Revascularization of Chronic Total Occlusions

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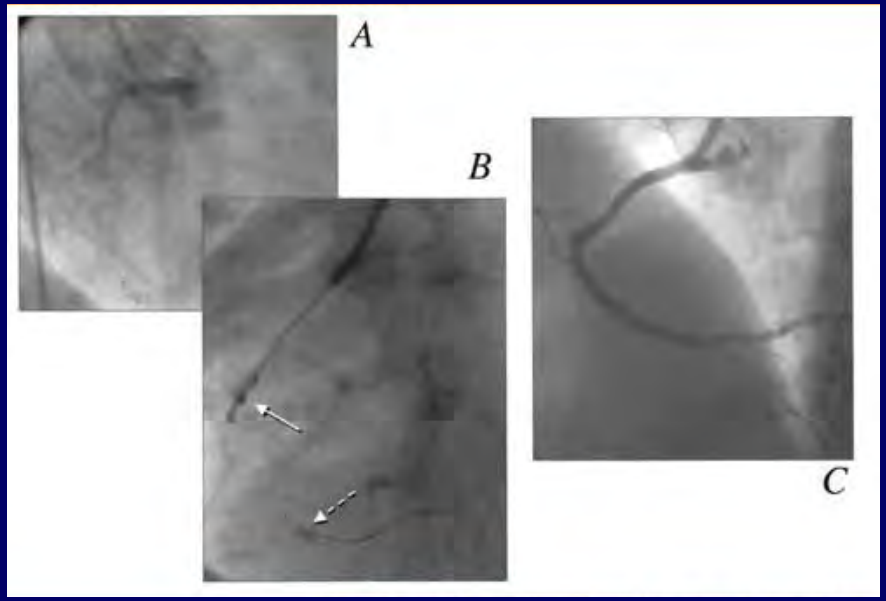


PCI for Chronic Total Occlusions

“The Last Great Frontier of Interventional Cardiology”

Chronic Total Occlusion - CTO

- 100% narrowing of the artery
- No angiographically detectable antegrade flow (TIMI flow = 0)
- > 1 month old

Baim DS, Ignatius EJ. Am J Cardiol 1998;61:3G-8G

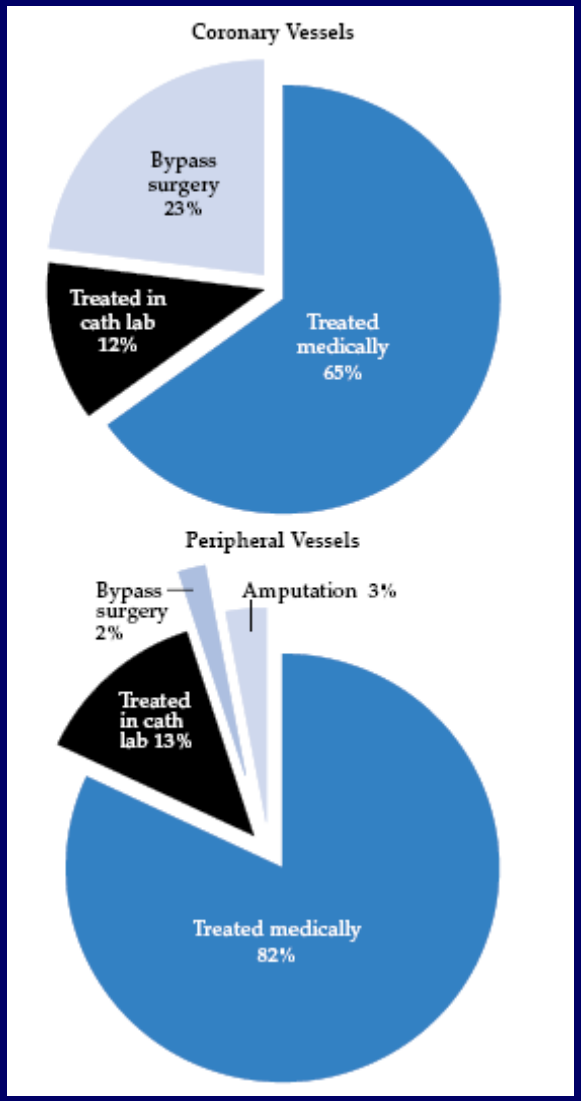
CTOs in Perspective

NHLBI Dynamic Registry and BARI study 1997-1999, n=1,761

- Presence of total occlusion 31%
- Attempted total occlusion 7.5%

Srinivas et al. Circulation 2002

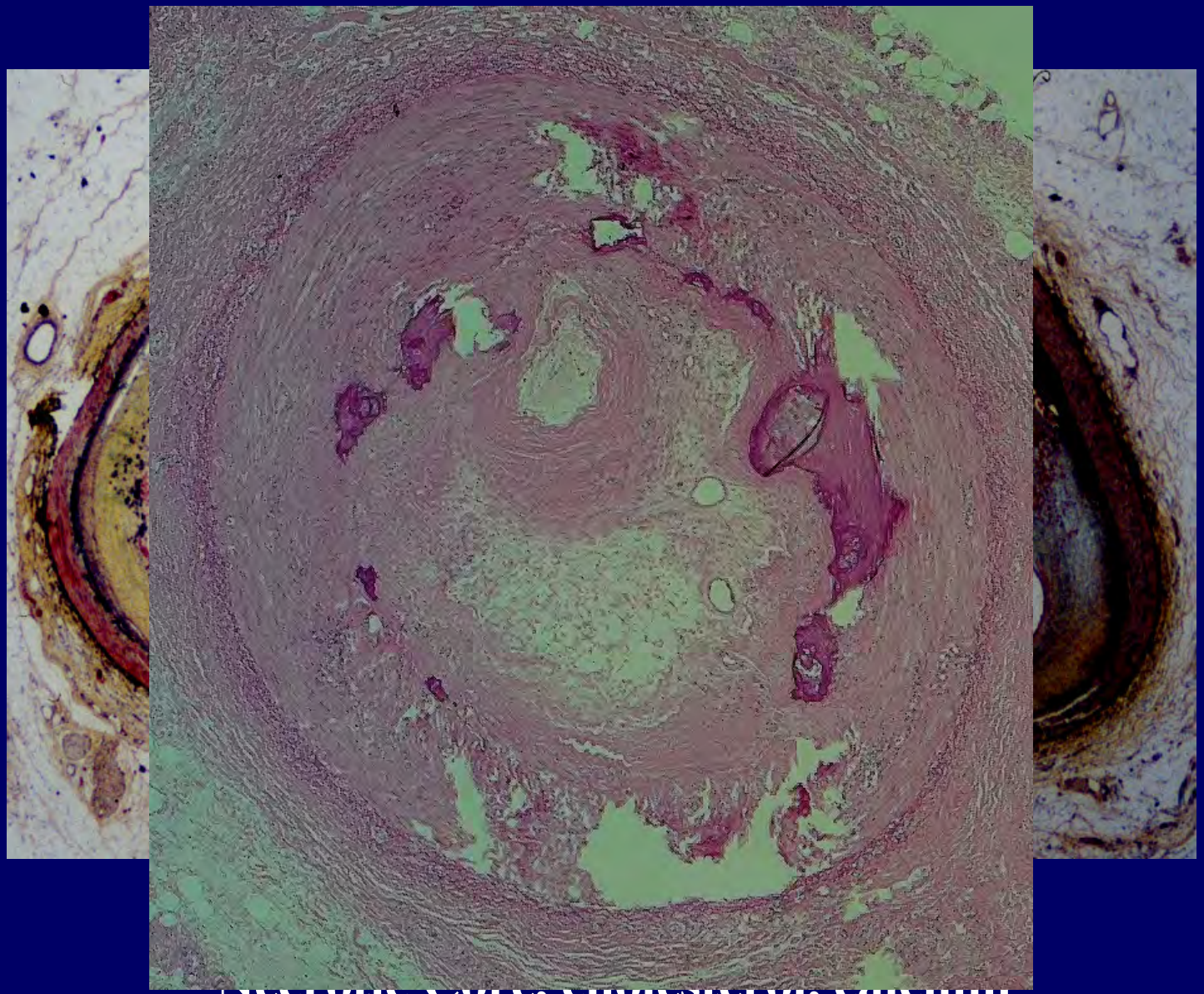
Current Treatment of CTO



30% coronary atherosclerosis and >50% peripheral atherosclerosis patients present with total occlusions

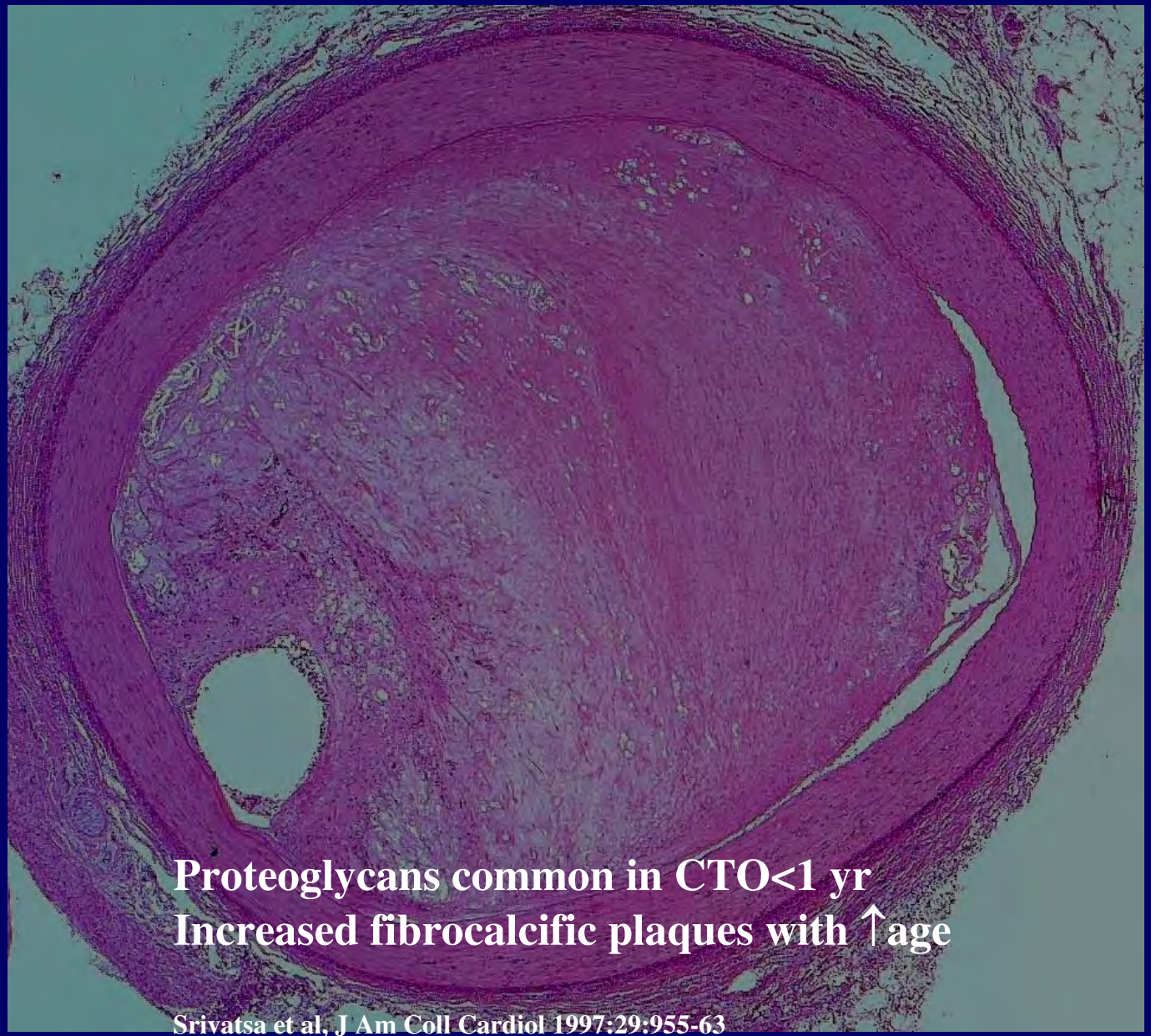
Only 12-13% pts currently treated in cath lab

CTO: What's In the Lumen?



Necrotic Core, cholesterol, calcium

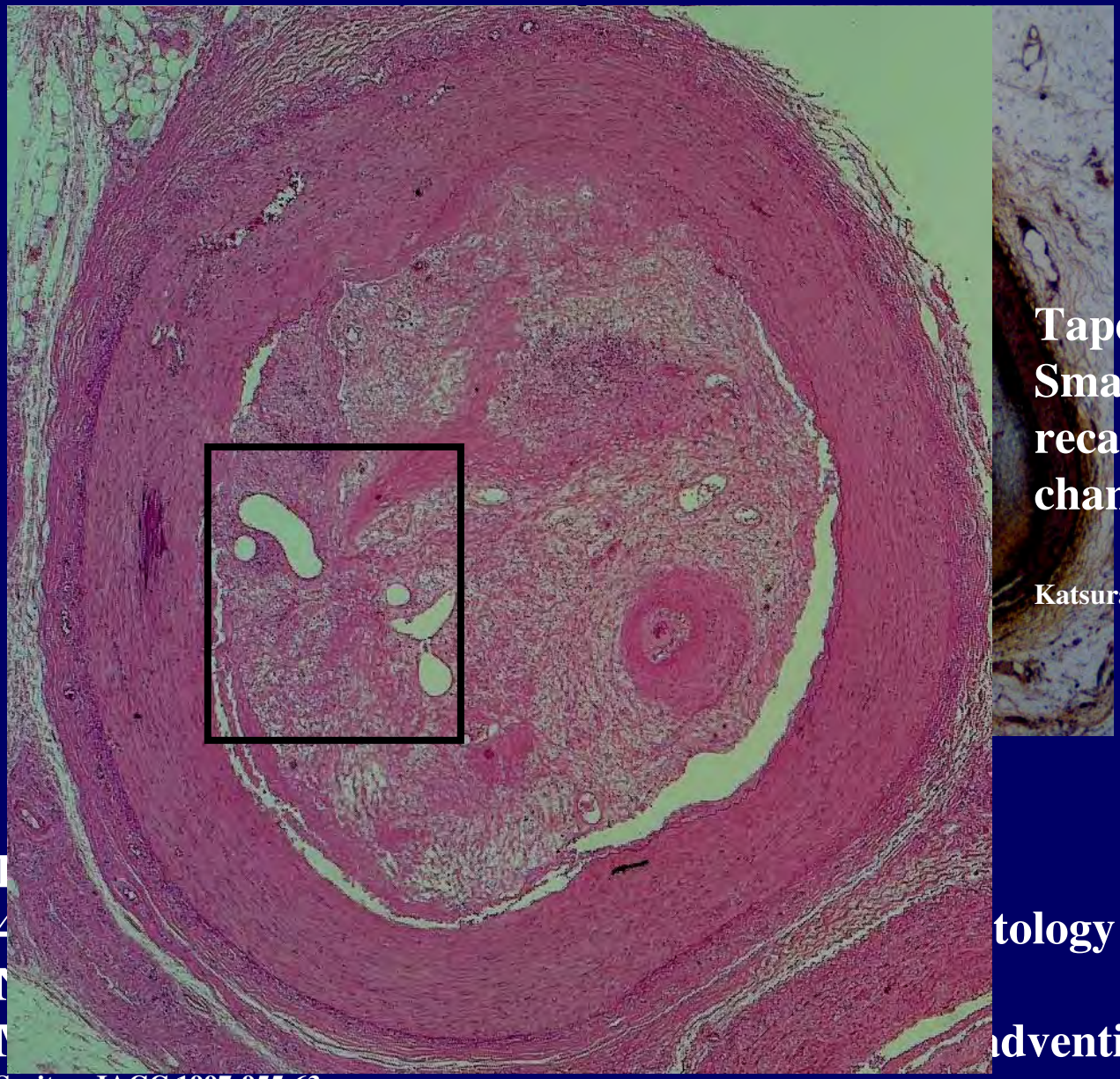
CTO: What's in the Lumen?



Proteoglycans common in CTO<1 yr
Increased fibrocalcific plaques with ↑age

Srivatsa et al, J Am Coll Cardiol 1997:29:955-63

CTO: What's in the Lumen?



Tapered CTO: Small luminal recanalization channels

Katsuragawa, JACC 1993

tology

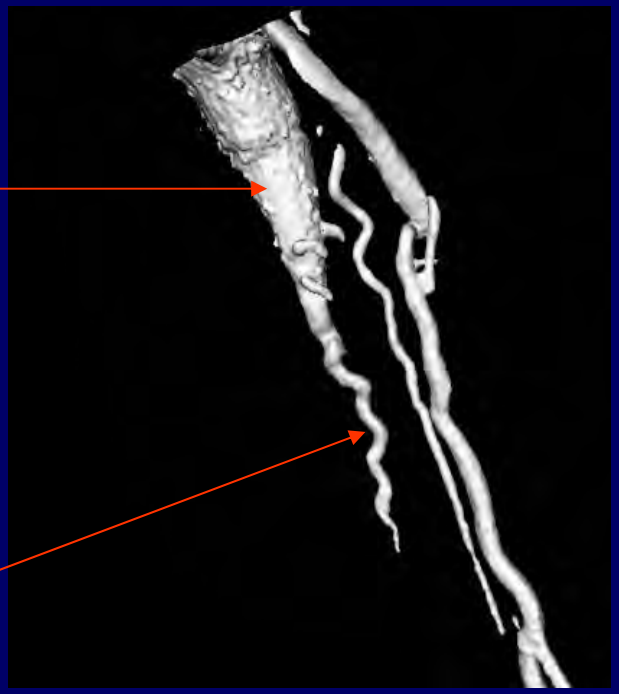
dventitia

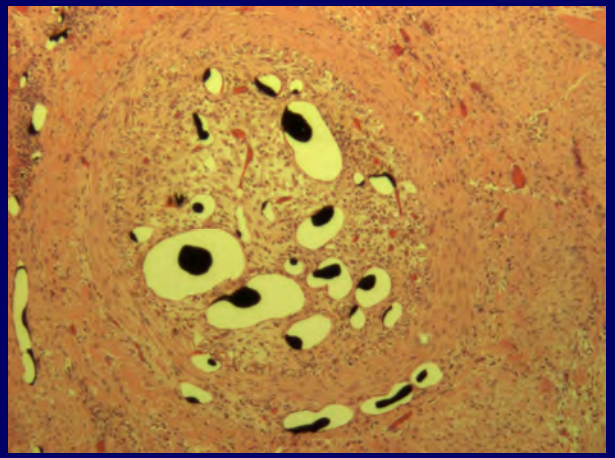
Srvitsa, JACC 1997:955-63

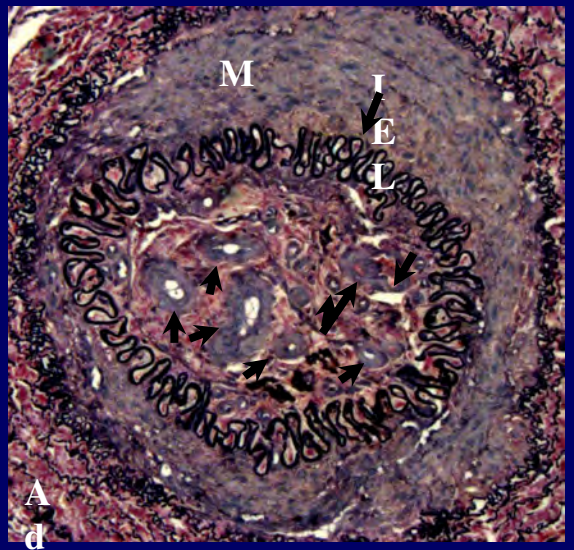
Microvessels
41% of all CTOs

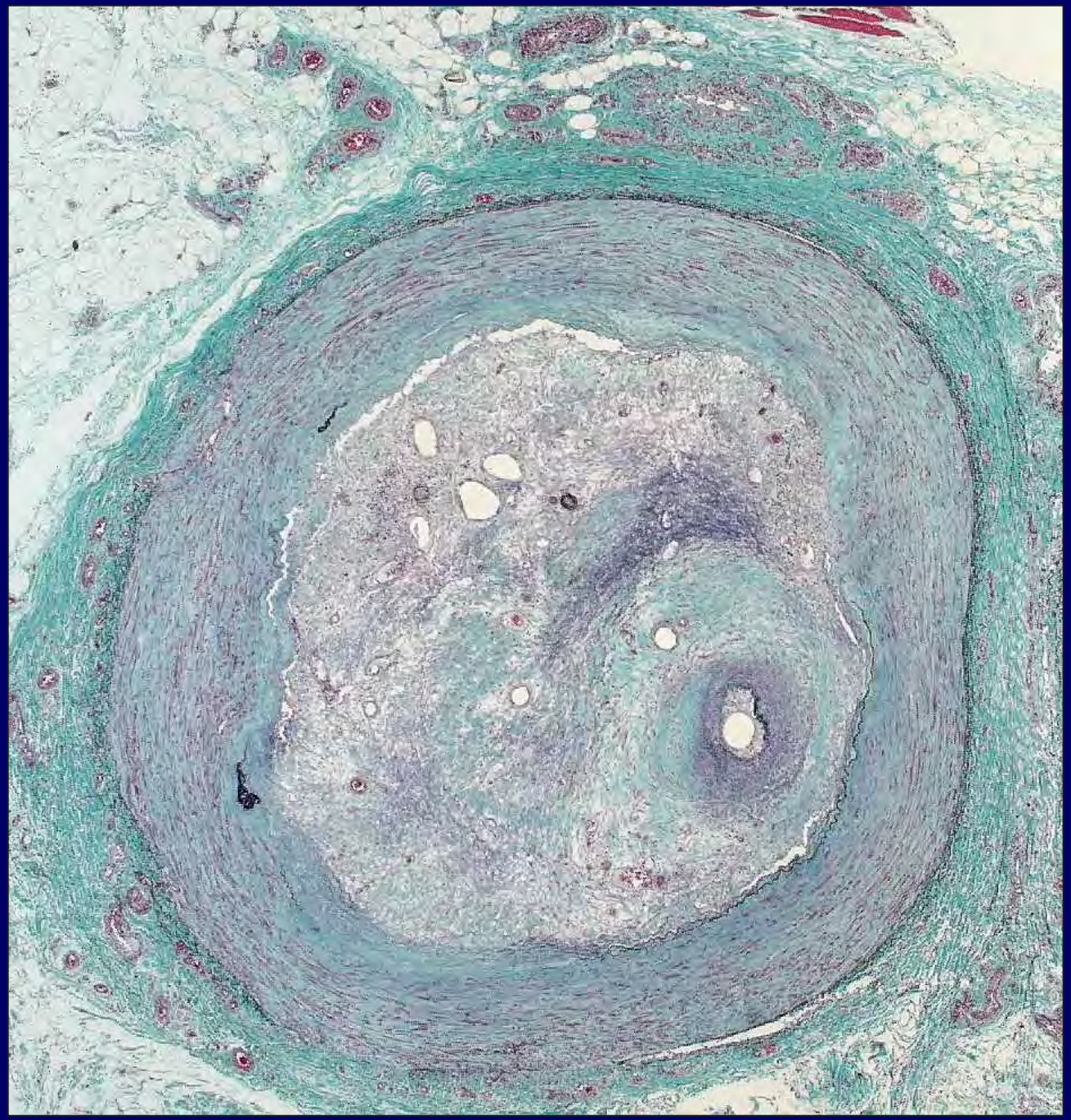
Proximal
"End"

Endoluminal
Microchannel





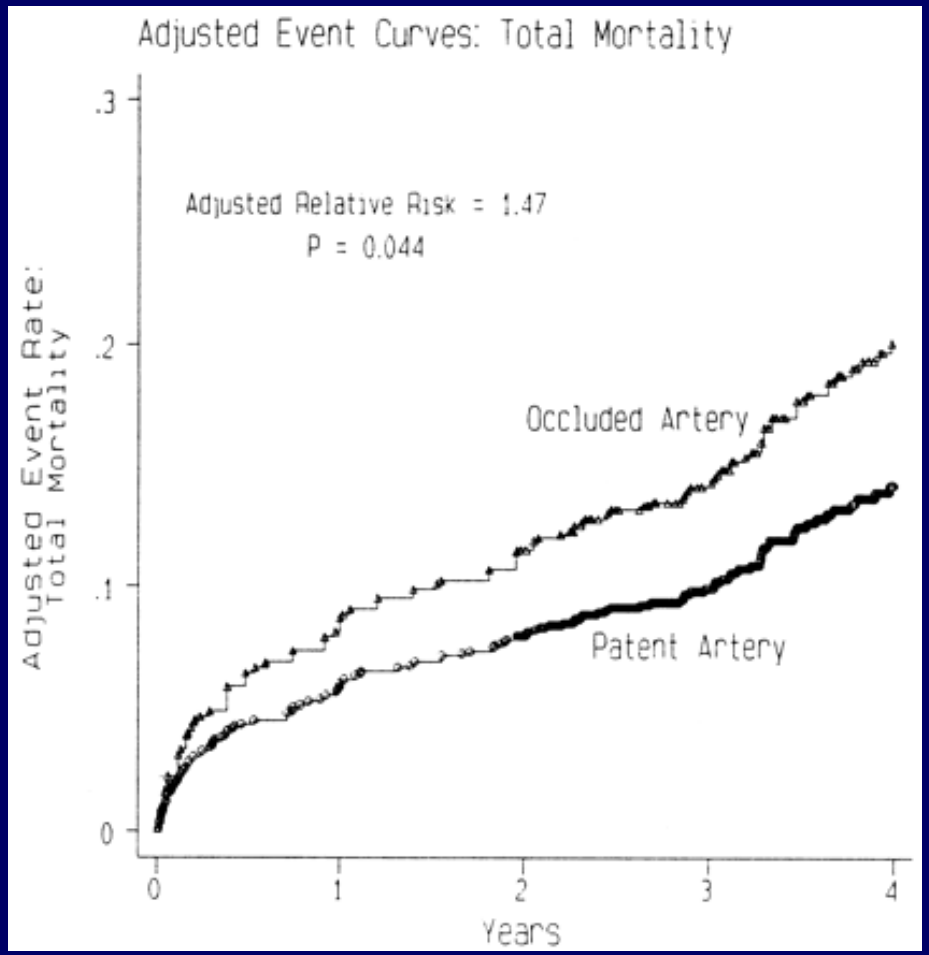




Theoretical rationale for CTO Revascularization

- Increased long-term survival
- Improved left ventricular function
- Electrical stability of myocardium and reduced predisposition to arrhythmic events
- Increased tolerance of future acute coronary syndromes, mainly occlusions

Clinical rationale for CTO intervention



Lamas GA et al, Circulation 1995

Long-term survival associated with successful CTO revascularization

Late open artery theory

Trial	Success N	Failure N	Follow-up years	Mortality,% Success	Mortality,% Failure	P
British Columbia Registry	1118	340	1	10.0	19.0	<0.001
Suerro et al.	1491	514	10	26.6	35.0	0.001
TOAST GISE	286	83	6	1.1	3.6	0.13

Long-term outcome after intended revascularization of non-acute CTOs

Multivariate mortality model

	Hazzard ratio	95% CI	p
Failure	2.27	1.56-3.30	<0.0001
Age (per decade)	1.33	1.12-1.58	0.001
LVEF<50%	2.33	1.58-3.43	<0.0001
Multivessel CAD	1.62	1.09-2.40	0.02
Prior CHF	1.73	1.10-2.76	0.02
ESRD	2.77	1.36-1.56	0.005
COPD	1.64	1.01-2.67	0.05
Diabetes	1.50	0.99-2.27	0.055

Ramanathan and Buller, TCT 2003

Technical Issues

- Technically challenging
  - Organized fibrocalcific atherosclerotic plaque
  - Difficult visualization
  - >75% - inability to cross with a guide-wire

- Time consuming
  - >60 min procedure
  - >20 min of fluoro time is typical

Guidelines – PCI of CTO

- ESC – class IIa level C

- Class III
  - Small area of viability
  - No ischemia
  - Low likelihood of success

PCI Limitations

- Success rate: 20-74% of attempted cases
- Predictors of success:
  - Age of occlusion
  - Vessel diameter
  - Location
  - Degree of calcification
  - Bridge collaterals
  - Operator dependent
    - Experience
    - Patience and persistence
- Time, radiation exposure, and difficulty often discourage CTO revascularization attempts

Angiographic predictors of poor outcome (traditional)

- Long gap
- Non-tapering stump
- Side-branch at occlusion
- Vessel turtuosity
- Calcification
- Ostial location
- Poor distal vessel visibility
- Bridge collaterals

Other factors to consider

- Access / backup (iliac and aortic turtuosity)
- Renal function
- Risk of CABG
- Operator experience

How to do (CTO) Angioplasty in 3 easy steps!!!

1. Cross CTO with 0.014” Guidewire

2. Inflate balloon that was advanced over the guidewire

3. Deploy stent that is mounted on a second angioplasty balloon catheter

Step #1: Advancing the guidewire through the blockage

- Usually like pushing through concrete
- Conventional guidewires usually unsuccessful

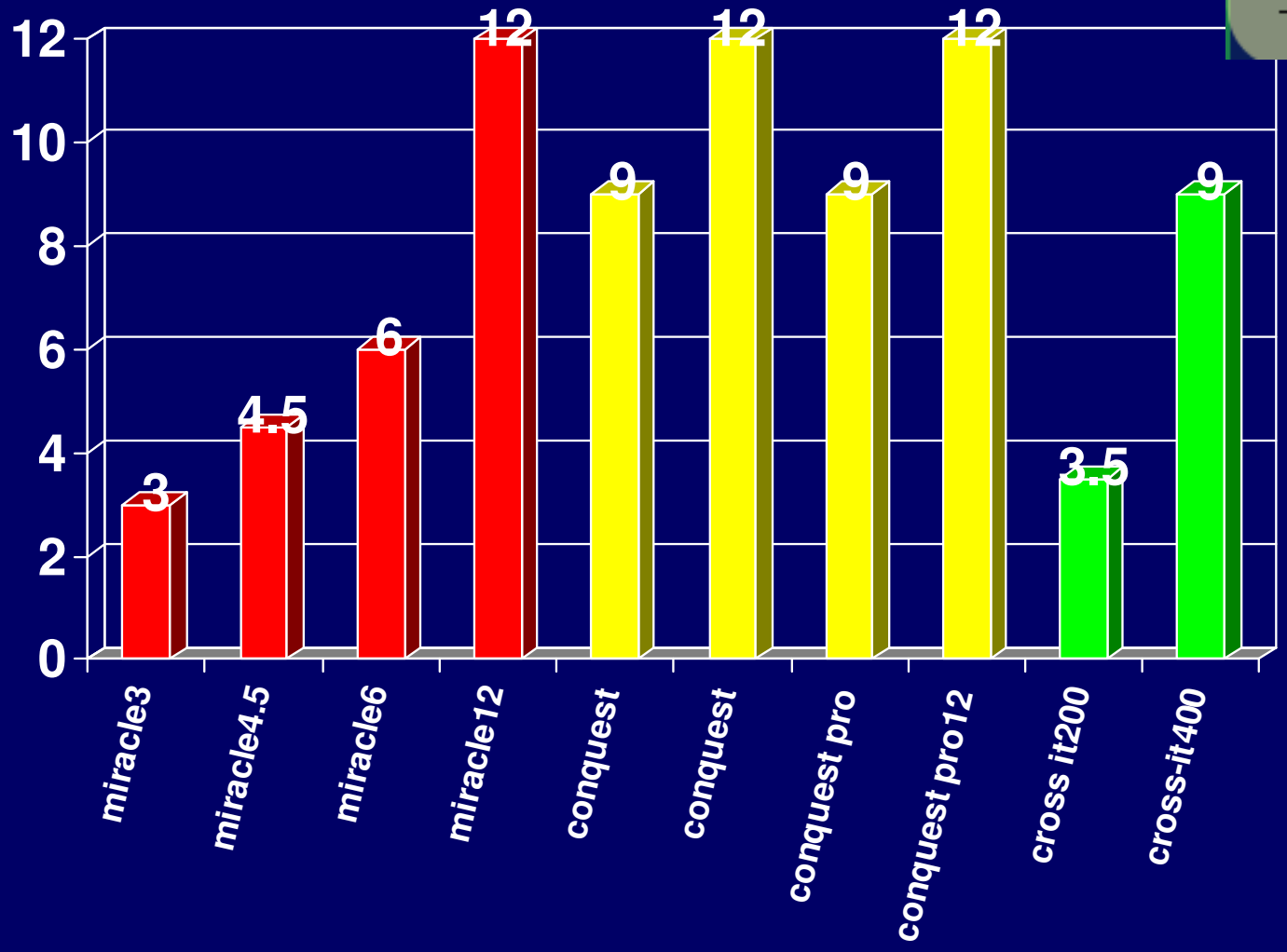
- Mechanical Approaches:
  - Dedicated CTO Guidewires
  - Specialty Guidewires
  - Specialty Devices

- Biological Approaches:
  - Plaque Softening
  - Intraluminal Angiogenesis

Guide-wire selection

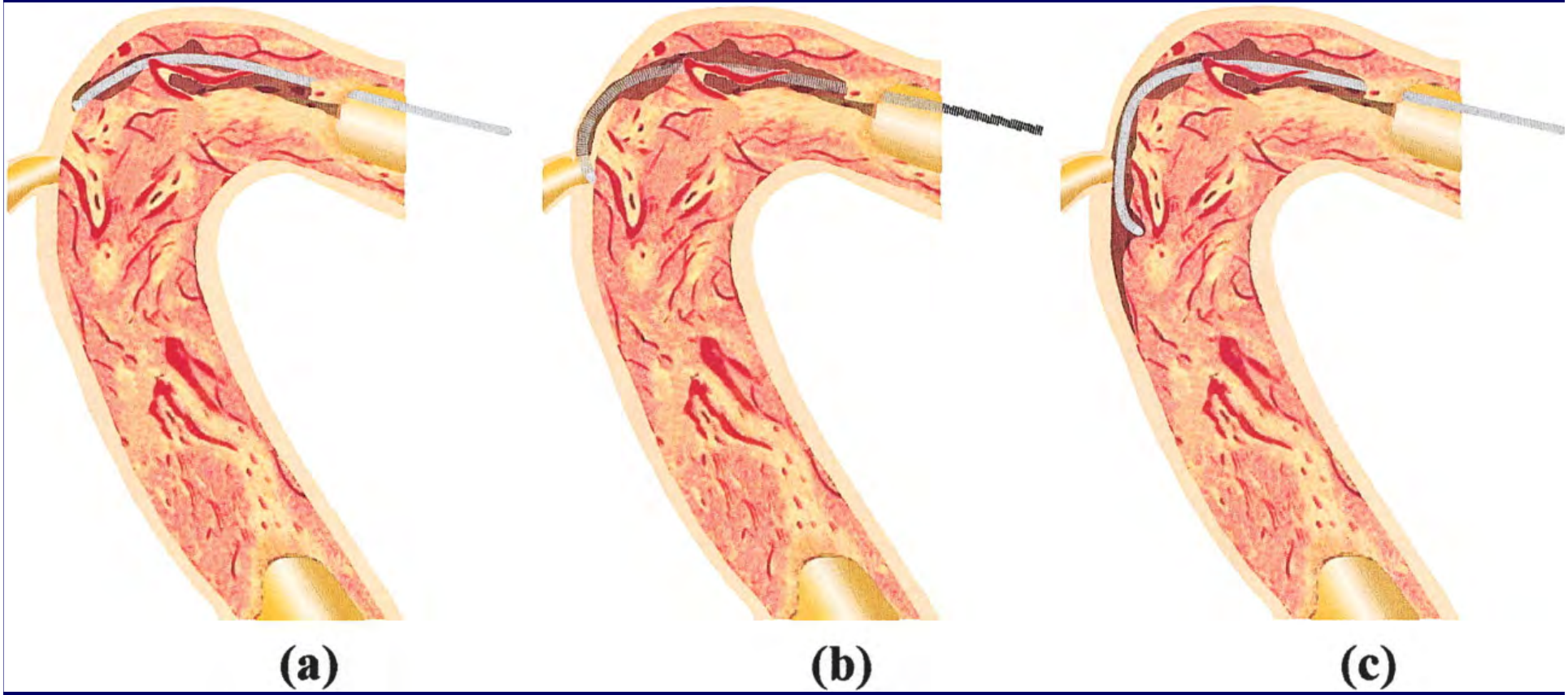
- Floppy tip – selection >> penetration
- Intermediate – selection > penetration
- Stiff tip – selection < penetration
- Ultra-stiff tip – selection << penetration
- Tapered tip – selection << penetration
- Coated wire – better torque

Comparison of wires

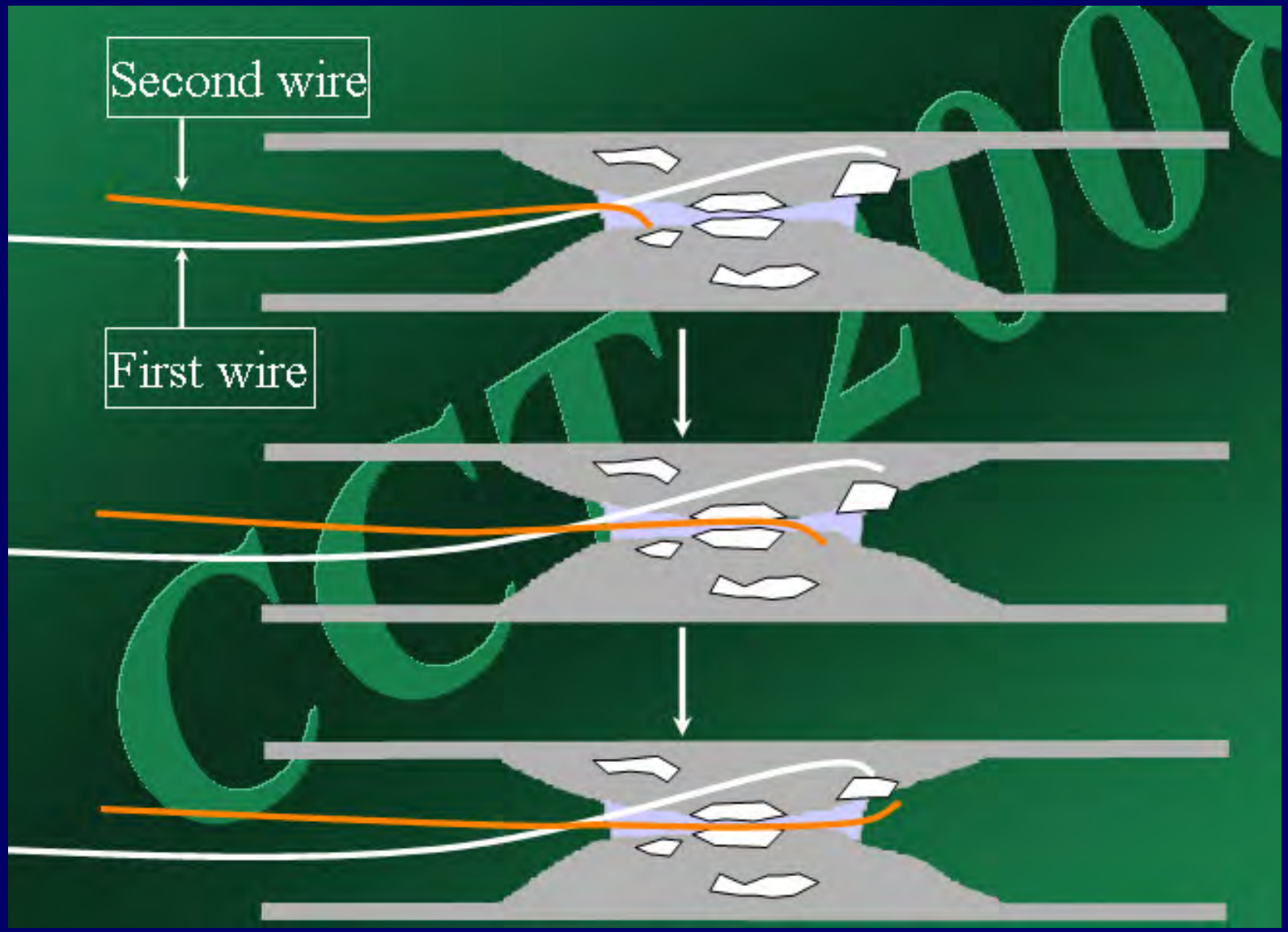


Antegrade wire techniques

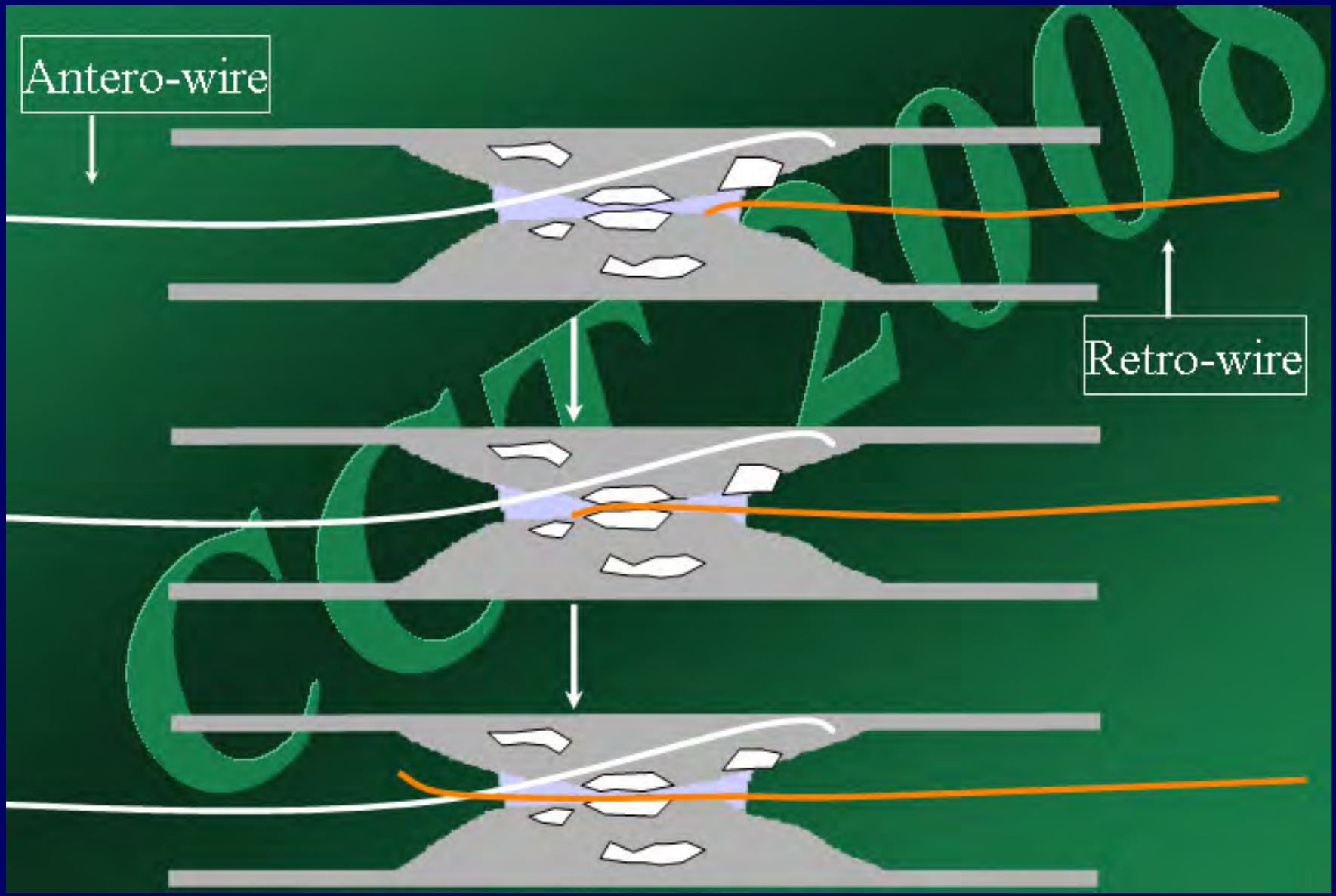
- One wire technique
- Parallel wire technique
- Multiple wire technique


(a)
(b)
(c)

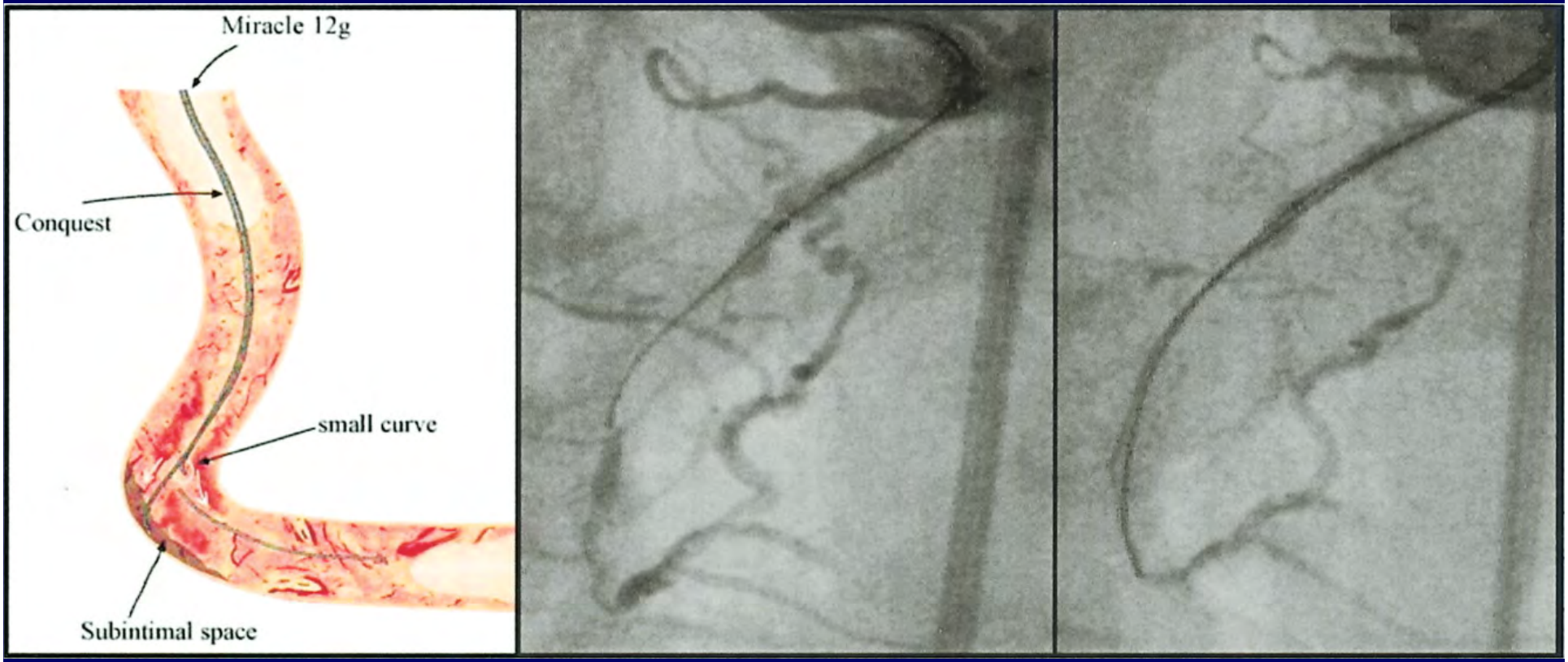
Parallel wire technique



Bilateral parallel wire technique

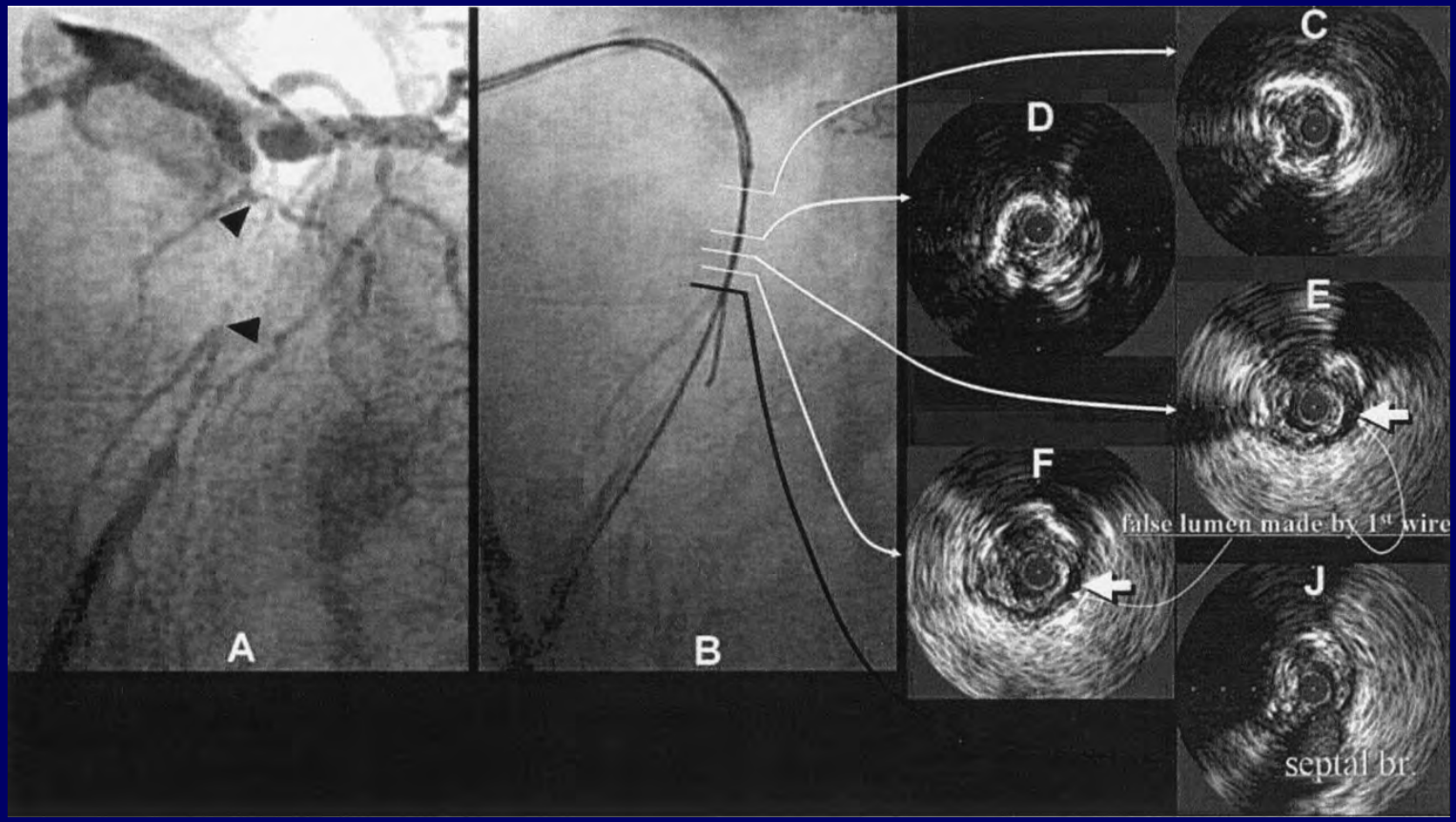


Parallel wire technique

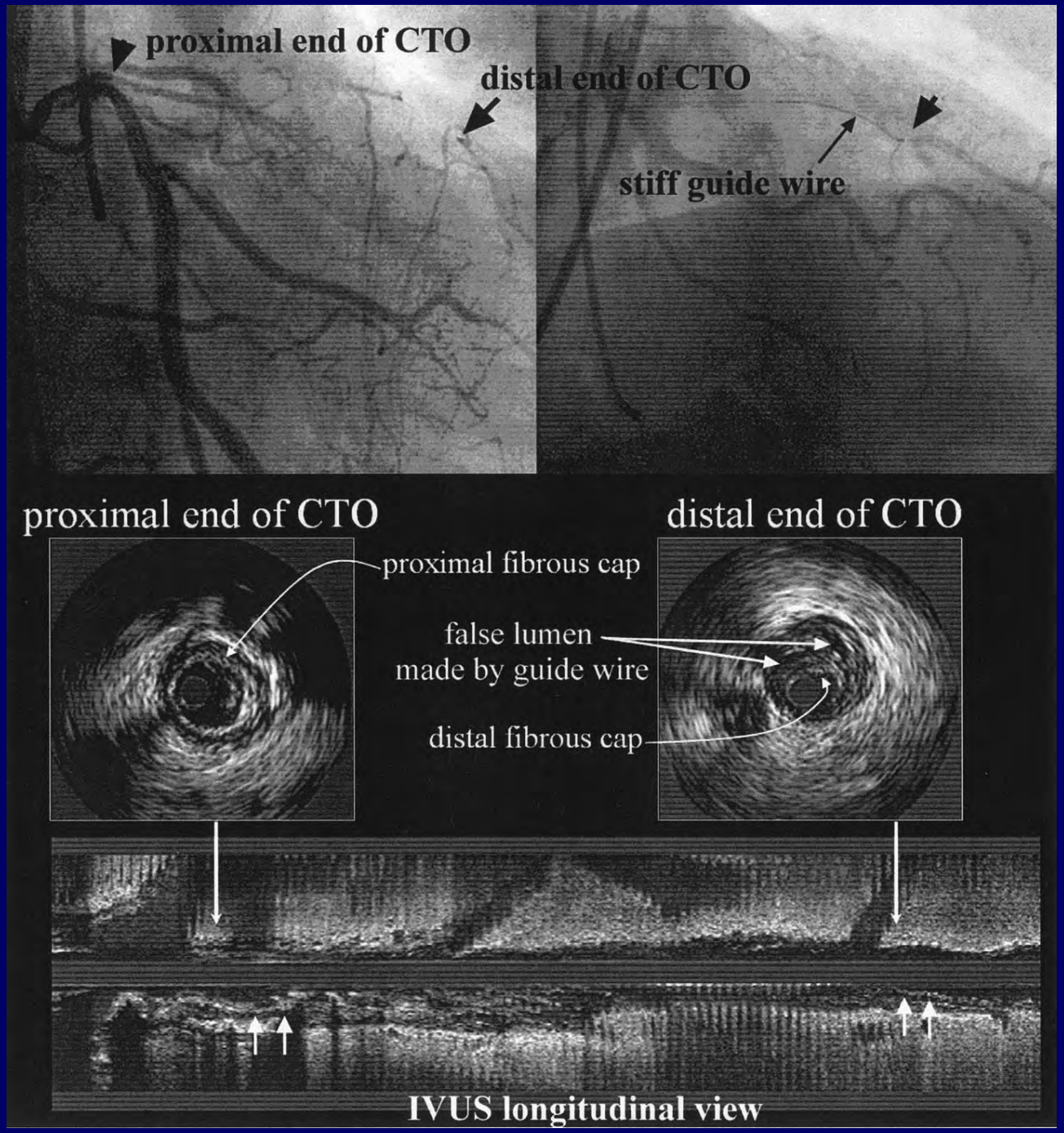


Utility of intravascular ultrasound

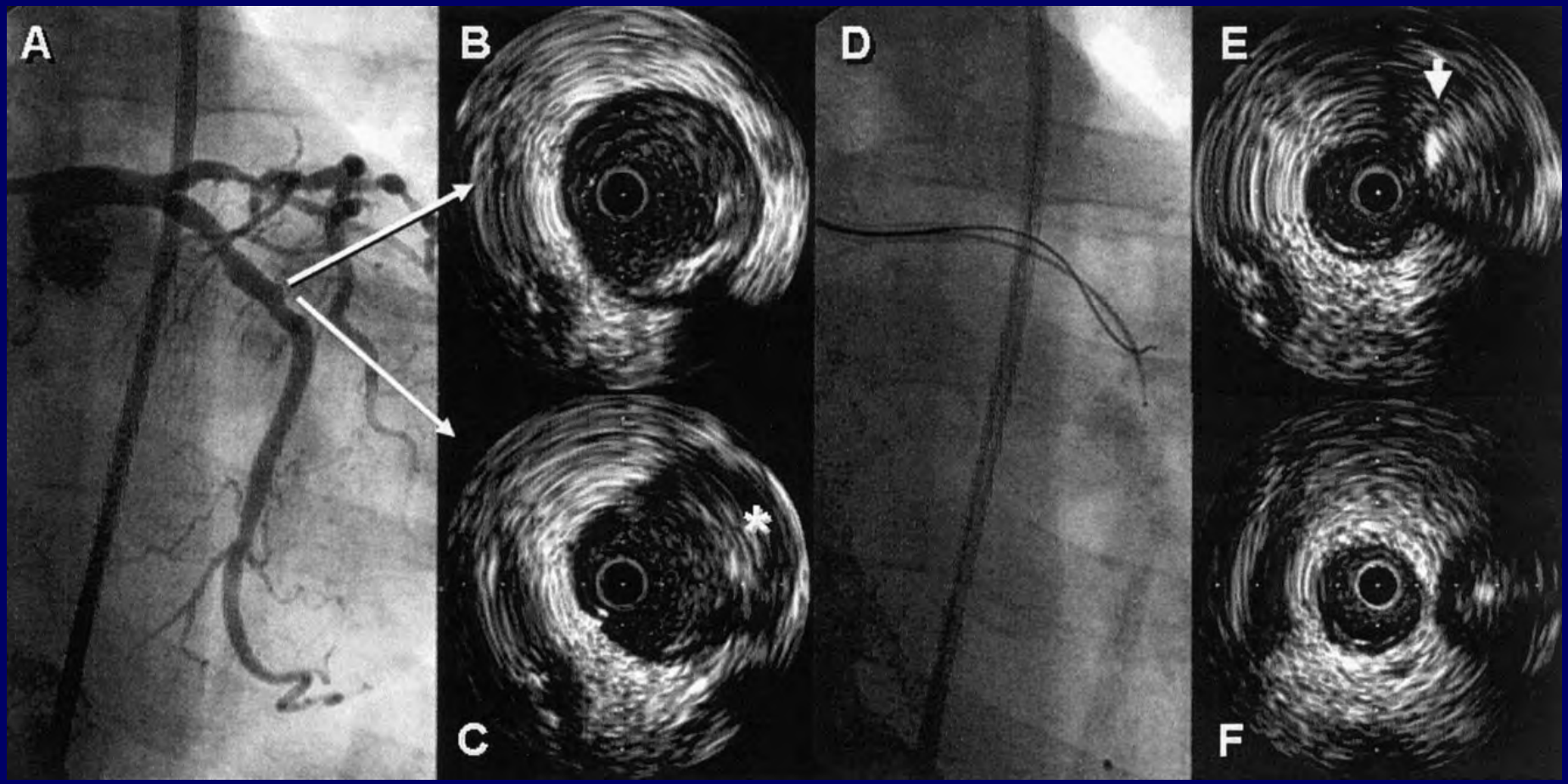
- IVUS can differentiate a true lumen from a false lumen by identifying side branches (which arise only from the true lumen) and intima and media (which surround the true lumen, but not the false lumen).
- IVUS can confirm when the guidewire has reentered the true lumen from a false lumen
- IVUS studies have also revealed that the major reason that it is difficult to penetrate the distal cap into the true lumen is that the guidewire tends to deflect into a false channel, not because of extensive calcification or fibrosis.



1st wire into false lumen
2nd wire in true lumen
C+D: wire is confirmed in true lumen
E+F: IVUS imaging of false lumen
J: septal branch

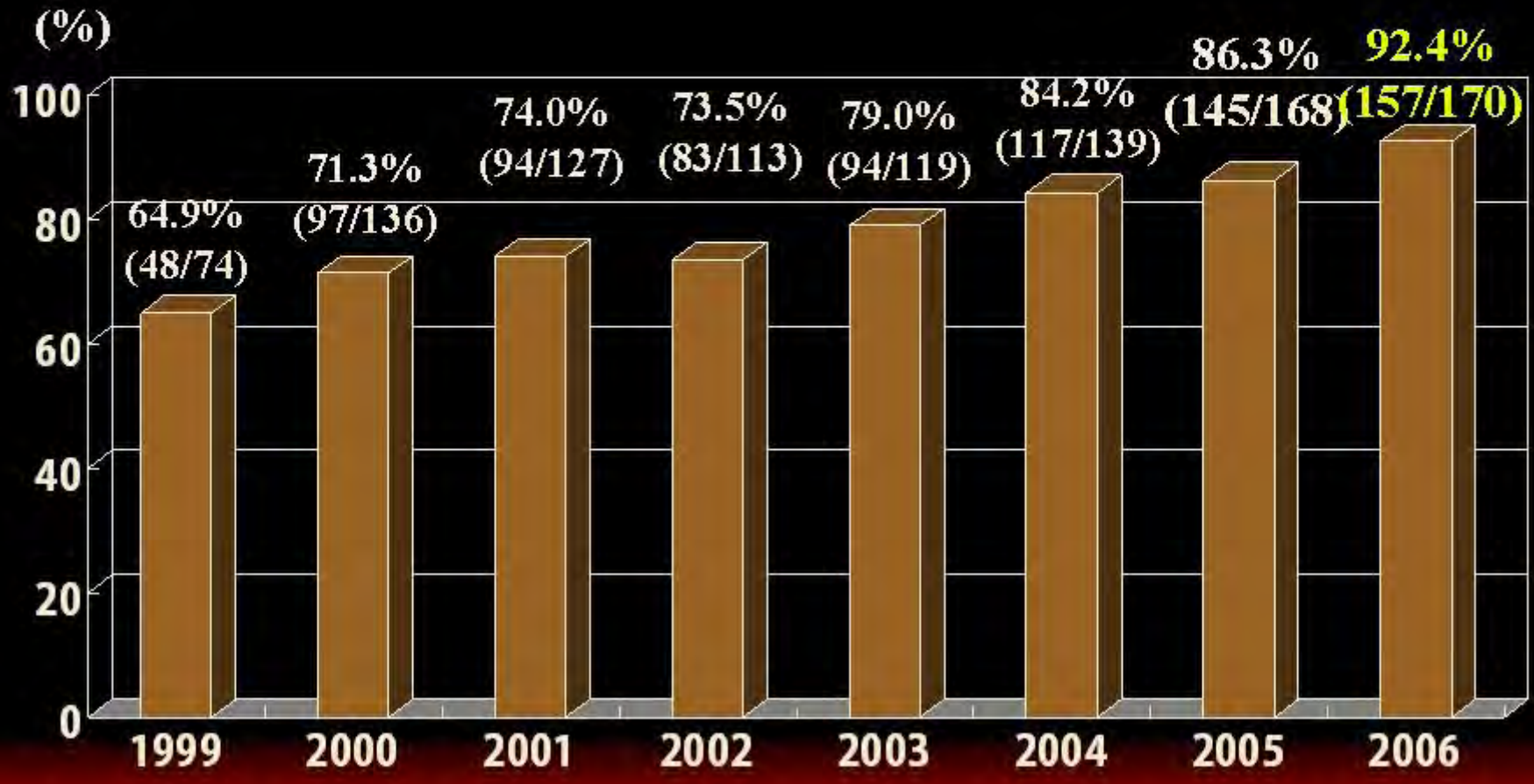

proximal end of CTO
distal end of CTO
stiff guide wire
proximal end of CTO
distal end of CTO
proximal fibrous cap
false lumen
made by guide wire
distal fibrous cap
IVUS longitudinal view

Ostial occlusion



Initial Success Rate

79.8% (835/1046)

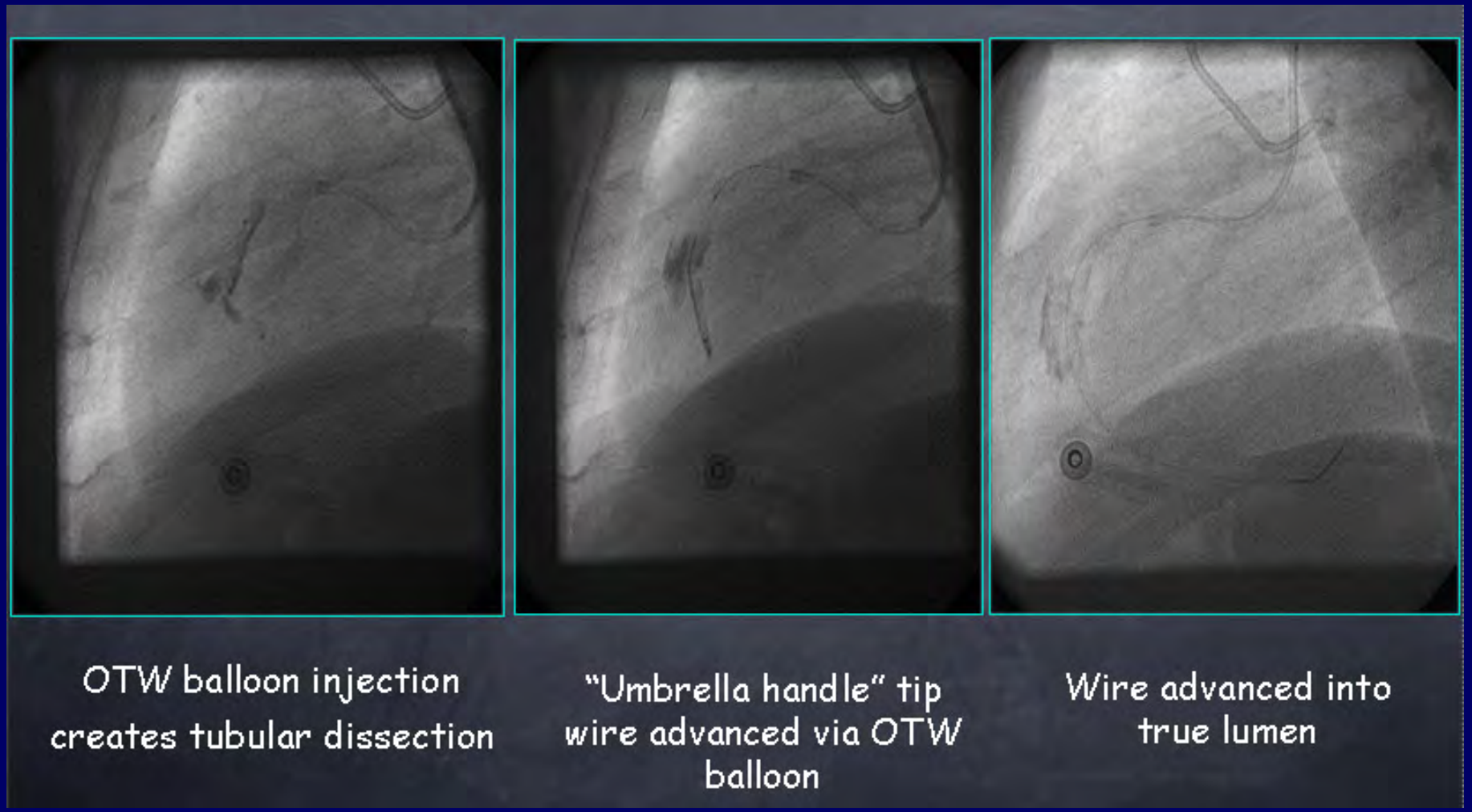


Guide wire crossing technique

(Jan. '06 – Dec. '06, n=170 lesions)

Antegrade single wire technique	167 (98%)
Parallel wire technique	50 (29%)
IVUS guide wire crossing	11 (6%)
Retrograde approach	50 (29%)

Subintimal Tracking and Reentry (STAR)



After crossing with wire…..

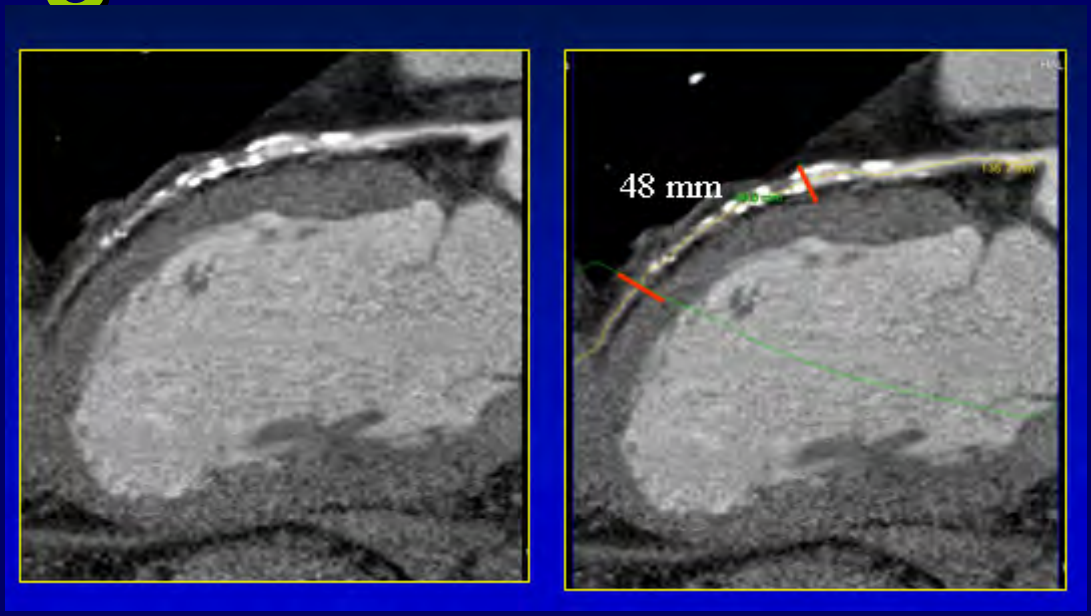
- Low profile micro-catheters
- Low profile balloon
  - Ryujin 1.25mm
  - Avion 1.25mm
- Tornus

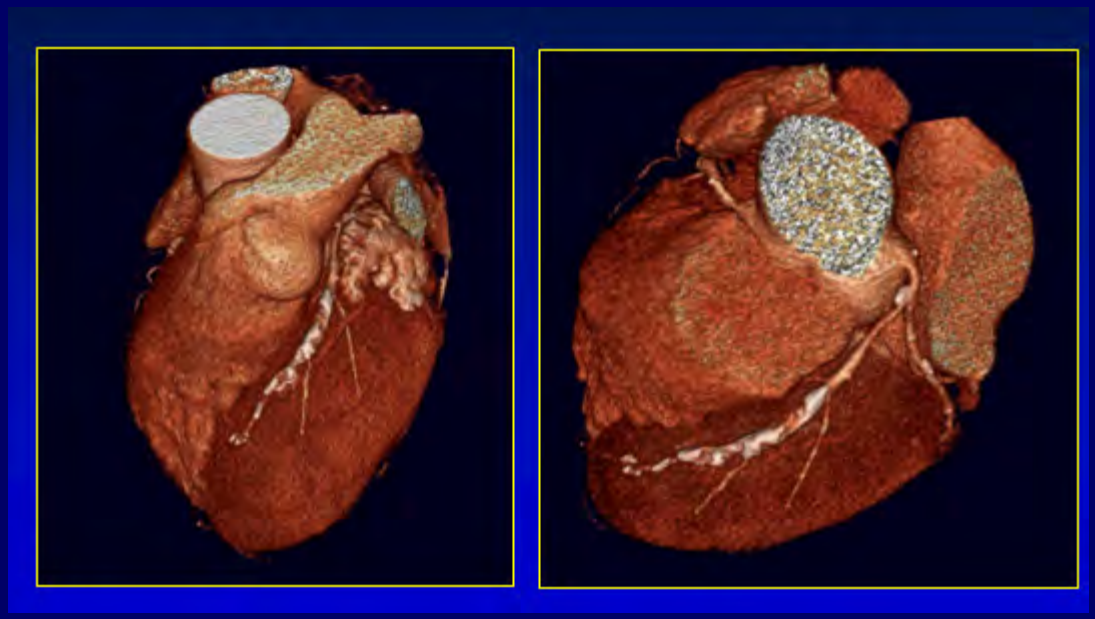
Role of CTA

- Predictors of failure
  - Length > 15 mm
  - Severe calcifications
- Angiographic predictors
  - Blunt entrance into occlusion
- CTA length was routinely longer than angiographic estimation

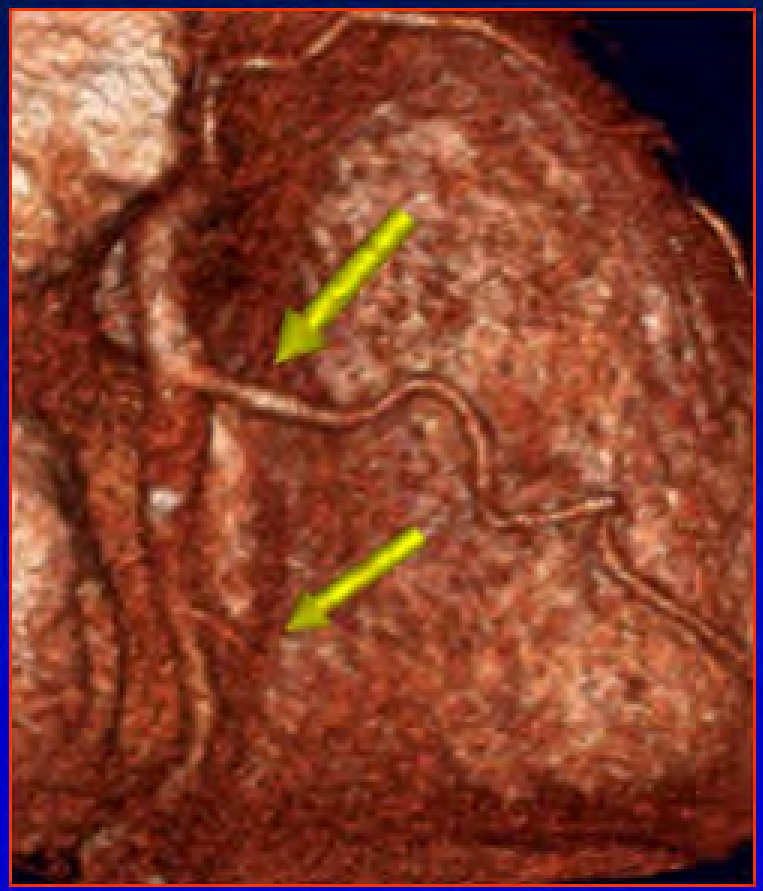
Mollet et al. Am J Cardiol 2005

Length of the Occlusion

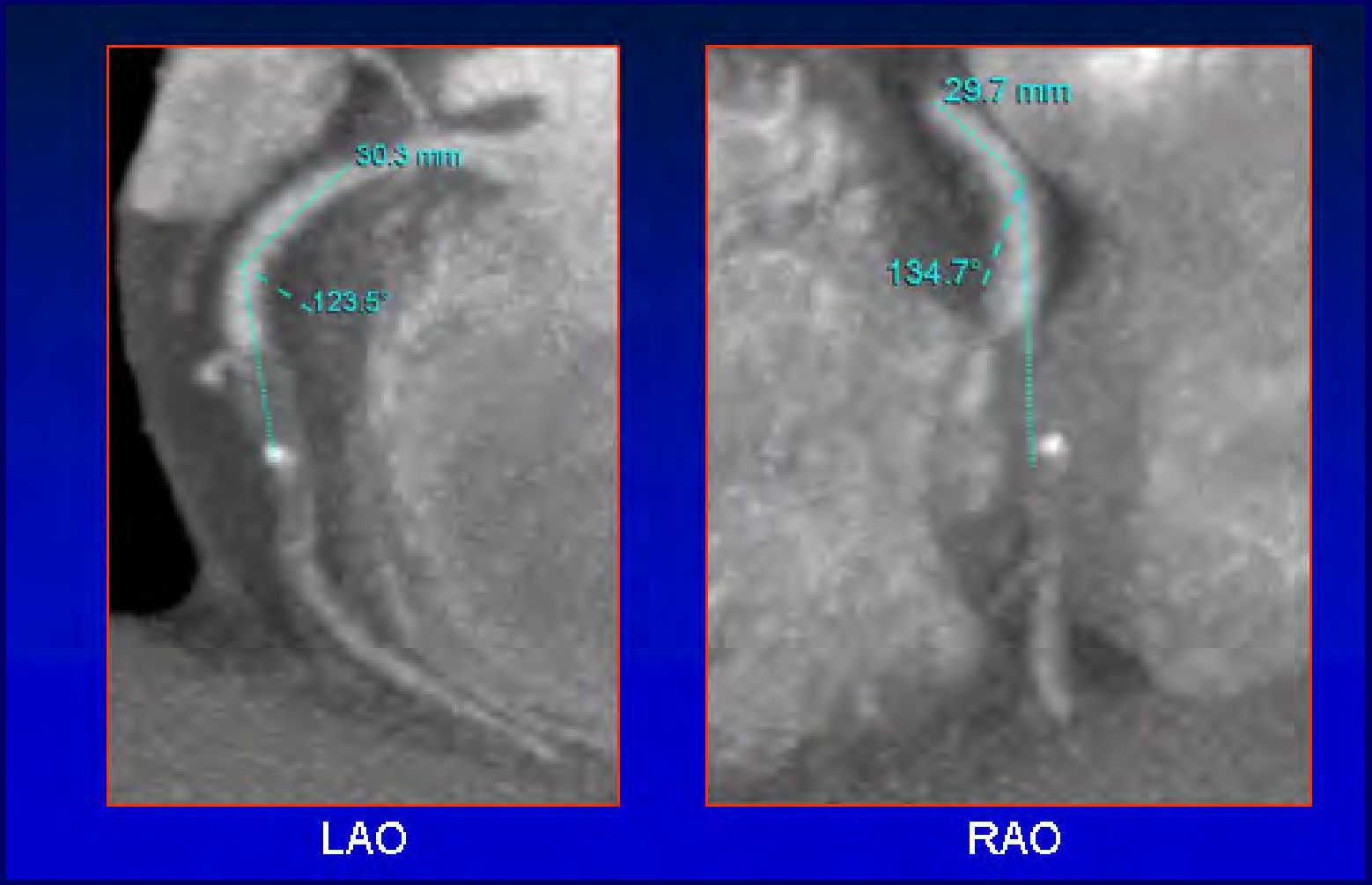




Assessment of distal vessel & sidebranches



Definition of intra-occlusion angle



Dedicated CTO Guidewires

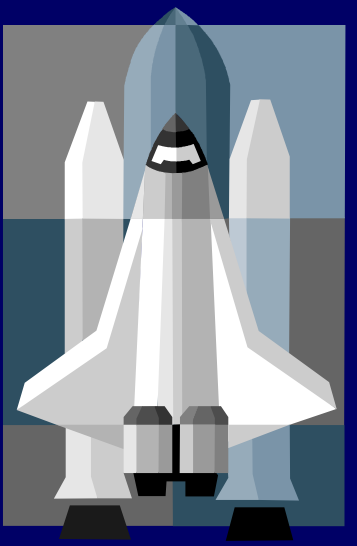
- Asahi
  - Miraclebros – excellent torque (3g-12 g)
  - Confienza, Confienza Pro- pentration (9g-12g)
- Medtronic
  - Persuader
- Cordis
  - Cross-it

Advantages are operator familiarity with conventional guidewires
However these are stiffer guidewires with risk of perforation

Specialty Guidewires

- Interesting novel technology
- Require some differences in techniques from conventional guidewires

CTO Technologies



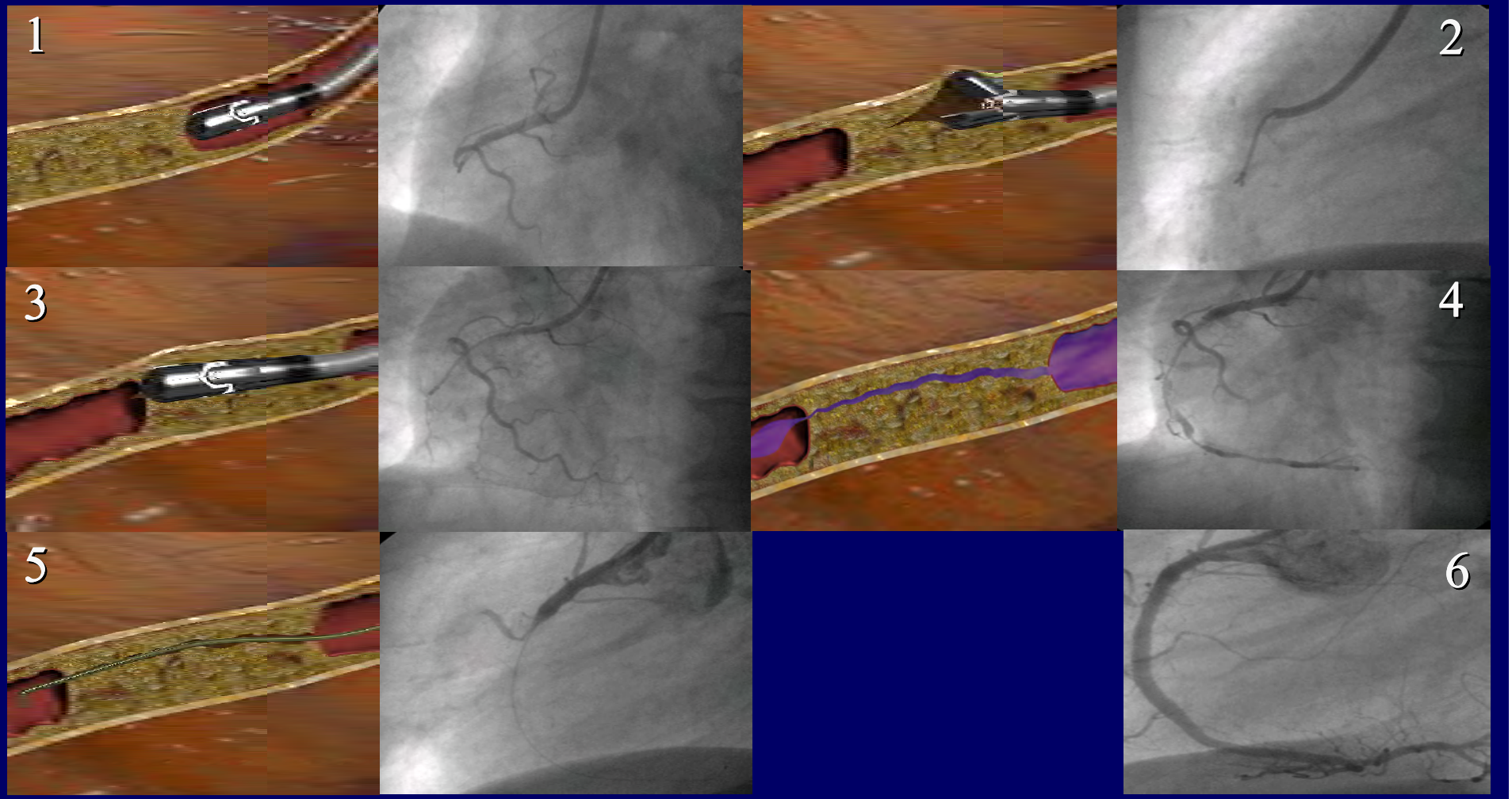
- Specialized guide-wires
  - Shinobi, Miracle Bros., Conquest…
- Lumend Frontrunner Catheter (blunt micro-dissection)
- Safe Cross system - Optical Coherence Reflectometry (OCT)
- US

LuMend Frontrunner Catheter

Controlled Blunt Micro-Dissection Technique

- Separates atherosclerotic plaque in various tissue planes, creating a passage through the CTO
- Uses the elastic properties of adventitia versus inelastic properties of fibrocalcific plaque to create fracture planes

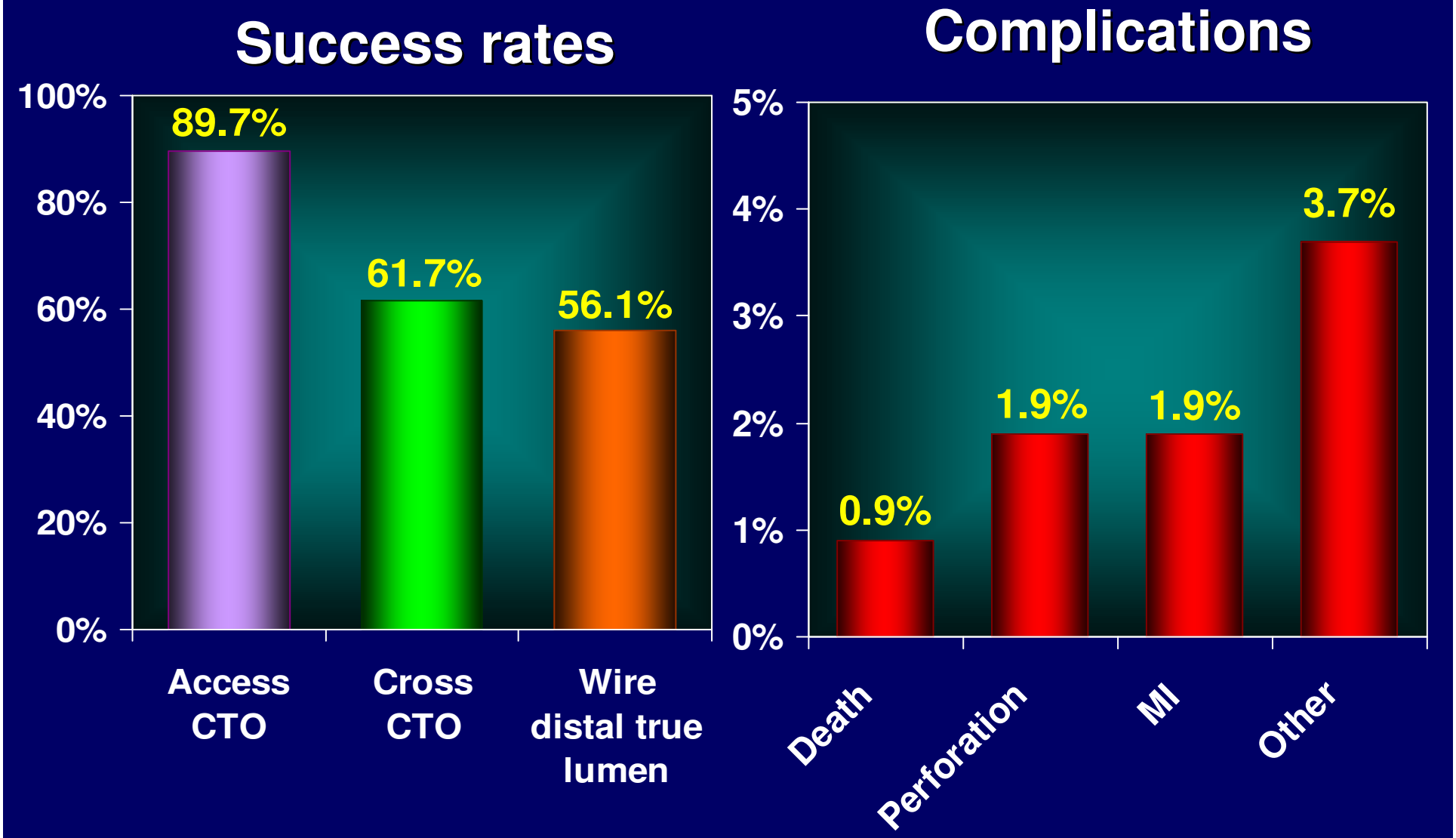
Frontrunner: Controlled Blunt Micro-Dissection



Frontrunner Catheter: Clinical Study

- Prospective, controlled multi-center trial
- 107 patients
- CTOs refractory to 10 min (fluoroscopy time) conventional GW attempt
- Success defined as placement of guide wire beyond CTO in the true vessel lumen
- Mean lesion length: 22 mm (range 2 – 53 mm)

Frontrunner Clinical Results



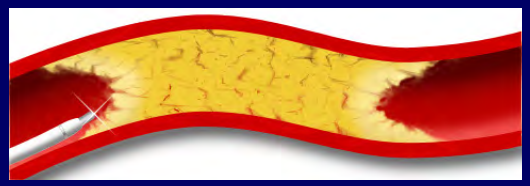
Feb 2002: FDA 510k Clearance

Safe Cross – IntraLuminal Therapeutics

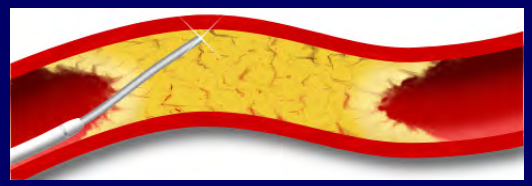
Optical Coherence Reflectometry (near-infrared light) guidance system
Coupled to pulse radiofrequency ablation
January 2004: 510k clearance from the FDA for coronary occlusions

OCR Waveform Displays

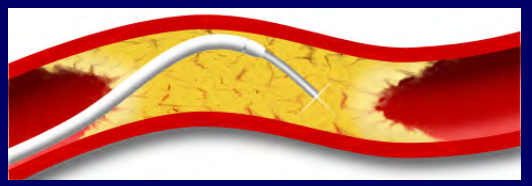
No artery wall detected

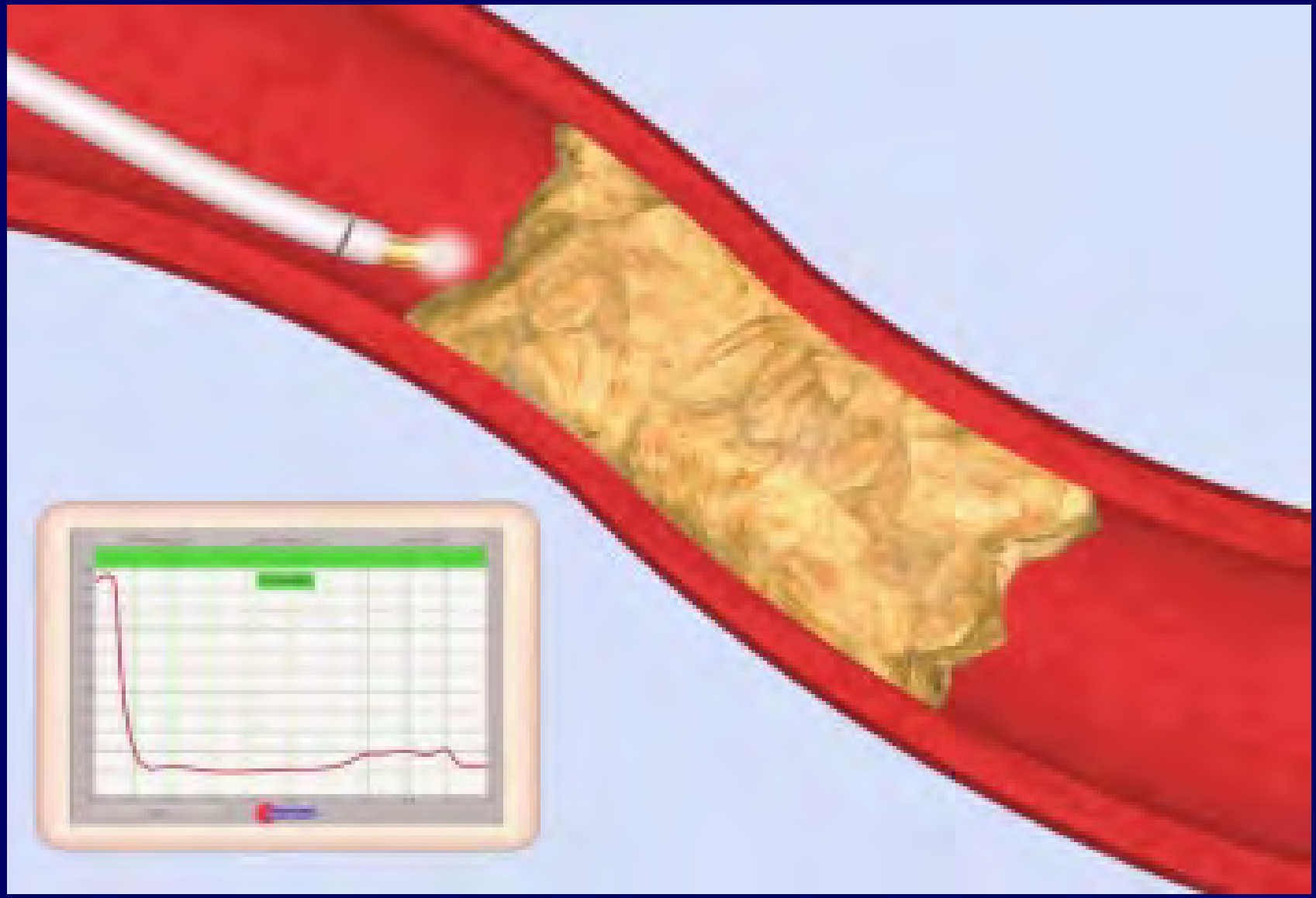


Artery wall detected



No artery wall detected





GREAT

Guided **R**adio Frequency **E**nergy
Ablation of **T**otal Occlusions

GREAT Study Overview

- Originally begun as a randomized trial at 10 sites
  - Native CTO (> 2.5 mm, < 30 mm length)
  - 1:1 randomization of treatment with the SAFE-CROSS™ RF versus current standard wires
  - 30 day safety and efficacy endpoints
  - Patients who failed the conventional wire can enter GREAT Registry after 30-days -> OCR
- Later converted to 116 patient registry, after a failed 10 minute attempt with a conventional wire (~Lumend study)

GREAT

- Device Success 55.7%
- Reasons for failure
  - Wire unable to progress 81%
  - Entry of false lumen 25%
  - Perforation 12%
    - Wire exit or local stain 6.7%
    - Extravasation 0.7%

GREAT

- Complications 6.0% (9)
  - Q-MI, CABG, Death 0%
  - MACE (all NQMI) 4.7% (7)
  - Clinical Perforations 2.6% (4)
    - Device related 0.7% (1)

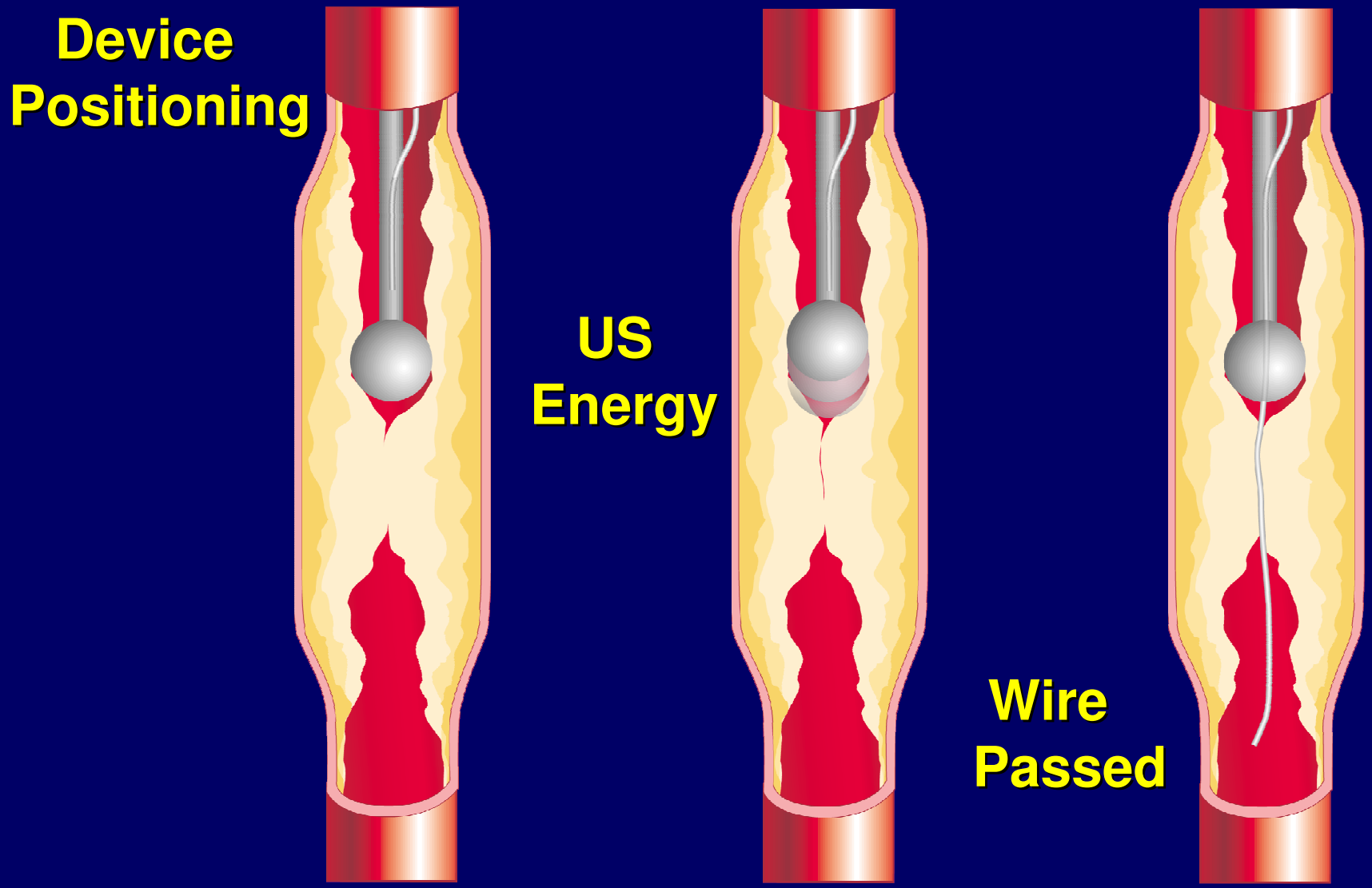
CROSSER System- FlowCardia Inc.

FlowCardia CROSSER System

High frequency mechanical revascularization

High frequency mechanical vibrations at 20 kHz
Vibrational energy provides cavitational effects

CTO: Therapeutic Ultrasound



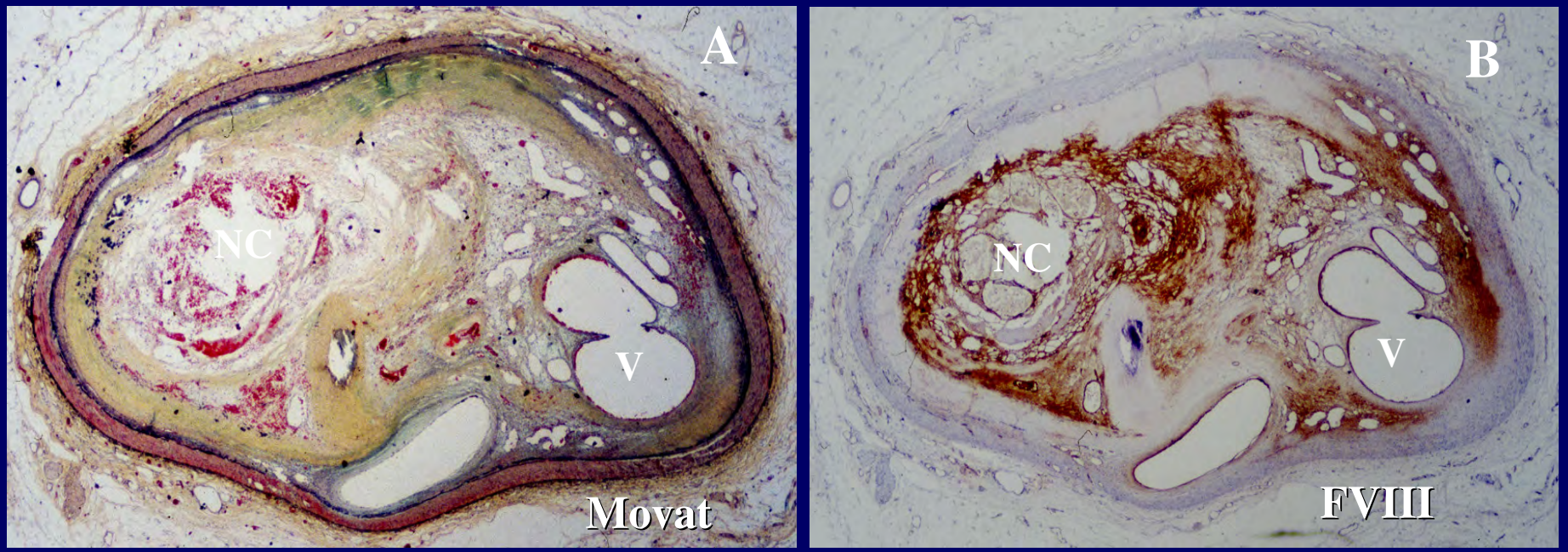
CTO - Results of New Technologies

	Device	Application	N	tech. success	perforations
LUMEND	Frontrunner	Coronary	105	56%	1.9%
GREAT	Safe-cross	Coronary	116	56%	2.6%
GRIP	Safe-cross	Peripheral	72	76%	0

Should we develop a non-mechanical, biological modality to facilitate CTO revascularization?

How about enzymatic degradation?

Pathology of Chronic Total Occlusions: Human Coronary Arteries

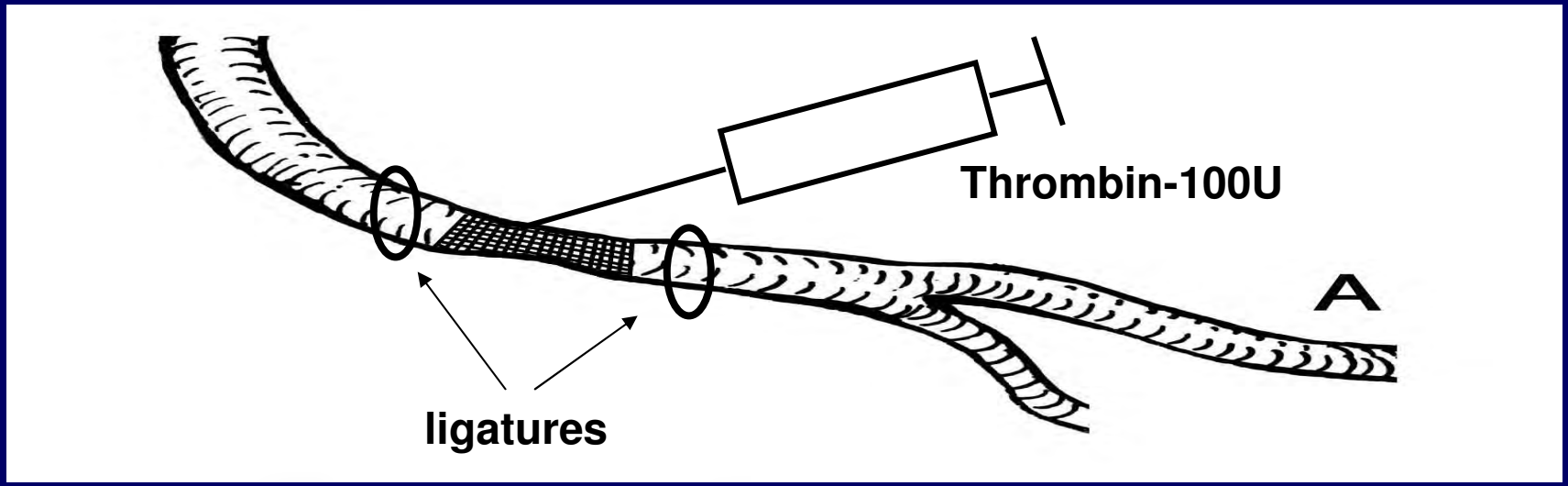


- Majority (78%) of angiographic CTO are ≈99% occluded by histology
- Collagen: Major structural components of the extracellular matrix
- Proteoglycans are common in CTO < 1 yr
- Intimal plaque micro-vascular channels are common in CTO (>75%)

Courtesy of Dr. Renu Virmani, AFIP, Bethesda

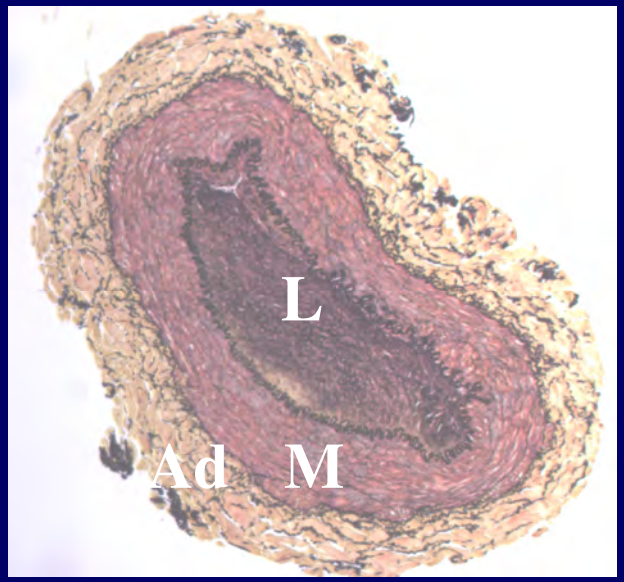
Rabbit Model of Femoral Artery CTO

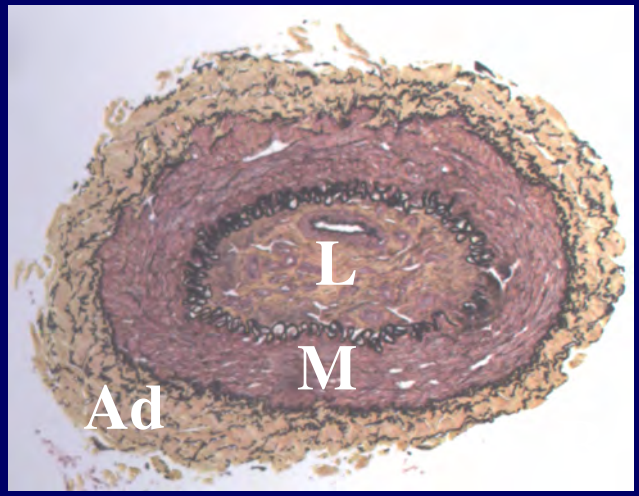
Rabbit femoral artery

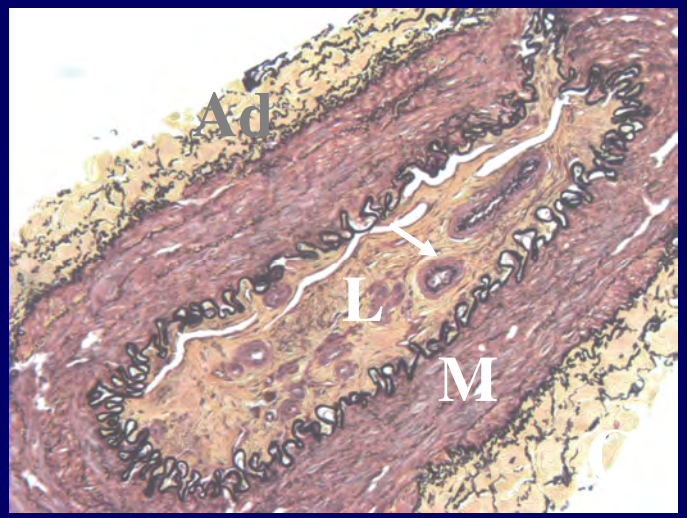


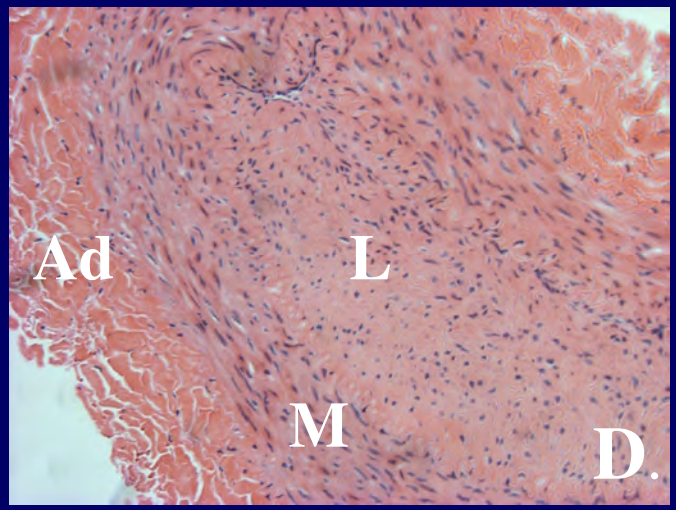
Thrombin injection
Restoration of blood flow after 1 hour
Angiographic confirmation of occlusion at 3-4 months
-thrombus / fibrin is replaced by fibrotic tissue (collagen)

Chronic Total Occlusions: Rabbit Femoral Model









Strauss BH et al, Circulation 2003;108:1259-62

CTO by MRI


3D
Ex: 1025
Se: 101
MIP No cut
SLA
SWCHSC SB
Rabbit-040708-two occlusions
? 12345
Jul 08 2004
1.00 x
R
A
S
L
P
I
No VOI
46552X2599/1.00 NEX
00:49
1.0 mm/1.0sp
DFOV 7.0cm
EC:1/1
TE:2.8/Fr
TR:9.4
GR/SS/GENESIS_SIGNA 3.0T
FAST_GEMS\VB_GEMS\PFF
W = 281 L = 144
AL
RA
LP
PR
IRP

Proteinases

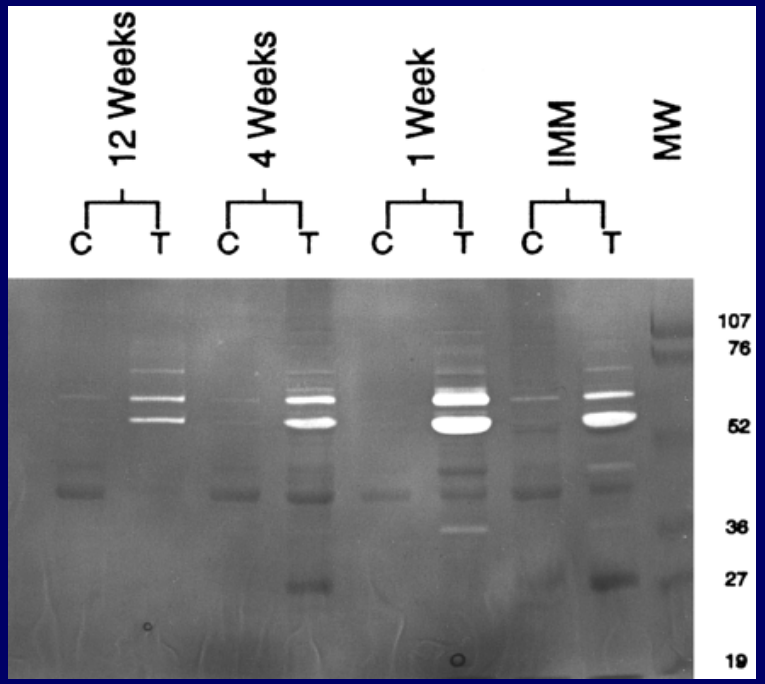
Enzymes that catalyze the breakdown of native proteins

Matrix Metalloproteinases

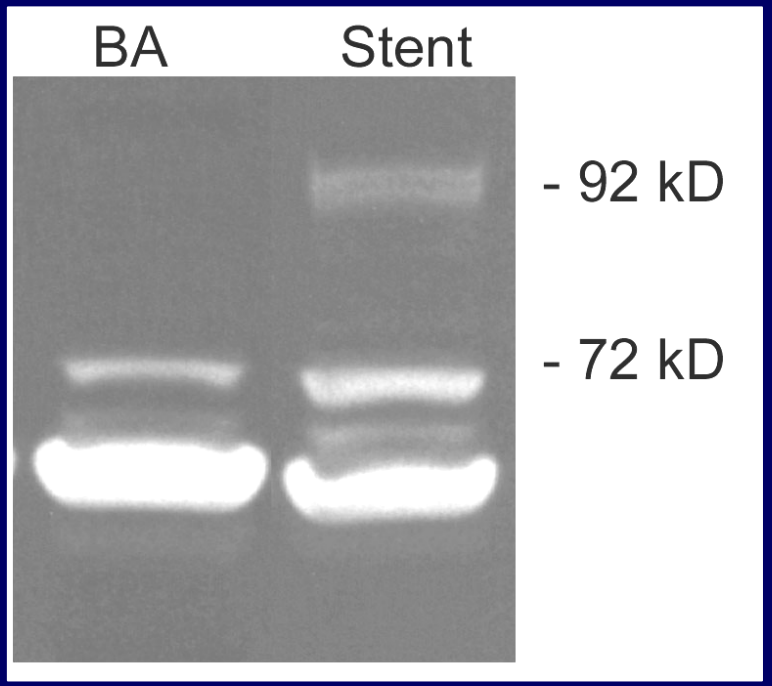
- Zinc and calcium-dependent enzymes
- >20 members
- MMP-1, MMP-2, MMP-9, MMP-3
- degrade all extracellular matrix components
- 3 broad categories:

  collagenases (MMP-1), gelatinase, and stromelysins

Gelatinase Activity After Arterial Injury



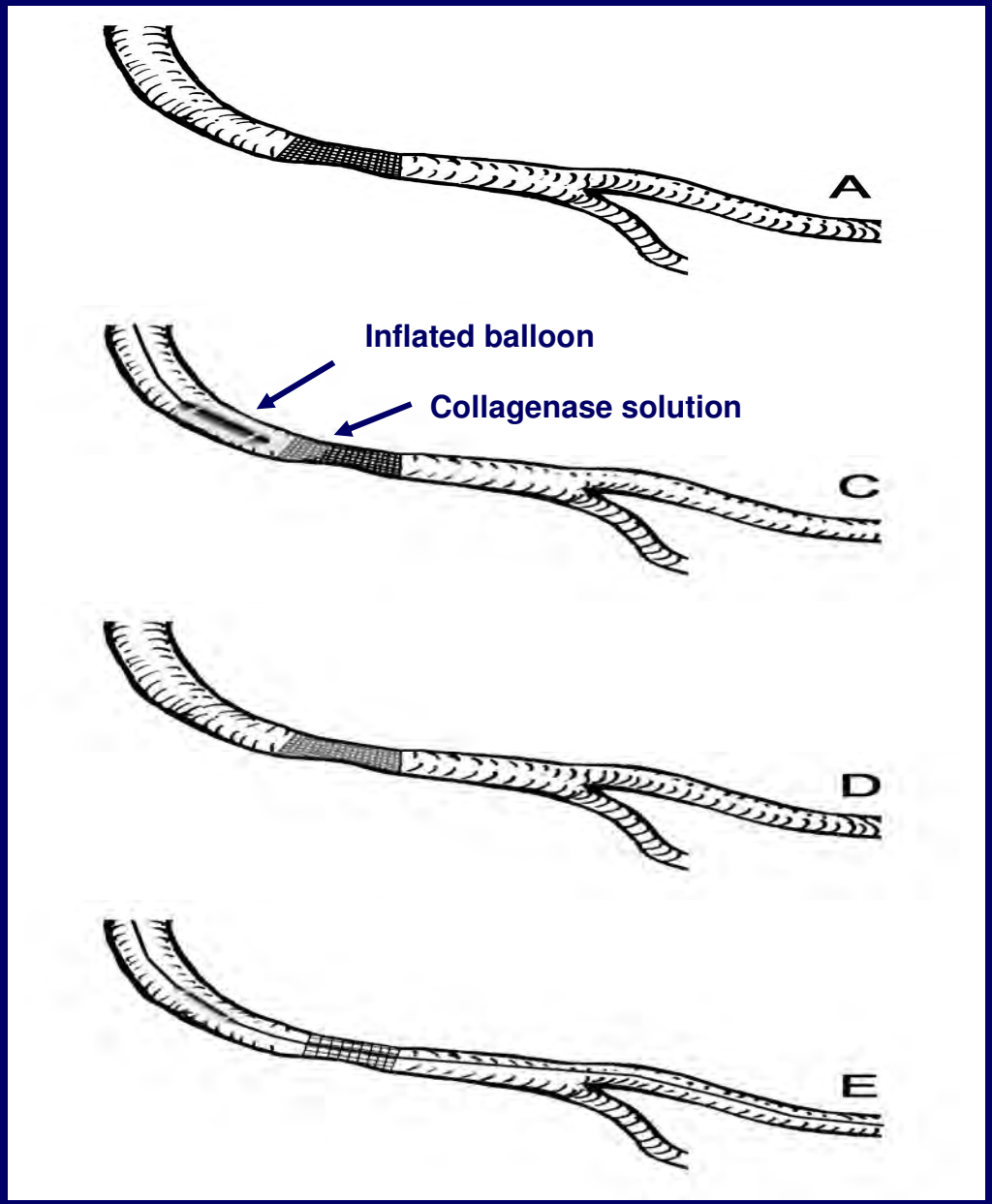
Strauss et al Circ Res 1996;79:541



Li C et al, JACC 2002;39:1852-8

Type IA Collagenase (Sigma)

- Source: Clostridium histolyticum
- Components
  - Collagenase
  - Clostripain
  - Neutral Protease
  - Trypsin-like activities



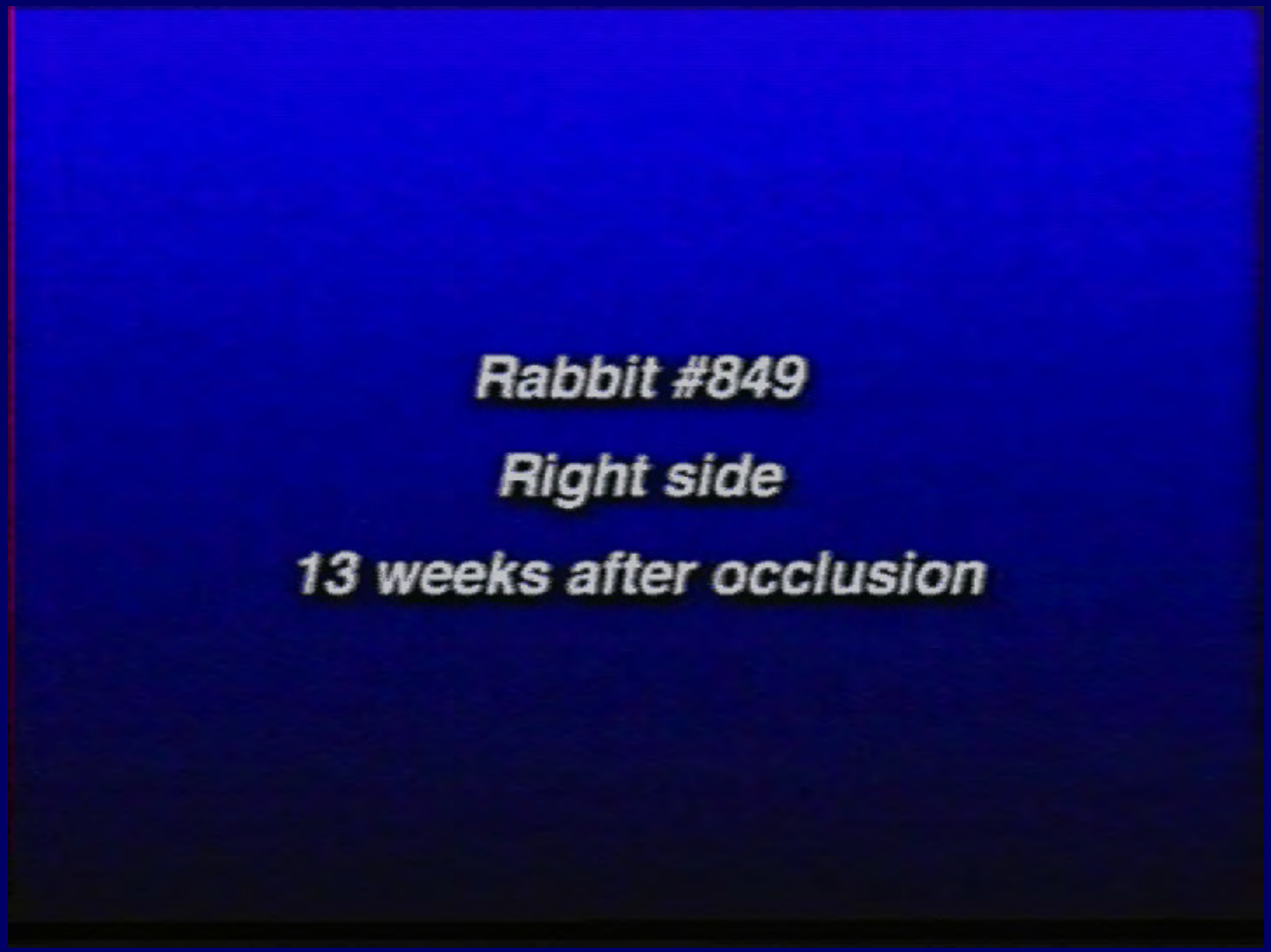
CTO in femoral artery

Advancement of an over-the-wire balloon and local injection of collagenase solution while balloon remains inflated (1 hour)

Balloon removal

Successful guide-wire crossing after 24 hours

Collagenase: Successful Guide Wire Crossing



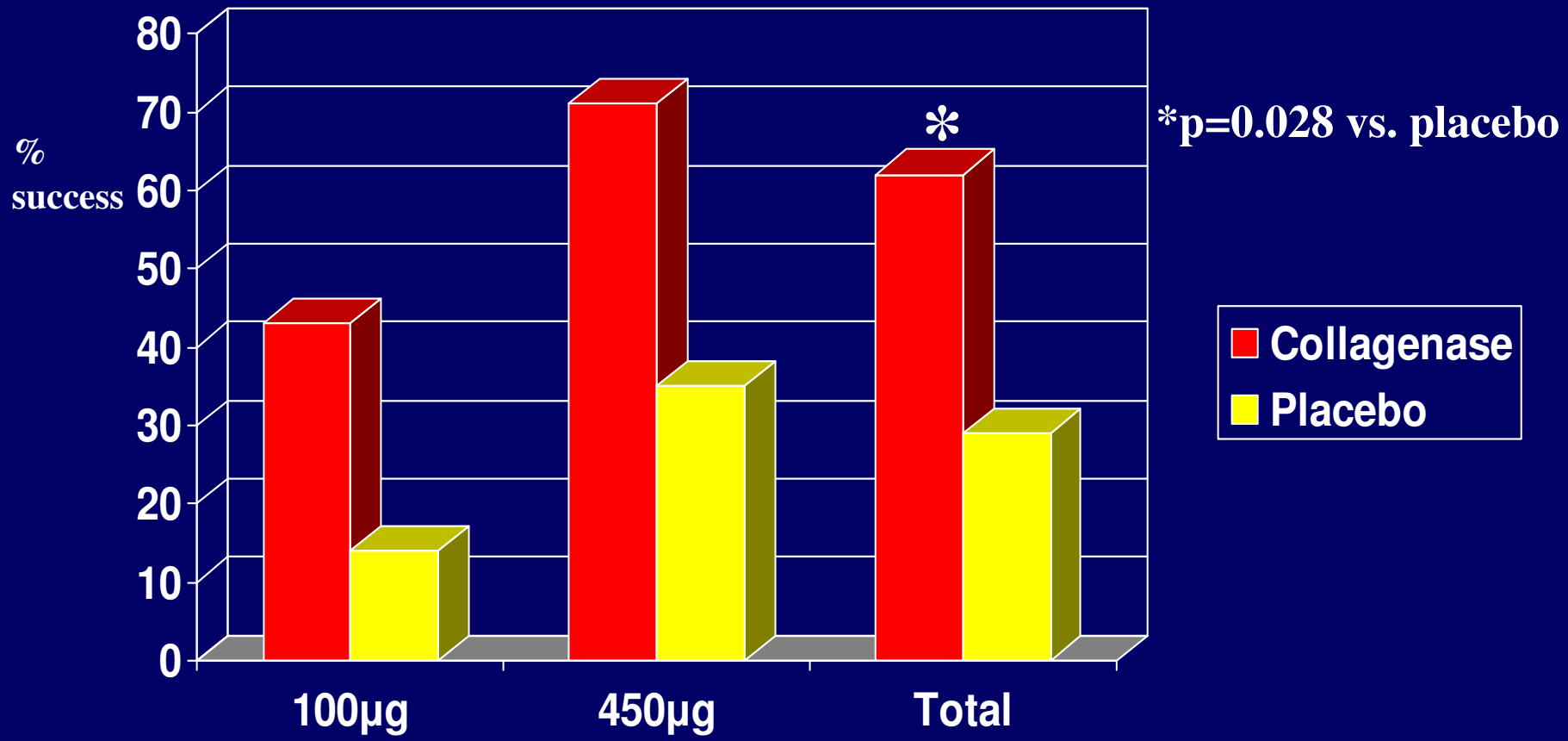
Rabbit 849 Right Femoral Artery

CTO Characteristics

- **Occlusion Age: 16 ± 5 weeks**
  (range 10-25 weeks)

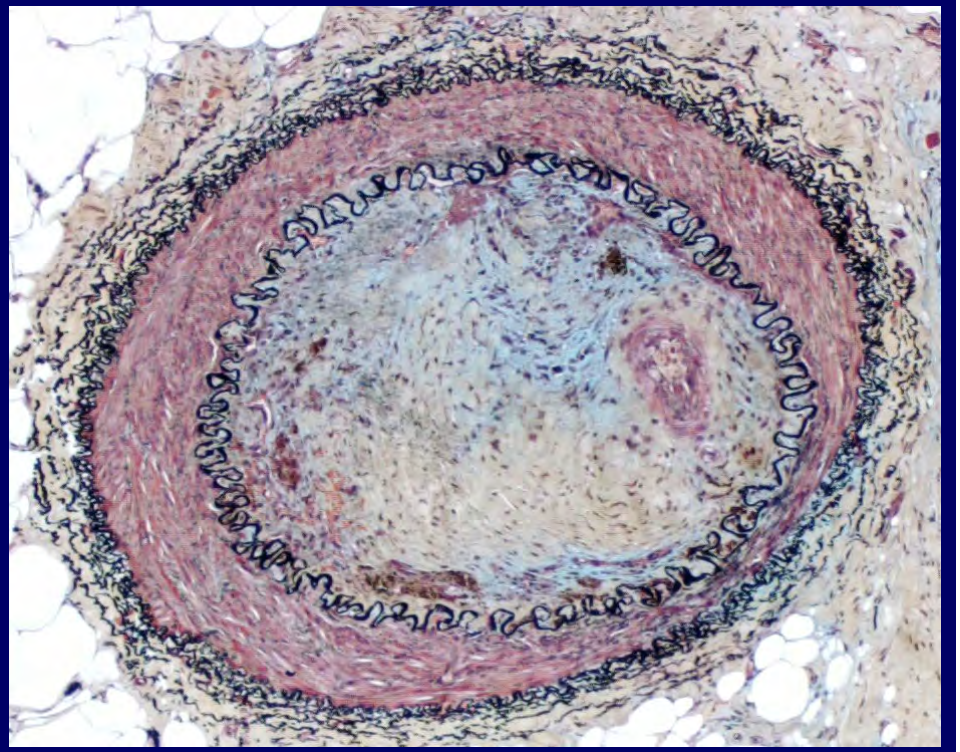
- **Mean occlusion length: 28 ± 9 mm**
  (range 14-46 mm)

Guide Wire Crossing Success Rates at 72 Hours Post Infusion



Guide Wire Crossing at 72 hours

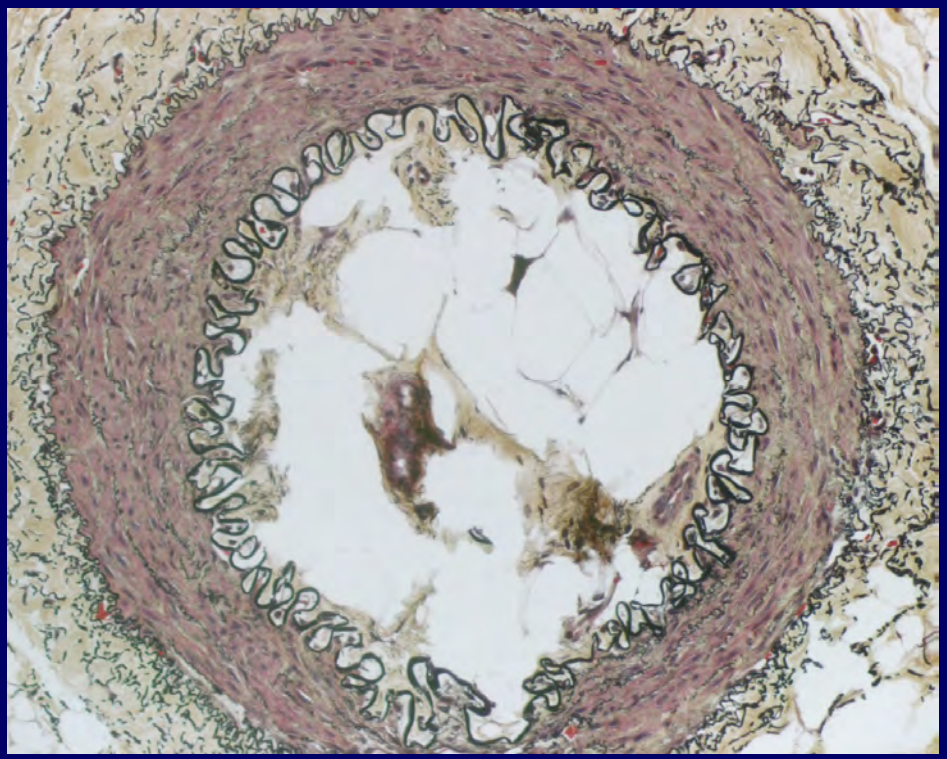
Success
Collagenase 450 µg

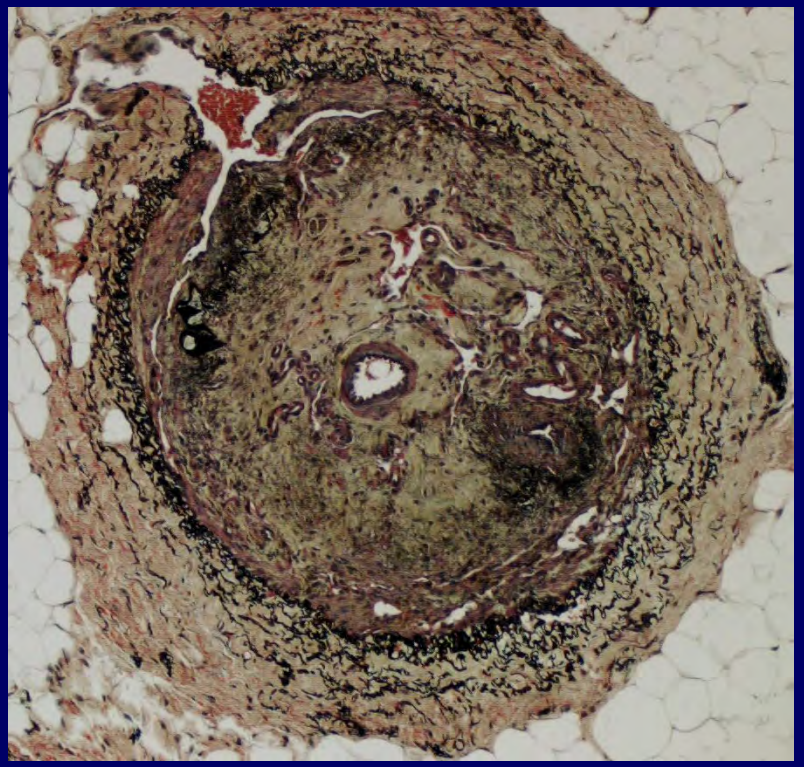


Failure
Placebo

Treatment Effects At 24 Hours

(No Guide Wire Attempt)





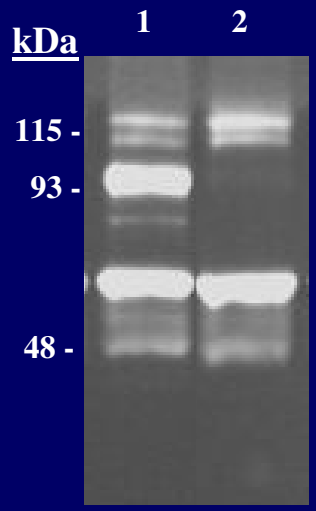
Collagenase 450 µg

Placebo

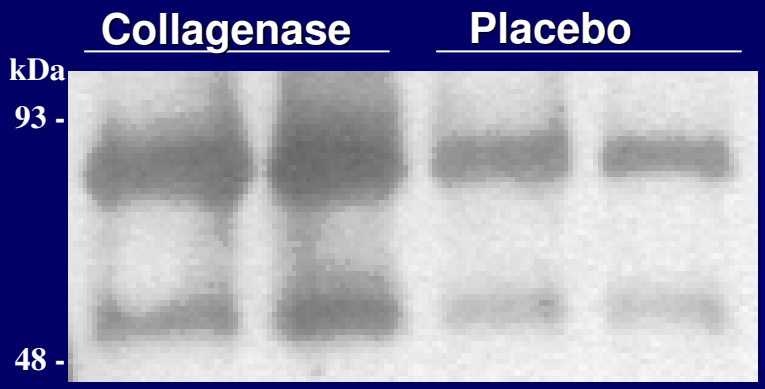
Strauss BH et al, Circulation 2003;108:1259-62

24 hours: Proteolytic Effects

Gelatin Zymogram



Collagen Fragments Western Immunoblot
COL 2 3/4 Against Carboxy Terminus



Lane 1- Collagenase artery

Lane 2- Placebo artery

Strauss BH et al, Circulation 2003;1081259-62

Purified Collagenase:

- 38-fold more potent than Sigma collagenase preparation
- No contaminating proteolytic activity
- Suitable for human studies

Rabbit Femoral CTO Model

Dosing Study:

100-200 µg (n=10) no or mild subcutaneous bruising

250-500 µg (n=7) moderate-severe sc bruising

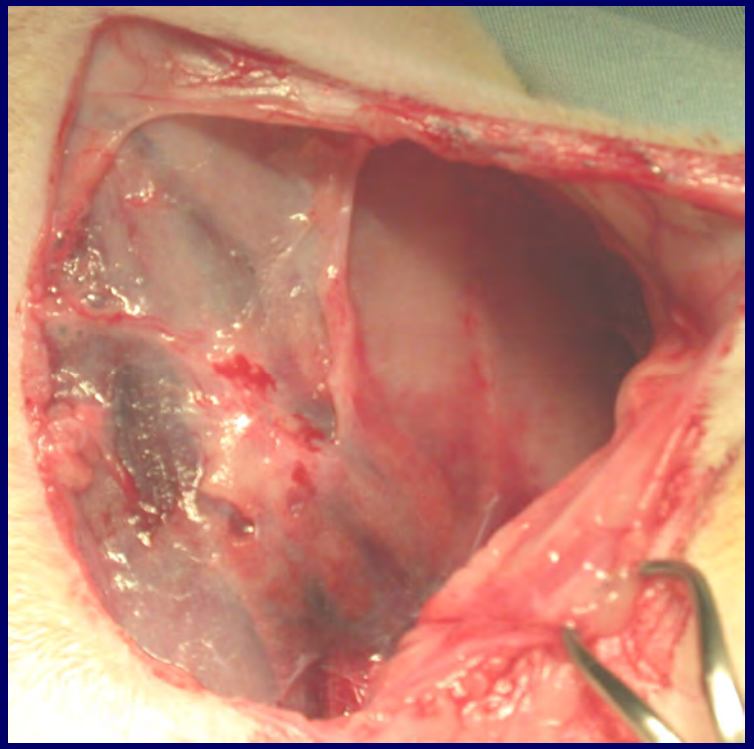
Guide Wire Crossing at 24 Hours

150 µg (n=10)

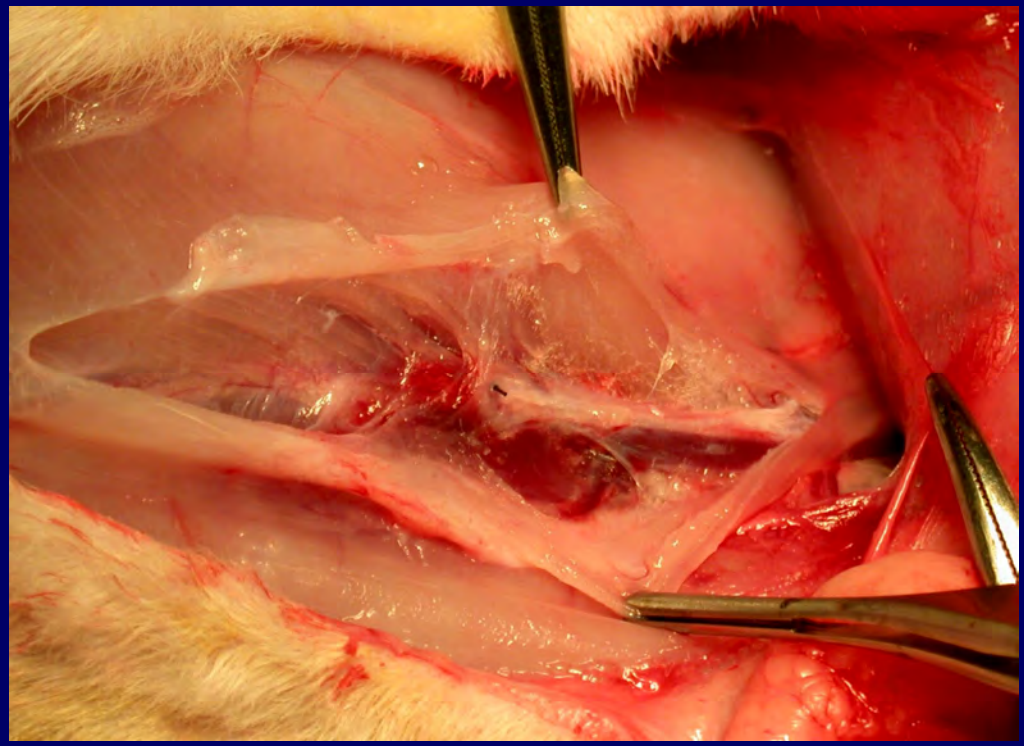
100% Successful !!

Segev A et al, JVIR, Submitted

Subcutaneous Bruising

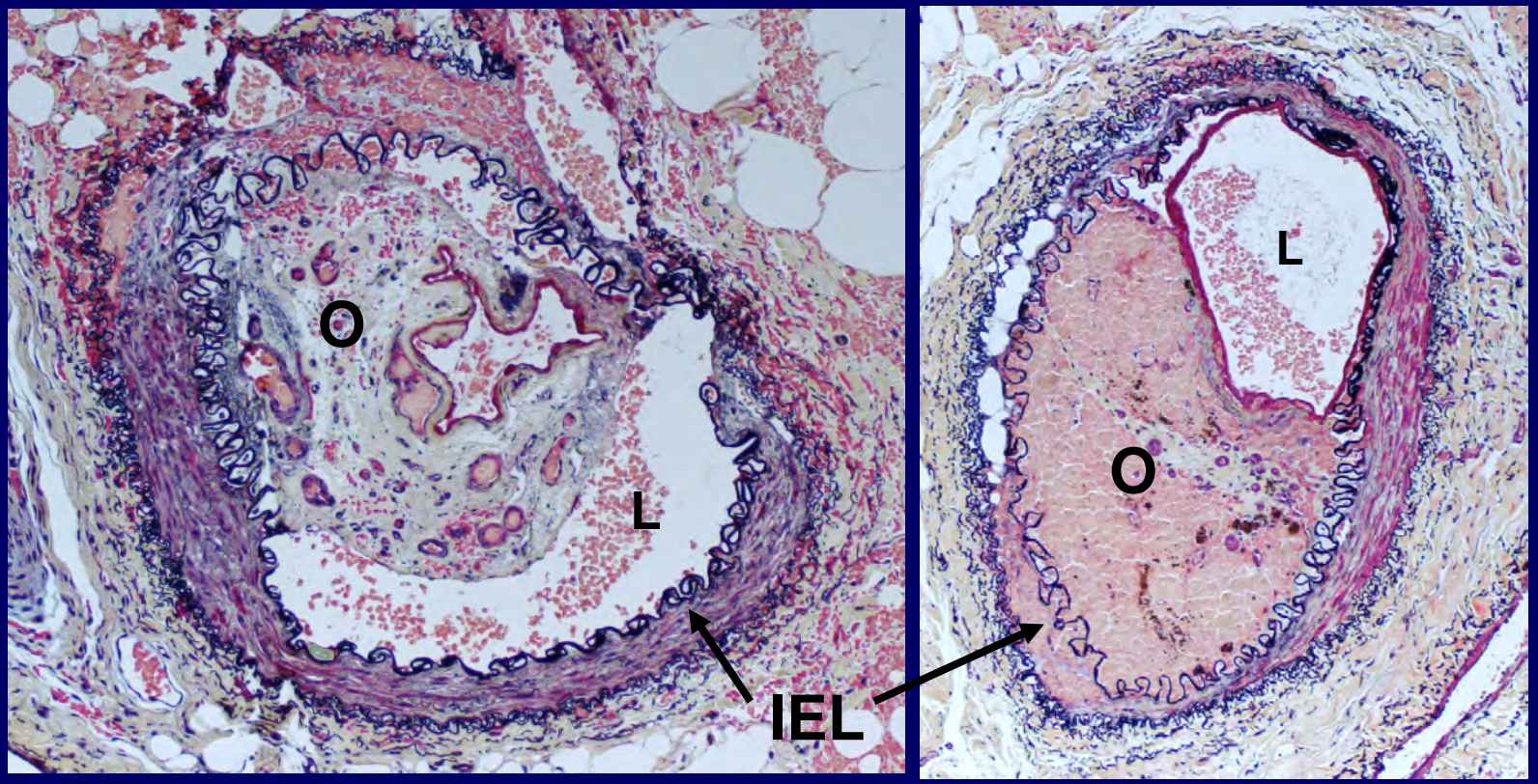


500 µg collagenase



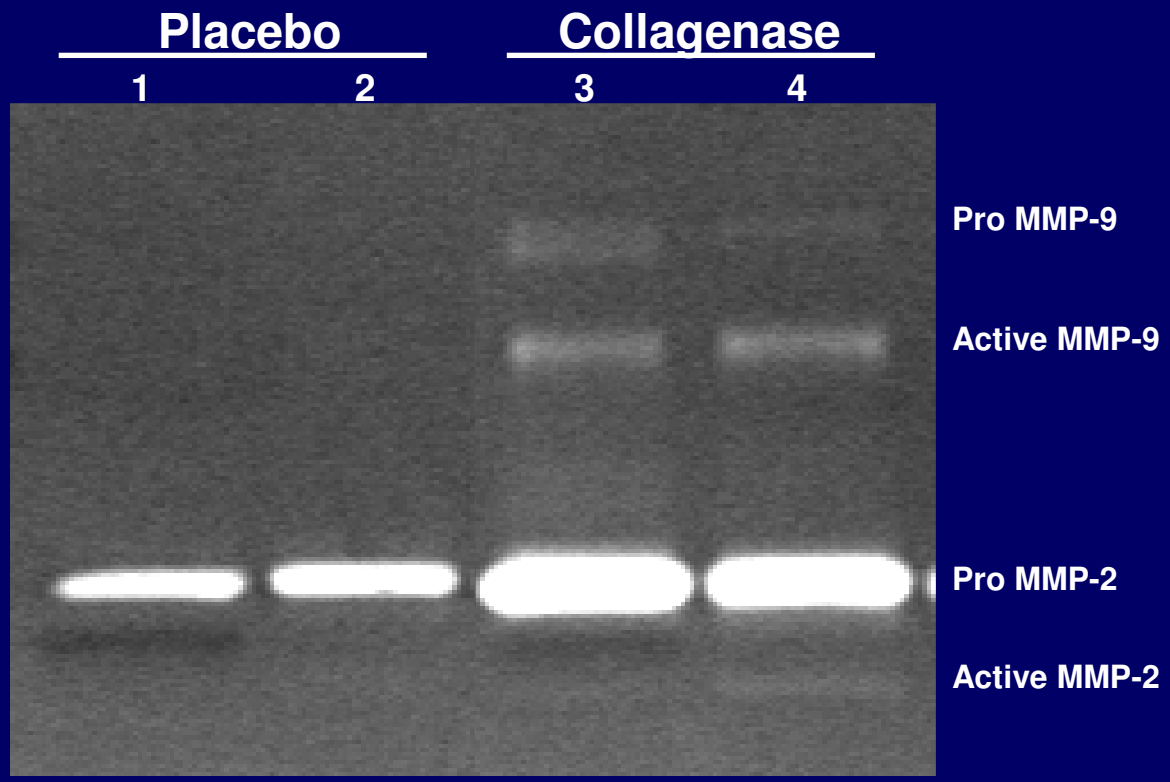
150 µg collagenase

Rabbit CTO cross sections with successful crossings



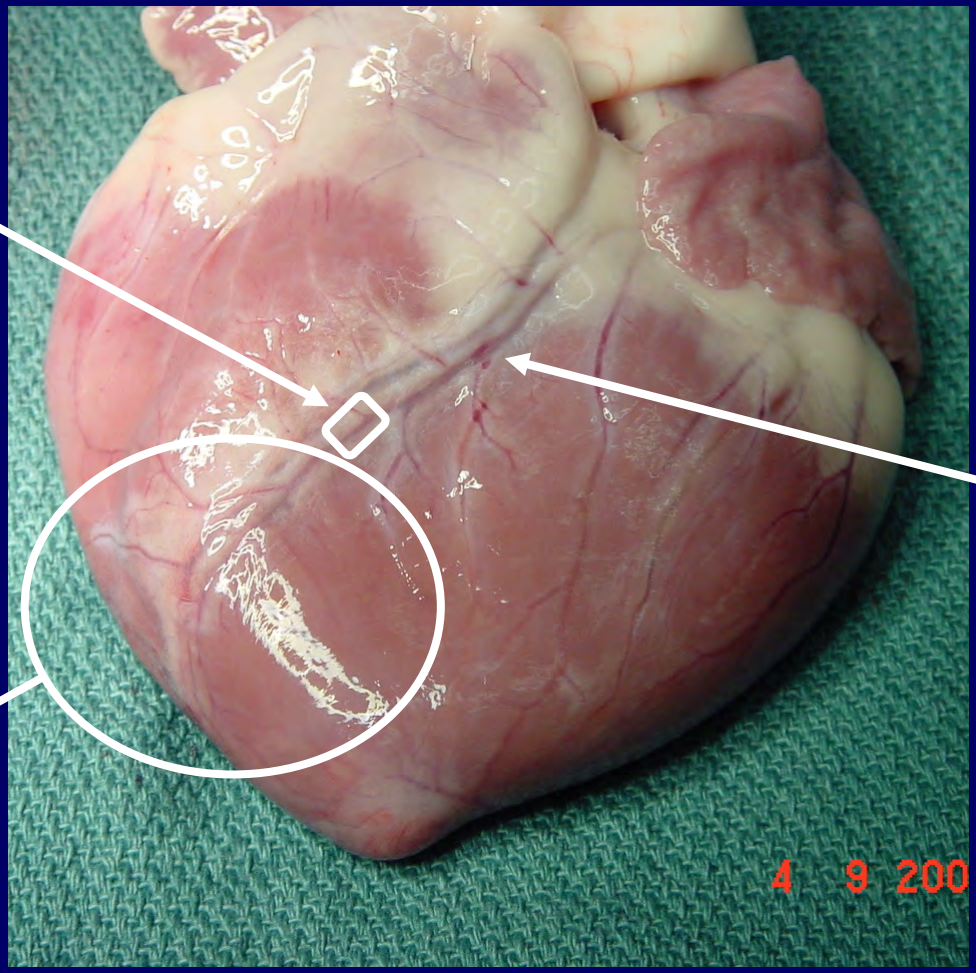
Segev A et al. JVIR, Submitted

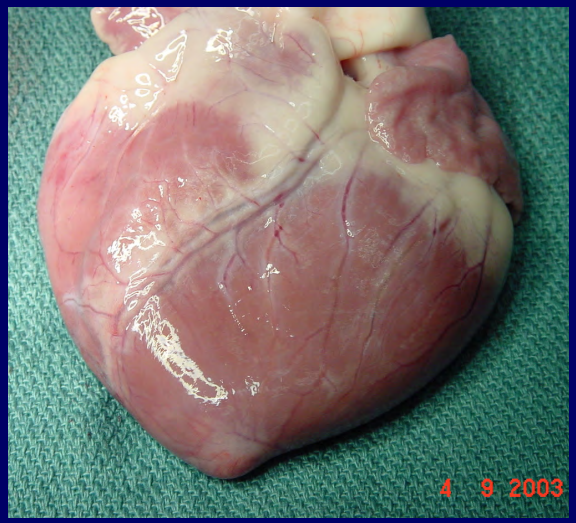
Gelatinase Activity at 24 Hours: 150 µg



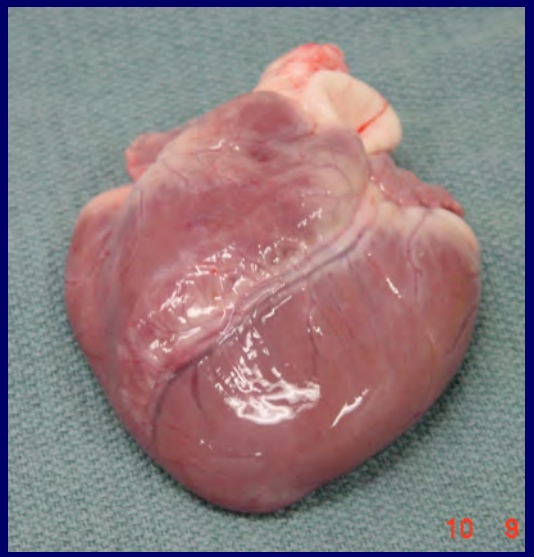
Segev A et al. Submitted

Intra-coronary Purified Collagenase: Swine Hearts





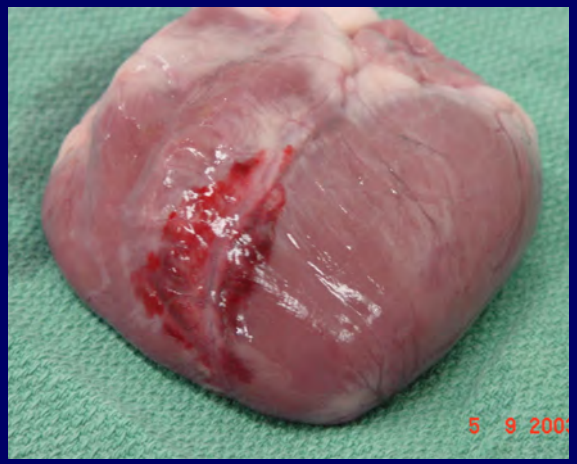
Control



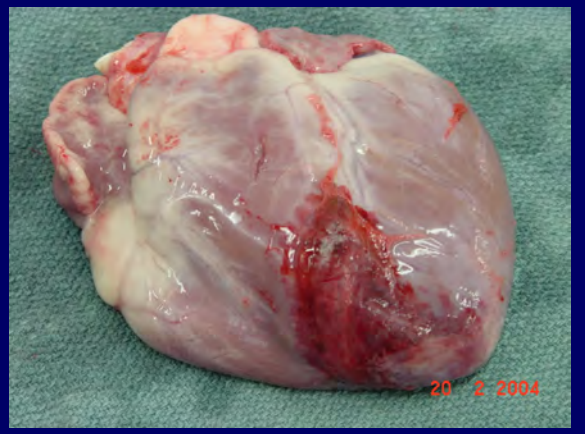
50µg

75µg

150µg



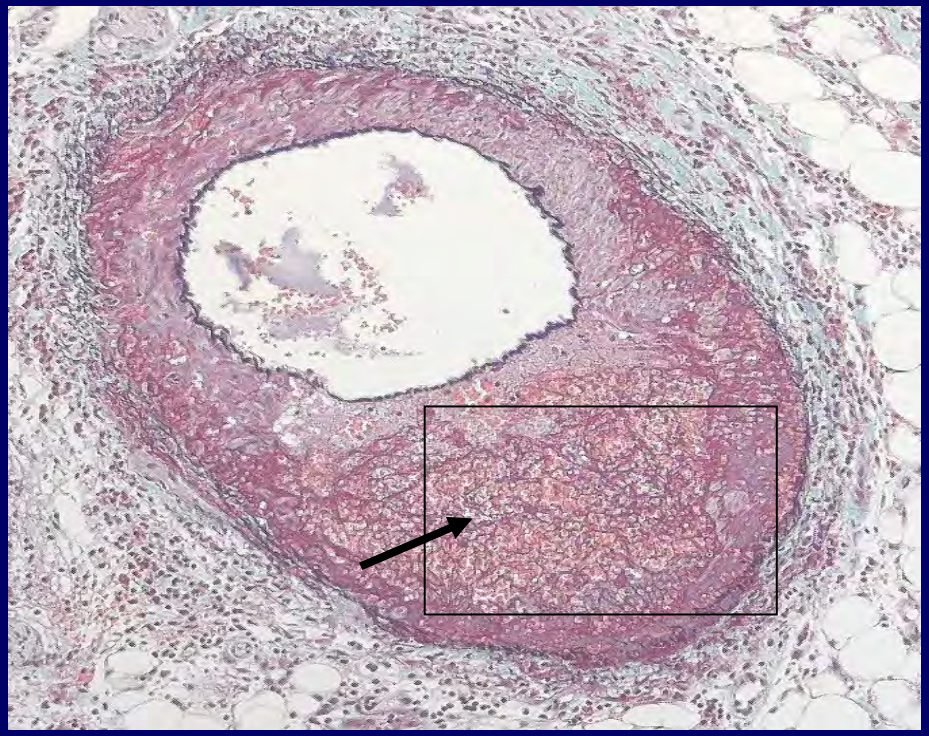
450µg

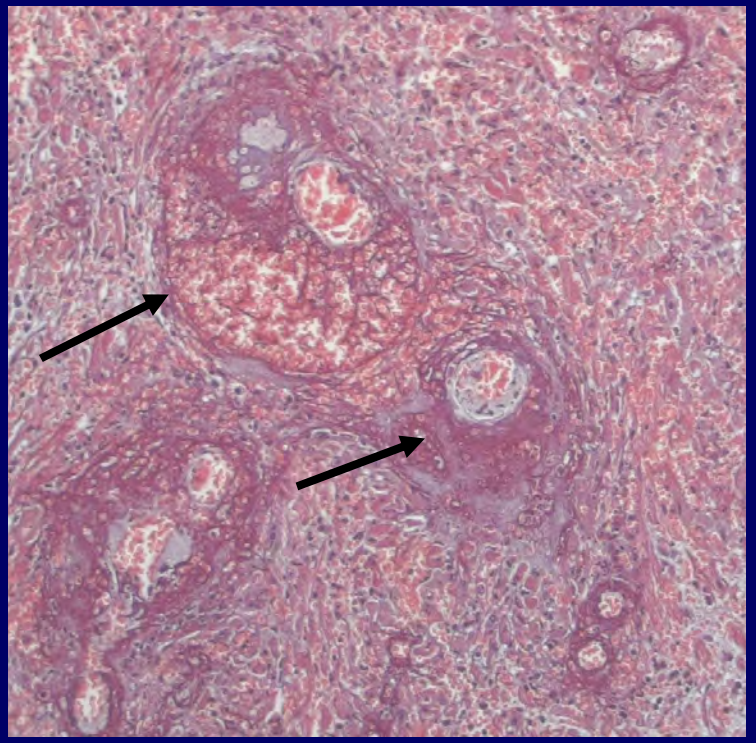


1000µg

Arterial Medial Damage

Only at High Dose (450 µg)





Segev A et al. Cardiovasc Pathol, Submitted

1-Month follow-up

- 9 pigs
- Intra-coronary collagenase:
  - 150, 450, 1000μg
- Macroscopically normal
- 2/3 pigs with high dose showed normal myocardium with no fibrosis.
- 1 pig showed mild fibrosis.

Conclusion

- Local delivery of collagenase facilitates guide-wire crossing in chronic total occlusions
- No adverse effects on arterial structure
- Local bruising is a dose related side effect
- Human phase I study is planned

Phase I Clinical Trial

- **Objective**
  - To determine the safety and efficacy of 3 different doses of a human-grade purified collagenase for the treatment of failed coronary chronic total occlusion (up to 1 year old).
- **Inclusion criteria:**
  - Patients with CTO with a clinical indication for revascularization.
  - CTO ≤ 1 year old.
  - Previously failed coronary intervention or if patient recruited as an ad hoc, failure to cross the occlusion with conventional wires after 10 minutes (FDA definition).
- **Exclusion criteria:**
  - Saphenous vein graft occlusion
  - True ostial LAD, LCX or RCA occlusions
  - Major side branch immediately proximal to the occlusion

Phase I Clinical Trial

- **Protocol:**
  - Confirmation of failed conventional PCI attempts and no exclusion criteria.
  - Advancement of a short over-the-wire balloon until against the occlusion and removal of wire.
  - Inflation of the balloon to nominal size.
  - Slow injection of collagenase solution through the balloon lumen.
  - The balloon remains inflated for up to 1 hour depending on patient's tolerability.
  - ACT>300 seconds throughout the procedure.
  - Balloon deflation.
  - Patient remains in hospital and will be ECG monitored and serial blood samples for cardiac enzymes taken
  - The day after, repeat conventional PCI

- Three different doses will be tested: 50µg, 75µg, and 100µg.
- Each group will consist of 6 patients. Total = 18 patients.
- The first dose to be assessed will be 50µg.

Future Research

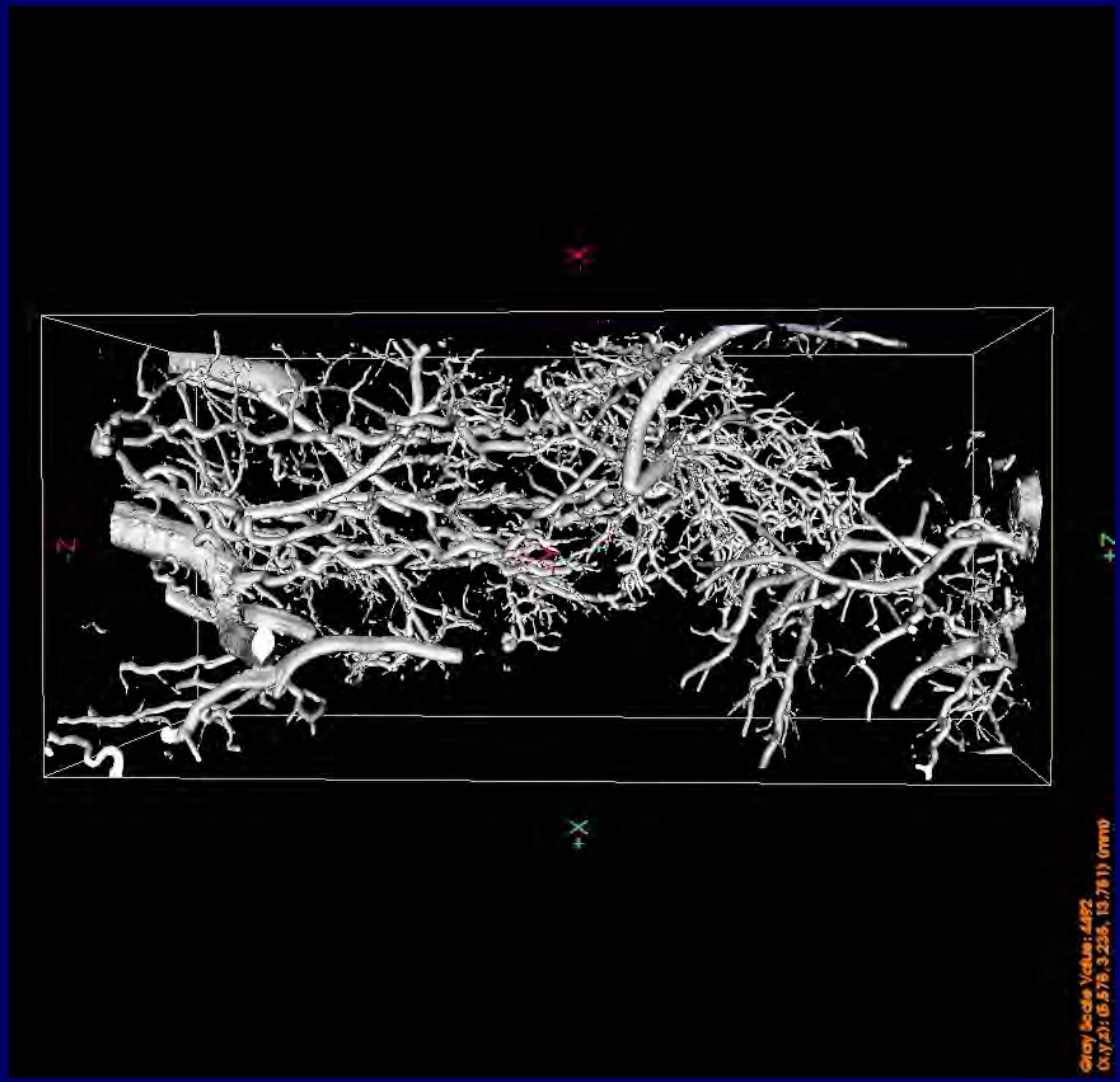
1) CTO imaging

2) Augmentation of CTO Micro-Vessels by Cell Therapy with Engineered EPCs

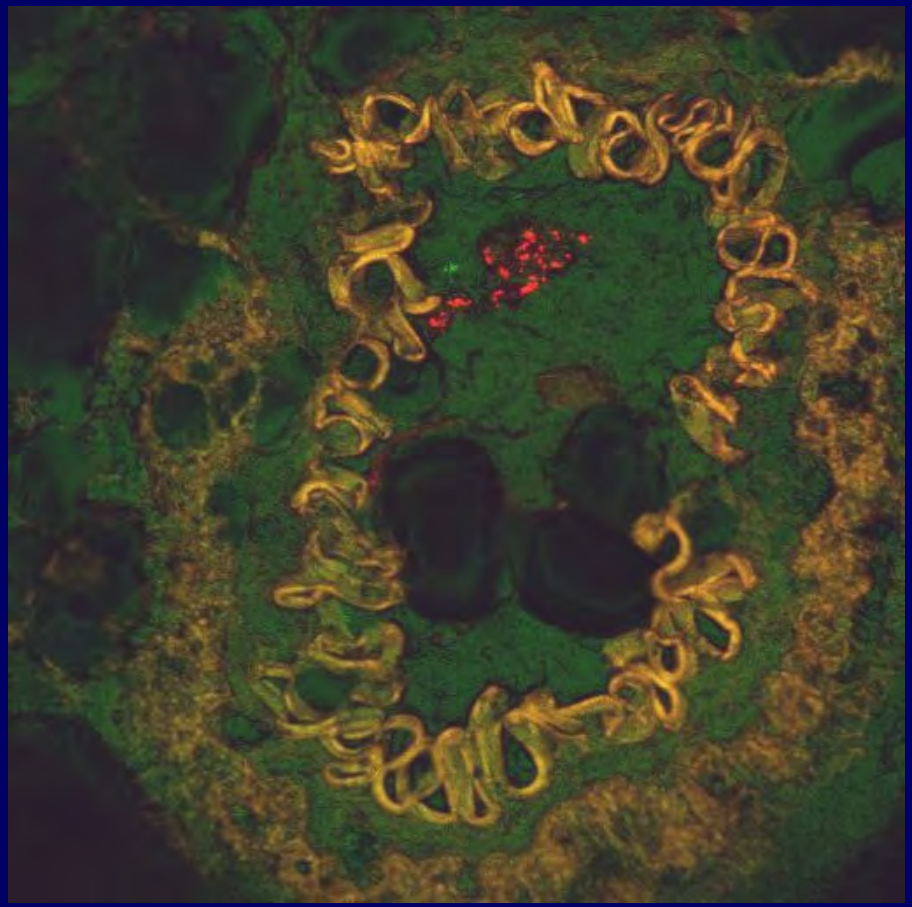
MRI

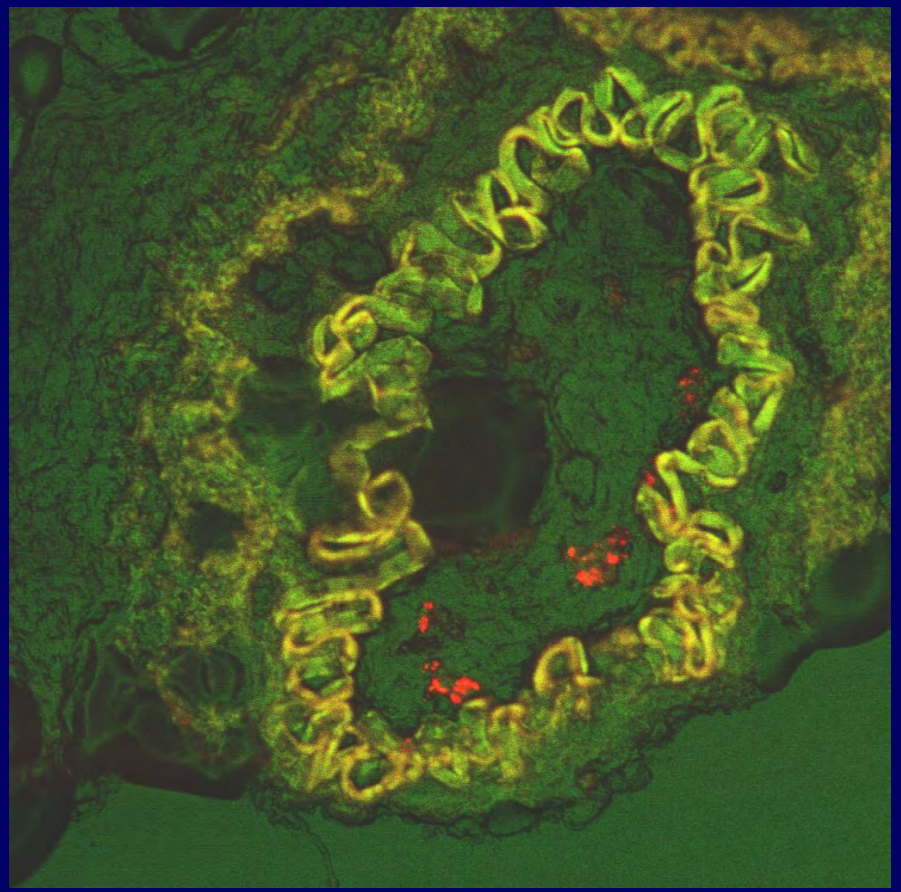

3D
Ex: 1025
Se: 101
MIP No cut
SLA
SWCHSC SB
Rabbit-040708-two occlusions
? 12345
Jul 08 2004
1.00 x
R
A
S
L
P
I
No VOI
46552X2599/1.00 NEX
00:49
1.0 mm/1.0sp
DFOV 7.0cm
EC:1/1
TE:2.8/Fr
TR:9.4
GR/SS/GENESIS_SIGNA 3.0T
FAST_GEMS\VB_GEMS\PFF
W = 281 L = 144
IRP
AL
RA
LP
PR

CTO by micro-CT



Fibroblasts delivery into CTO





UNITED STATES PROVISIONAL PATENT APPLICATION

Inventors: Bradley H. Strauss of Toronto, Canada;, and Amit Segev of Raanana, Israel.

AUGMENTATION OF INTRALUMINAL MICROVESSEL FORMATION TO FACILITATE GUIDE WIRE CROSSING IN CHRONIC TOTAL OCCLUSIONS

Conclusions

- Remember the pathology
- Clinical indication !!!
- Favorable angiographic appearance
- Consider CTA
- Advanced guide-wires techniques
  - No room for dedicated devices – so far…
- STAR and retrograde techniques – only if your last name rimes with SUZUKI