IVUS and IVUS/VH in Acute Coronary Syndromes: How to Interpret and Apply PROSPECT to Clinical Care

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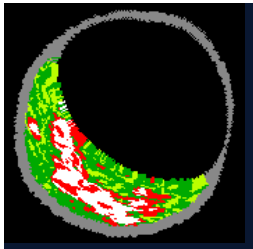
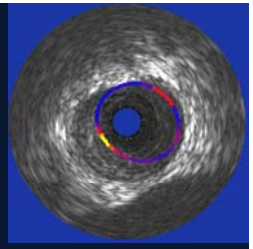
What I learned from PROSPECT. . .



The PROSPECT Trial



700 pts with ACS (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

PROSPECT: Pre-specified Primary Endpoints

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*

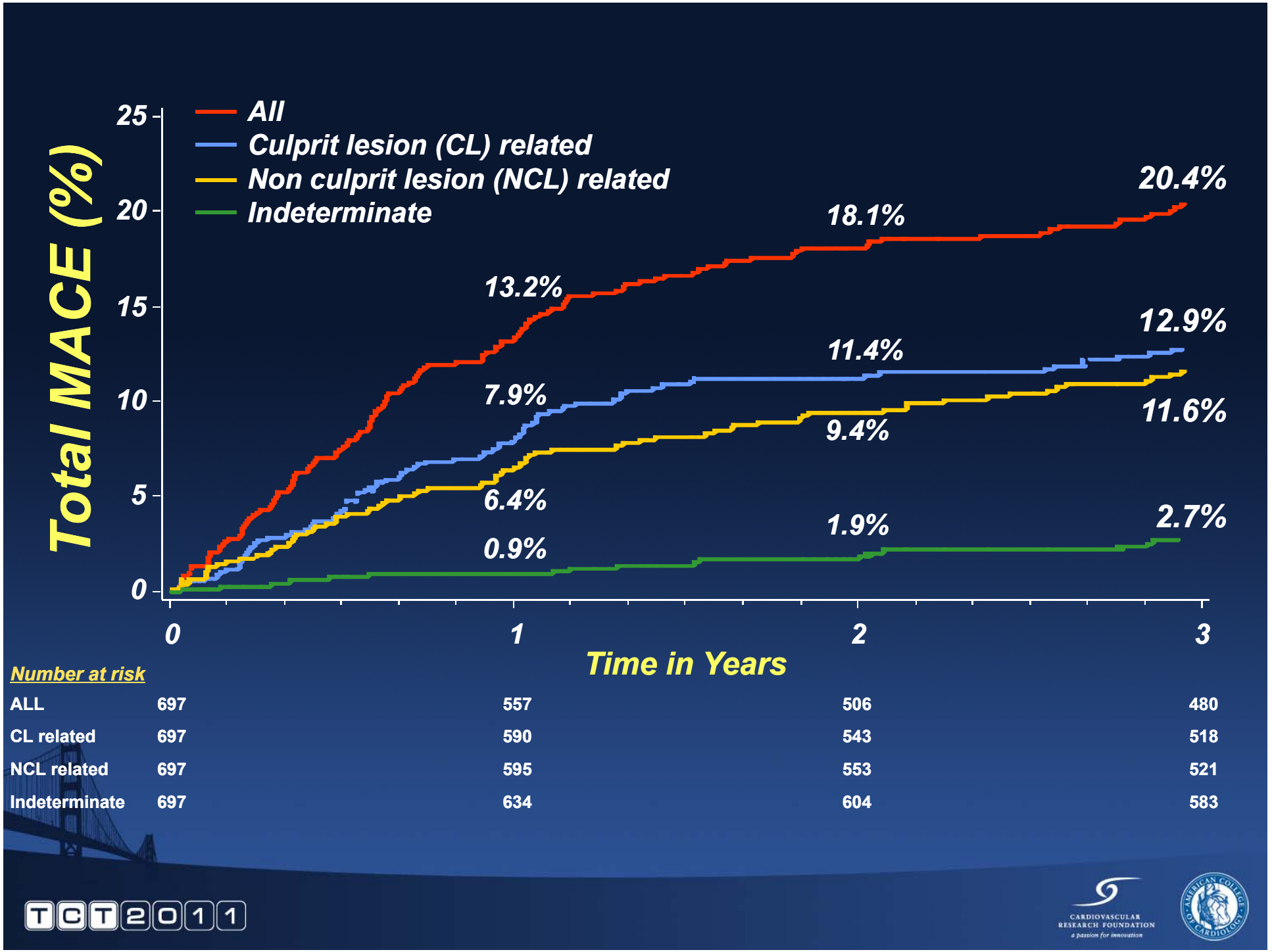
MACE during FU were adjudicated by the CEC as attributable to culprit lesions (treated during or before index hospitalization) or non culprit lesions (untreated areas of the coronary tree) based on angiography (+ECGs, etc.) at the time of the event; events occurring in pts without angiographic follow-up 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: Modern Medical Therapy Works

With modern medical therapy in the setting of a prospective registry of patients treated with primary PCI for STEMI or NSTEMI, the subsequent hard non-culprit lesion events (death/MI) occurred in only 1% of patients per year.



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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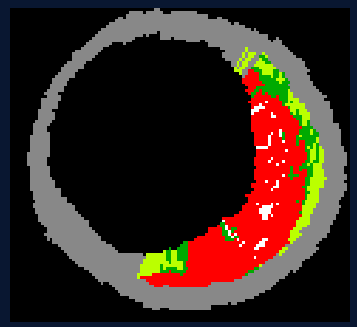
PROSPECT: Independent Predictors of Non Culprit Lesion Related Events

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

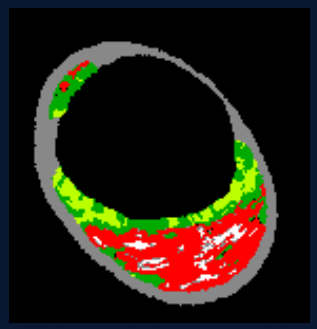
Variables entered into the model: minimal luminal area (MLA) ≤4.0 mm^2; plaque burden at the MLA (PB_{MLA}) ≥70%; external elastic membrane at the MLA (EEM_{MLA}) <median (14.1 mm^2); lesion length ≥median (11.2 mm); distance from ostium to MLA ≥median (30.4 mm); remodeling index ≥median (0.94); VH-TCFA.

VH-TCFA and Non Culprit Lesion Events



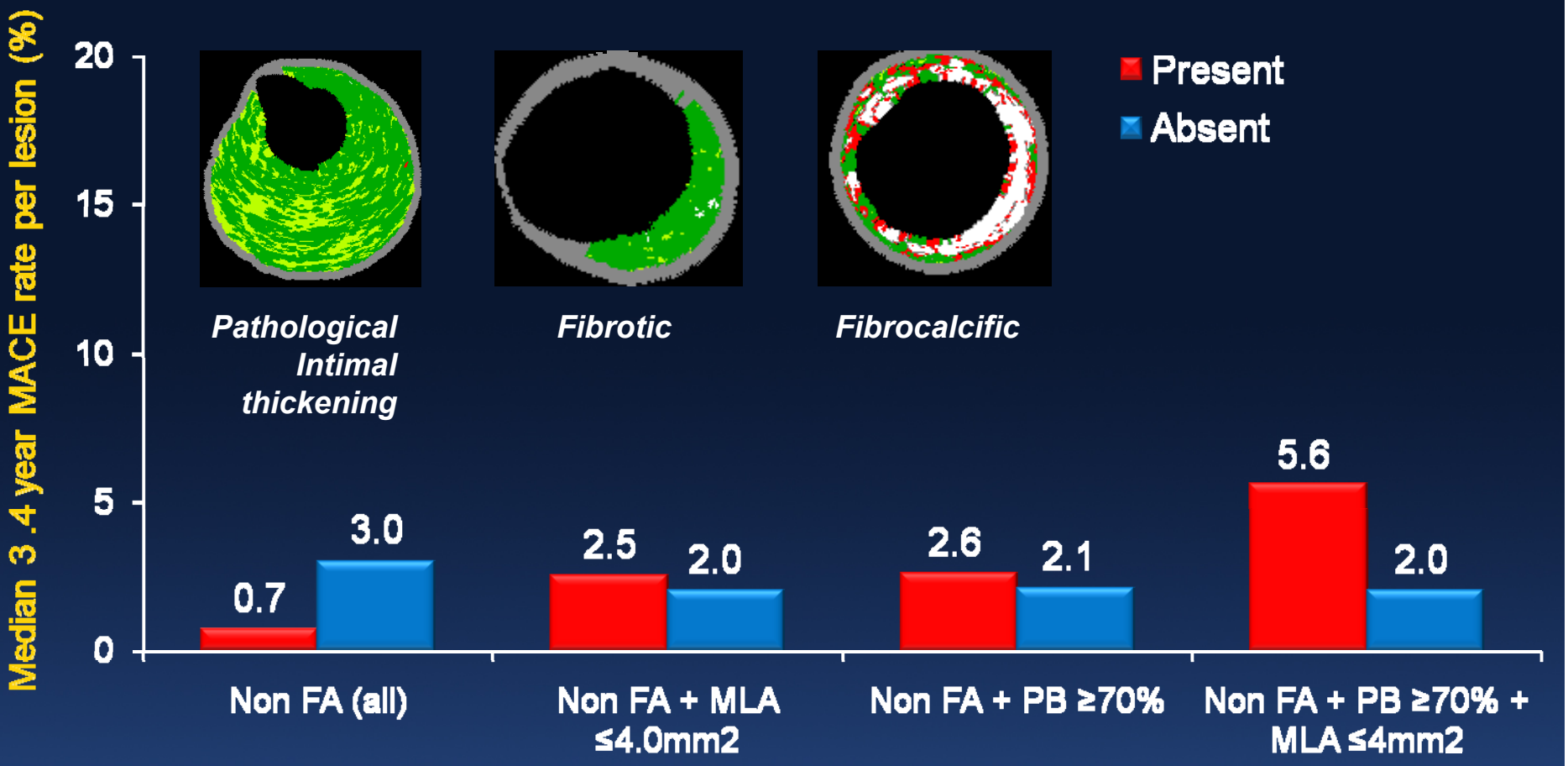
Lesion HR	3.90 [2.25, 6.76]	6.55 [3.43, 12.51]	10.83 [5.55, 21.10]	11.05 [4.39, 27.82]
P-value	<0.0001	<0.0001	<0.0001	<0.0001
Prevalence	4.67%	15.9%	10.1%	4.2%

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



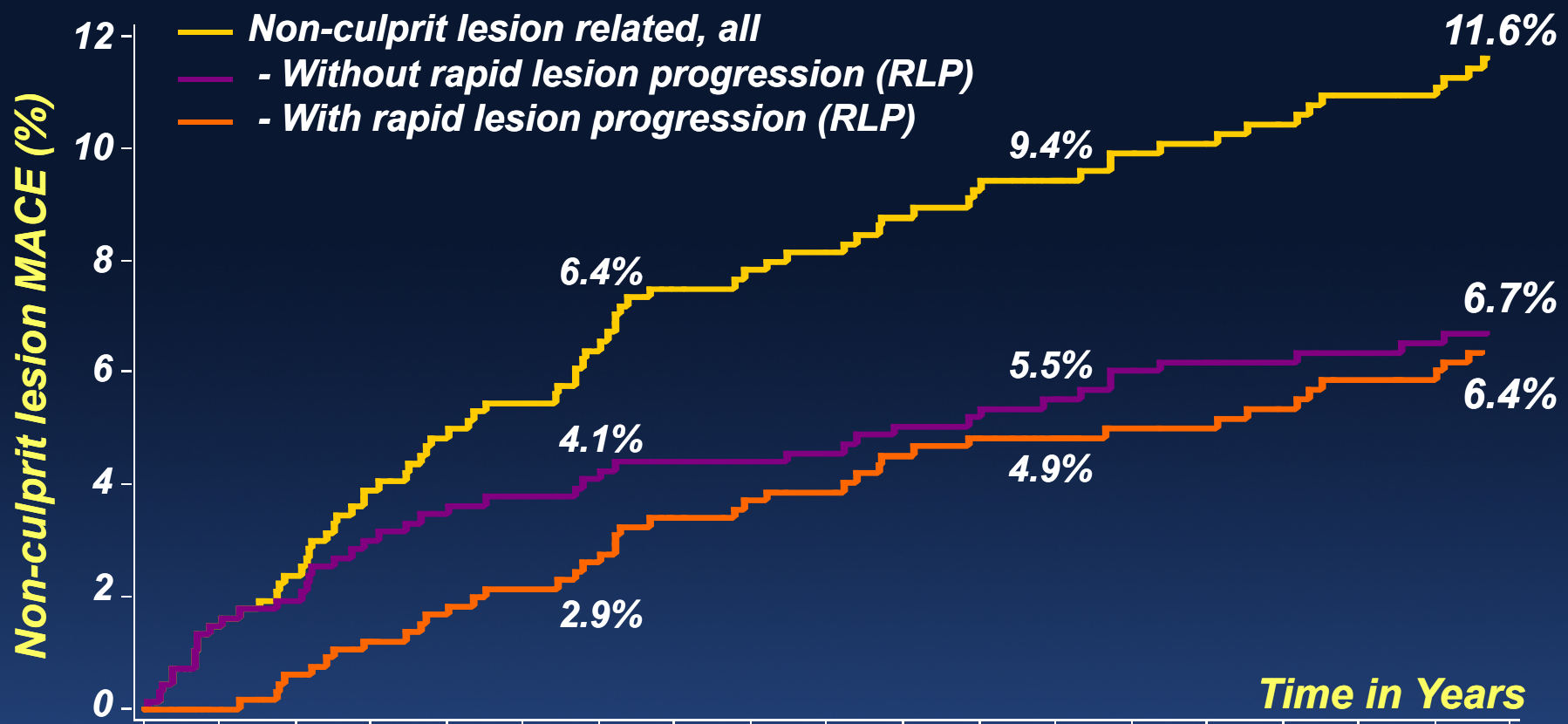
Lesion HR	0.22 [0.10, 0.49]	1.49 [0.44, 3.39]	1.25 [0.17, 9.01]	2.60 [0.36, 18.84]
P-value	0.0002	0.70	0.83	0.34
Prevalence	67.9%	19.7%	5.6%	2.7%

Lesson #2

VH-IVUS tissue characterization and the vulnerable plaque ("TCFA") hypothesis are real.

Conversely, a ThFCA phenotype is "neutral" and phenotypes of PIT and fibrotic and fibrocalcific plaque are "protective" and are not associated with events – including the need for repeat revascularization – at 3 years.

PROSPECT: Lesions responsible for non-culprit MACE had plaque burden ≥40%; and 33% had ≥50% QCA DS at baseline.



Number at risk	0	1	2	3
NCL related, all	697	595	553	521
- without RLP	697	610	577	551
- with RLP	697	620	579	550

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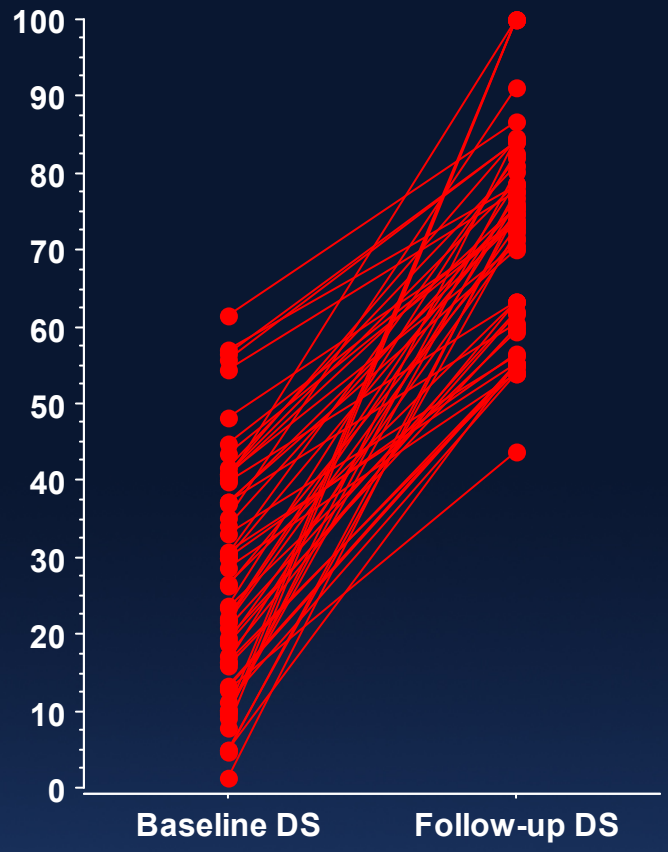
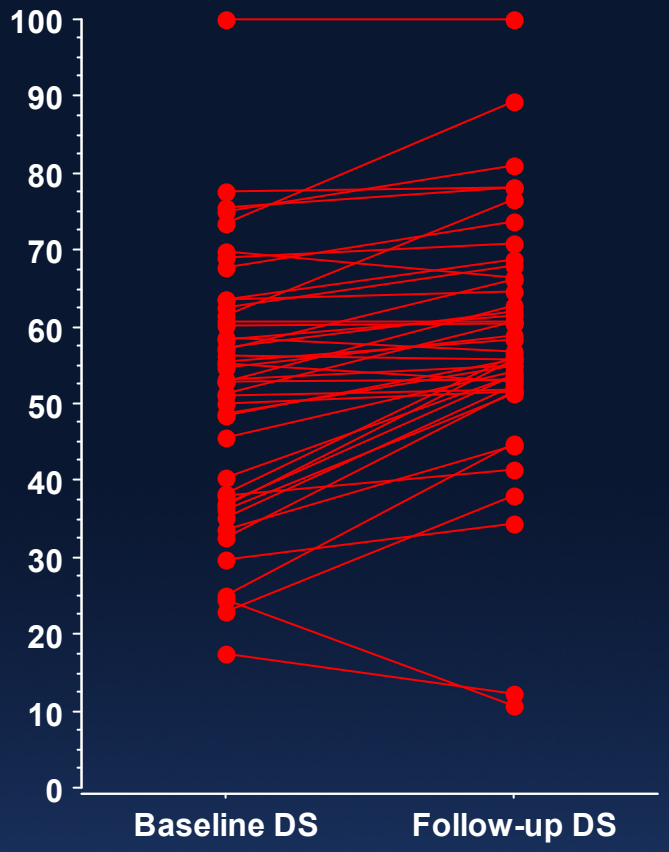




	Significant Progression	p	No Significant Progression
Time to events (median)	401	0.07	223
Baseline DS	27±16%	<0.0001	49±19%
Follow-up DS	72±14%	0.0001	59±16%
DS progression	44±18%	<0.0001	5±8%

Sanidas et al. JACC Cardiovasc Imaging 2012;5:S95-S105

Lesson #3

Non-culprit lesion events occurred only at sites with >40% plaque burden by IVUS - disease that was angiographically silent in 2/3 of lesions because of positive remodeling.

Two-thirds of non-culprit lesion events in the 1st year (those without significant progression) were attributable to disease that was present, and perhaps should have been treated, at the time of the original PCI.

Although uncommon, the composite of death, cardiac arrest, or MI occurred only in the setting of significant lesion progression.

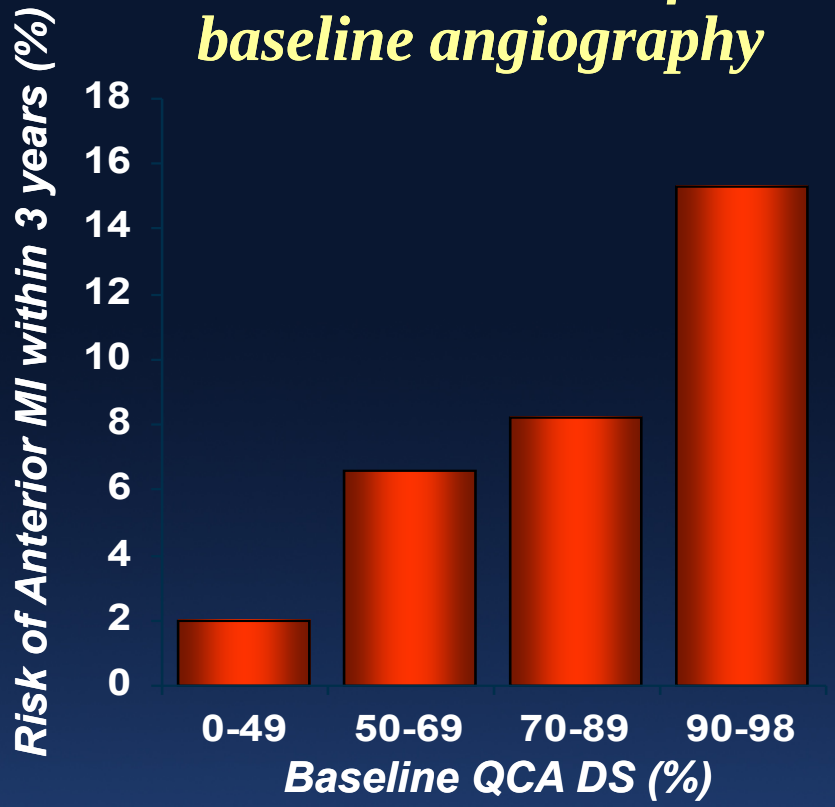
Risk of MI

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



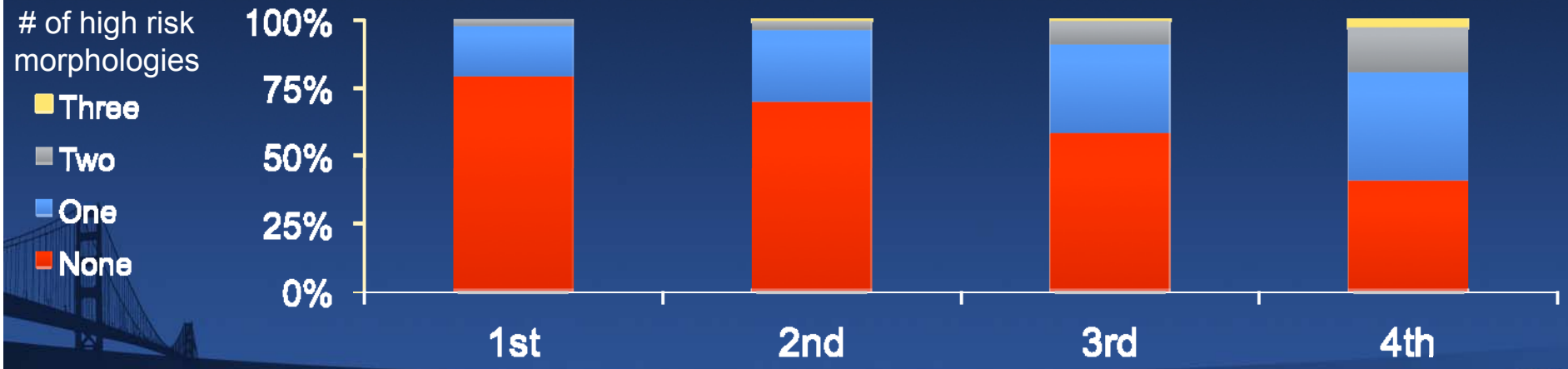
Ellis et al. J Am Coll Cardiol 1988;11:908-16

"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."

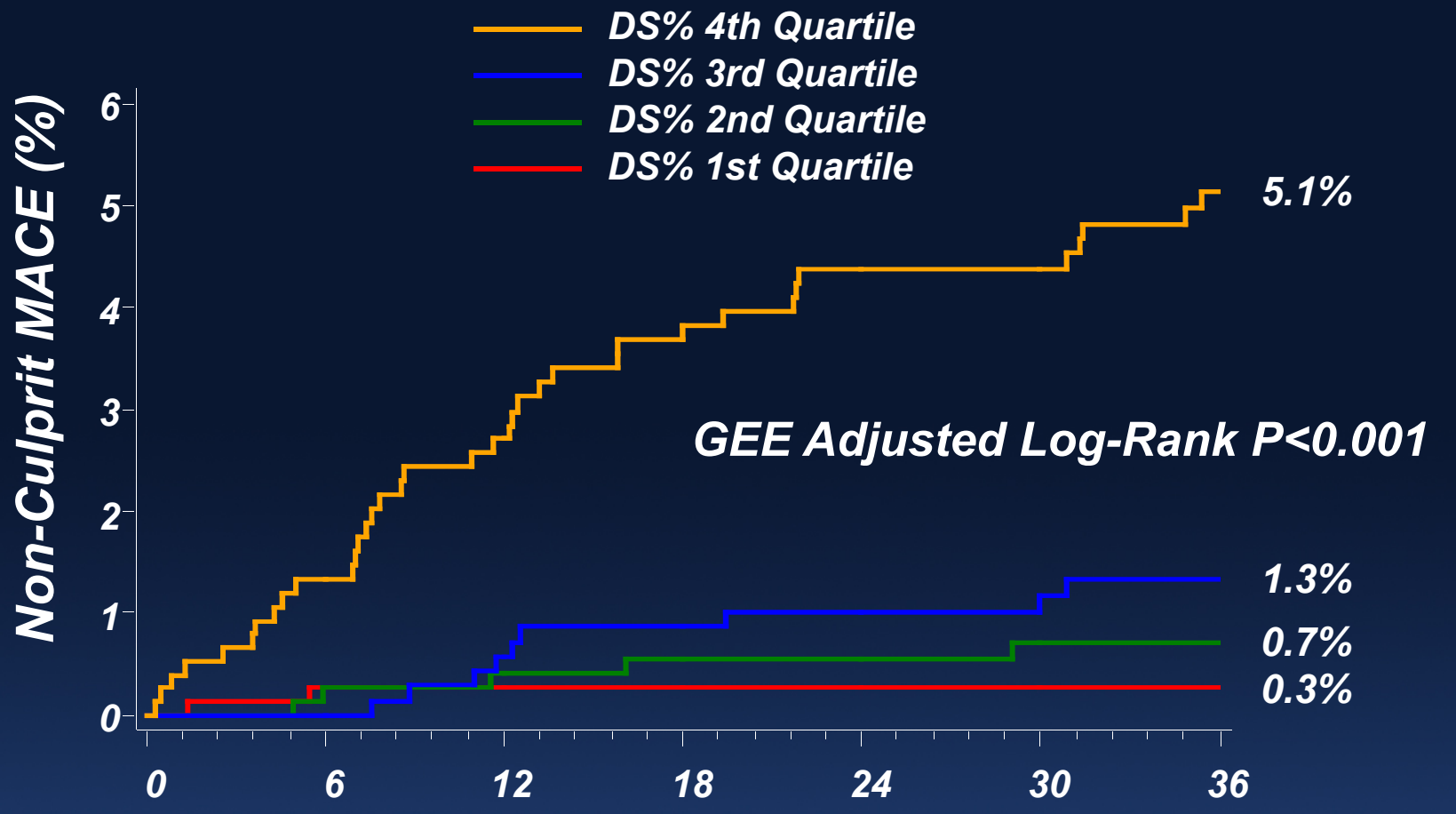
Kern and Meier. Circulation 2001;103:3142-9

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, in press



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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Yun et al. Am J Cardiol, in press

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Lesson #4

The angiographic severity of a nonculprit lesion is a marker of lesion vulnerability.

But. . . . .

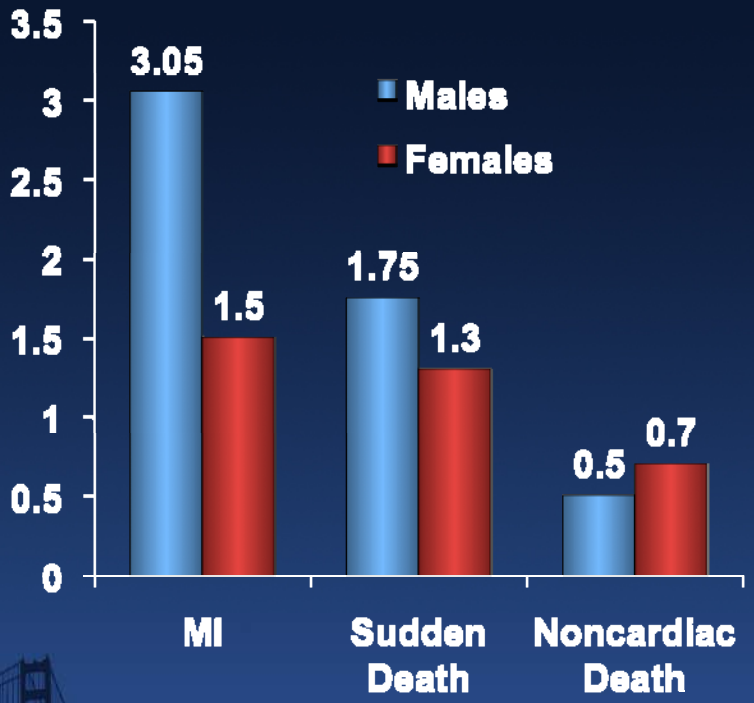
The Limits of Opening Arteries

NYTimes March 28, 2004

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

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

Cross-sectional analysis

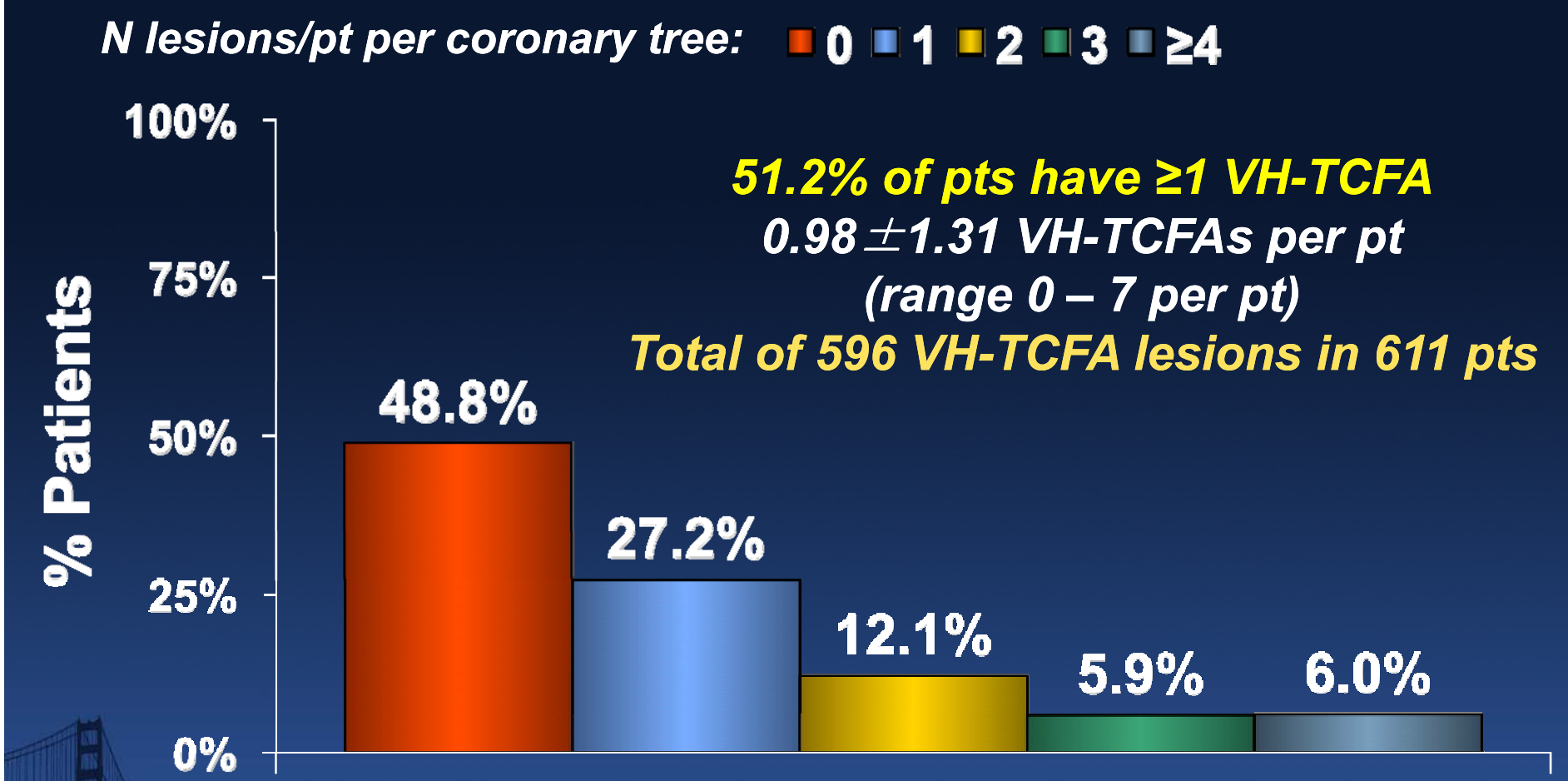


Longitudinal analysis

	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

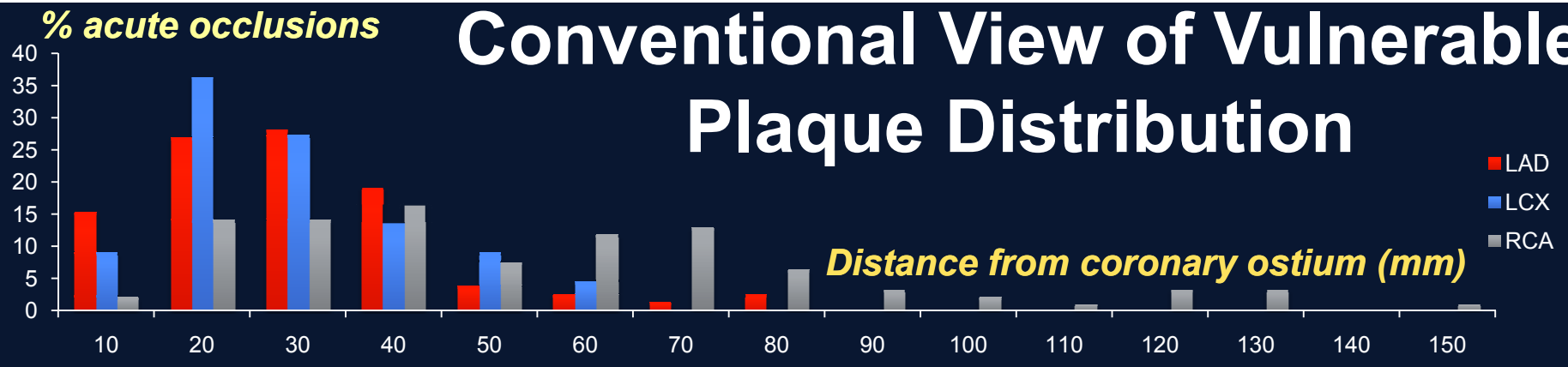
PROSPECT: Per patient incidence of VH-TCFAs



Lesson #5

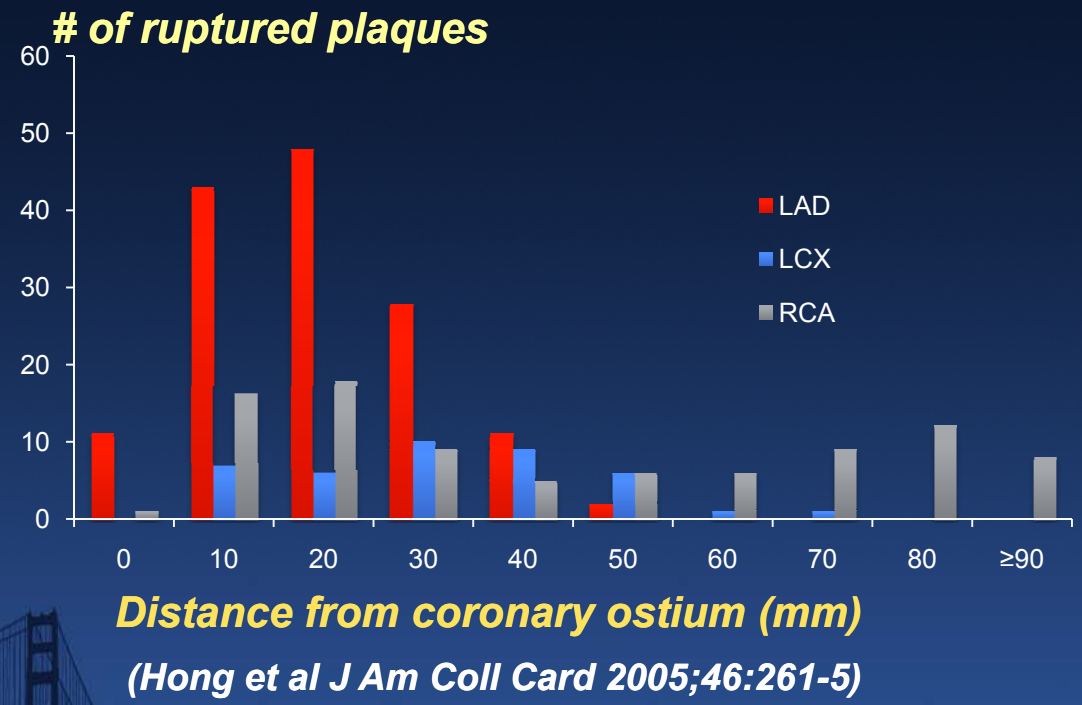
Vulnerable plaques are limited in number and are <u>focal</u> manifestations of a systemic disease.

Conventional View of Vulnerable Plaque Distribution

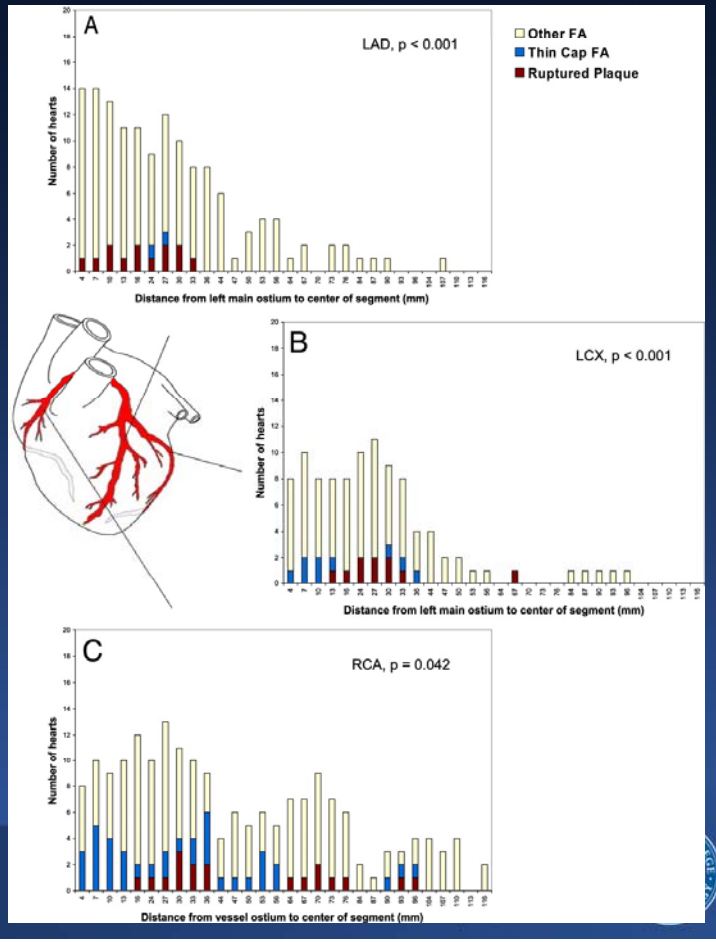


(Wang et al., Circulation 2004;110:278-84)

(Cheruvu et al. J Am Coll Cardiol 2007;50:940-9)



(Hong et al J Am Coll Card 2005;46:261-5)



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PROSPECT: Location of MACE

	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.

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

Lesson #6

After stenting the culprit lesions and treating patients with modern medical therapy, there is a shift in the location of non-culprit lesions from proximal major epicardial vessels to more distal vessels and sidebranches so that 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, but the complication rate decreased with operator experience

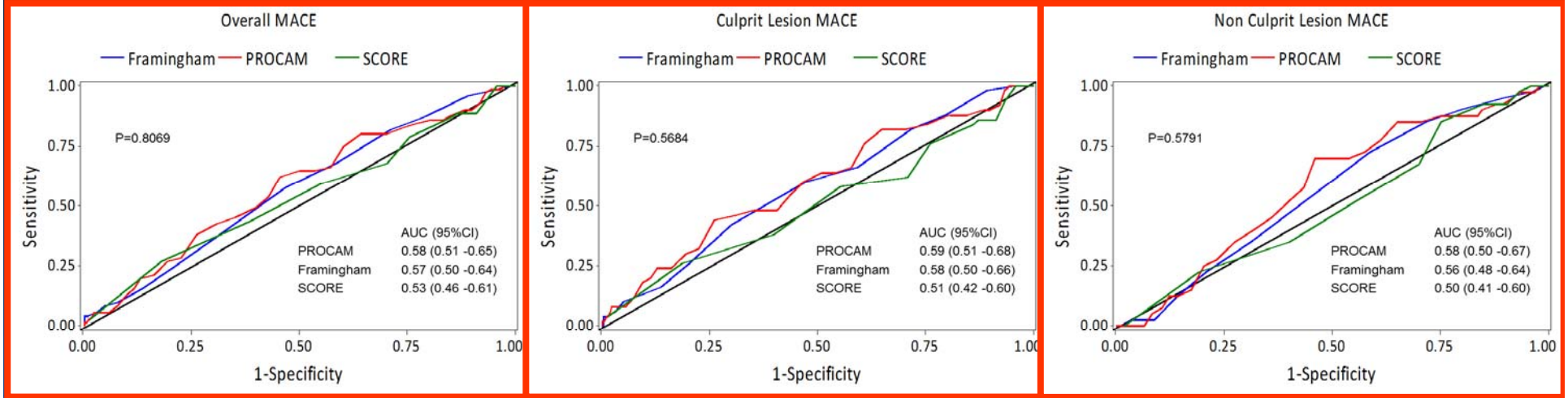
Lesson #7

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

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



Lesson #8

While we have the tools to identify vulnerable plaques, it is hard to justify it as current "standard of care"; and current risk scores do not tell us which patients are more likely to have a vulnerable plaque.