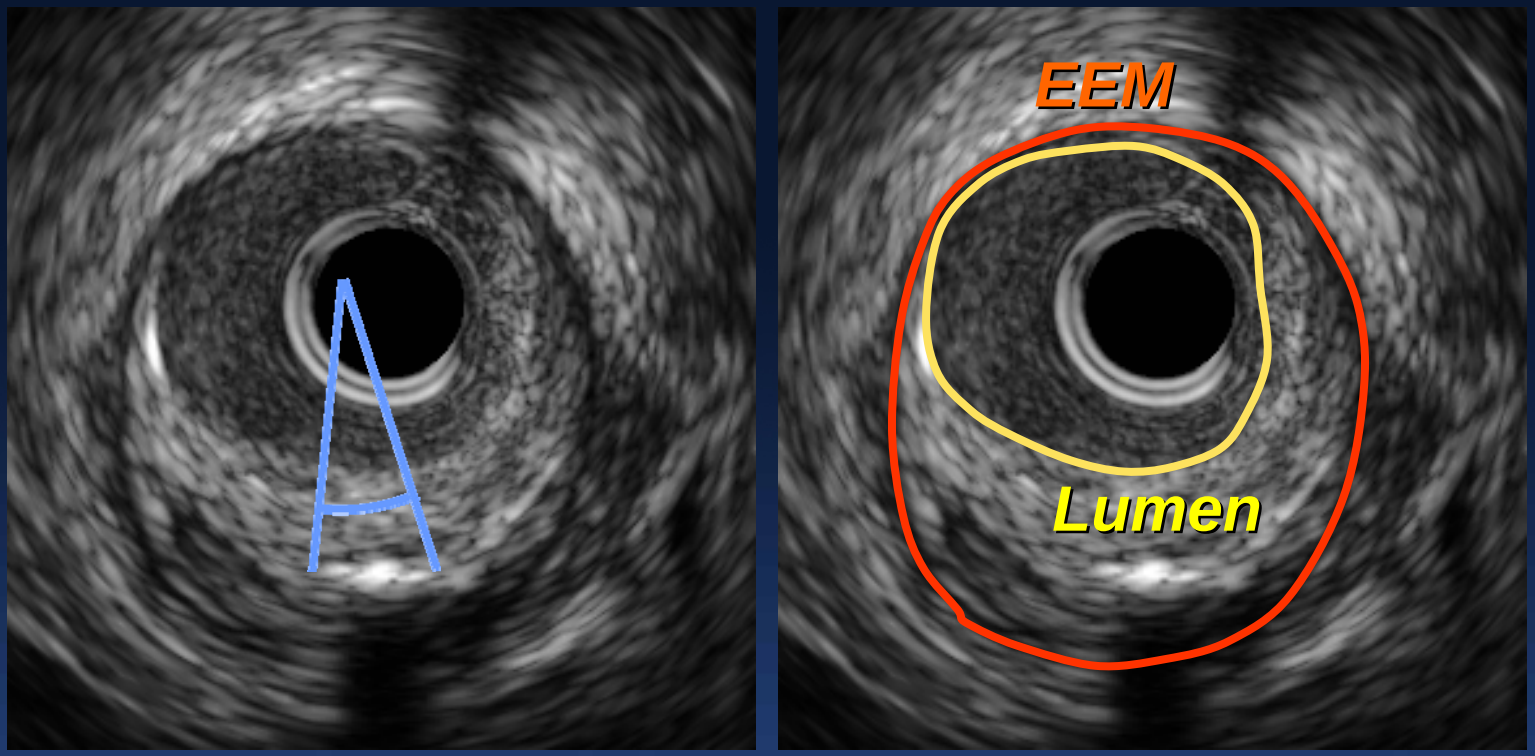
Hands-On Session: Core Lab Analysis

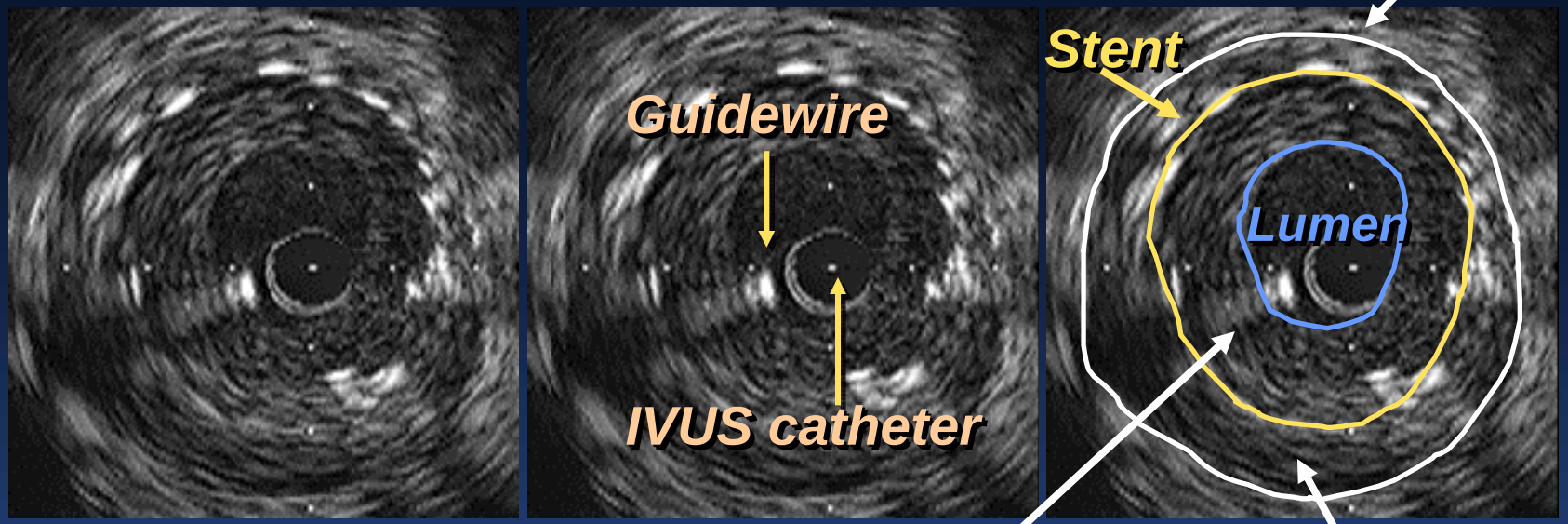
Gary S Mintz, MD

Cardiovascular Research Foundation

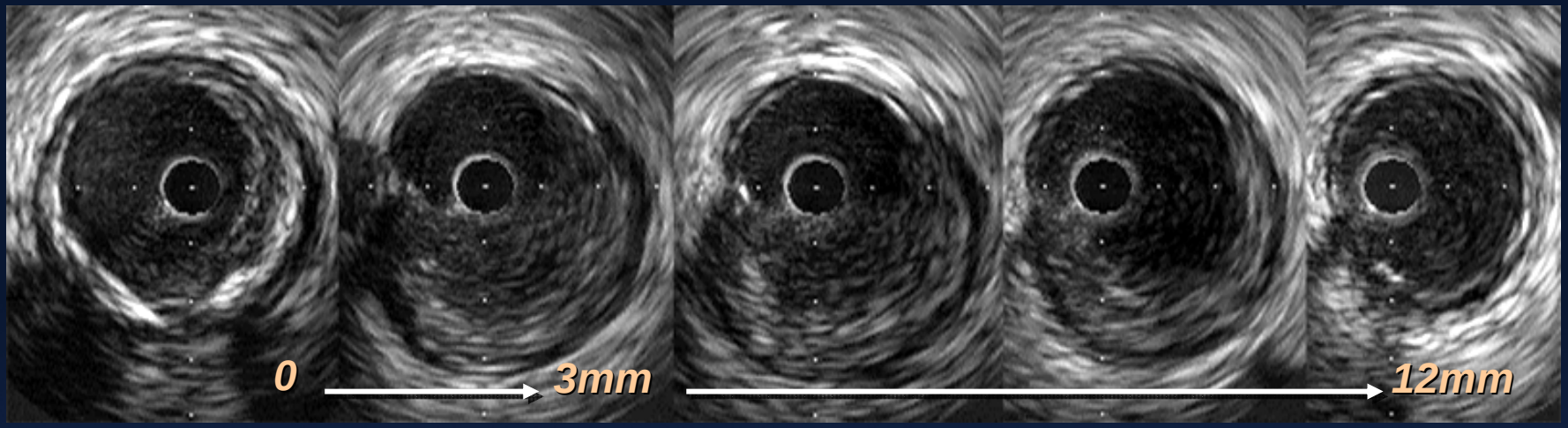
New York City


EEM
Lumen

Stented Artery



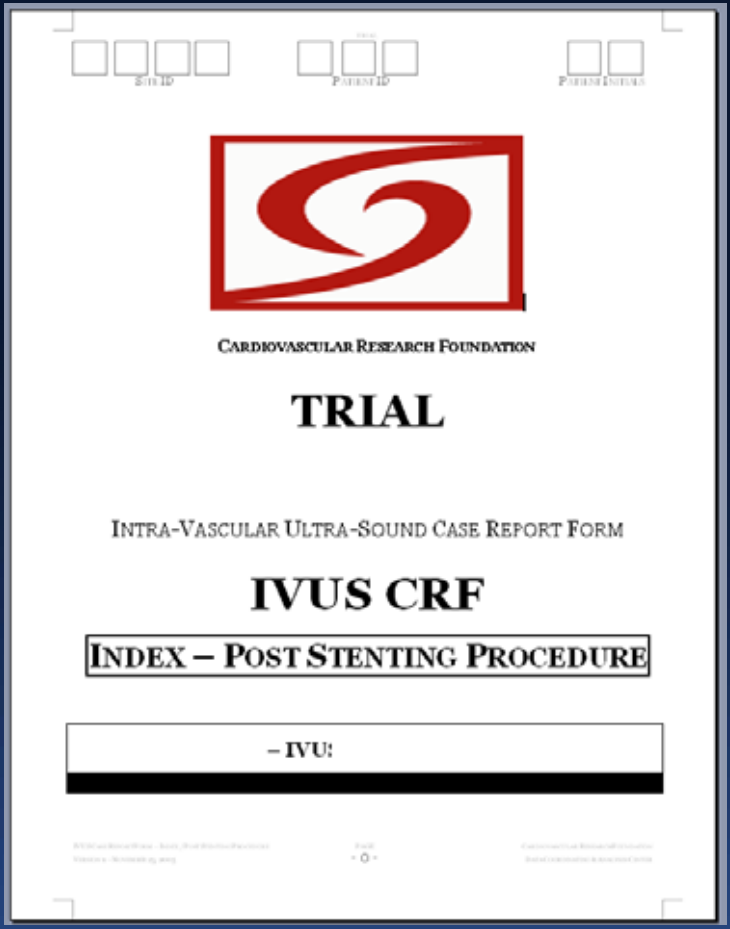
Proximal Reference	Lesion Site	Distal Reference



Proximal Reference	Lesion Site	Distal Reference
EEM CSA = 20.4	EEM CSA = 21.6	EEM CSA = 13.3
Lumen CSA = 9.7	Lumen CSA = 4.5	Lumen CSA = 8.9
Max lumen diam = 3.7	Max lumen diam = 32.8	Max lumen diam = 3.6
MLD = 3.1	MLD = 2.3	MLD = 3.0
P+M CSA = 10.7	P+M CSA = 17.1	P+M CSA = 4.4
Eccentricity = 1.0/0.3	Eccentricity = 3.0/0.1	Eccentricity = 0.6/0.2
Plaque burden = 0.52	Plaque burden = 0.79	Plaque burden = 0.33
Arc of Ca = 60		

Average Reference EEM CSA = 16.9
Remodeling Index = 1.3
Average Reference Lumen CSA = 9.3
Area Stenosis = 52%

CRF off-line analysis “Case report form”



Site ID Patient ID Patient Initials

CARDIOVASCULAR RESEARCH FOUNDATION

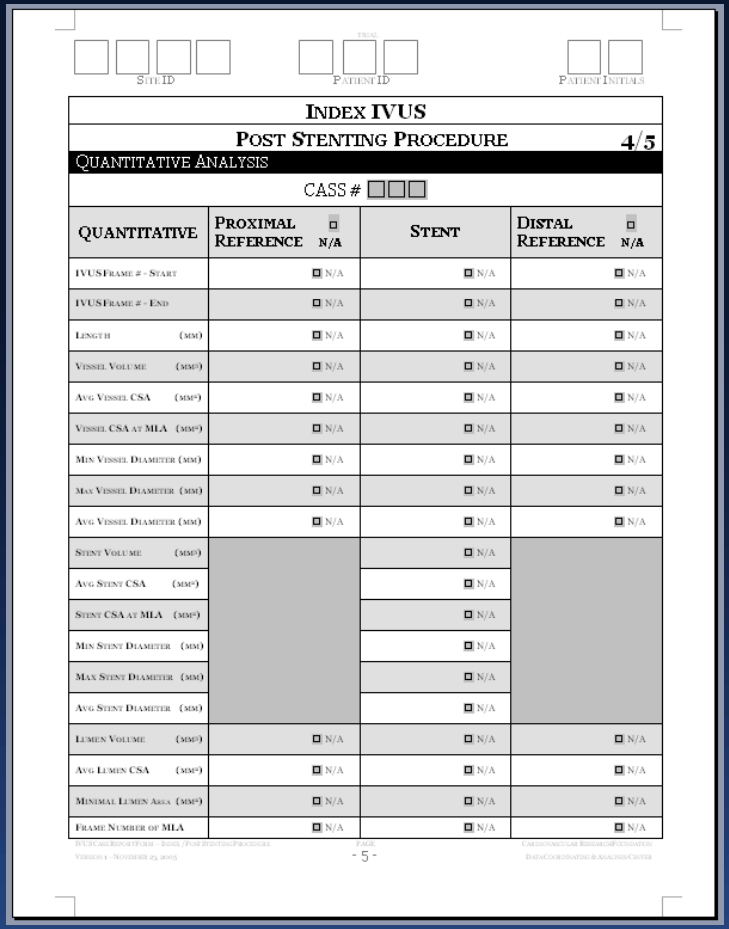
TRIAL

INTRA-VASCULAR ULTRA-SOUND CASE REPORT FORM

IVUS CRF

INDEX – POST STENTING PROCEDURE

– IVU:



Site ID Patient ID Patient Initials

INDEX IVUS

POST STENTING PROCEDURE 4/5

QUANTITATIVE ANALYSIS

CASS # ☐☐☐

QUANTITATIVE	PROXIMAL REFERENCE ☐ N/A	STENT	DISTAL REFERENCE ☐ N/A
IVUS FRAME # - START	☐ N/A	☐ N/A	☐ N/A
IVUS FRAME # - END	☐ N/A	☐ N/A	☐ N/A
LENGTH (MM)	☐ N/A	☐ N/A	☐ N/A
VESSEL VOLUME (MM³)	☐ N/A	☐ N/A	☐ N/A
AVG VESSEL CSA (MM²)	☐ N/A	☐ N/A	☐ N/A
VESSEL CSA AT MLA (MM²)	☐ N/A	☐ N/A	☐ N/A
MIN VESSEL DIAMETER (MM)	☐ N/A	☐ N/A	☐ N/A
MAX VESSEL DIAMETER (MM)	☐ N/A	☐ N/A	☐ N/A
AVG VESSEL DIAMETER (MM)	☐ N/A	☐ N/A	☐ N/A
STENT VOLUME (MM³)		☐ N/A	
AVG STENT CSA (MM²)		☐ N/A	
STENT CSA AT MLA (MM²)		☐ N/A	
MIN STENT DIAMETER (MM)		☐ N/A	
MAX STENT DIAMETER (MM)		☐ N/A	
AVG STENT DIAMETER (MM)		☐ N/A	
LUMEN VOLUME (MM³)	☐ N/A	☐ N/A	☐ N/A
AVG LUMEN CSA (MM²)	☐ N/A	☐ N/A	☐ N/A
MINIMAL LUMEN AREA (MM²)	☐ N/A	☐ N/A	☐ N/A
FRAME NUMBER OF MLA	☐ N/A	☐ N/A	☐ N/A

- 5 -

11 pages!!!

CARDIOVASCULAR RESEARCH FOUNDATION
A Passion for Innovation

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

- What you analyze and how you analyze it depends on the question that you want to answer.
- It is important to have the question or hypothesis in mind before you start your analysis and, even better, before you collect your data
  - IVUS predictors of ischemia or events
  - IVUS predictors of restenosis or stent thrombosis
  - Mechanisms of restenosis
  - Progression/regression

- Pre-specify the analysis and definitions. This is especially important in unblinded and non-randomized studies.
- Analysis software
  - Commercial systems
  - Freeware/shareware. . . NIH Image (or ImageJ for Mac)
- Understand the limitations of your project before you start
- The more you plan in advance, the less you will have to repeat before you are finished.
- Read the literature. Standards documents exist. Read them and follow their guidelines.

VERDICT Pilot

Vascular **E**valuation for **R**evascularization:
Defining **I**ndications for **C**oronary **T**herapy

Prospective, multicenter, non-randomized, non-blinded study in 300 intermediate coronary lesions

(DS ≥40% - <80%, RVD 2.75 – 4.0 mm)

FFR and VH-IVUS assessment of all lesions

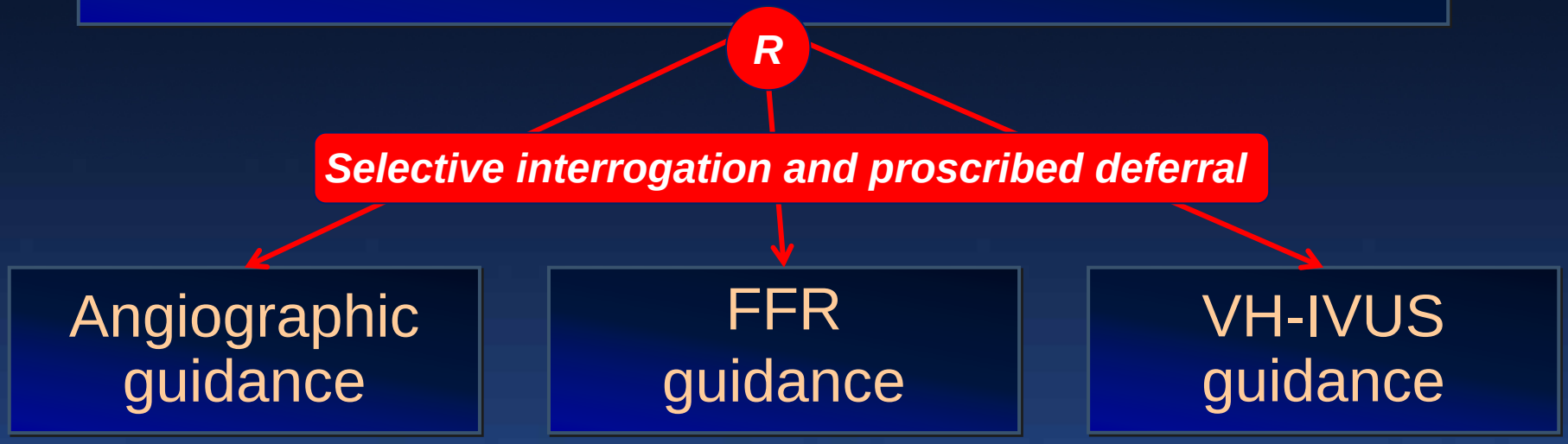
10 sites in US and EU; Sponsor: Volcano Corp.

Study Endpoints and Objectives:

1. Examine concordance between FFR and VH-IVUS parameters
2. Establish IVUS values for MLA/length/volume to predict ischemia (ROC)
3. ? Incremental correlative value of fibroatheromas for ischemia
4. Inform a large-scale, randomized trial

VERDICT Randomized Trial

Patients undergoing PCI with one or more additional intermediate lesions (≥40% - <80%) in a vessel with RVD 2.75 - 4.0 mm



1 year follow-up

Endpoints: MACE, cost-effectiveness

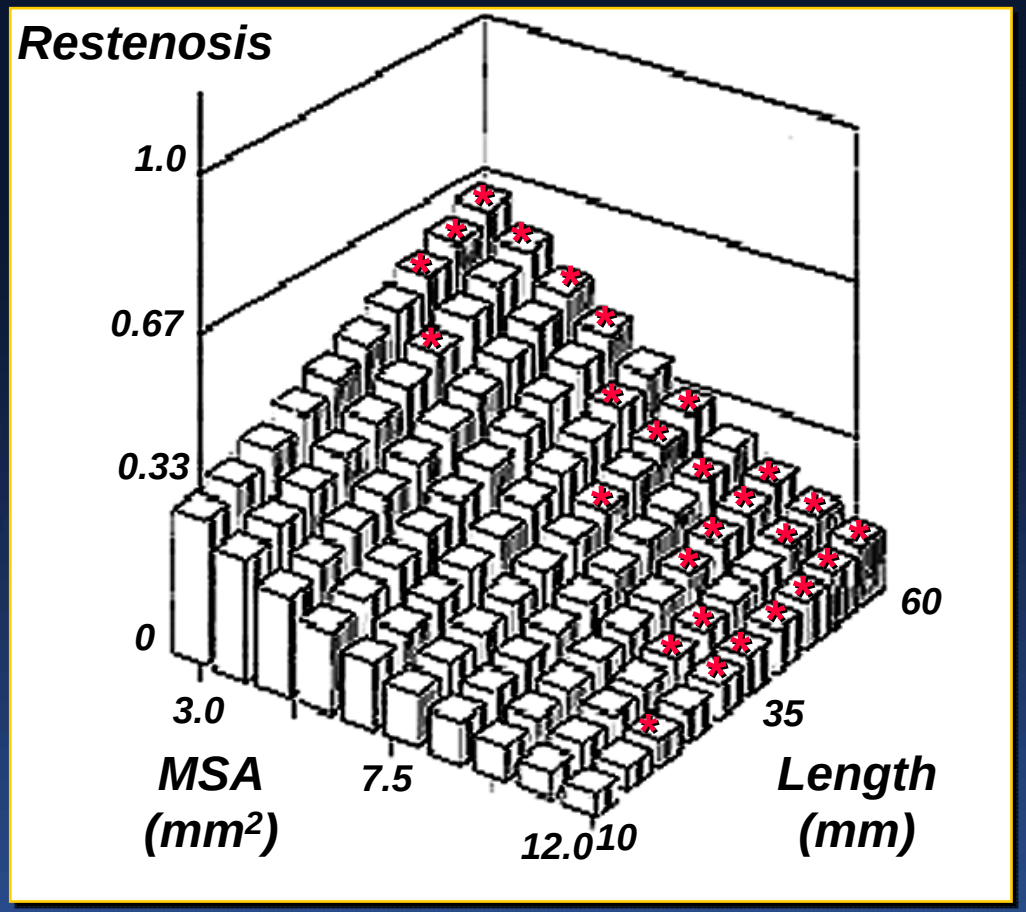
Powered for superiority of both FFR and VH-IVUS vs. angio (α=0.025)

Note: Trial design not finalized

Assessment of Predictors of Thrombosis & Restenosis

	DES Thrombosis	DES Restenosis
Underexpansion	•*Fujii et al. J Am Coll Cardiol 2005;45:995-8)* •*Okabe et al., Am J Cardiol. 2007;100:615-20* •*Liu et al. JACC Cardiovasc Interv. 2009;2:428-34* •*Choi et al. Circulation Cardiovascular Interventions (in press)*	•*Sonoda et al. J Am Coll Cardiol 2004;43:1959-63* •*Hong et al. Eur Heart J 2006;27:1305-10* •*Doi et al JACC Cardiovasc Interv. 2009;2:1269-75* •*Fujii et al. Circulation 2004;109:1085-1088*
Edge problems (geographic miss, secondary lesions, large plaque burden, etc)	•*Fujii et al. J Am Coll Cardiol 2005;45:995-8)* •*Okabe et al., Am J Cardiol. 2007;100:615-20* •*Liu et al. JACC Cardiovasc Interv. 2009;2:428-34* •*Choi et al. Circulation Cardiovascular Interventions (in press)*	•*Sakurai et al. Am J Cardiol 2005;96:1251-3* •*Liu et al.Am J Cardiol 2009;103:501-6* •*Costa et al, Am J Cardiol, 2008;101:1704-11*

Impact of lesion length and final minimum stent area (MSA) on restenosis



*No actual observations in this range

de Feyter et al. Circulation 1999;100:1777-83

	ST	No ST	p
Reference segment			
Most normal looking			
Lumen CSA, mm^2	9.2	9.3	0.6
EEM CSA, mm^2	14.4	15.3	0.7
Plaque burden, %	41.7	37.0	0.3
Most diseased			
Lumen CSA, mm^2	3.5	5.9	<0.001
EEM CSA, mm^2	13.5	12.2	0.8
Plaque burden, %	67.5	49.5	<0.001
Stent			
MLA slice			
Stent CSA, mm^2	6.3	7.1	0.5
Lumen CSA, mm^2	4.4	6.7	0.013
MSA slice			
Stent CSA, mm^2	6.3	7.1	0.3
<5.0mm^2	41.7%	17.0%	

Choi et al. Circulation Cardiovascular Interventions (in press)

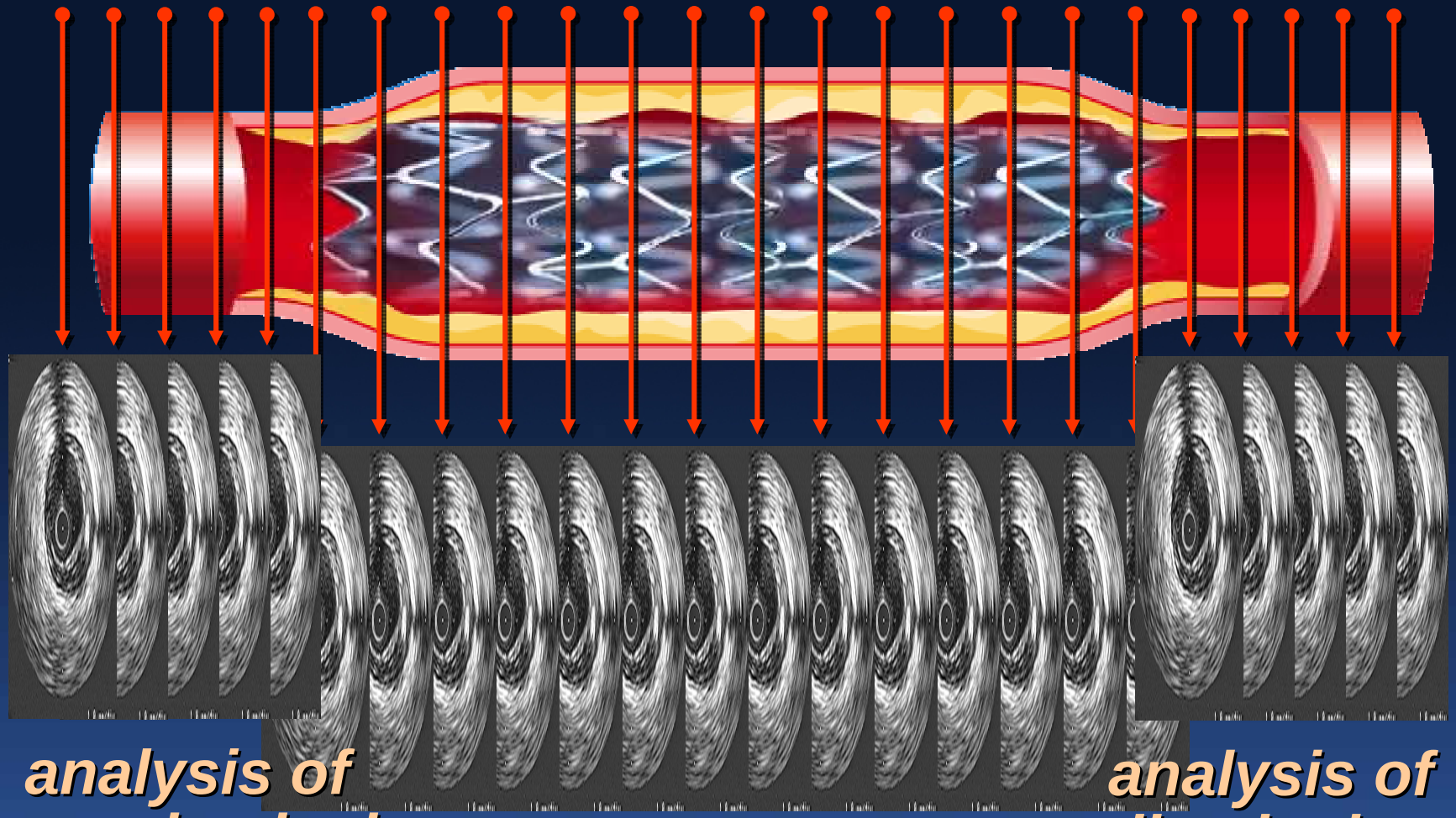
Assessment of *Mechanisms* of Restenosis

- Identify the site of the minimum lumen CSA at follow-up because this defines restenosis. Then "go backwards" to identify the same cross-section post-PCIand pre-PCI
- Conversely, it is not correct to identify the site of the minimum lumen CSA pre-PCI and "go forward" to indentify the same cross-section post-PCI and at follow-up. This may not represent the restenosis process.
- The MLA migrates from pre-PCI to post-PC to follow-up.

What measurements are important?

Non-stented lesions	Stented lesions	Stent edges
ΔEEM	ΔStent	ΔEEM
ΔLumen	ΔLumen	ΔLumen
ΔP&M	ΔIH	ΔP&M
	ΔEEM	
	ΔP&M	
	ΔMalapposition	

Volumetric analysis and planar (mm x mm) analysis are complementary

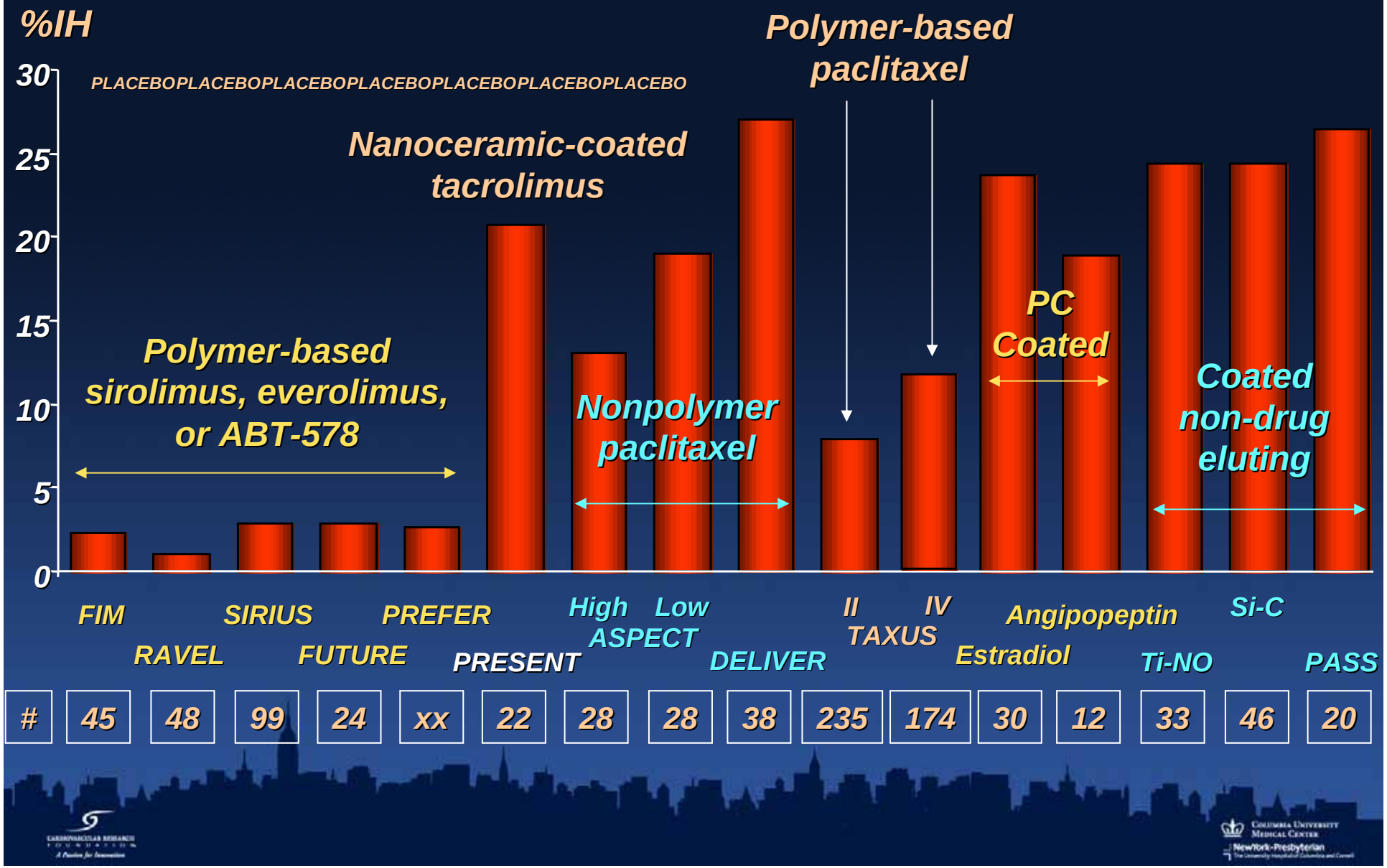


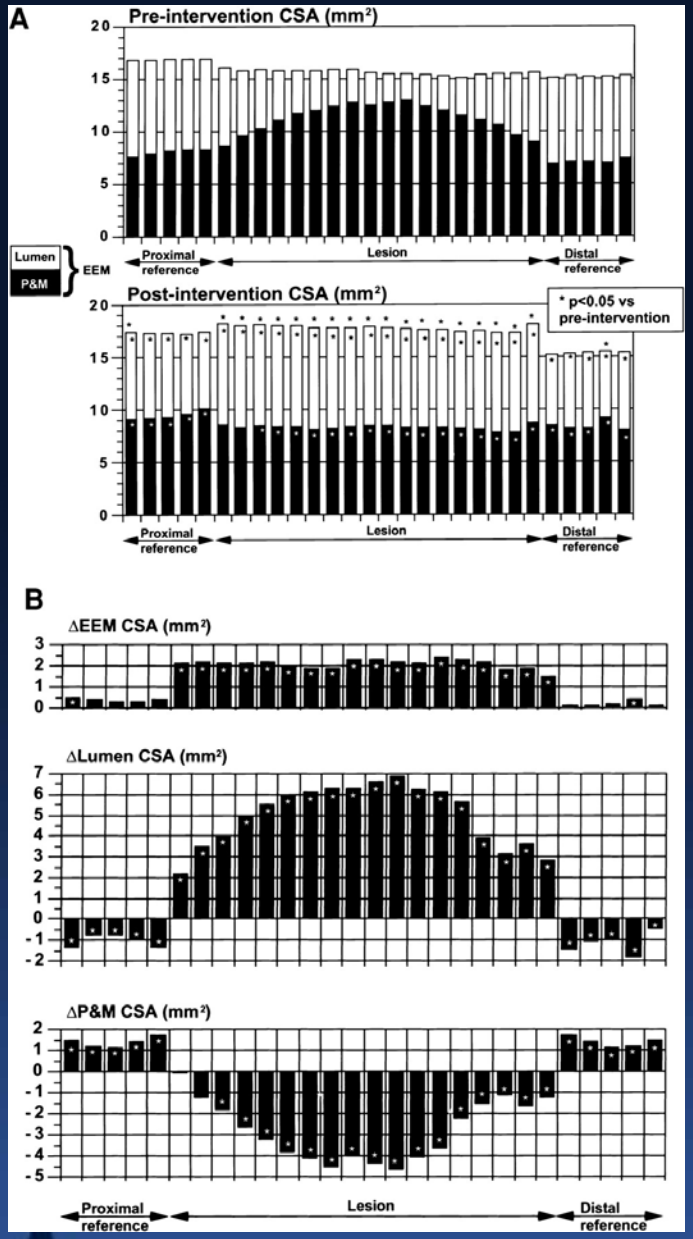
analysis of proximal edge

analysis in-stent

analysis of distal edge

%IH in various DES trials

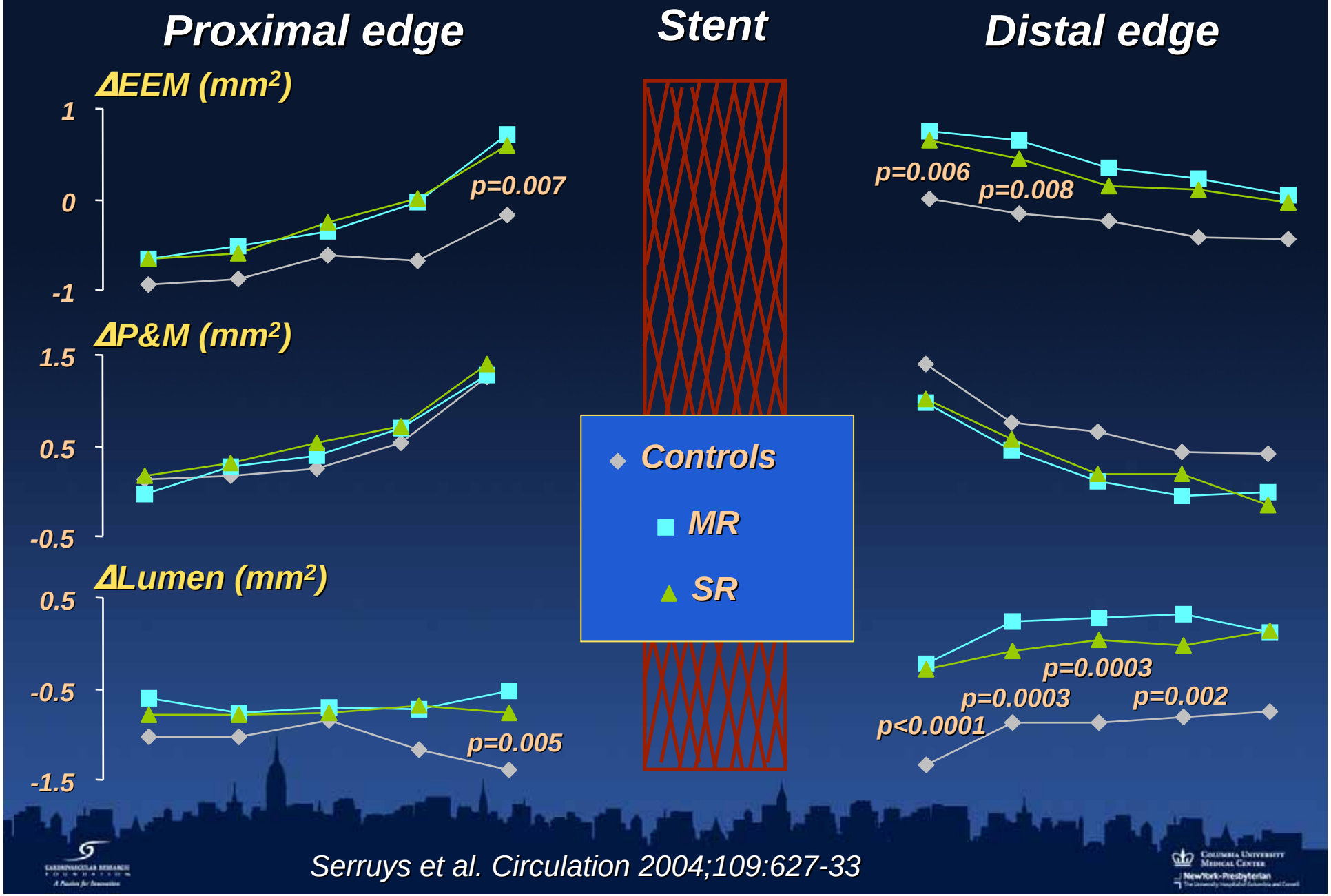




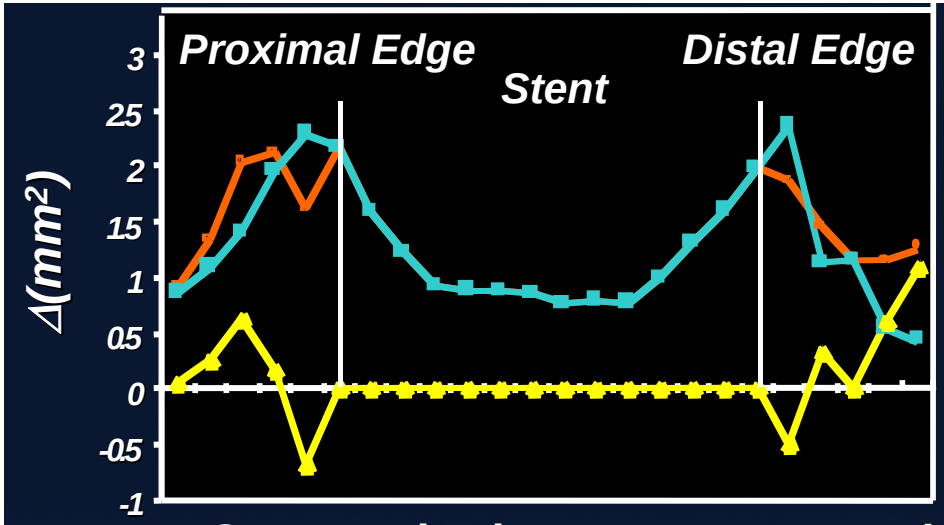
Mechanism of Lumen Enlargement During Intracoronary Stent Implantation

Ahmed et al. Circulation 2000;102:7-10

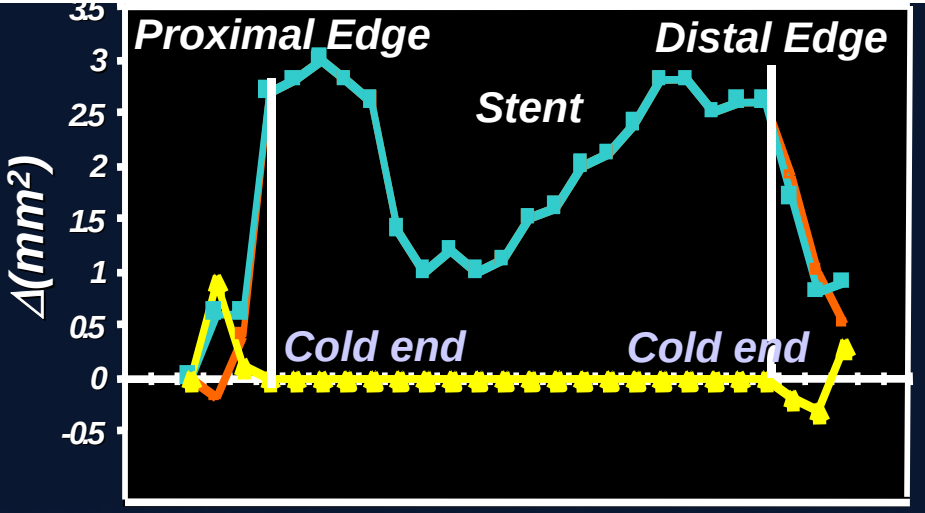
Serial edge analysis in TAXUS-II



Serruys et al. Circulation 2004;109:627-33



Stent and Edges per mm

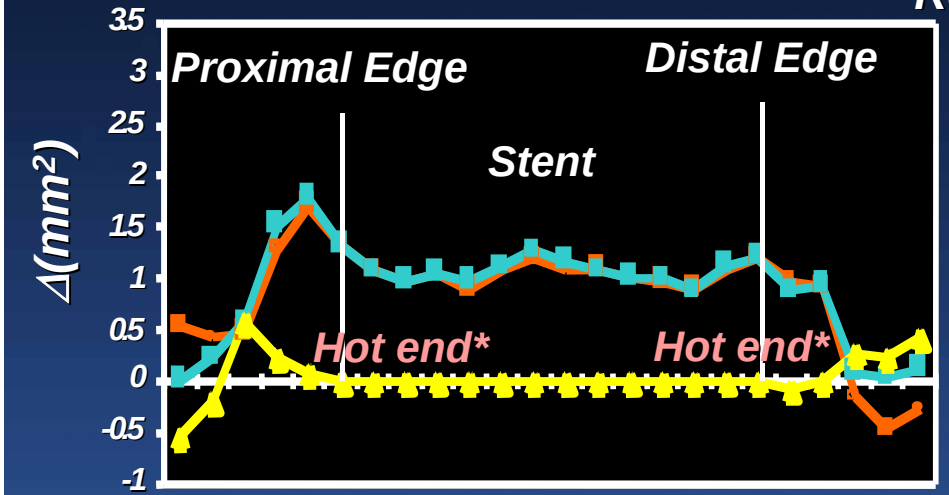


Stent and Edges per mm

Lumen loss

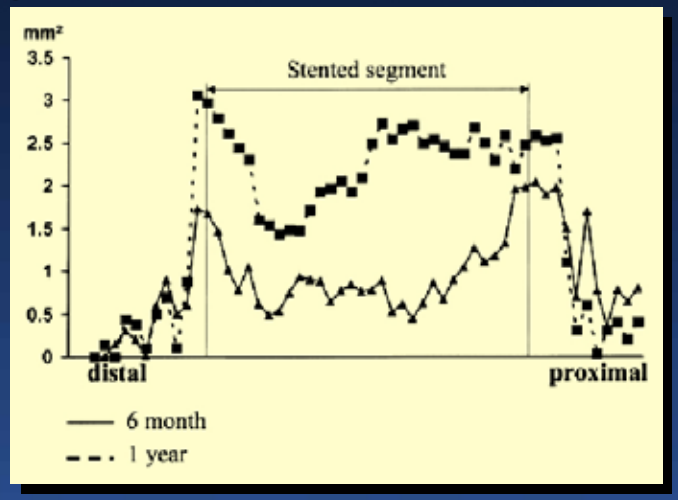
Plaque gain

Remodeling



Stent and Edges per mm

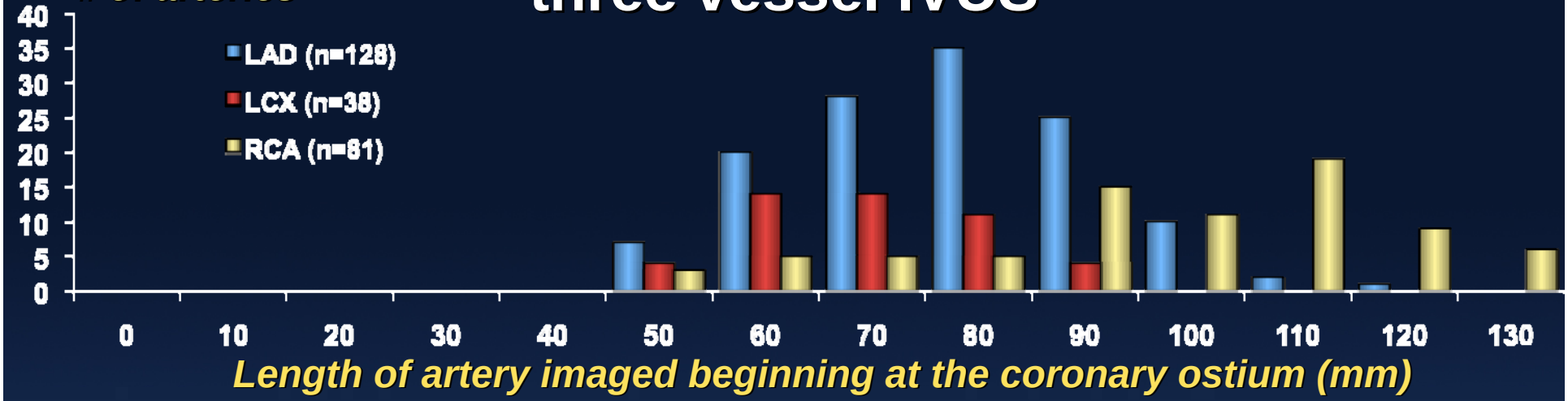
* 20% incidence of late malapposition

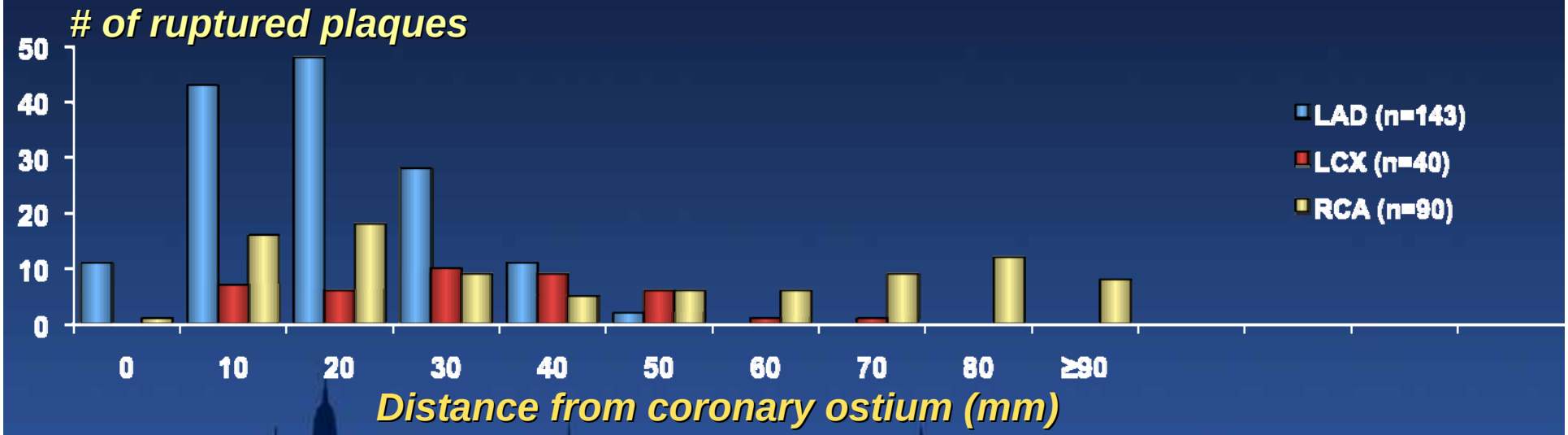


Weissman et al unpublished

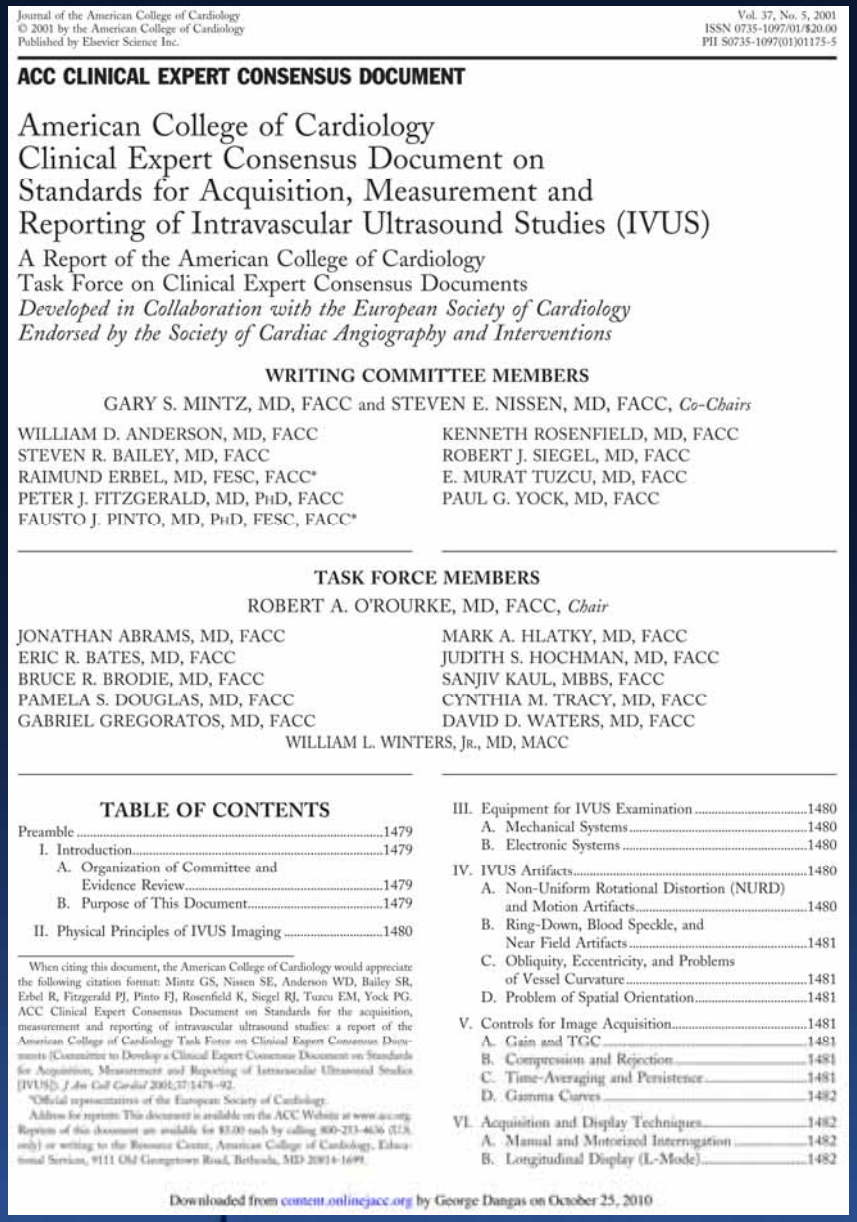
Kay et al. Circulation 2001;103:14-7

Location of 273 ruptured plaques in 158 patients with ACS and 48 patients with stable angina and three vessel IVUS





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



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ACC CLINICAL EXPERT CONSENSUS DOCUMENT

American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS)

A Report of the American College of Cardiology
Task Force on Clinical Expert Consensus Documents
Developed in Collaboration with the European Society of Cardiology
Endorsed by the Society of Cardiac Angiography and Interventions

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*Official representatives of the European Society of Cardiology.

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Use well-established greyscale IVUS definitions and measurements

Don't re-invent the wheel!

Clinical research

EuroIntervention

Clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound regression/progression studies

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Rationale for a consensus document

Atherosclerotic cardiovascular disease is a leading cause of morbidity and mortality despite the widespread use of established medical therapies. This has prompted the search to identify new therapeutic approaches to achieve more effective prevention of cardiovascular events. Considerable interest has focused on the role of surrogate markers of therapeutic efficacy in the early evaluation of novel anti-atherosclerotic therapies.

Monitoring changes in the extent of coronary atherosclerosis with intravascular ultrasound (IVUS) has been increasingly employed in clinical trials to assess progression and regression of atherosclerosis. This is based on the pivotal role that atherosclerotic plaque plays in the natural history of cardiovascular disease and the acceptance of validated arterial imaging approaches including coronary angiography and carotid intimal-medial thickness by regulatory authorities. The ability to generate high-resolution imaging of the entire thickness of the coronary artery wall permits evaluation of the entire burden of atherosclerotic plaque.

In order to understand the differences, similarities, limitations and pitfalls of the IVUS technique among different academic core laboratories, a number of meetings of representatives from these groups were convened in 2007 and 2008. This document is the result of those IVUS methodology meetings that assembled experts from core laboratories to discuss standards for image acquisition, definitions, criteria, analyses, and primary and secondary endpoints.

Equipment

Early studies that employed coronary IVUS imaging typically involved the use of one imaging system in terms of both catheter and console. With technological advances a number of systems and catheters are now available that permit high-resolution imaging within the coronary arteries. Given that studies often involve a large network of sites, there is likely to be marked heterogeneity in terms of imaging systems available among institutions and within each catheterisation laboratory. As a result, there is now a much greater risk that an individual subject is imaged with different systems at different time points. It is critical that every possible effort is made to ensure that an individual is imaged with the same equipment (catheters and consoles and pullback devices) for baseline and follow-up studies.

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E-mail: p.w.j.c.serruys@erasmusmc.nl

- ***Use the absolute change in % atheroma volume of a >30mm long segment with well-defined proximal and distal fiduciary points as the primary endpoint***

- ***Even though the most diseased subsegments contain the largest mean plaque burden, do not use for the primary endpoint:***
  - ***No consistent proximal and distal fiduciary points***
  - ***MLA, maximum plaque burden, and the most-diseased segment can shift during follow-up***
  - ***variability increases when the segment length is short***

Focus article

EuroIntervention

Tissue characterisation using intravascular radiofrequency data analysis: recommendations for acquisition, analysis, interpretation and reporting

Héctor M. García-García[1], MD, MSc; Gary S. Mintz[2], MD, FACC; Amir Lerman[3], MD, FACC; D. Geoffrey Vince[4], PhD; M. Paulina Margolis[4], MD, PhD; Gerrit-Anne van Es[5], PhD; Marie-Angèle M. Morel[5], BSc; Anuja Nair[4], PhD; Renu Virmani[6], MD, FACC; Allen P. Burke[6], MD, FACC; Gregg W. Stone[2], MD, FACC; Patrick W. Serruys[1]*, MD, PhD, FACC, FESC

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Paulina Margolis is vice president of scientific affairs and medical director of Volcano Corporation. She and her husband declare ownership interest. D. Geoffrey Vince and Anuja Nair are also Volcano Corporation employees. Gary Mintz declares ownership interest and is also a consultant of the company. Renu Virmani is consultant to Volcano Corporation and she has received research support from Volcano Corporation. Gregg Stone is consultant to Volcano Corporation. He has received research support from Boston Scientific and Abbott Vascular.

KEYWORDS
Imaging, patients, plaque, radiofrequency data analysis, ultrasonics

Abstract

This document suggests standards for the acquisition, measurement, and reporting of radiofrequency data analysis (virtual histology – VH) intravascular ultrasound (IVUS) studies. Readers should view this document as the authors' best attempt in an area of rapidly evolving investigation, an area where rigorous evidence is not yet available or widely accepted. Nevertheless, this document is based on known pathologic data as well as previously reported imaging data; where practical, this data is summarised in the current document, a document which will also include recommendations for future evolution of the technology.

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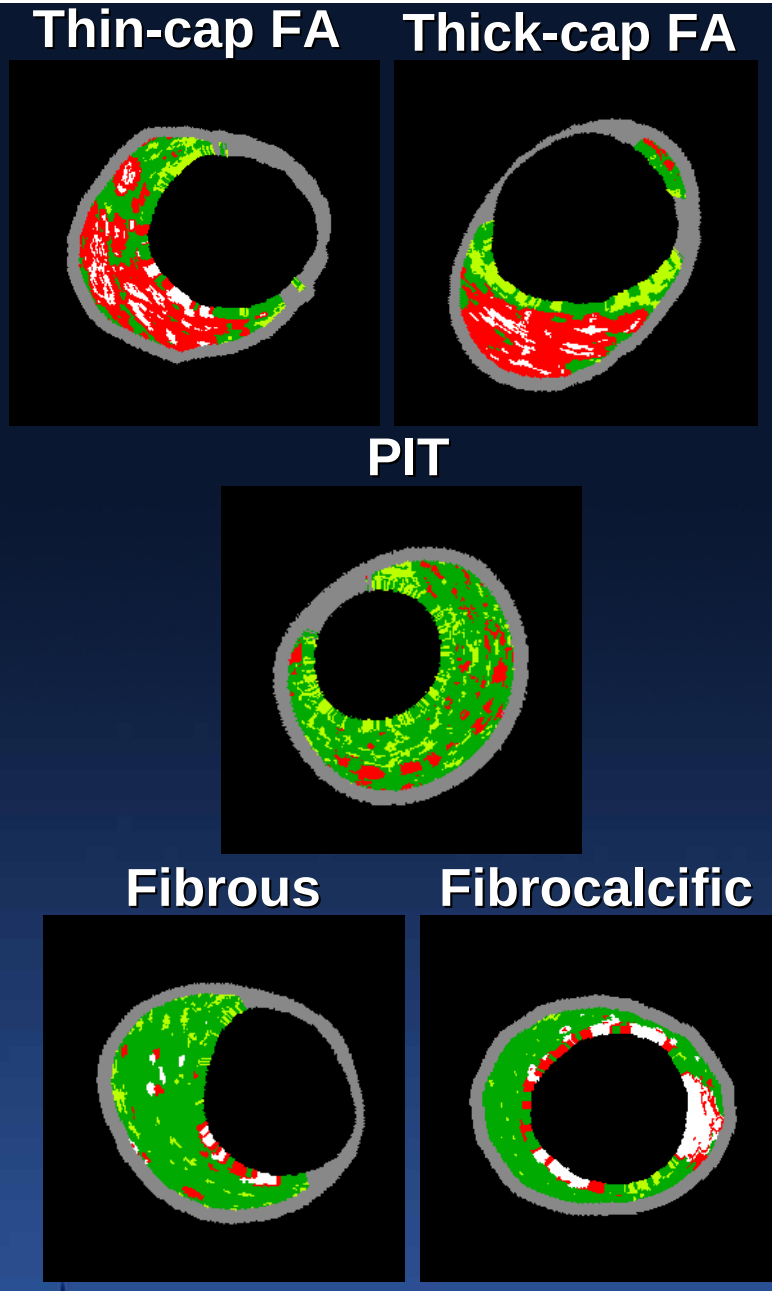

Pre-specify the definitions

Catheterization and Cardiovascular Interventions 65:233–239 (2005)

Impact of Different Definitions on the Interpretation of Coronary Remodeling Determined by Intravascular Ultrasound

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The objective of this study was to compare the categorizations and determinants related to remodeling by the three definitions commonly used. Several morphological and intravascular ultrasound (IVUS) studies have demonstrated the fundamental importance of arterial remodeling in atherosclerosis. However, lack of consensus on how to define remodeling has led to conflicting analyses of factors that influence this process. Analysis of preinterventional IVUS images of 514 lesions in native coronary arteries was performed. Arterial remodeling was defined as outward by definition 1, when [cross-sectional area (CSA) of the external elastic membrane (EEM) at the lesion site (EEM_{lesion})]/[EEM CSA either at the proximal ($EEM_{prox\ ref}$) or distal ($EEM_{distal\ ref}$) reference site with the least amount of plaque] was > 1.05, intermediate when this ratio was between 0.95 and 1.05, and inward when < 0.95. Remodeling was defined as outward by definition 2 when EEM_{lesion} > both $EEM_{prox\ ref}$ and $EEM_{distal\ ref}$, inward when EEM_{lesion} < both $EEM_{prox\ ref}$ and $EEM_{distal\ ref}$, and intermediate when EEM_{lesion} was intermediate between $EEM_{prox\ ref}$ and $EEM_{distal\ ref}$. By definition 3, vessel remodeling was defined as outward when EEM_{lesion} > ($EEM_{prox\ ref}$ + $EEM_{distal\ ref}$)/2 and intermediate/inward when $EEM_{lesion} \leq (EEM_{prox\ ref} + EEM_{distal\ ref})/2$. The frequency of outward remodeling was significantly higher by definitions 1 and 3 than by definition 2, whereas a higher frequency of inward remodeling was observed in definition 1, resulting in significantly different remodeling distributions between the three definitions ($P < 0.0001$). By multivariate logistic analysis, the only clinical determinants related to outward remodeling was younger age, and only by definition 3. IVUS determinants varied significantly between the three definitions. The only consistent determinants among the three definitions were smaller lumen CSA at the reference site and larger plaque + media CSA at the lesion site. This study demonstrates the significant impact of different remodeling definitions on the incidence and determinants of remodeling patterns. The marked variability in categorization of remodeling underscores the importance of developing a standard methodology. © 2005 Wiley-Liss, Inc.

Key words: atherosclerosis; coronary disease; ultrasonics

INTRODUCTION

Intravascular ultrasound (IVUS) studies have demonstrated that the remodeling response is critical in determining lumen size in de novo atherosclerosis [1,2] or in vessels after intervention [3–5]. Recent studies have indicated that outward remodeling may be associated

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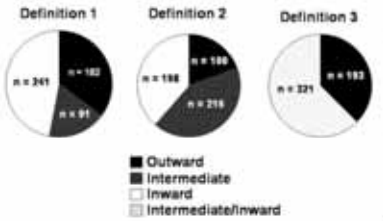

Fig. 2. Frequency distribution and type of remodeling pattern for each remodeling definition.

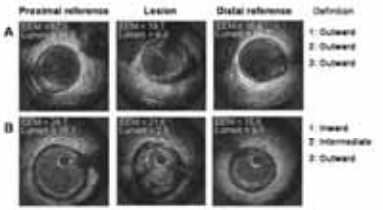

Fig. 3. Representative IVUS images of coronary arteries showing consistent (top) and inconsistent (bottom) remodeling pattern between the three remodeling definitions.

inward remodeling in 198 (38.5%) lesions. By definition 3, outward remodeling was observed in 193 (37.5%) lesions and intermediate/inward remodeling in 321 (62.5%) lesions. There was a lower frequency of lesions with intermediate remodeling and a higher frequency of lesions with inward remodeling by definition 1 than by definition 2 ($P < 0.0001$). The frequency of lesions with outward remodeling was significantly higher by definition 1 and definition 3 than by definition 2 (both $P < 0.0001$).

Examples of categorization of lesion remodeling are shown in Figure 3. The lesion in the top panel was consistently defined as outward remodeling by all definitions (Fig. 3A). In contrast, the category of remodeling assigned to the lesion in the bottom panel was inconsistent (Fig. 3B). By definition 1, this lesion was assigned to inward remodeling using the proximal reference site to calculate the RI. The same lesion was assigned to intermediate remodeling by definition 2, whereas definition 3 defined this lesion as outward remodeling (Fig. 3B).

Determinants of Arterial Remodeling

The characteristics of the 514 lesions among the lesions with outward, intermediate, and inward remodeling are summarized in Table II. Only those parameters showing significant differences between groups by any of the three definitions are presented. When clinical variables were compared between vessel remodeling subgroups, no difference was noted. As expected from the definitions of remodeling patterns, lesions with outward remodeling had consistently larger P+M CSA and plaque burden at the lesion site than those with intermediate/inward remodeling ($P < 0.0001$ by any definition). Lumen CSAs at the reference site were consistently smaller in lesions with outward remodeling than in those with intermediate/inward remodeling ($P < 0.0001$ for definition 1, $P = 0.002$ for definition 2, and $P = 0.001$ for definition 3). Several parameters showed inconsistency between the three definitions for detecting the differences between remodeling subgroups: diseased vessel distributions, number of diseased vessels, P+M CSA at the reference site, plaque burden at the reference site, and lumen area stenosis (Table II).

By multivariate logistic analysis, the clinical and IVUS factors associated with positive remodeling varied significantly between the three definitions (Table III). Younger age and noncalcification at the lesion site were significantly associated with outward remodeling by definition 3 (odds ratio = 0.97 and 0.57, respectively); however, these factors did not remain significant by either definition 1 or definition 2. Similarly, left descending artery (LAD) lesion was associated with outward remodeling by definition 1 (odds ratio = 2.36), but not by definition 2 or 3. Smaller P+M CSA at the reference site was significantly associated with outward remodeling by definition 1 and definition 2 (odds ratio = 0.85 and 0.29, respectively), but not by definition 3. Furthermore, larger lumen CSA at the lesion site was significantly associated with outward remodeling by definition 2 only (odds ratio = 1.91). The only consistent associations with outward remodeling across all three definitions were smaller lumen CSA at the reference site and larger P+M CSA at the lesion site.

DISCUSSION

This study demonstrates that categorization and quantification of remodeling response is critically dependent on the method used to define remodeling. Consequently, correlation between remodeling response