
Will imaging the proximal and mid segments of the three major epicardial vessels detect all vulnerable plaques?

Pathology spatial Distribution of Advanced Coronary Lesions

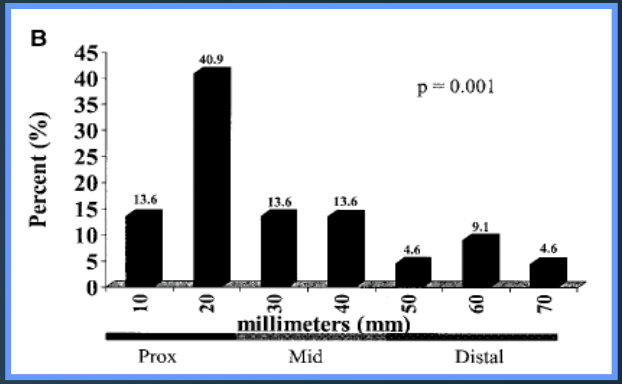


Angiographic location of acute coronary occlusions

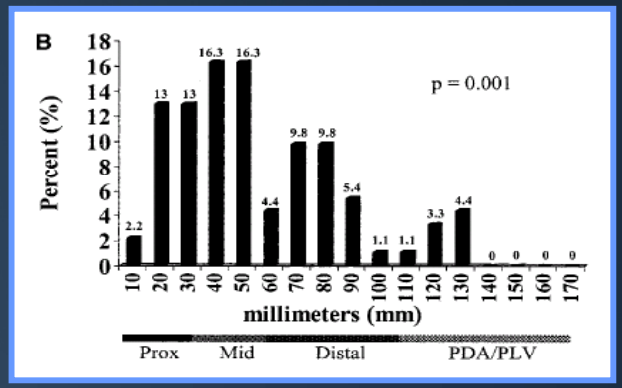
LAD



LCX



RCA



(Cheruvu et al. J Am Coll Cardiol 2007;50:940-9)
(Wang et al. Circulation 2004;110:278-84)

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PROSPECT: Completeness of 3-vessel IVUS and VH-IVUS imaging

Event type	Total # of events	Baseline QCA at event site	Baseline IVUS at event site	Baseline VH at event site
All MACE	245	227	140	132
Culprit lesion related	120	120	84	76
Non culprit lesion related	**107**	**107**	**56**	**56**
- With RLP	51	51	31	31
- Without RLP	56	56	25	25
Indeterminate	18	0	0	0

Location of MACE Events

	All (n=228)	Culprit lesion related (n=121)	Non culprit lesion related (n=107)
LM	4 (1.8%)	1 (0.8%)	3 (2.8%)
LAD	82 (36.0%)	48 (39.7%)	34 (31.8%)
LCX	63 (27.6%)	30 (24.8%)	33 (30.8%)
RCA	79 (34.6%)	42 (34.7%)	37 (34.6%)
Proximal vessel	69 (30.3%)	43 (35.5%)	26 (24.3%)
Mid vessel	51 (22.4%)	30 (24.8%)	21 (19.6%)
Distal vessel	35 (15.4%)	18 (14.9%)	17 (15.9%)
Branch*	73 (32.0%)	30 (24.8%)	43 (40.2%)

Excludes indeterminate lesions. Includes, diagonal, ramus, obtuse marginal, R/L PDA, R/L PLAS.

Is three vessel invasive imaging safe?

Complications attributed to the 3-vessel IVUS imaging procedure (n=697, non-hierarchical)

Death	0 (0%)
MI	3 (0.4%)
- Q-wave (from dissection)	1
- non Q-wave (from dissection)	2
PCI or CABG	10 (1.4%)
- CABG (from perforation)	1
- CABG (from dissection)	2
- PCI (from dissection)	9
Any imaging complication*	11 (1.6%)

*Some pts had more than one complication

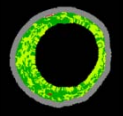
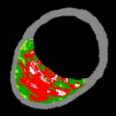
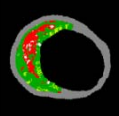
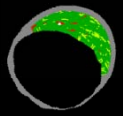
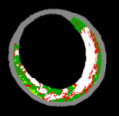
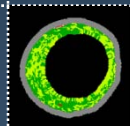
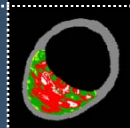
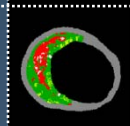
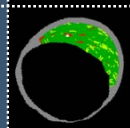
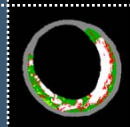
Safety becomes an even more important concern if imaging must be repeated periodically.

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

- 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 were PIT and 6 were ThFA at baseline.
- No fibrotic or fibrocalcific plaque evolved into a TCFA.

Kubo et al. J Am Coll Cardiol 2010;55:1590-7

Follow-up

Baseline		PIT (n=48)	TCFA (n=17)	ThCFA (n=109)	Fibrotic (n=23)	Fibrcalcific (n=20)
						
PIT (n=62)		44	6	12	0	0
TCFA (n=20)		0	5	14	2	0
ThCFA (n=93)		0	6	83	3	1
Fibrotic (n=22)		4	0	0	18	0
Fibrocalcific (n=19)		0	0	0	0	19

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Kubo et al. J Am Coll Cardiol 2010;55:1590-7

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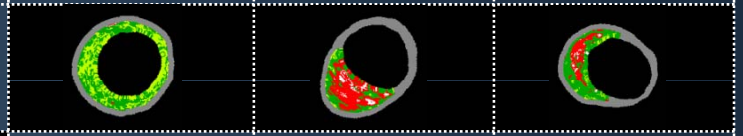
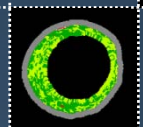
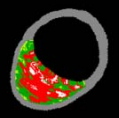
Change in non-culprit lesion phenotype in 100 pts (100 lesions: plaque burden >40%) from HORIZONS: Baseline and 13-month follow-up VH-IVUS

			Follow-up		
			PIT (n=11)	TCFA (n=54)	ThCFA (n=32)
					
Baseline	PIT (n=16)		6	3	7
	TCFA (n=43)		2	33	8
	ThCFA (n=40)		1	19	20

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Zhao et al. J Am Coll Cadiol 2011;57:E907

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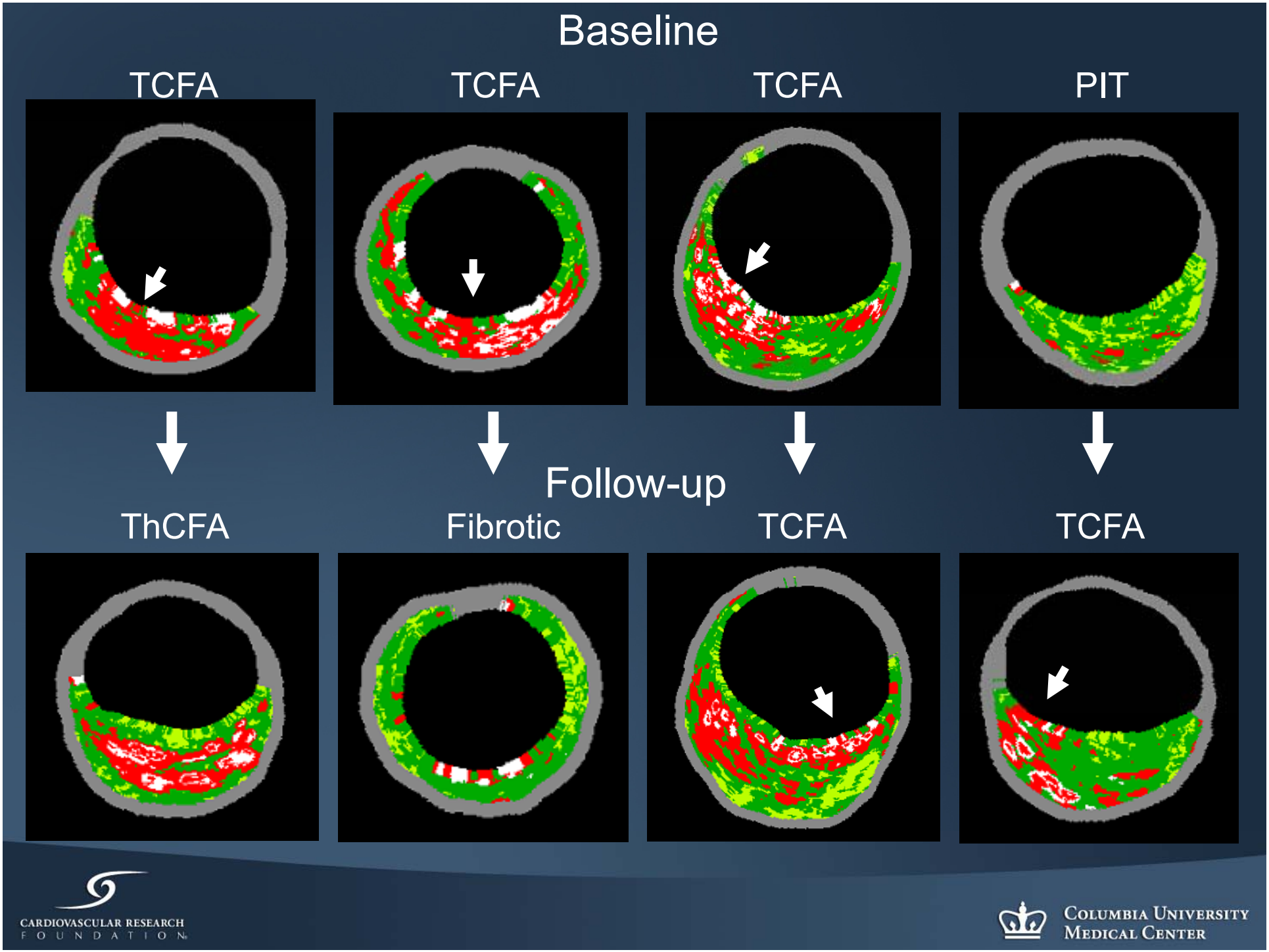
Baseline
TCFA
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Follow-up
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Fibrotic
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TCFA
CARDIOVASCULAR RESEARCH FOUNDATION
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And some vulnerable plaques rupture asymptomatically and are detected incidentally while others heal and contribute disease progression

- *Maehara et al. J Am Coll Cardiol 2002;40:904-10*
- *Rioufol et al. Circulation. 2002;106:804-8*
- *Hong et al. Circulation 2004;110:928-33*
- *Fuji et al. Circulation 2003;108:2473-8*
- *Burke et al. Circulation 2001;103;934-40*
- *Rioufol et al. Circulation 2004;110:2875-80*
- *Hong et al. Atherosclerosis. 2007;19:107-14*

How common are major vulnerable plaque events (death/MI) in 2012, really?

PROSPECT: 3-year follow-up hierarchical MACE assuming indeterminate events (ie., death) are non-culprit lesion related

	All	Culprit lesion related	Non culprit lesion related
Cardiac death	1.9% (12)	0.2% (1)	1.8% (11)
Cardiac arrest	0.3% (2)	0.3% (2)	0% (0)
MI (STEMI or NSTEMI)	2.7% (17)	1.7% (11)	1.2% (7)
Rehospitalization for unstable or progressive angina	15.4% (101)	10.4% (69)	10.5% (67)
Composite MACE	20.4% (132)	12.9% (83)	13.3% (85)
Cardiac death, arrest or MI*	**4.9% (31)**	**2.2% (14)**	**2.9% (18)**

*In patients post-PCI for STEMI/NSTEMI and treated with optimal medical therapy and followed as part of a clinical study

VIVA: Virtual Histology in Vulnerable Atherosclerosis

- 932 non-culprit lesions in 170 pts were identified with 3-vessel IVUS imaging
- At a median follow-up of 625 days, there were 18 culprit and non-culprit MACE in 16 pts
  - 14 revascularizations, 2 MIs, and 2 deaths

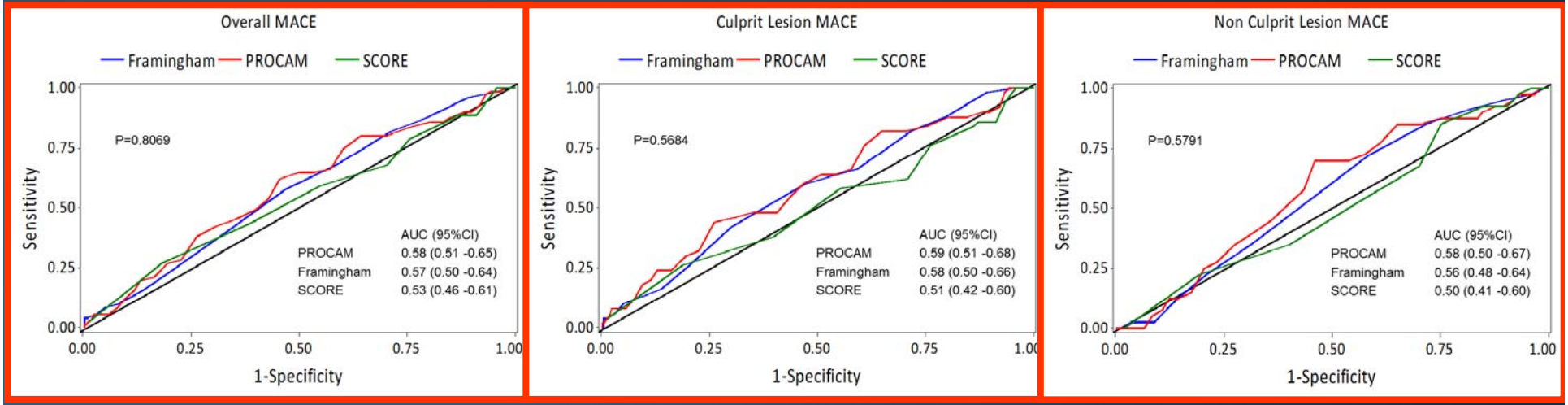
Calvert et al. JACC Cardiovasc Imaging 2011;4:894-901

Who should we study? Primary prevention versus secondary prevention?

PROSPECT: Independent predictors of patient level events

	Hazard ratio	P value
Insulin dependent diabetes mellitus	3.32	0.005
Prior PCI	2.03	0.02

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



Conclusion

- We can now say with confidence that we are able to detect TCFAs.
- However, that does not mean that searching for a vulnerable plaque in patients will ever make clinical sense unless we can identify a truly high risk patient population or one that does not respond to conventional medical therapy in order to justify invasive imaging – especially, since we do not have a focal therapy to offer.

Reference: Vancraeynest et al. Imaging the vulnerable plaque. J Am Coll Cardiol 2011;57:1961-79