Natural History of Vulnerable Plaque: Imaging Study

Angioplasty Summit – Seoul

April 29, 2010

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Virtual Histology

Clinical Uses Now and in the Future

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Essence of 2004 Talk

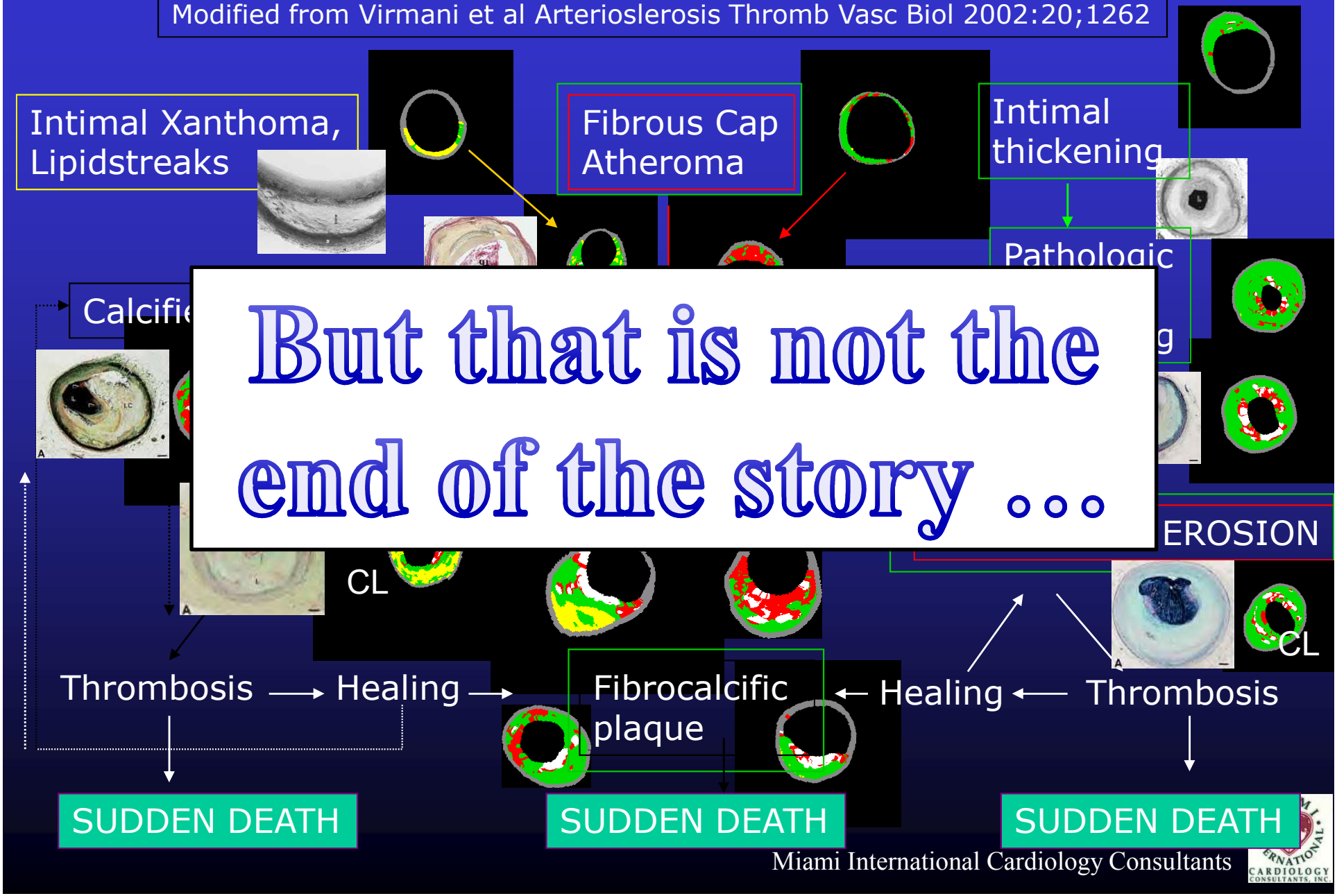
- Plaque rupture is major cause of acute MI and sudden death.
- VH-IVUS could identify plaque components (fibrous, fibro-fatty, necrotic core and calcium) with 95% predictive accuracy.
- VH could possibly identify culprit lesions and even predict plaques that were likely to rupture in the future.
- Studies planned and in progress were designed to validate these bold claims.

Natural History of Vulnerable Plaque

- It all starts with endothelial dysfunction.
- Early lesion is positively remodeled without lumen compromise until plaque burden reaches ca. 40%.
- Expanding necrotic core eventually ruptures:
- When rupture occurs into the lumen, thrombus forms – this may be partially or totally occlusive.
- Thrombus organizes, the rupture is covered, and the cycle repeats.
- All of these phenomena can be demonstrated by VH.

Progression of Atherosclerosis

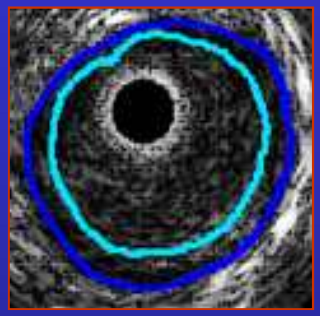
Modified from Virmani et al Arterioslerosis Thromb Vasc Biol 2002:20;1262

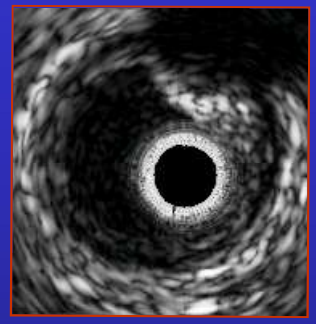


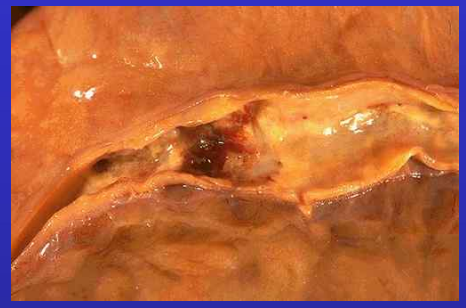
Culprit of the Culprit

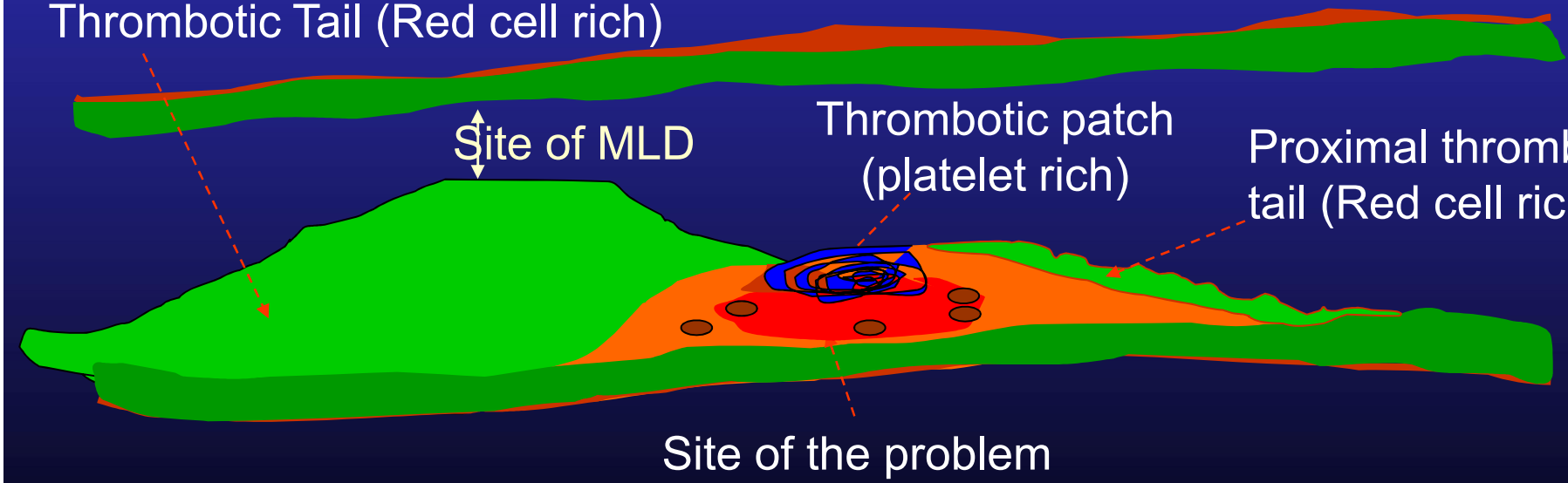
- The site of plaque rupture is generally not the site of maximal arterial narrowing.
- When a plaque ruptures, thrombus forms not only at the rupture site but also proximally and distally.
- The greatest narrowing is usually at the site of the distal thrombotic tail, which may be a centimeter or more from the rupture site.

Rupture of an Eccentric TCFA



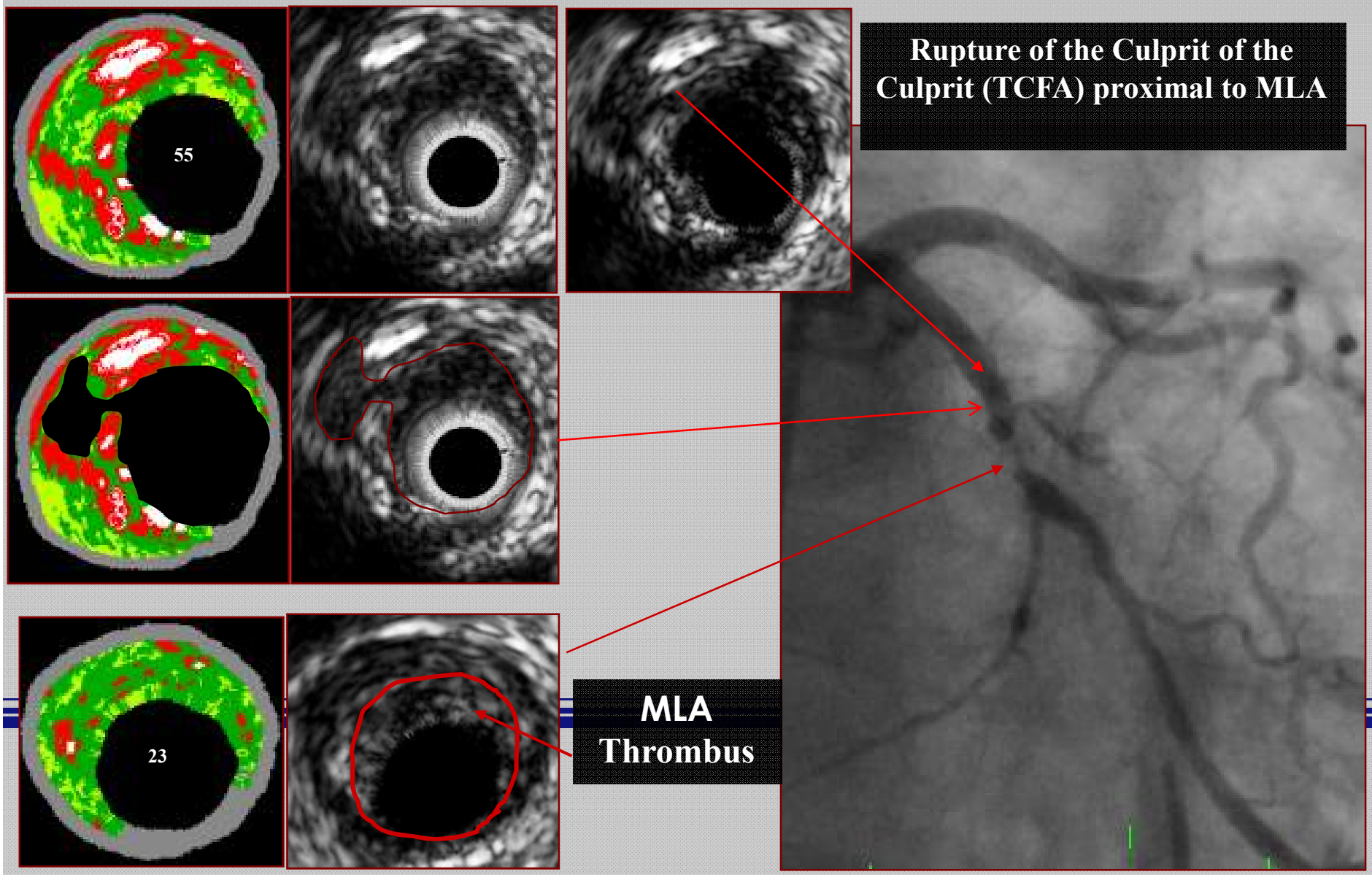




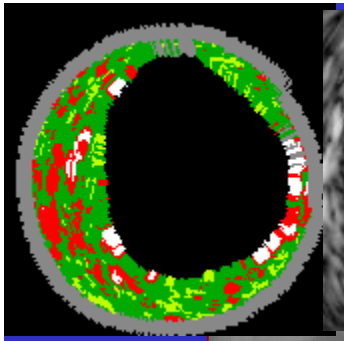


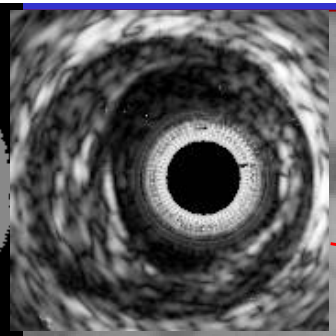
R Virmani, CVPath and
P Margolis, Volcano Corp.

Clinical Presentation NSTEMI



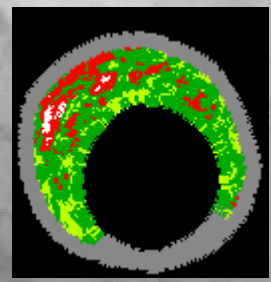
Thrombus Study In Japan

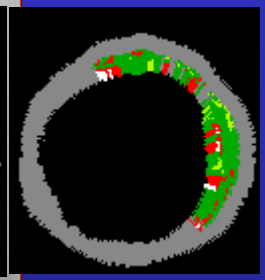




Rupture site

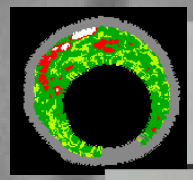
Thick fibrous plaque with necrotic core

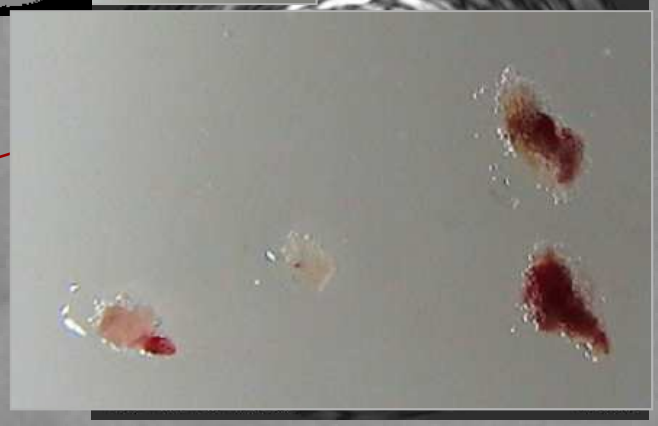




Pre DCA

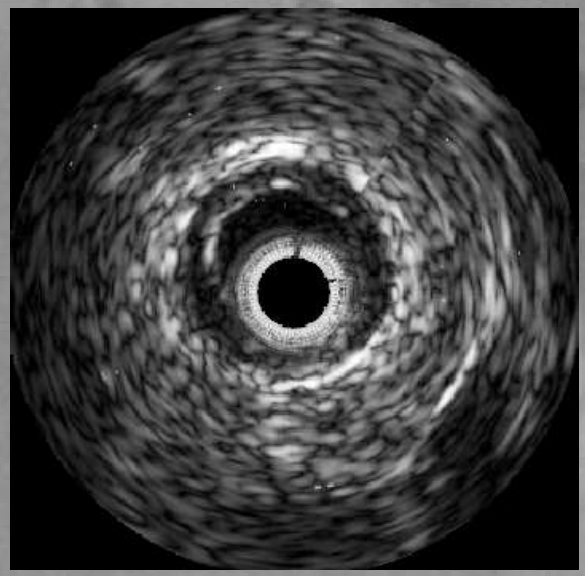
Post DCA





Red cell rich thrombotic tail

Pre thrombectomy



Post thrombectomy

Courtesy:
O. Katoh
P. Margolis

nsultants

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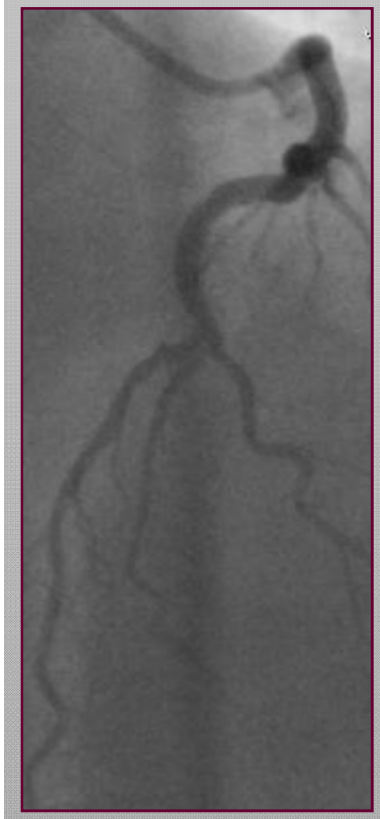
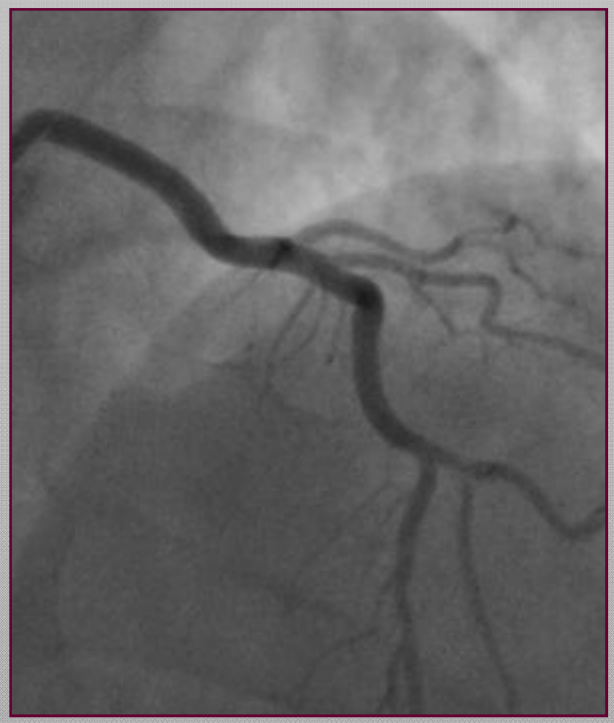
How often do we fail to see and miss treating the ruptured TCFA because the thrombus obscures our scenery?

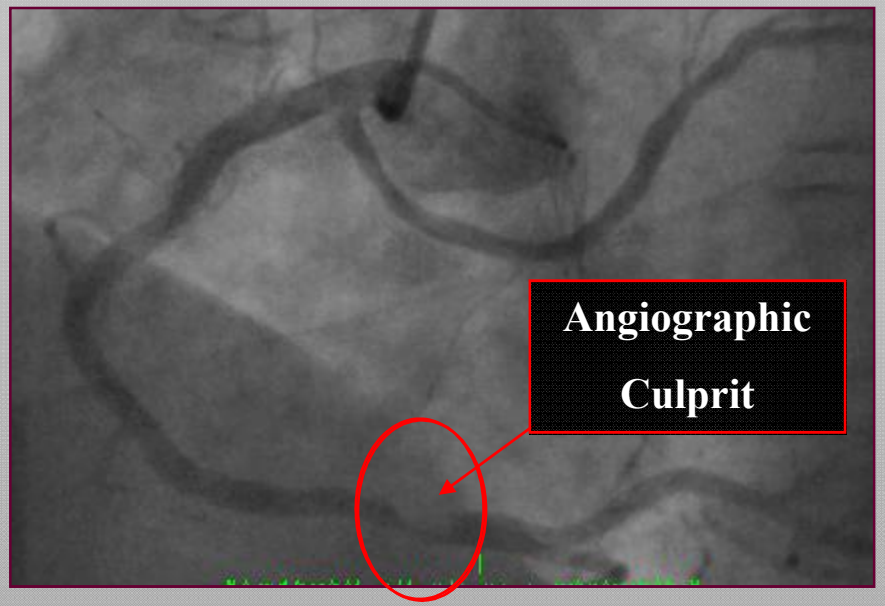
- D. Dudek, et al.
  - n=40
    - n=20 STEMI
    - n=20 NSTEMI
  - Aspiration if feasible
  - VH IVUS
  - Stenting by angio guidance only
  - VH IVUS

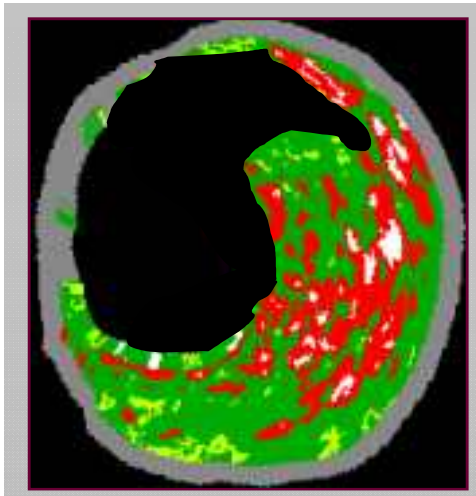
Case 13→ Clinical Presentation STEMI

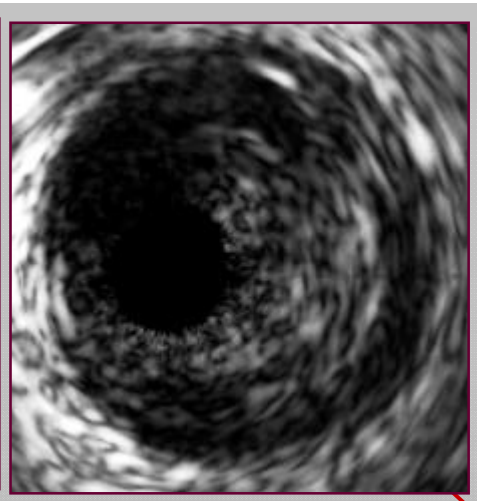
Angiographic findings

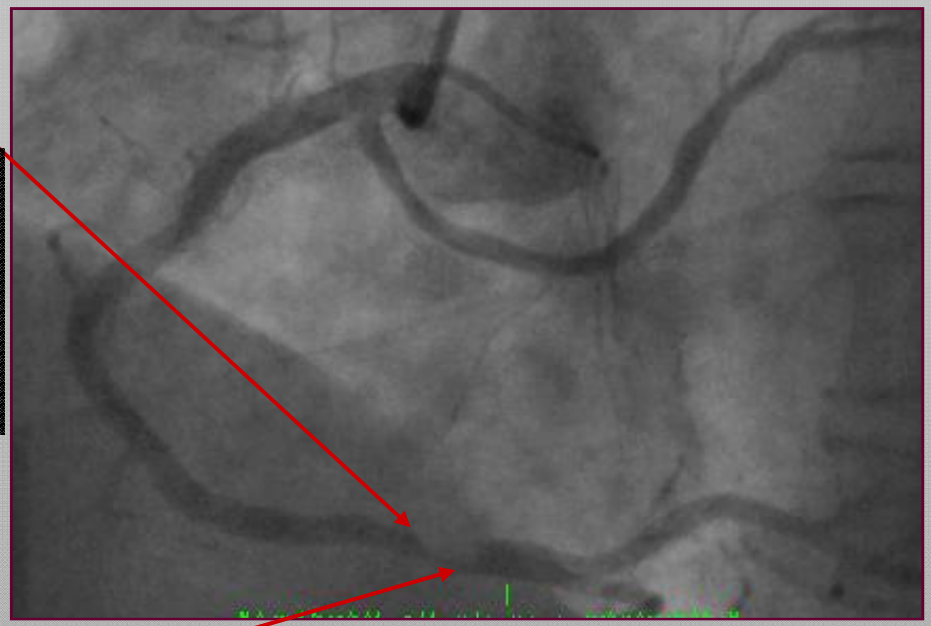




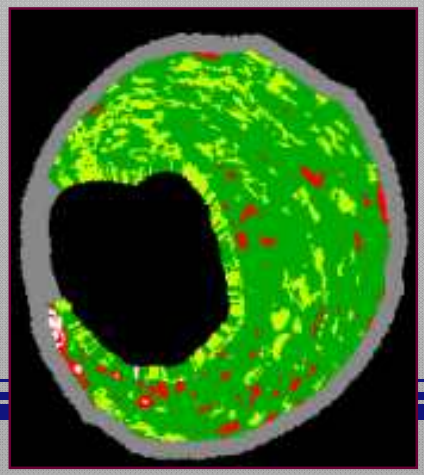


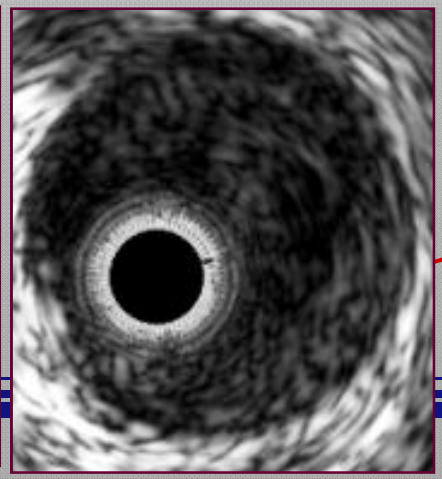






Rupture of the Culprit of the Culprit: 2 mm proximal to MLA, still at the angiographically significant lesion site, atheroma volume = 65%



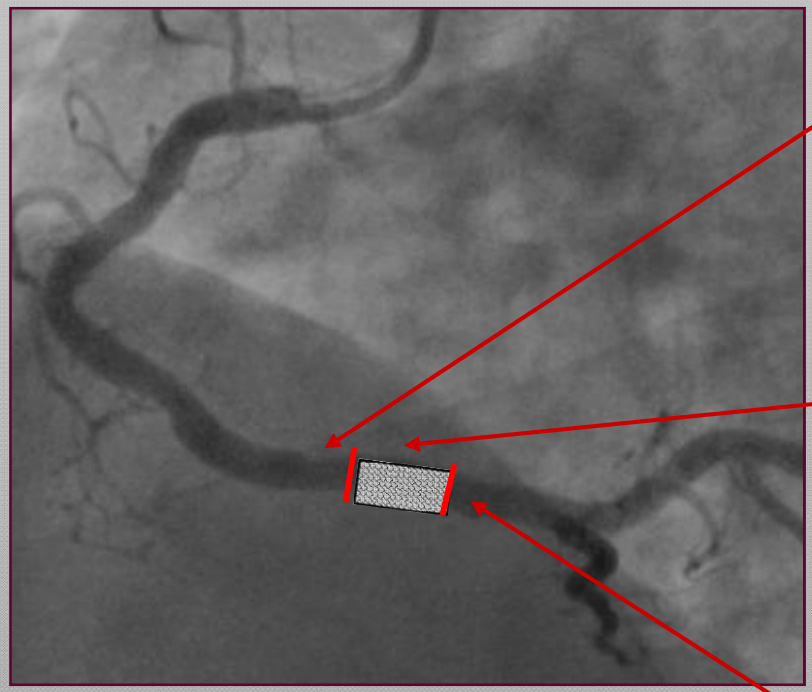


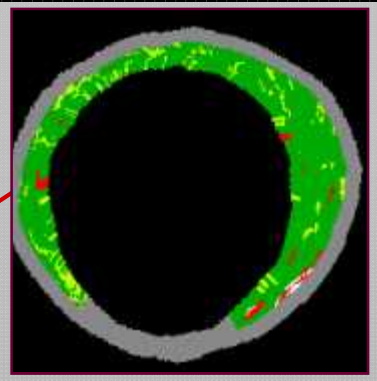
MLA (thrombus) **atheroma volume = 89%**

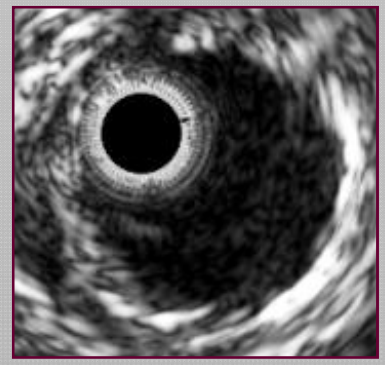
Case 13, treatment / Stenting

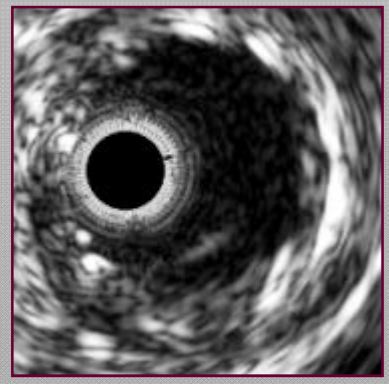
Just proximal to stent

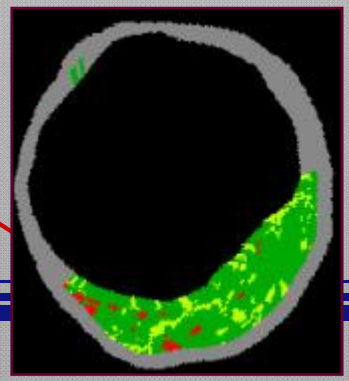
Final angiogram









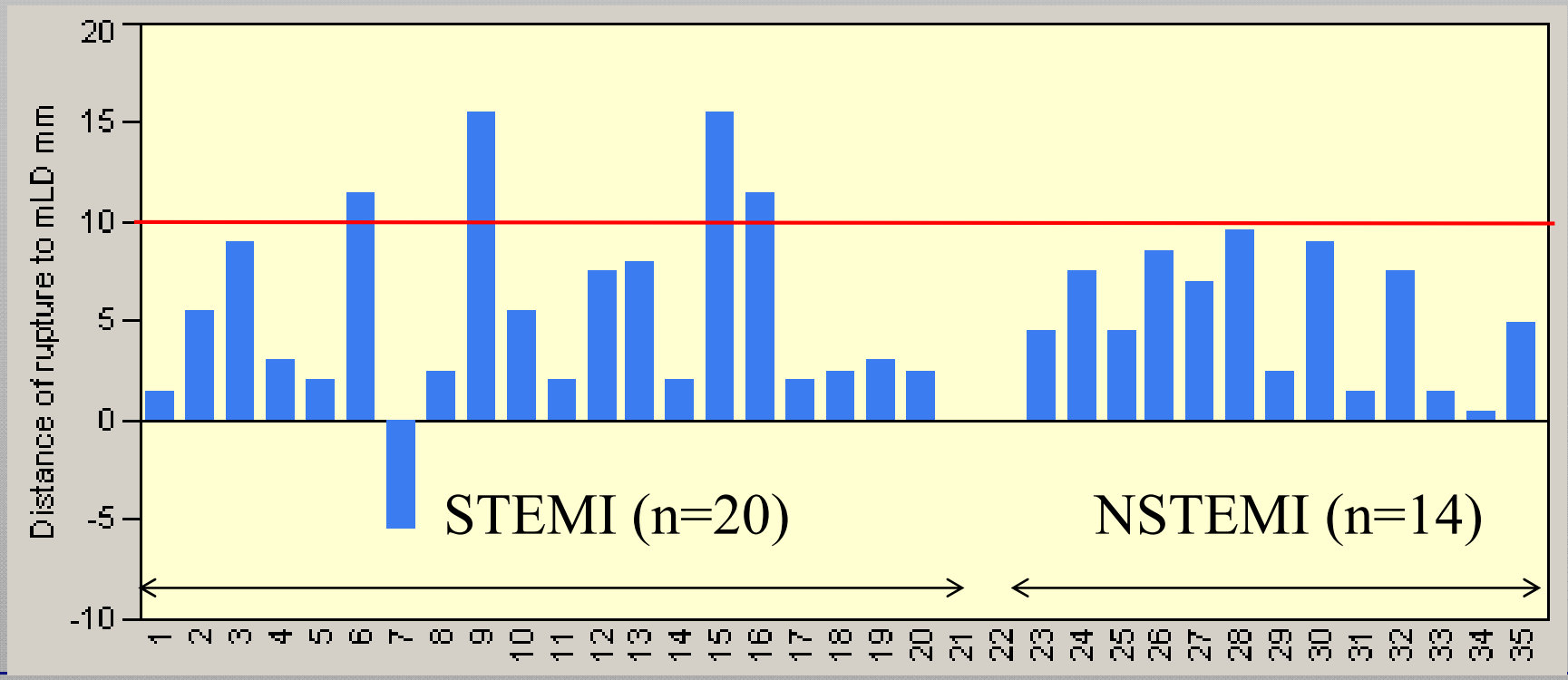


BMS 4,5 x 13 mm
Plaque/thrombus protrusion within stent

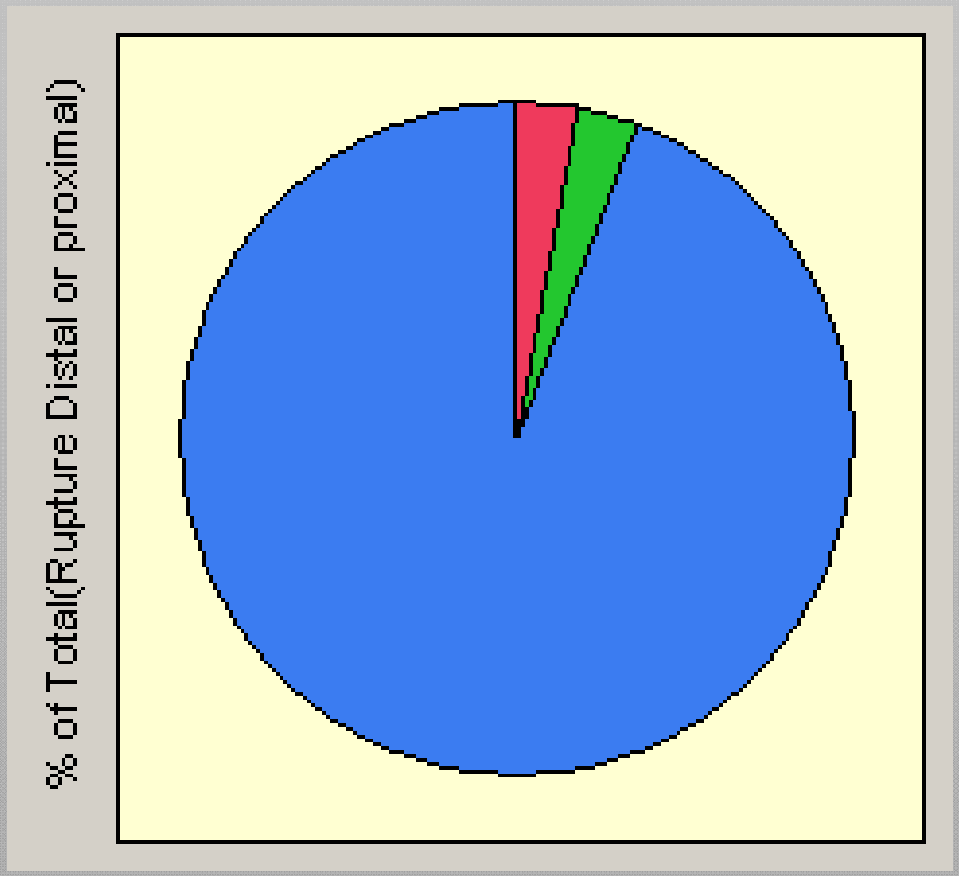
Just distal to the stent

Distance of the Plaque Rupture Site from the Min Lumen Diameter

No statistical significant difference between STEMI and NSTEMI



The location of the Rupture Site with Reference to the Min Lumen Cross Sectional area (CSA)

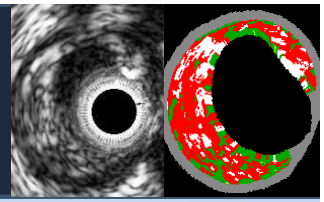


Korea 2004

Virtual Histology Can Differentiate Between Low and High Risk Lesions in These Patients?

All PROSPECT slides courtesy of Gregg Stone, M.D.

The PROSPECT Trial



700 pts with ACS

UA (with ECGΔ) or NSTEMI or STEMI >24º

undergoing PCI of 1 or 2 major coronary arteries

at up to 40 sites in the U.S. and Europe

Metabolic S.
- Waist circum
- Fast lipids
- Fast glu
- HgbA1C
- Fast insulin
- Creatinine

PCI of culprit lesion(s)

Successful and uncomplicated

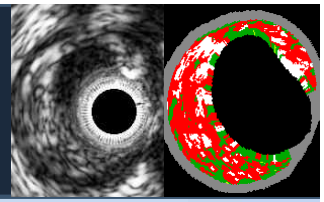
Biomarkers
- Hs CRP
- IL-6
- sCD40L
- MPO
- TNFα
- MMP9
- Lp-PLA2
- others

Formally enrolled

PI: Gregg W. Stone

Sponsor: Abbott Vascular; Partner: Volcano

The PROSPECT Trial



3-vessel imaging post PCI

Culprit artery, followed by non-culprit arteries

Angiography (QCA of entire coronary tree)

IVUS

Virtual histology

Palpography (n=~350)

Proximal 6-8 cm of each coronary artery

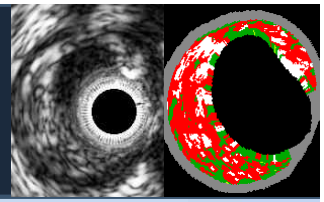
Meds rec
Aspirin
Plavix 1yr
Statin
Repeat biomarkers
@ 30 days, 6 months

F/U: 1 mo, 6 mo, 1 yr, 2 yr, ±3-5 yrs

MSCT Substudy N=50-100

Repeat imaging in pts with events

PROSPECT: Primary Endpoint



MACE attributable to <u>non-culprit</u> lesions*

- **Cardiac death**
- **Cardiac arrest**
- **Myocardial infarction**
- **Rehospitalization due to**
  - **- Unstable angina**
  - **- Progressive angina**

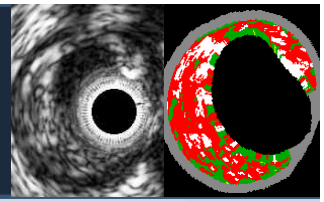
Most severe

Hierarchical

Least severe

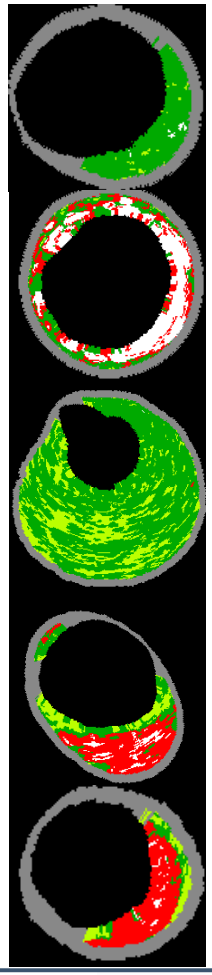
MACE during FU were adjudicated by the CEC as attributable to culprit lesions (those treated during or before the index hospitalization) or non culprit lesions (untreated areas of the coronary tree) based on angiography (+ECGs, etc.) at the time of the event; events occurring in pts without angiographic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

PROSPECT: Methodology



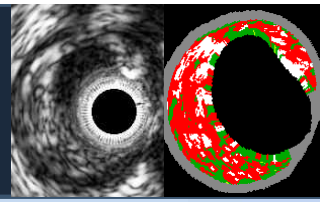
Virtual histology lesion classification

Lesions are classified into 5 main types

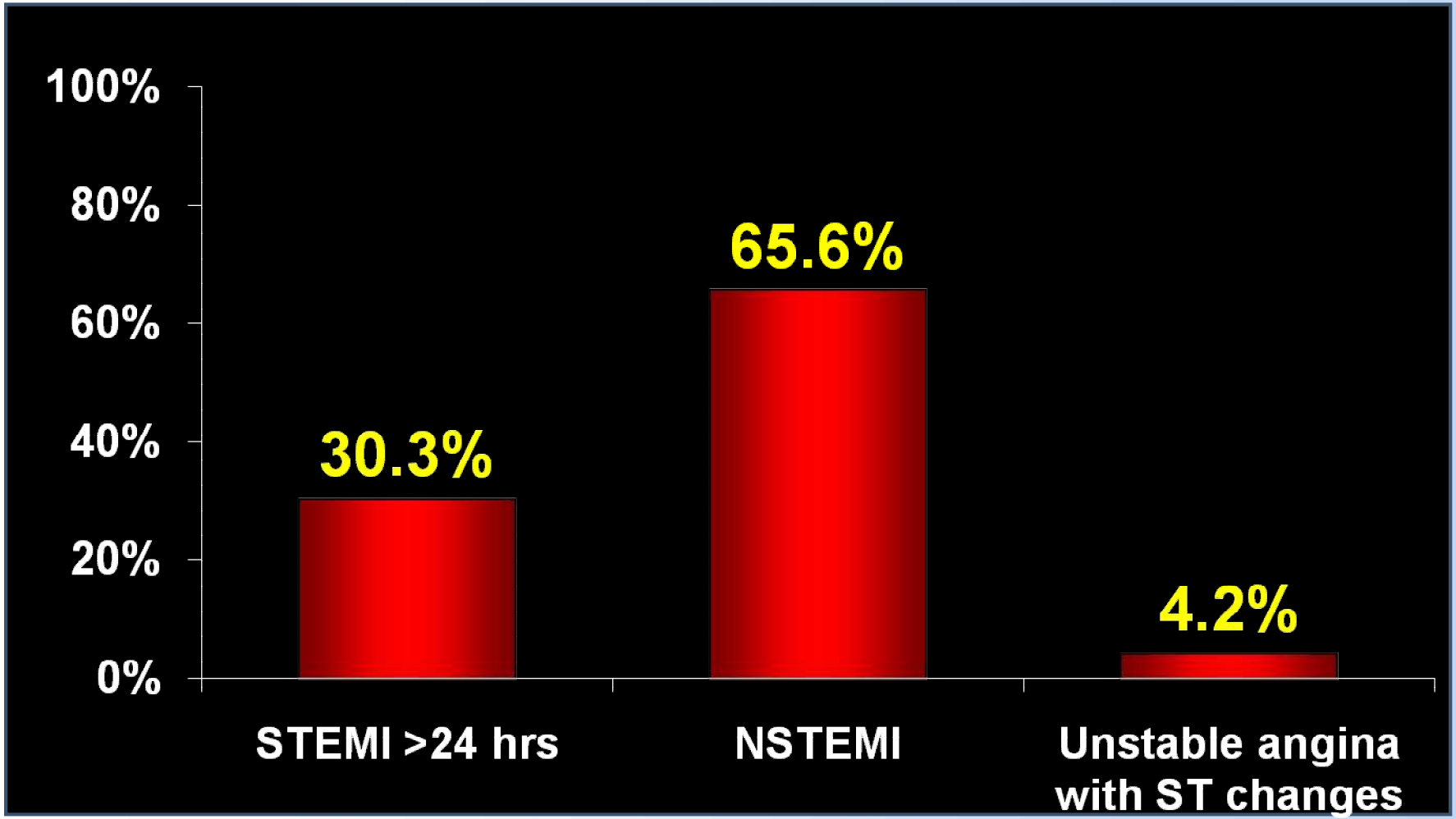


1. **Fibrotic**
2. **Fibrocalcific**
3. **Pathological intimal thickening (PIT)**
4. **Thick cap fibroatheroma (ThCFA)**
5. **VH-thin cap fibroatheroma (VH-TCFA)**
   (presumed high risk)

PROSPECT: Baseline Features

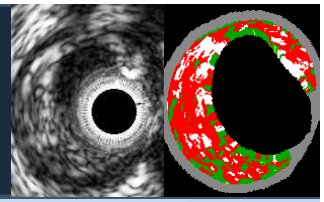


N = 697*



*3 patients who were never consented were de-registered

PROSPECT: Imaging Summary

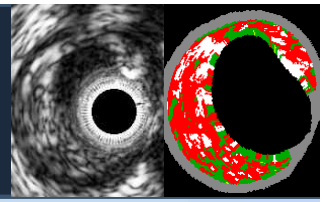


Length of coronary arteries analyzed (core lab)

Mean (mm)	Angiography (N=697)	IVUS (N=673)	VH data* (N=623)
LM	9.3 ± 4.3	12.8 ± 9.8	12.8 ± 9.7
LAD	153.5 ± 41.1	73.3 ± 34.1	73.8 ± 33.7
LCX	132.7 ± 49.9	63.3 ± 36.1	63.6 ± 36.0
RCA	148.3 ± 45.1	85.2 ± 39.6	85.5 ± 39.4
Total per pt	437.9 ± 86.4	192.0 ± 97.7	206.7 ± 85.4
Total all pts	305,228.3	129,216.8	128,757.9

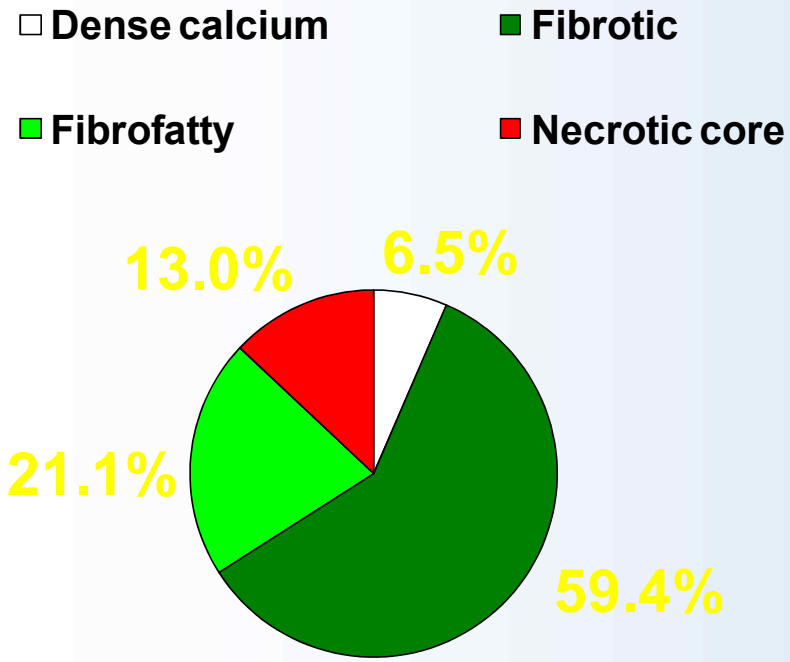
* Note: VH data doesn't register if there is no plaque

PROSPECT: Imaging Summary



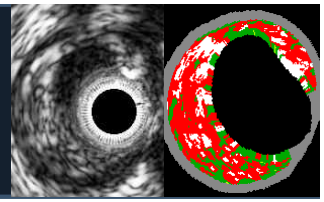
Virtual histology (N=2811 lesions in 611 pts)

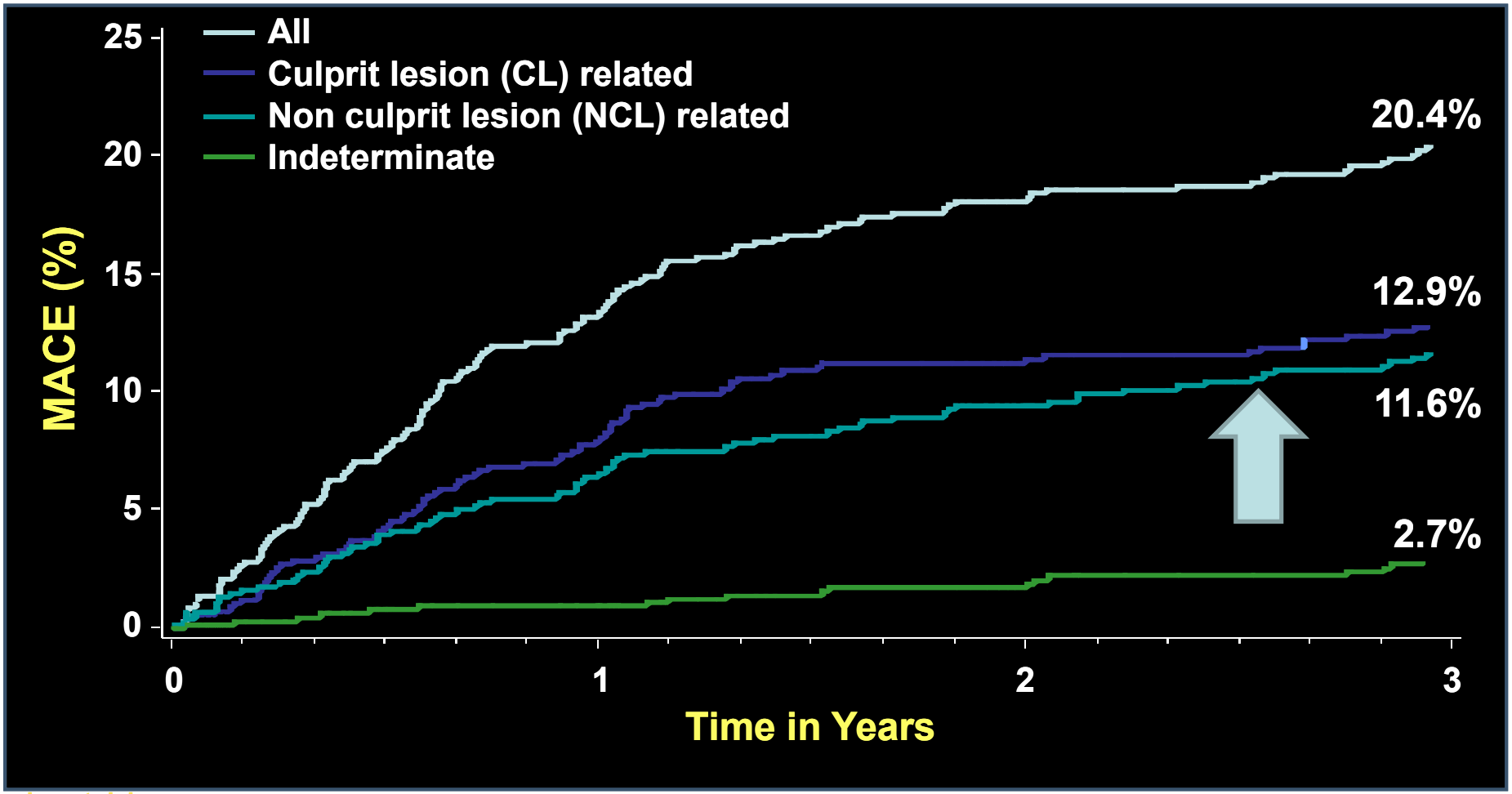
- Mean plaque composition-



Plaque subtype	N=2811
Fibrotic	2.5%
Fibrocalcific	1.2%
PIT	35.9%
Fibroatheroma	57.4%
- Thick cap	36.2%
- VH-TCFA	18.9%
- Single, - Ca	5.2%
- Single, + Ca	0.5%
- Multiple, - Ca	9.5%
- Multiple, + Ca	6.1%

PROSPECT: MACE

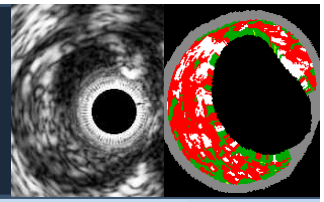




Number at risk

ALL	697	557	506	480
CL related	697	590	543	518
NCL related	697	595	553	521
Indeterminate	697	634	604	583

PROSPECT: MACE

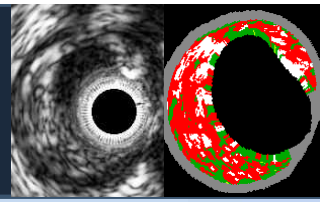


3-year follow-up, hierarchical

	All	Culprit lesion related	Non culprit lesion related	Indeter-minate
Cardiac death	1.9% (12)	0.2% (1)	0% (0)	1.7% (11)
Cardiac arrest	0.3% (2)	0.3% (2)	0% (0)	0% (0)
MI (STEMI or NSTEMI)	2.7% (17)	1.7% (11)	1.0% (6)	0.2% (1)
Rehospitalization for unstable or progressive angina	15.4% (101)	10.4% (69)	10.7% (68)	0.8% (5)
Composite MACE	20.4% (132)	12.9% (83)	11.6% (74)	2.7% (17)

Rates are 3-yr Kaplan-Meier estimates (n of events)

PROSPECT: Correlates of Non Culprit Related Events



Baseline variables examined (n=152)

Demographic, history and PE (n=19)

Labs (n=7; including CrCl, lipids, hgbA1C, CRP)

Angio non core lab (n=1; visible lesions >30% DS)

QCA measures (n=12)

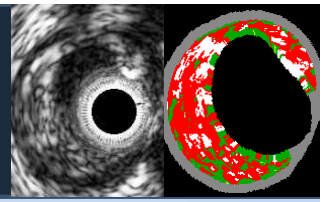
IVUS area and volumetric measures (n=22)

Virtual histology measures (n=74)

Treatment related (n=1; # vessels stented)

Medications in-hosp. and at discharge (n=16)

PROSPECT: Multivariable Correlates of Non Culprit Lesion Related Events

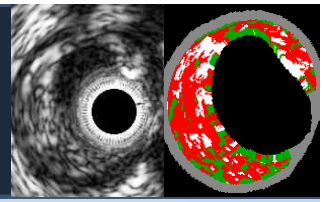


Independent predictors of patient level events by Cox Proportional Hazards regression

Variable	HR [95% CI]	P value
Insulin dependent diabetes	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

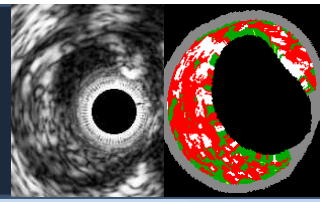


Independent predictors of lesion level events by Cox Proportional Hazards regression

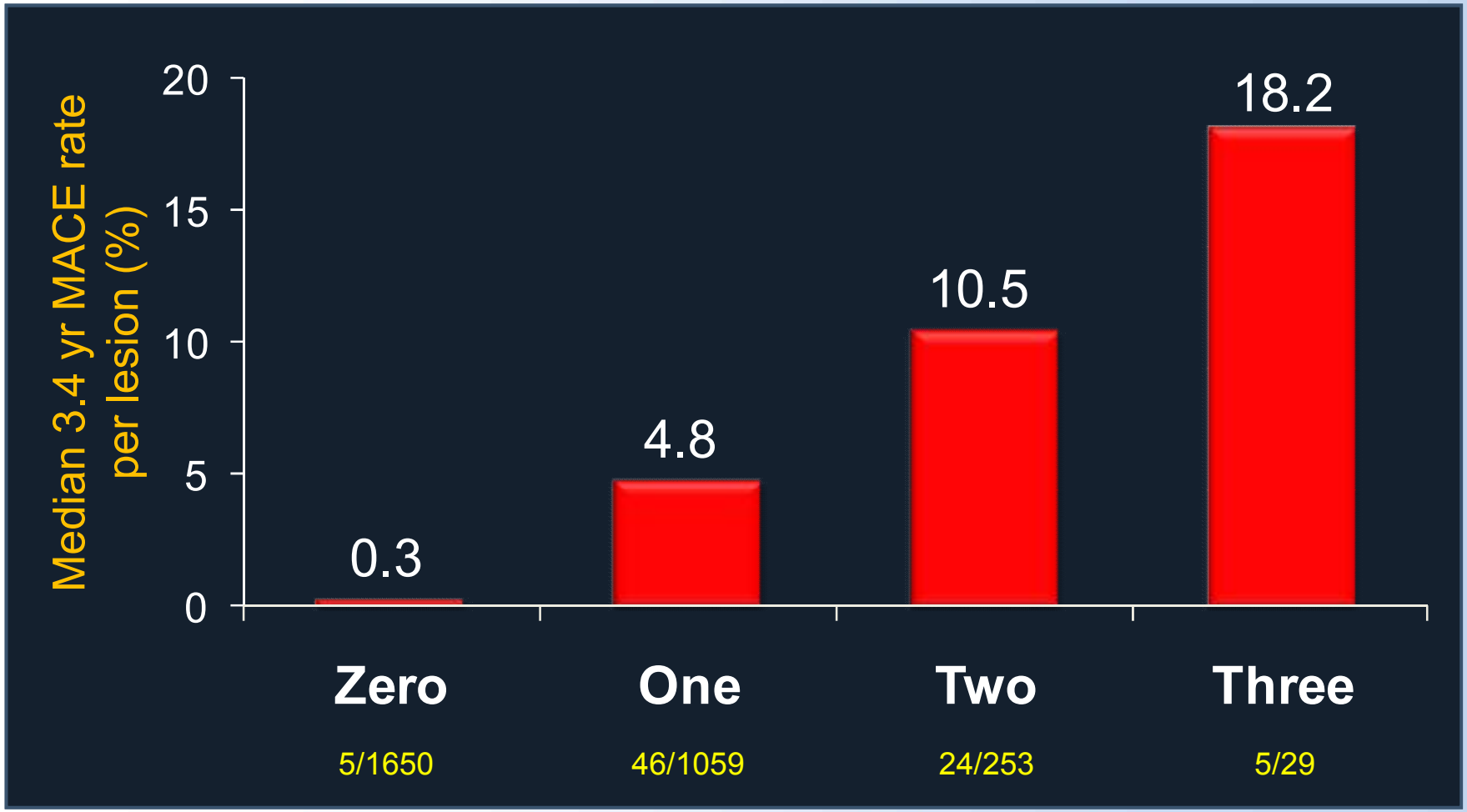
Variable	HR [95% CI]	P value
PB_{MLA} ≥70%	5.03 [2.51, 10.11]	<0.0001
VH-TCFA	3.35 [1.77, 6.36]	0.0002
MLA ≤4.0 mm^2	3.21 [1.61, 6.42]	0.001

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.

PROSPECT: Correlates of Non Culprit Lesion Related Events

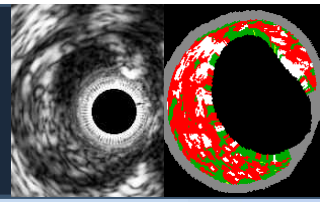


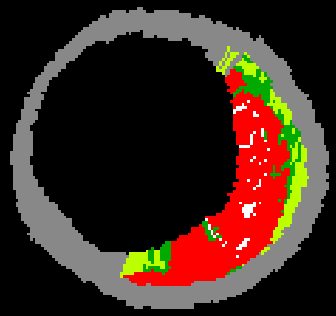
Number of factors present: PB_{MLA} ≥70%, MLA ≤4.0mm^2 or TCFA



PB = plaque burden at the MLA

PROSPECT: VH-TCFA and Non Culprit Lesion Related Events

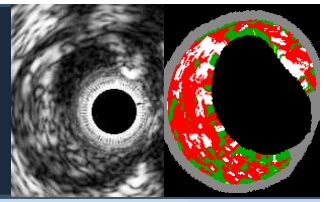


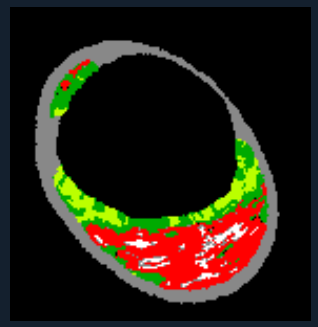


	TCFA	TCFA + MLA ≤4.0mm2	TCFA + PB ≥70%	TCFA + PB ≥70% + MLA ≤4mm2
Lesion HR	3.90 (2.25, 6.76)	6.55 (3.43, 12.51)	10.83 (5.55, 21.10)	11.05 (4.39, 27.82)
P value	<0.0001	<0.0001	<0.0001	<0.0001
Prevalence*	46.7%	15.9%	10.1%	4.2%

*Likelihood of one or more such lesions being present per patient. PB = plaque burden at the MLA

PROSPECT: Thick CFA and Non Culprit Lesion Related Events

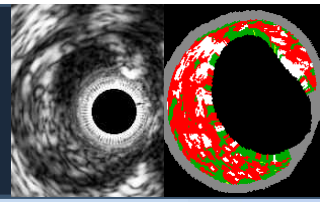


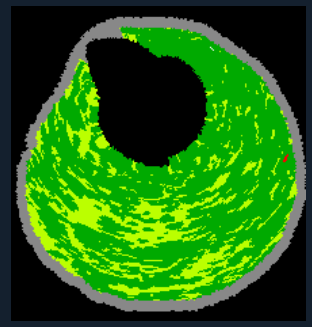


	ThCFA	ThCFA + MLA ≤4.0mm2	ThCFA + PB ≥70%	ThCFA + PB ≥70% + MLA ≤4mm2
Lesion HR	0.92 (0.52, 1.63)	3.41 (1.75, 6.65)	5.17 (2.59, 10.32)	5.02 (1.99, 12.63)
P value	0.77	0.0003	<0.0001	<0.0001
Prevalence*	67.6%	22.7%	15.6%	8.3%

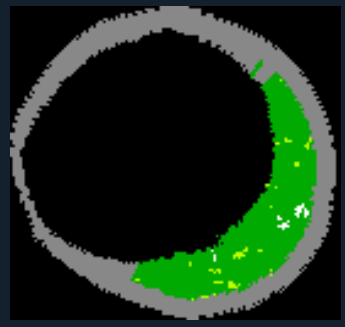
*Likelihood of one or more such lesions being present per patient. PB = plaque burden at the MLA

PROSPECT: Non Fibroatheromas and Non Culprit Lesion Events

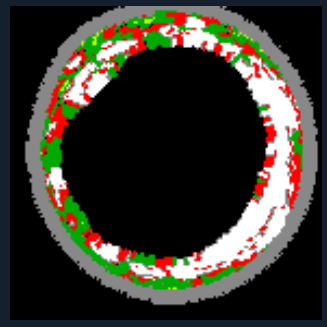




Pathological Intimal thickening



Fibrotic

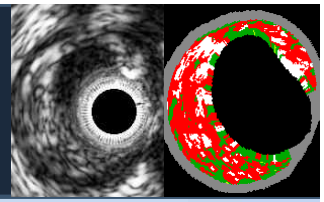


Fibrocalcific

	Non FA (all)	Non FA + MLA ≤4.0mm2	Non FA + PB ≥70%	Non FA + PB ≥70% + MLA ≤4mm2
Lesion HR	0.22 (0.10, 0.49)	1.22 (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%

*Likelihood of one or more such lesions being present per patient. PB = plaque burden at the MLA

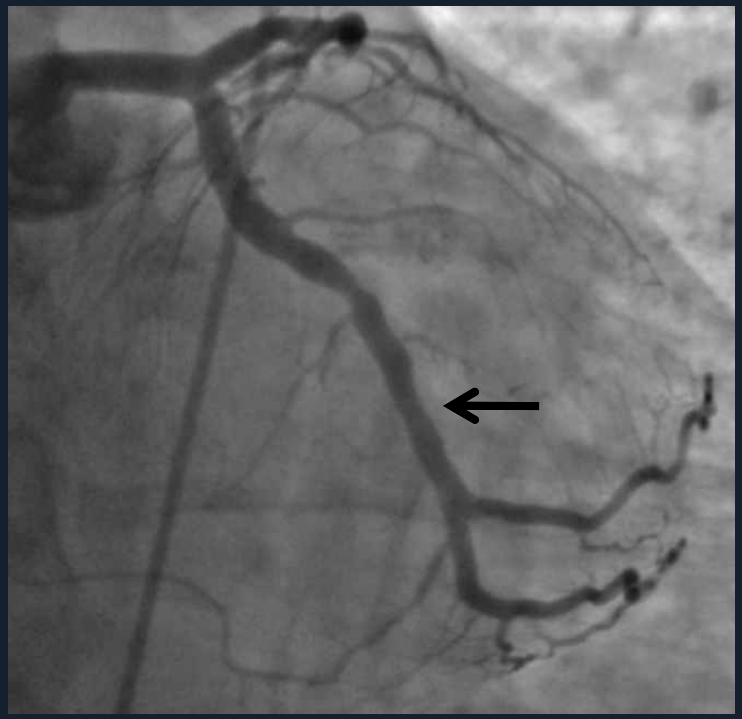
PROSPECT 82910-012: 52 yo♂



2/13/06: NSTEMI, PCI of MLAD

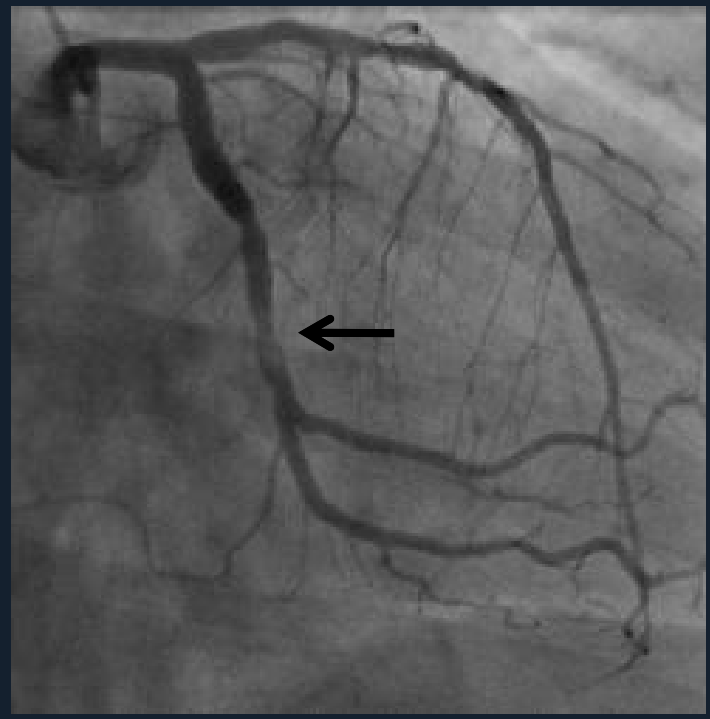
2/6/07 (51 weeks later): NSTEMI attributed to LCX

Index 2/13/06



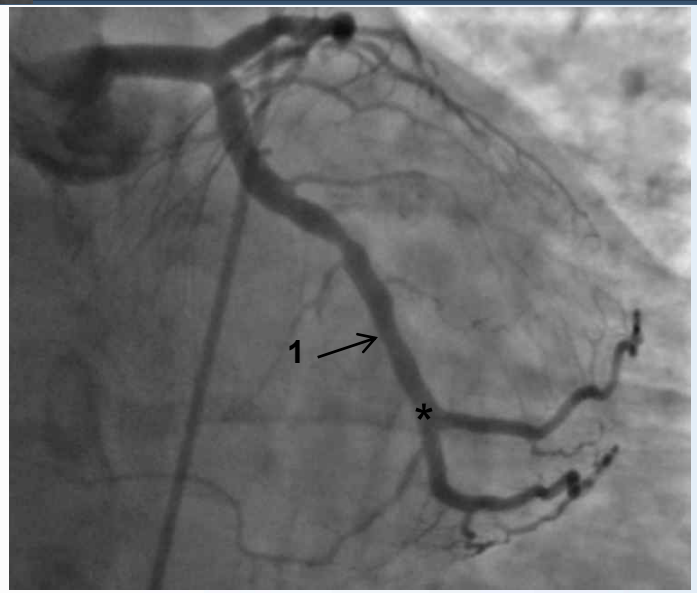
QCA PLCX DS 28.6%

Event 2/6/07



QCA PLCX DS 71.3%

PROSPECT 82910-012: Index 2/13/06



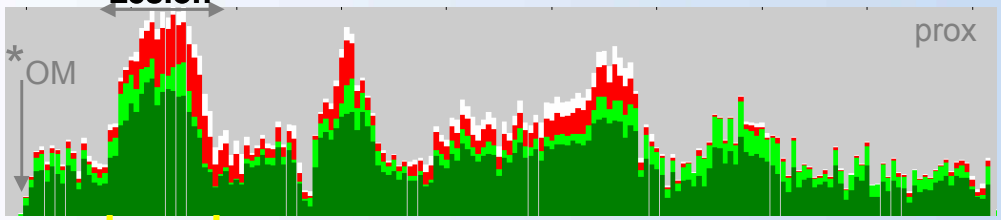
Baseline PLCX

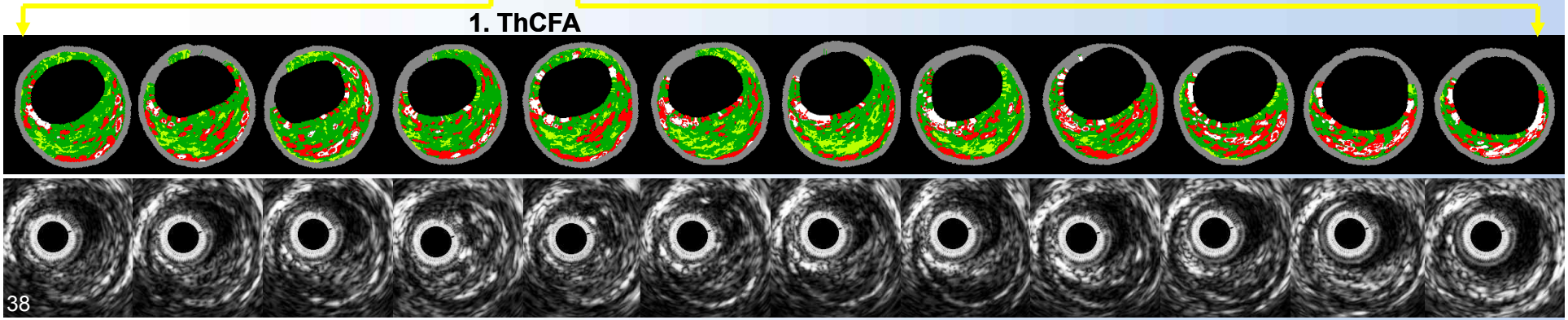
QCA: RVD 2.82 mm,

DS 28.6%, length 6.8 mm

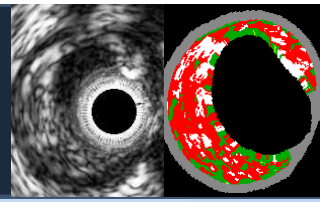
IVUS: MLA 5.3 mm²

VH: ThCFA

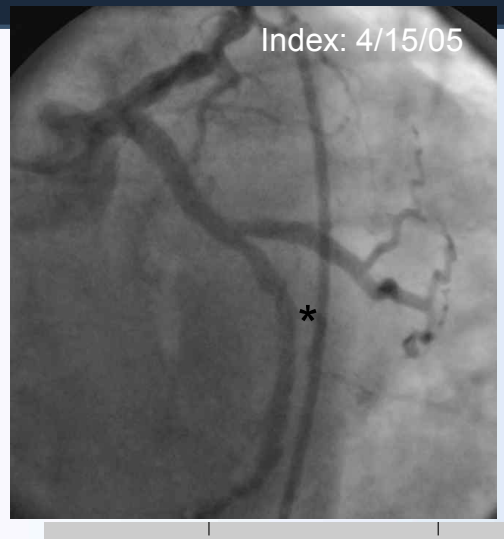


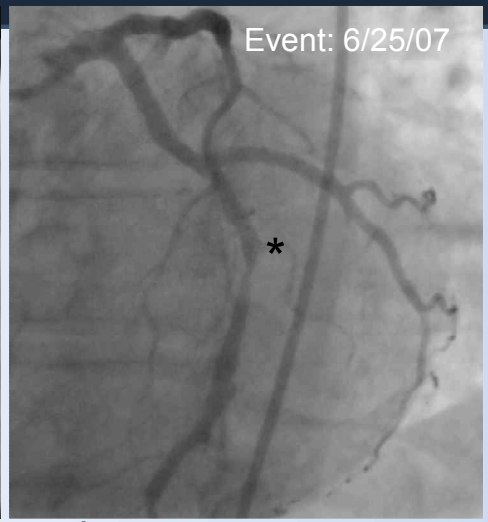


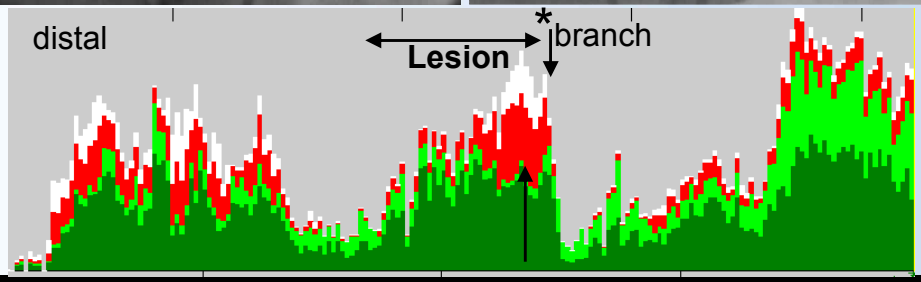
27662-003 CASS22

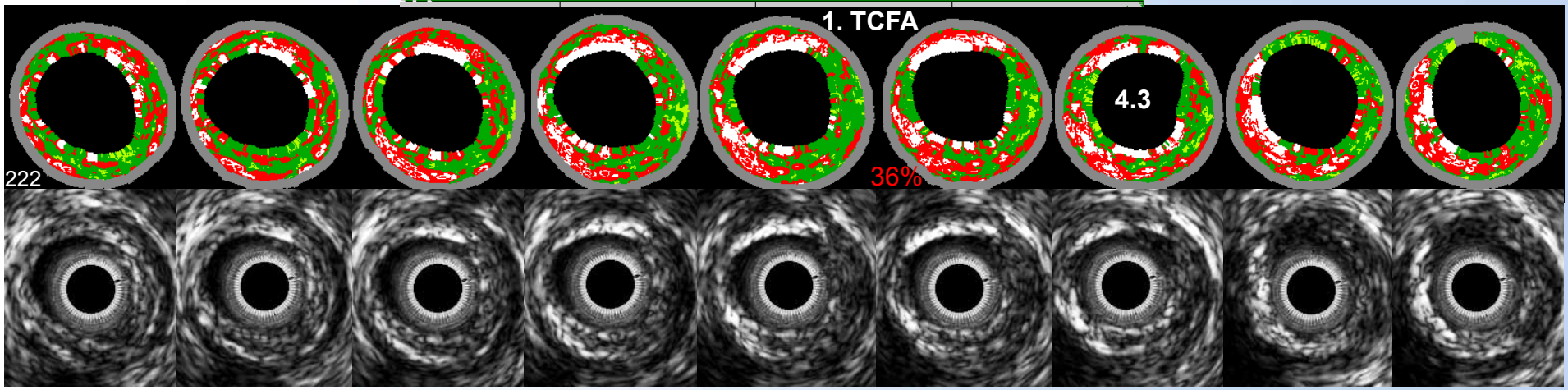


Lesion: TCFA
Culprit sub-lesion: TCFA



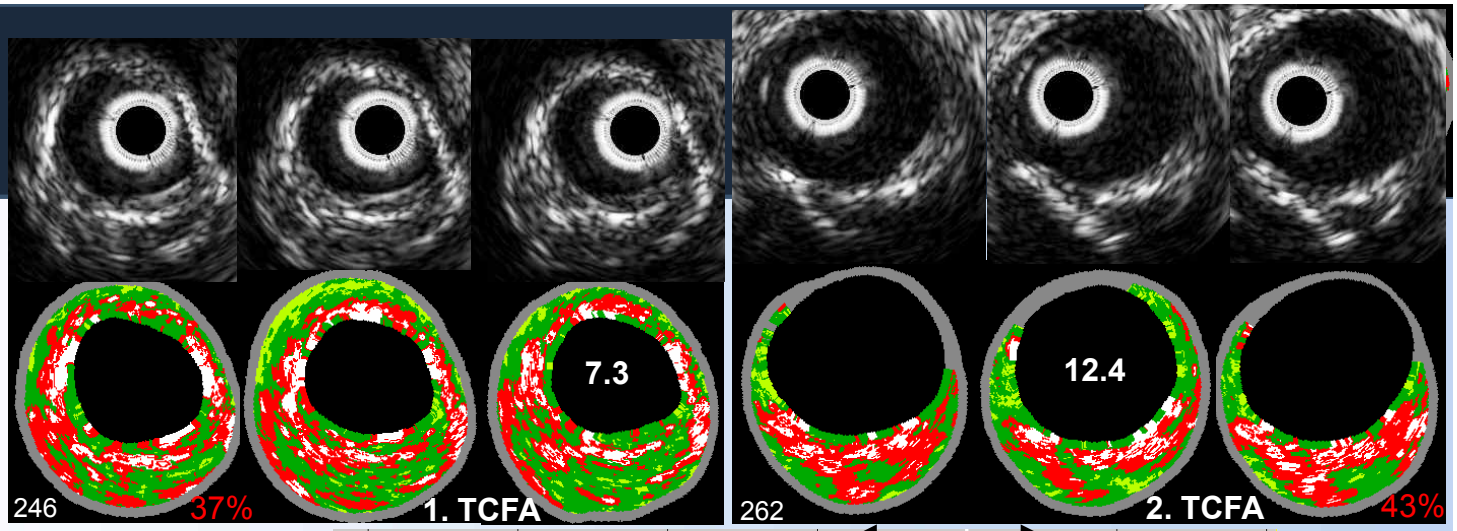


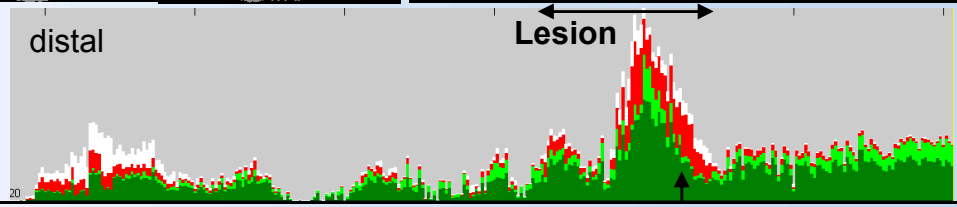


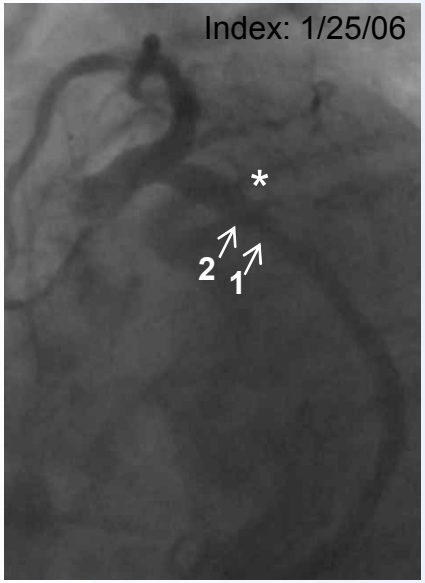


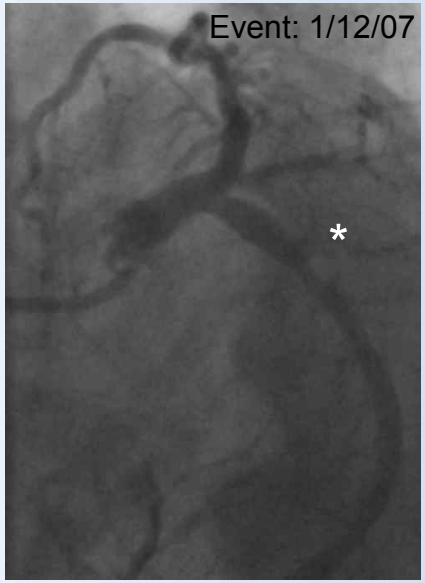
28930-031
CASS18

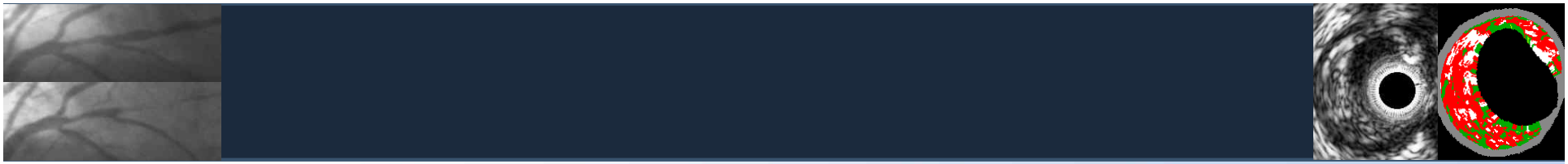
Lesion: TCFA
Culprit sub-lesion: TCFA





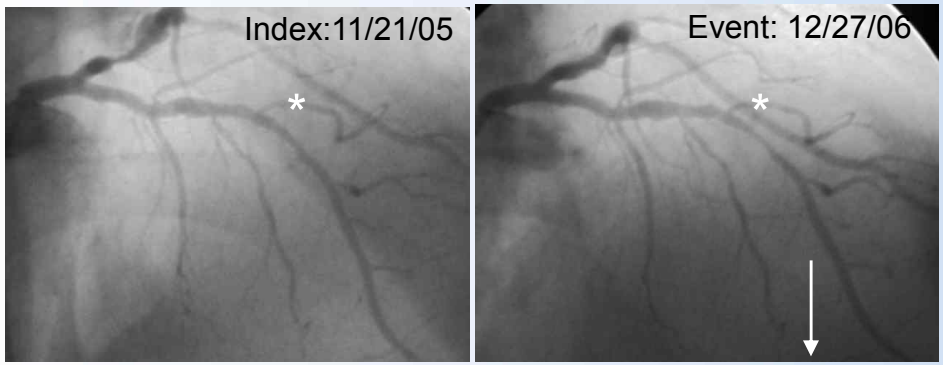


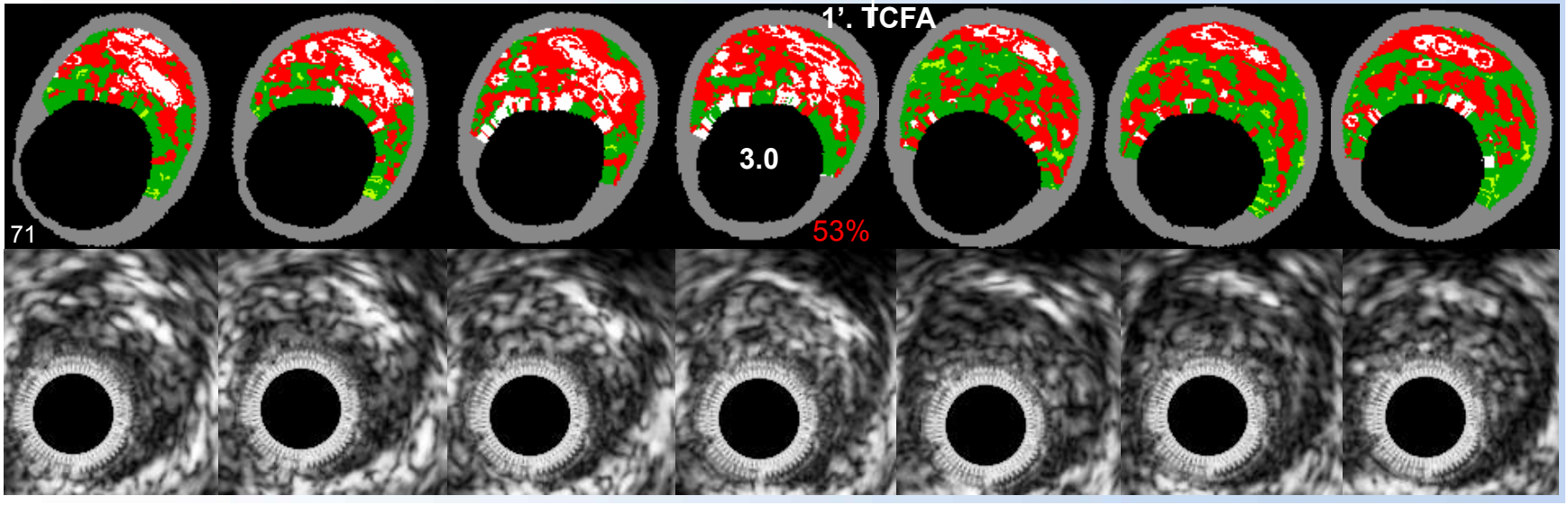




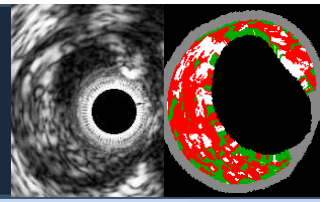
32674-016
CASS 13

Lesion:CaThCFA/
Echolucent
Plaque





PROSPECT: Conclusions

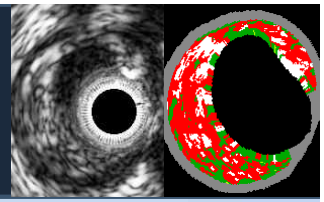


Approximately 20% of pts with ACS successfully treated with stents and contemporary medical Rx develop MACE within 3 years, with adverse events equally attributable to recurrence at originally treated culprit lesions (treatment failure) and to previously untreated non culprit coronary segments

Approximately 12% of pts develop MACE from non culprit lesions during 3 years of follow-up

Patients treated with contemporary medical therapy who develop non culprit lesion events present most commonly with progressive or unstable angina, and rarely with cardiac death, cardiac arrest or MI

PROSPECT: Conclusions



- While plaques which are responsible for unanticipated future MACE are frequently angiographically mild, most untreated plaques which become symptomatic have a large plaque burden and a small lumen area (which are detectable by IVUS but not by angiography)
- The prospective identification of non culprit lesions prone to develop MACE within 3 years can be enhanced by characterization of underlying plaque morphology with virtual histology, with VH-TCFAs representing the highest risk lesion type
- The combination of large plaque burden (IVUS) and a large necrotic core without a visible cap (VH-TCFA) identifies lesions which are at especially high risk for future adverse cardiovascular events

Summary

- Six years and >150 publications later, the predictions we made here are proving to be accurate.
- VH can identify culprit lesions and even predict plaques that are likely to rupture in the future.
- Suppositions regarding the natural history of vulnerable plaque, that had been formed on the basis of postmortem data have now been demonstrated *in vivo*.
- With our new understanding of *in vivo* histology, we are able to plan and perform PCI in a more intelligent way with the hope of significantly reducing MACE events in the future.