

OrbusNeich Lunch Symposium

TCTAP 2012 CVRF

25th April 2012

A Scientific and Rational Approach To Delineate Future Stent Platform

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Disclosure Statement of Financial Interest

I, Stephen WL Lee DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

THE NEXT ERA: COMBO DUAL THERAPY STENT

COMBO™

**A Safe, No Compromise Solution
for You and Your Patients**

ANGIOPLASTY SUMMIT
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OrbusNeich Lunch Symposium

Wednesday, 25th April, 2012

THE NEXT ERA: COMBO DUAL THERAPY STENT

Endovascular Arena, Level 1

The Convention Center of Sheraton Grande Walkerhill Hotel, Seoul, Korea

Chairpersons: Seung Jung Park and Harry Suryapranata

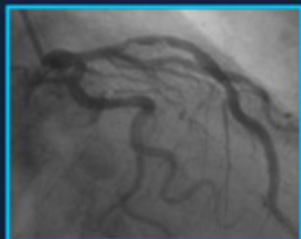
- 12:45 - 12:50 Opening address - Seung Jung Park
- 12:50 - 13:00 The Next Era: COMBO Dual Therapy Stent - Roxana Mehran
- 13:00 - 13:15 COMBO - a combination sirolimus eluting and anti - CD34 antibody coated stent: technology, development, and clinical data - Stephen M Rowland
- 13:15 - 13:35 A Scientific and Rational Approach to Delineate Future Stent Platforms - Stephen W L Lee
- 13:35 - 13:45 Q & A followed by Closing Remarks - Harry Suryapranata

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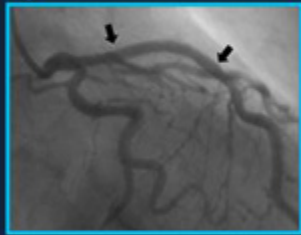
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CE mark pending

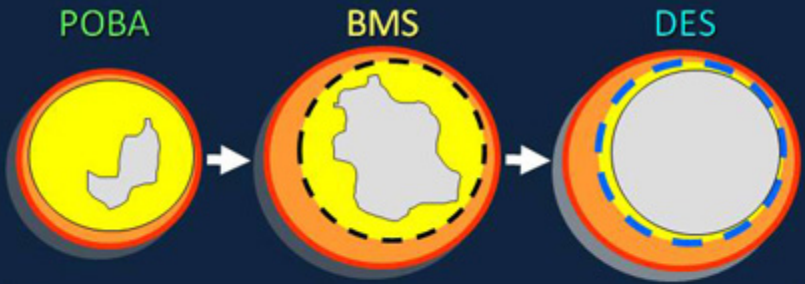




Pure revascularization



Without TVF:-
acute closure
restenosis / TLR
stent thrombosis / MI
death



Acute Closure		
Restenosis	30-50%	25-35%
		3-10% !!

LATE Stent Thrombosis
AMI DEATH

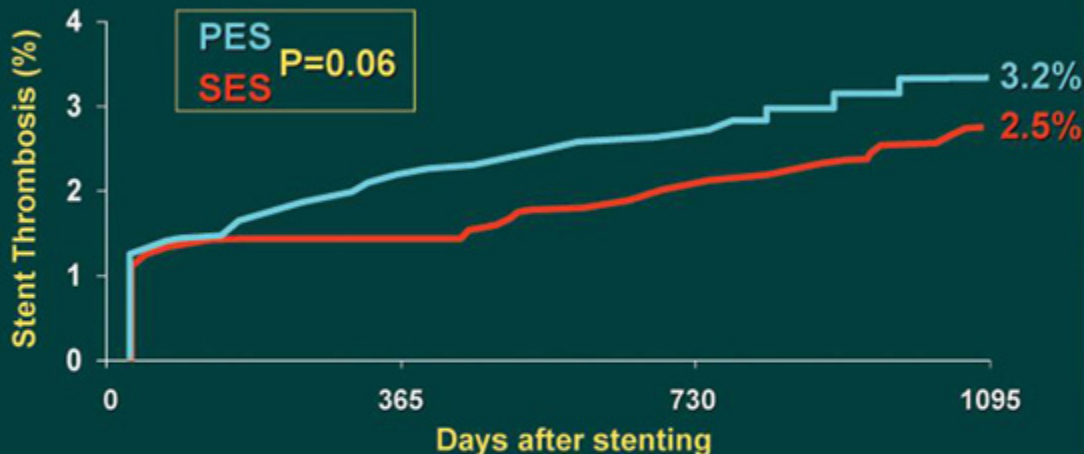
Major GI or CNS bleeding ?
Sudden need for surgery ??
Traffic accident ???
Cost & non-compliance ?

Prolonged DAPT
RESISTANCE

Any better choice ? achieving
(1) neointimal suppression without non-healing (e.g. Dual Therapy Combo Stent)
(2) scientifically predicting future stent thrombosis in new stent platform

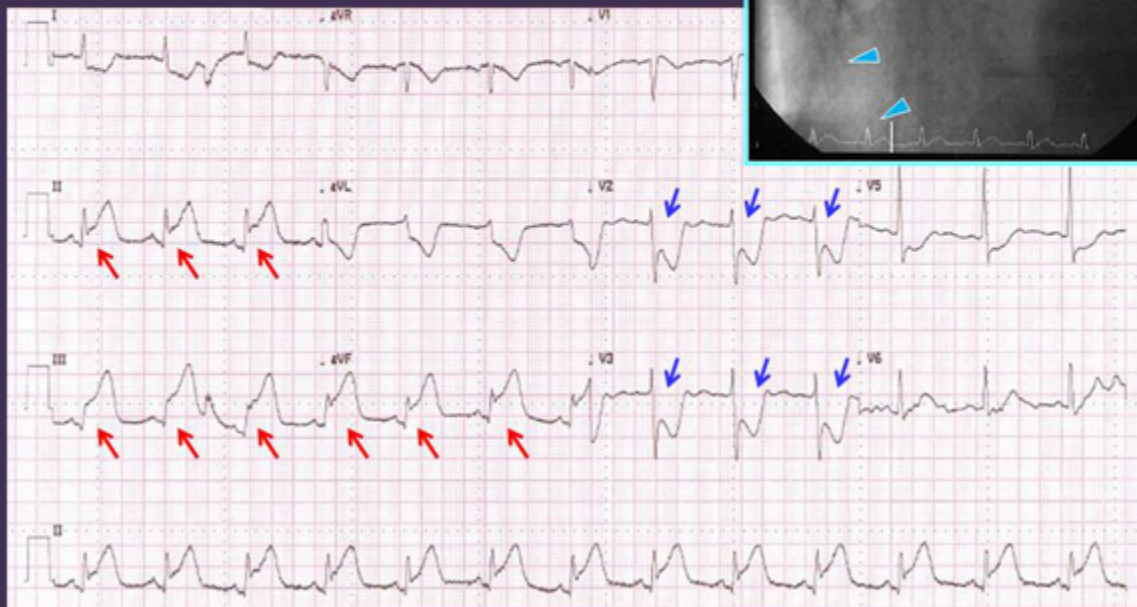
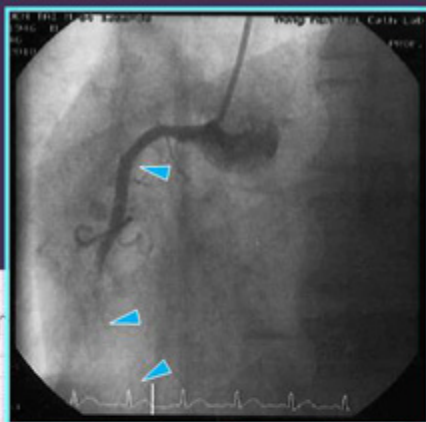
Bern – Rotterdam cohort study

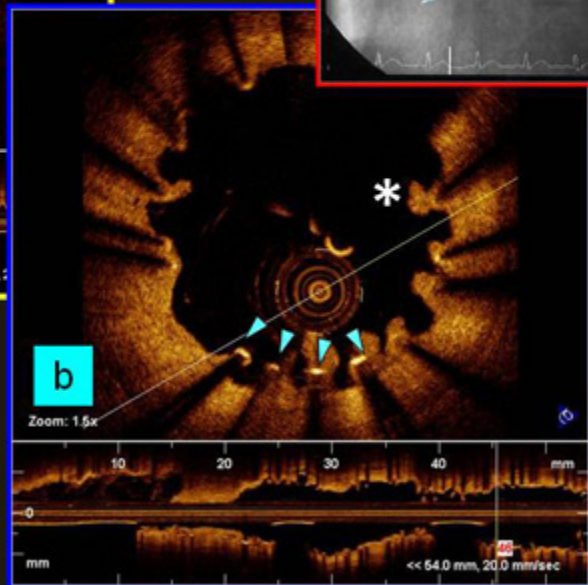
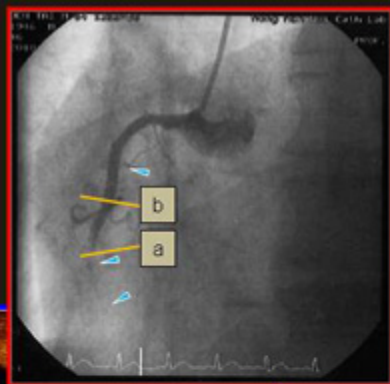
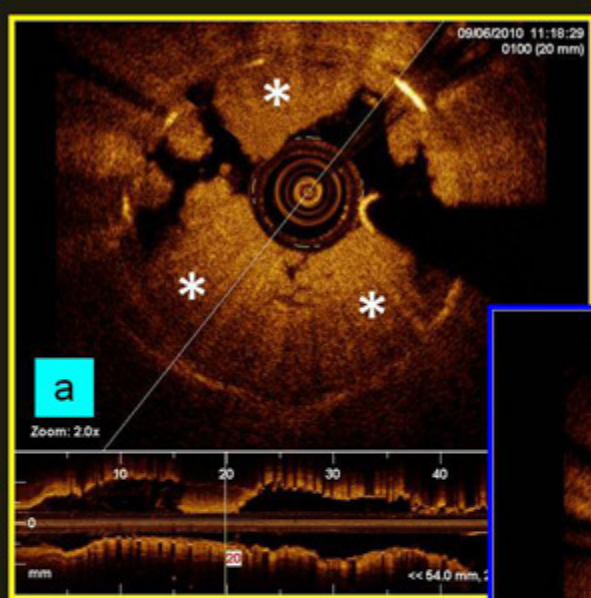
Angiographic DES Stent Thrombosis

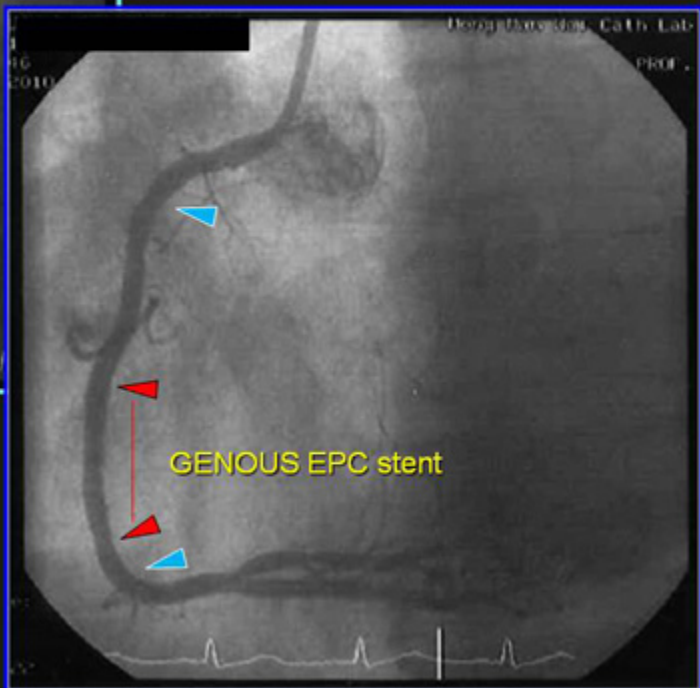
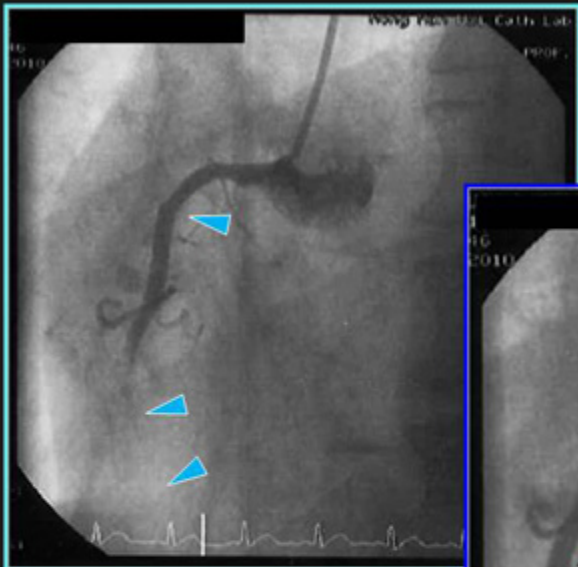


Days after PCI	9	30	365	730	1095
Incidence SES (%)	1.0	1.1	1.3	1.9	2.5
Incidence PES (%)	1.2	1.3	2.0	2.7	3.2
Pts at risk	8146	7162	7002	2841	971

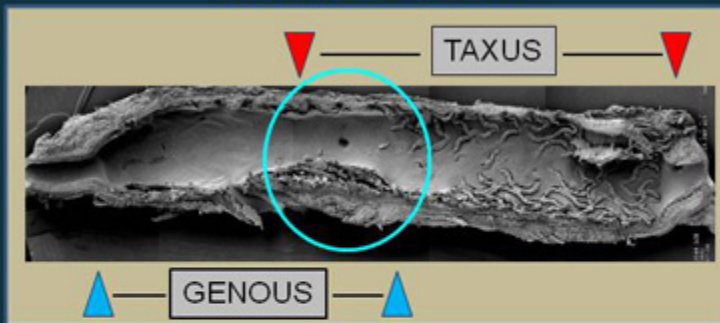
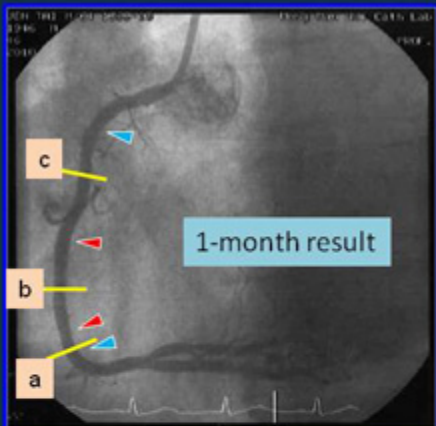
2 first generation DES implanted 3 years ago.
Completed dual anti-platelet therapy for 1 year.
Acute MI 3 years later.







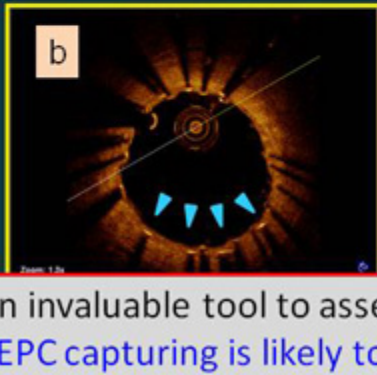
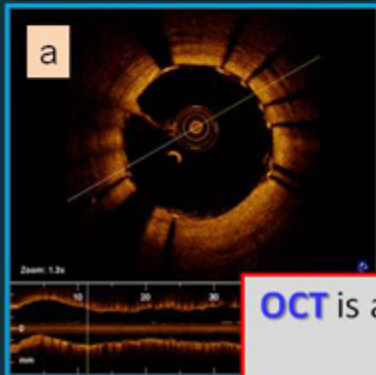
Porcine overlapping model 14 days explants



Distal DES – still uncovered

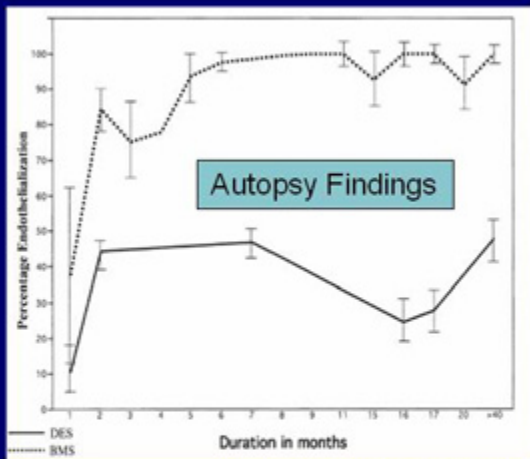
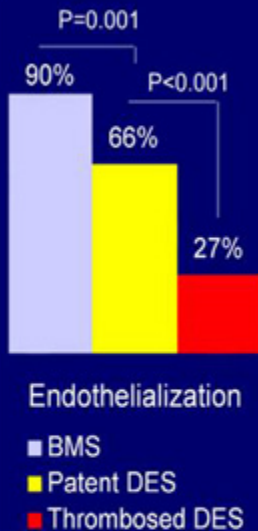
Mid EPC GENOUS – covered

Prox. DES – still uncovered

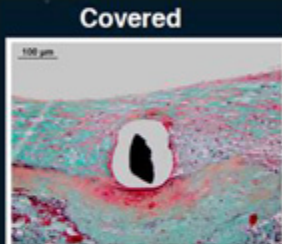


OCT is an invaluable tool to assess **stent healing in-vivo**
EPC capturing is likely to be pro-healing

Vascular Healing following Stent (especially DES) implantation



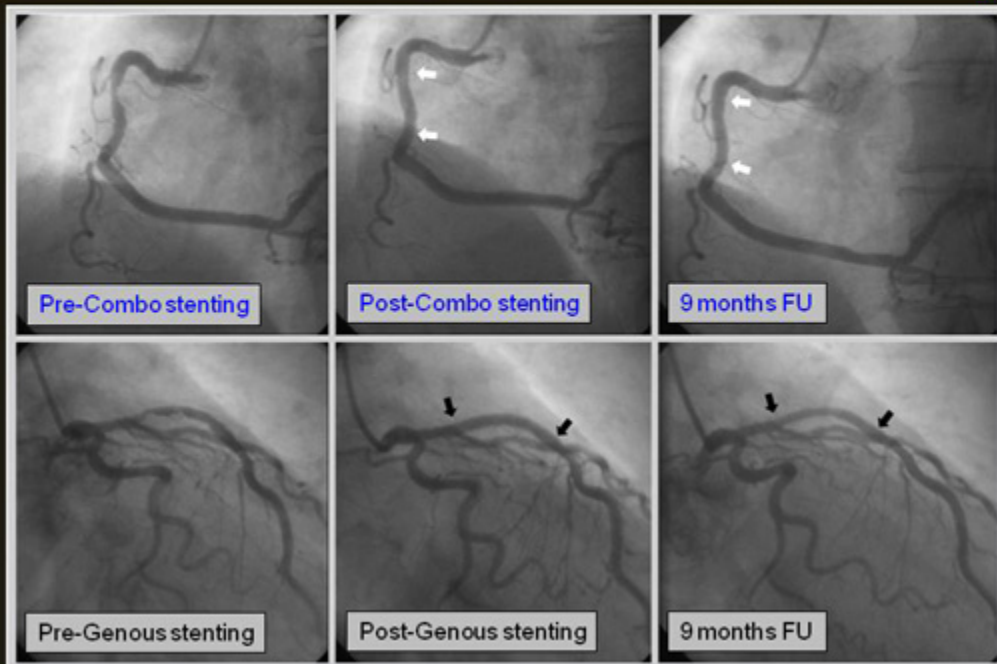
Joner et al. JACC 2006;48(1):193-202



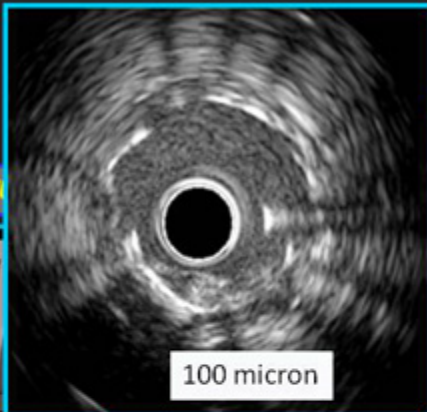
- Most powerful histological predictor of stent thrombosis = *endothelial coverage*
- Most powerful surrogate indicator of endothelialization = *neointimal coverage*
- Best morphometric predictor of LST = *ratio of uncovered to total stent struts*

Coronary angiogram (quantitative coronary analysis) remains the gold standard in detecting coronary atherosclerotic disease & assessment of treatment results.

Totally impossible to reveal the composition of atherosclerotic plaque.
Totally incapable to show the healing responses after stenting (DES).

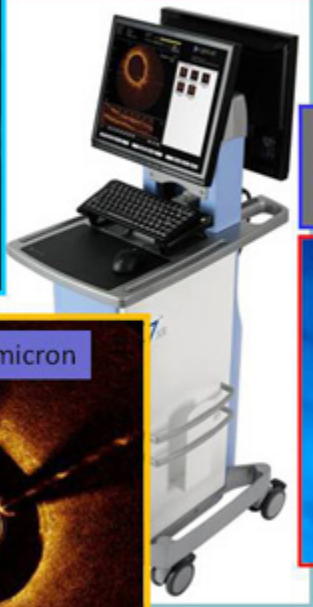


Volcano *sS/sSI IV*

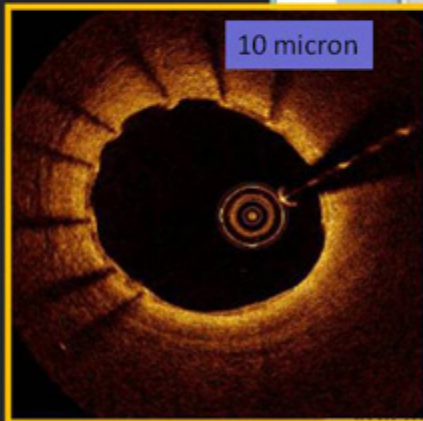
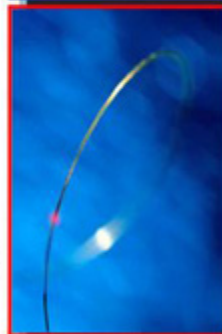


100 micron

St. Jude Medical LightLab
C7 XR FD-OCT system



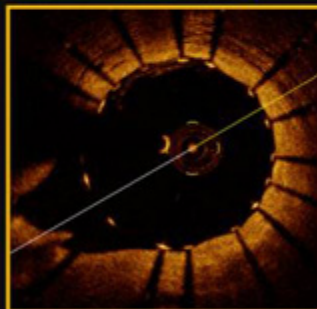
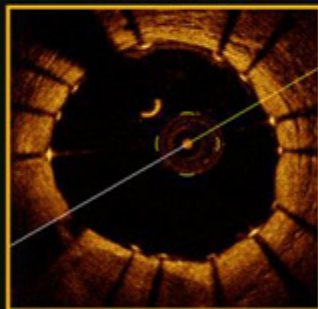
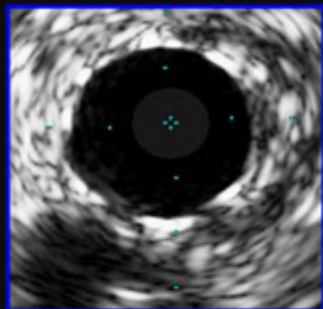
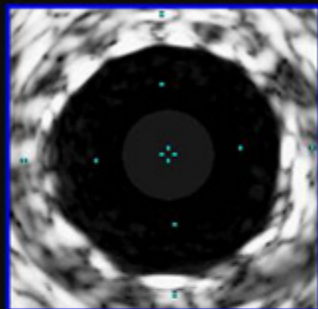
Dragonfly
*non-occlusive
OCT catheter*



10 micron

o FD-OCT (OFDI) System
o-Axsun Technology System

Identical frames in a “newly implanted” COMBO stent
IVUS resolution (100um) versus OCT resolution (10um)

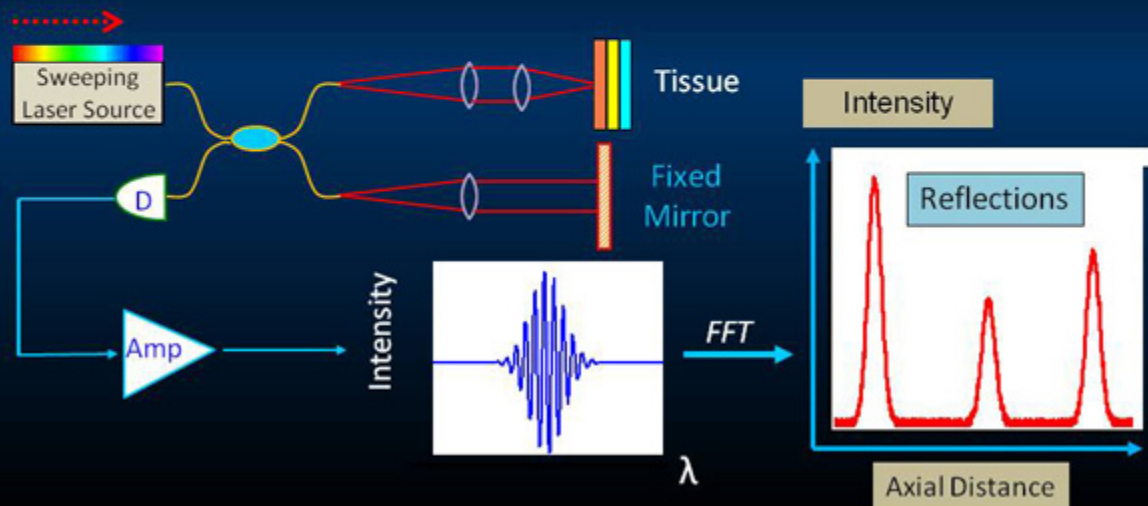


IVUS has never been useful in detecting early stent coverage (healing)

FD-OCT is an invaluable tool assessing treatment results & vascular healing

Frequency Domain OCT

- Measure interference pattern: spectrum + Fourier transform
- Signal generated from all depths simultaneously
- Fixed mirror & fast image acquisition without loss of quality
- Takes only 3 seconds

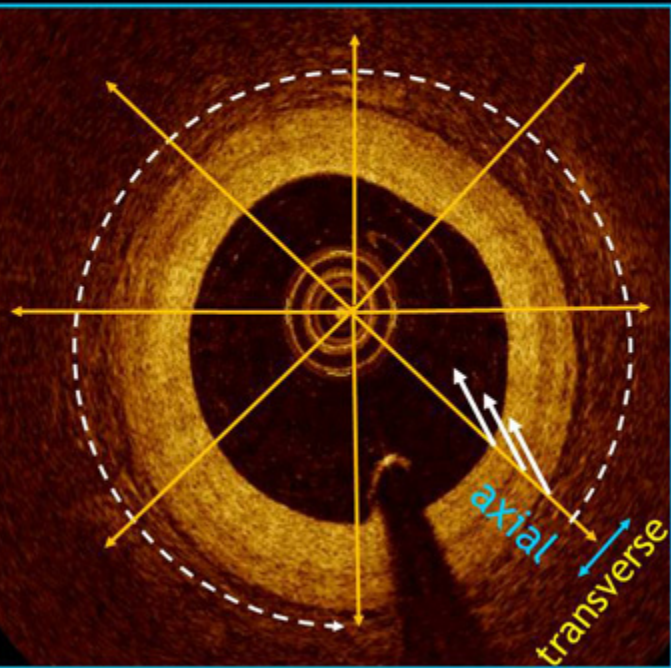


C7-XR FD-OCT Image Resolution

Measure echo delay of reflected light waves

- 1 frame = 500 axial lines
- 1 axial line = 1024 pixels
- 1 pixel = 5 x 19 μm
- *Optical resolution:-*
 - **axial = 10 - 15 μm** ←
 - transverse = 20 to 40 μm*

An invaluable tool for very thin neointimal tissue, strut coverage and stent healing



Usefulness of OCT

Baseline Information

- Tissue and plaque characterization
(fibrous, lipid core, calcium, cap thickness, thrombus)
- Aiding PCI strategy (stent size & length, vulnerable plaque)

During and After PCI

- Stent strut apposition / mal-apposition, dissection, thrombus

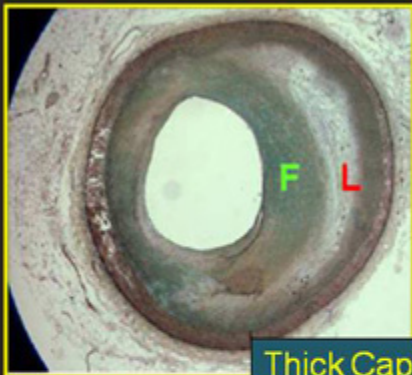
Follow-Up Assessment

- Neointimal coverage, neointimal thickness & area, restenosis
- Late thrombosis

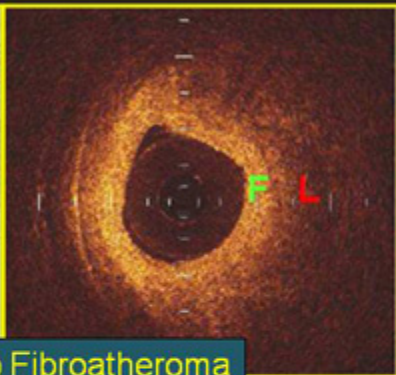
Research Next Generation stent development, DAPT duration

Bio-absorbability, polymer, optimal drug dosages, eluting kinetics

Tissue Characterization & Fibroatheroma



Thick Cap Fibroatheroma

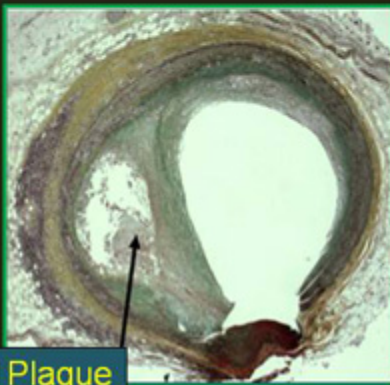


Lipid

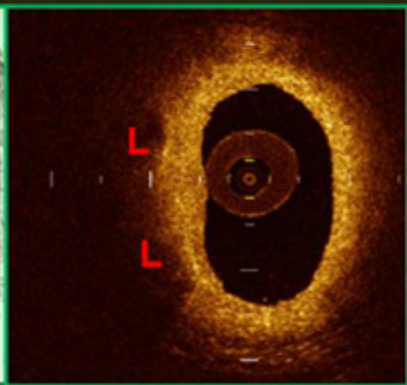
- *low back scattering*
- *high attenuation*
- *top is bright*
- *body is black*
- *diffuse border*

Fibrous tissue

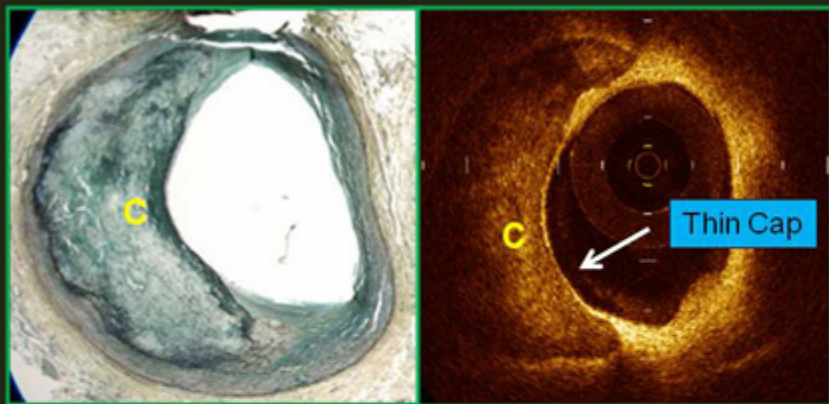
- *bright signal*
- *homogenous*
- *inner lumen*



Lipid Plaque

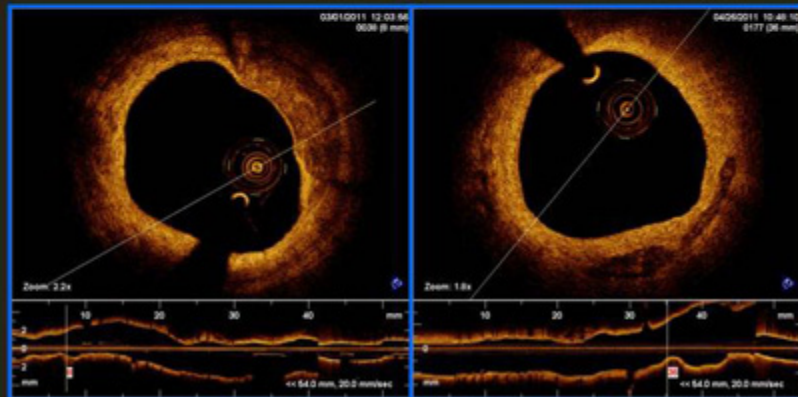


Tissue Characterization & Calcification

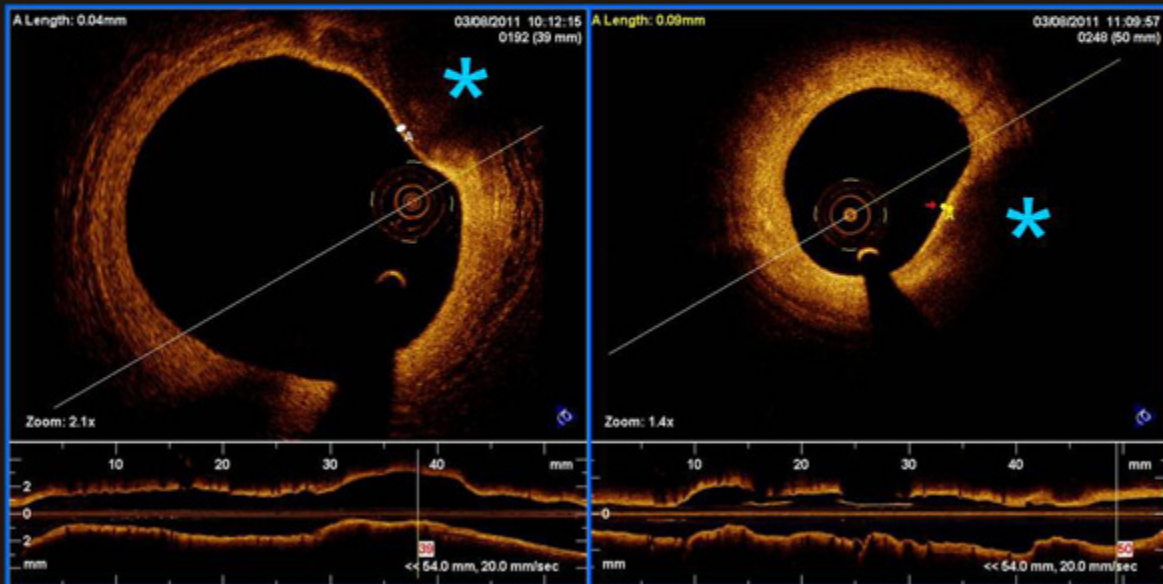


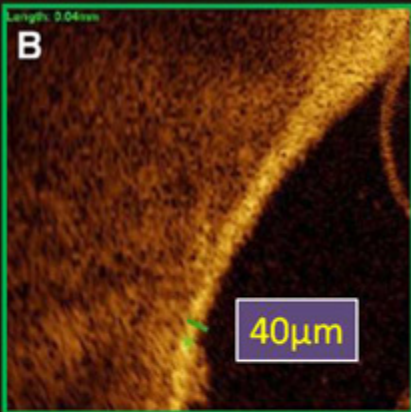
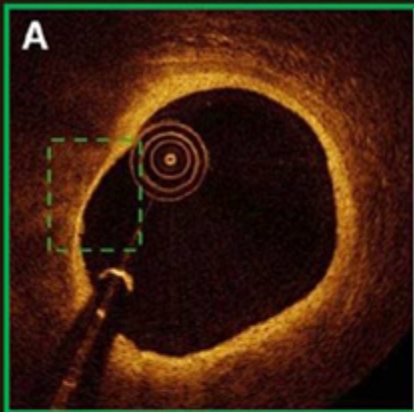
Calcified Plaque

- *low backscattering (dark signal)*
- *low attenuation*
- *sharp border*
- *heterogeneous*



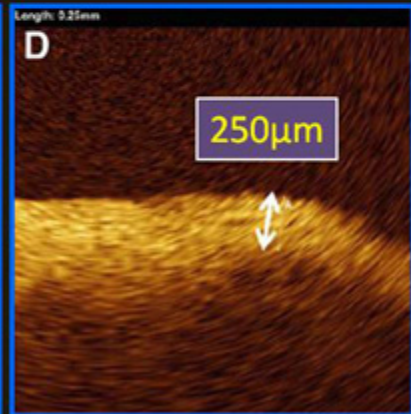
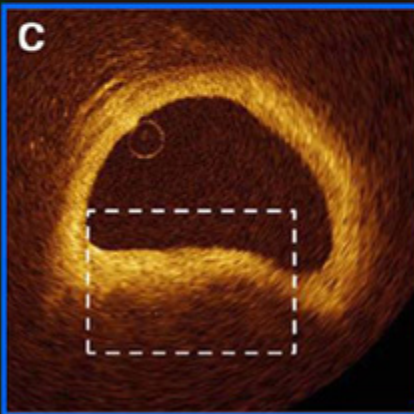
Lipid plaque with thin cap





Thin Cap
Fibroatheroma

Cut off = 65micron



Thick Cap
Fibroatheroma

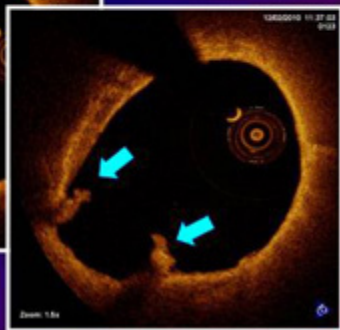
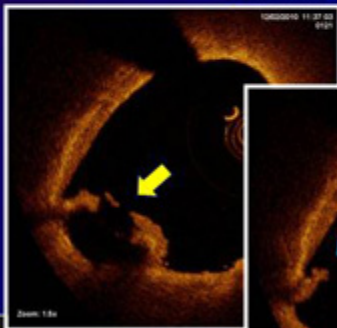
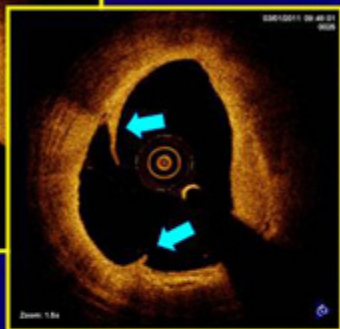
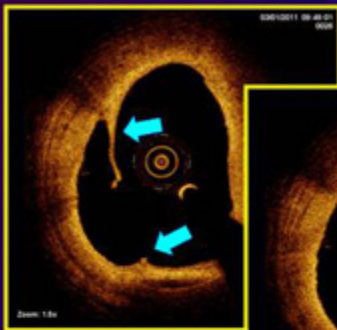
Understanding of ACS

Vulnerable Plaque

Thin-cap fibroatheroma
Large lipid core

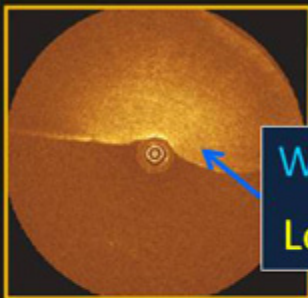
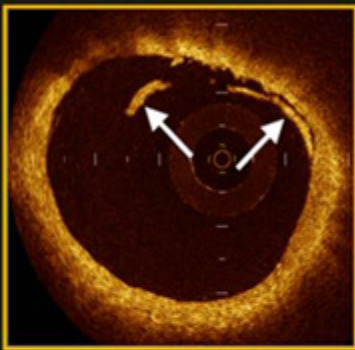
Fibrous Cap

Lipid Core

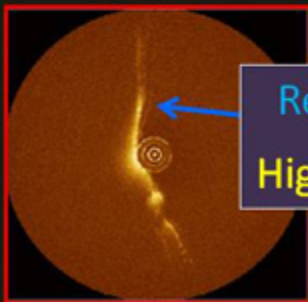
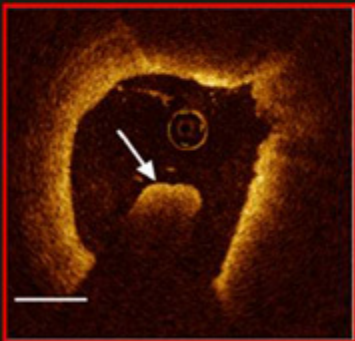


- Large lipid pool + thin fibrous cap $\leq 65 \mu\text{m}$
- Necrotic core $> 10\%$.

Red and White Thrombus

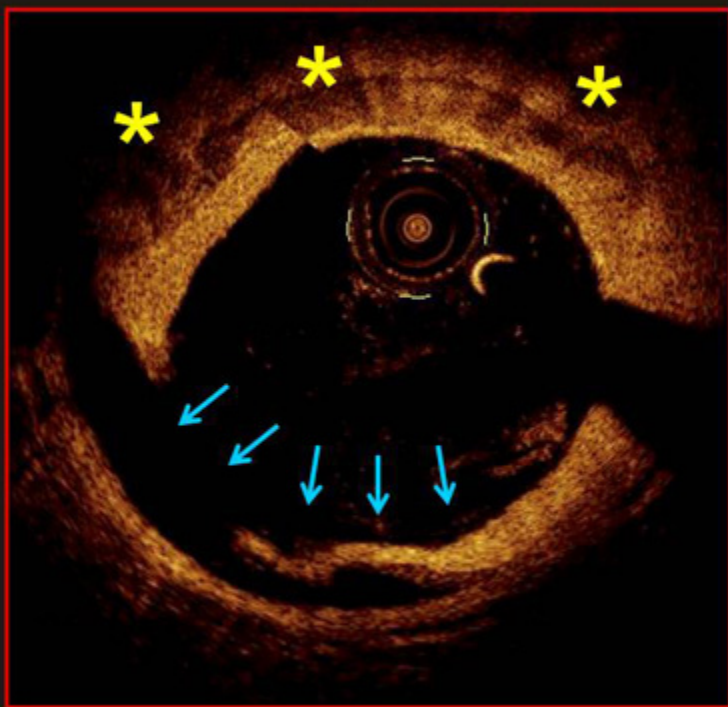


White Thrombus
Low attenuation



Red Thrombus
High attenuation

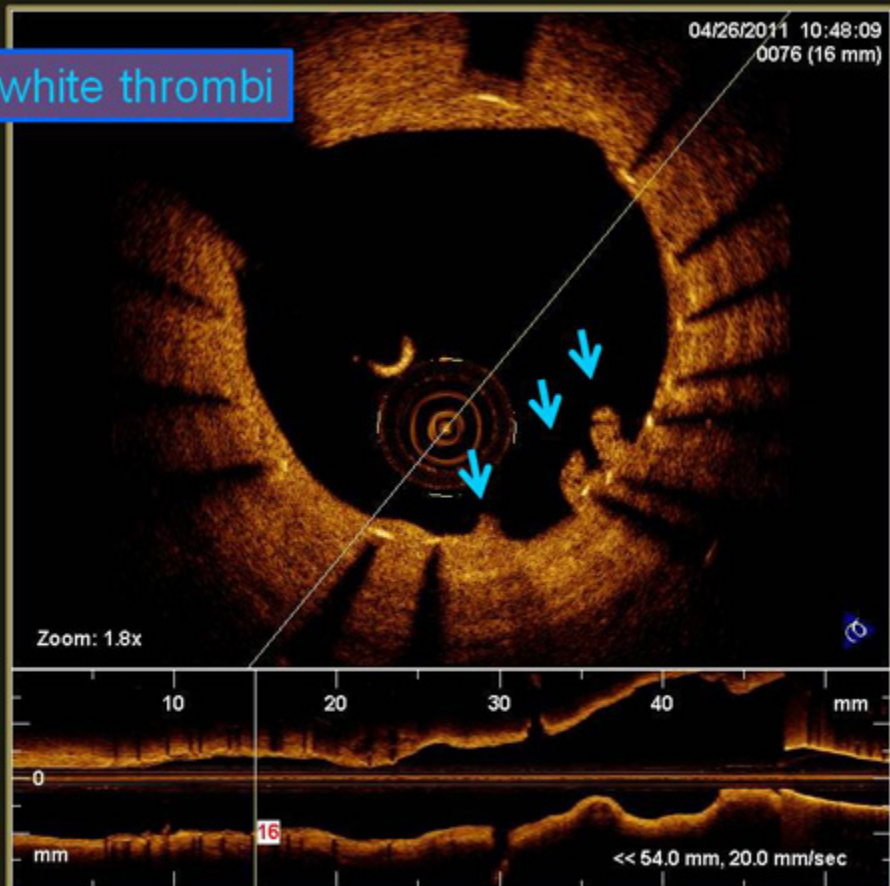
Circumferential mixed plaque

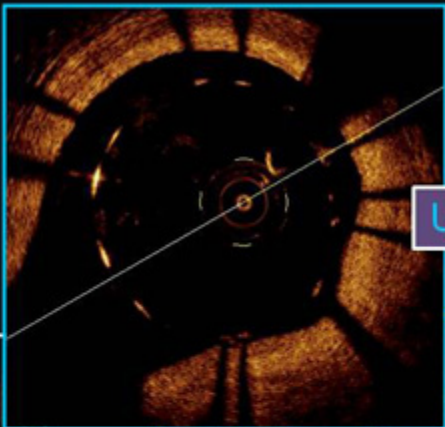


Already ruptured with spontaneous dissection

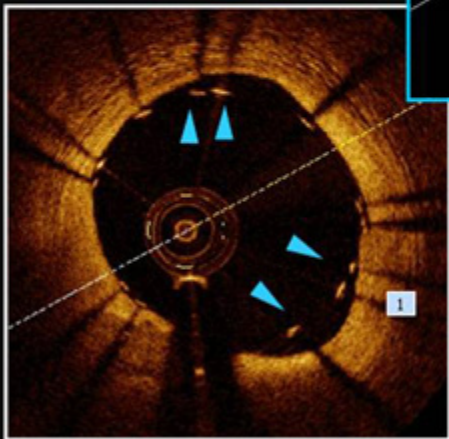
04/26/2011 10:48:09
0076 (16 mm)

Stent with white thrombi

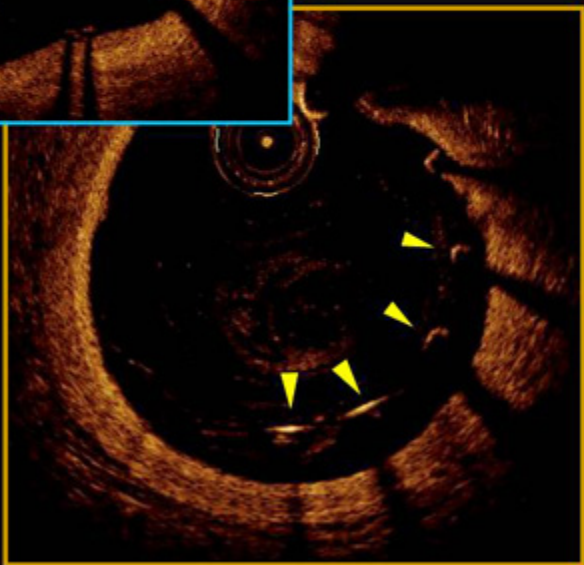




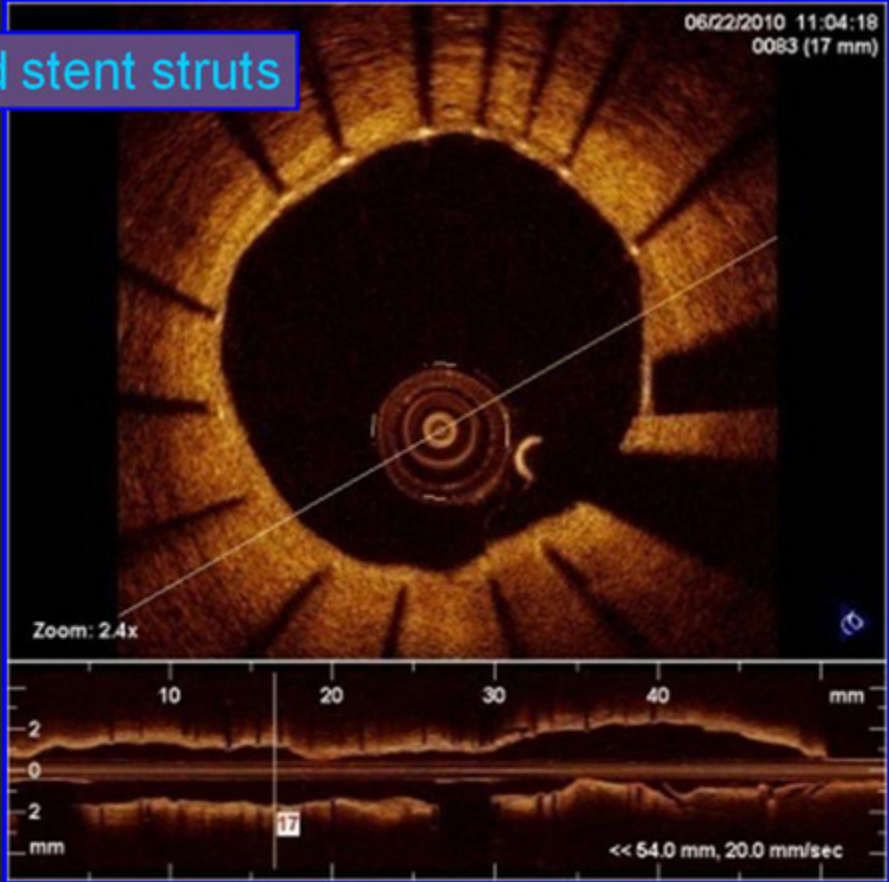
Under expansion



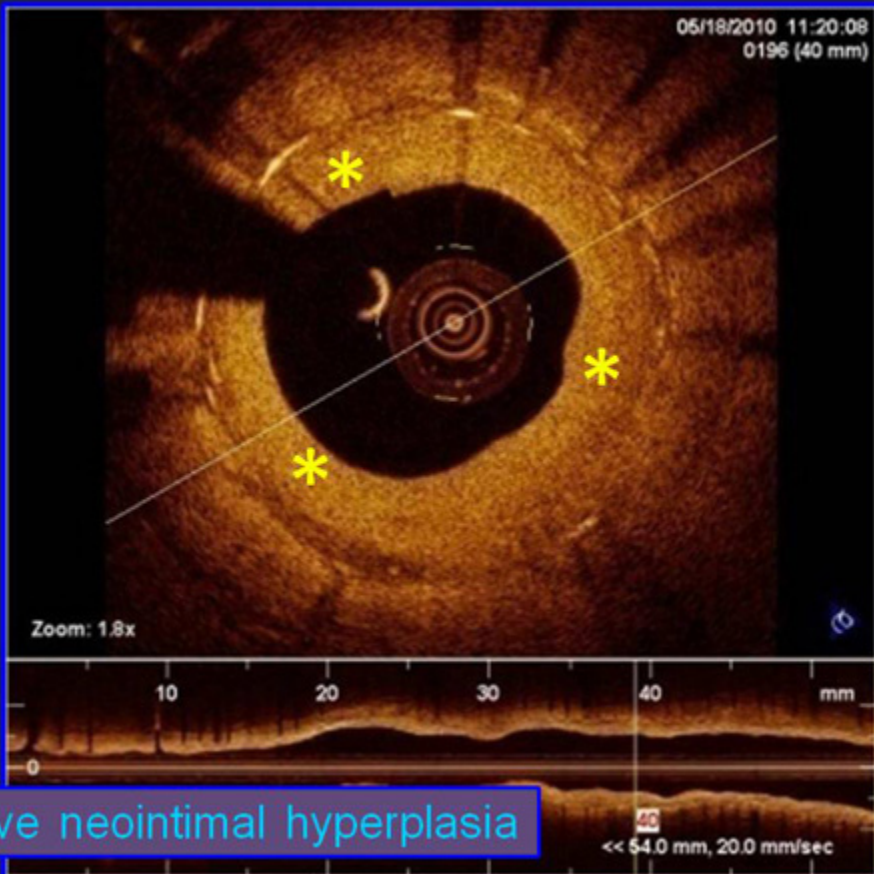
Malapposed stent struts



Covered stent struts

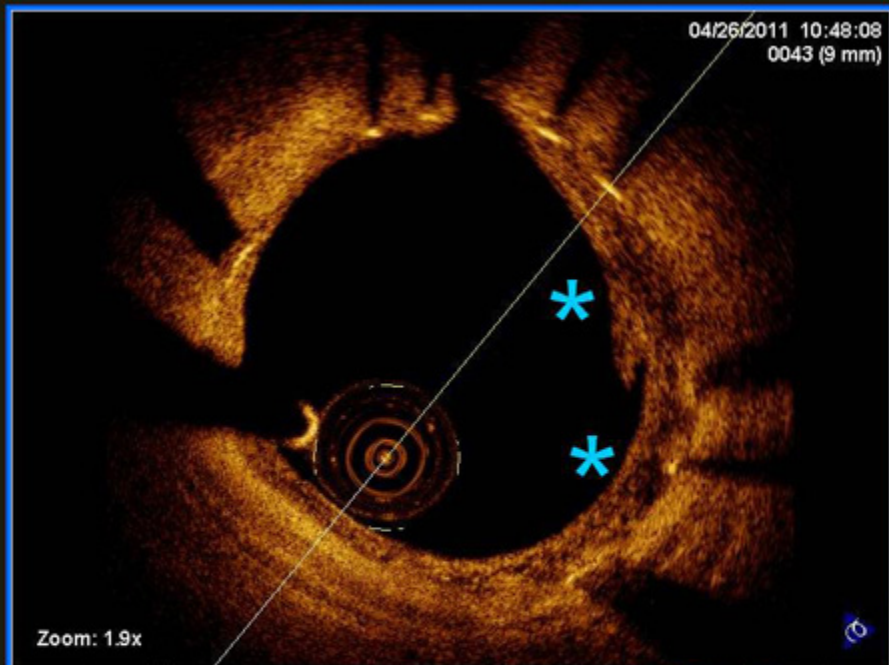


05/18/2010 11:20:08
0196 (40 mm)

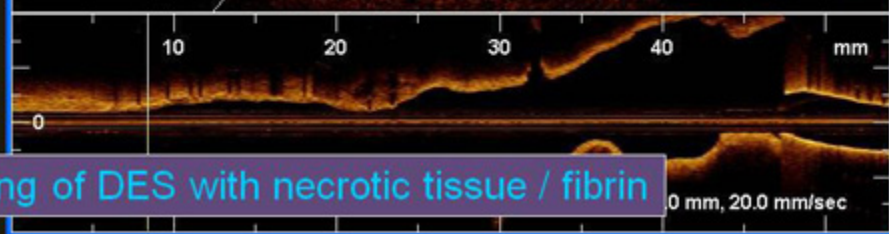


Proliferative neointimal hyperplasia

04/26/2011 10:48:08
0043 (9 mm)

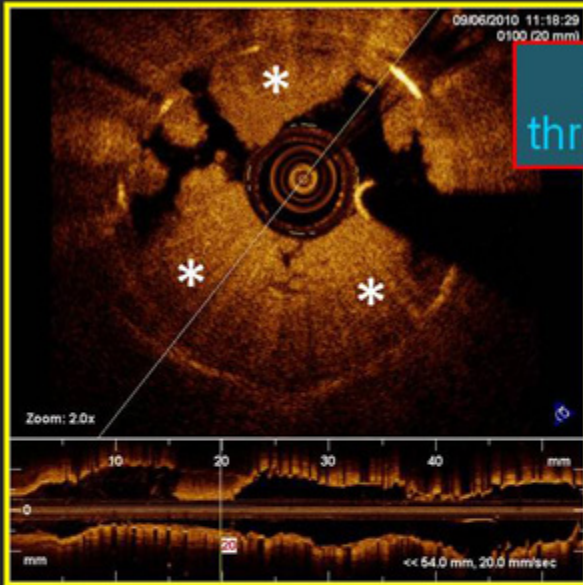


Zoom: 1.9x

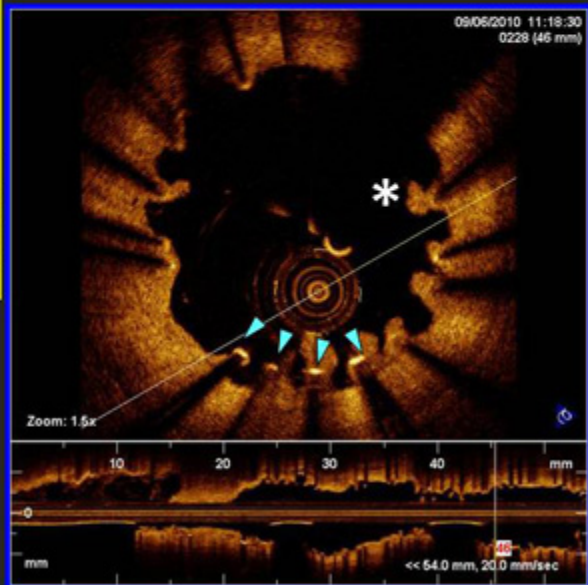


Poor healing of DES with necrotic tissue / fibrin

0 mm, 20.0 mm/sec

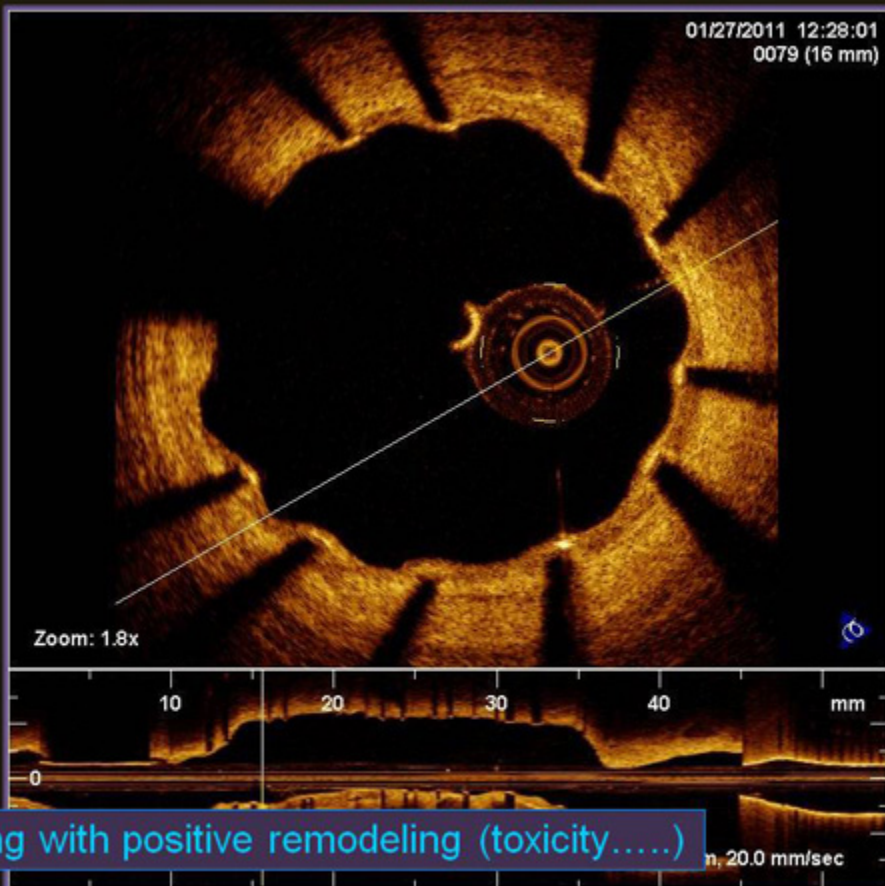


Stent
thrombosis



Non-healing
Malapposition

01/27/2011 12:28:01
0079 (16 mm)



DES healing with positive remodeling (toxicity.....)

Strut Paucity

06/03/2010 11:02:04
0097 (18 mm)

Thin fibrous cap

Zoom: 2.1x

10 20 30 40 mm



Tissue Prolapse

06/03/2010 11:02:06
0154 (31 mm)

Zoom: 2.1x

10 20 30 40 mm



Fibrous cap

09/07/2010 14:34:42
0100 (20 mm)

Zoom: 1.8x

10 20 30 40 mm



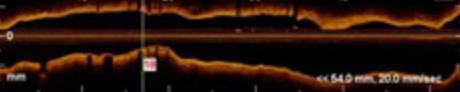
Biomatrix Stent at 3 months

xx 64.0 mm, 20.0 mm/sec

09/07/2010 14:37:55
0086 (18 mm)

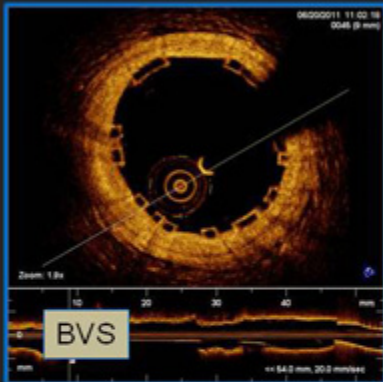
Zoom: 1.8x

10 20 30 40 mm



xx 64.0 mm, 20.0 mm/sec

Bioresorbable Vascular Scaffold (BVS)



In 2 years' time, OCT will definitely discern any residual non-absorption, with 100% accuracy.

Usefulness of OCT

Baseline Information

- Tissue and plaque characterization
(fibrous, lipid core, calcium, cap thickness, thrombus)
- Aiding PCI strategy (stent size & length, *vulnerable plaque*)

During and After PCI

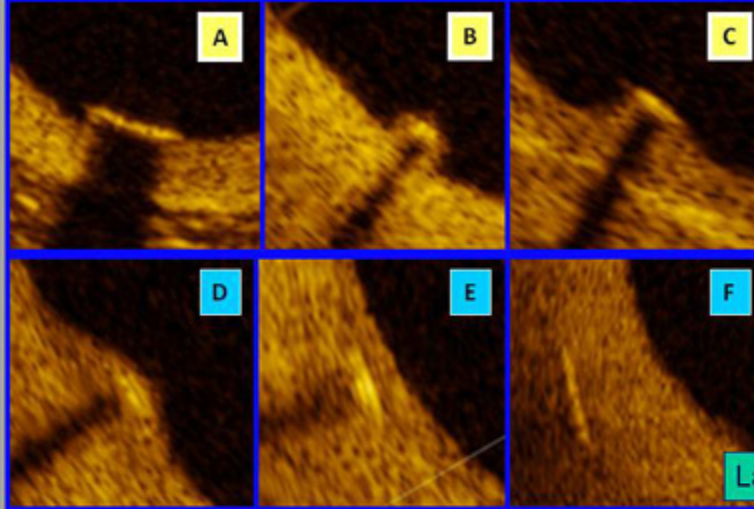
- Stent strut apposition / mal-apposition, dissection, thrombus

Follow-Up Assessment

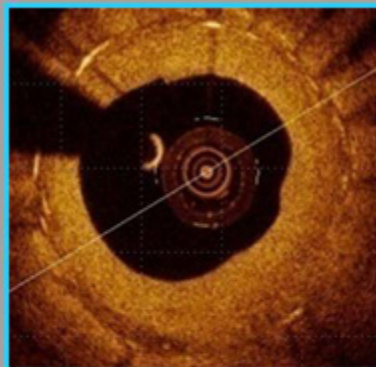
- Neointimal coverage, neointimal thickness & area, restenosis
- Late thrombosis

Research Next Generation stent development, DAPT duration

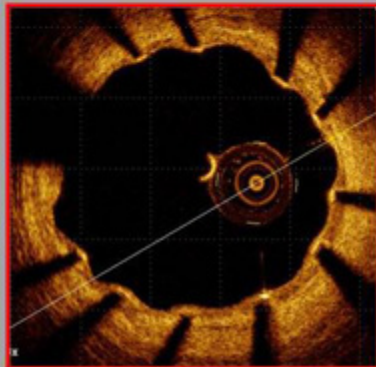
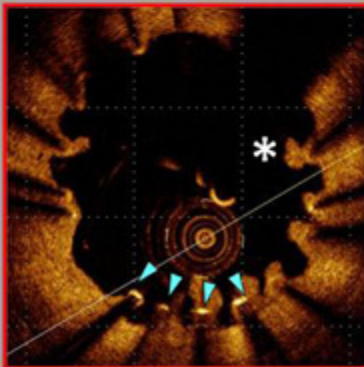
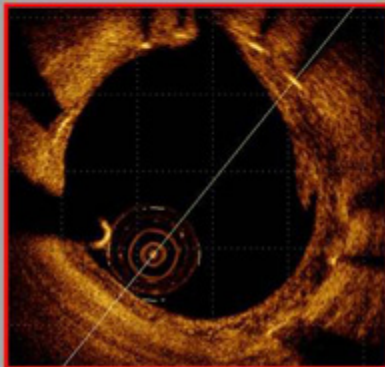
Bio-absorbability, polymer, optimal drug dosages, eluting kinetics



Early Healing / Coverage



Late Non-Healing / Proliferation



Validation of OCT (Terumo) on Stent Coverage / Healing Comparing to Light and Electronic Microscopy

Validated in porcine model

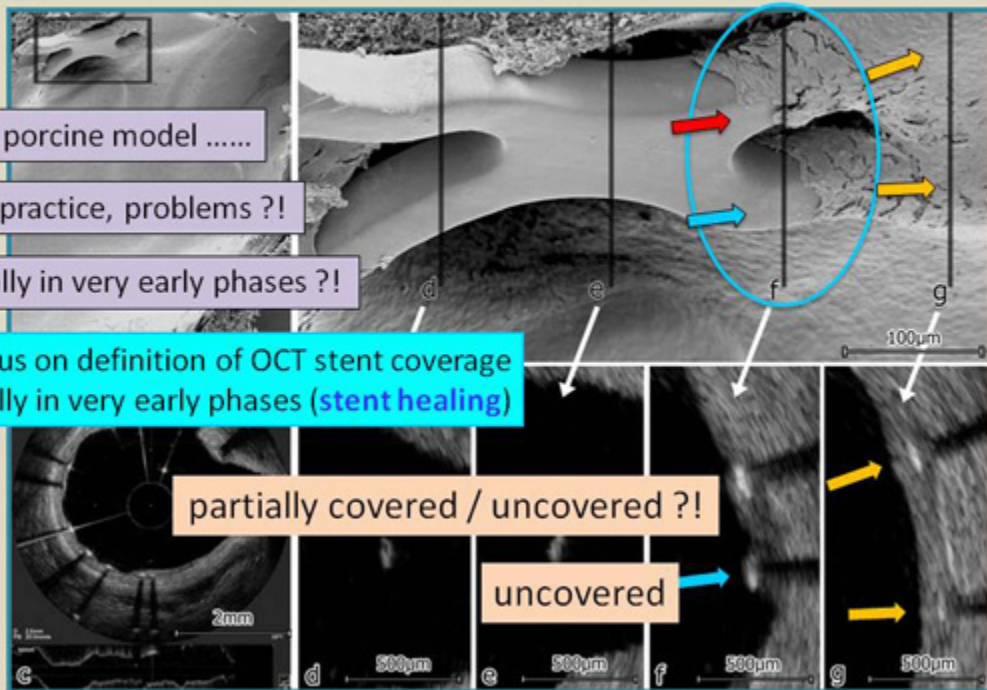
..... clinical practice, problems ?!

..... especially in very early phases ?!

No consensus on definition of OCT stent coverage
especially in very early phases (**stent healing**)

partially covered / uncovered ?!

uncovered



The EGO-Genous Study

Evaluation of Early Healing of Endothelial Progenitor Cell Capturing (GENOUS) Stent by Optical Coherence Tomography

Design: Prospective, single centre study

Treatment by GENOUS stent for stable angina or ACS/AMI

50 patients randomly assigned to 5 groups (10 patients each)

Restudy OCT evaluation at 2, 3, 4, 5, 6 weeks

Core laboratory OCT analysis (*blinded to clinical data*)

Endpoints:- % Strut Coverage, NIT, and NIA

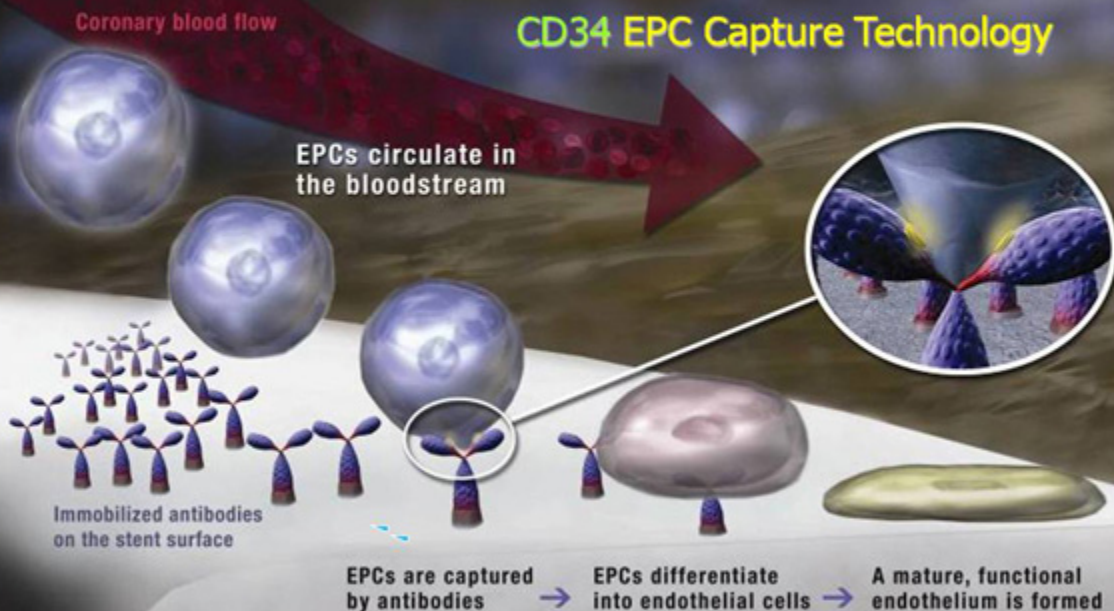
Status: Study completed; 53 patients enrolled altogether;
pending Core Lab OCT Analyses

Stable angina 11 (37%), NSTEMI 6 (20%), STEMI 13 (43%)



Genous Healing Approach

CD34 EPC Capture Technology



Genous stent strut

Endothelial Progenitor Cell (EPC)



Anti-CD34 Antibody (Clone561 / Qbend 10)

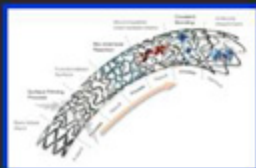
CD34 Cell Surface Antigen



Endothelium

Stent Outer Surface

EPC Capture Coating



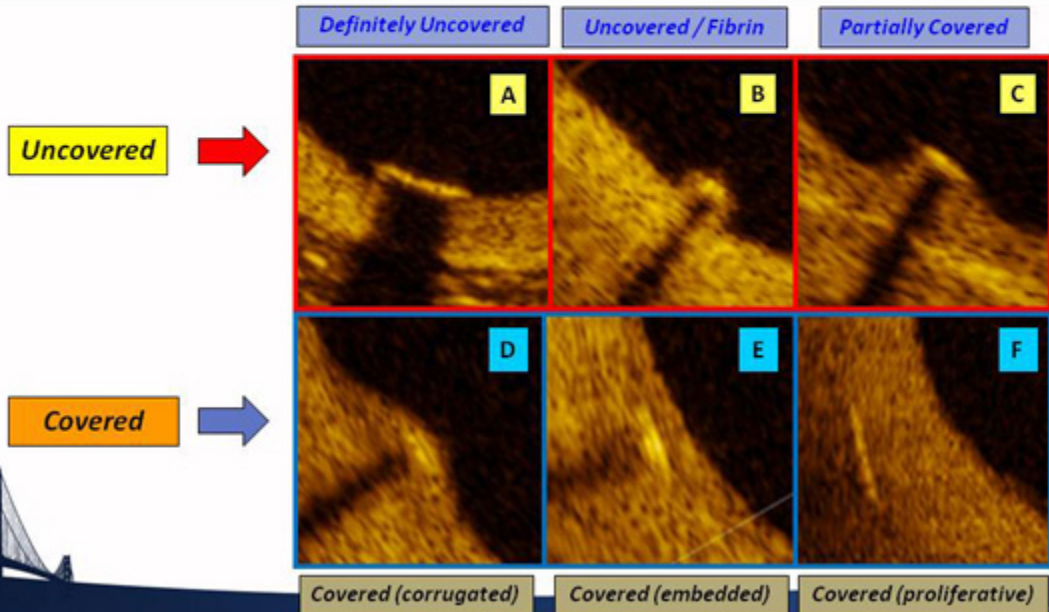
Core Laboratory (Dr. Harry Suryapranata)

(1) Malapposed Frames

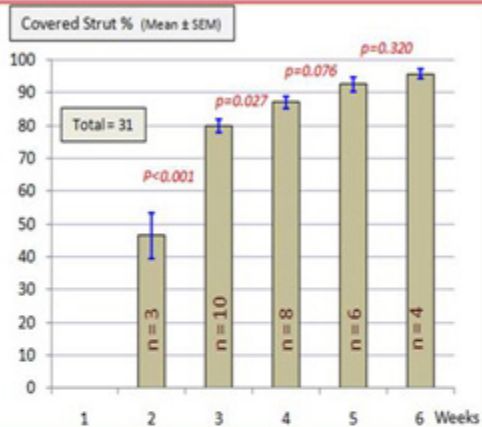
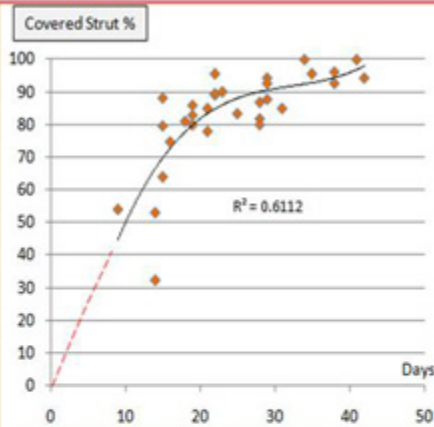
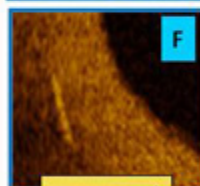
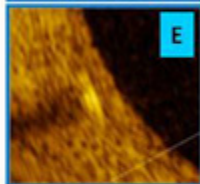
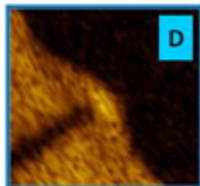
(2) Frames over Side-branches

(3) Properly Apposed Frames

The EGO-Genous Study



The EGO-Genous Study (interim results)

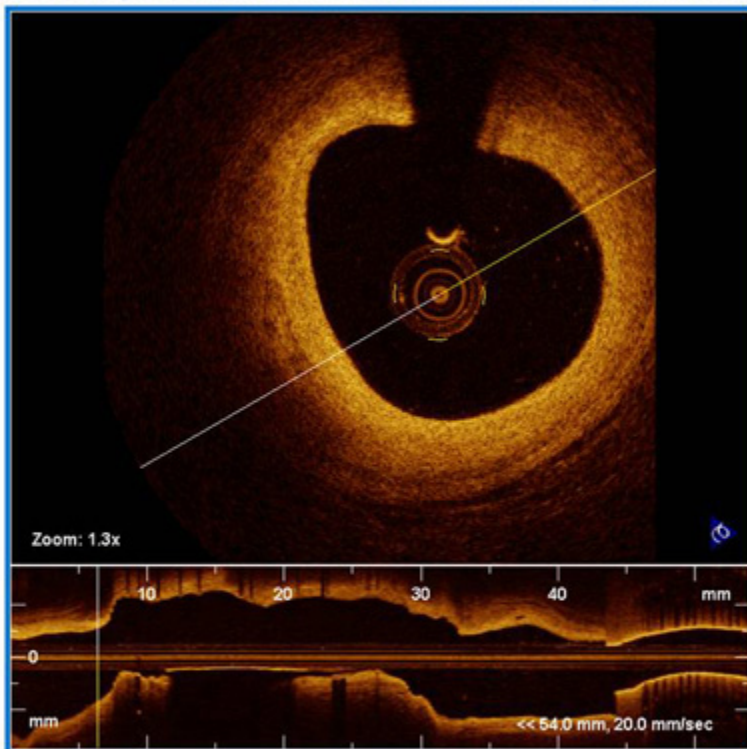


Approaching 70% strut coverage by 15 days, & 100% by 6 weeks

6 weeks DAPT could be more than adequate for EPC stent

For the first time the healing profile of an intra-coronary stent was established, supporting possible pro-healing benefits of EPC-capturing GENOUS Stent, as already been shown by other studies

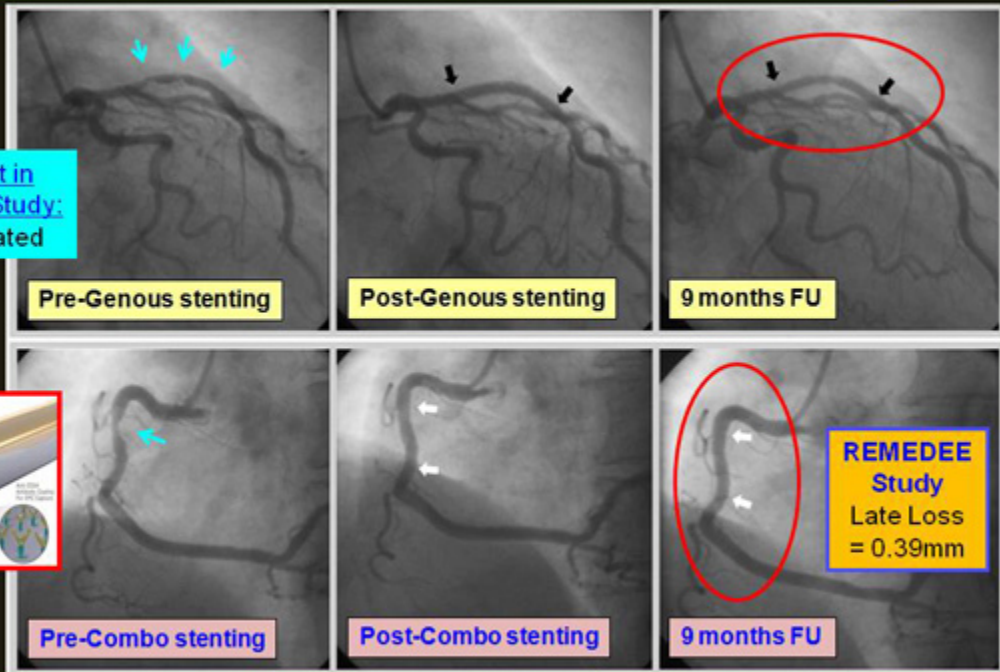
EGO Study: Genous Stent at 15 days after AMI



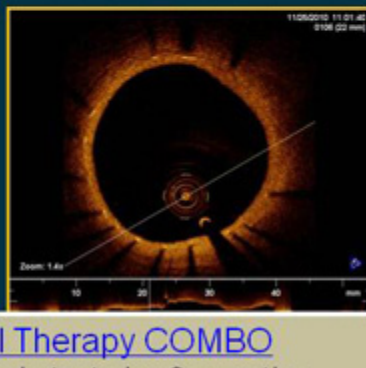
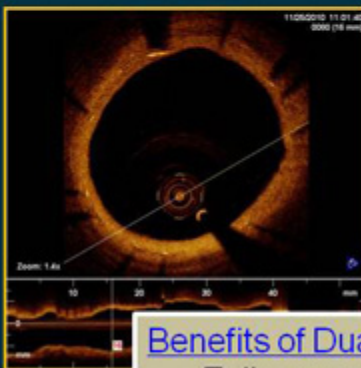
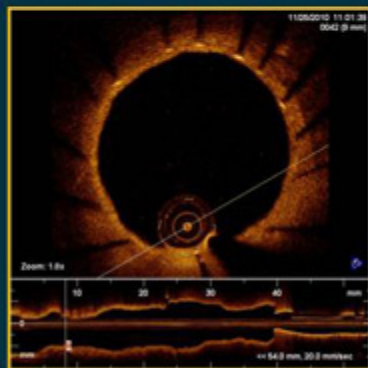
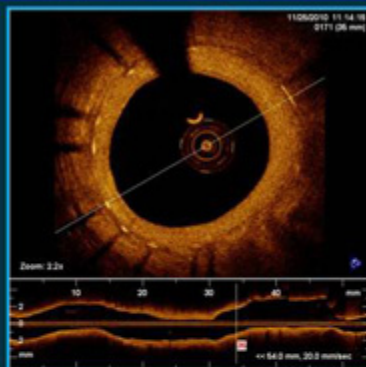
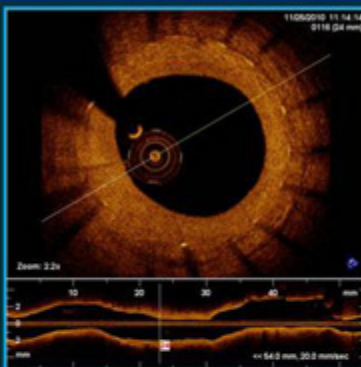
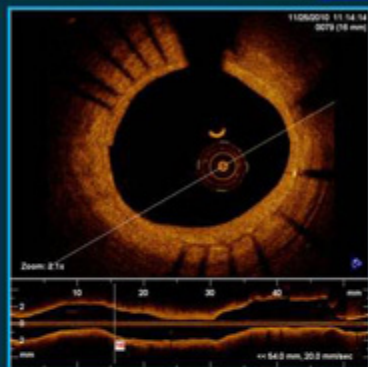
Genous Stent:- a pro-healing EPC capturing stent

But similar to a bare metal stent still with some late loss

Same patient in
REMEDEE Study:
2 lesions treated



Dual Therapy COMBO Stent:- a DES with EPC capturing + sirolimus coating
Benefits of pro-healing + neointimal suppression & less late loss like DES.



Benefits of Dual Therapy COMBO

- Fully covered struts by 9 months
- Low neointimal hyperplasia as a DES

The EGO-COMBO Study

Combo stent
Baseline OCT

4 groups (2 to 5 months)
OCT strut coverage

9-month OCT
(late loss NIH)

Early endothelialization

Shorter dual anti-platelet treatment

? A Novel Stent

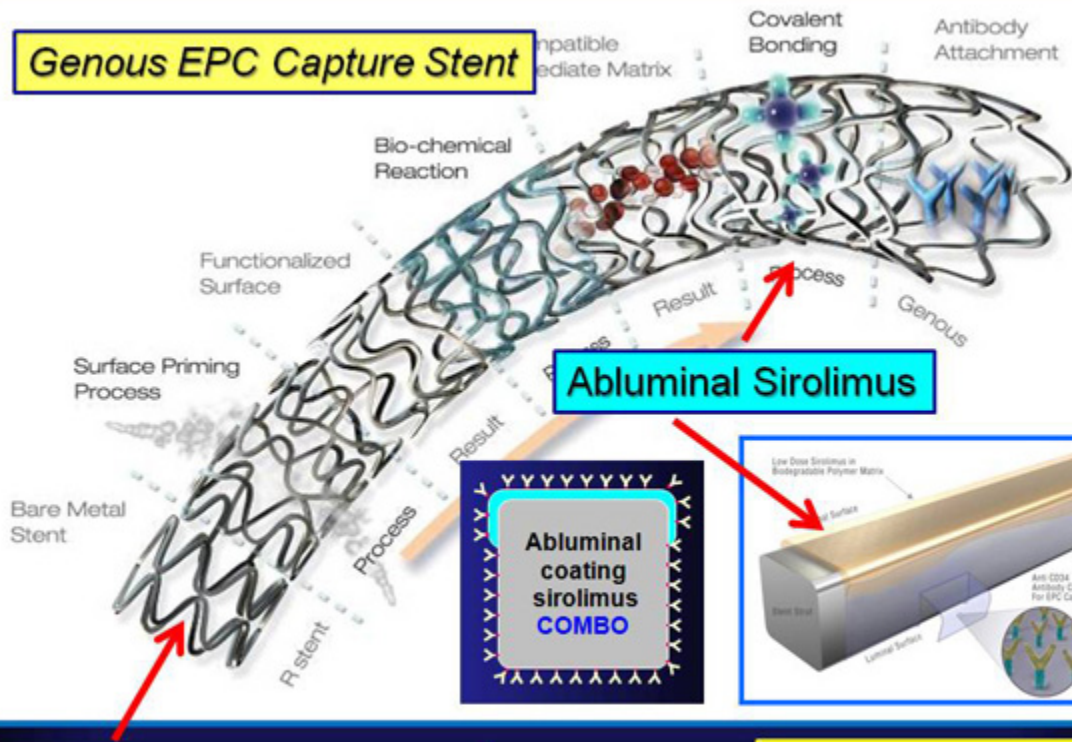
Less late stent thrombosis

Little late loss as a DES

Methods: Prospective, single center study, 60 patients treated by COMBO stent randomly assigned to 4 monthly groups. FD-OCT performed serially at baseline post-stenting, at early follow-ups in 4 groups at 2nd, 3rd, 4th, and 5th month (for early neointimal healing), and at 9 months (for OCT late loss). Independent OCT core laboratory (blinded to the clinical data) performed the covered strut % and neointima analyses, while in-house analysis further classified the early strut coverage into 6 categories (A to F).

Status: Study completed (61 patients), 100% FU rate, pending Core Lab.

Genous EPC Capture Stent



Anti-CD34 EPC Capture Coating

Combo stent

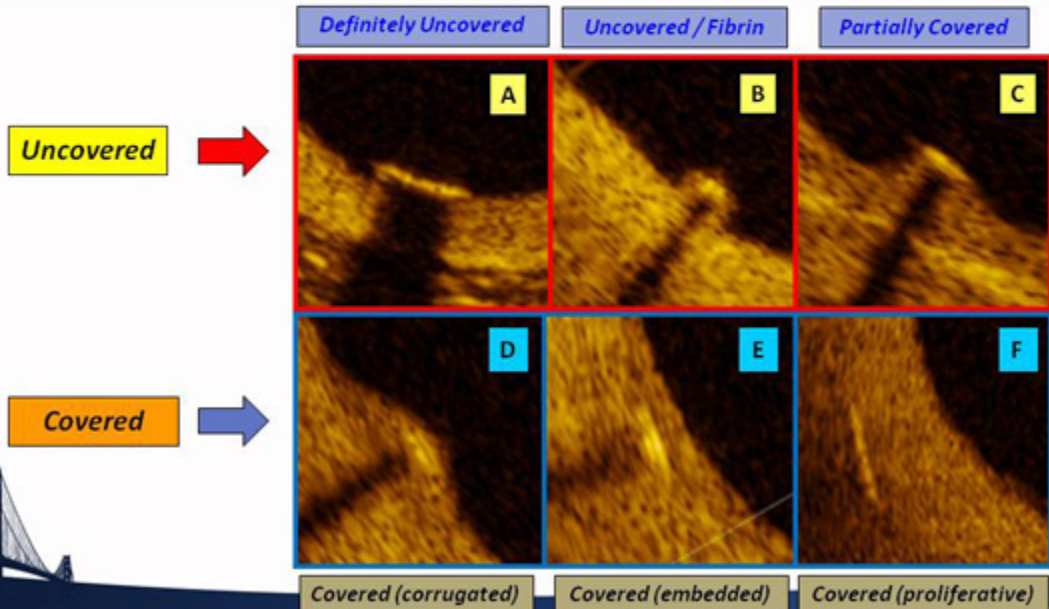
CRF Core Laboratory (Drs. Akiko Maehara & Roxana Mehran)

(1) Malapposed Frames

(2) Frames over Side-branches

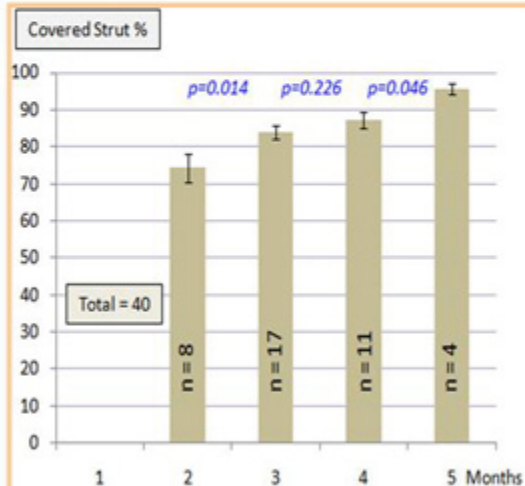
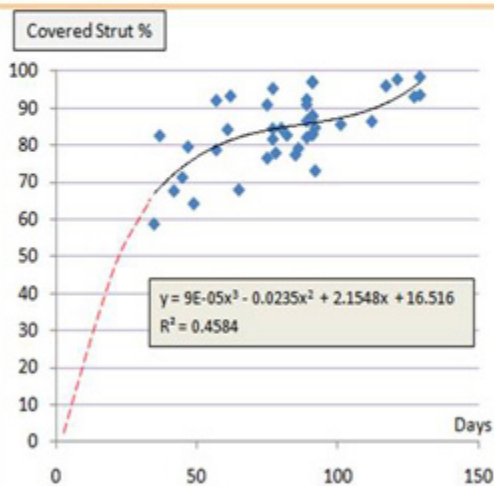
(3) Properly Apposed Frames

The EGO-Combo Study



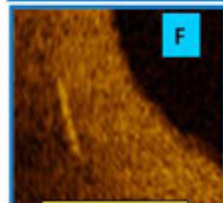
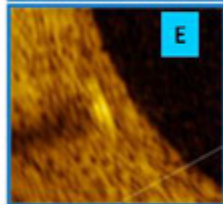
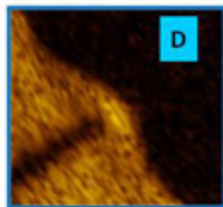
The EGO-COMBO Study

Interim Results: As of the date of abstract submission, all 60 patients (30% diabetic, 87 COMBO stents) were enrolled and 40 had the first OCT restudy. A total of 7,004 frames and 60,069 struts were analyzed. The mean percentages of covered struts (with properly apposition) were 74.4%, 84.0%, 87.4%, & 95.6%, $p = 0.014$, 0.226 , & 0.046 , between 2nd to 5th month, respectively. No MACE was recorded.

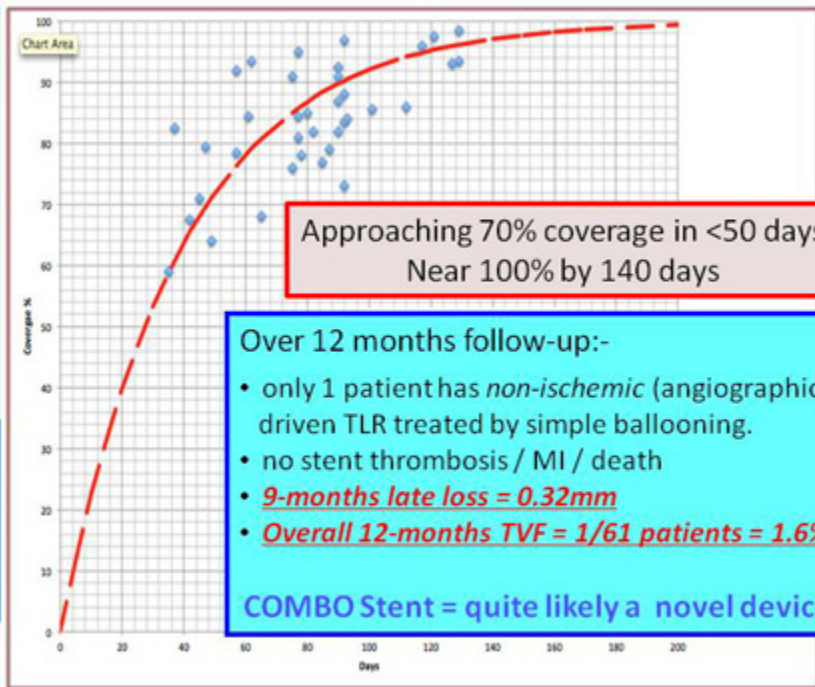


Approaching 70% coverage in <50 days
Near 100% by 140 days

The EGO-COMBO Study (exponential plot)

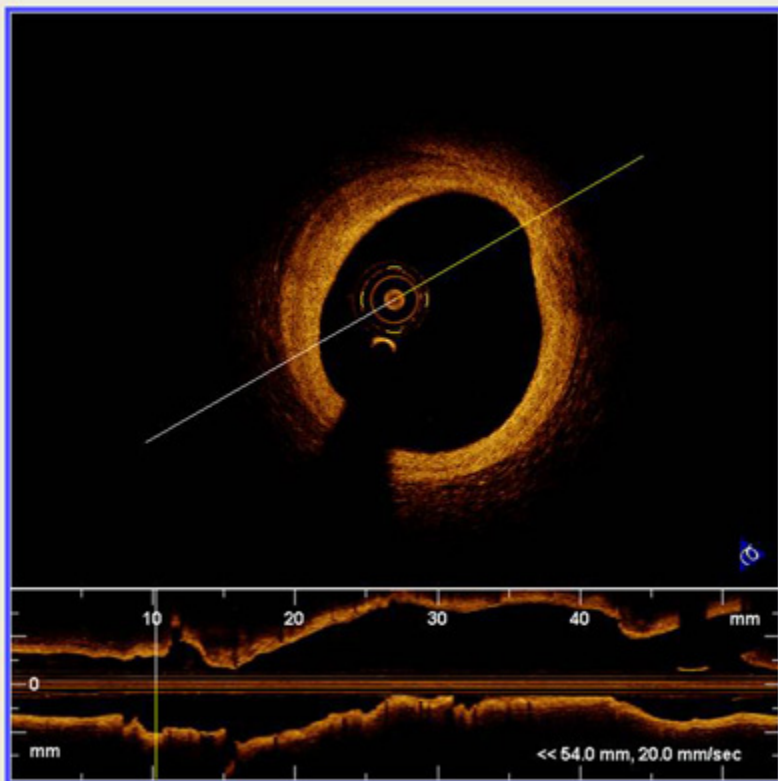


covered

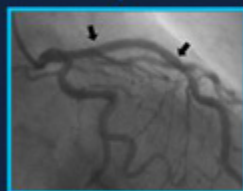
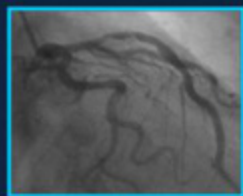


More results : EuroPRC2012

EGO-Combo Study: Dual Therapy Stent at 90 days



Conclusions



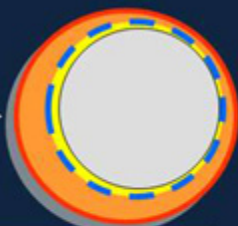
Pure Ballooning



BMS



DES



Acute Closure

Bail-out + BMS

Restenosis 30-50%

25-35%

3-10% !!

All current DES = can achieved neointimal suppression

PCI objective = purely for achieving revascularization
= without complicated issues of

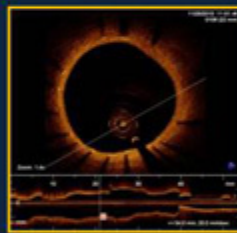
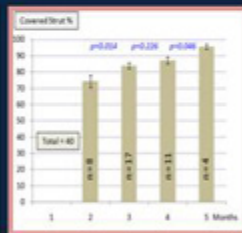
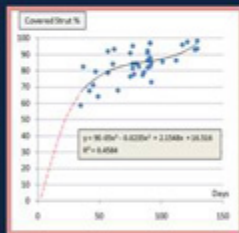
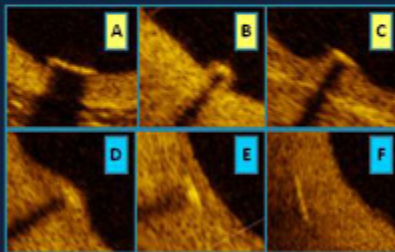
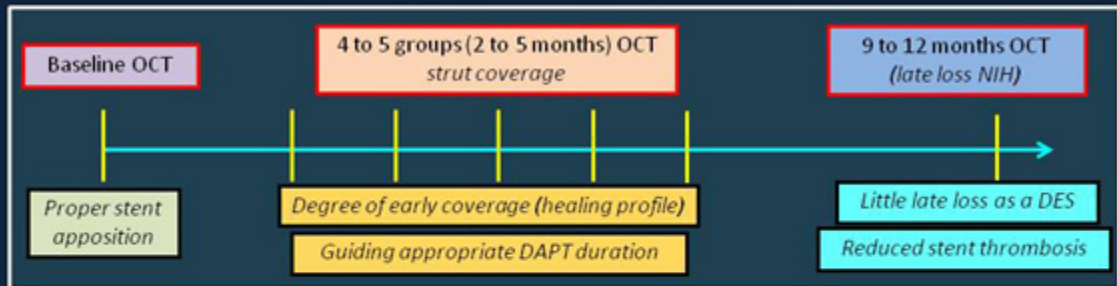
But many DES still show poor Stent Healing =

drug cytotoxicity, polymer hypersensitivity, local inflammatory reactions, loss endothelial and vasomotor functions

- Acute failure
- Restenosis
- Stent thrombosis
- Prolonged DAPT

- Stent thrombosis
- MACE

Sequential longitudinal OCT FU with a very stringent strut coverage classification should be adopted as a vigorous & novel step for guiding any new stent platform.



Very stringent strut coverage classification

May predict / prevent late stent thrombosis, rather than waiting for years to observe for adverse effects.

