Lessons Learned from Current Imaging Trials

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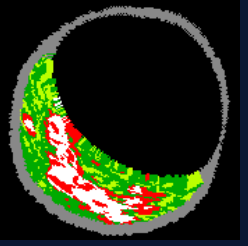
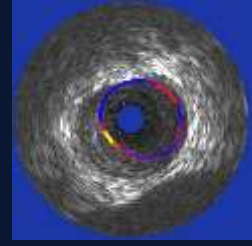


The PROSPECT Trial



700 pts with ACS UA (with ECG Δs) or NSTEMI or STEMI
>24º
undergoing 1 or 2-vessel PCI followed by 3-vessel imaging

QCA of entire coronary tree

IVUS

Virtual Histology

Proximal 6-8 cm of each coronary artery

Medications
Aspirin
Plavix ≥1yr
Statins

F/U: Until there were 100 VP events

Repeat imaging in patients with events

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

PROSPECT: 3-year follow-up hierarchical MACE (assuming indeterminant events 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)**

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Rehospitalization for unstable or progressive angina	15.4% (101)	10.4% (69)	10.5% (67)
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Stone et al. N Engl J Med 2011;361:226-35

Lesson #1

With modern medical therapy in the setting of a prospective registry, the rate of hard, non-culprit lesion events (death/MI) was less than predicted and occurred in only 1% of high risk patients per year.

PROSPECT: Multivariable Correlates of Non Culprit Lesion Related Events

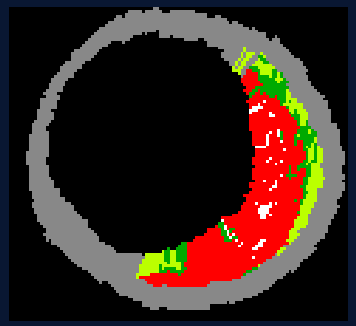
Independent predictors of lesion level events by Cox Proportional Hazards regression

Variable	HR [95% CI)	p
PB_{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

Variables entered into the model: minimal luminal area (MLA) ≤4.0 mm^2; plaque burden at the MLA (PB_{MLA}) ≥70%; external elastic membrane at the MLA (EEM_{MLA}) <median (14.1 mm^2); lesion length ≥median (11.2 mm); distance from ostium to MLA ≥median (30.4 mm); remodeling index ≥median (0.94); VH-TCFA.

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

VH-TCFA and Non Culprit Lesion Events



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	4.67%	15.9%	10.1%	4.2%

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

VIVA: Virtual Histology in Vulnerable Atherosclerosis

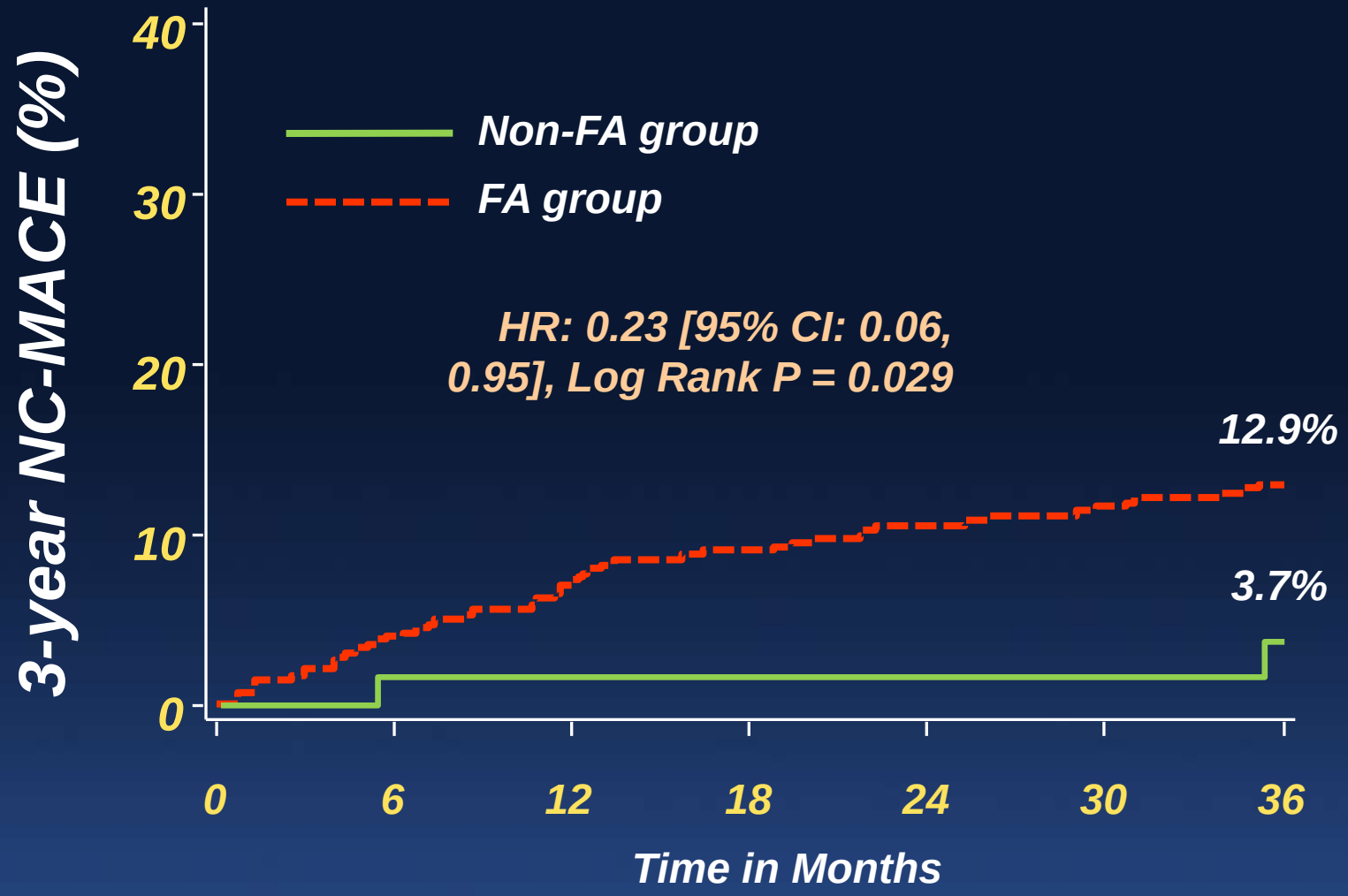
- 932 non-culprit lesions in 170 pts were identified with 3-vessel IVUS imaging
- At a median follow-up of 625 days, there were 18 culprit and non-culprit MACE in 16 pts (14 revascularizations, 2 MIs, and 2 deaths)
- *Univariate* predictors of non-culprit MACE
  - Non-calcified VH-TCFA (p=0.025)
  -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

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

European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis – IVUS (ATHEROREMO-IVUS) study - I

- 1 non-culprit artery imaged in 581 pts (stable CAD or ACS): LAD>RCA>LCX
- At 1 year of follow-up, 56 pts had at least 1 event: 4 PCI in pts without baseline PCI, 11 culprit events, 27 non-culprit events, 18 indeterminate events
- 18 deaths, 8 from cardiac or unknown causes; 14 ACS (7 MI); 24 unplanned revascularization
- Presence of VH-TCFA was significantly associated with the composite of Death/ACS (adjusted HR=2.51, p=0.021)

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



Number at risk

Non-FA group	67	62	61	61	60	57	29
FA group	542	485	463	443	424	406	248

Dohi et al. JACC Cardiovasc Imaging 2013;6:908-16

Lesson #2

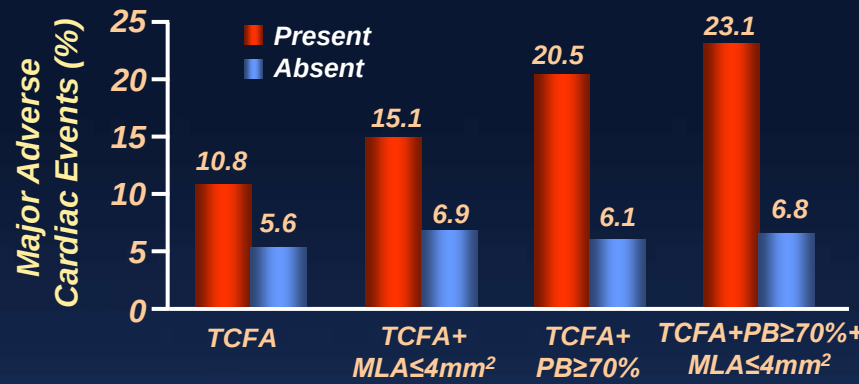
The vulnerable plaque hypothesis and VH-IVUS tissue characterization, particularly VH-TCFA classification, are real. VH-IVUS phenotypes of ThFCA, PIT, and fibrotic and fibrocalcific plaque are associated with few if any events

Non-culprit lesions responsible for MACE (n=107 in 76 patients)

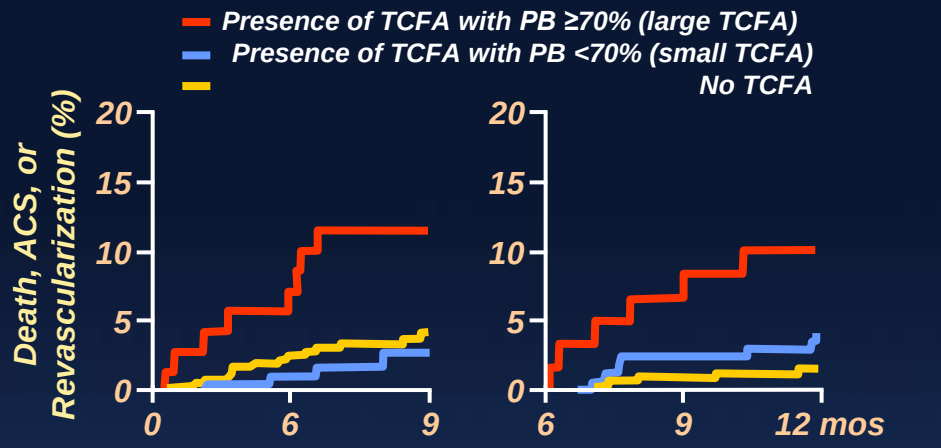
- *While 72 of 107 non-culprit MACE lesions (67.0%) had <50% DS by angiography, all sites responsible for non-culprit MACE had plaque burden ≥40% by IVUS imaging.*
- *No imaged coronary segment with <40% plaque burden resulted in a non-culprit event during the median 3.4 year follow-up period.*
- *Among non-culprit lesions with a plaque burden 40-70%, only 1% caused non-culprit MACE*

McPherson et al. JACC Cardiovasc Imaging 2012;5:S76-85

European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis – IVUS (ATHEROREMO-IVUS) study - II



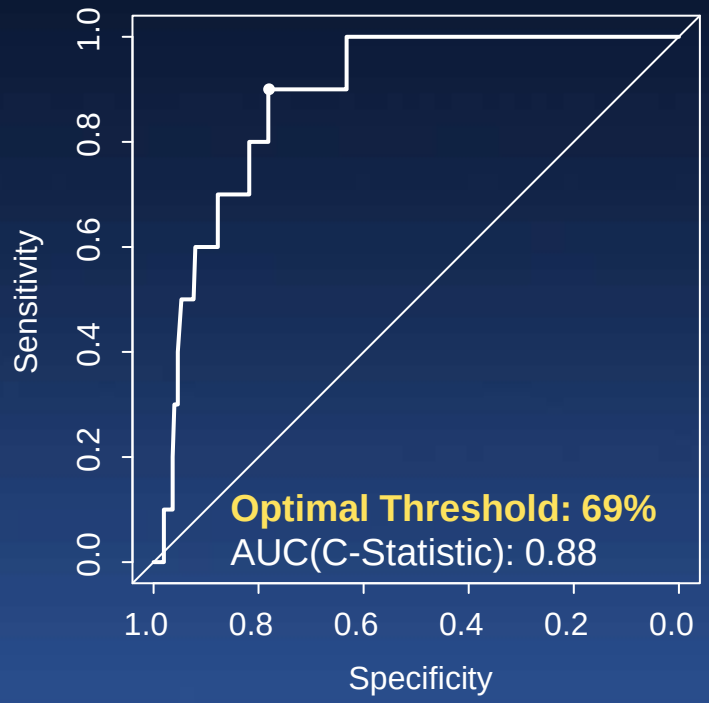
	TCFA		TCFA+ MLA≤4mm²		TCFA+ PB≥70%		TCFA+PB≥70%+ MLA≤4mm²	
Prevalence (%)	41.7	58.3	10.5	89.5	11.9	88.1	6.0	94.0
No. at risk at 1 yr (n)	211	312	50	473	52	471	52	471
HR	1.96		2.26		3.47		3.70	
P value	0.024		0.025		<0.001		<0.001	



- 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), while smaller TCFA lesions were only associated with a higher MACE rate after 6 months (P=0.033)

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

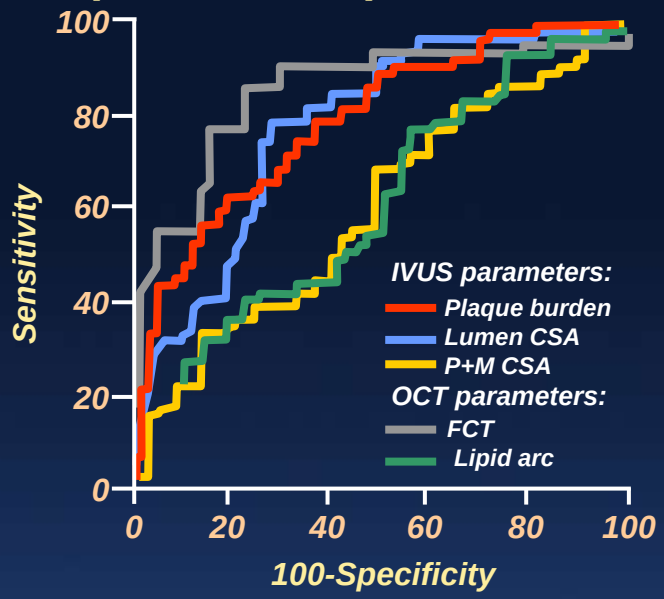
Plaque burden predictor of TCFA in 271 atherosclerotic lesions from 106 fresh coronary arteries in 54 patients at necropsy.



Inaba, unpublished

126 Plaques from 82 ACS Pts were Assessed using OCT and IVUS and Classified as Ruptured Culprit Plaques (RCP), Ruptured Non-culprit Plaques (RNCP), or Non-ruptured TCFAs

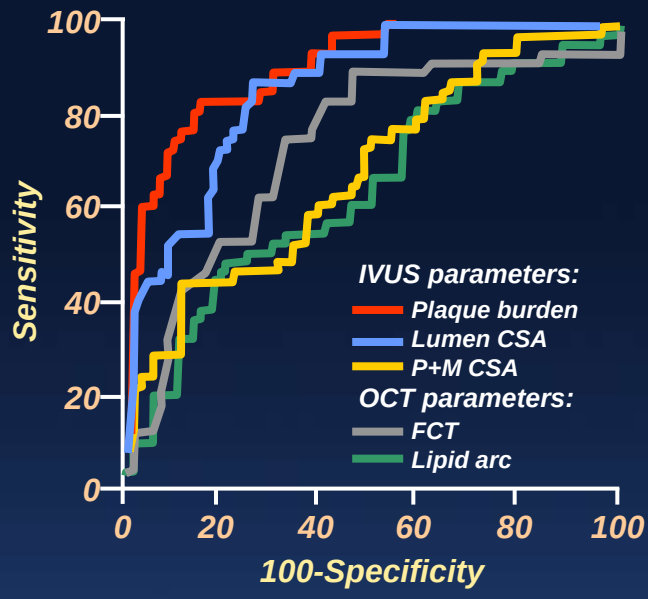
Plaque Rupture (RCP+RNCP) vs TCFA



	RCP	RNCP	TCFA
N	49	19	59
Plaque burden	82%	64%	62%
MLA, mm^2	2.1	4.6	5.1
P+M, mm^2	10.8	8.0	8.9
Fibrous cap thickness	43µ	41µ	56µ
Lipid arc	241°	214°	207°

Plaque burden	72%	0.79	<0.001
MLA	3.7mm^2	0.78	<0.001
P+M	7.2mm^2	0.61	0.034
Fibrous cap thickness	52µ	0.86	<0.001
Lipid arc	197°	0.61	0.029

Culprit Plaque Rupture vs RNCP+TCFA

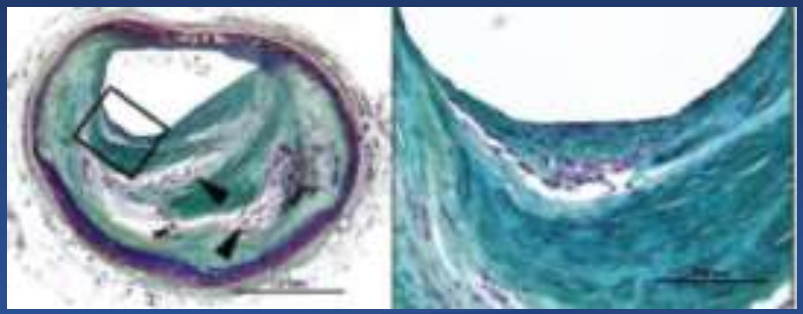


Plaque burden	76%	0.91	<0.001
MLA	2.6mm^2	0.96	<0.001
P+M	12mm^2	0.68	0.034
Fibrous cap thickness	38µ	0.74	<0.001
Lipid arc	247°	0.64	0.005

Tian et al. J Am Coll Cardiol. 2014;63:2209-16

Fate of secondary plaque ruptures

- 14 pts with 28 plaque ruptures with MLA >4.0mm^2 treated with statins and DAPT. At 22±13 months, no clinical events and half had healed
  - (Rioful et al. Circulation 2004;110:2875-80)
- 28 pts with non-culprit plaque ruptures (half treated with statins) followed for 11.9±1.3 months. No TLR in statin-treated pts (p=0.11).
  - (Hong et al. Atherosclerosis. 2007;19:107-14)
- The event rate in 93 pts with at least 1 secondary plaque rupture was the same as in 567 pts with no secondary plaque ruptures.
  - (Xie et al. JACC Cardiovasc Imaging 2014;7:397-405)
- 142 men with sudden cardiac death had 44 acute rupture sites - 9 had 1, 9 had 2, 9 had 3, and 6 had 4 healed previous rupture sites.
  - (Burke et al. Circulation 2001;103:934-40)
- In 31 men with sudden cardiac death, 16/99 non-culprit plaques with <20% DS had previous plaque rupture vs 18/86 plaques with 20-50% DS vs 52/71 plaques with >50% DS
  - (Mann and Davies. Heart199;82:265-8)



Lesson #3

Vulnerable plaque events do not occur at sites of minimal disease. Rather they occur only at sites of >40% plaque burden by IVUS (and mostly at sites with >70% plaque burden) - disease that is angiographically silent in 2/3 of lesions because of positive remodeling. Most TCFAs rupture silently and lead to disease progression, but not ACS.

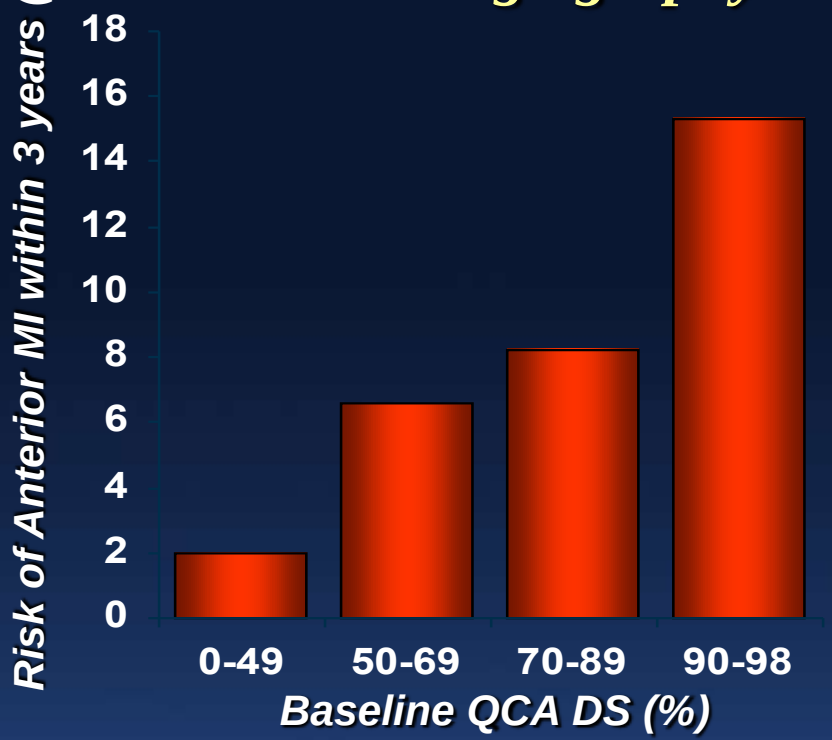
Risk of MI

42 Consecutive pts with angiography both before and after MI

- 29 patients had a newly occluded artery
  - In 19 pts, the artery previously had a <50% DS
  - In only 10 pts the occlusion was at the site of the most severe stenosis

Little et al. Circulation 1988;78:1157-66

118 Pts in CASS after baseline angiography



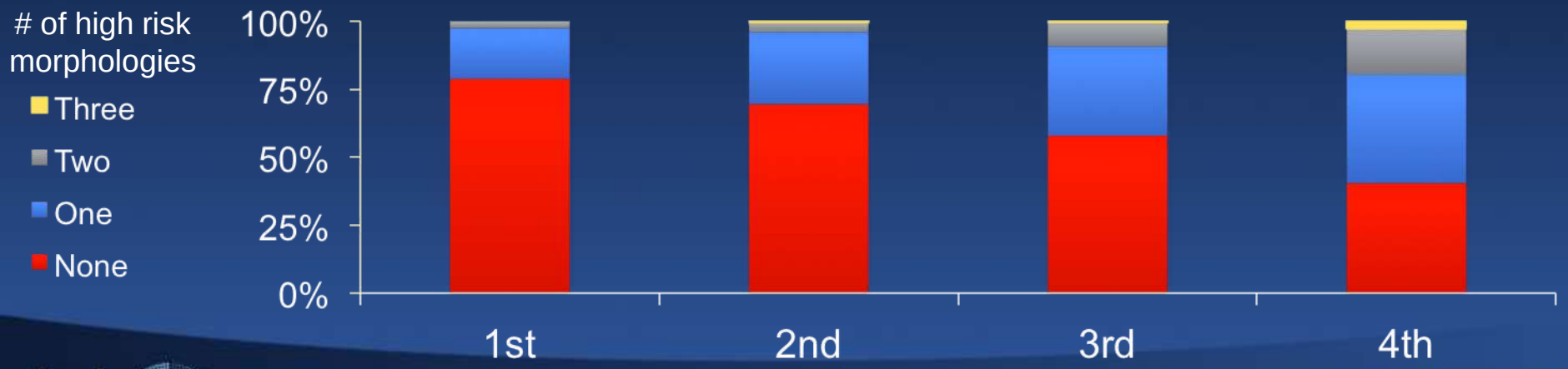
Ellis et al. J Am Coll Cardiol 1988;11:908-16

"Because the aggregate risk of rupture associated with many non-significant lesions (each with an admitedly lower individual risk potential) exceeds that of the fewer significant lesions, an MI will more likely originate from a nonsignificant lesion."

Kern and Meier. Circulation 2001;103:3142-9

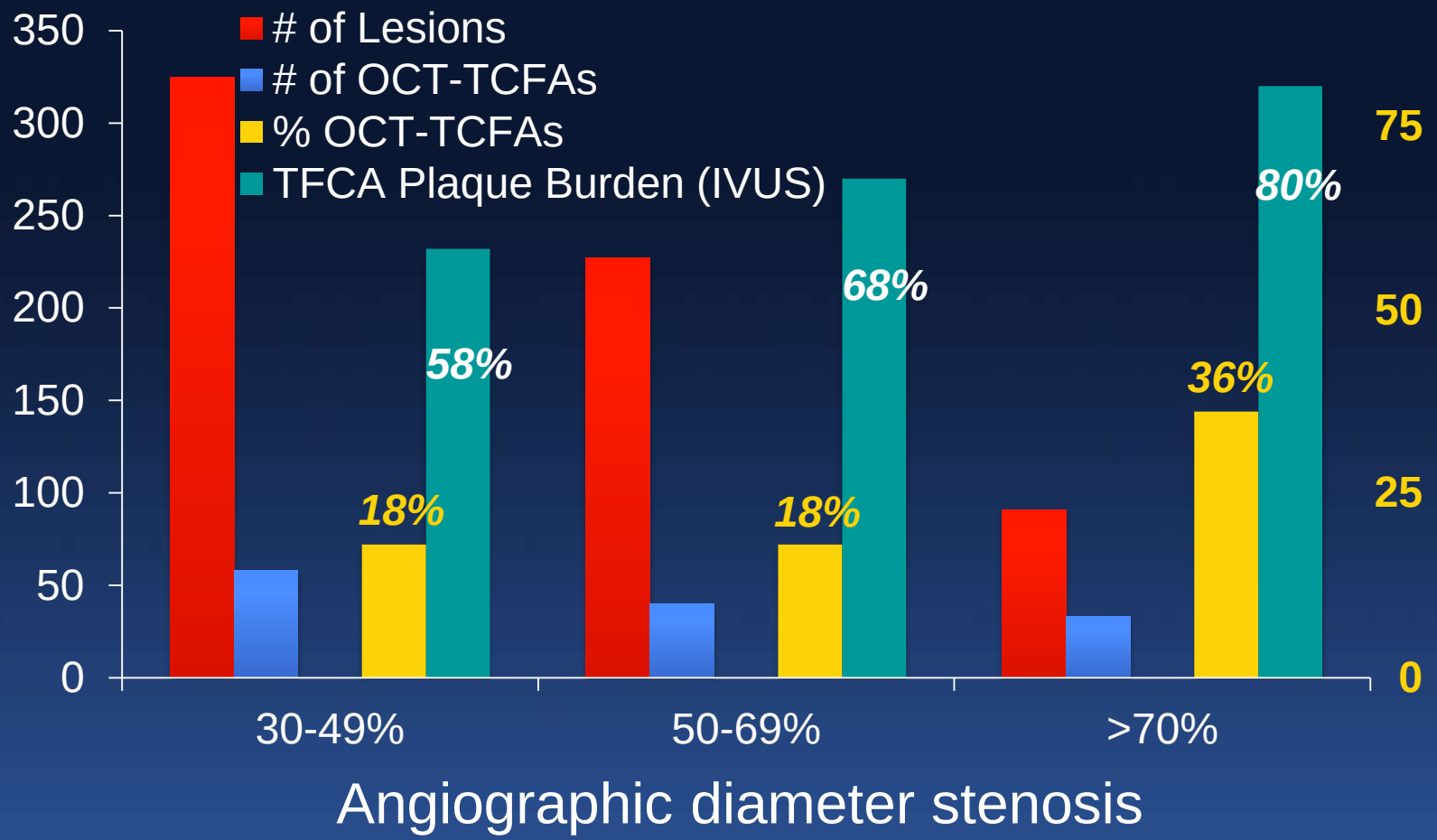
PROSPECT: Angiographic severity vs high risk morphology (n=3115)

	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%



Yun et al. Am J Cardiol 2012;110:471-7

Prevalence of TFCA vs Angiographic DS



Tian et al. J Am Coll Cardiol 2004;64:672-80

Lesson #4

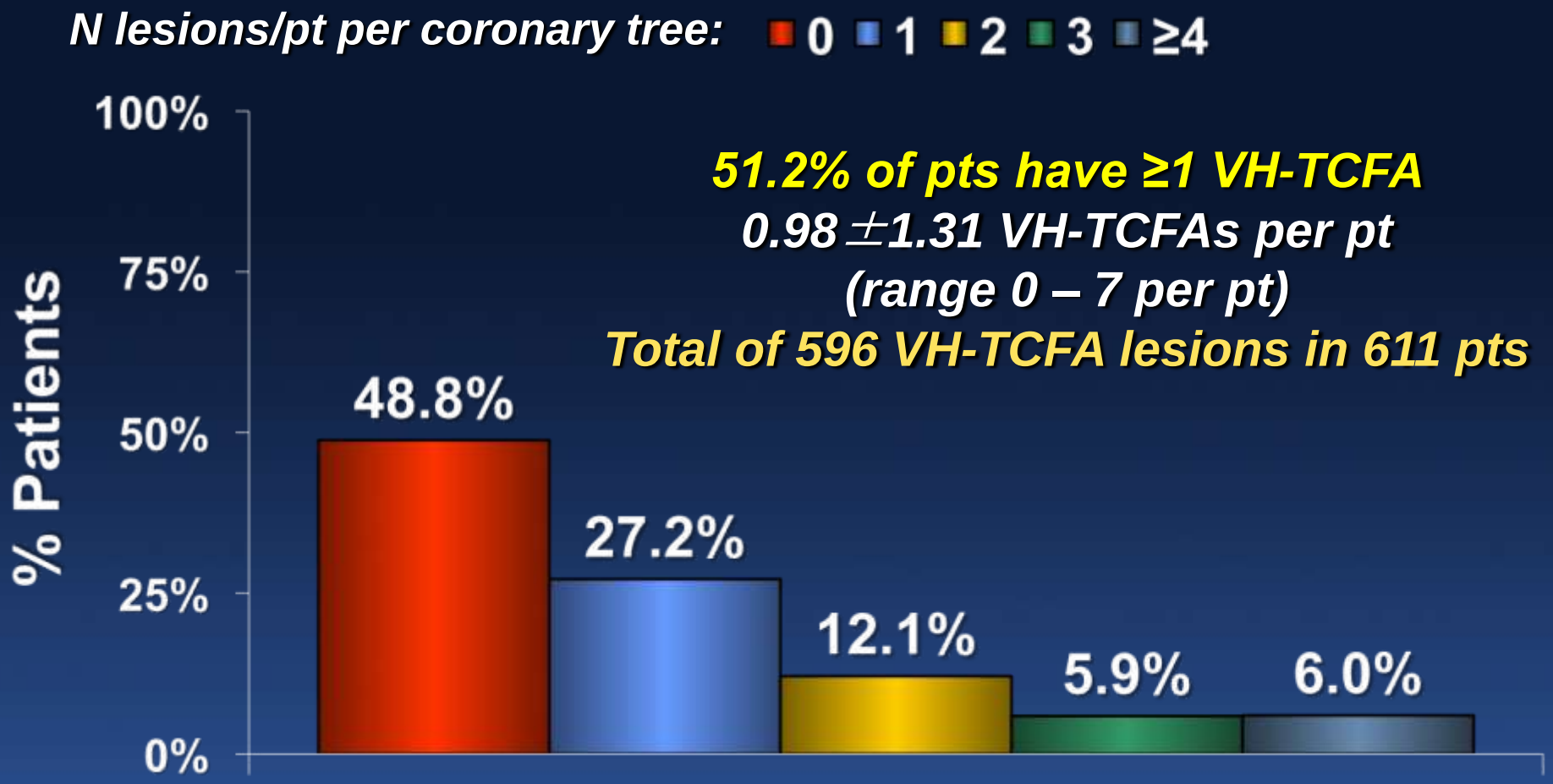
The angiographic severity of a nonculprit lesion may be a marker of lesion vulnerability.

The Limits of Opening Arteries

NYTimes March 28, 2004

(Patients) may have hundreds of vulnerable plaques that are more apt to burst and trigger a heart attack . . . . .

Per patient incidence of VH-TCFAs



51.2% of pts have ≥1 VH-TCFA

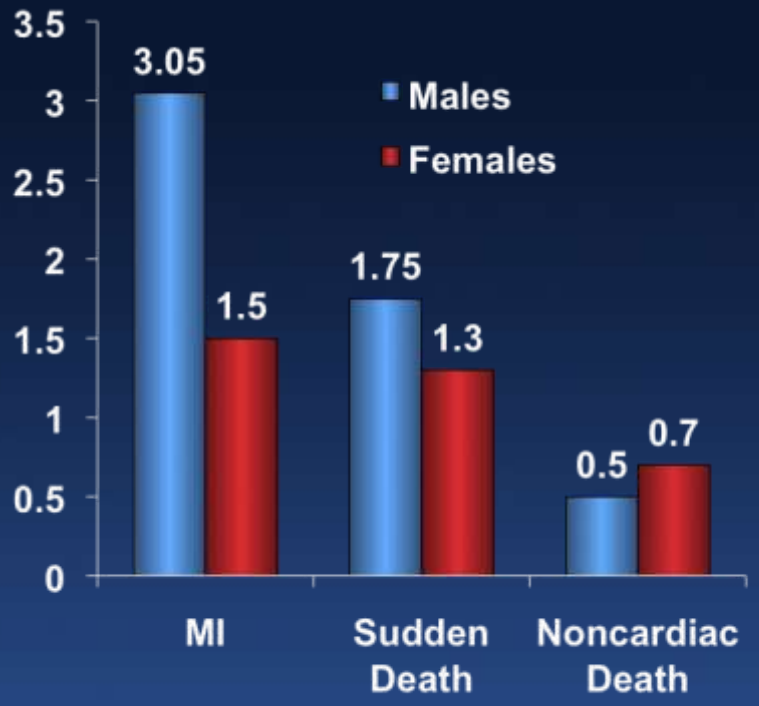
0.98 ±1.31 VH-TCFAs per pt

(range 0 – 7 per pt)

Total of 596 VH-TCFA lesions in 611 pts

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)

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

Lesson #5

Vulnerable plaques are limited in number and are <u>focal</u> manifestations of a systemic disease.

But. . . . .

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 Event Lesions

	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.

Lesson #6

In PROSPECT, even pre-specified 3-vessel invasive imaging was incomplete and detected only 50% of lesions that caused non-culprit events

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

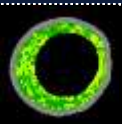
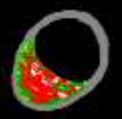
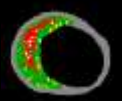
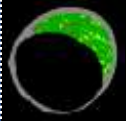
Death	0 (0%)
MI	3 (0.4%)
- Q-wave (from dissection)	1
- non Q-wave (from dissection)	2
PCI or CABG	10 (1.4%)
- CABG (from perforation)	1
- CABG (from dissection)	2
- PCI (from dissection)	9
Any imaging complication*	11 (1.6%)

Some pts had more than one complication

Lesson #7

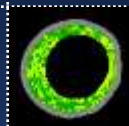
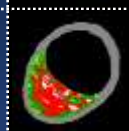
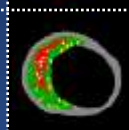
There is a small, but finite risk associated with instrumenting all 3 coronary arteries – even when done by experts. This must be balanced against the value of vulnerable plaque detection.

8-month change in non-culprit lesion phenotype in 106 pts (201 lesions) with stable CAD with plaque burden >40% from the Global VH Registry

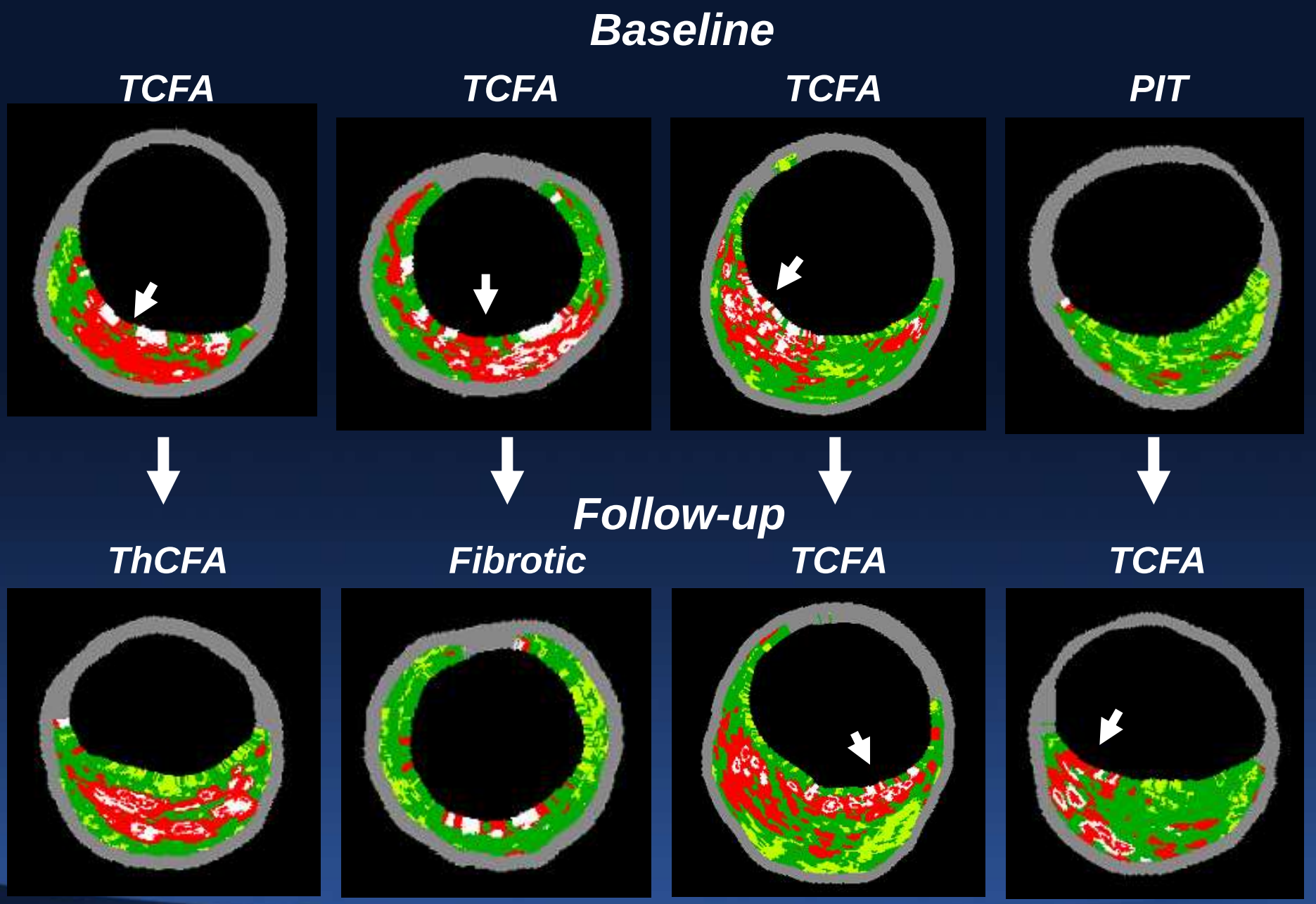
Baseline		Follow-up: PIT (n=48)	TCFA (n=17)	ThCFA (n=109)	Fibrotic (n=23)	Fibrcalcific (n=20)
PIT (n=62)		44	6	12	0	0
TCFA (n=20)		0	5	14	2	0
ThCFA (n=93)		0	6	83	3	1
Fibrotic (n=22)		4	0	0	18	0
Fibrocalcific (n=19)		0	0	0	0	19

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

13-month change in non-culprit lesion phenotype in 100 pts (100 lesions) with plaque burden >40% from the HORIZONS-AME Trial

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

Kubo et al. JACC Cardiovasc Imaging 2013;6:86-95


Baseline
TCFA
TCFA
TCFA
PIT
Follow-up
ThCFA
Fibrotic
TCFA
TCFA

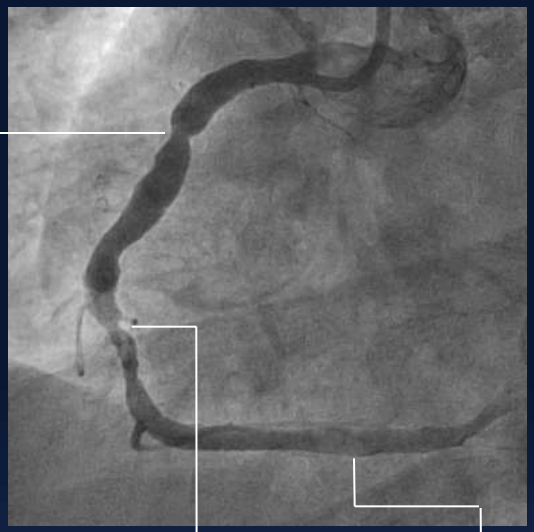
Lesson #8

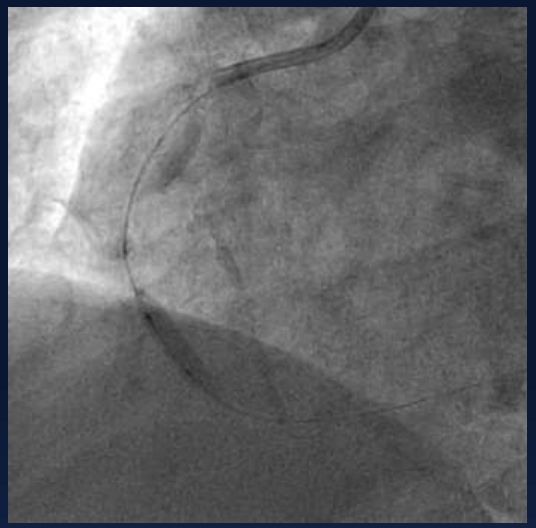
Lesion phenotype is "unstable." In particular, VH-TCFAs in stable patients can heal or rupture asymptomatically; and new TCFAs can develop in as short a period as 8 months while VH-TCFAs in unstable patients tend not to change.

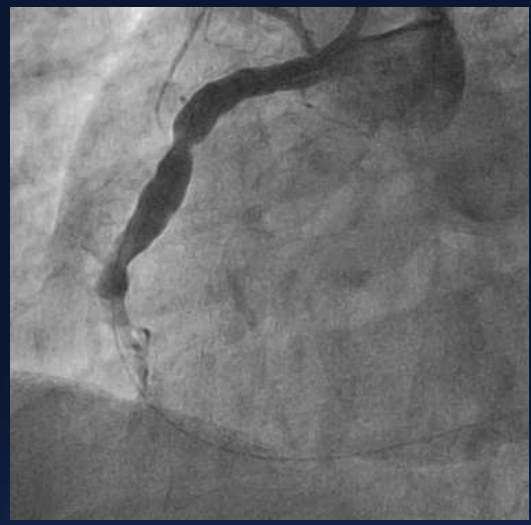
Probability of distal embolization predictable by

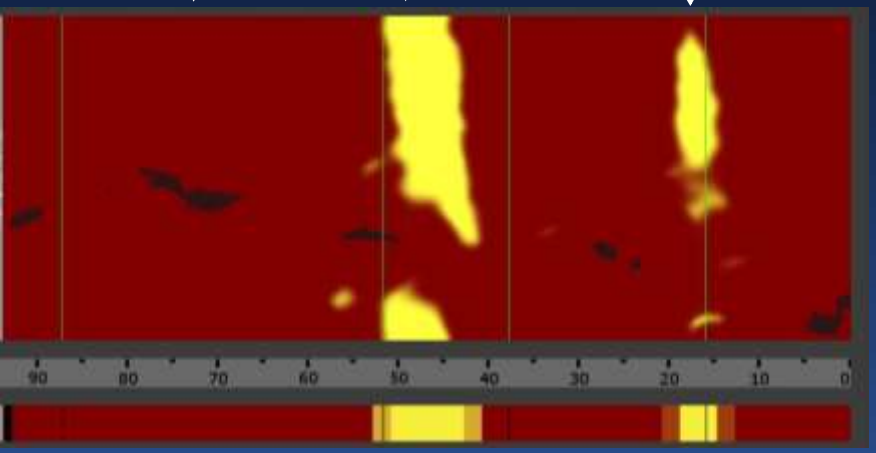
- **Attenuated plaque – grayscale IVUS**
  - Lee et al. JACC Cardiovasc Interv. 2009;2:65-72
  - Wu et al, Am J Cardiol 2010;105:48-53
  - Okura et al, Circ J 2007;71:648-53
  - Wu et al. JACC Cardiovasc Interv 2011;4:495-502
  - Lee et al JACC Cardiovasc Interv. 2011;4:483-91
  - Kubo et al. Cardiol Res Pract. 2011;687515
  - Shiono et al, JACC Cardiovasc Interv 2013;6:847-53
  - Jang et al. Am J Cardiol 2013;111:968-72
- **VH-TCFA or large necrotic core**
  - Claessen et al. JACC Cardiovasc Imaging 2012;5:S111-8
- **OCT-TCFA or plaque rupture**
  - Tanaka et al. Eur Heart J 2009;30:1348-55
  - Yonetsu et al. Int J Cardiol 2011;146:80-5
  - Lee et al. Circ Cardiovasc Intv 2011;4:378-86
  - Lee et al. J Am Coll Cardiol Intv 2011;4:483-91
  - Porto et al. Circ Cardiovasc Intv 2012;5:89-96
  - Imola et al. Am J Cardiol 2013;111:526-31
- **Large lipid core plaque - NIRS**
  - Goldstein et al. Circ Cardiovasc Interv 2011;4:429-437
  - Dohi et al. ACC2014

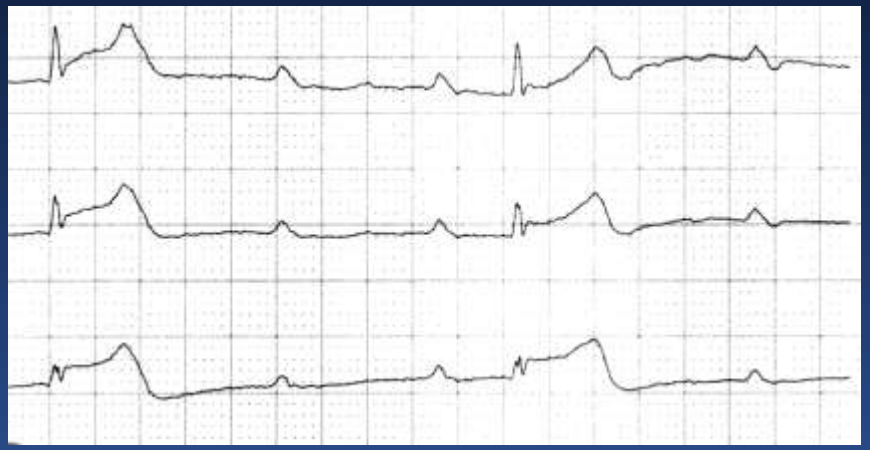
The common denominator is the presence of a TCFA











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Goldstein et al. JACC Cardiovasc Imaging. 2009;2:1420-4

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Lesson #9

TCFAs do more than just cause MI and cardiac death. They are responsible for distal embolization and no-reflow in patients undergoing percutaneous coronary intervention that, in turn, is associated with a four-fold increase in peri-procedural mortality.

Final Lesson

Remember…..There are other causes of ACS besides a TCFA: erosions, calcified nodules, spontaneous coronary dissection, and severe stenoses can, collectively, account for up to 50% of events.