5TH JMC - Joint Meeting with Mayo Clinic

15TH—16TH OCTOBER 2009 TURIN, ITALY

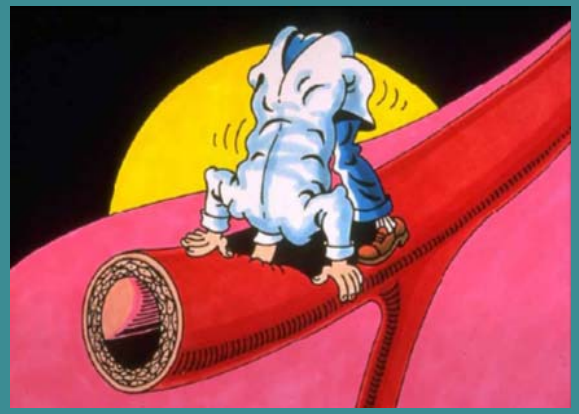
The role of IVUS in the detection and treatment of vulnerable plaque

Dott. Massimo Fineschi

U.O. Emodinamica

Azienda Ospedaliera-Universitaria Senese

Siena



BACKGROUND

- Rupture of vulnerable plaque is the main cause of ACS and AMI. Identification of these vulnerable plaque is therefore essential to enable the development of treatment modalities to stabilize them.

BACKGROUND

- The pathologic features of plaque prone to ropture are positively remodelled vessel,including a large necrotic core,a thin fibrous cap (<65μm), and macrophage infiltration into the cap.This entity is usually known as thin-cap fibroatheroma (TCFA).

LESION VS LUMEN: I LIMITI DELLA CORONAROGRAFIA

- Ambrose et al reported that minor to moderate luminal irregularities with an irregular ulcerative contour were the most prominent angiographic finding predictive of subsequent occlusion.

- However ,elucidation of the precise morphology of the ATS plaque associated with ACS has remained difficult,because angiography provides only a silhouette of the vessel lumen,not precise intramural plaque morphology.

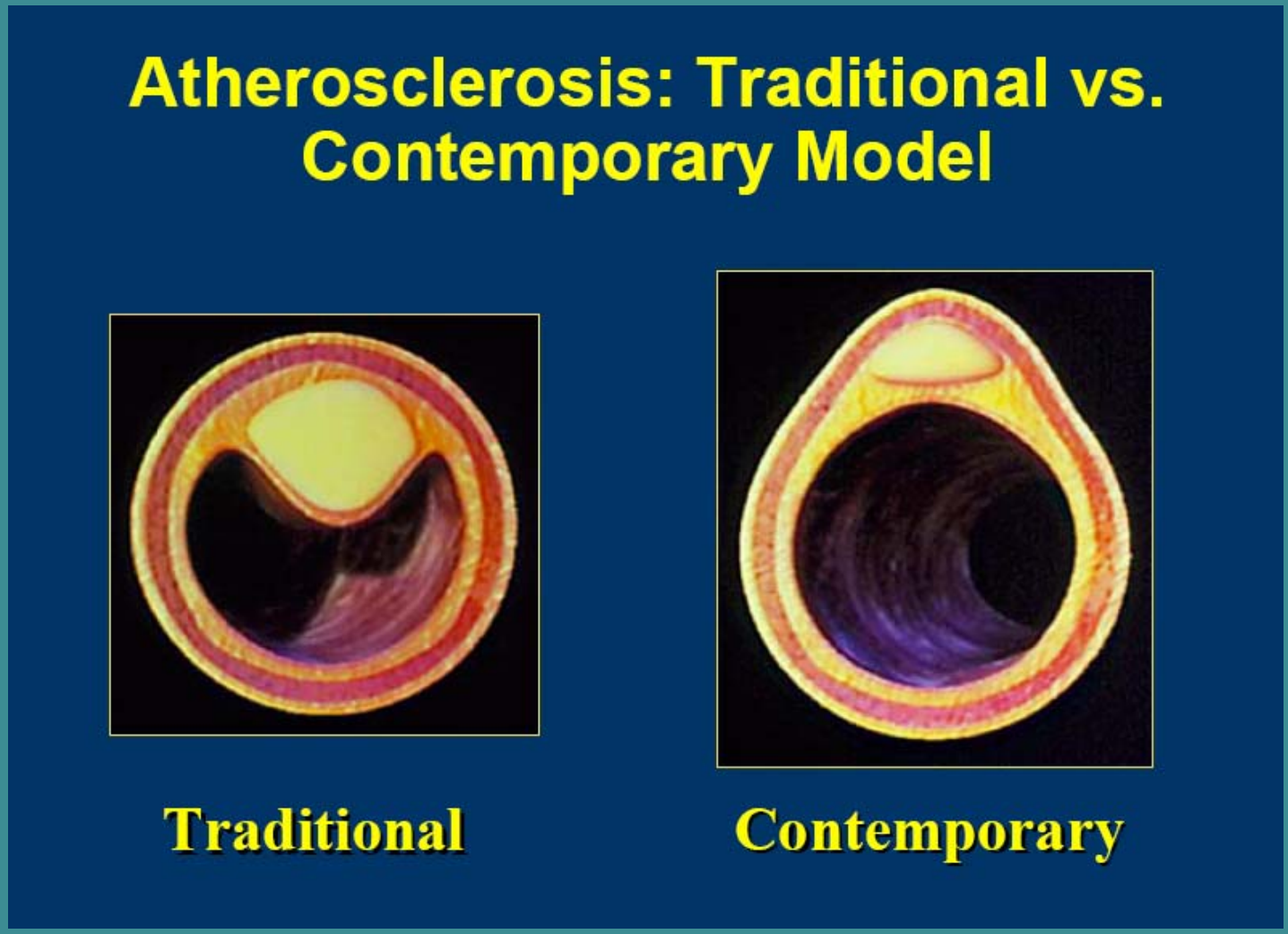
TABLE I. Comparison of Catheter-Based Techniques for Detection of Individual Features of Vulnerable Plaque

Technique	Thin-cap detection	Inflammation	Lipid core	Remodeling
Intravascular ultrasounds	+	–	+	+++
Echogenecity	–	–	+	–
Palpography	++	++	+	–
Virtual histology	++	–	+++	+++
Optical coherence tomography	+++	+	+	–
Thermography	–	+++	–	–
Angioscopy	–	–	++	–
Intravascular MRI	–	–	++	–
Spectroscopy	–	++	++	–

IVUS: *lesion vs lumen*

- ***Positive remodelling***
- ***Plaque burden***
- ***Large lipid necrotic core***
- ***Thin cap***
- ***Inflammation***

POSITIVE REMODELING: A LESION EEM GREATER THAN THE REFERENCE (lesion EEM area/reference EEM area>1)



-THE CORONARY LUMEN IS USUALLY PRESERVED UNTIL THE PLAQUE INVOLVEMENT REACHES ABOUT 40% OF VESSEL CIRCUMFERENCE.

-POSITIVE REMODELING IS ASSOCIATED WITH GREATER LIPIDIC CORE AND WITH THIN FIBROUS CAP.

ELSEVIER

Atherosclerosis 202 (2009) 476–482

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

Impact of vascular remodeling on the coronary plaque compositions: An investigation with in vivo tissue characterization using integrated backscatter-intravascular ultrasound

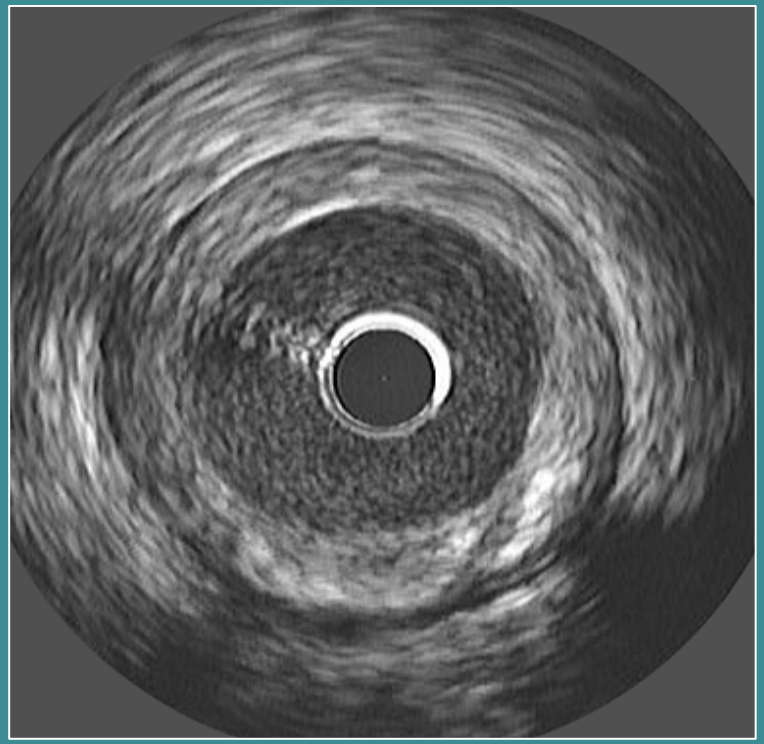
Hiroki Takeuchi, Yoshihiro Morino *, Takashi Matsukage, Naoki Masuda, Yota Kawamura, Satoshi Kasai, Tadashi Hashida, Daisuke Fujibayashi, Teruhisa Tanabe, Yuji Ikari

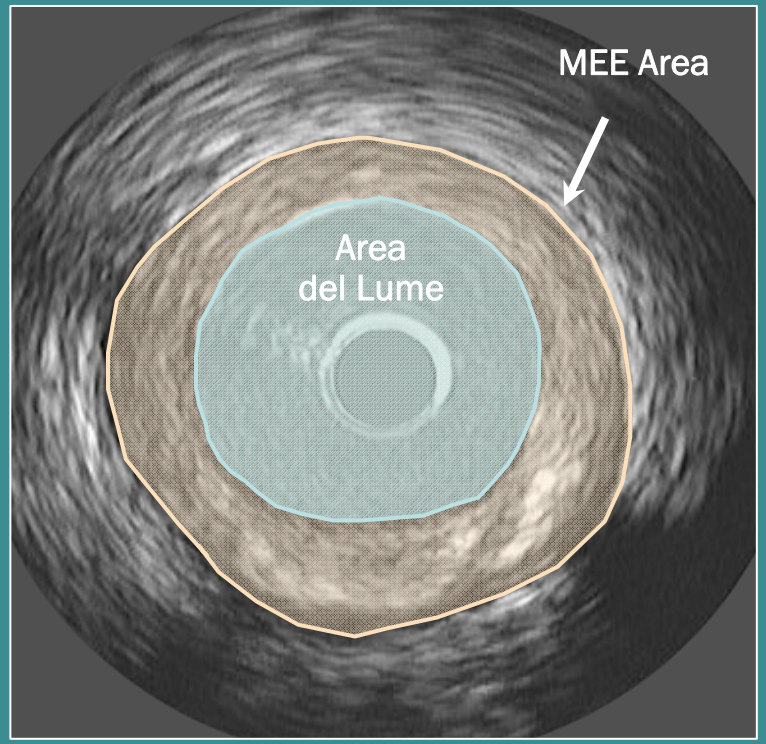
Importantly, our study showed that PR lesions had a greater content of lipid and lower content of hard plaque tissue component, consistent with previous pathological studies and clinical experiences [3,12,21], which explain the potential mechanism behind the high incidence of ACS seen in the PR lesion. In contr

pattern and medication usage in this study, several previous studies had indicated that some pharmacological intervention might affect the patterns of remodeling and changes in plaque compositions, including angiotensin-converting enzyme inhibitors and statins [22,23].

Determinazione dell'area dell'ateroma mediante IVUS

Plaque burden



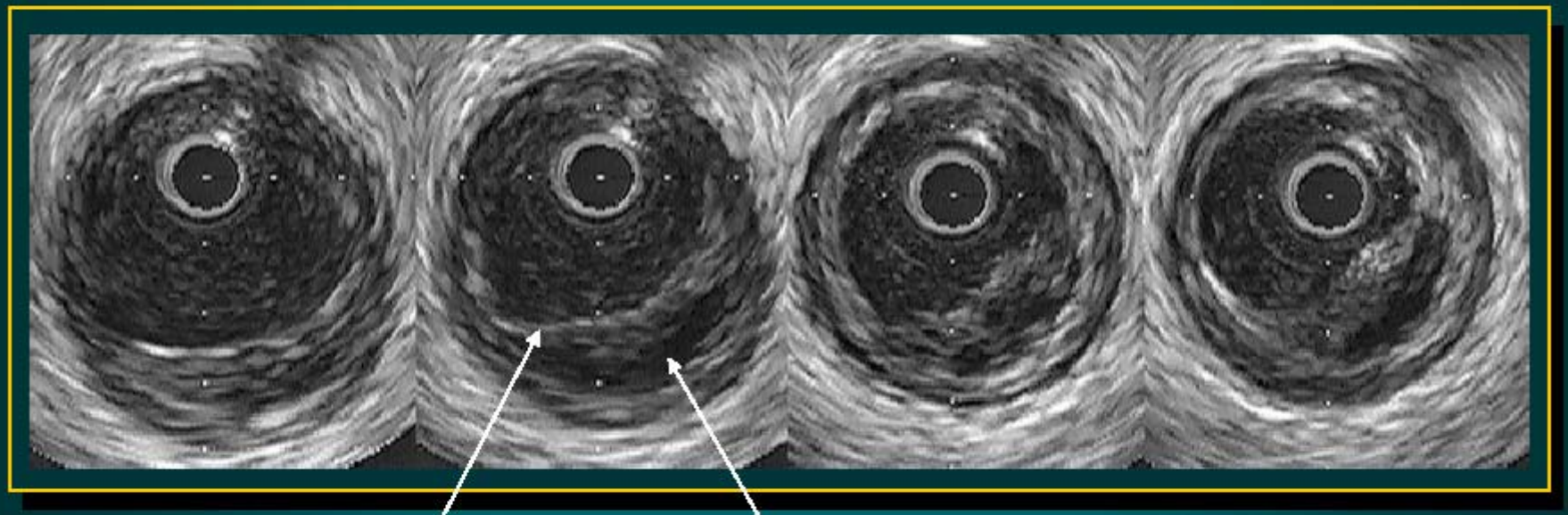


MEE=Membrana Elastica Esterna

(MEE Area – Area del Lume)=area ateroma

LIPID CORE

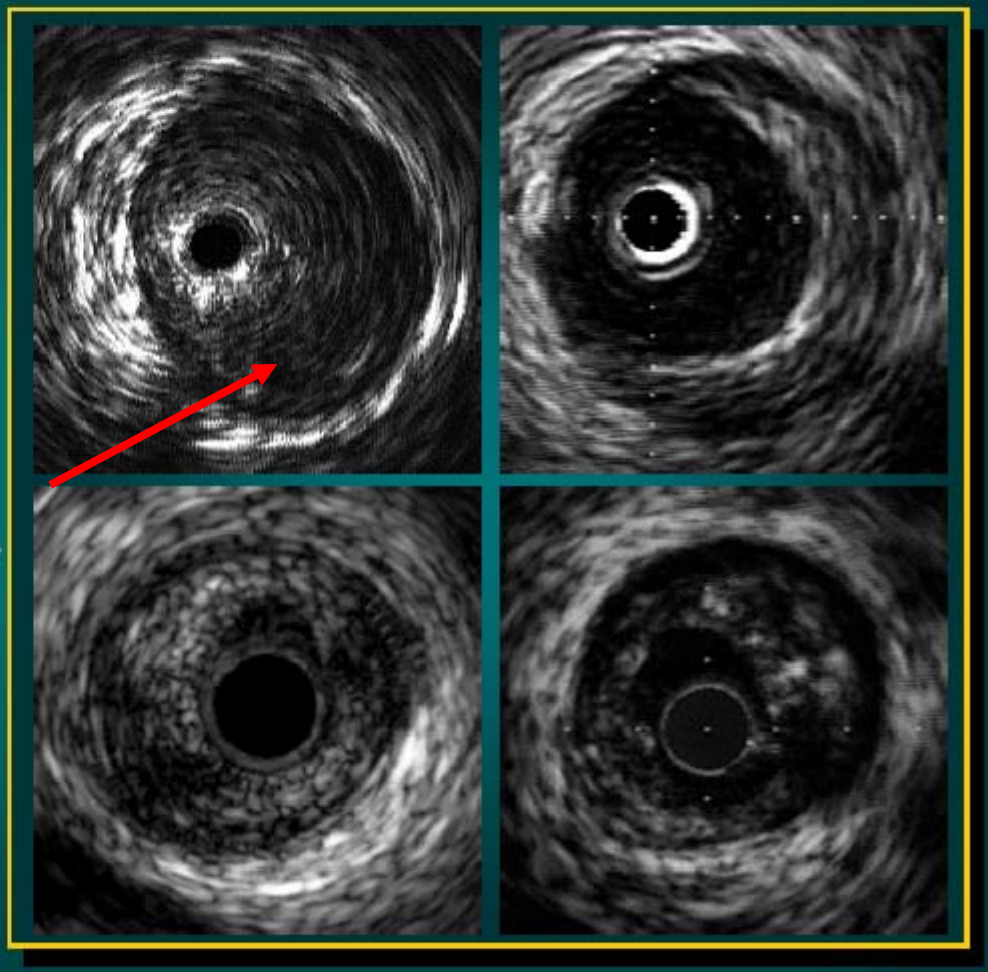
Vulnerable Plaque



ECHOLUCENT ZONE CLOSE TO THE LUMINAL SURFACE:
"SHALLOW SURFACE"

Soft Plaque

- Not as bright as the adventitia (hypoechoic)
- "Soft" refers to the low echogenicity, generally due to high lipid content in a mostly cellular lesion.
- Reduced echodensity may also be due to:
  - necrotic zone within plaque
  - intramural hemorrhage
  - thrombus



EuroIntervention

In vivo characterisation of coronary plaques with conventional grey-scale intravascular ultrasound: correlation with optical coherence tomography

Adrian F. Low[1], MBBS; Yoshiaki Kawase[1], MD; Yiong-Huak Chan[2], PhD; Guillermo J. Tearney[3], MD, PhD; Brett E. Bouma[3], PhD; Ik-Kyung Jang[1]*, MD, PhD.

1. Cardiology Division, Massachusetts General Hospital, Boston, MA, USA; 2. Biostatistics Unit, National University of Singapore, Singapore; 3. Department of Pathology, Wellman Center for Photomedicine, Massachusetts General Hospital, MA, USA

IDENTIFICATION OF LIPID POOLS
IVUS vs OCT

IVUS consistently under-reported lipid content when compared to OCT

SENSITIVITY 24.1%
SPECIFICITY 93.9%

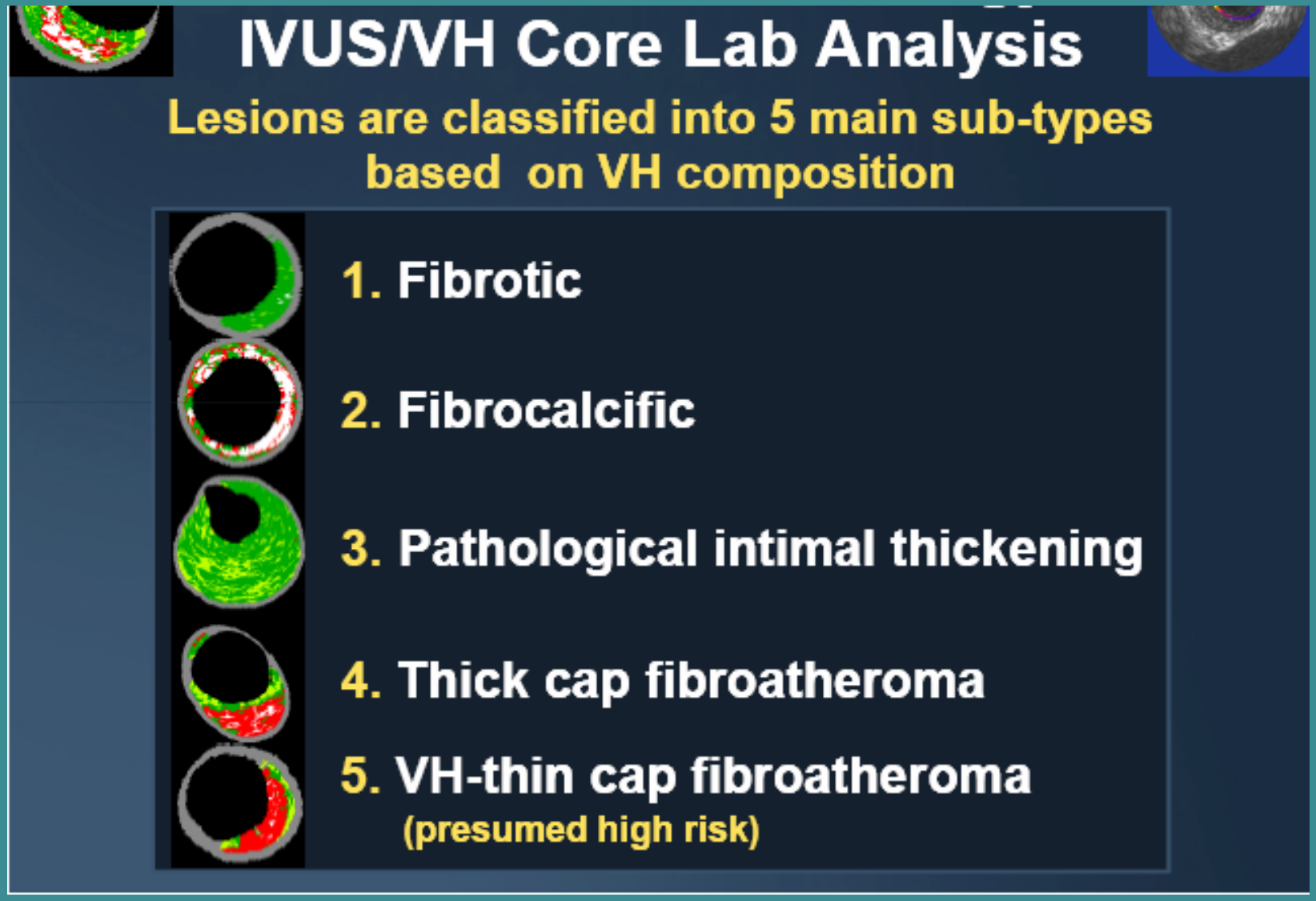
Abstract

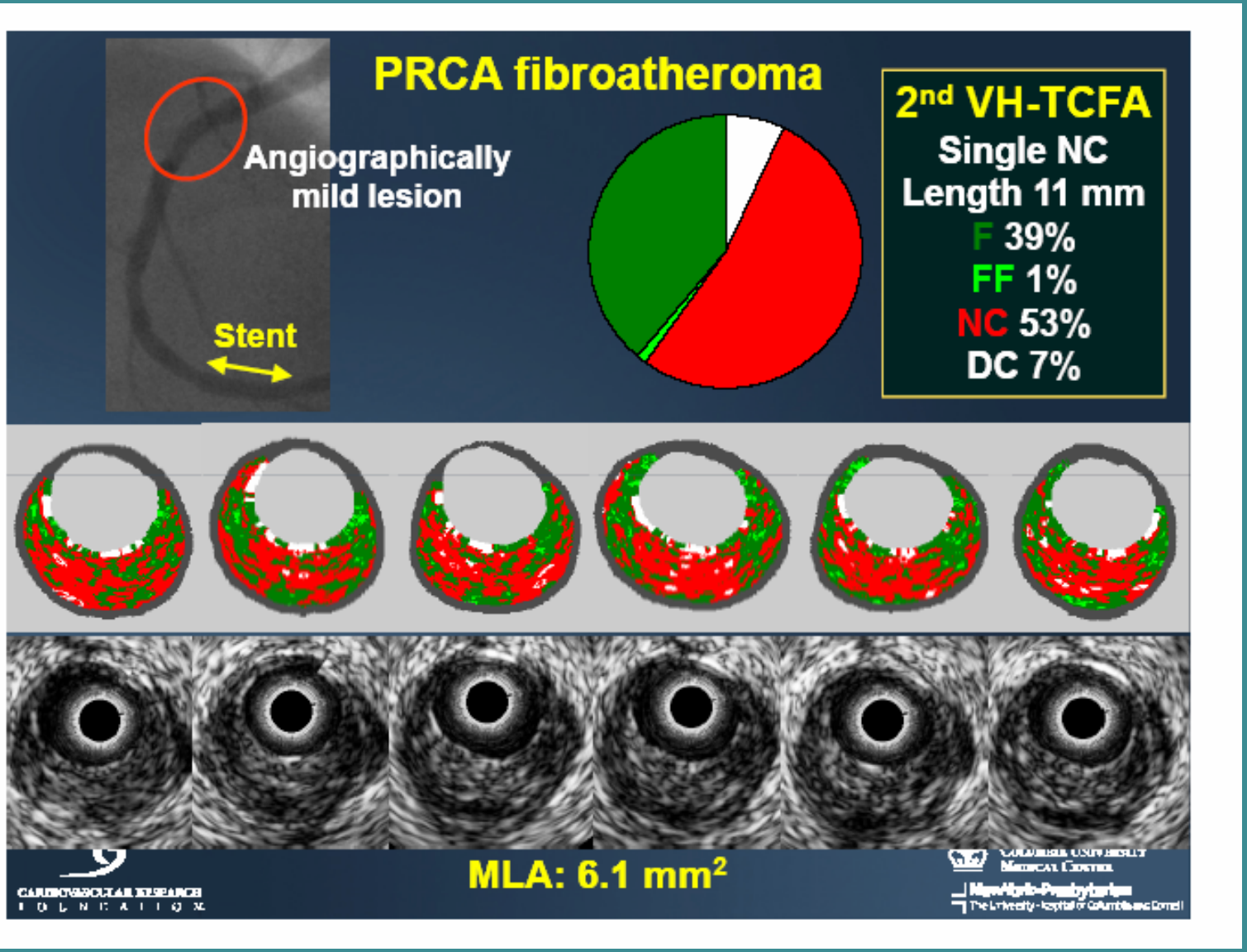
Aims: Although intravascular ultrasound (IVUS) is widely used, there is limited published data on its accuracy in defining plaque characteristics *in vivo*. Optical coherence tomography (OCT) is a high-resolution imaging technique that takes advantage of the pronounced optical contrast between the components of normal and diseased vessels. The aim of this study was to evaluate the ability of conventional grey-scale IVUS in identifying *in vivo* coronary plaque characteristics, in particular lipid content as a marker of the vulnerable plaque, when compared to OCT.

Methods and results: In patients undergoing cardiac catheterisation, IVUS and OCT imaging was performed. Detailed qualitative analysis of lipid-rich plaque, calcific plaque, and plaque disruption were performed at corresponding sites using both modalities. A total of 146 matched sites were available for analysis. When compared to OCT, sensitivity of IVUS for identification of lipid pools was low (24.1%) but specificity was high (93.9%). The sensitivity and specificity of IVUS for detection of calcific plaque and plaque disruption were respectively 92.9%; 66.4%, and 66.7%; 96.1%.

Conclusions: Conventional grey-scale IVUS may not be a reliable imaging modality for detection of lipid-rich and hence vulnerable plaques. This has important implications in using conventional grey-scale IVUS to identify the vulnerable plaque.

IVUS-VH offers an in vivo opportunity to assess plaque morphology and histology





Rimodellamento positivo con lume conservato,NC e TCFA

How common are vulnerable plaques?

Are vulnerable plaque locations predictable?

When vulnerable plaques rupture, do they always cause events?

Multiple Atherosclerotic Plaque Rupture in Acute Coronary Syndrome

A Three-Vessel Intravascular Ultrasound Study

G. Rioufol, MD, PhD; G. Finet, MD, PhD; I. Ginon, MD; X. André-Fouët, MD; R. Rossi, MD; E. Vialle, MD; E. Desjoyaux, MD; G. Convert, MD; J.F. Huret, MD; A. Tabib, MD, PhD

Background—To test the hypothesis of general atherosclerotic plaque destabilization during acute coronary syndrome (ACS), the present study sought to analyze the 3 coronary arteries by systematic intravascular ultrasound scan (IVUS).

Methods and Results—Seventy-two arteries were explored in 24 patients referred for percutaneous coronary intervention after a first ACS with troponin I elevation. Fifty plaque ruptures (mean, 2.08 per patient; range, 0 to 6) were diagnosed by the association of a ruptured capsule with intraplaque cavity. Plaque rupture on the culprit lesion was found in 9 patients (37.5%). At least 1 plaque rupture was found somewhere other than on the culprit lesion in 19 patients (79%). These lesions were in a different artery than the culprit artery in 70.8% and were in both other arteries in 12.5% of these 24 patients. Complete IVUS examination of all 3 coronary

that multiple atherosclerotic plaque ruptures were detecte

neously with the culprit lesion; they were frequent and loc

trunks; and the multiple plaque ruptures in locations other

less calcified.

Conclusion—Although one single lesion is clinically activ

associated with overall coronary instability. (*Circulation.*

. (*Circulation*. 2002;106:804-808.)

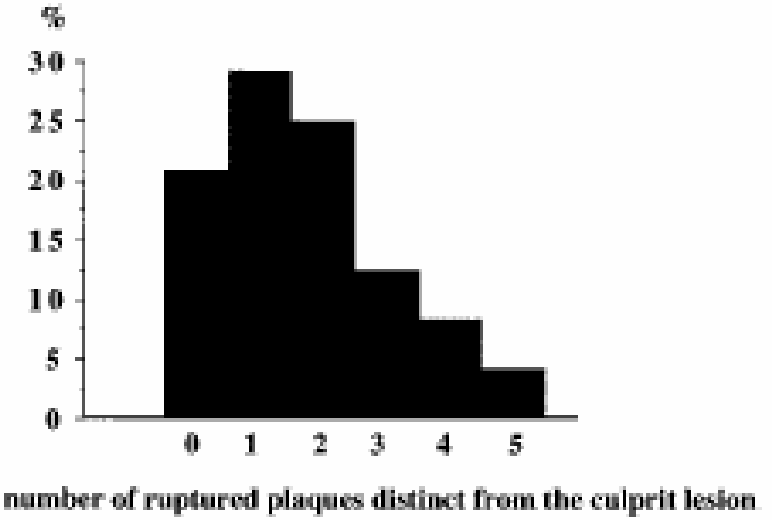
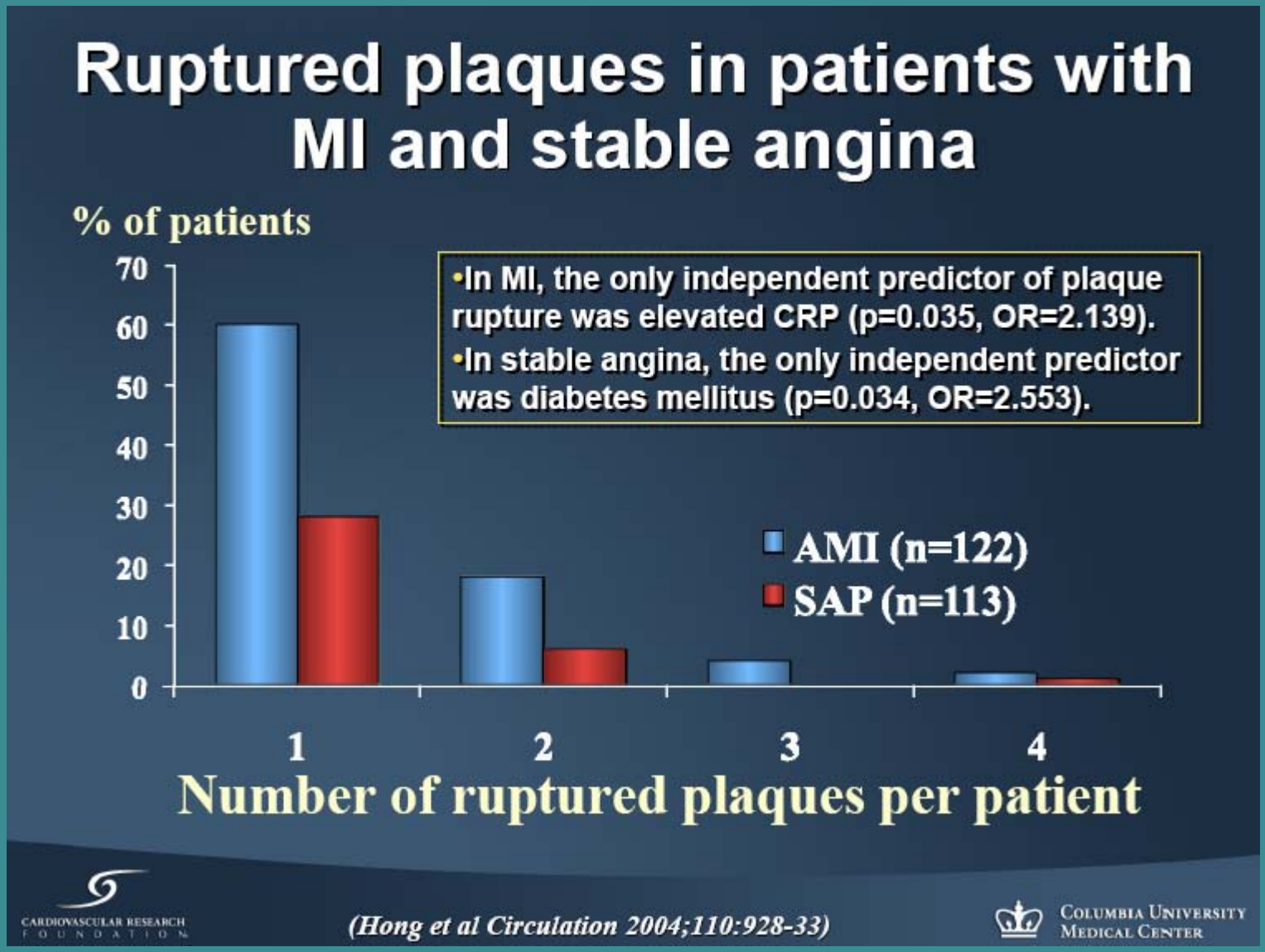


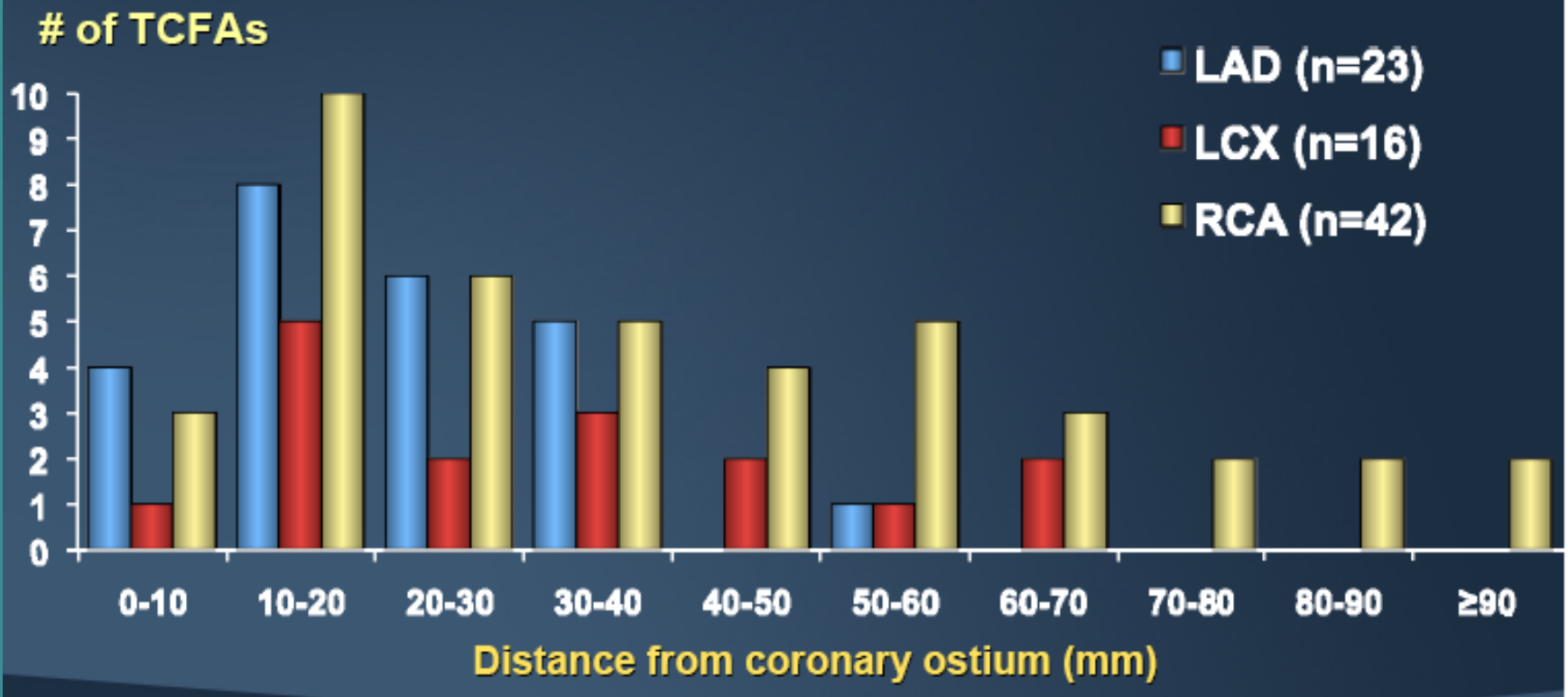
Figure 1. Percentage distribution of coronary atherosclerotic plaque ruptures other than the culprit lesion. In 79% of cases, at least 1 such plaque rupture was found.



multiple plaque rupture in 20% of AMI

Location of 82 TCFAs in 34 patients with AMI and 17 patients with stable angina and three vessel OCT:

Vulnerable plaques tend to cluster in predictable "hot spots" within the proximal segments of the LAD and LCX and the entire length of the RCA



CARDIOVASCULAR RESEARCH FOUNDATION

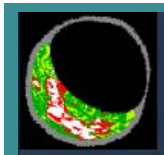
(Fujii et al AHA 2007)

COLUMBIA UNIVERSITY MEDICAL CENTER

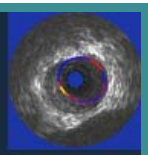
Linking Plaque Composition to Events: Insights from PROSPECT

ESTABLISHMENT OF THE NATURAL HISTORY OF HIGH-RISK VULNERABLE PLAQUES

Identification of lesions with morphological characteristic of "vulnerable plaques" is not sufficient; we need to observe the natural history of these lesions and confirm the hypothesis of their potential clinical instability. Only prospective observation could reliably identify which plaque is prone to rupture and change our approach to the treatment of coronary atherosclerotic disease.



The PROSPECT Trial



700 pts with ACS

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

1-2 vessel CAD undergoing PCI

at up to 40 sites in U.S., Europe

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

PCI of culprit lesion(s)

Successful and uncomplicated

Formally enrolled

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

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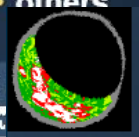
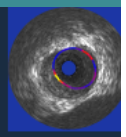
PI: Gregg W. Stone
Sponsor: Abbott Vascular; Partner: Volcano



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

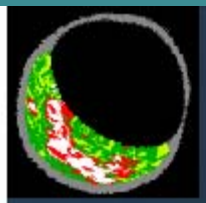
F/U: 1 mo, 6 mo, 1 yr, 2 yr, ±3-5 yrs

MSCT Substudy
N=50-100

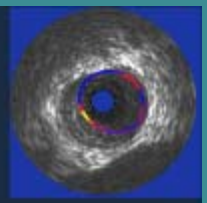
Repeat imaging in pts with events

CARDIOVASCULAR RESEARCH FOUNDATION

Columbia University Medical Center
NewYork-Presbyterian

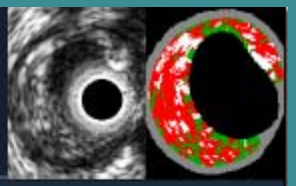


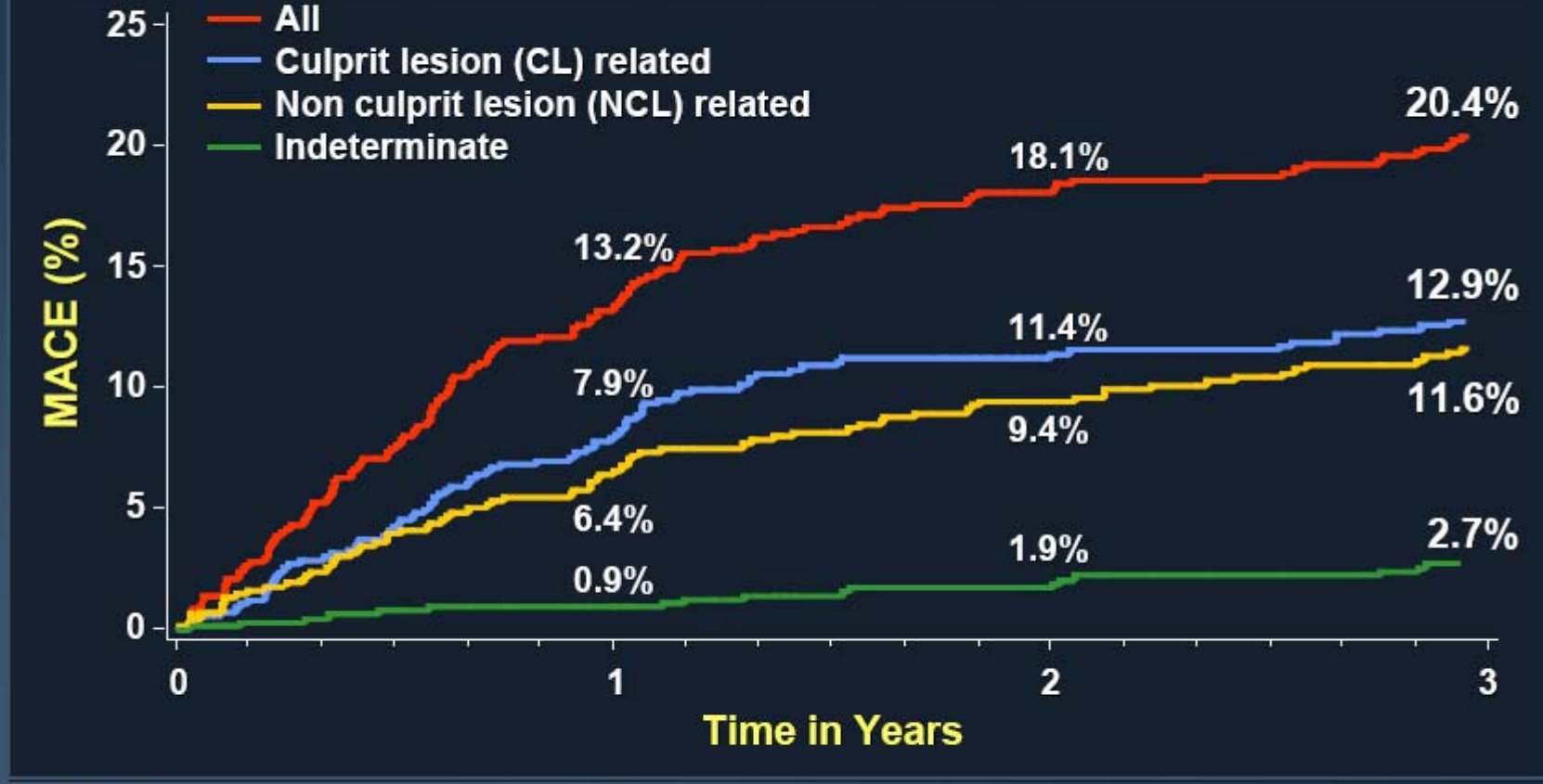
PROSPECT Baseline Analysis Conclusions



- Insights derived from the baseline findings from PROSPECT include the facts that:
  - At least one non-culprit lesion with an IVUS MLA <4.0 mm^2 was identified in ~43% of pts
  - VH-TCFAs were identified in the coronary tree in ~52% of pts (mean 0.99 ± 1.3, range 0-7 per pt), and were more widespread than previously described.
- Follow-up is ongoing to determine whether baseline demographics, biomarkers, angiography, IVUS, and VH can identify pts and lesions at risk for future adverse CV events

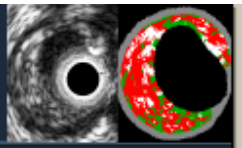
PROSPECT: MACE





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

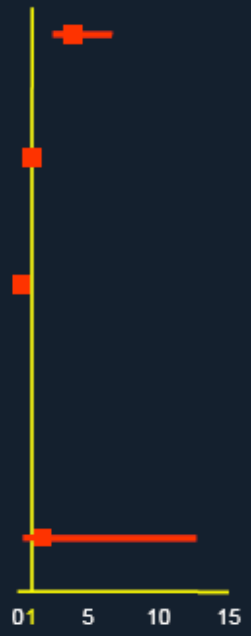
PROSPECT: Correlates of Non Culprit Lesion Related Events



Lesion level events (51 events from 2655 lesions in 609 pts at median 3.4 yrs)

Virtual Histology Plaque Type

Variable	Rate (n)	HR [95% CI]	P
VH-TCFA (n=590)	4.4% (26)	3.84 [2.22, 6.65]	<0.0001
Not VH-TCFA (n=2065)	1.2% (25)		
ThCFA (n=1005)	1.8% (18)	0.89 [0.50, 1.58]	0.69
Not ThCFA (n=1650)	2.0% (33)		
PIT (n=964)	0.6% (6)	0.23 [0.10, 0.53]	0.001
Not PIT (n=1691)	2.7% (45)		
Fibrotic (n=67)	0% (0)	-	0.99
Not Fibrotic (n=2588)	2.0% (51)		
Fibrocalcific (n=29)	3.4% (1)	1.75 [0.24, 12.63]	0.58
Not fibrocalcific (n=2626)	1.9% (50)		



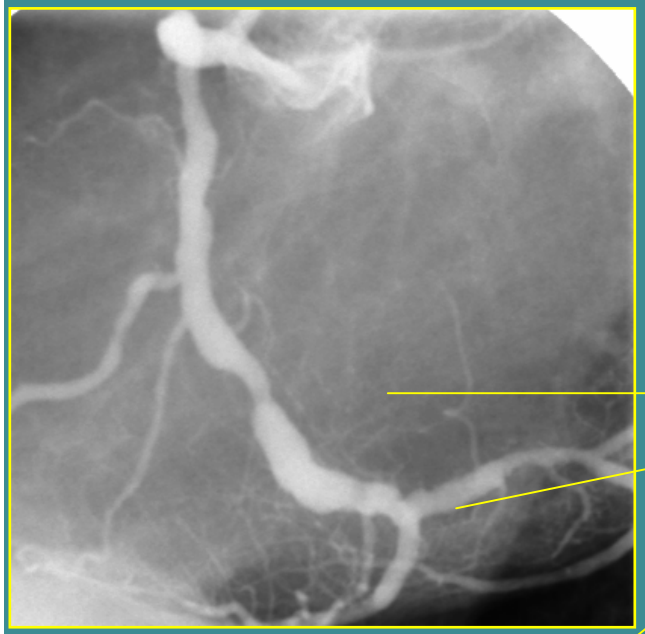
TCFA = thin cap fibroatheroma; ThCFA = thick cap fibroatheroma; PIT = pathologic intimal thickening. Univariate, unadjusted.

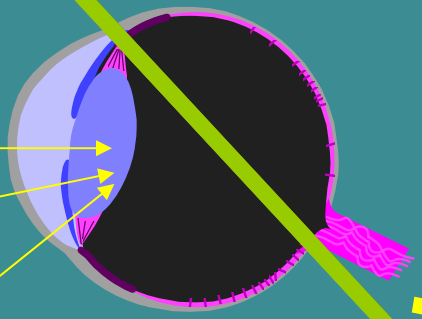
- The prospective identification of non culprit lesions prone to develop MACE within 3 years can be enhanced by characterization of underlying plaque morphology with virtual histology, with VH-TCFAs representing the highest risk lesion type
  - The combination of large plaque burden (IVUS) and a large necrotic core without a visible cap (VH-TCFA) identifies lesions which are at especially high risk for future adverse cardiovascular events

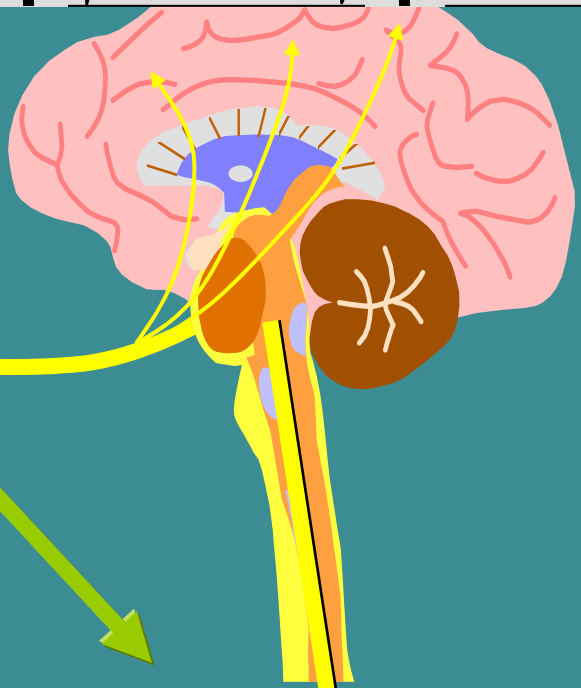
FROM IDENTIFICATION TO MANAGEMENT

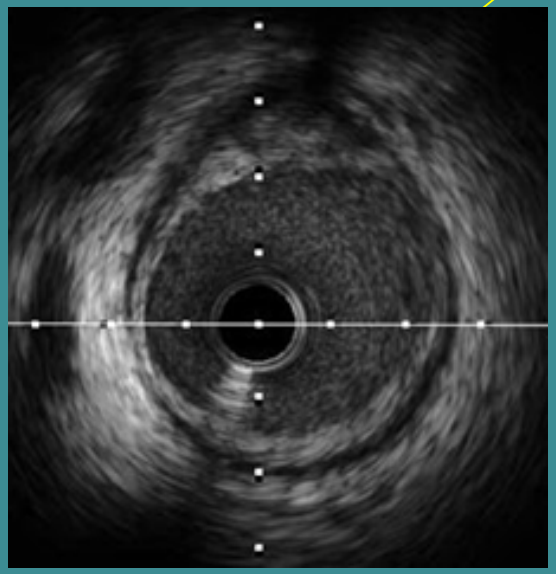
- LOCAL TREATMENT
- SYSTEMIC TREATMENT

Oculo-Stenotic Reflex









OCULO-VULNERABLE REFLEX

Case Study

Nature Reviews Cardiology **6**, 374-378 (May 2009) | doi:10.1038/nrcardio.2009.34

Subject Categories: Angina and coronary artery disease | Intervention

First case of stenting of a vulnerable plaque in the SECRITT I trial—the dawn of a new era?

Steve Ramcharitar[1], Nieves Gonzalo[1], Robert Jan van Geuns[2], Hector M. Garcia-Garcia[1], Joanna J. Wykrzykowska[1], Jurgen M. R. Ligthart[1], Evelyn Regar[1] & Patrick W. Serruys[1]

Effects of the Direct Lipoprotein-Associated Phospholipase A_2 Inhibitor Darapladib on Human Coronary Atherosclerotic Plaque

Patrick W. Serruys, MD, PhD; Héctor M. García-García, MD, MSc; Pawel Buszman, MD, PhD; Paul Erne, MD, PhD; Stefan Verheye, MD, PhD; Michael Aschermann, MD; Henrikus Duckers, MD, PhD; Oyvind Bleie, MD; Dariusz Dudek, MD; Hans Erik Bøtker, MD; Clemens von Birgelen, MD, PhD; Don D'Amico, MA; Tammy Hutchinson, MSc; Andrew Zambanini, MD; Frits Mastik; Gerrit-Anne van Es, PhD; Antonius F.W. van der Steen, PhD; D. Geoffrey Vince, PhD; Peter Ganz, MD; Christian W. Hamm, MD; William Wijns, MD, PhD; Andrew Zalewski, MD, PhD; for the Integrated Biomarker and Imaging Study-2 Investigators

Background—Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is expressed abundantly in the necrotic core of coronary lesions, and products of its enzymatic activity may contribute to inflammation and cell death, rendering plaque vulnerable to rupture.

IBIS-2 Imaging Methodology

Imaging beyond measuring plaque size

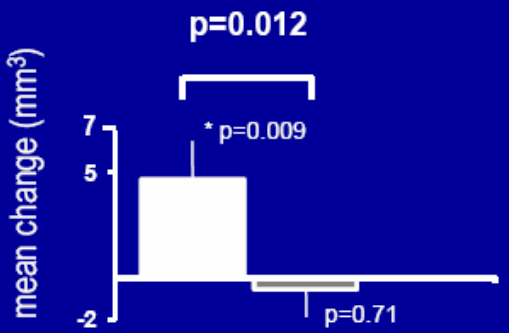
Plaque Composition

by IVUS - VH

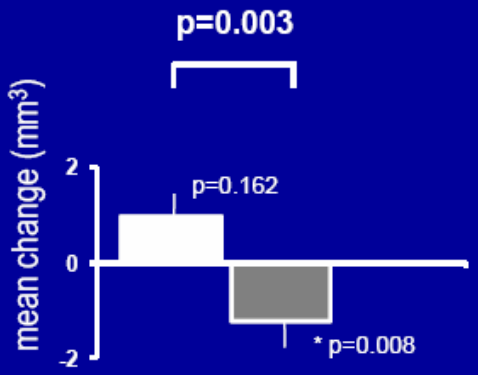
change from baseline in necrotic core volume

entire region of interest [mean 48 mm]

key secondary endpoint



the worst 10 mm subsegment



placebo (plus standard of care) n=110

darapladib 160 mg (plus standard of care) n=129

Welcome to the ESC Congress 2009
29 Aug 2009 - 02 Sep 2009 , Barcelona - Spain

900 : Natural course of lipid-rich plaques assessed with combination of intra-vascular ultrasound and optical coherence tomography

Authors:
K. Ishibashi (Wakayama /Japan), **S. Takarada** (Wakayama /Japan), **T. Tanimoto** (Wakayama /Japan), **H. Kitabata** (Wakayama /Japan), **T. Kubo** (Wakayama /Japan), **K. Hirata** (Wakayama /Japan), **N. Nakamura** (Wakayama /Japan), **M. Mizukoshi** (Wakayama /Japan), **T. Imanishi** (Wakayama /Japan), **T. Akasaka** (Wakayama /Japan)

Topic(s):
Invasive coronary imaging

Citation:
European Heart Journal (2009) 30 (Abstract Supplement), 152

Purpose: Identification of coronary lesions with morphological characteristic of "rupture-prone plaques" is not sufficient. The purpose of this study to examine the natural history of non-culprit lipid-rich plaques in patients with non-ST elevated acute coronary syndrome (NSTEACS).

Methods: Consecutive 80 patients with NSTEACS who underwent percutaneous coronary intervention (PCI) were enrolled. We assessed the volume change of residual non-culprit lipid-rich plaques and the change of the corresponding fibrous cap thickness (FCT) by use of intra-vascular ultrasound (IVUS) and optical coherence tomography (OCT), respectively, at baseline and after 9-months.

Results: From the analysis study of natural history, the change in total atheroma volume (TAV) of lipid-rich plaques was 0.42±0.6% and the change in the corresponding FCT was 14±12% during 9 months follow-up periods. Percent change in TAV showed a significant positive correlation with percent LDL/HDL ratio reduction (R=0.37, P<0.01). In contrast, the change in FCT demonstrated no correlation with LDL/HDL ratio level, but had a significant positive correlation with percent change in high sensitive CRP (R=0.39, P<0.01). And between TAV and FCT changes, no significant correlation was observed. Furthermore, in a multivariable analysis including age, sex, diabetes mellitus, hypertension, several concomitant drugs, only statin-use was the independent predictor for changing well-stabilized plaques, which obtained both TAV reduction and FCT increase.

Conclusion: The change in TAV and in FCT of coronary plaques during 9-months was related to the two different independent factor (reduction rate of LDL-C and high sensitive CRP, respectively). Furthermore, lipid lowering therapy by use of statin has a potential to stabilize them by both plaque reduction and fibrous cap thickening.

PLAQUE STABILIZATION / PLAQUE REGRESSION

Effects of Statin Treatments on Coronary Plaques Assessed by Volumetric Virtual Histology Intravascular Ultrasound Analysis

Statin-naïve patients with angiographically mild to moderate coronary disease (N=100)

1:1 randomization (double-blinded)

Simvastatin 20 mg n=50

Rosuvastatin 10 mg n=50

Serial VH-IVUS at baseline and 12 month

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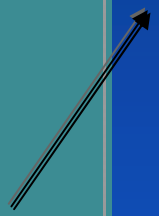
Baseline characteristics

	Simvastatin (N=50)	Rosuvastatin (N=50)	P-value
Lipid profiles at baseline			
Total cholesterol (mg/dL)	191 ± 34	189 ± 27	0.7
LDL cholesterol (mg/dL)	119 ± 30	116 ± 28	0.6
HDL cholesterol (mg/dL)	43 ± 10	43 ± 11	0.8
Triglycerides (mg/dL)	149 ± 69	152 ± 75	0.9
Lipid profiles at 12-month follow-up			
Total cholesterol (mg/dL)	142± 22	128 ± 20	0.002
LDL cholesterol (mg/dL)	78 ± 20	64 ± 21	0.002
HDL cholesterol (mg/dL)	48 ± 12	52 ± 14	0.127
Triglycerides (mg/dL)	115 ± 50	107 ± 96	0.6



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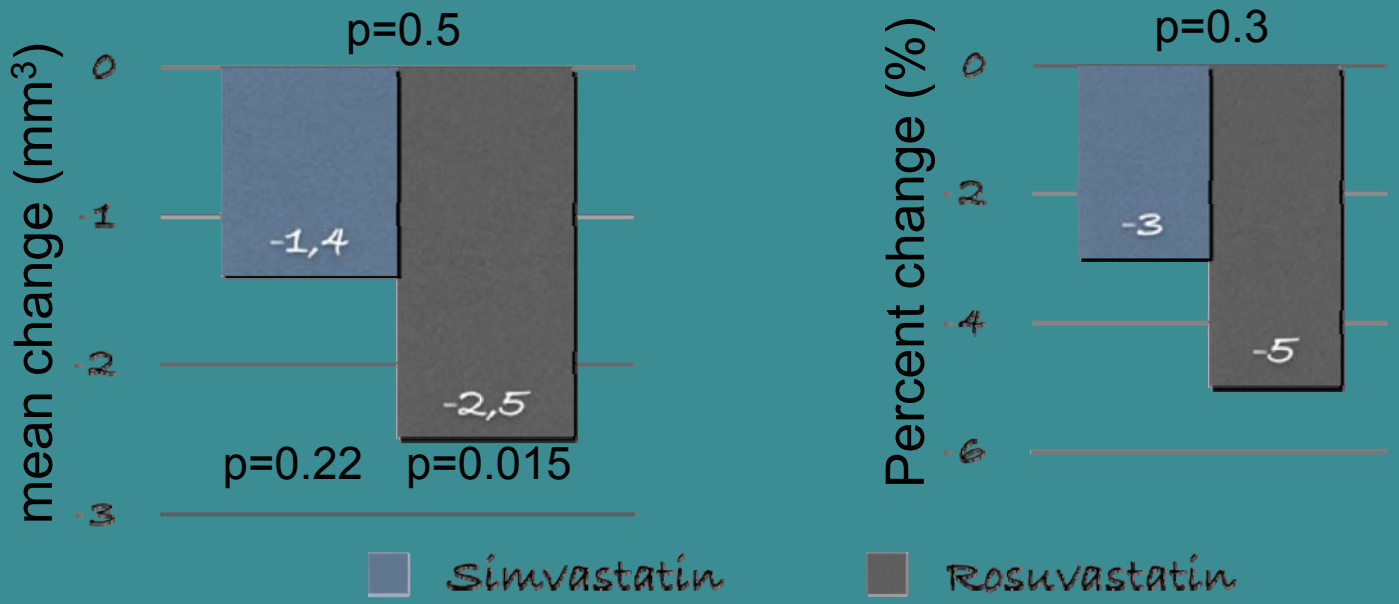
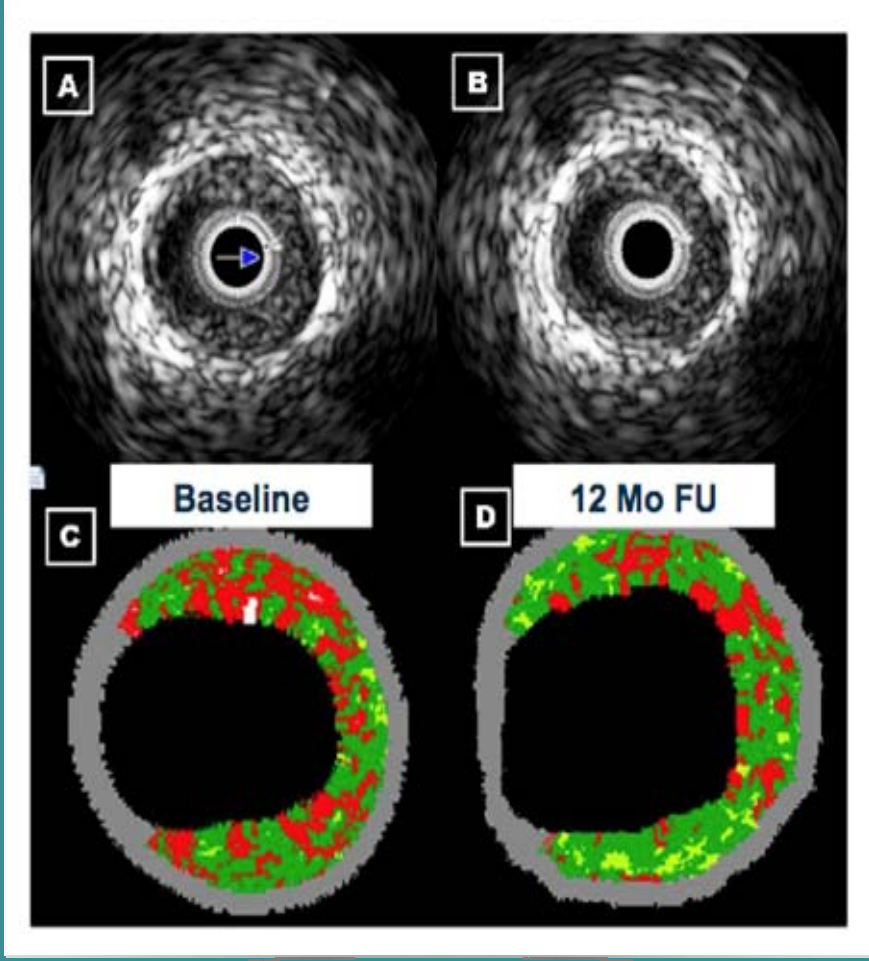
Plaque Composition by IVUS-VH
change from baseline in necrotic core volume
The worst 10 mm Segment



There was no significant treatment effect among statin groups. However, by intra-group serial analysis, there was significant reduction of NC in the rosuvastatin group.

Representative case: Rosuvastatin group



NC 2,3 mm^2 (47%) **NC 1,1 mm^2 (24%)**

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Conclusion

- A desire to identify the potential lethal aspects of atherosclerotic plaques is driving investigators into more innovative imaging technology.
- Seeing more will verify and validate pathology and mechanisms
- Seeing more will permit aterosclerotic researcher to identify best therapies for better outcome
- The clinical value to medicine will reside in the linkage between image and outcome, the study of which will remain at the farefront of our attack on acute and cronic coronary heart disease.

CONCLUSIONI

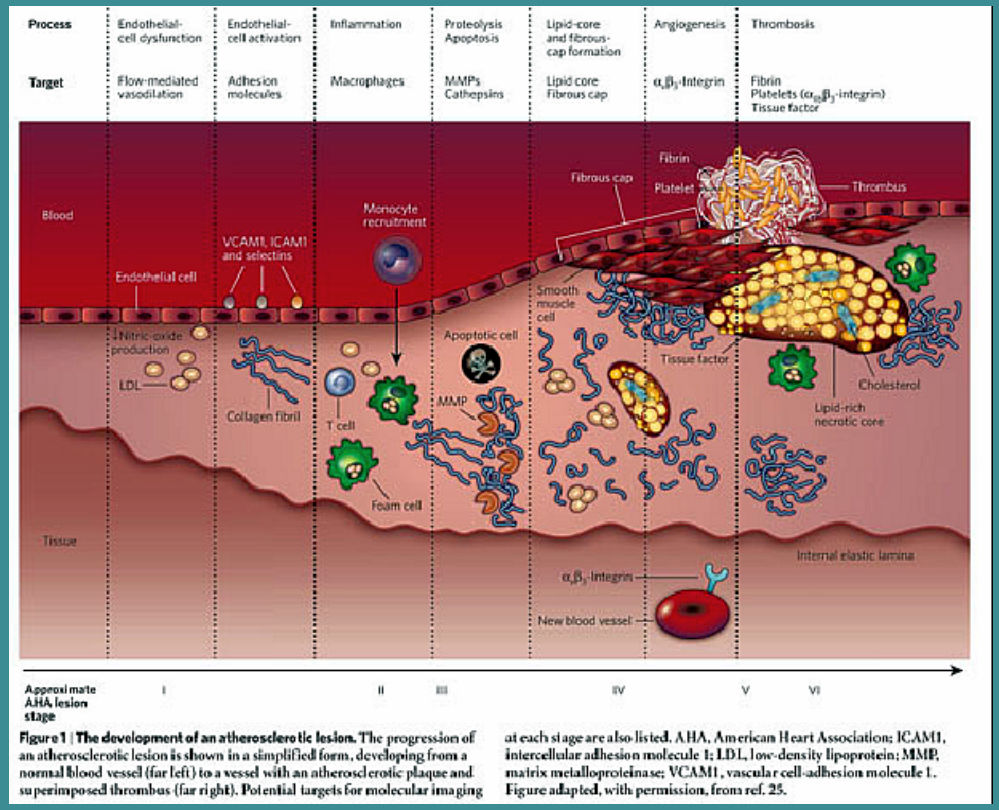

Figure 1 | The development of an atherosclerotic lesion. The progression of an atherosclerotic lesion is shown in a simplified form, developing from a normal blood vessel (far left) to a vessel with an atherosclerotic plaque and superimposed thrombus (far right). Potential targets for molecular imaging at each stage are also listed. AHA, American Heart Association; ICAM1, intercellular adhesion molecule 1; LDL, low-density lipoprotein; MMP, matrix metalloproteinase; VCAM1, vascular cell-adhesion molecule 1. Figure adapted, with permission, from ref. 25.

The prolonged course of ATS disease provides a widow of opportunity for diagnosis before symptoms occur.

Developments in imaging technology offer many enticing prospect,including detecting ATS early,grouping individuals by the probability that they will develop symptoms of ATS,assessing the results of treatment and improving the current understanding of the biology of ATS

Just as IVUS was a step beyond angiography, it is now fashionable to point to new imaging modalities such as virtual histology or integrated backscatter IVUS, palpography, optical imaging, spectroscopy, and so on as technologies that are a step beyond IVUS. Although in their relative infancy, these techniques have the potential to assess changes in plaque composition and stability rather than just overall changes in atherosclerosis volume. It is the instability of the disease, not just the increase in plaque mass, that is different in high-risk patient subsets. However, these new techniques will yield significant information only with careful patient and coronary artery segment selection, the proper analysis, and correlation with clinical events.

THIN CAP

- Although the most accepted threshold to define a cap as “thin” has been set at 65μm by pathology investigation,a number of important ex vivo studies used higher (200 μm) threshold.

	IVUS	OCT
Risoluzione	100 μm	10 μm
Penetrazione	Buona	Scarsa
Cappuccio fibroso	+	+++
Nucleo lipidico	++	+++

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CLINICAL RESEARCH
Coronary heart disease

Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002

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A recent Swedish study showed that only 1% of an over-50% decrease CHD mortality between 1986 and 2002 could be attributed to *local treatment of stenotic lesion* by PCI or CABG surgery !

Linking Plaque

ents:

SPECT

- I make the assumption that we will be able to detect TCFAs. After all, we are smart people, and a lot of money and time is being spent on this problem.
- However, that does not mean that this makes sense and will become a clinical

Gary S. Mintz, MD

ESTABLISHMENT OF THE NATURAL HISTORY OF HIGH-RISK VULNERABLE PLAQUES

Identification of lesions with morphological characteristic of "vulnerable plaques" is not sufficient; we need to observe the natural history of these lesions and confirm the hypothesis of their potential clinical instability. Only prospective observation could reliably identify which plaque is prone to rupture and change our approach to the treatment of coronary atherosclerotic disease.