Perspectives on the Evolution of IVUS Into a Clinical Tool

Gary S. Mintz, MD
Cardiovascular Research Foundation
New York, NY

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Eras of IVUS Discovery and Usage

- Invention and validation
- Early experiences
  - Mechanisms of intervention
  - Comparisons with angiography
- Mechanisms and predictors of restenosis
  - PTCA, DCA, rotational atherectomy, and ELCA
  - BMS implantation
  - DES implantation

- Clinical Utility
  - LM disease
  - Intermediate lesions
  - Unusual angiographic morphology
  - PCI optimization
    - Calcification
    - Eccentricity
    - Final lumen/stent dimensions and residual plaque burden
    - Complications

- Technology improvement
- Mechanisms of disease
- Progression and regression

Invention and Validation

- In the beginning there were
  - InterTherapy
  - CardioVascular Imaging Systems
  - Diasonics/Mansfield
  - Endosonics
- The seminal validation studies were. . .

- Mallery JA, Tobis JM, Griffith J, et al., Assessment of normal and atherosclerotic arterial wall thickness with an intravascular ultrasound imaging catheter. *Am Heart J* 1990; 119: 1392-400.
- Hodgson JMcB, Eberle M, Savakus A, Validation of a new real time percutaneous intravascular ultrasound imaging catheter. *Circulation* 1988; 78: II-21 (abstract).
- Hodgson JMcB, Graham SP, Sarakus AD, et al., Clinical percutaneous imaging of coronary anatomy using an over-the-wire ultrasound catheter system. *In J Cardiac Imaging* 1989; 4: 186-93.
- Gussenhoven EJ, Essed CE, Lancee CT, et al., Arterial wall characteristics determined by intravascular ultrasound imaging: An in vitro study. *J Am Coll Cardiol* 1989; 14: 947-52.
- Tobis JM, Mallery JA, Gessert J, et al., Intravascular ultrasound cross-sectional arterial imaging before and after balloon angioplasty in vitro. *Circulation* 1989; 80: 873-82.
- Potkin BN, Bartorelli AL, Gessert JM, et al., Coronary artery imaging with intravascular high-frequency ultrasound. *Circulation* 1990; 81: 1575-85.
- Nishimura RA, Edwards WD, Warnes CA, et al., Intravascular ultrasound imaging: in vitro validation and pathologic correlation. *J Am Coll Cardiol* 1990; 16: 145-54.
- Wenguang L, Gussenhoven WJ, Zhong Y, et al., Validation of quantitative analysis of intravascular ultrasound images. *In J Card Imaging* 1991; 6: 247-53.
- DiMario C, The SH, Madretsma S, et al., Detection and characterization of vascular lesions by intravascular ultrasound: An in vitro study correlated with histology. *J Am Soc Echocardiogr* 1992; 5: 135-46.
- Tobis JM, Mallery J, Mahon D, et al., Intravascular ultrasound imaging of human coronary arteries in vivo. Analysis of tissue characterizations with comparison to in vitro histological specimens. *Circulation* 1991; 83: 913-26.
- Gussenhoven EJ, Essed CE, Frietman P, et al., Intravascular echographic assessment of vessel wall characteristics: A correlation with histology. *Int J Card Imag* 1989; 4: 105-16.

Mechanisms of Intervention - I

- Balloon angioplasty
  - Vessel expansion
  - Axial plaque redistribution
  - Dissection
- Stand-alone DCA
  - Plaque excision (limited by calcium, even angiographically invisible calcium)
  - Dissection
- DCA+adjunct PTCA
  - Plaque excision (limited by calcium, even angiographically invisible calcium)
  - Vessel expansion
  - Dissection

Mechanisms of Intervention - II

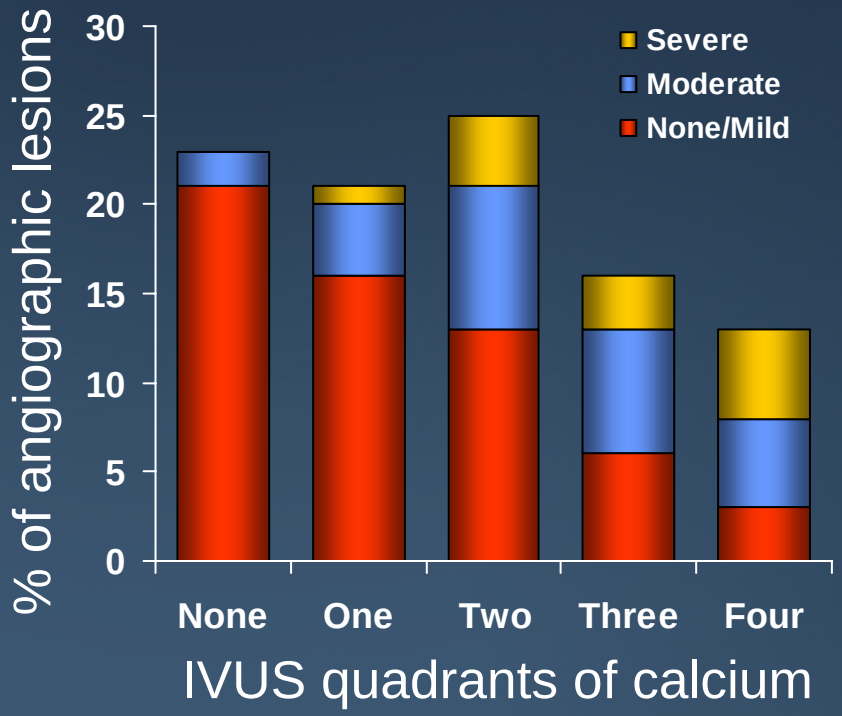
- Rotational Atherectomy
  - Limited plaque ablation
  - Significant residual plaque burden
  - Most of the lumen enlargement came with adjunct PTCA and vessel expansion
- Excimer Laser Coronary Angioplasty
  - Minimal plaque ablation
  - No calcium ablation
  - Fracture within calcium deposits
  - Forced vessel expansion
  - Most of the lumen enlargement came with adjunct PTCA and vessel expansion

Mechanisms of Intervention - III

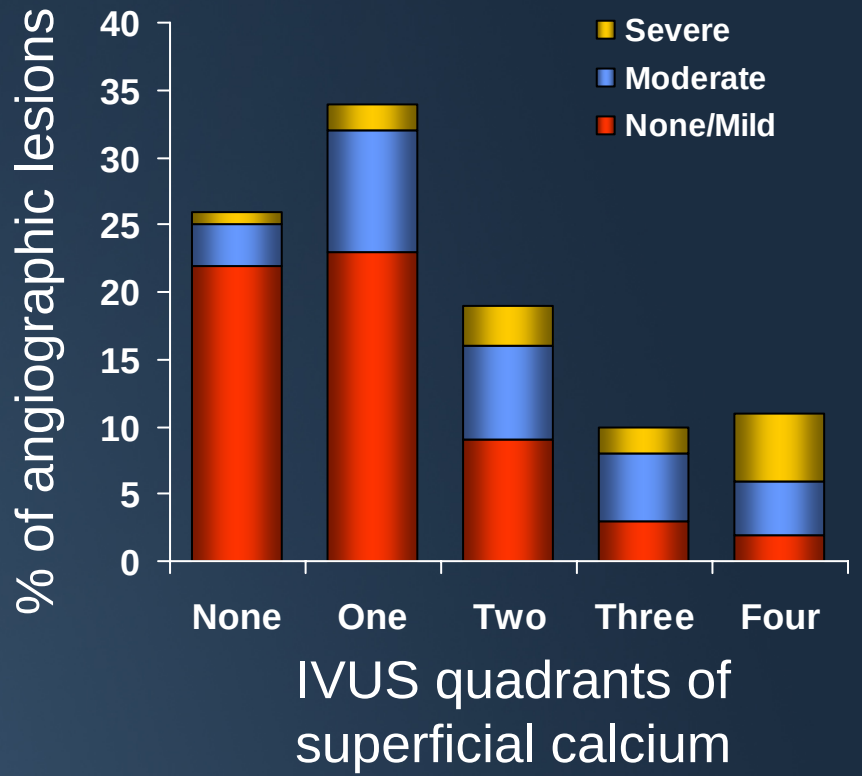
- Stent implantation
  - Vessel expansion
  - Axial plaque redistribution
- Treatment of in-stent restenosis
  - DCA, RA, and ELCA all removed tissue
  - Balloon angioplasty, adjunct balloon angioplasty, or additonal stent implantation additionally expanded the stent
  - Lumen of the original stent implantation procedure was rarely recovered

Lesion Calcification

Calcification



Superficial calcification



The only predictor of IVUS calcium was angiographic calcification elsewhere in the coronary tree. (Tuzcu et al. J AM Coll Cardiol 1996;27:832-8)

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Mintz et al. Circulation1995;91:1959-65.

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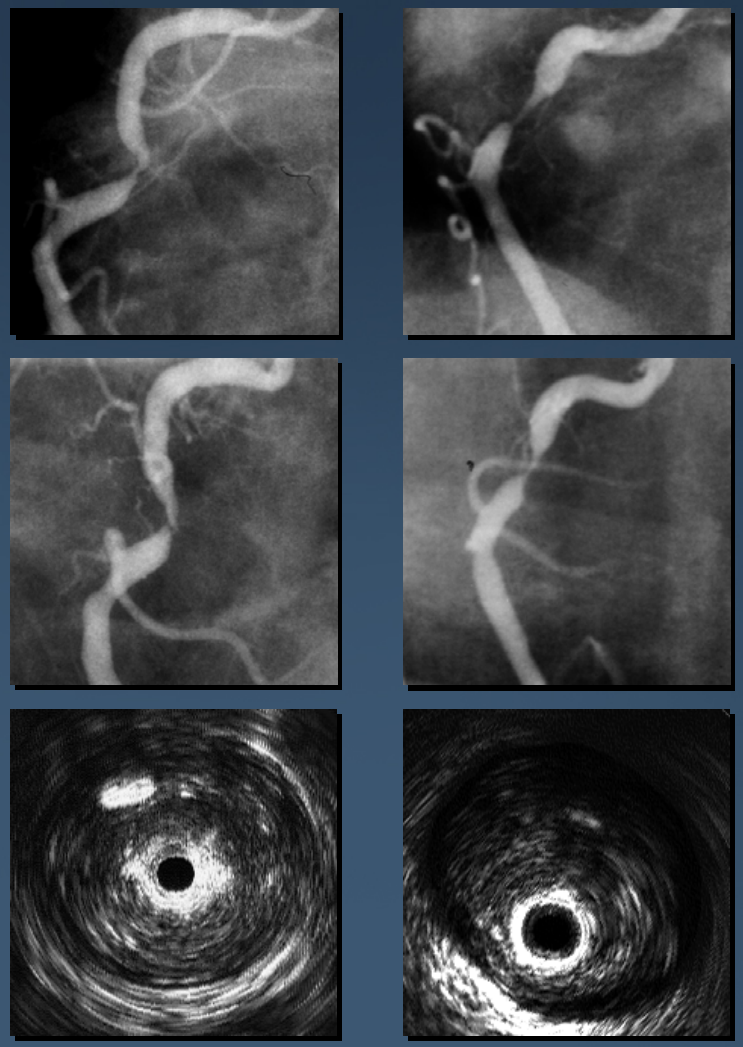
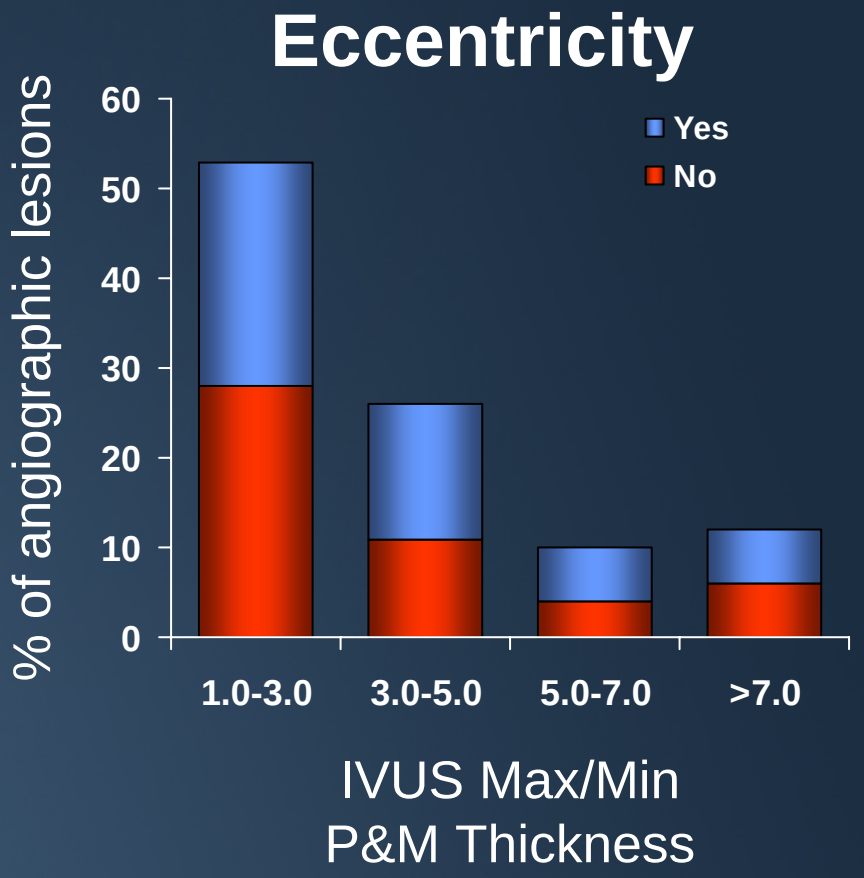
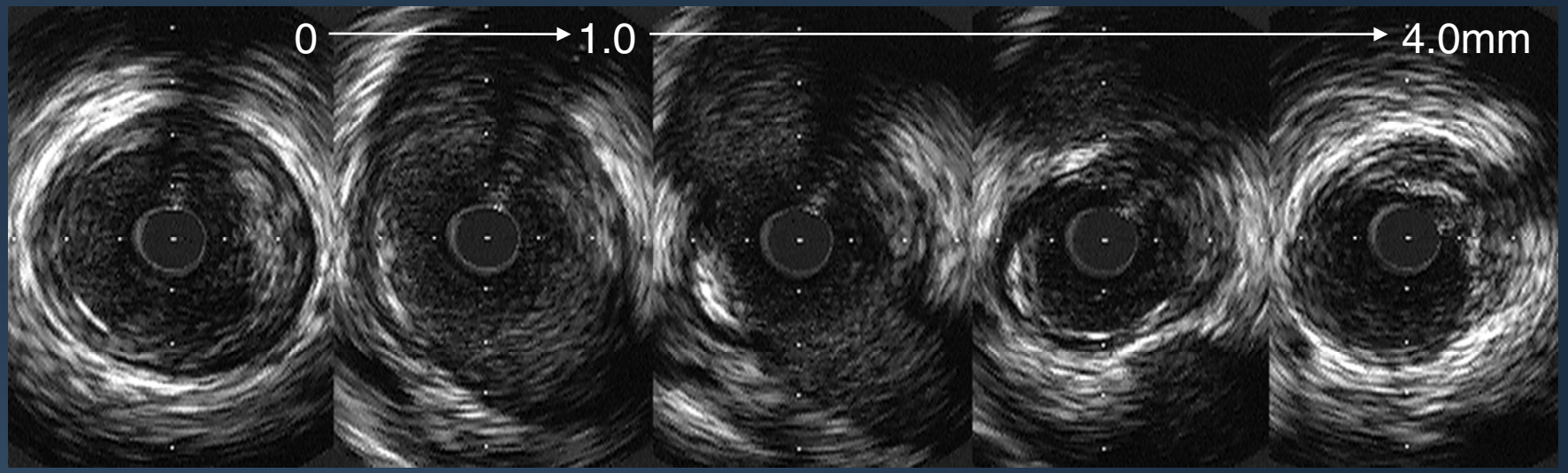
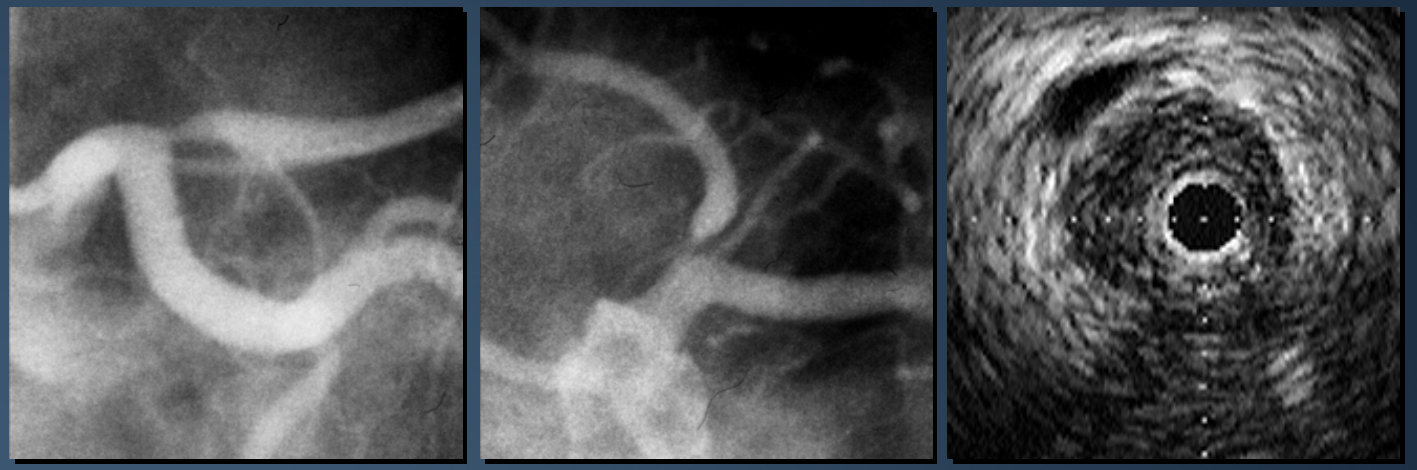
Lesion Eccentricity





Mintz et al. Circulation1996;93:924-931





Maximum plaque thickness spares the flow divider in nearly all cases and plaque deposition is usually opposite the sidebranch.

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Kimura et al. J Am Coll Cardiol 1996;27:825-31

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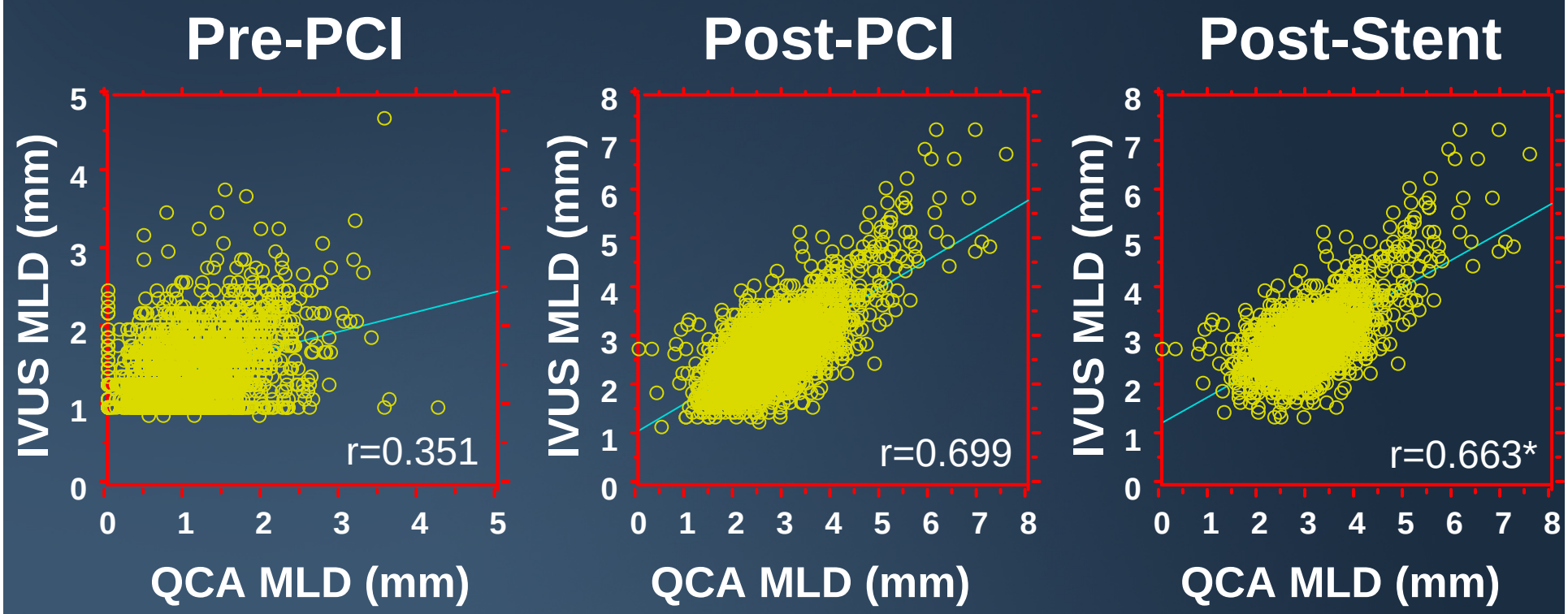
QCA vs IVUS MLD



*worse for >2 stents

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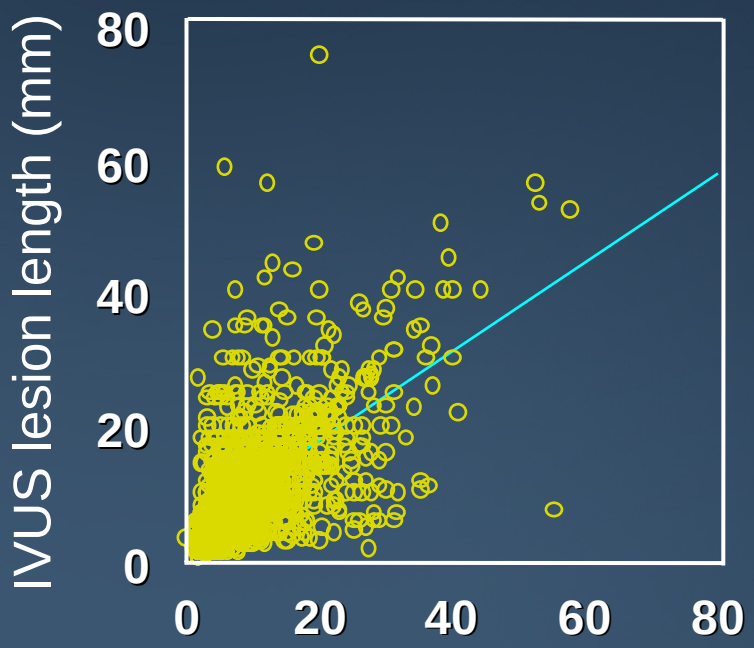
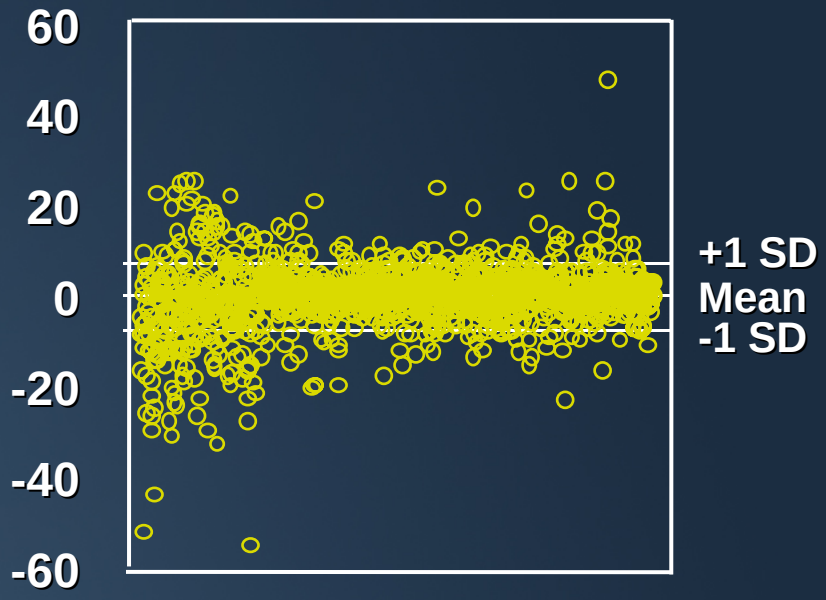
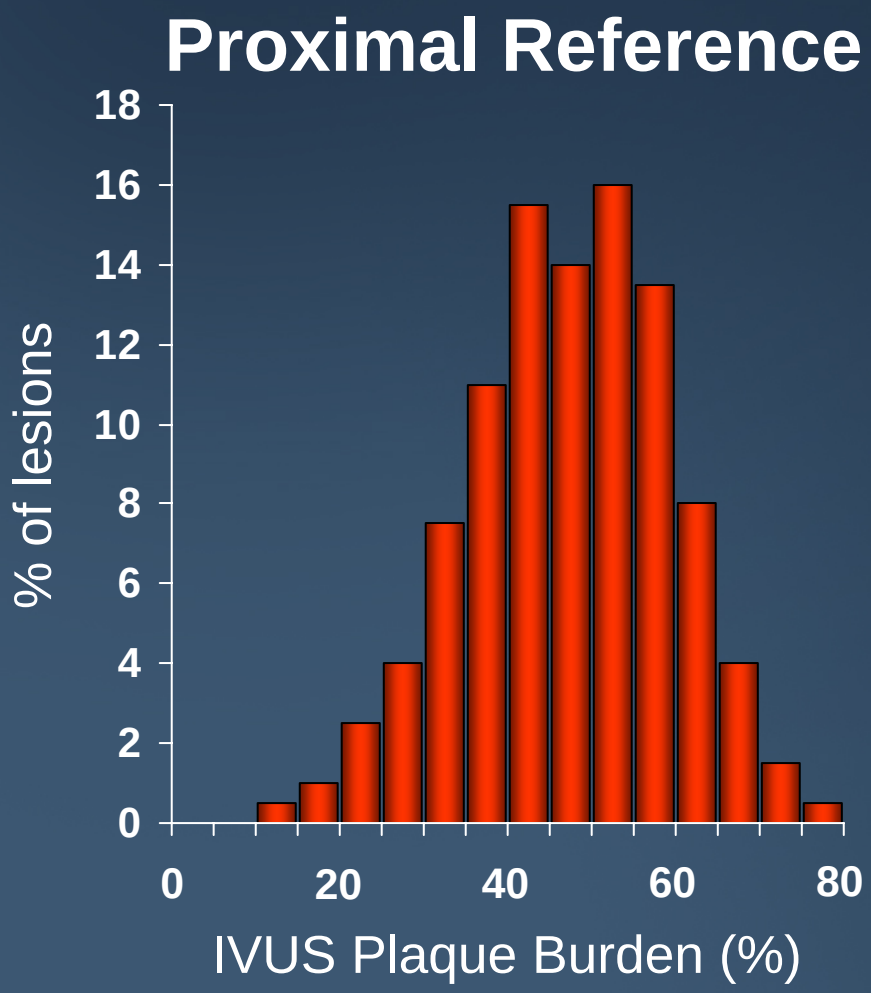
Lesion Length

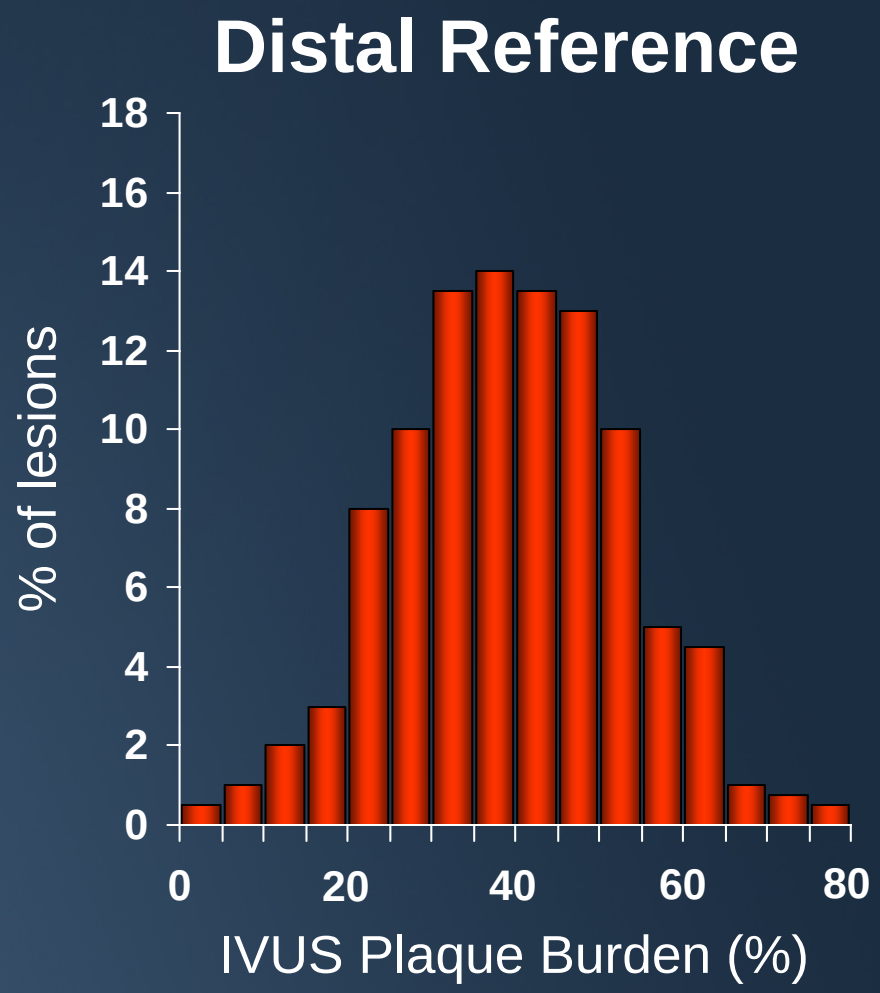




IVUS-QCA lesion length=0.6±7.2mm

Reference Segment Plaque Burden





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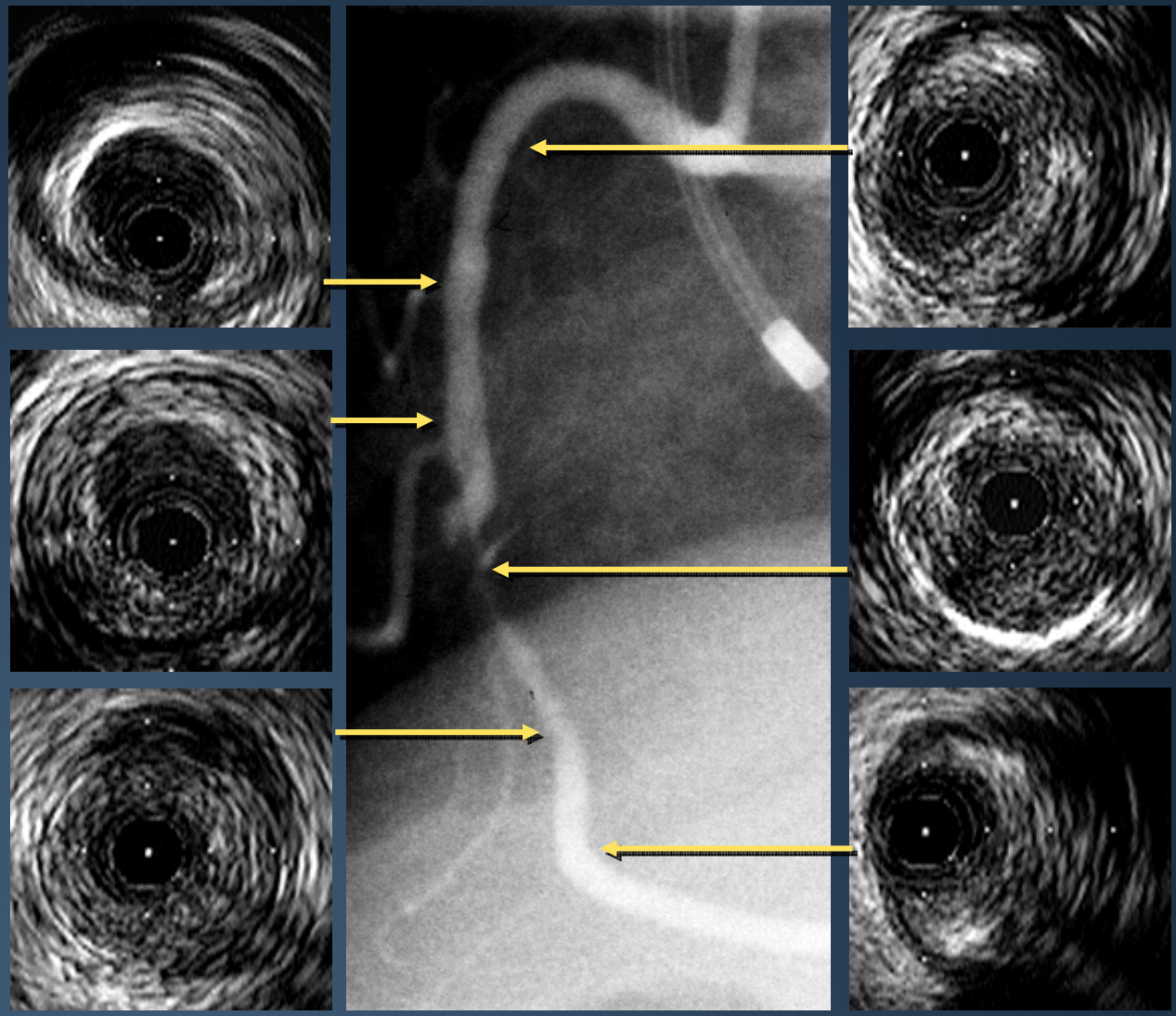

Mintz et al. J Am Coll Cardiol 1995;25:1479-85

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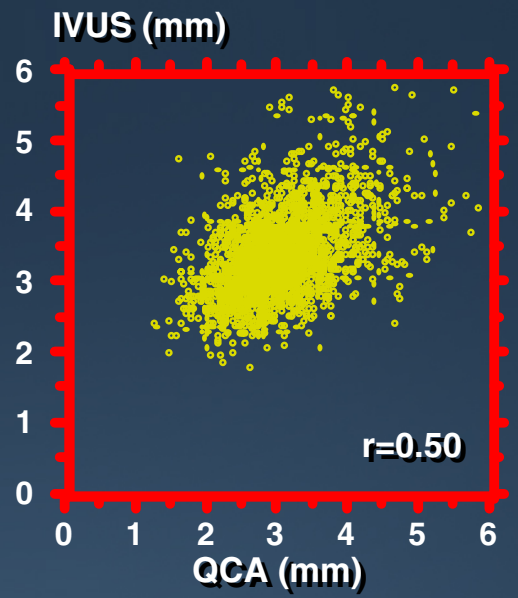
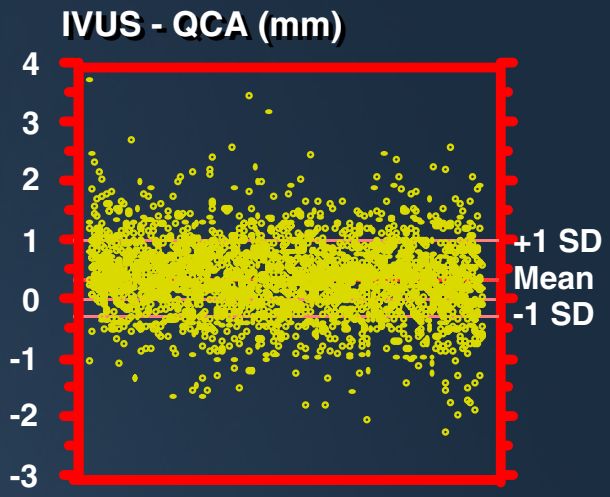
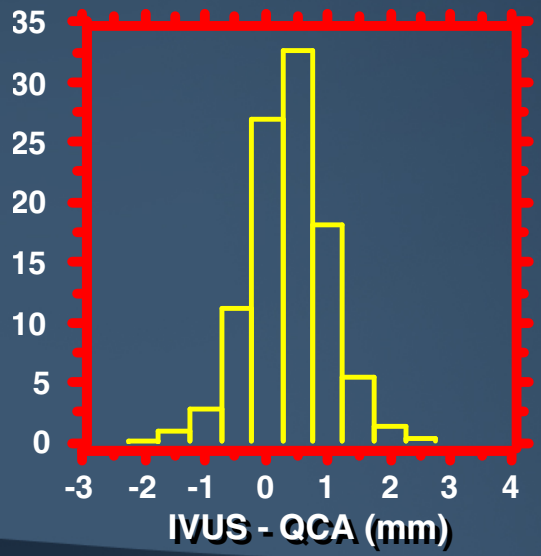
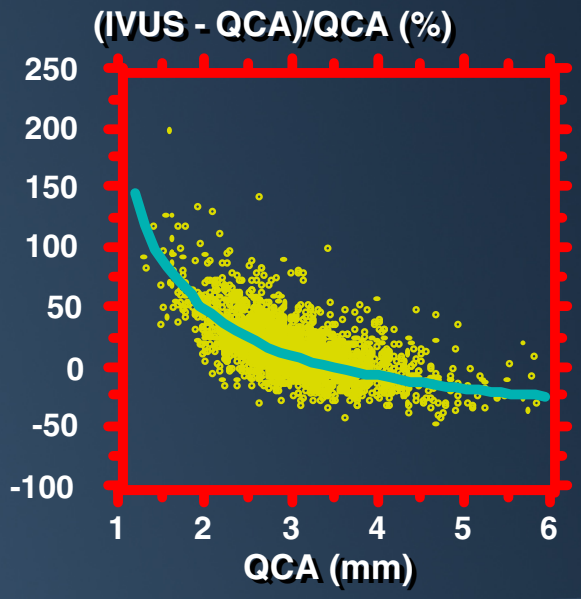
Reference Lumen Sizes









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Mechanisms of Restenosis

- Balloon angioplasty
- Atherectomy
- BMS
- In-stent restenosis
- Brachytherapy
- DES

Prior to the seminal serial IVUS studies, it was believed that intimal hyperplasia was the cause of restenosis in non-stented lesions and that chronic stent recoil was the cause of restenosis in stented lesions.

Mechanisms of Restenosis - I

- (Except, perhaps, in diabetic patients, who have more intimal hyperplasia than non-diabetics) late arterial responses to nonstent coronary interventions are determined less by tissue growth than by the direction and magnitude of arterial remodeling (increase or decrease in EEM).
- Early (w/i 1 month) positive remodeling prevents lumen loss.
- Early positive remodeling is followed by late negative remodeling (vessel contraction) that is distinct from passive elastic recoil and that is responsible for 70% of late lumen loss in non-stented lesions.
- The residual plaque burden is the strongest predictor of restenosis in non-stented lesions.

Mintz et al. Circulation 1996;94:35-43
Kimura et al Circulation 1997;96:475-83
Kornowski et al. Circulation 1997;95:1366-9
Mintz et al J Am Coll Cardiol 1996;27:1678-87

Editorial

Vascular Remodeling

Honey, I Think I Shrunk the Artery

Jeffrey M. Isner, MD

The mechanisms responsible for both favorable and unfavorable outcomes of balloon angioplasty continue to invite controversy. Nowhere is this more profound than in the case of restenosis, clearly the most frequent complication of percutaneous revascularization. Despite the fact that 185 patents describing treatment strategies designed to limit restenosis have been issued during the past decade,[1] until recently successful clinical application of derivative therapies has been virtually without success. There can be little doubt that our lack of understanding regarding the mechanisms responsible for restenosis has provided the underpinnings of our inability to successfully prevent its recurrence.

See p 2816

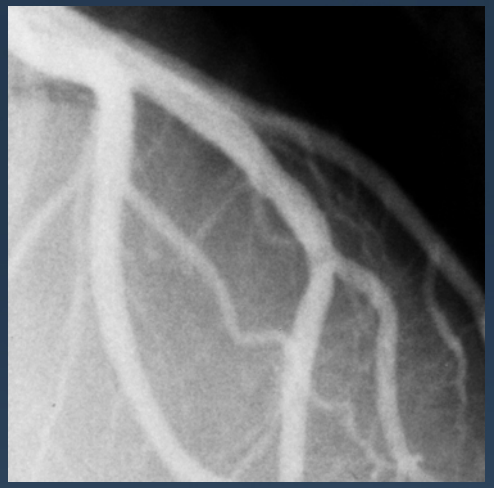
The vast majority of medical therapies designed to preempt restenosis have been predicated on the assumption that smooth muscle cell (SMC) proliferation constitutes the principal pathogenetic basis for restenosis. This concept has its origins in the fundamental studies of human atherosclerotic arteries that identified SMC accumulation within the neointima of (primary) lesions obtained at necropsy[2-4] and in supportive experimental observations in a variety of animal models.[5-10] Subsequently, beginning with the report of Austin et al,[11] necropsy examination of sporadic patients dying at various intervals after percutaneous revascularization[12-21] disclosed foci of hypercellularity, including cells with phenotypic characteristics of vascular SMCs, at the original site of balloon angioplasty.

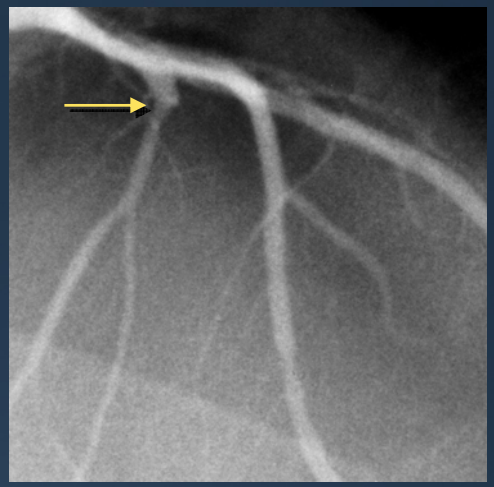
These reports were subsequently amplified by system-

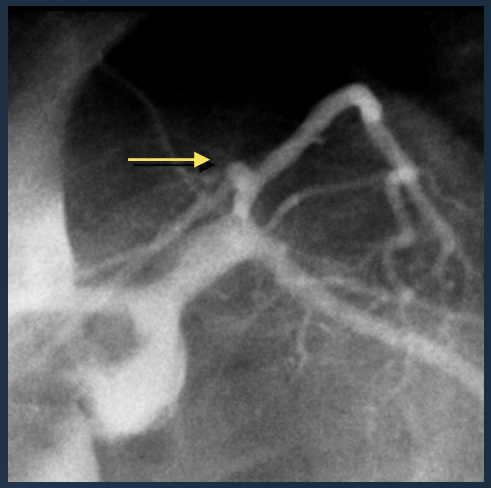
vascular SMCs, and the matrix surrounding these cells typically had a distinctly lighter hue and less-compact appearance than the matrix of primary or adjacent plaque.[26]

These contrasting findings regarding primary and restenotic lesions were perhaps best illustrated in a group of 18 patients studied in our laboratory[27] in whom directional atherectomy had been performed both as the primary intervention and again when the patient returned with restenosis. These 18 patients thus offered a unique opportunity to study the same lesion site in the same artery of the same patient at two different points in time. Light microscopic examination documented distinctive features, including hypercellular foci consisting of proliferative vascular SMCs surrounded by a loose neomatrix in 13 of 18 cases (72%). In 5 important exceptions, however, neither the primary nor the restenotic specimen demonstrated such a "restenosis focus." Of 253 restenosis specimens (65%) retrieved by directional atherectomy and studied in our laboratory,[27] a similar restenosis focus was identified in 165 (65%); among the remaining 88 specimens (35%), however, no distinctive histological features were observed.

Additional evidence supporting the proliferative nature of restenosis versus primary lesions is derived from ex vivo studies of SMCs cultured directly from explanted fragments of human atherectomy specimens.[28-38] These studies documented that the outgrowth kinetics of SMCs cultivated in this manner were indeed a reflection of the lesion type. Among 41 lesions retrieved by directional atherectomy and used in our laboratory to

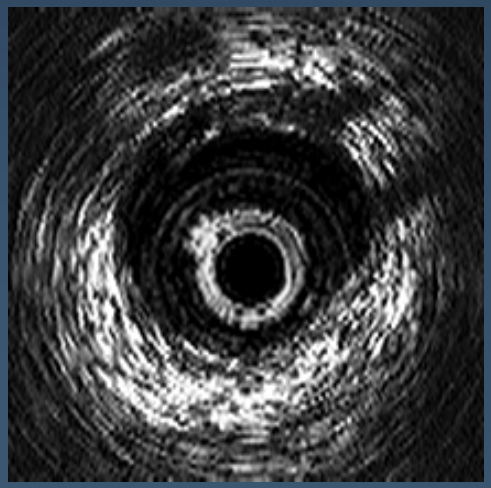




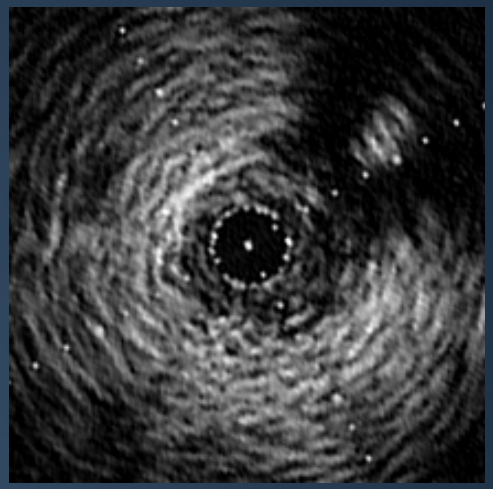


Post DCA+PTCA

7 month F/U



EEM =14.7mm²
Lumen = 10.2mm²
P&M = 4.6mm²



EEM = 5.5mm²
Lumen= 1.0mm²
P&M = 4.5mm²

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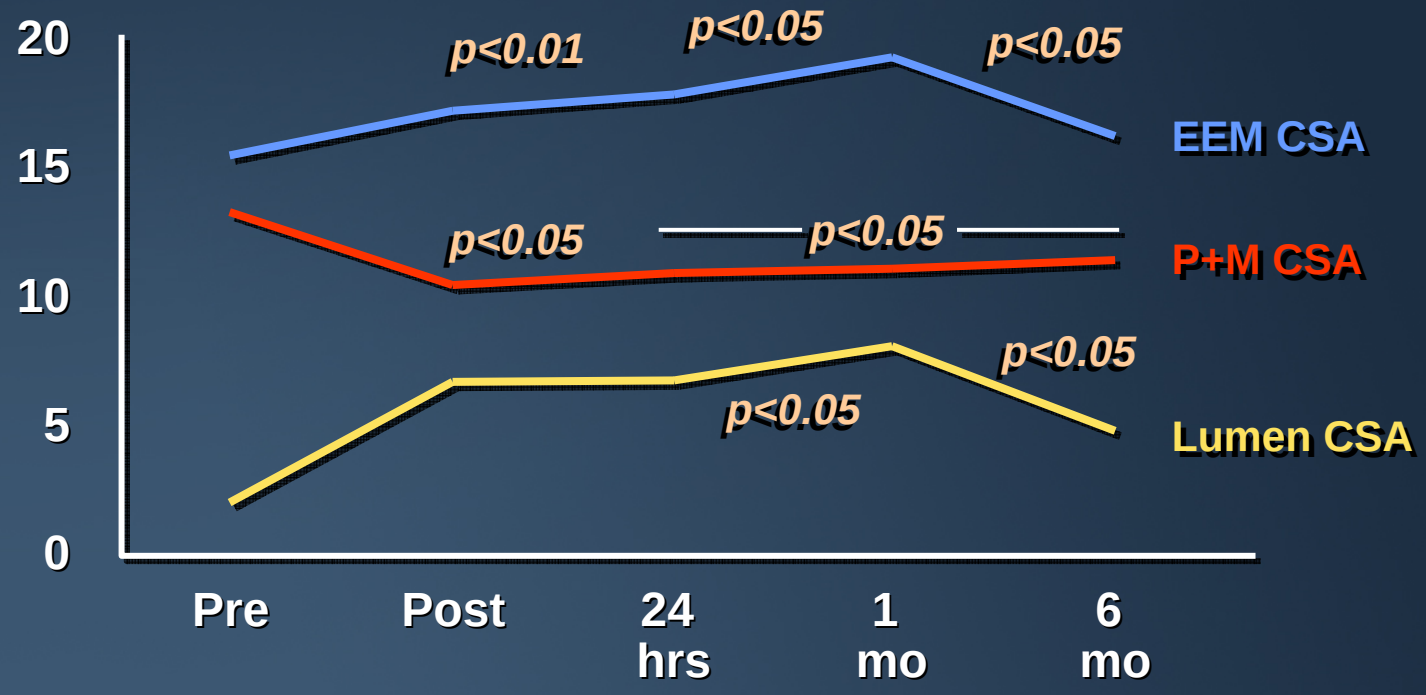
SURE Trial: Restenosis in non-stented lesions

Average of the two image slices with the smallest pre-intervention and follow-up lumen CSA



61 native vessel lesions (26 DCA, 35 PTCA) with complete serial IVUS studies (out of 79 lesions enrolled in the study)

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Kimura et al. Circulation 1997;96:475-83

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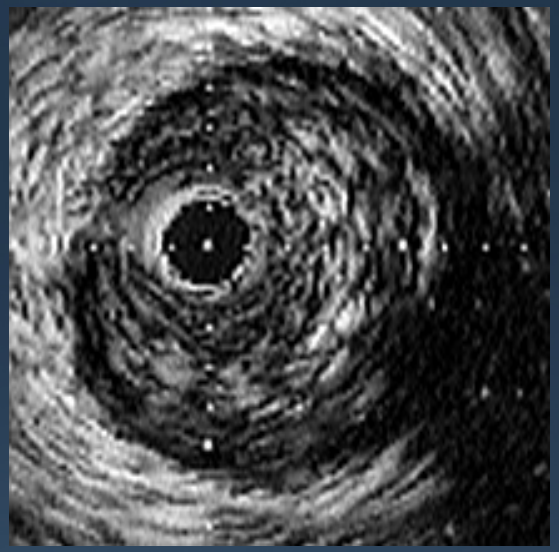
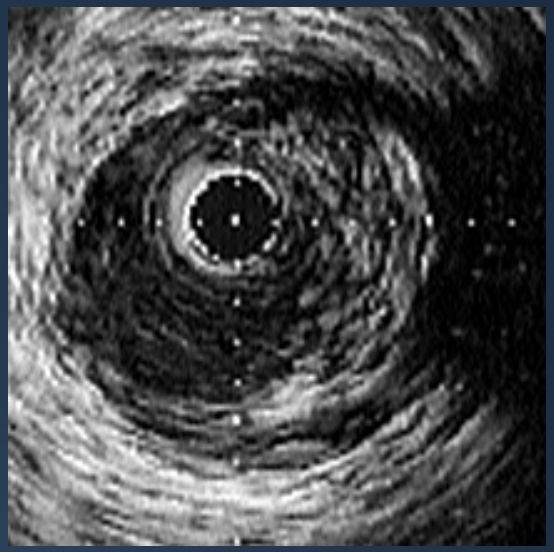
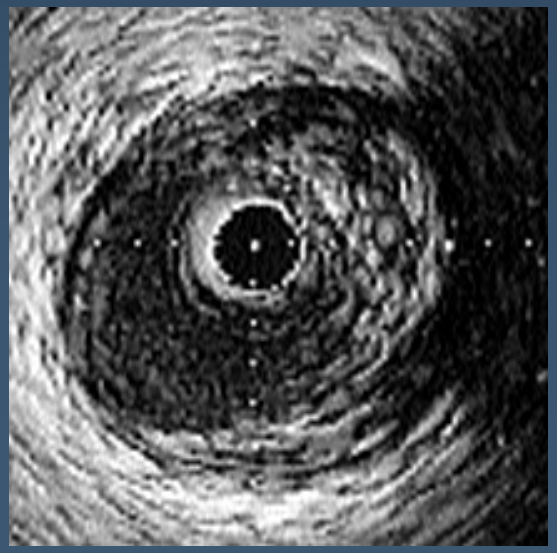


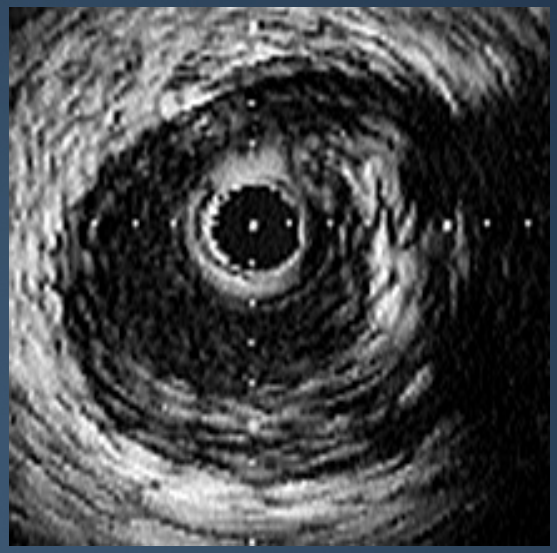
Pre DCA



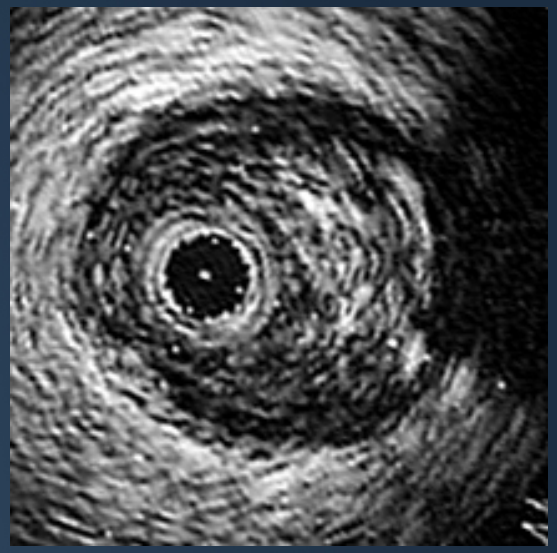
Post DCA+PTCA



24 hours



1 month



6 months

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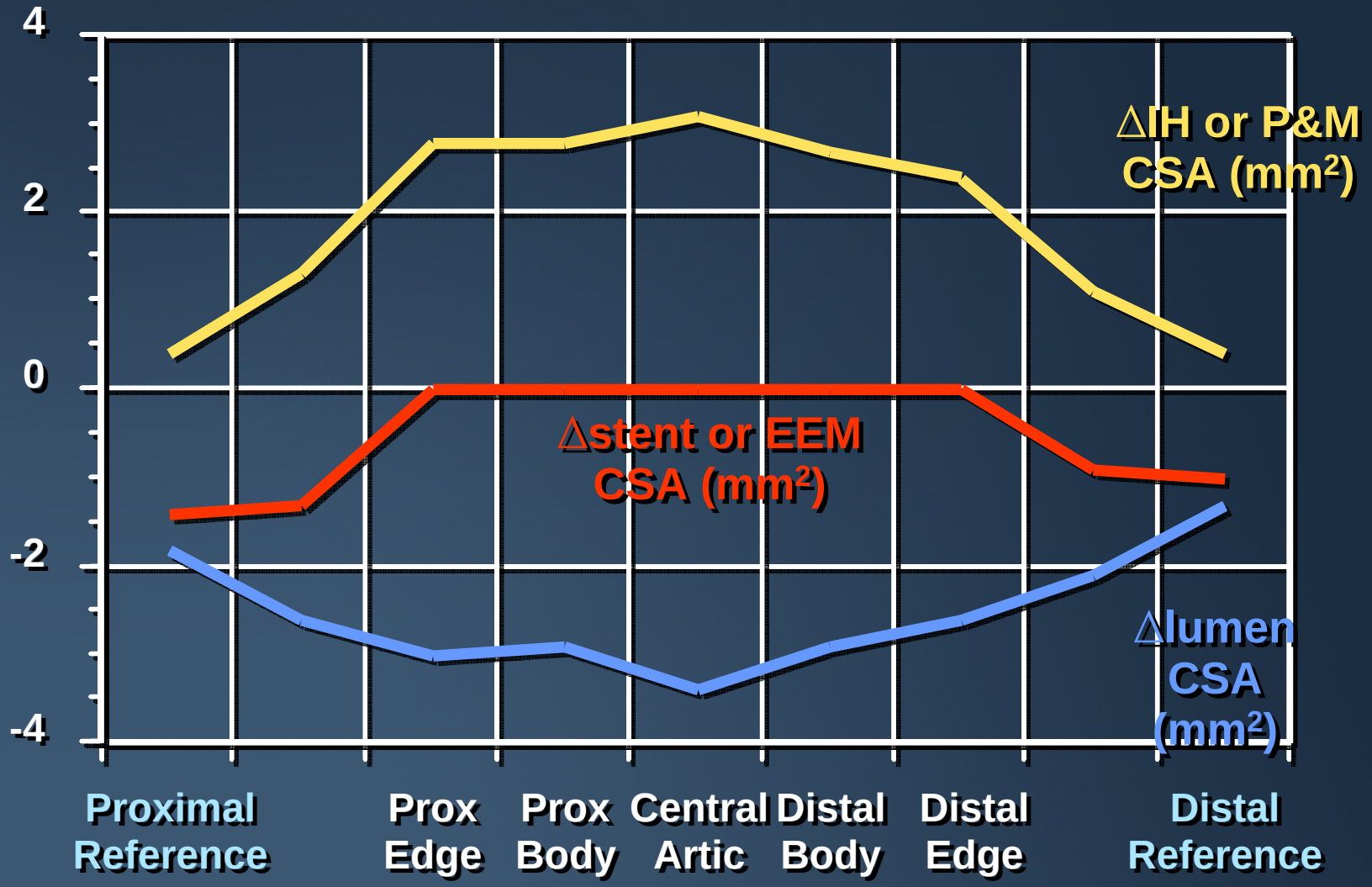
Mechanisms of Restenosis - II

- **Stents reduce restenosis by achieving a better post-procedural result and by *eliminating* remodeling. This offsets a stent-related *increase* in tissue growth.**
- **In-stent restenosis is *solely* the result of tissue growth. However, stent edge restenosis is a combination of negative remodeling and intimal hyperplasia and is determined, in part, by the plaque burden at the edge at the time of implant**
- **Mechanical problems - that occurred at the time of stent implantation - are present in a significant percentage of in-stent restenosis lesions**
- **The strongest predictor of in-stent restenosis is the final minimum stent CSA**

Hoffmann et al. Circulation 1996;94:1247-54
Hoffmann et al Am J Cardiol 1997;79:951-3
Mintz et al. AM J Cardiol 1996;78:18-22
Castagna et al. Am Heart J 2001;142:970-2
De Feyter et al. Circulation 1999;100:1777-83

Restenosis in Stented Lesions



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Hoffmann et al. Circulation 1996;94:1247-54

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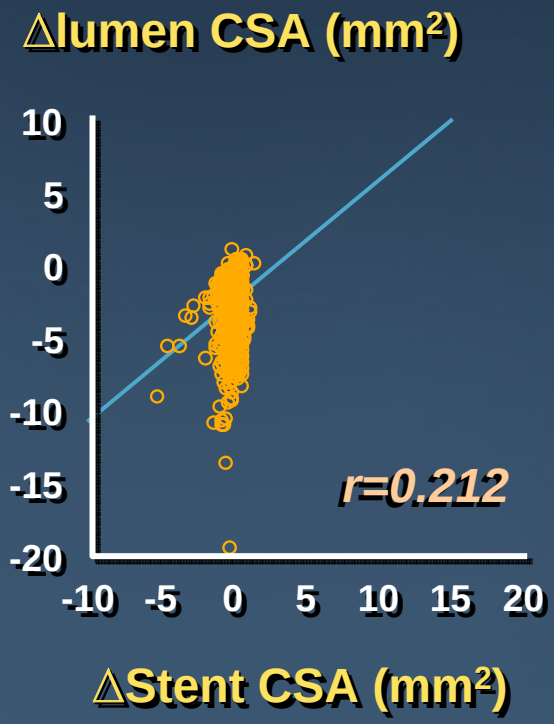
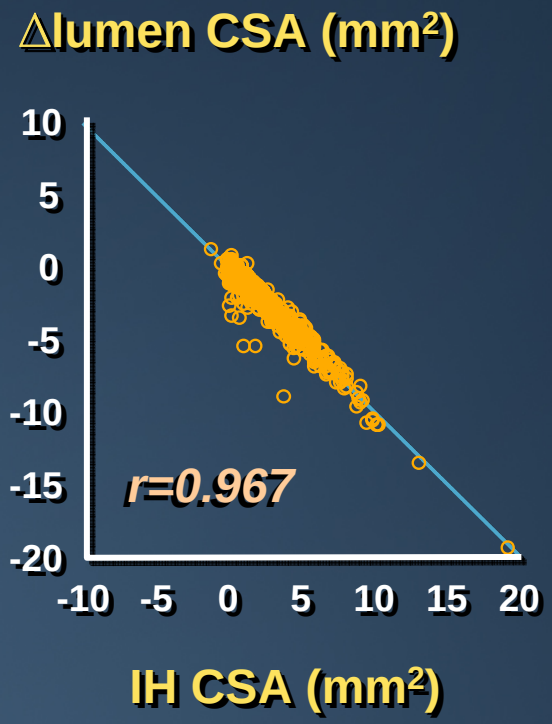
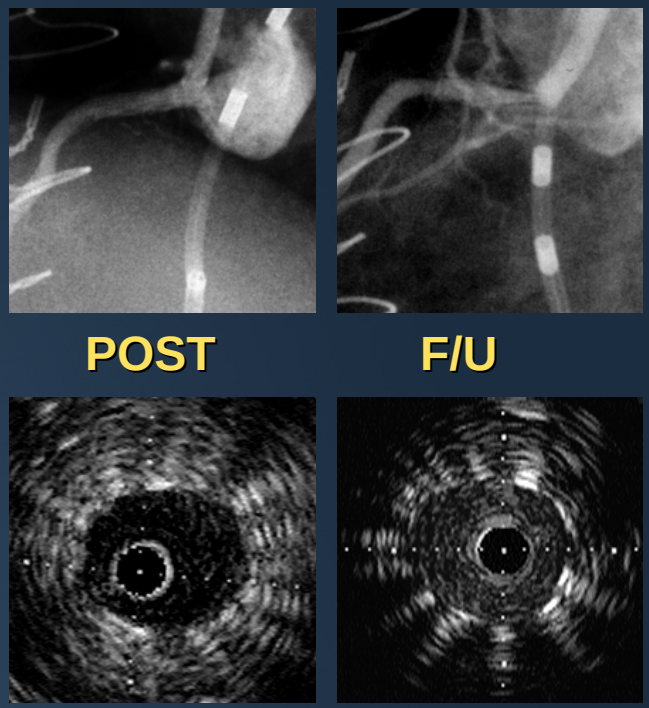
Therefore, in-stent restenosis is all intimal hyperplasia







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Hoffmann et al. Circulation 1996;94:1247-54

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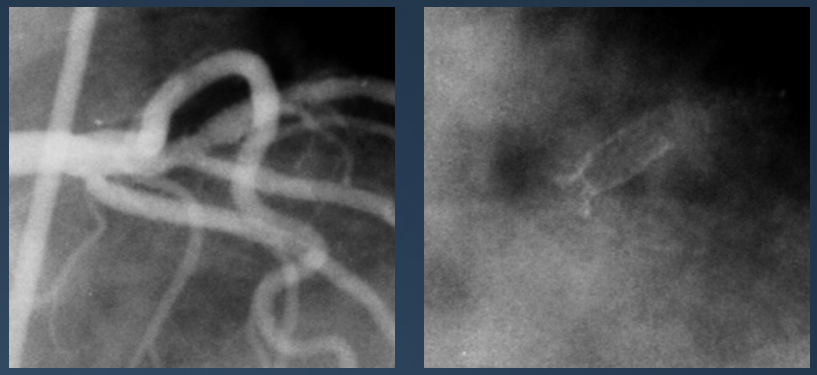
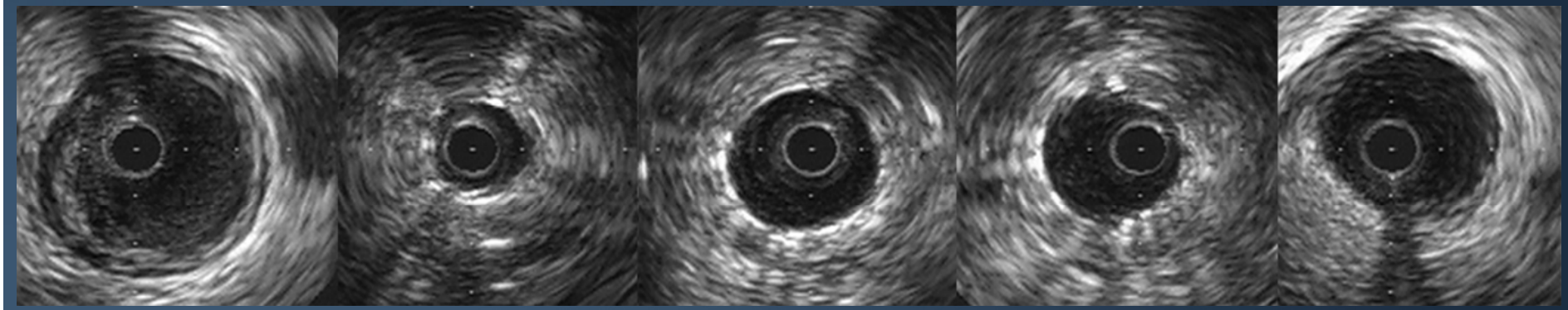


Proximal



0 → 5.0mm → 20.0mm

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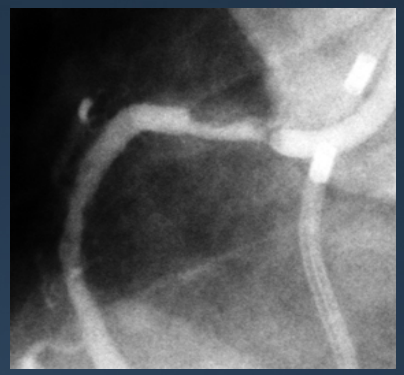
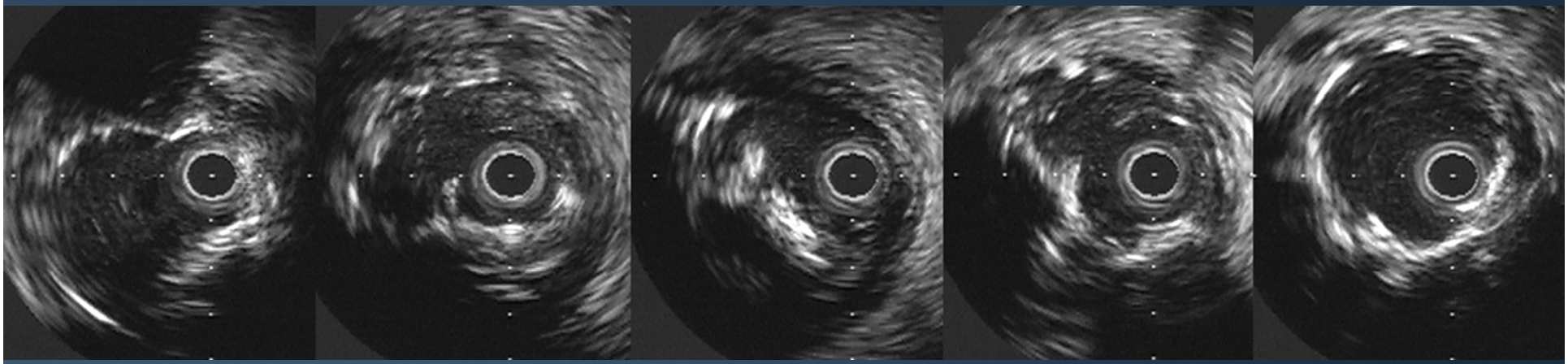


Proximal



0 → 2.5mm → 10.0mm

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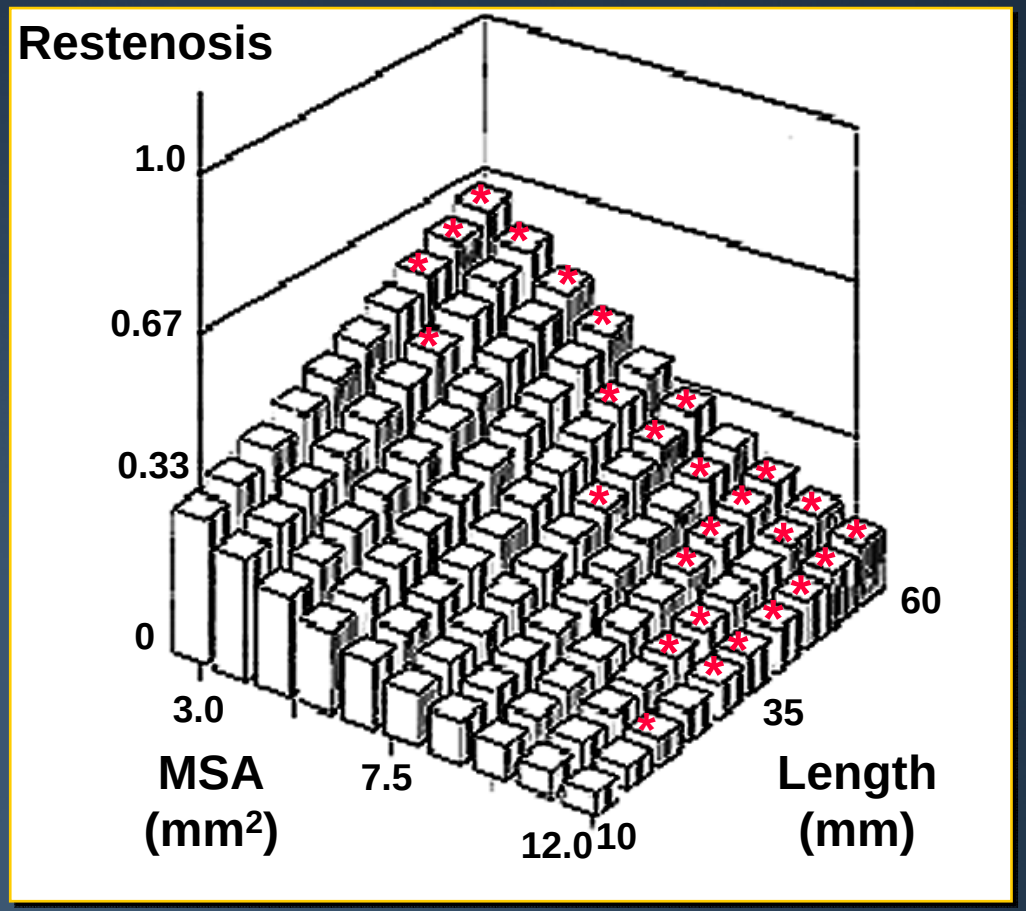
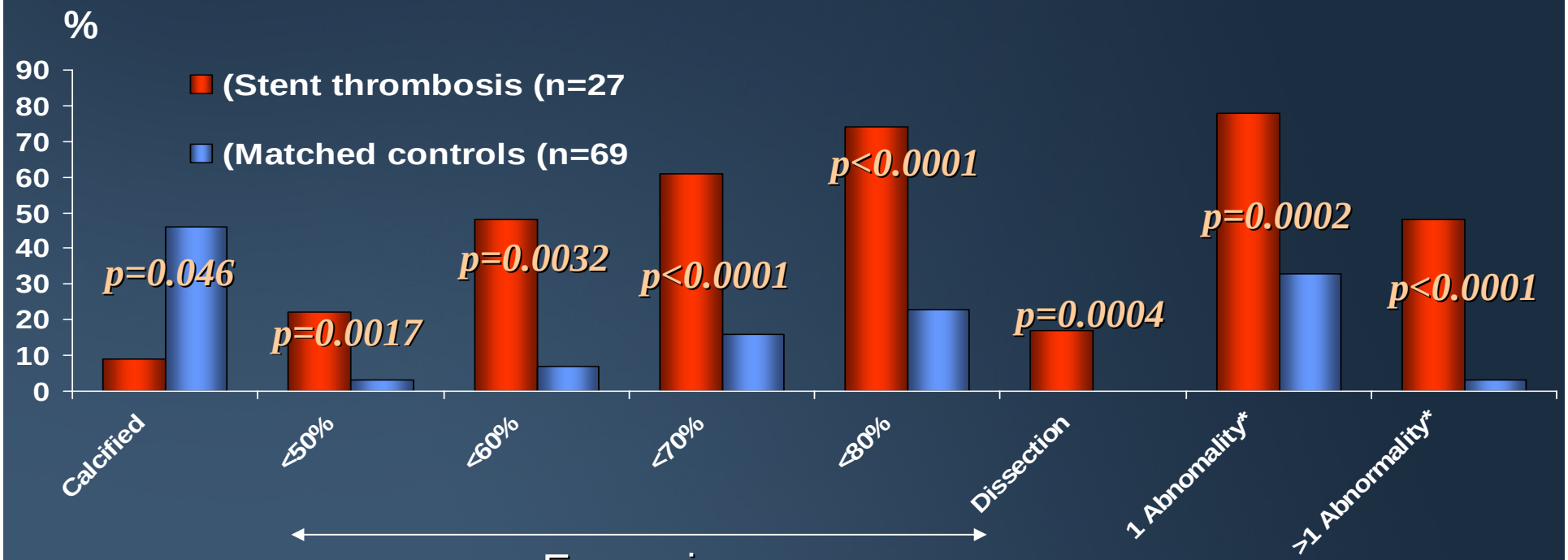
Impact of lesion length and final minimum stent area (MSA) on restenosis



**No actual observations in this range*

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

IVUS Predictors of Stent Thrombosis (27/7484=0.4%)



(MSA=6.4 vs 7.7mm^2, p=0.047)

***Expansion defined as <90% of reference lumen or <80% if MLA>9.0mm^2**

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Cheneau et al. Circulation 2003;108:43-47

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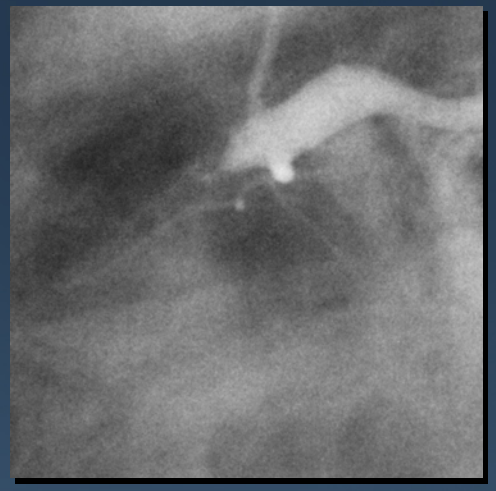
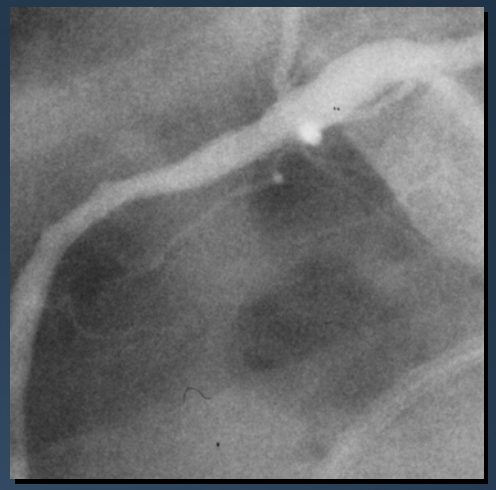
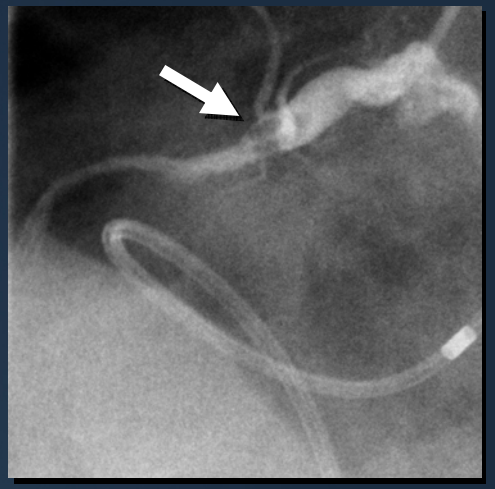
Crushed stent leading to subacute thrombosis



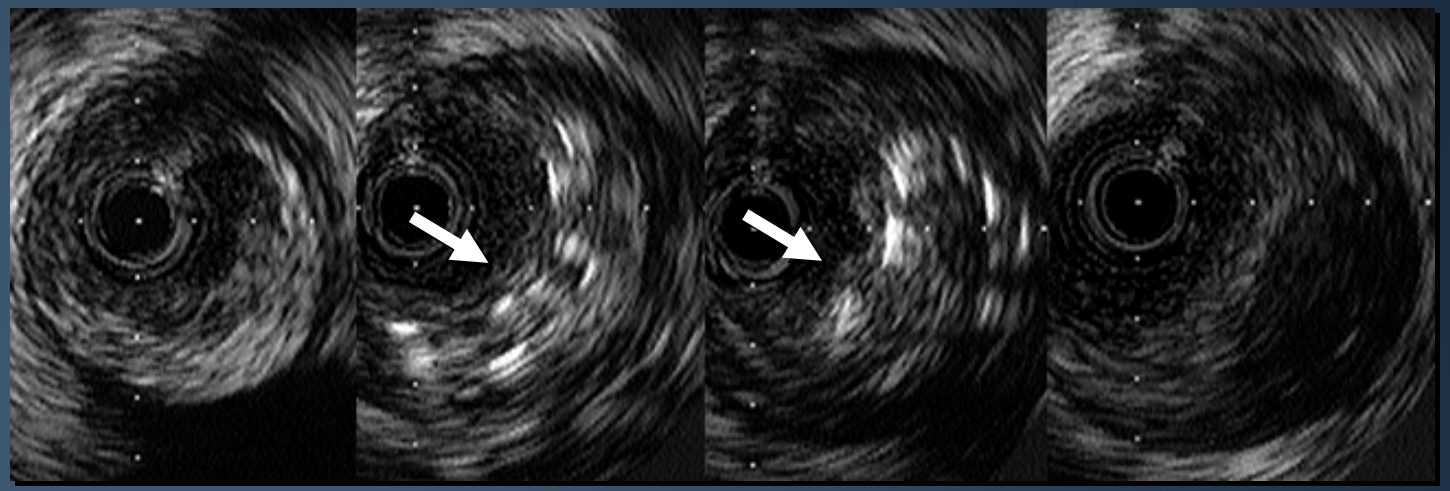
Pre-intervention



s/p JJIS+PTCA



2 week follow-up



0 → 4mm → 20mm

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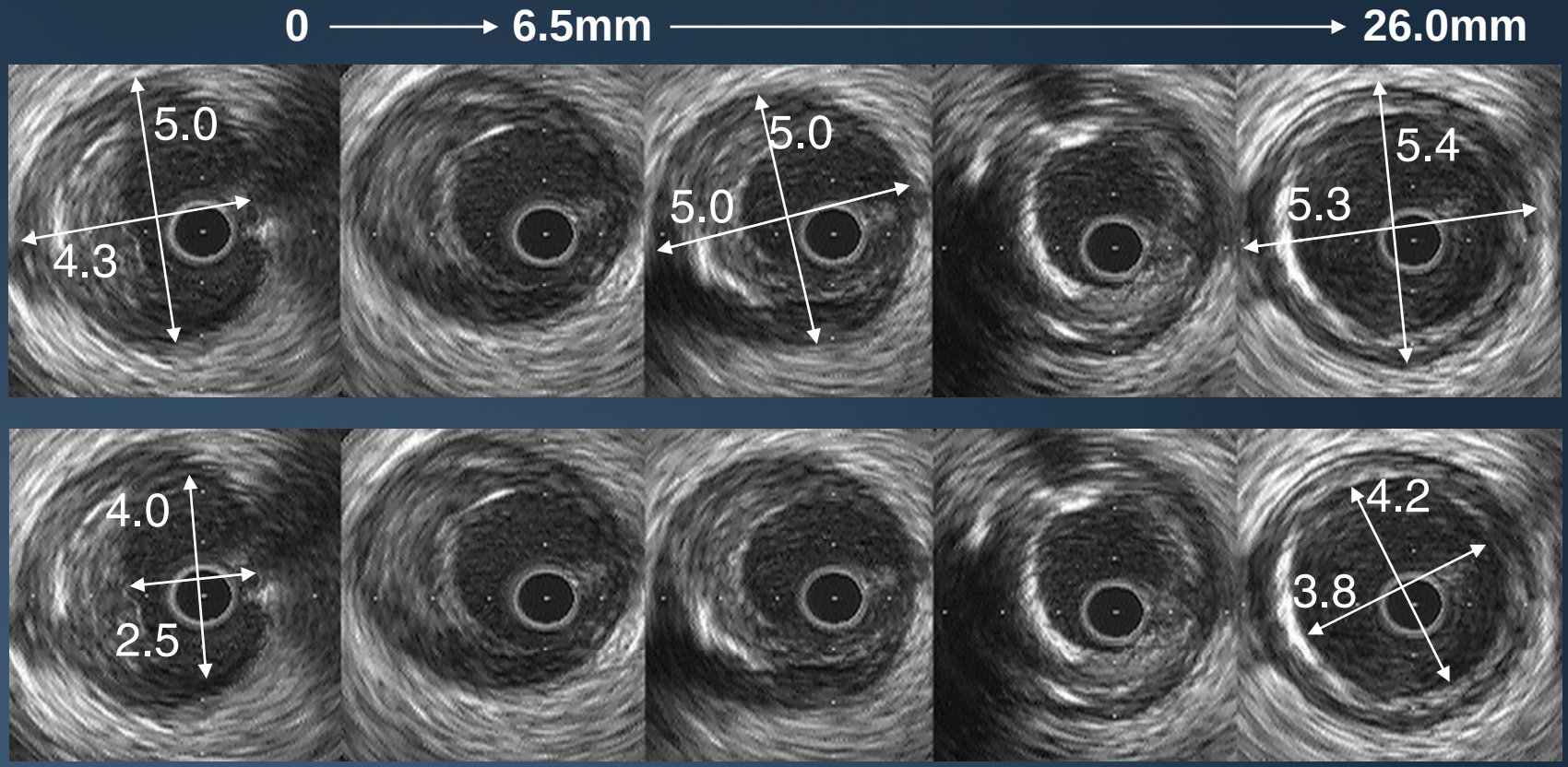
Clinical Utility

- Assess lesion severity
- Assess LM disease severity
- Whenever the angiogram, non-invasive tests, and clinical symptoms do not agree or whenever the angiogram is difficult to interpret
  - Hazy lesions
  - Aneurysms
  - Filling defects
  - ACS patients
- Select device and size
- Optimize procedural results
  - Maximize stent and lumen dimensions
  - Detect and treat complications



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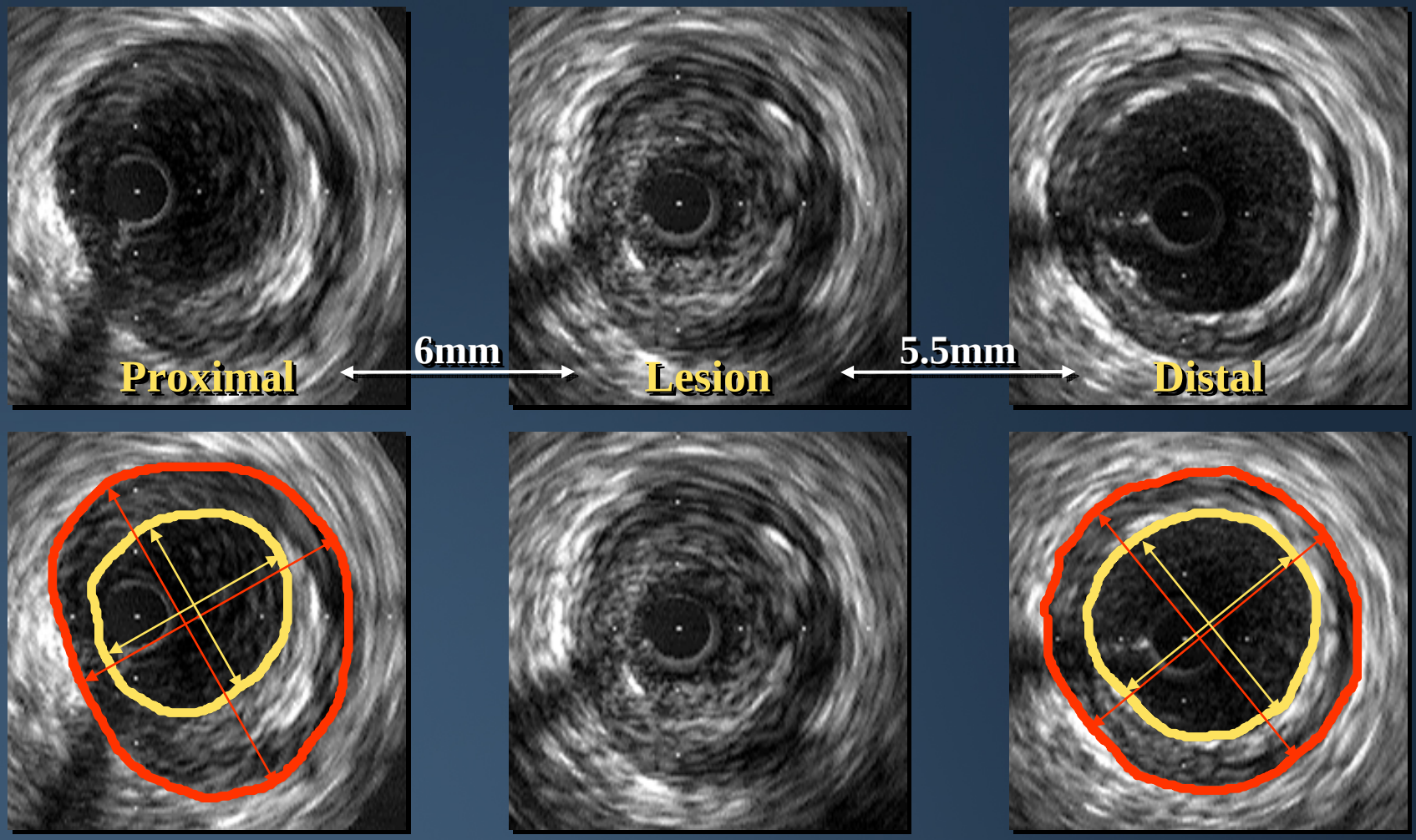
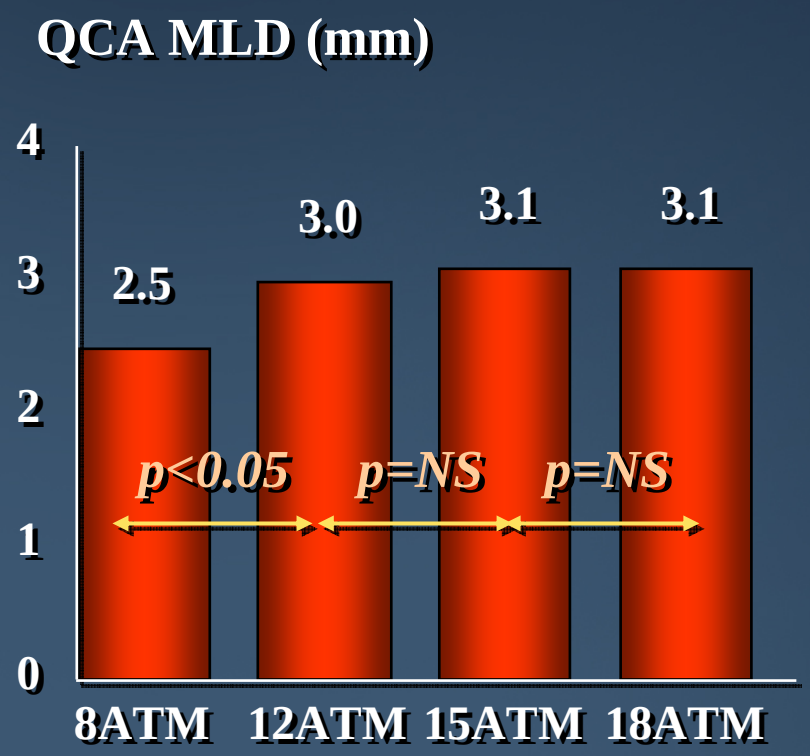
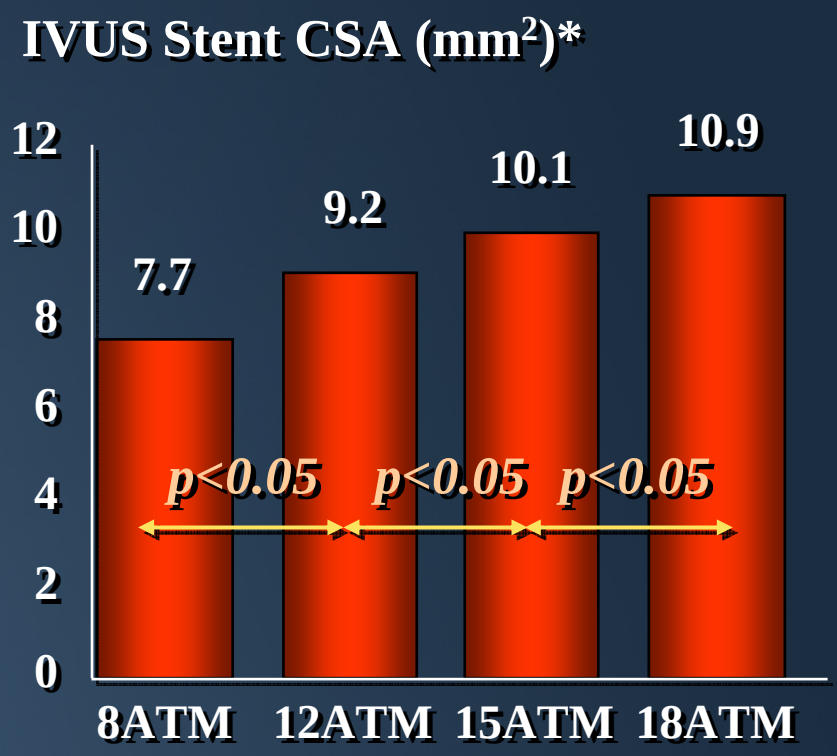
Stent sizing using IVUS

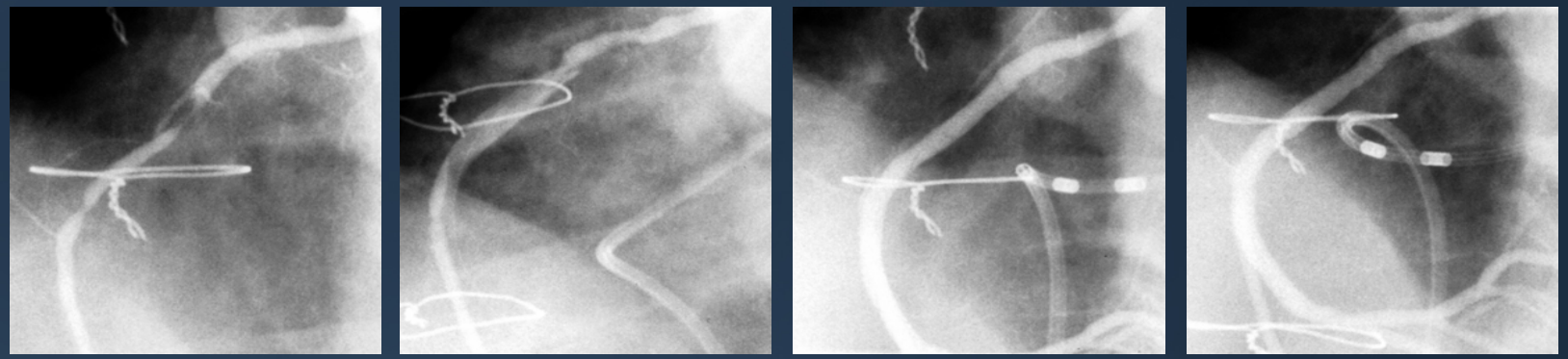


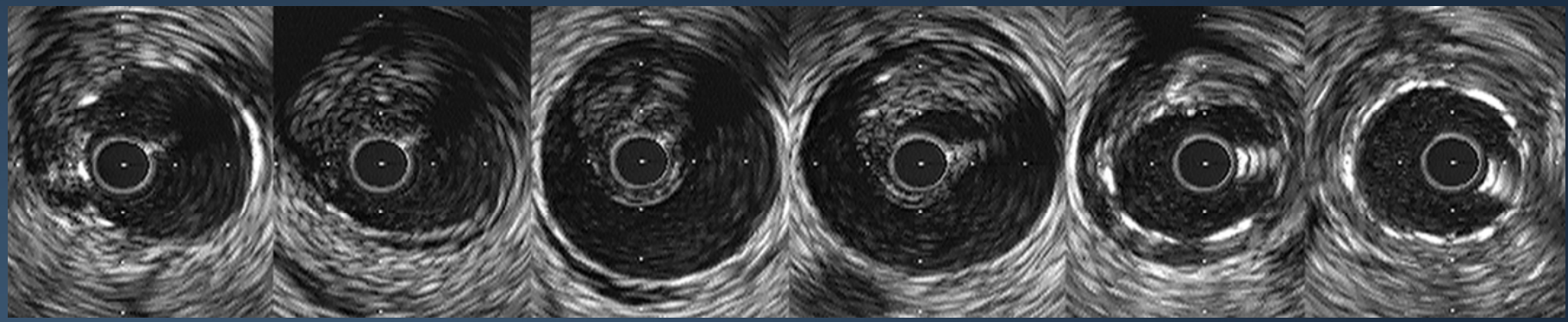
Iterative IVUS can be used to ‘fine-tune’ the final MSA during stent implantation - Angio cannot



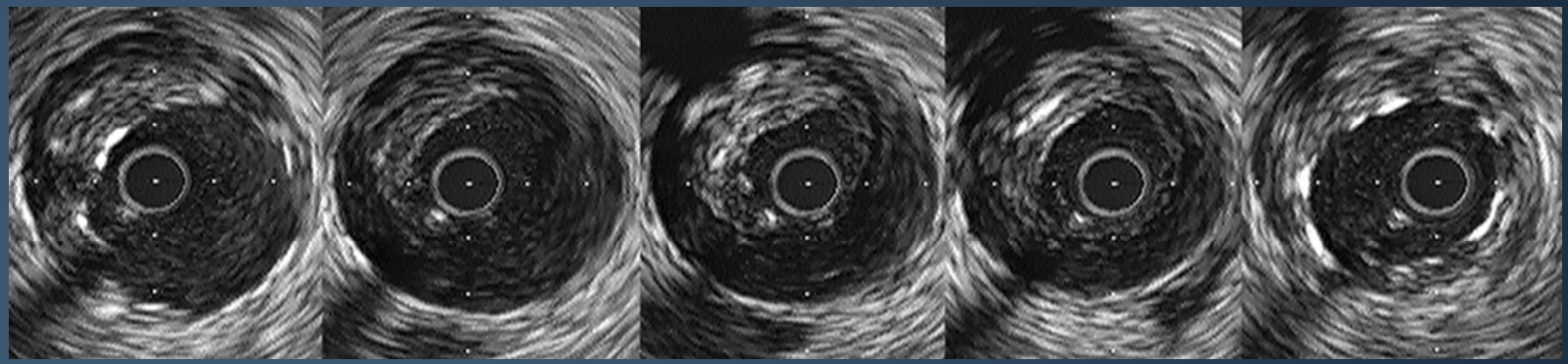


*ANOVA P<0.0001





0 → 5.0mm → 25.0mm



0 → 1.0mm → 4.0mm

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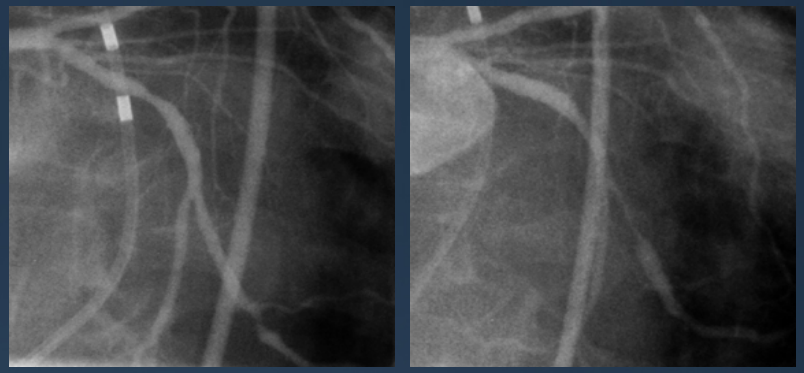
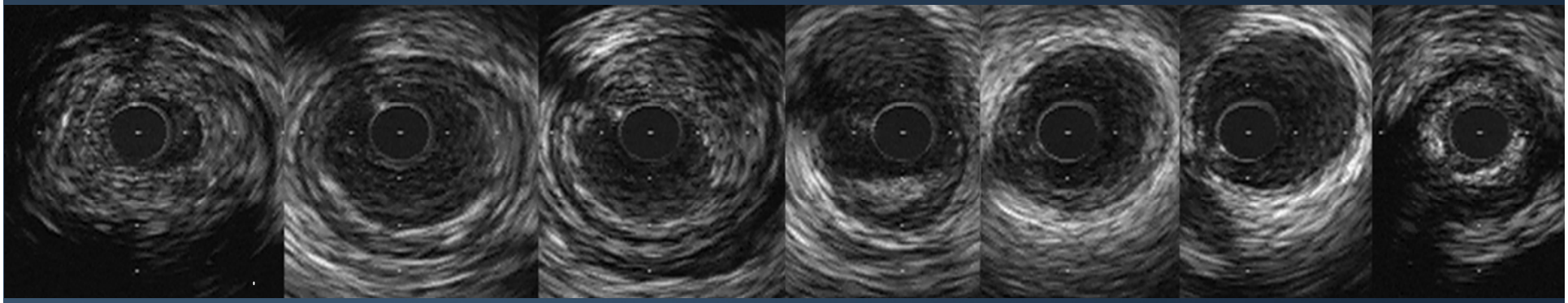
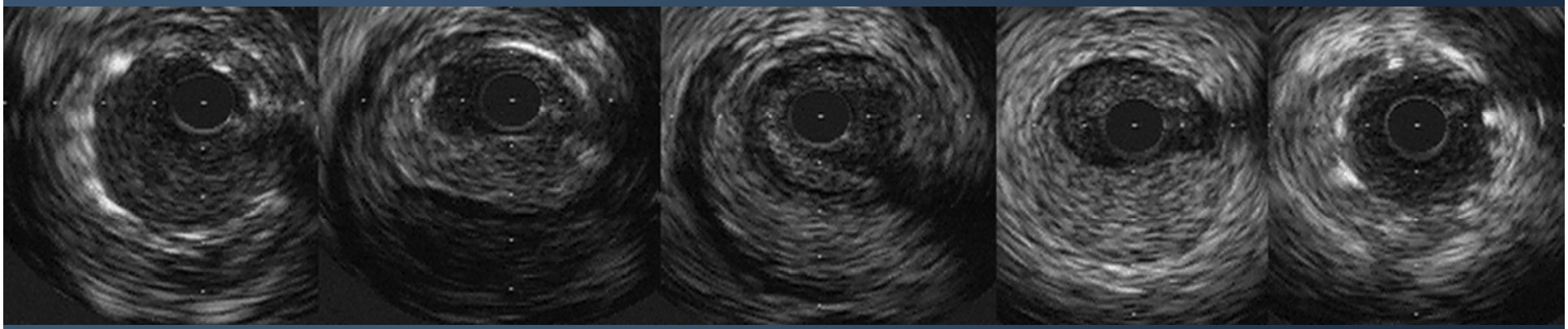




0 → 7.5mm → 45.0mm



0 → 8.0mm → 32.0mm

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	Angio Better	IVUS Better	IVUS Also Cheaper
Choi et al (AHJ 2001;142:112-8)		x	
CENIC (JACC 2002;39:54A)		X	
CRUISE (Circulation 2000;102:523-30)		X	
SIPS (Circulation 2000;102:2497-502 and AJC 2003;91:143-7)		X	X
AVID (Circ Cardiovasc Intervent 2009; 2:113-123)		X	
Gaster et al (Scan Cardiovasc J 2001;35:80-5 & Heart 2003;89:1043-9)		X	x
RESIST (JACC 1998;32:320-8 & Int J Cardiovasc Intervent 2000;3:207-13)		X	
TULIP (Circulation 2003;107:62-7)		X	
BEST (Circulation2003;107:545-551)		X	
OPTICUS (Circulation. 2001;104:1343-9)	x		
PRESTO (Am Heart J. 2004;148:501-6)	x		
DIPOL (Am Heart J. 2007;154:669-75)		X	

Safety of Intracoronary Ultrasound

n = 2207	Certain	Uncertain
Spasm	63 (2.9%)	0
Acute complications	6 (0.3%)	9 (0.4%)
Major complications*	3 (0.1%)	5 (0.2%)

*MI, CABG, or death

Safety

- **Gorge et al.,** J Am Coll Cardiol 1996;27:155A.
  - 7085 IVUS studies at 51 centers
  - 10 (0.1%) major complications other than spasm (7 dissection, 1 thrombus, 1 VF, 1 severe unresponsive spasm)
- **Batkoff et al.,** Cath Cardiovasc Diagn 1996;38:238-41
  - 718 IVUS studies at 12 centers
  - 8 (1.1%) major complications (4 spasm, 2 dissection, 2 guidewire entrapment)

Essentials of an IVUS Program

- Director
- Dedicated Technicians, Nurses, and/or Fellows
- Procedure standards
- Image acquisition protocol(s)
- Identify ways to make imaging more efficient and effective*
- Reports
- Housekeeping issues

* will vary from laboratory to laboratory

Director

- **Overall responsibility for the clinical IVUS service* including selection of equipment, staff, standards, protocols, and education.**

* Not just a cath lab or an echo lab, but a combination both. . .

Dedicated Technicians*, Nurses, and/or Fellows

- Knowledge of imaging systems, catheters, and imaging protocol(s)
- Immediately available and patient care and flow of PCI procedure not interrupted
  - System and catheter preparation
  - System controls and image optimization
  - Annotation
  - *Make measurements, interpret images, and provide feedback to physician during procedure*
- Care of systems, catheters, video tapes, CDs, etc.
- Archive cases onto CDs
- Keep procedure logs
- Aware of research protocols
- Generate reports
- Teach residents, fellows, and attending physicians

* Technicians often “run” an echo lab, why not an IVUS service

Imaging Procedure

- Remember to give heparin prior to inserting guidewire and IVUS catheter – avoid thrombosis
- Remember to give intracoronary NTG prior to imaging (even if blood pressure is borderline) – avoid spasm
- Remember to disengage guiding catheter when imaging aorto-ostial lesions – avoid confusing the guiding catheter with the ostium

Image Acquisition Protocol(s)

- Important for
  - Viewing, understanding, and comparing studies at a later date
  - Serial IVUS analysis
  - Multicenter studies - often have their own protocols
- Accurate voice annotation
- Label studies completely
  - Vessel (e.g., LAD) and lesion location (e.g., proximal)
  - Device use (stent type, size, length, pressure)
  - Temporal relationship between imaging run and procedure (e.g., pre-intervention, post-stent #1, etc.)
- Perform complete imaging runs back to aorto-ostial junction at least once during the procedure
  - Free look at proximal vessel and at LMCA if imaging LAD or LCX
- Motorized vs. Manual pullback

Motorized Pullback

- 0.5mm/sec is recommended
- Advantages
  - Images acquired in a distal to proximal sequence – avoids “sightseeing” up and down the vessel
  - Steady, slow transducer pullback to avoid imaging any segment too quickly
  - Ability to concentrate on images without having to worry about catheter manipulation
  - Length and volume measurements
  - Mandatory for most multicenter and all serial studies
- Disadvantages
  - Inadequate examination of important regions of interest because transducer does not remain long at any one specific site in the vessel

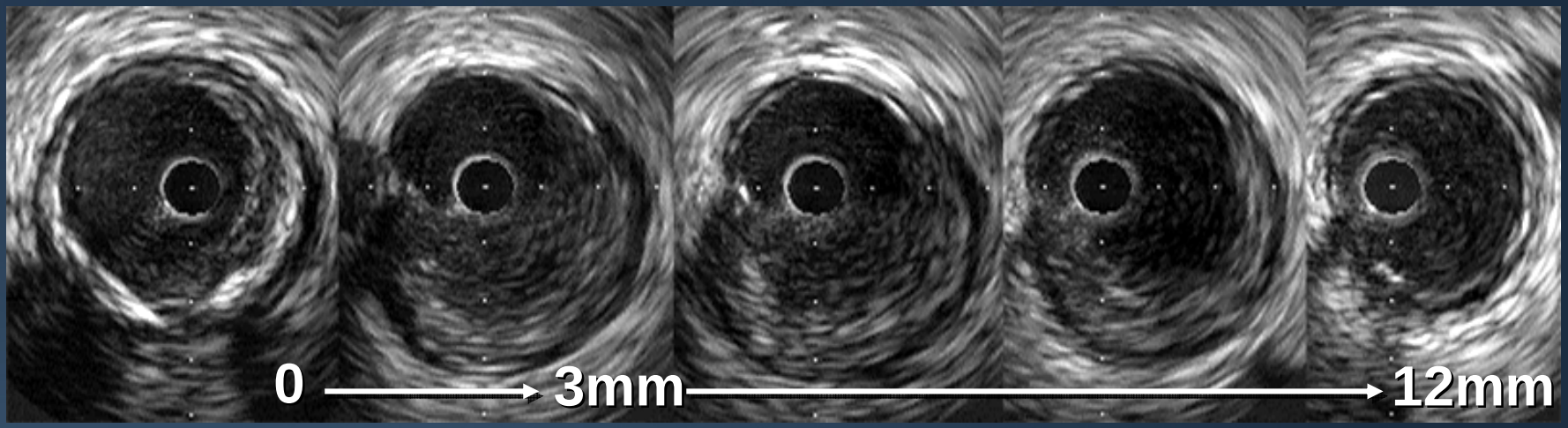
Basic Report

- Patient demographics
- Indications
- Brief description of IVUS procedure
  - Equipment
  - Vessels(s) imaged
- Basic findings
  - Basic measurements (e.g., MLA, MSA, MSD, plaque burden, etc.)
  - Notable morphology (e.g., plaque rupture, thrombus, calcium, dissection, intramural hematoma, etc.)
- Changes in therapy because of IVUS imaging
- IVUS-related complications and consequent therapy

Comprehensive Report

- In addition to information contained in Basic Report. . .
- Pre-intervention and/or post-intervention quantitative analysis of three cardinal images slices: distal reference, lesion, proximal reference
  - EEM CSA
  - Lumen CSA
  - Plaque&media CSA and plaque burden
  - Area stenosis
  - Stent measurements
  - Lesion length

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%

Imaging Efficiency and Effectiveness - I

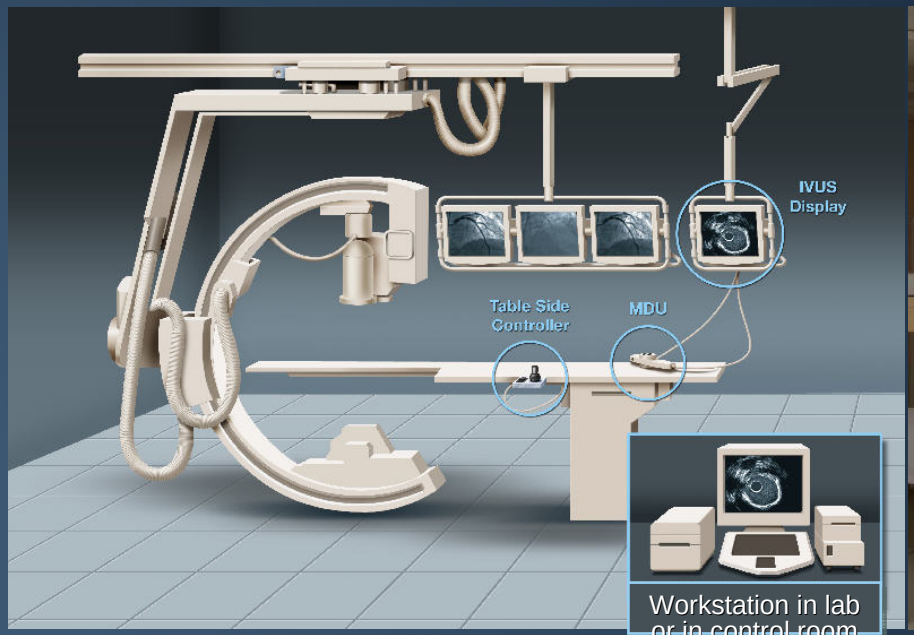
- Perform imaging run(s), remove IVUS catheter, and make measurements from video tape or digital replay - NOT during live imaging
  - Less patient ischemia
  - More efficient use of cath lab time
  - Additional measurements can easily be made and additional questions easily answered
- Display images on angiographic monitors
  - Superior monitors
  - Easier to see
  - Get IVUS system away from table
  - Requires separate roadmap or reference monitors
- Full system integration

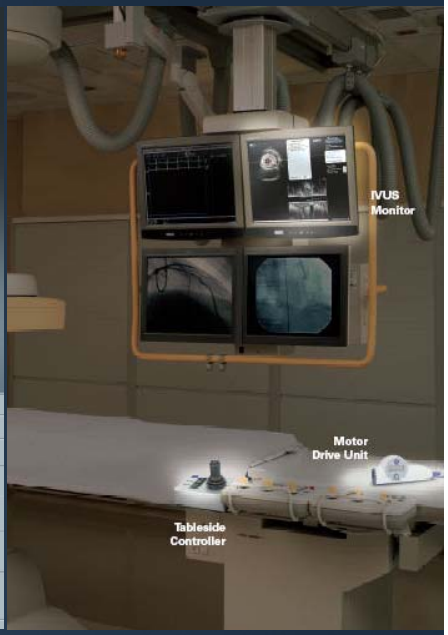
Full System Integration

- Easier for staff
  - Turn on system once a day
  - Eliminate looking for equipment and/or transporting equipment between rooms
  - Access is constant
  - No cables or wires between system and angiographic table
- Less hassle for physicians
  - Ready when they are
  - Minimize time added to procedure
  - Controls can be located within sterile field
  - Simply plug in the catheter and begin
- Customizable
- Cost
- (But not a new concept)

Volcano V-Fusion

BSC iLab





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