Natural History Study of Vulnerable Plaque: Nine Lessons from PROSPECT (and other studies)

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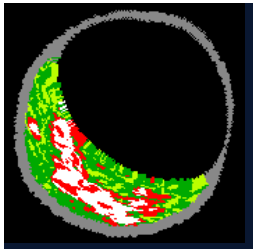
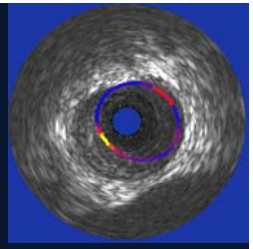


The PROSPECT Trial



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
Statin

F/U: Until there were 100 VP events

Repeat imaging in patients with events

PROSPECT: Pre-specified Primary Endpoint

100 MACE events attributable to rapid angiographic progression of a non-culprit lesion*

- *Cardiac death*
- *Cardiac arrest*
- *Myocardial infarction*
- *Unstable angina*
  - *Requiring revascularization*
  - *Requiring rehospitalization*
- *Increasing angina*
  - *Requiring revascularization*
  - *Requiring rehospitalization*

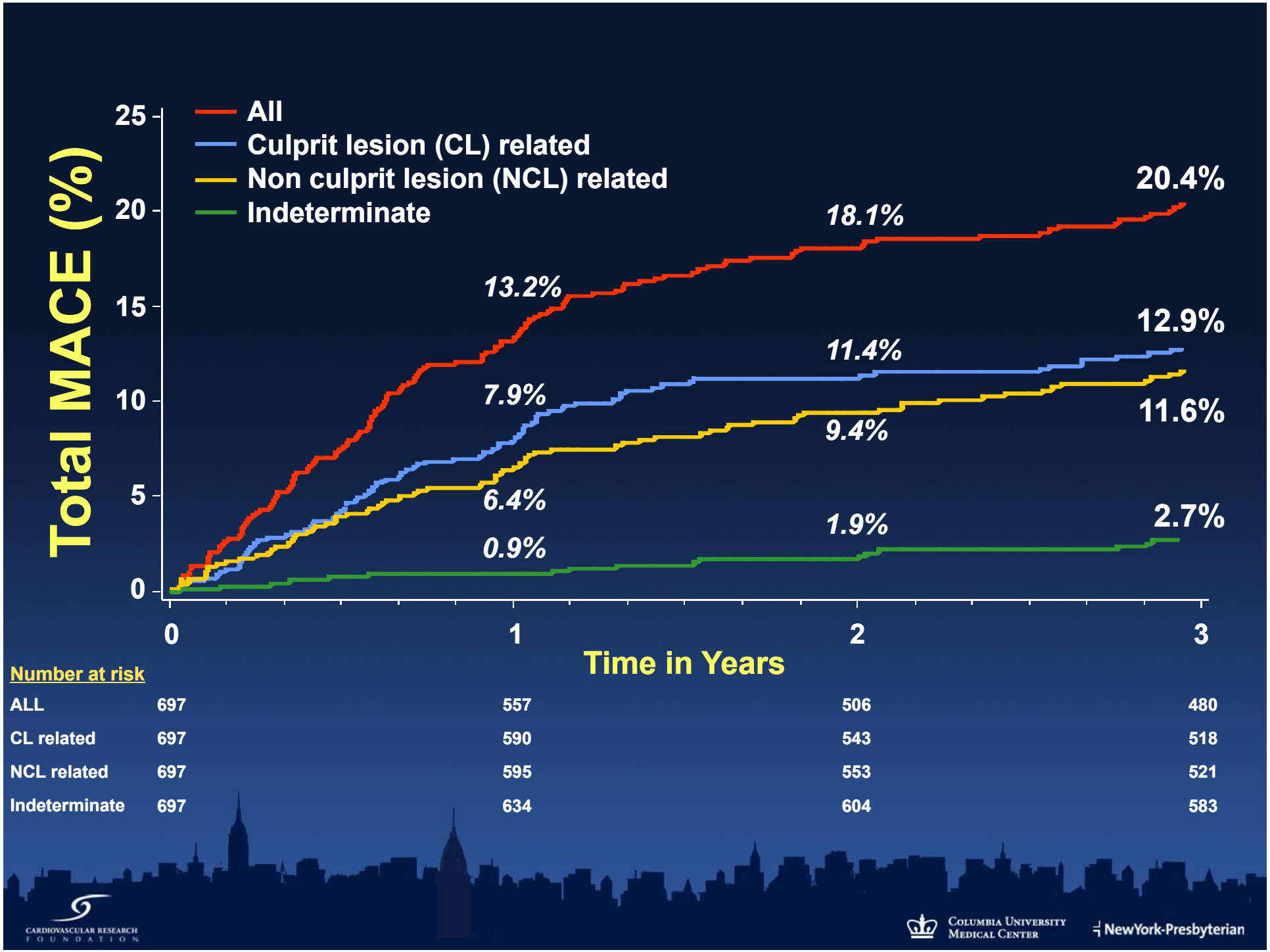
MACE during FU were adjudicated by the CEC as attributable to culprit lesions (treated during or before index hospitalization) or non culprit lesions (untreated areas of the coronary tree) based on angiography (+ECGs, etc.) at the time of the event; events occurring in pts without angiographic follow-up were considered indeterminate in origin. Rapid lesion progression = ↑ in QCA DS by >20% from baseline to FU.

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)**

Lesson #1

With modern medical therapy the rate of non-culprit lesion events was less than predicted – and most of those events are angina and revascularization, not hard events of death and MI. The hard events of death and MI occurred in only 1% of high risk patients per year.


All
Culprit lesion (CL) related
Non culprit lesion (NCL) related
Indeterminate
Total MACE (%)
25
20
15
10
5
0
0
1
2
3
Time in Years
20.4%
18.1%
13.2%
12.9%
11.4%
7.9%
11.6%
9.4%
6.4%
2.7%
1.9%
0.9%
Number at risk
ALL 697 557 506 480
CL related 697 590 543 518
NCL related 697 595 553 521
Indeterminate 697 634 604 583
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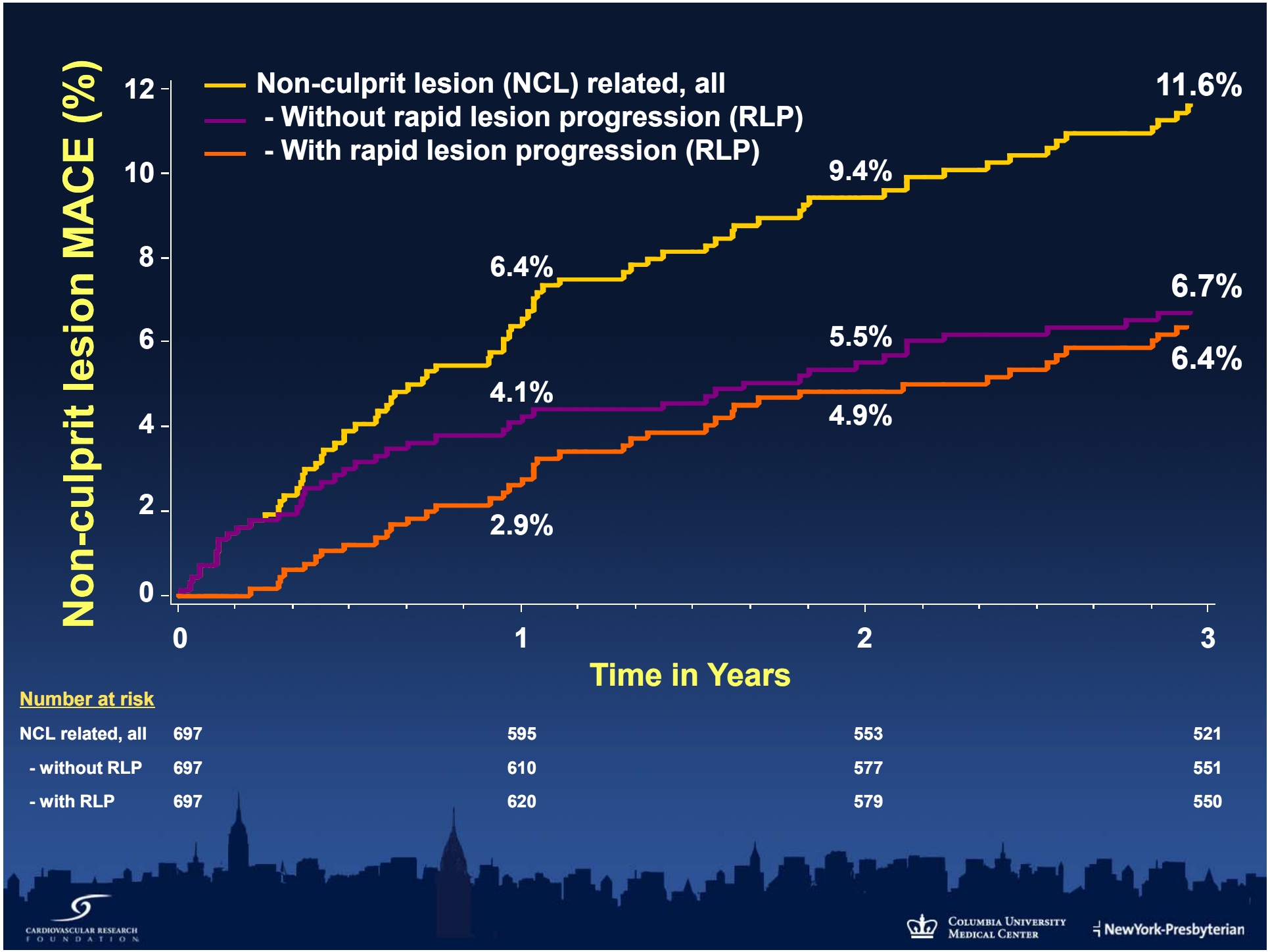
Non-culprit lesions responsible for MACE (n=107 in 76 patients)

- 35 of the 107 non-culprit MACE lesions (33.0%) had ≥50% DS by baseline angiography.
- All sites responsible for non-culprit MACE had plaque burden ≥40% by baseline 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.

Lesson #2

Non-culprit lesion events occur only at sites of at least 40% plaque burden by IVUS - disease that is angiographically silent in 2/3 of lesions, presumably because of positive remodeling.


Non-culprit lesion MACE (%)
12
10
8
6
4
2
0
Non-culprit lesion (NCL) related, all
- Without rapid lesion progression (RLP)
- With rapid lesion progression (RLP)
11.6%
9.4%
6.4%
6.7%
5.5%
4.1%
6.4%
4.9%
2.9%
0
1
2
3
Time in Years
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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	Rapid Lesion Progression	No Rapid Lesion Progression	P-value
Time to events (median)	401	223	0.07
Baseline QCA			
MLD (mm)	1.83±0.64	1.32±0.67	0.0001
DS	27±16%	49±19%	<0.0001
Follow-up QCA			
MLD (mm)	0.73±0.43	1.03±0.50	0.0023
DS	72±14%	59±16%	0.0001
DS progression	44±18%	5±8%	<0.0001

Lesson #3

Two-thirds of non-culprit lesion events in the first year (those without rapid lesion progression) are attributable to disease that was present (an more significant) at the time of the original PCI.
Importantly and although uncommon, death, cardiac arrest, or MI occurred only in the setting of rapid lesion progression.

PROSPECT: Multivariable Correlates of Non Culprit Lesion Related Events

Independent predictors of patient level events by Cox Proportional Hazards regression

Variable	HR [95% CI)	p
Insulin dependent DM	3.32 [1.43, 7.72]	0.005
Prior PCI	2.03 [1.15, 3.59]	0.02

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

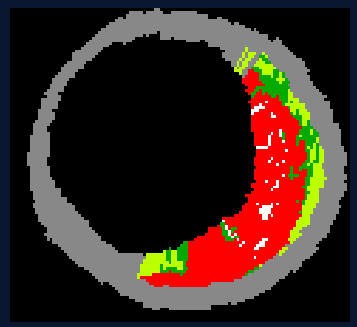
PROSPECT: Multivariable Correlates of Non Culprit Lesion Related Events

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

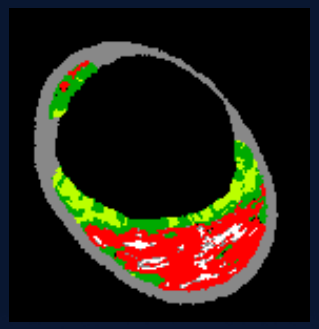
Variables entered into the model: minimal luminal area (MLA) ≤4.0 mm^2; plaque burden at the MLA (PB_{MLA}) ≥70%; external elastic membrane at the MLA (EEM_{MLA}) <median (14.1 mm^2); lesion length ≥median (11.2 mm); distance from ostium to MLA ≥median (30.4 mm); remodeling index ≥median (0.94); VH-TCFA.

VH-TCFA and Non Culprit Lesion Events



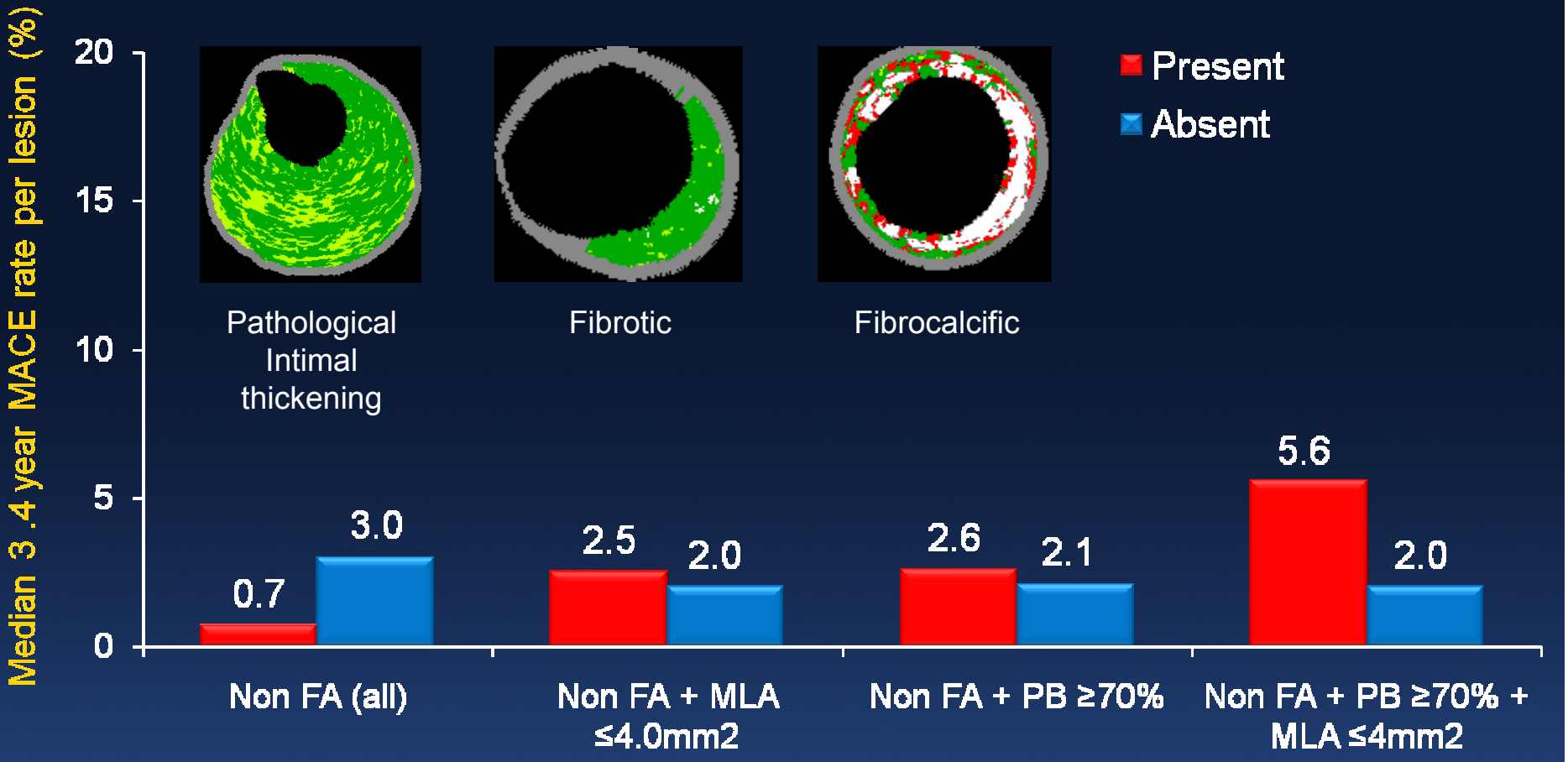
Lesion HR	3.90 [2.25, 6.76]	6.55 [3.43, 12.51]	10.83 [5.55, 21.10]	11.05 [4.39, 27.82]
P-value	<0.0001	<0.0001	<0.0001	<0.0001
Prevalence	4.67%	15.9%	10.1%	4.2%

Thick-cap FA and Non Culprit Lesion Events



Lesion HR	0.92 [0.52, 1.63]	3.41 [1.75, 6.65]	5.17 [2.59, 10.32]	5.02 [1.99, 12.63]
P-value	0.77	0.0003	<0.0001	<0.0001
Prevalence	67.6%	22.7%	15.6%	8.3%

Non Fibroatheromas and Non Culprit Lesion Events



Lesion HR	0.22 [0.10, 0.49]	1.49 [0.44, 3.39]	1.25 [0.17, 9.01]	2.60 [0.36, 18.84]
P-value	0.0002	0.70	0.83	0.34
Prevalence	67.9%	19.7%	5.6%	2.7%

Lesson #4

VH-IVUS tissue characterization and the vulnerable plaque hypothesis are real. This validates years if not more than a decade of work and lays to rest many of the questions about how the algorithm was built and validated and its ability to detect vulnerable (or stable) plaques.

But. . . . .

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 #5

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.

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.

Lesson #6

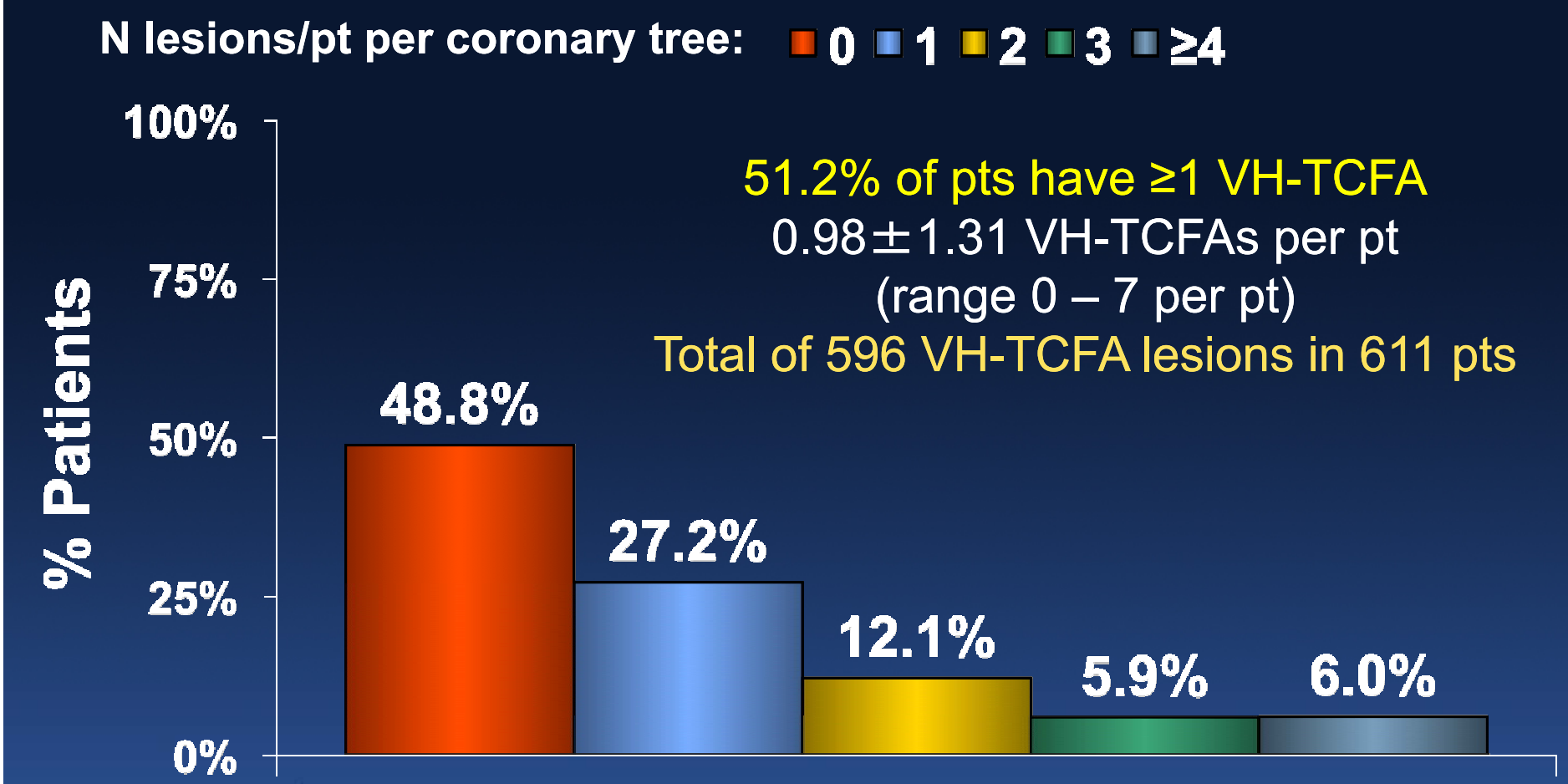
Even pre-specified 3-vessel invasive imaging is incomplete and detected only 50% of vulnerable plaques, in part because many vulnerable plaques are more distal than previously believed.

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

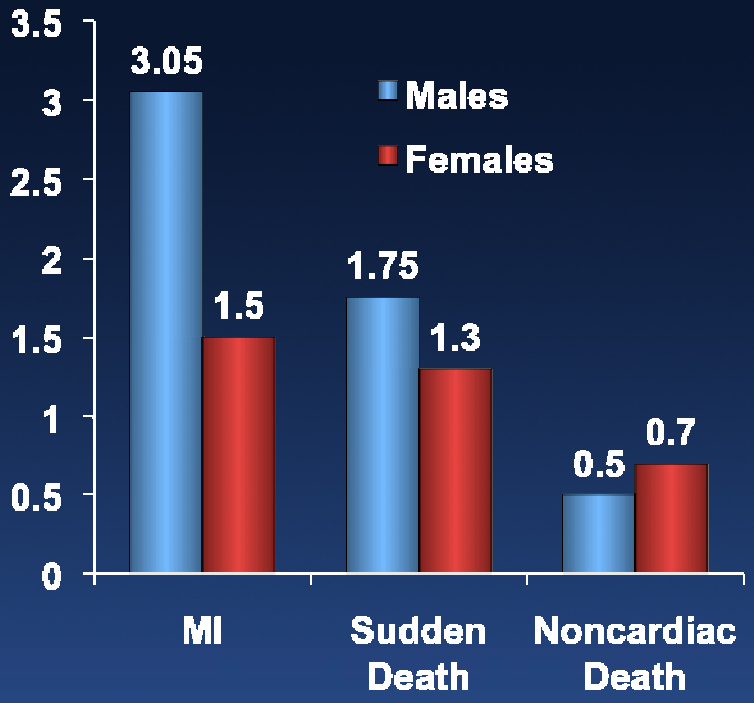
0.98±1.31 VH-TCFAs per pt

(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

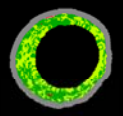
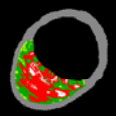
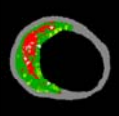
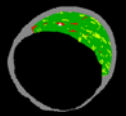
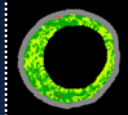
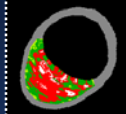
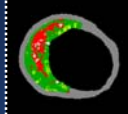
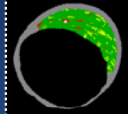
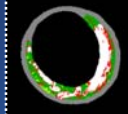
Lesson #7

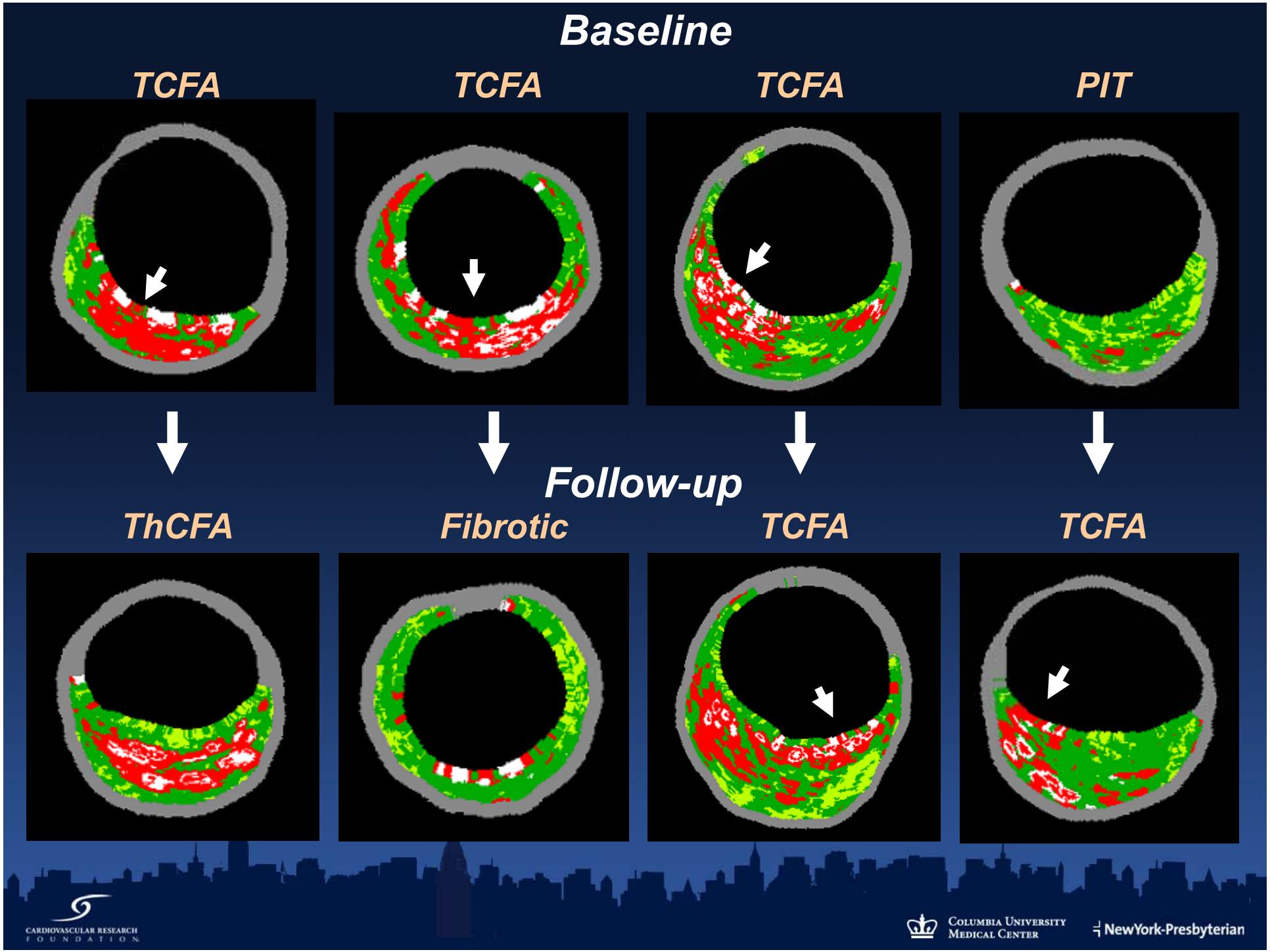
Vulnerable plaques are limited in number and are *focal* manifestations of a systemic disease.

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

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


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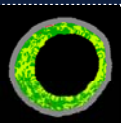
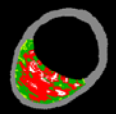
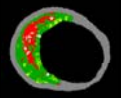
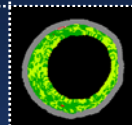
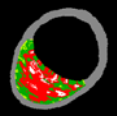
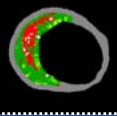
Change in non-culprit lesion phenotype in 100 pts (100 lesions: plaque burden >40%) from HORIZONS: Baseline and 13-month follow-up VH-IVUS

			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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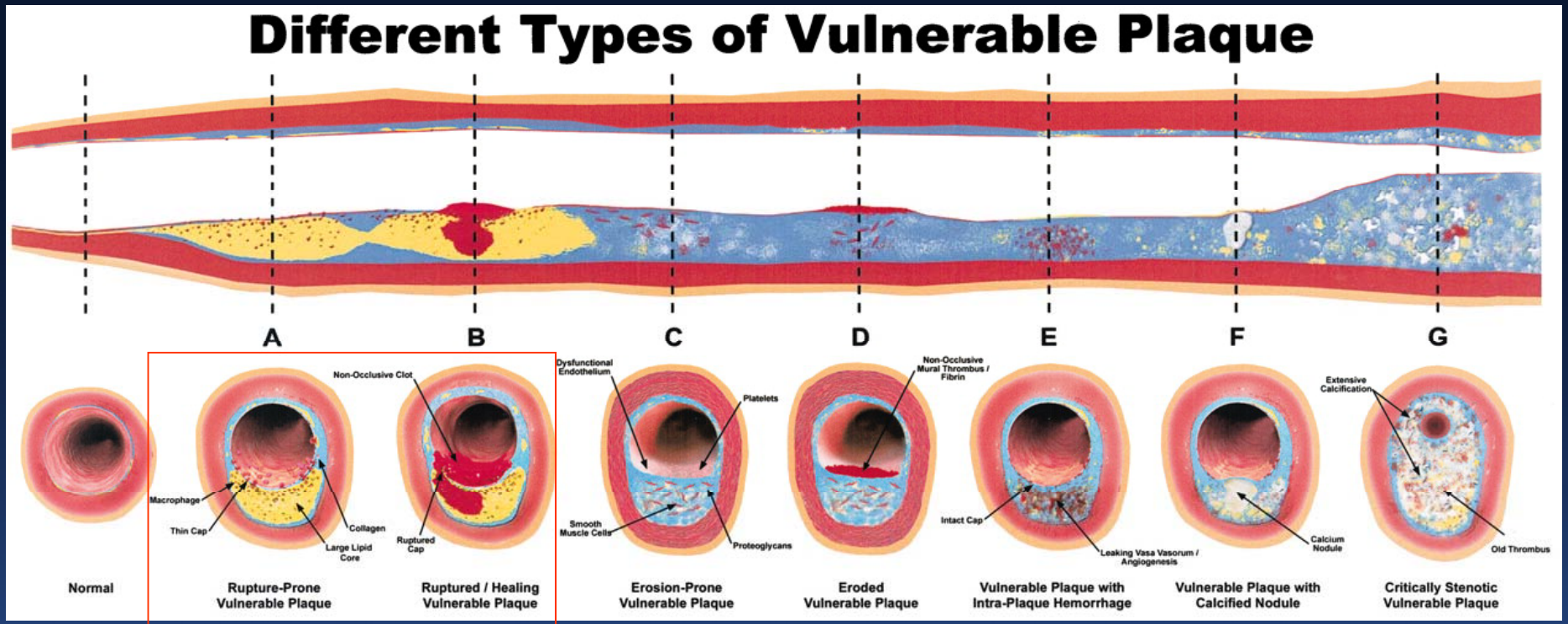
And some vulnerable plaques rupture asymptomatically or heal and contribute disease progression

- *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*

Lesson #8

Lesion phenotype is “unstable.” In particular, TCFAs can heal or rupture asymptomatically, and new TCFAs can develop in as short a period as 8 months.

"Vulnerable Plaque" = thrombosis-prone plaque and plaque with a high probability of undergoing rapid progression

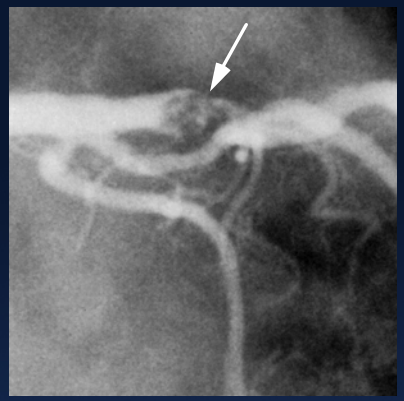


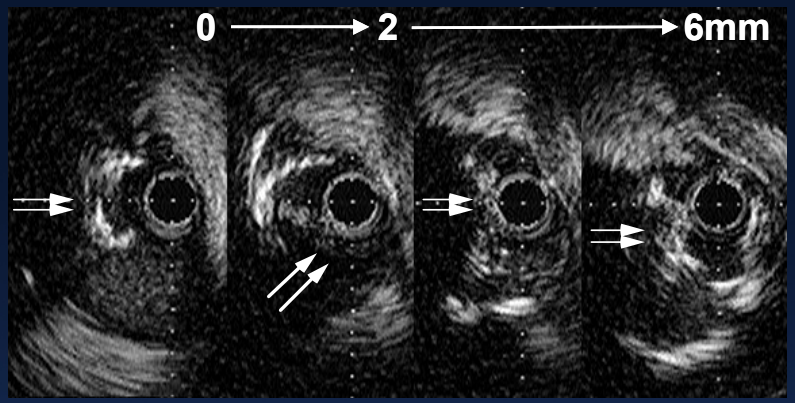
70% of ACS culprit lesions

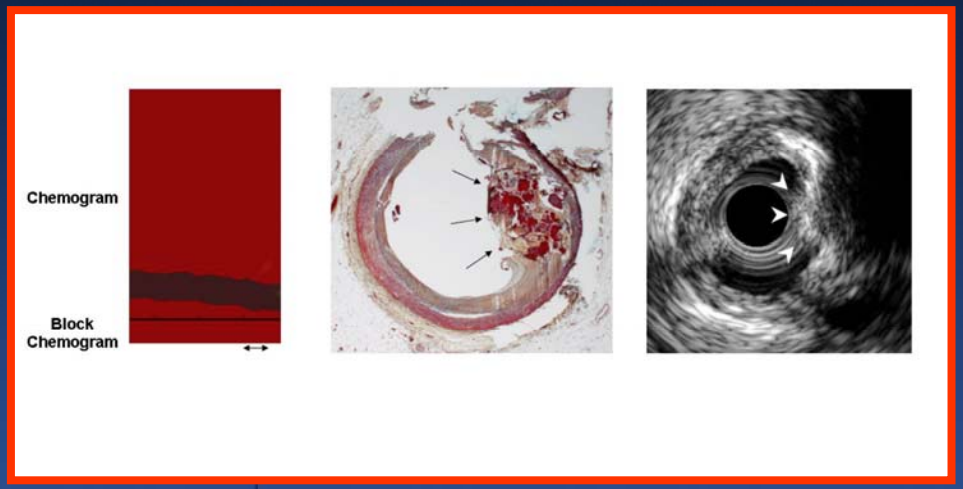
30% of ACS culprit lesions

Naghavi et al. Circulation 2003;108:1664-72

Not all ACS events are caused by TCFA rupture. Some are erosions, some thrombose without rupture, and some are calcific nodules

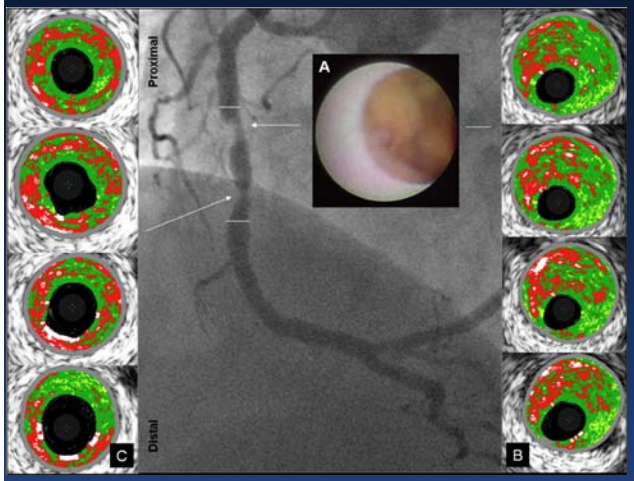




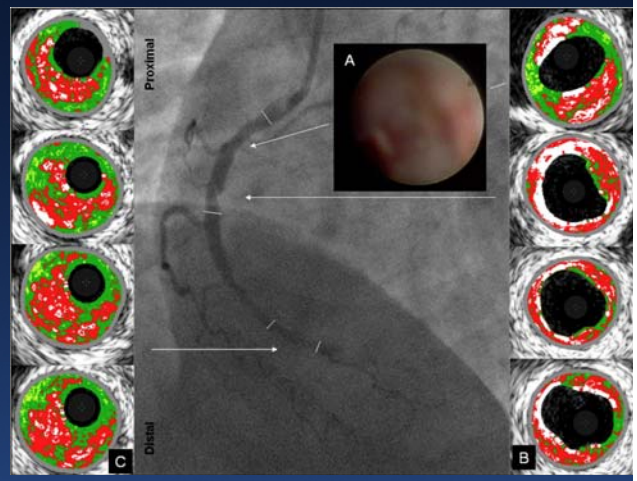


Duissaillant et al. Am Heart J 1996;132:687-9
Lee et al. Circulation, in press.

VH-IVUS and angioscopic assessment of culprit lesion phenotype morphology underlying coronary thrombosis



	Thrombus - rupture (n=23)	Thrombus + rupture (n=19)
VH-TCFA	17	11
ThCFA	5	7
PIT	1	1



Lesson #9

Not all vulnerable plaques are TCFAs.

Lessons learned

1) Modern medical therapy works. The annual rate of hard events (death/MI) is only 1% per year in high risk pts with established CAD. 700 patients followed for 3 years is insufficient and underpowered for a secondary detection/prevention natural history study.
2) Two-thirds of non-culprit lesion events in the first year are attributable to disease that was present at the time of the original PCI.
3) Non-culprit lesion events occur only at sites of at least 40% IVUS plaque burden - disease that may be angiographically silent (because of positive remodeling).
4) VH-IVUS and the vulnerable plaque hypothesis are real
5) There is a small, but finite risk associated with instrumenting all 3 coronary arteries.
6) Pre-specified 3-vessel invasive imaging is incomplete and detects only half of vulnerable plaques
7) Vulnerable plaques are limited in number and are *focal* manifestations of a systemic disease.
8) Vulnerable plaques lack temporal stability. They heal, rupture asymptomatically, or develop in as short a period of time as 8 months.
9) Not all vulnerable plaques are TCFAs.