

Can Biodegradable Polymer DES Be Better than 2nd Generation DES?

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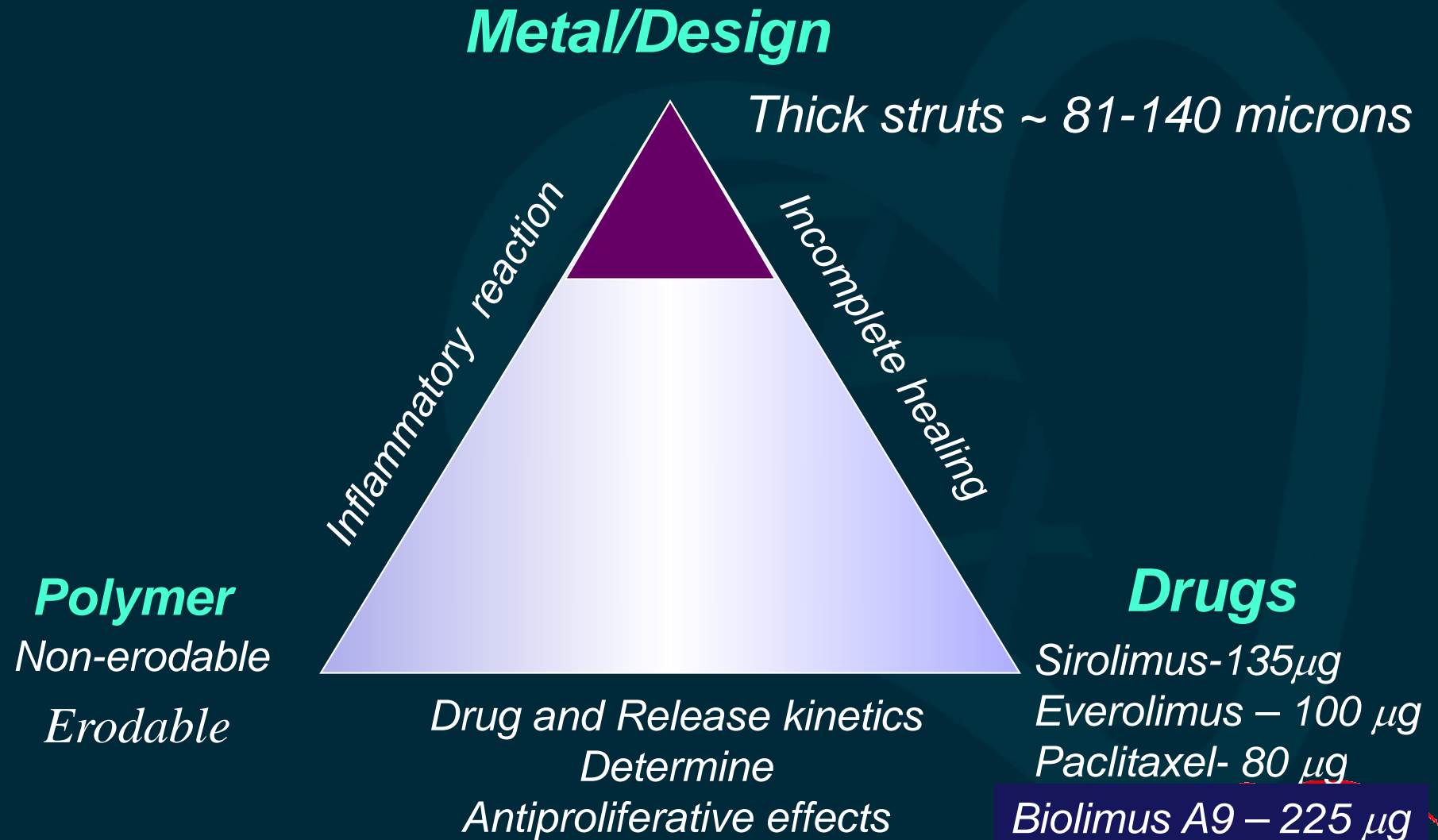
Receiving Research Grant From

Abbott Vascular Japan
Boston Scientific Japan
Medtronic Vascular Japan
Cordis Johnson & Johnson
Terumo Corp.
Biosensors Japan

Advisory Contract With

Abbott Vascular Japan
Terumo Corp.

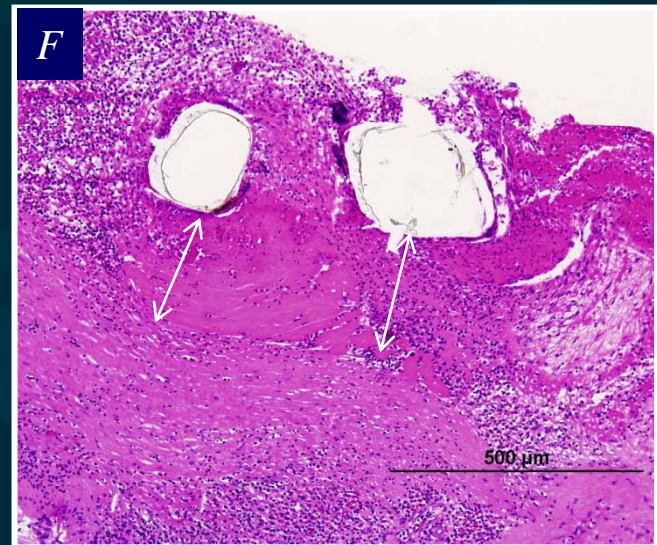
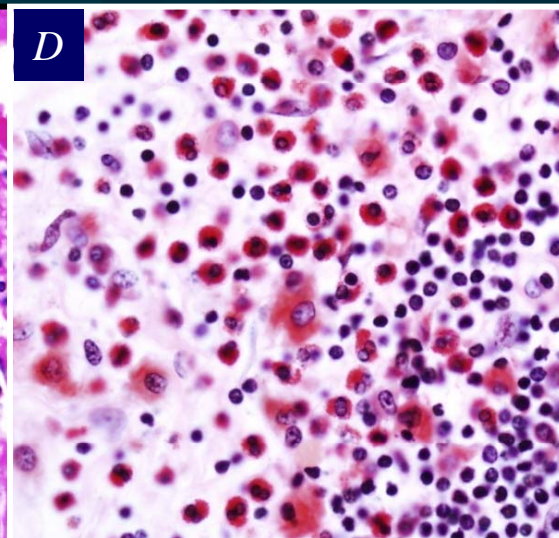
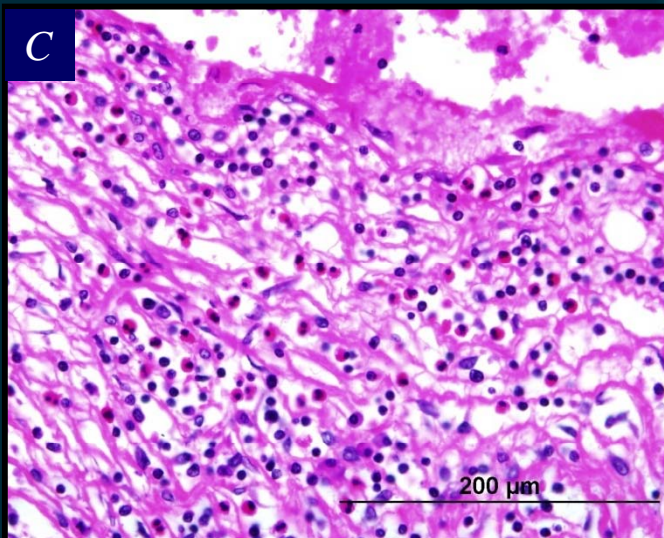
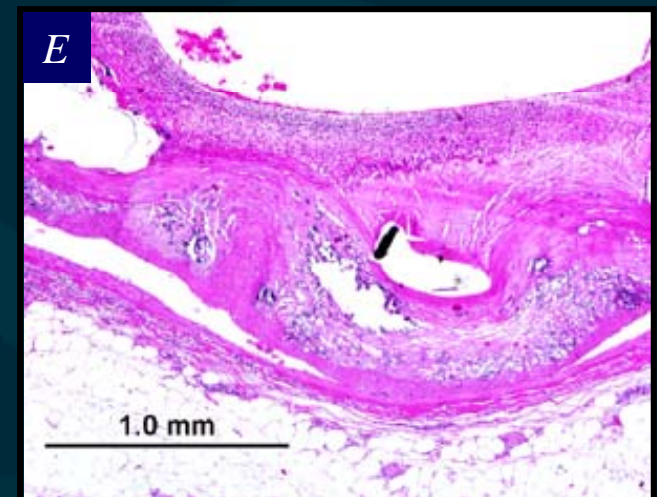
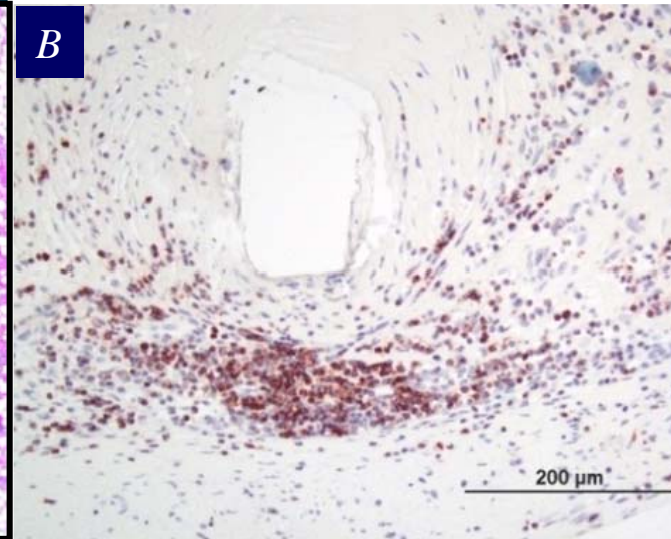
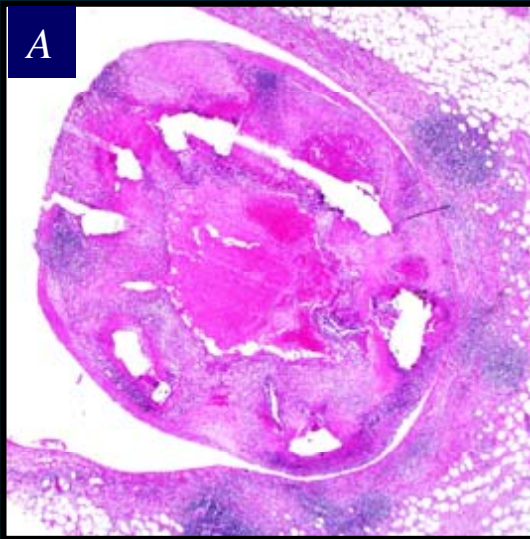
Components of DES



Localized Hypersensitivity Reaction in Cypher

LAD: Cypher (17months)

RCA: Cypher (17months)

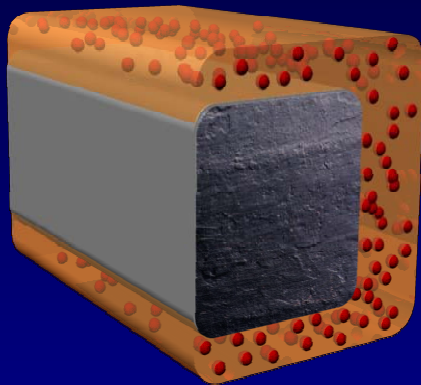


Nakazawa, G et al. J Am Coll Cardiol 2011; 57(4): 401-408

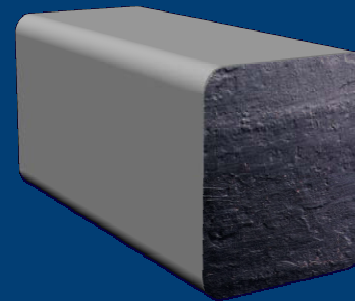
Long Term Safety : Future Directions

Long-Term Safety of DES: Future Directions

Asymmetric Biodegradable Polymer



No Polymer
No Drug



General criteria for selecting a polymer for use as biomaterial

- Does not evoke an inflammatory/toxic response, disproportionate to its beneficial effect
- Is metabolized in the body after fulfilling its purpose, leave no trace
- Is easily processed into the final product form
- Has acceptable shelf life
- Is easily sterilized

Synthetic Biodegradable Polymers

- Poly(lactide) (PLA)
- Poly(glycolide) (PGA)
- Poly(glycolic-co-lactic acid) (PLGA)
- Poly(ϵ -caprolactone) (PCL)
- Poly(dioxanone) (PDS)
- Poly(glycolide-co-trimethylene carbonate) (PGA-TMC)

Degradation Speed in Various Biodegradable Polymers

Material	Degradation Period
Poly(lactic acid (PLA)	9 months
Polyglycolic acid (PGA)	2-3 months
Poly-L-lactic acid (PLLA)	12-18 months
Poly(d,l-lactide/glycolide) copolymer (PGLA)	2-3 months
Polyorthoester (POE)	10 months (60%)
Poly(hydroxybutyrate/hydroxyvalerate)copolymer (PHBV)	6 months
Polycaprolactone (PCL)	36 months

Degradation

- ✓ The degradation-absorption mechanism is the result of many interrelated factors, including:
 - ✧ The chemical stability of the polymer backbone
 - ✧ The presence of catalysts
 - ✧ Additives
 - ✧ Impurities or plasticizers
 - ✧ Geometry of the device
 - ✧ Location of the device
- ✓ *Factors which accelerate polymer degradation are the following:*
 - ✧ *More hydrophilic monomers*
 - ✧ *More hydrophilic, acidic endgroups*
 - ✧ *More reactive hydrolytic group in the backbone*
 - ✧ *Less crystallinity*
 - ✧ *Small device size*

PLA Metabolic Pathway

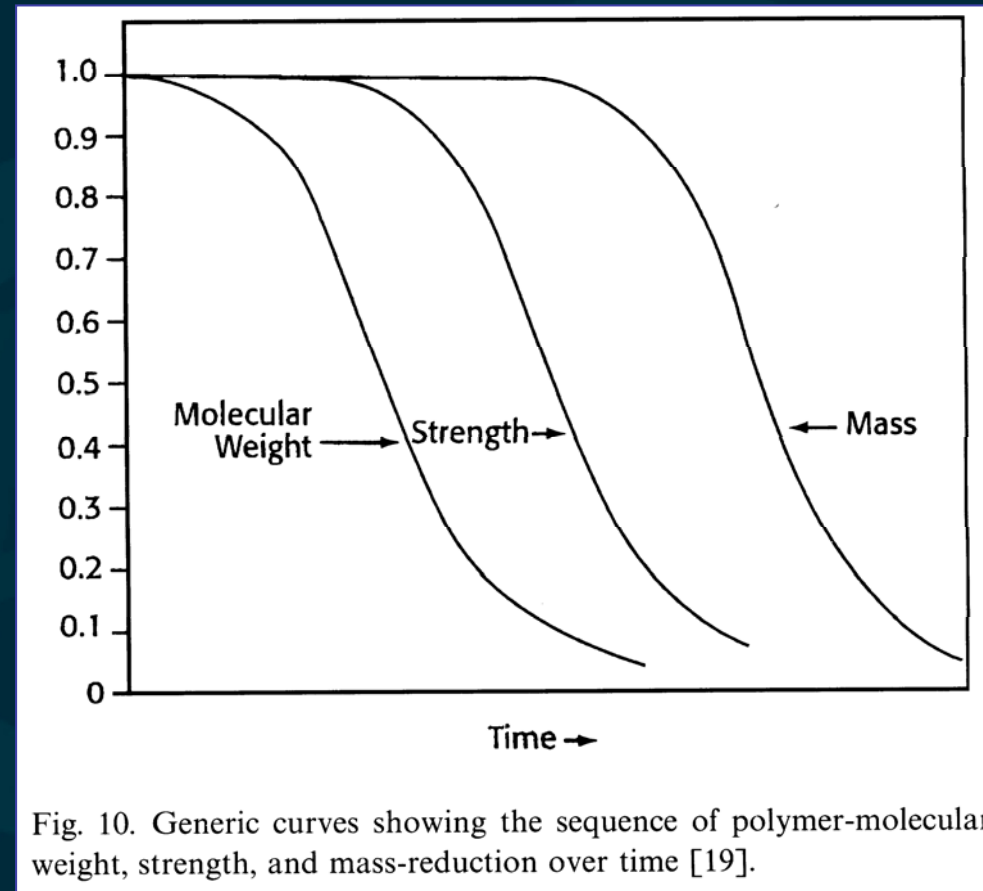
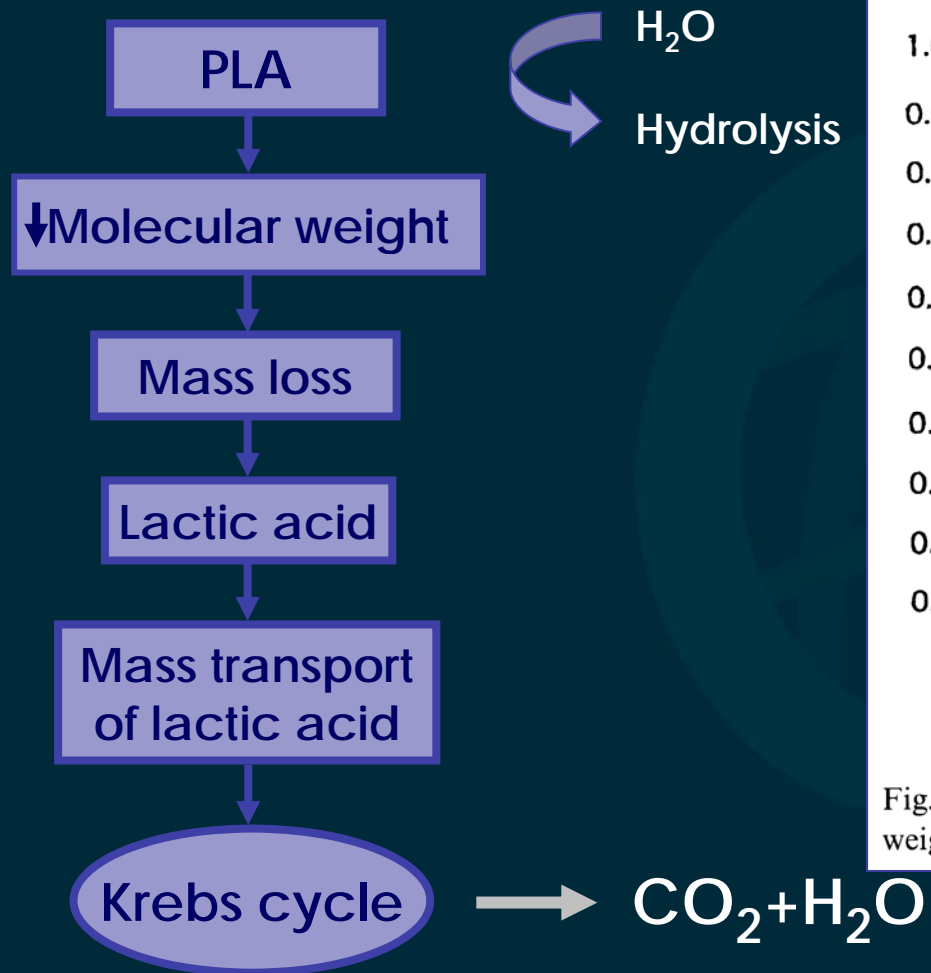
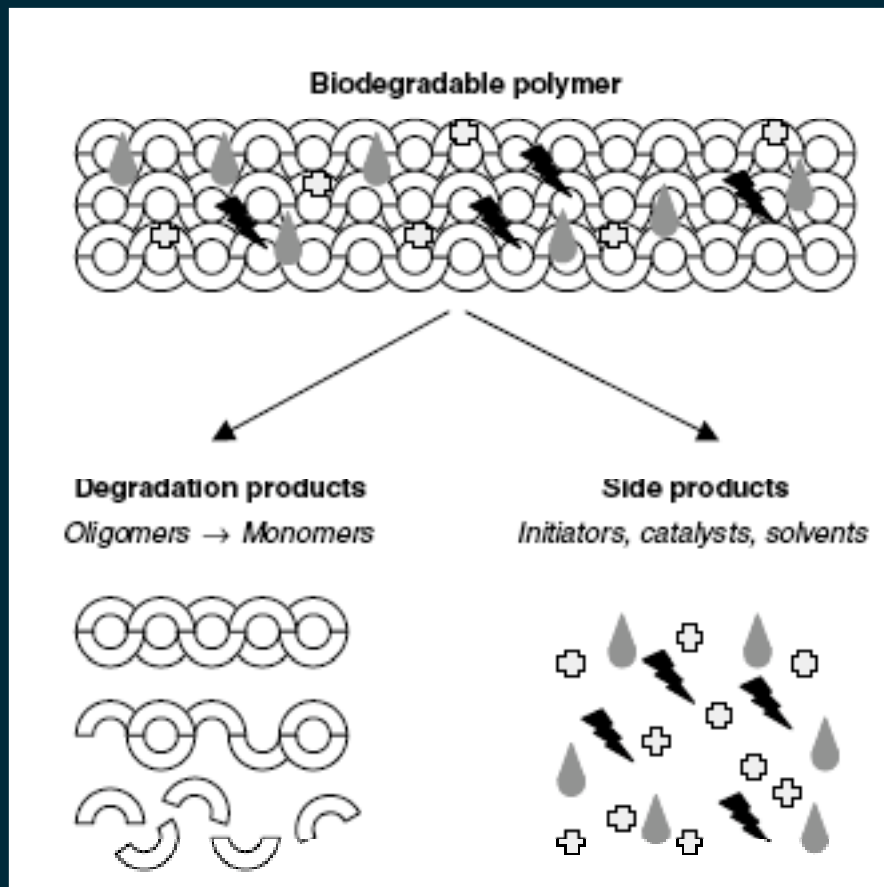
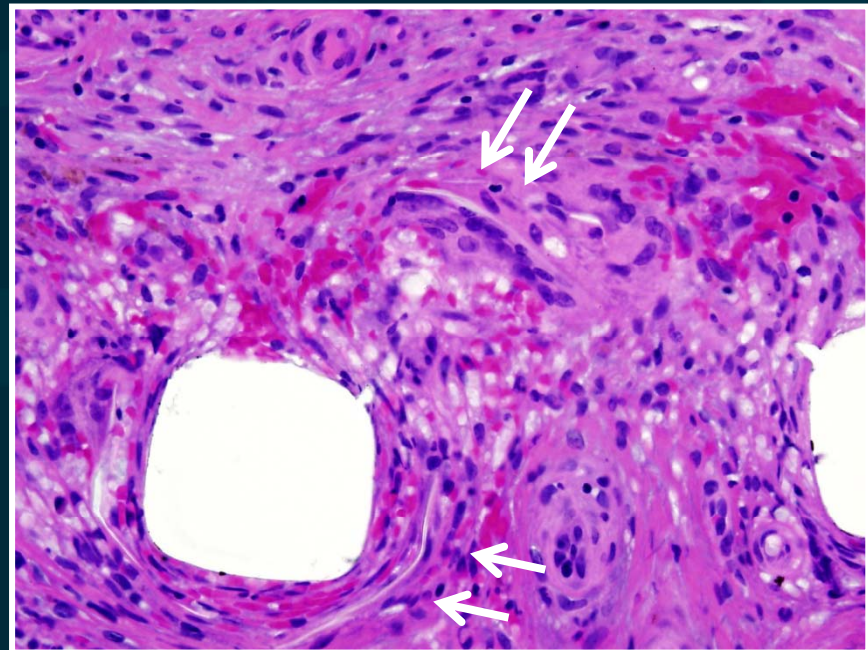
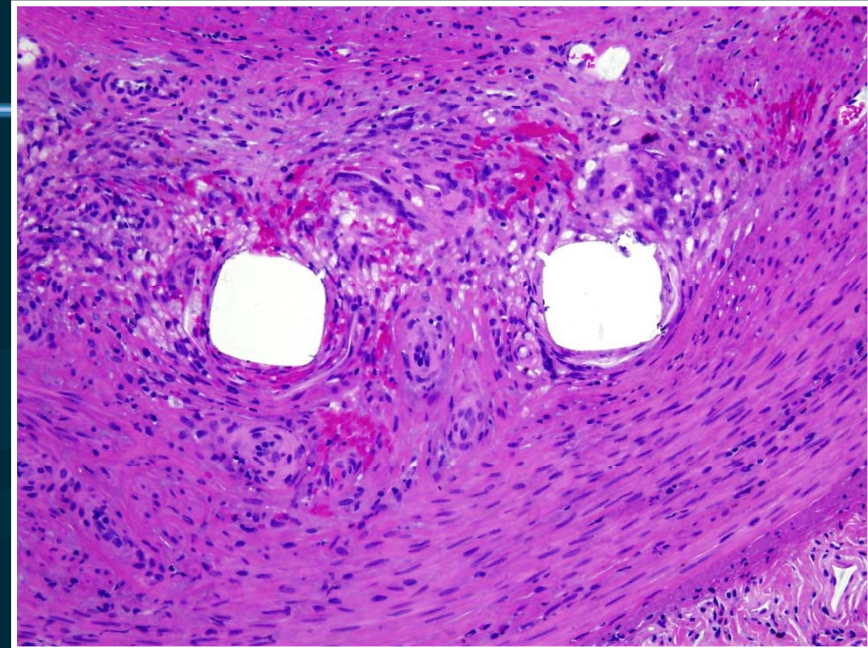


Fig. 10. Generic curves showing the sequence of polymer-molecular weight, strength, and mass-reduction over time [19].

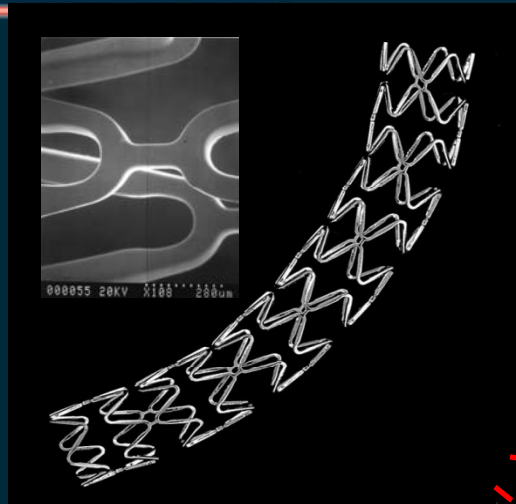
Bioerodable polymer breaks down into Polymer degradation products and side products. The side products, mostly responsible for toxic effects



Commandeur S, J Interven Cardiol 2006



NOBORI Stent Platform



Biodegradable Drug/Carrier:

- Biolimus A9[®] / Poly (Lactic Acid) 50:50 mix
- abluminal surface only (contacts vessel wall)
- 11 μ meter coating thickness
- degrades in 9 months releasing CO₂+ water

S-Stent[™] Platform:

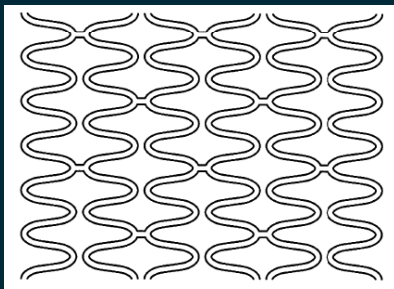
- Stainless steel (129 μ m)
- Open cell design
- Quadrature-link[™] connectors
- Different models for small and large vessels



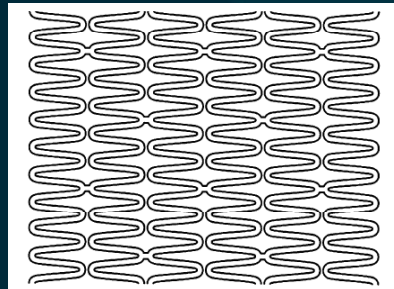
Parylene C

Drug: Biolimus A9

15.6 μ g/mm-stent length

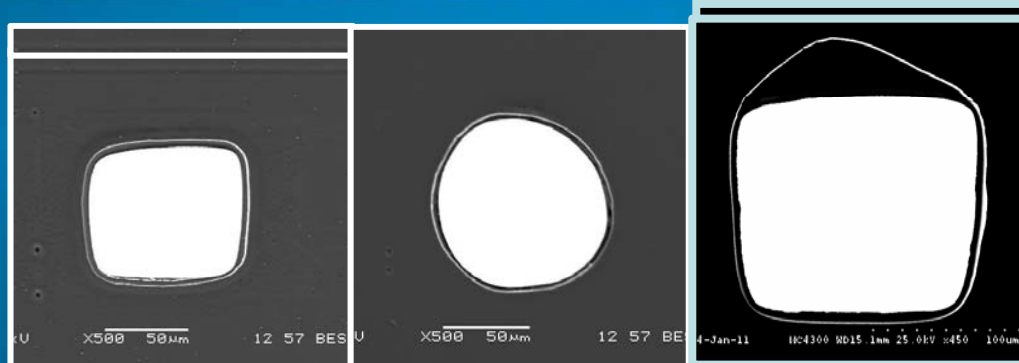


2.5-3.0mm (6 crown 2 link)



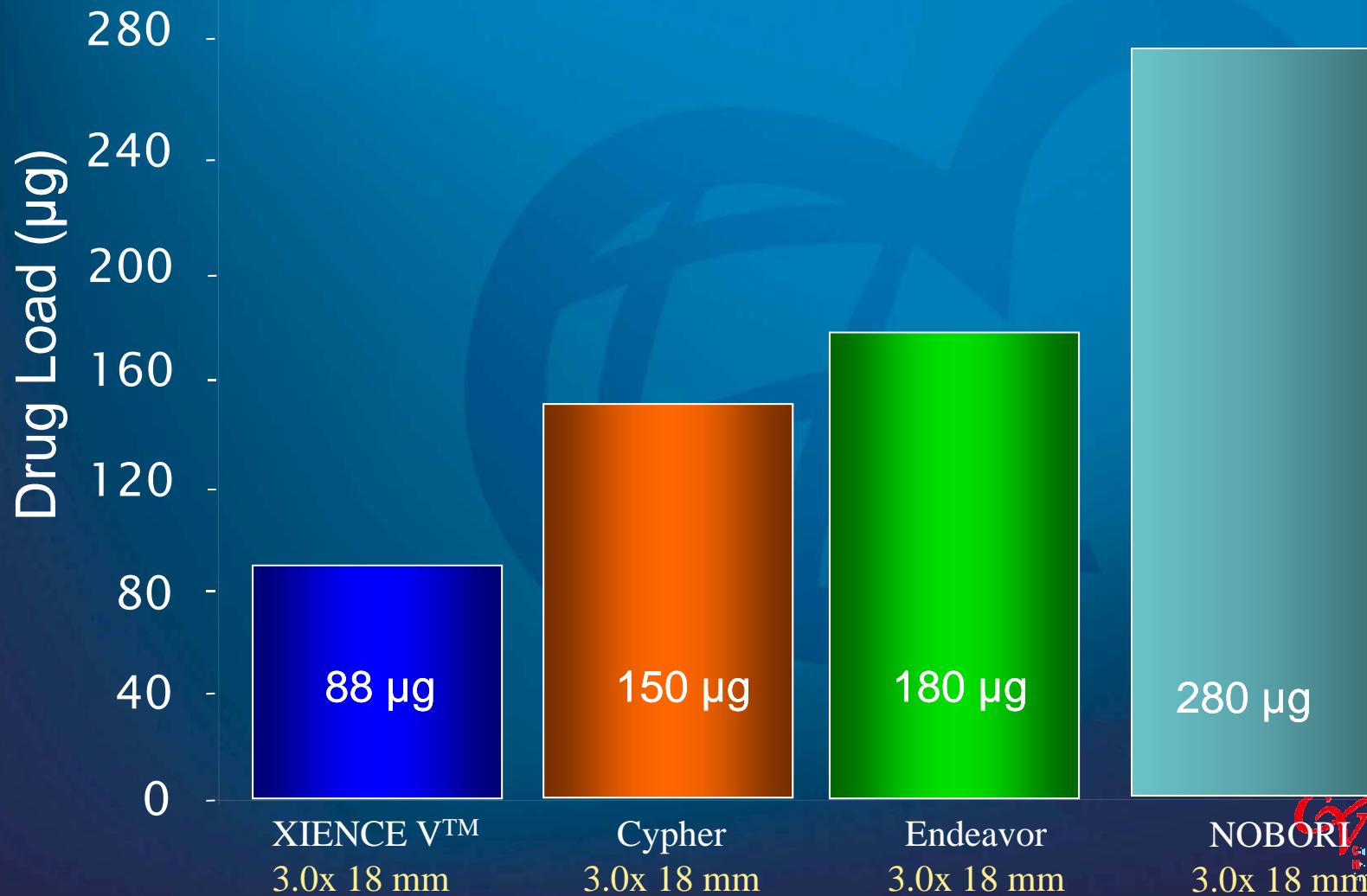
3.5mm (10 crown 2 link)

NOBORI– Strut and polymer thickness

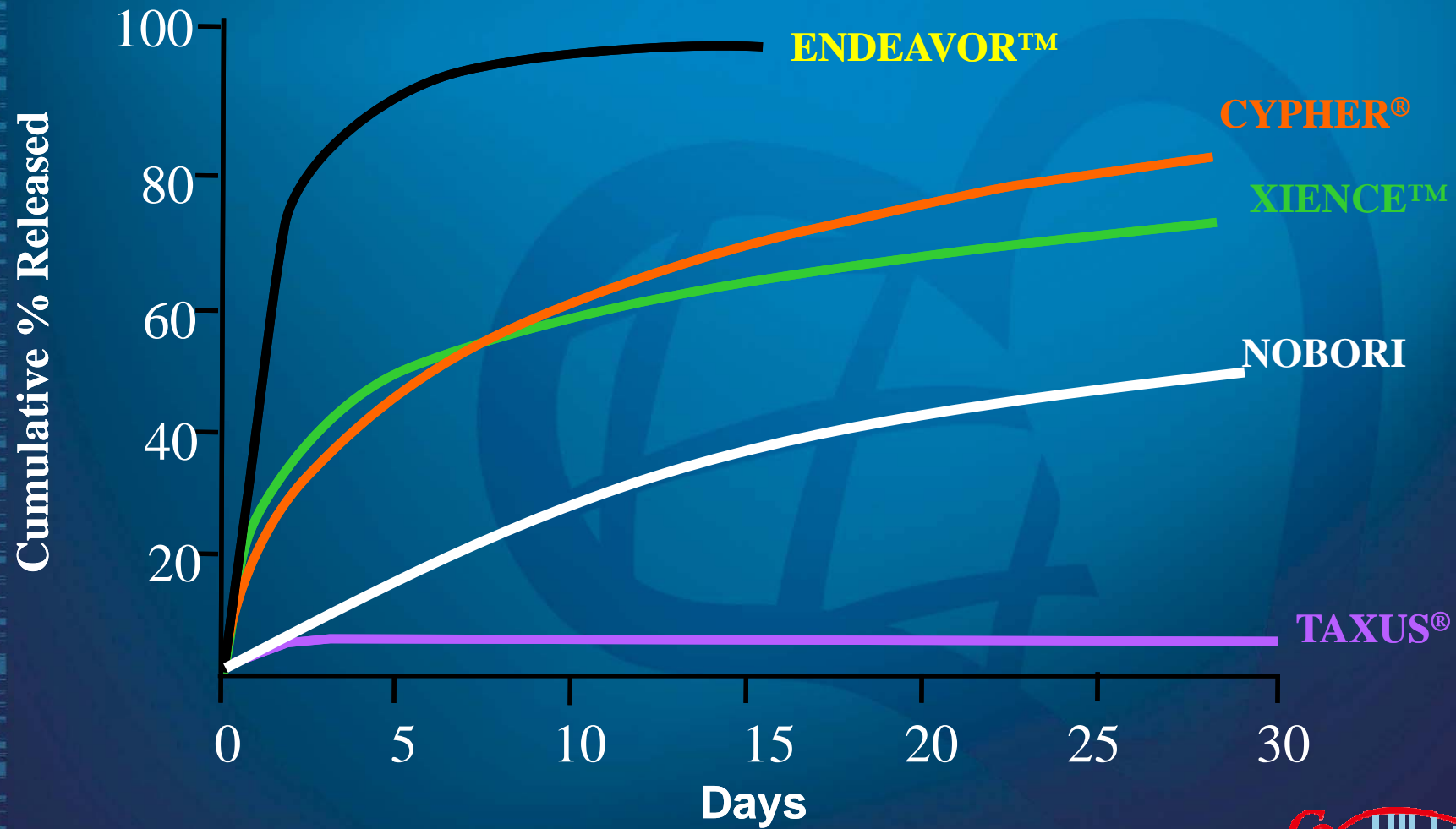


DES	Xience Stent	ENDEAVOR® Stent	NOBORI
Stent Material	Cobalt Chromium	Cobalt Chromium	Stainless Steel
BMS Strut Thickness (in.)	0.0032”	0.0036”	0.0053”
BMS Strut Thickness (µm)	81µm	91µm	130µm
Polymer Thickness (µm)	7µm	6µm	18µm

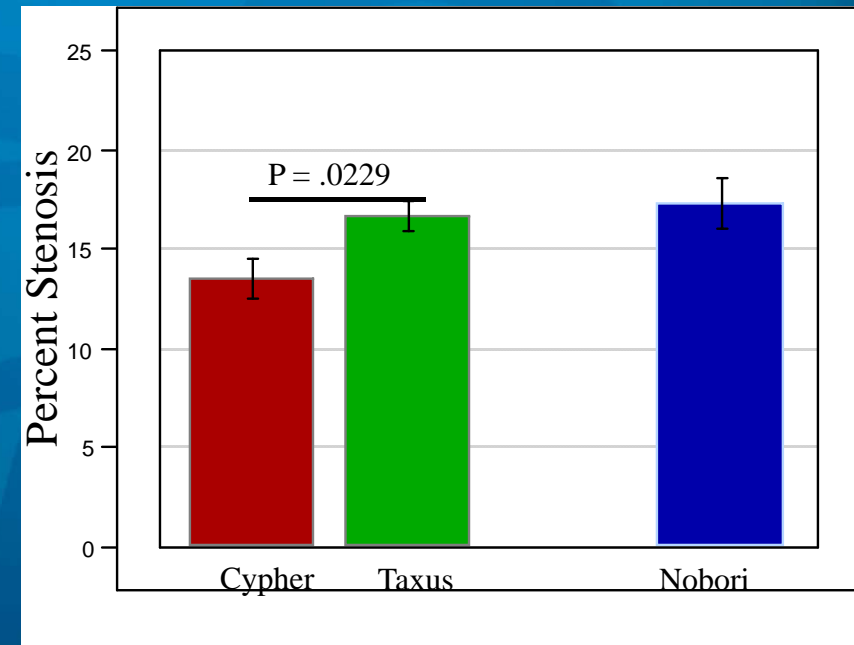
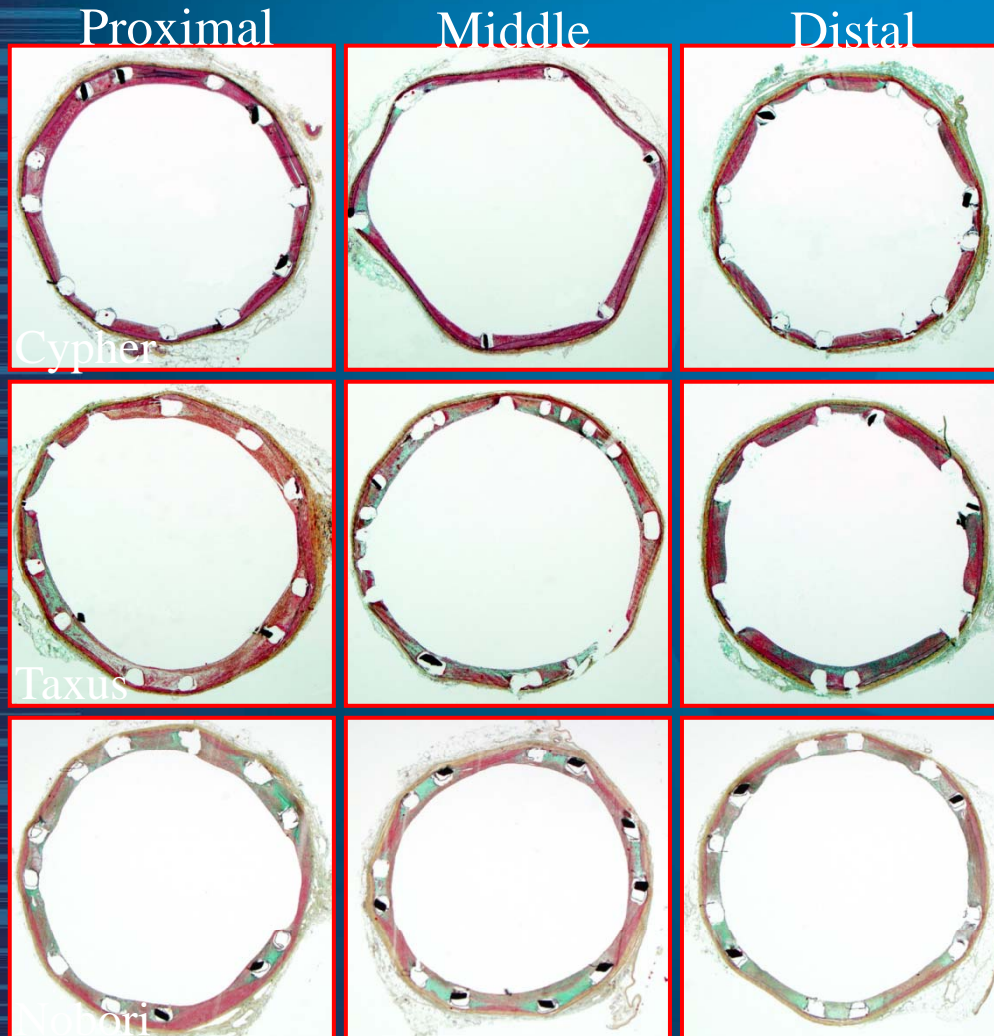
Drug Dose in various DES



Comparative Elution Profiles



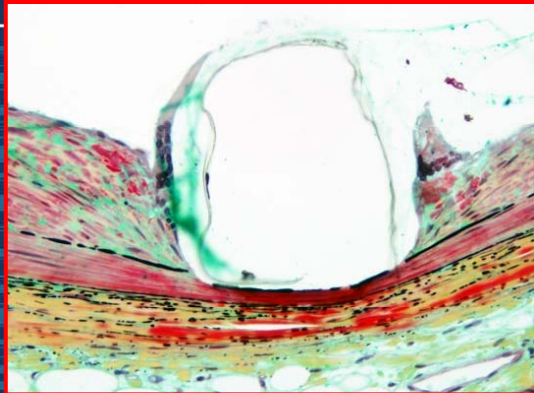
Percent Stenosis in Single DES in Rabbit Iliac Arteries following Deployment of Cypher, Taxus and Nobori stents at 28-days



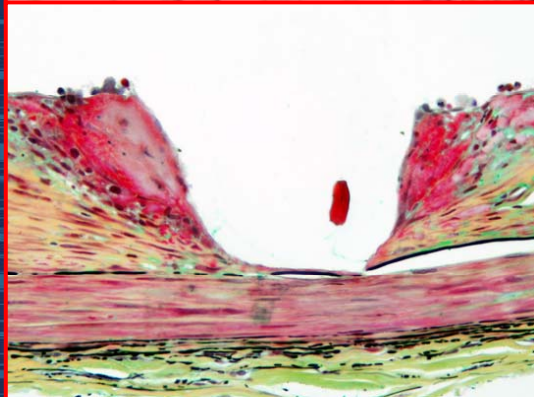
Data from CVPATH Institute, Inc.



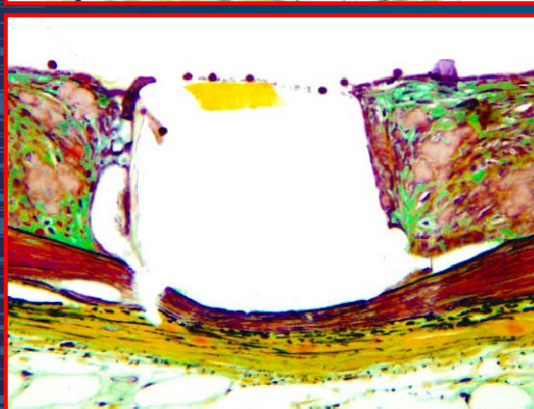
Fibrin Deposition in Single DES in Rabbit Iliac Arteries at 28-days



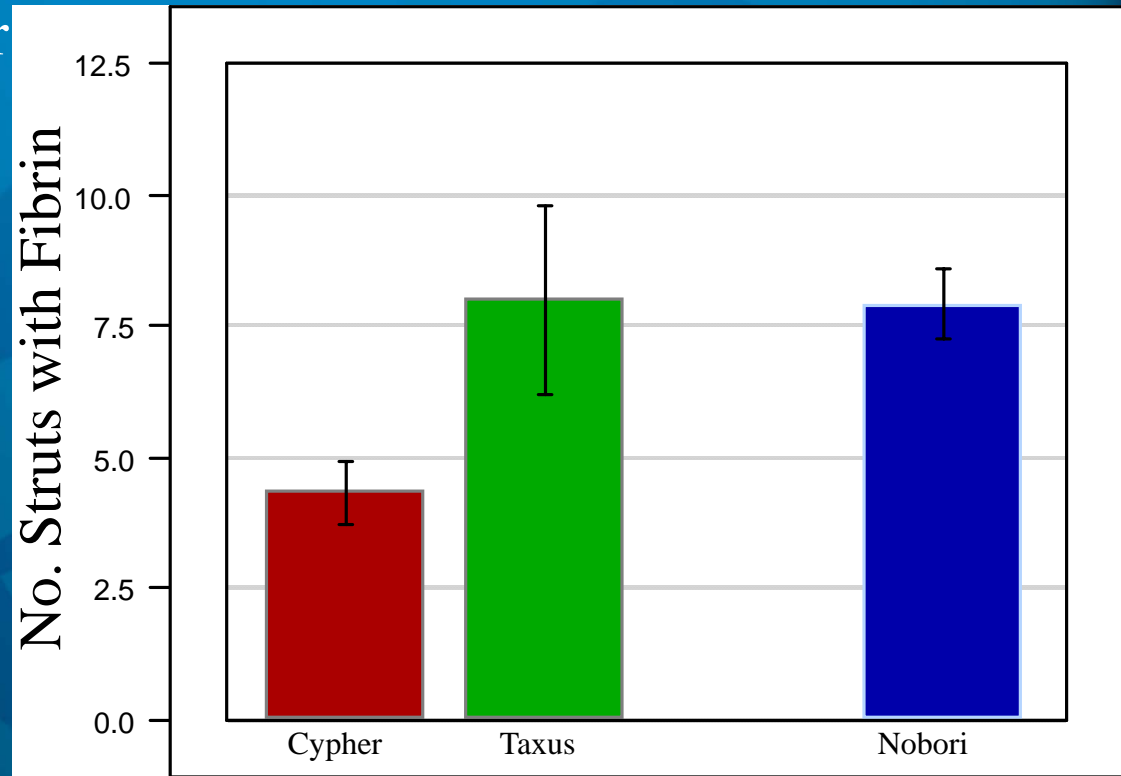
Cypher



Taxus



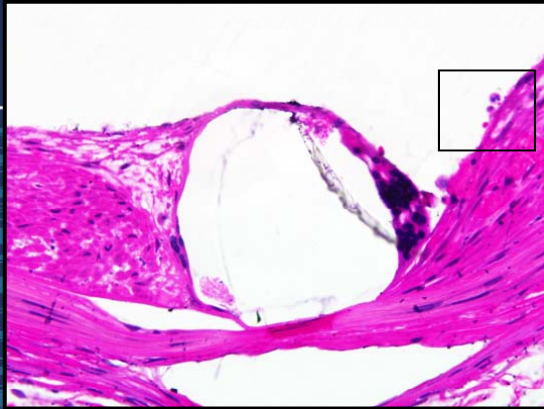
Nobori



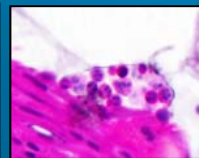
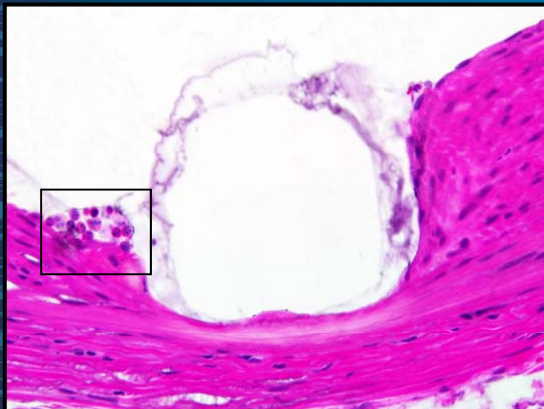
Data from CVPPath Institute, Inc.



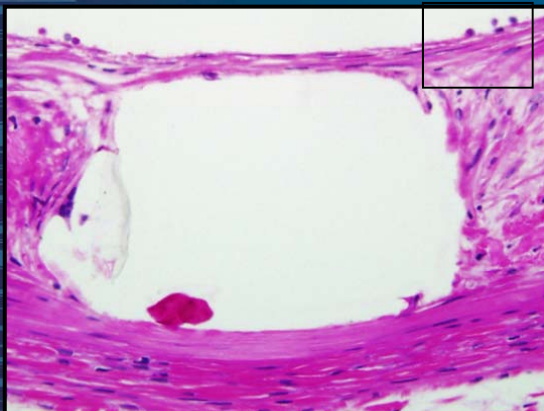
Inflammation in Single DES



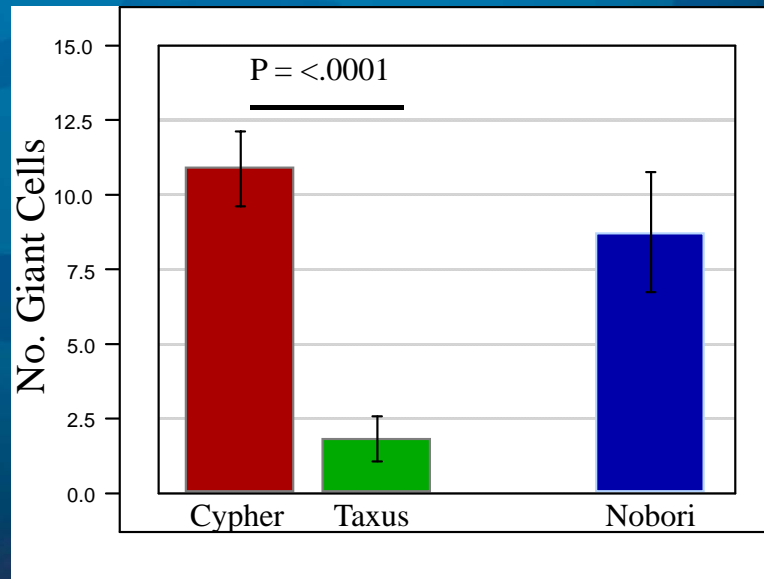
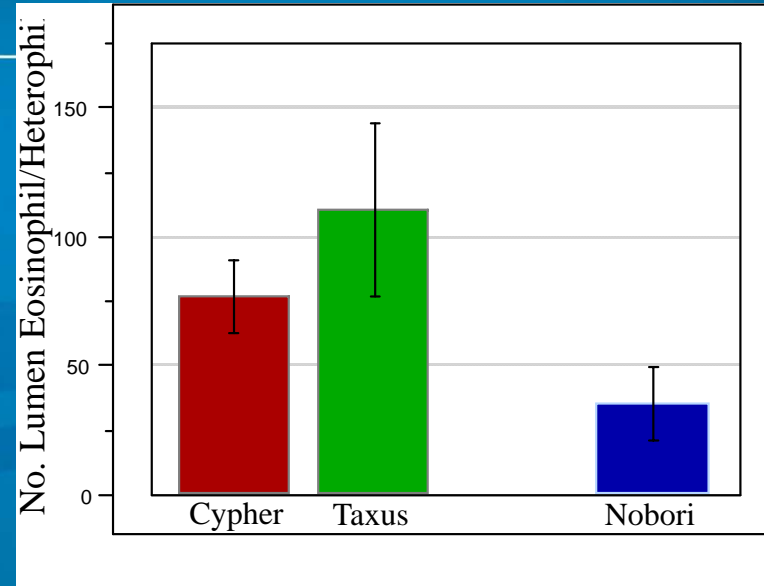
Cypher



Taxus



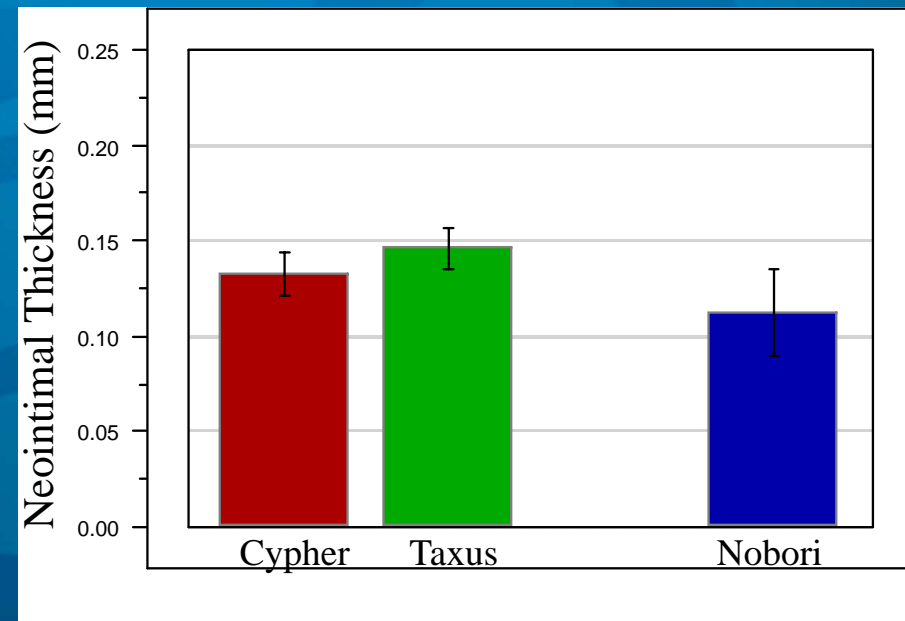
Nobori



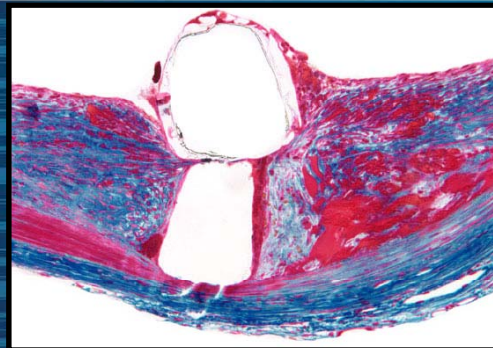
Data from CVPPath Institute, Inc.



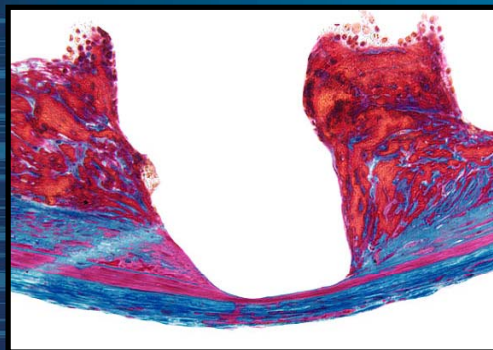
Overlapping Drug-Eluting Stents (Cypher, Taxus and Nobori) at 28-day



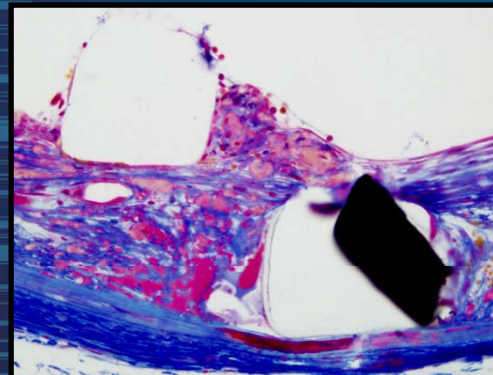
Fibrin Deposition in Overlapped DES at 28 days



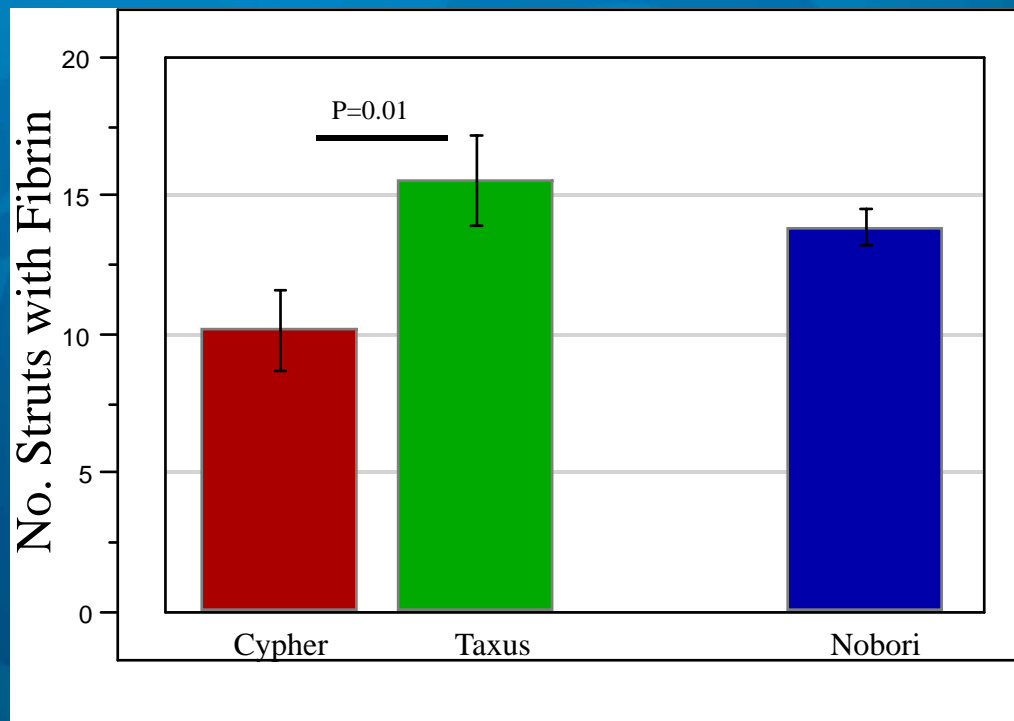
Cypher™



Taxus™



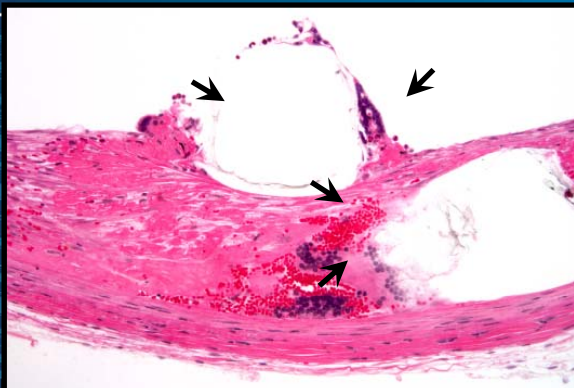
Nobori™



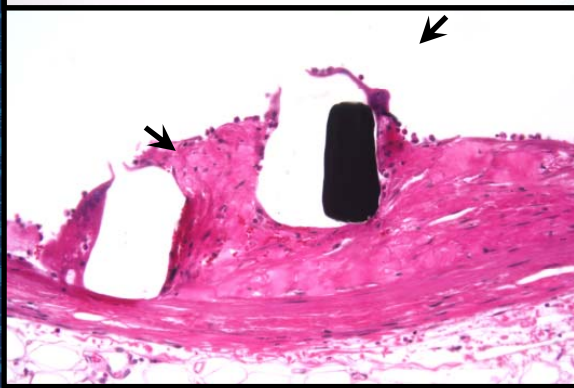
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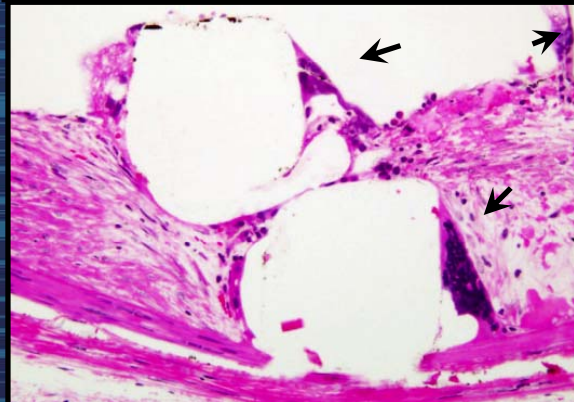
Giant cells in Overlapped DES at 28-Days



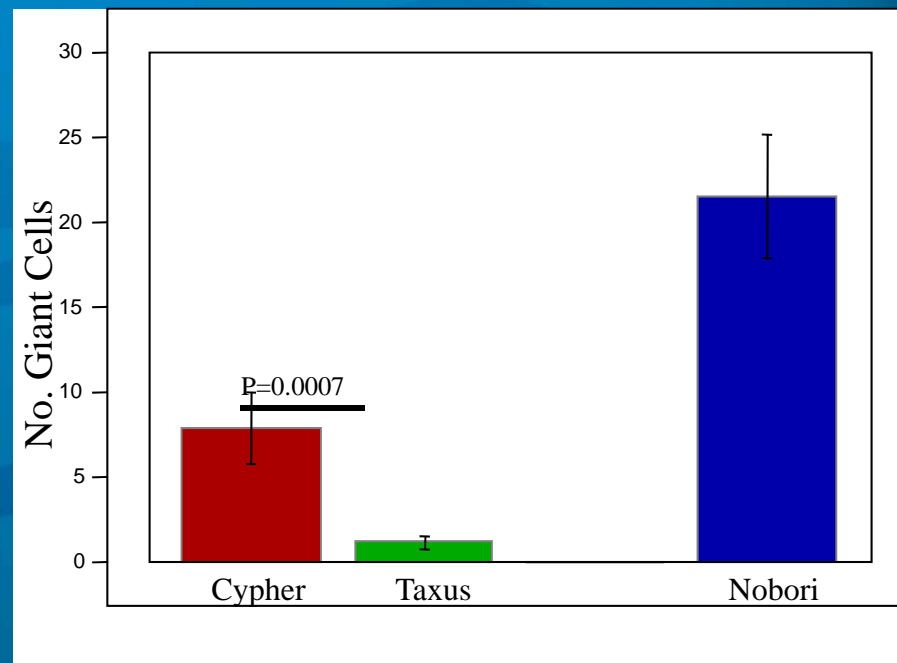
Cypher™



Taxus™



Nobori™



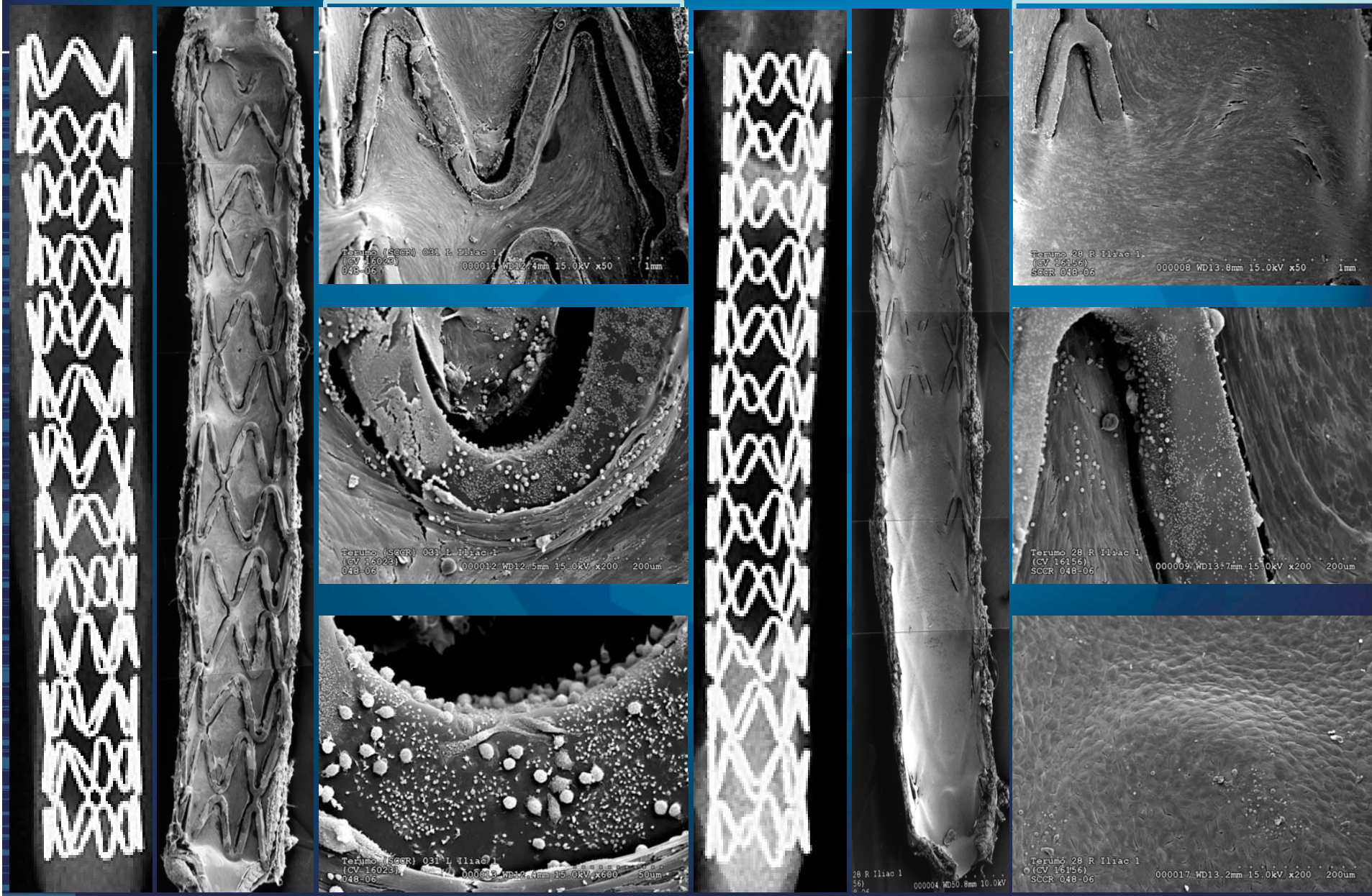
Data from CVPPath Institute, Inc.



Single Nobori™ Biolimus A9-Eluting Coronary Stents

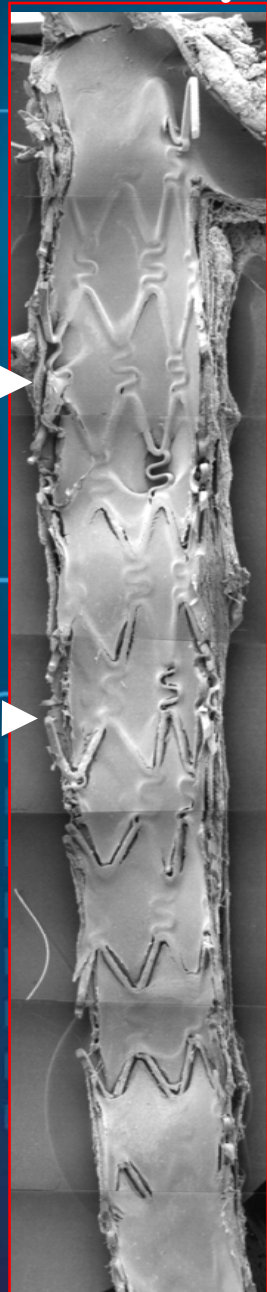
14 Day Single

28 Day Single



Comparison of Various BMS and DES In Rabbit Iliac Arteries at 28-days

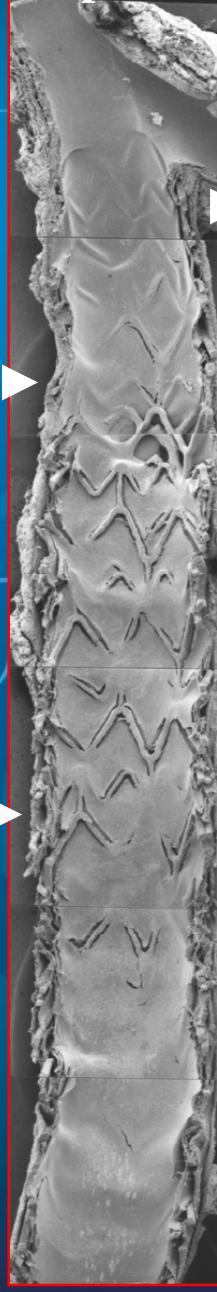
Bx Velocity



Cypher



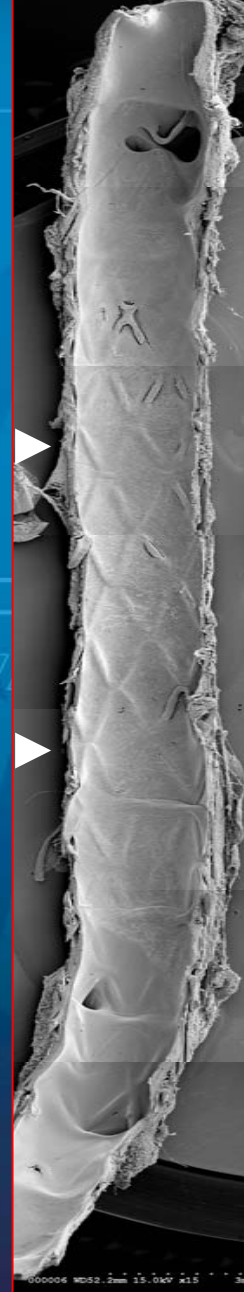
Express



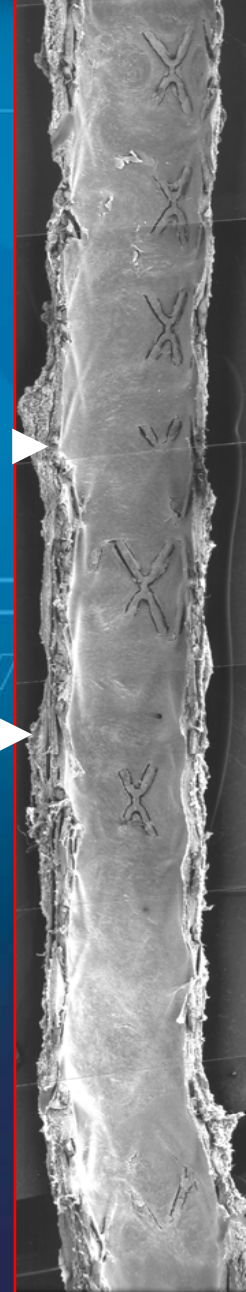
Taxus



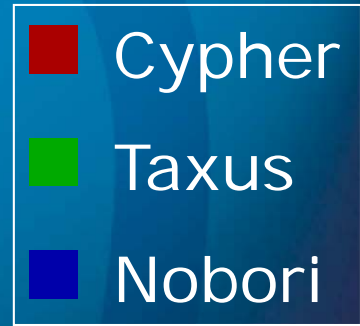
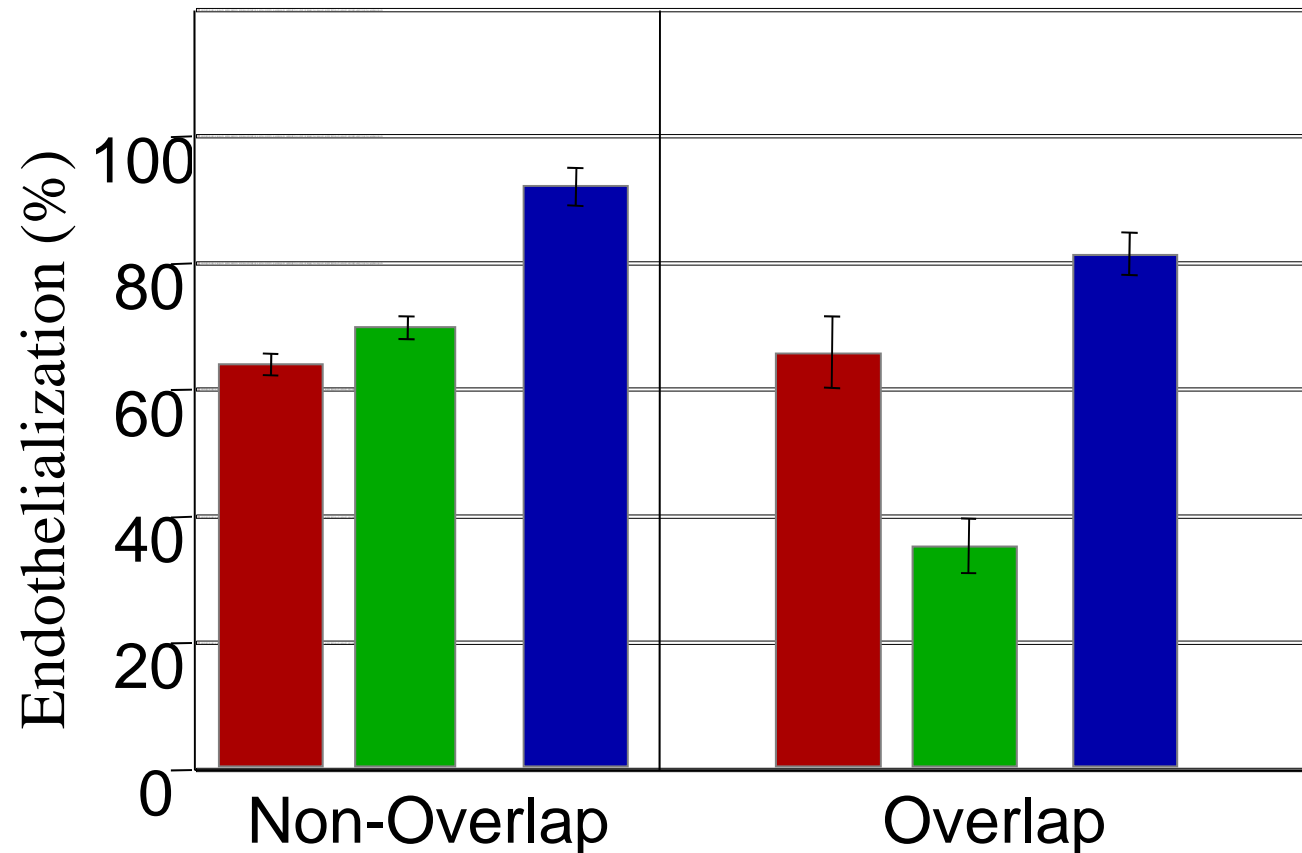
Tsunami



Nobori



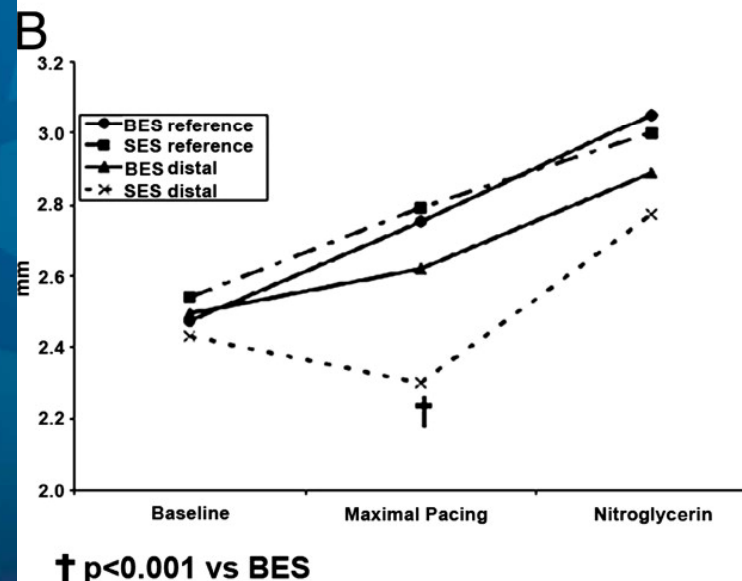
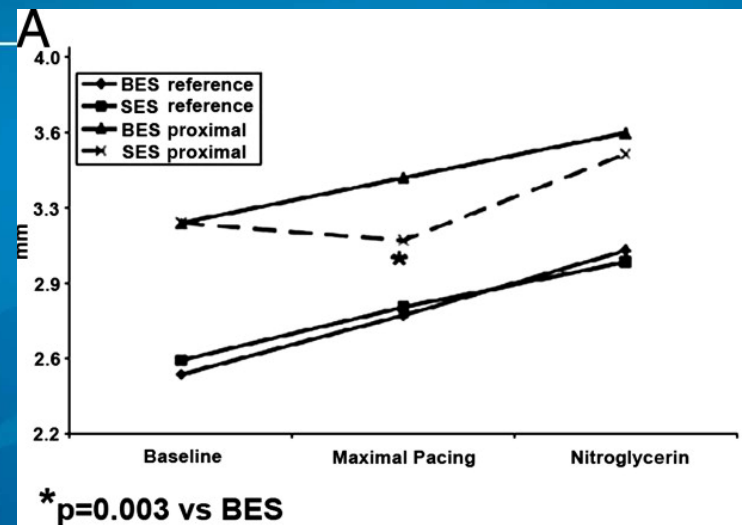
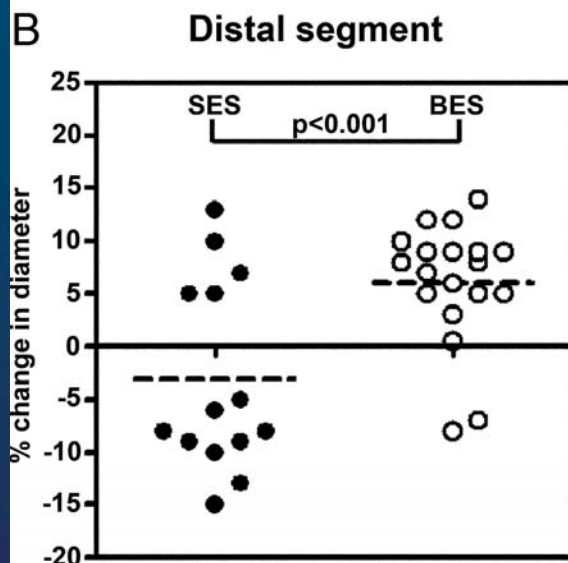
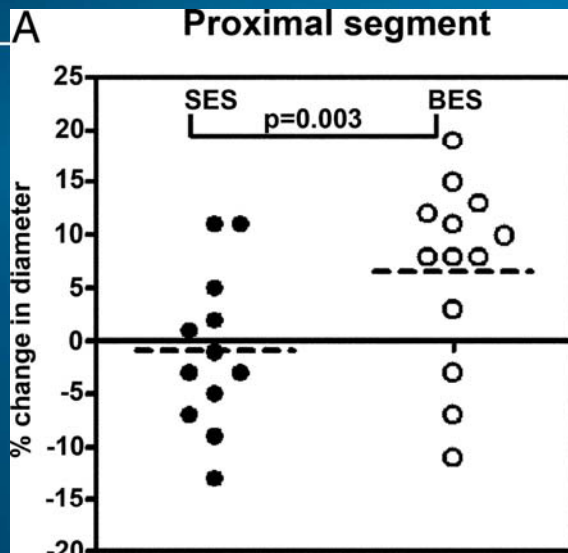
28 Day Endothelialization



Data from CVPPath Institute, Inc.



Endothelial Function in NOBORI



Hamilos, MI et al. J Am Coll Cardiol 2008;51:2123-9



Is the biodegradable polymer really better than durable ones?

Ongoing Pre-clinical Study

Study Title: Comparison of long-term safety following new generation drug eluting stents implantation in porcine coronary artery

Purpose: Hypersensitivity reaction due to lack of biocompatibility has emerged as one of the major concerns in 1st generation drug-eluting stents (DES). Newer generation DES has applied better polymer but the long-term safety is still unclear. **The aim of this study is to evaluate the long-term safety following Xience V, Cypher, and Nobori DES in porcine coronary artery model.**

Test Articles:

1. Xience V everolimus eluting stent
2. Cypher Select sirolimus eluting stent
3. Nobori Biolimus eluting stent

Collaborators

Kobe University Graduate School of Medicine

Toshiro Shinke, MD (Study Co-Director)

Daisuke Matsumoto, MD

Hiromasa Otake, MD

Junya Shite, MD

Tokai University School of Medicine

Takeshi Ijichi, MD

Abbott Vascular Japan

Masaharu Osa

Masaru Uchiyama

Akihi Kato

Yoshihiro Odagawa

GOODMAN CO., LTD.

Kentaro Asada

Toshio Kimura



Study Design

Implantation of DES
Animal N=12
Each animal receives 3 DESs
(XV, CS, and NB)

Sacrifice 6 animals for Histo
• Ach challenge test
• OCT observation
Before sacrifice

N=6

0

3M

N=6

0

1M

6M

• Acetylcholine challenge test
• OCT observation
6 animals for 6M

Sacrifice 6 animals for Histo
• Ach challenge test
• OCT observation
Before sacrifice

Protocol for Acetylcholine challenge test

Baseline Angiography

10^{-6} mol/l of acetylcholine
(1ml/min)

2.5 mins

10^{-5} mol/l of acetylcholine
(1ml/min)

2.5 mins

ISDN (200-400ug)

Final Angiography

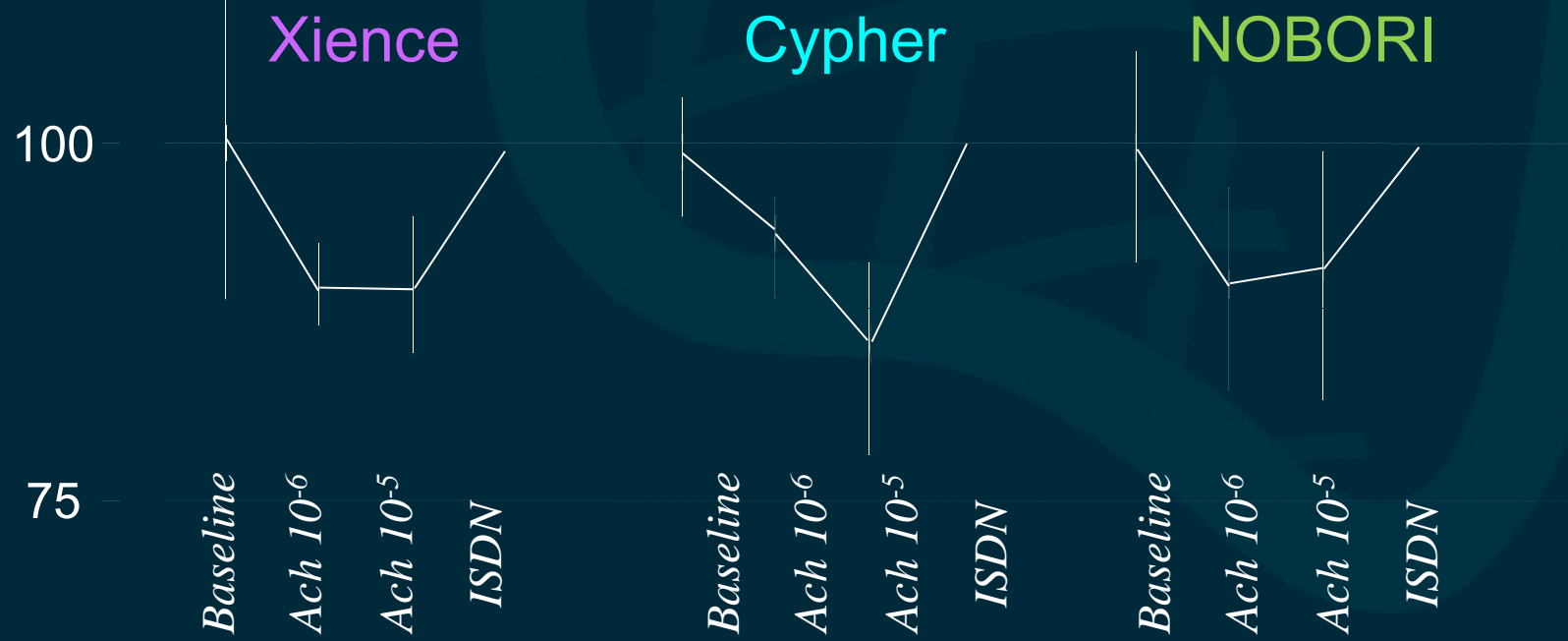
OCT Imaging

MLD following Ach Challenge@1M

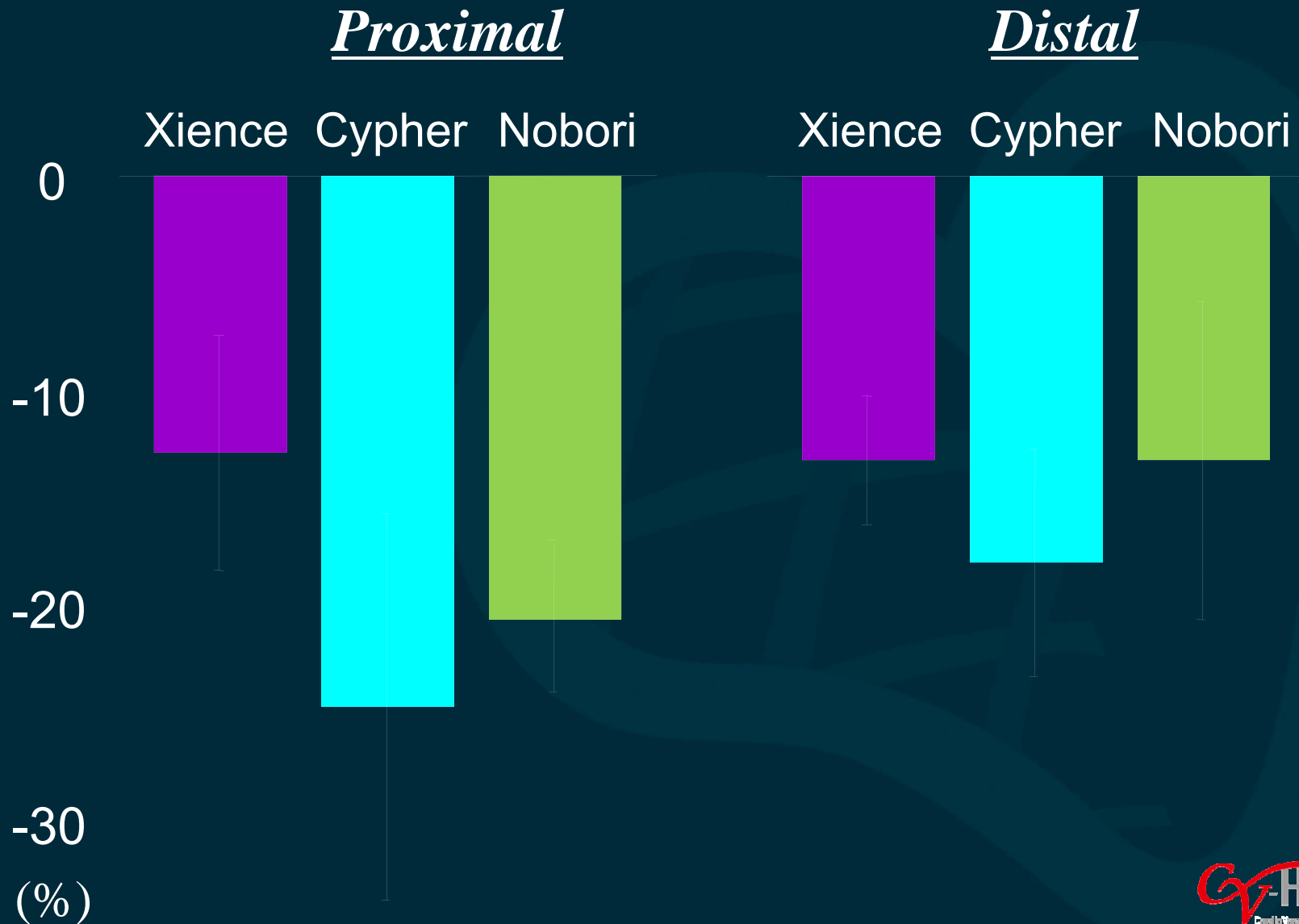
Proximal



Distal



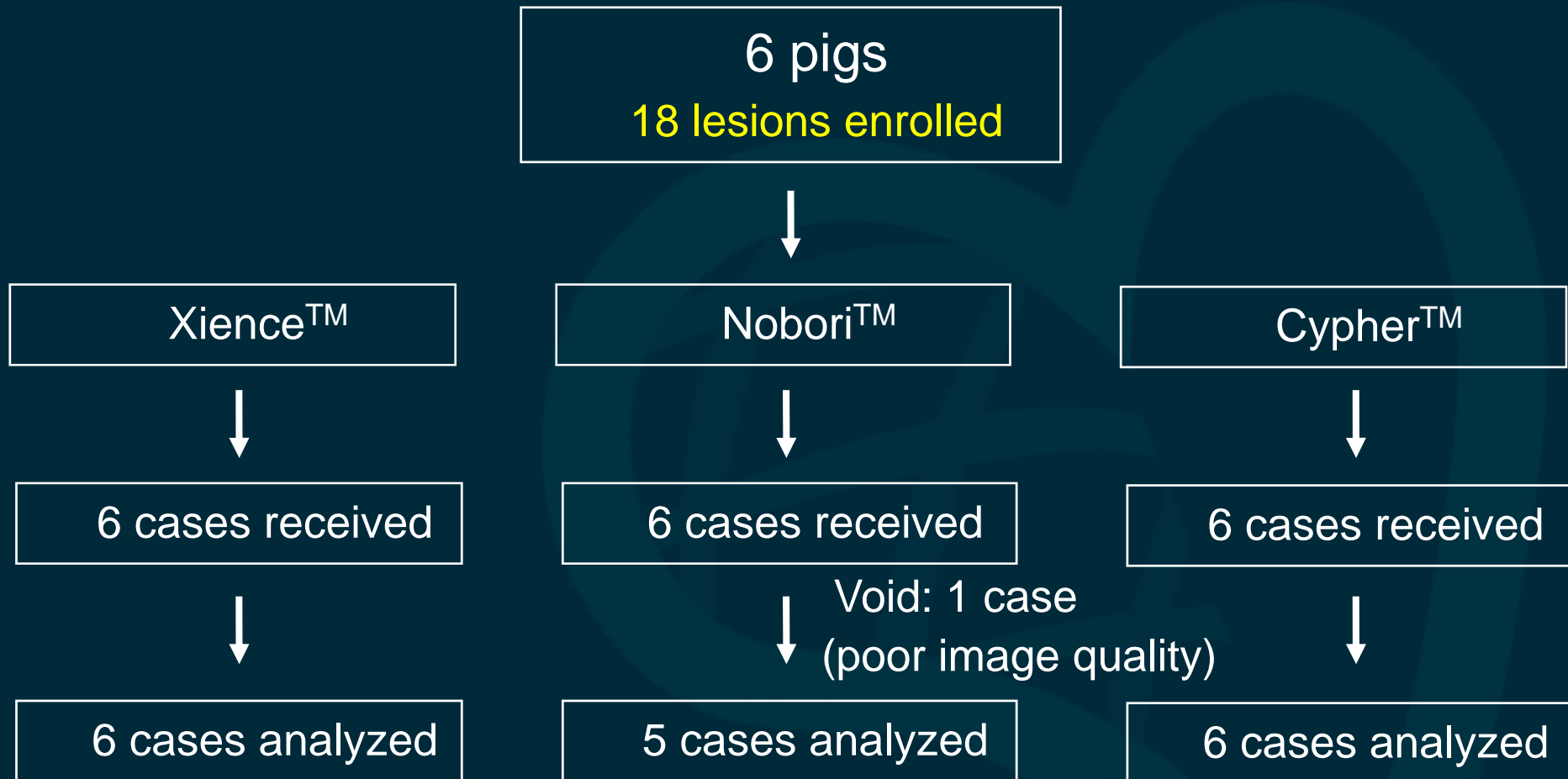
Maximum Change in MLD following Ach Challenge@1M



- Preliminary OCT results-

1 and 3 months

1-month group OCT Analysis Status

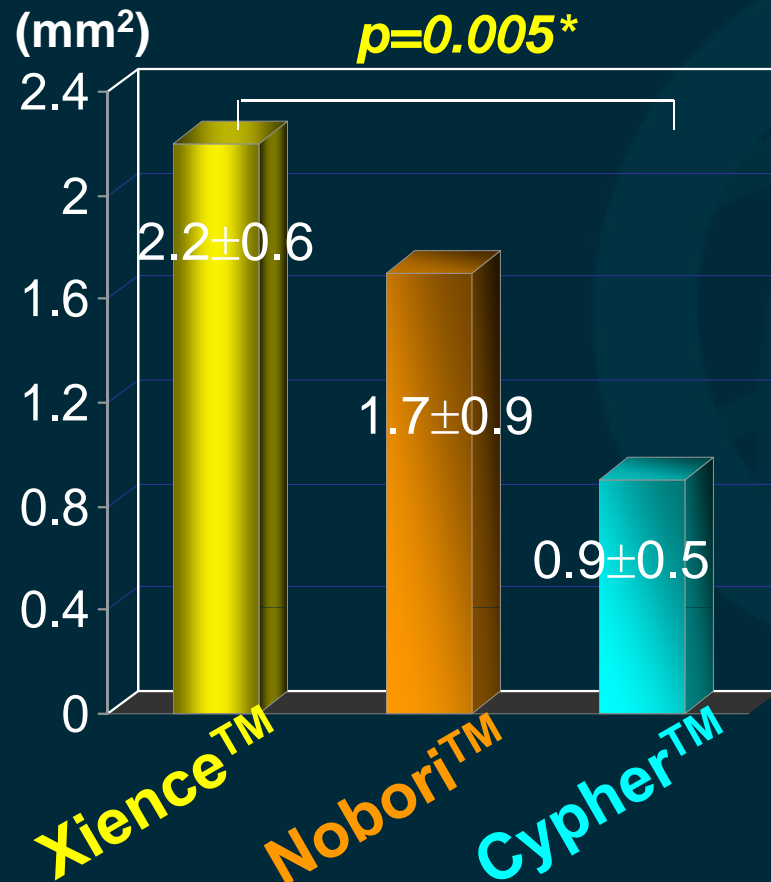


17 lesions available

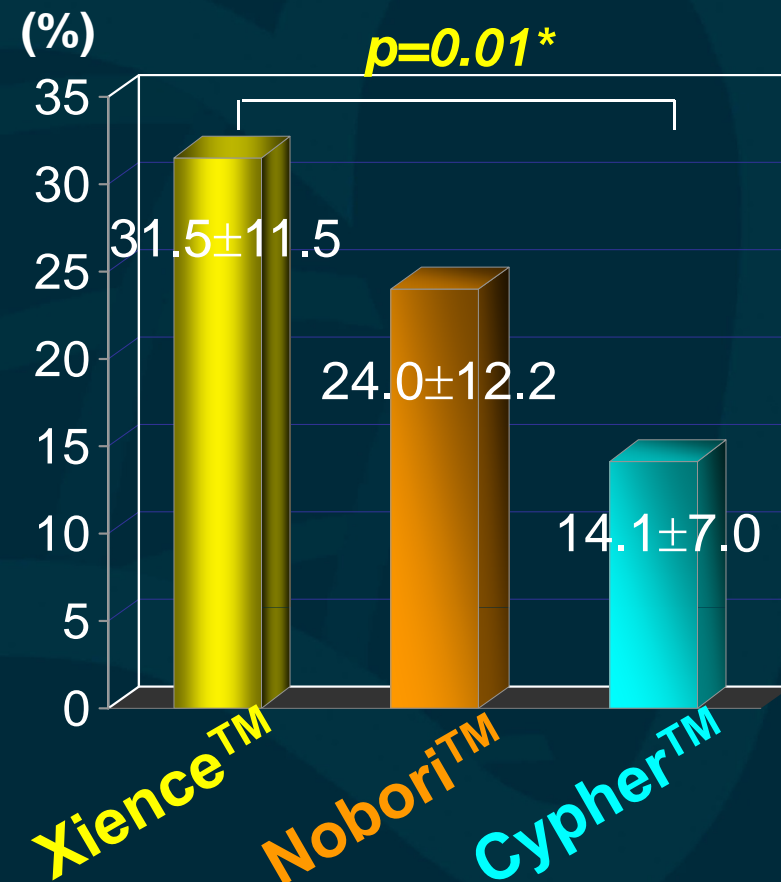
Follow-up OCT Results

~ Neointima proliferation ~

Average Neointimal Area



Average %Neointimal Area
(NIA /Stent area)

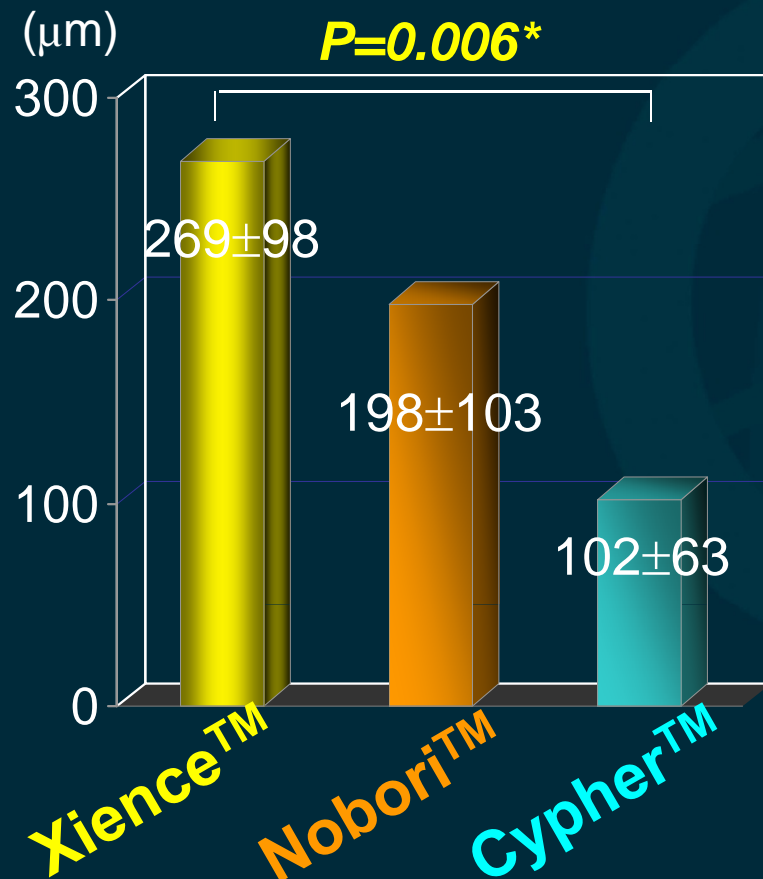


* Bonferoni/Dunn test

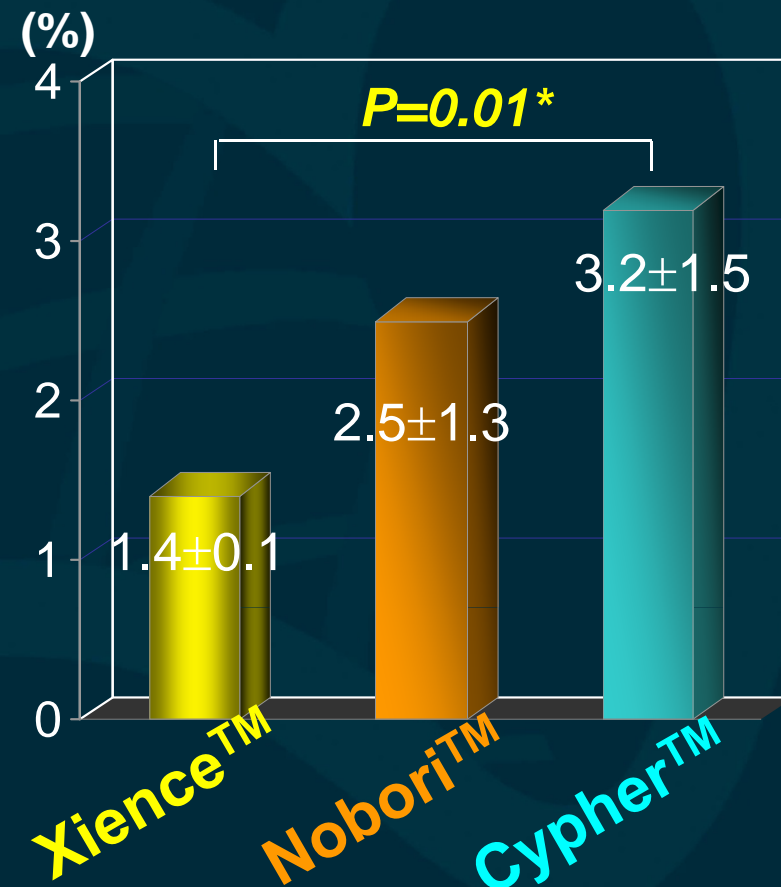
Follow-up OCT Results

~ Neointima proliferation ~

Average neointima thickness



Neointimal Unevenness Score



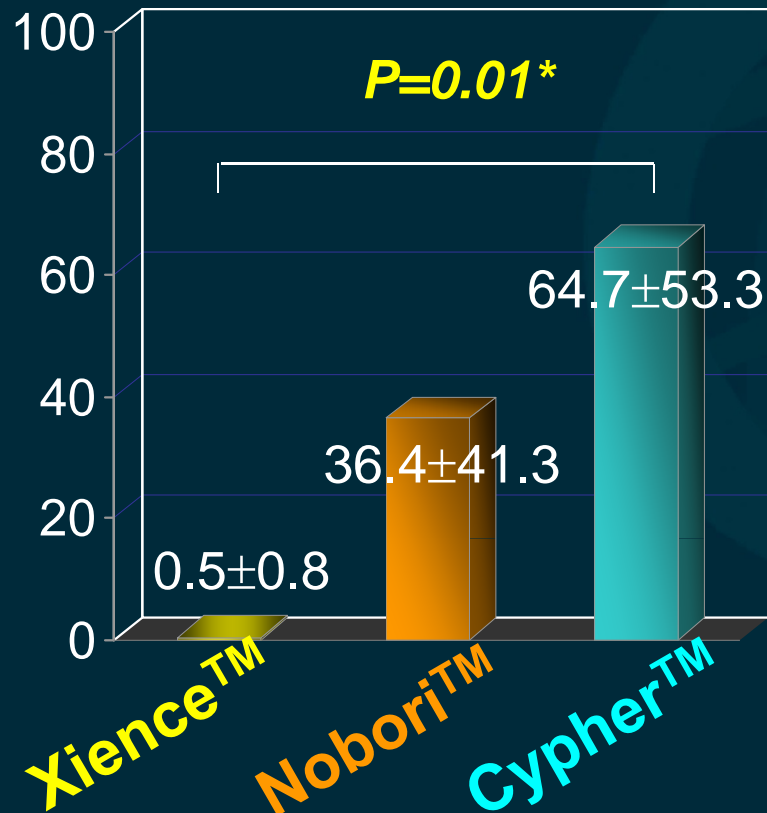
* Bonferoni/Dunn test

Follow-up OCT Results

~ Neointimal coverage ~

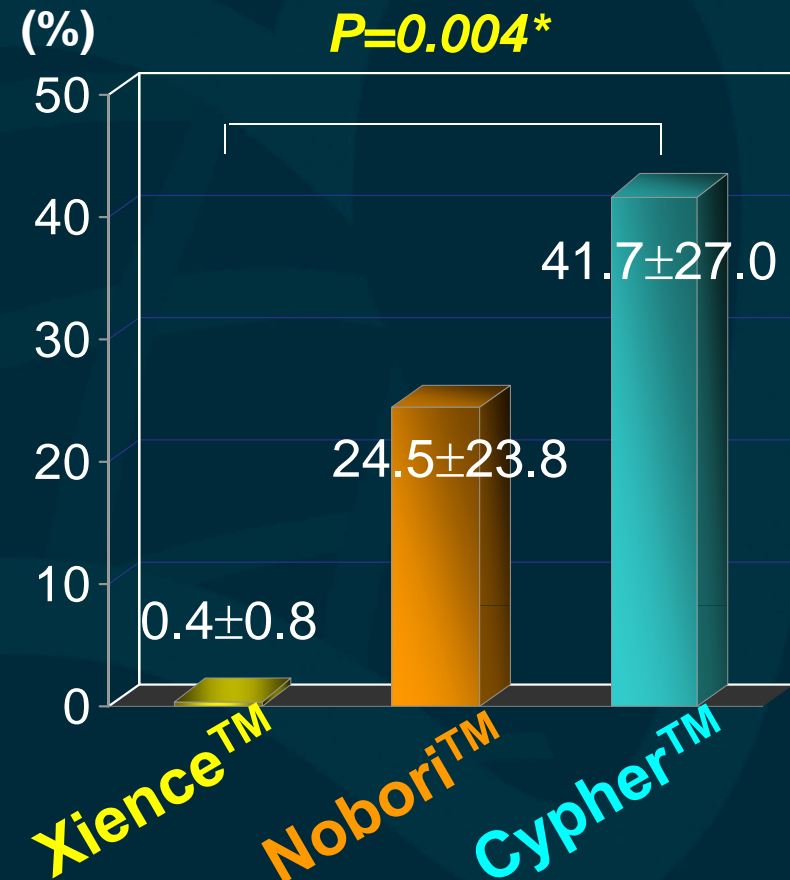
Number of
Uncovered struts

(/ stent)



%Uncovered Struts

(%)

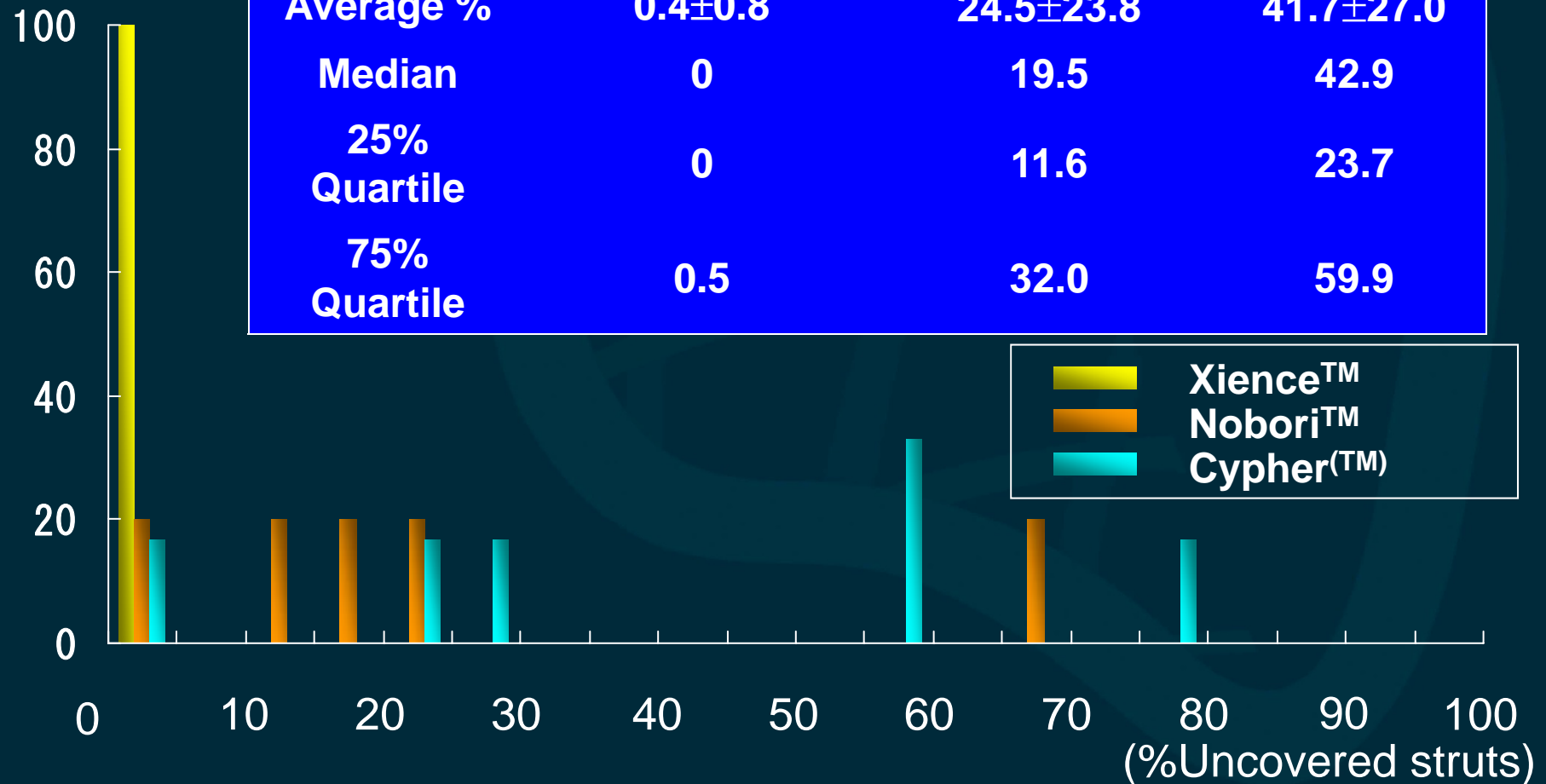


* Bonferoni/Dunn test

Histogram of %Uncovered struts

(No of Uncovered struts/ total no of struts)

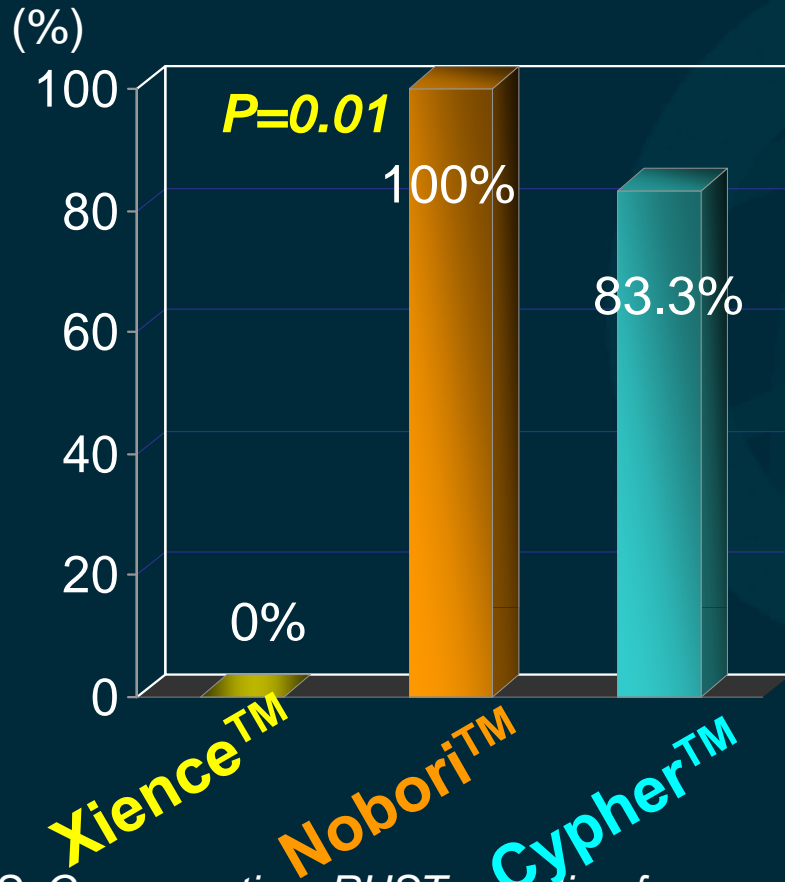
(% of lesions)



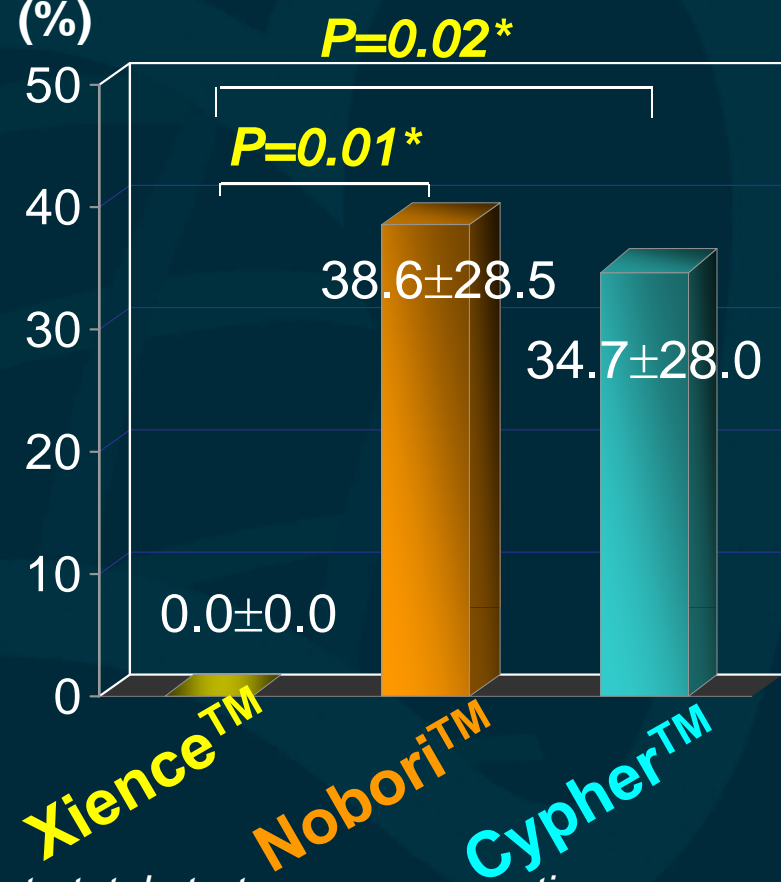
Follow-up OCT Results

~ Neointimal coverage ~

% of stents with at least 1 CS with RUST > 30%



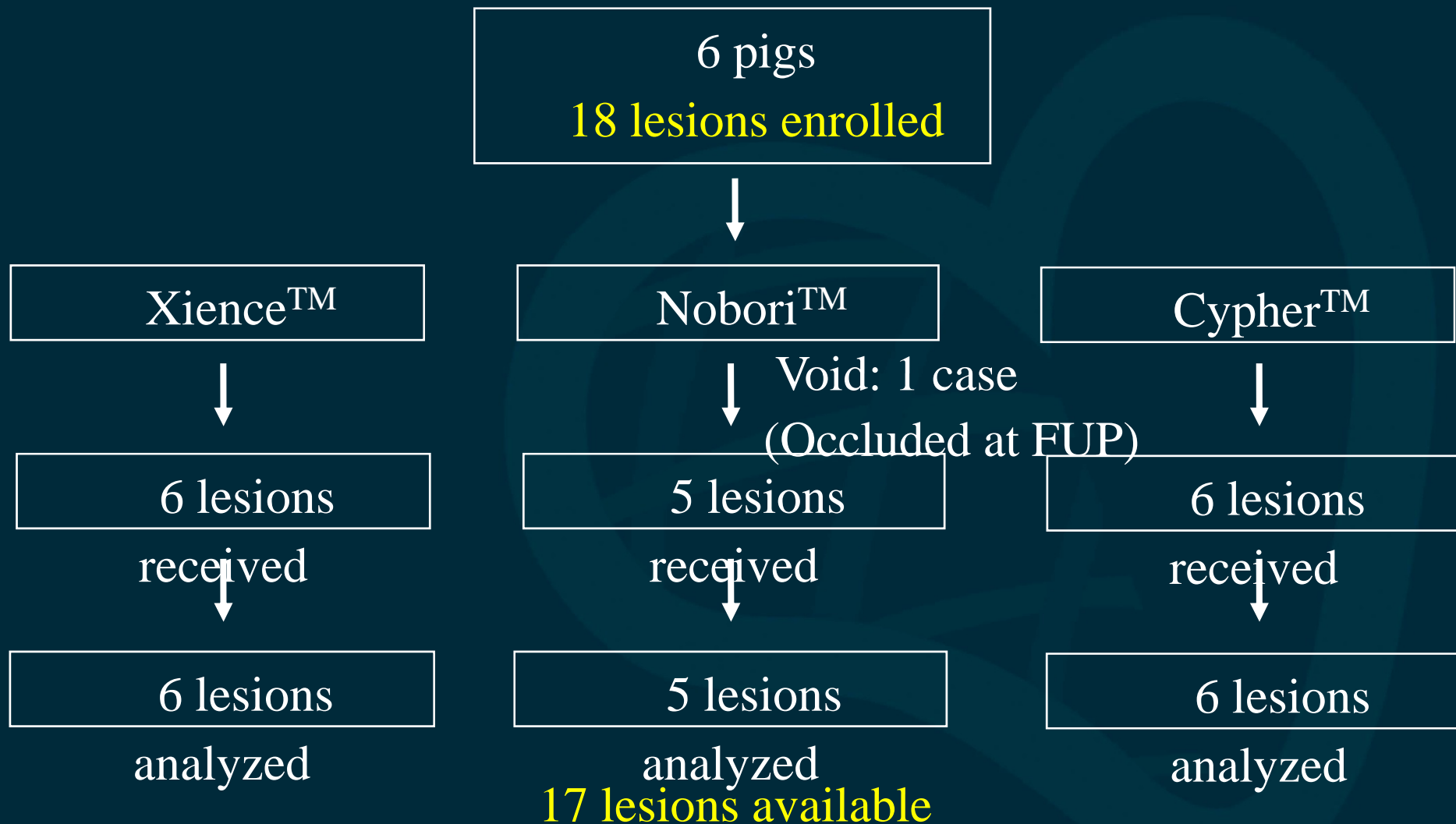
Average %CS with RUST > 30%



CS: Cross-section, RUST: a ratio of uncovered struts to total struts per cross section

* Bonferoni/Dunn test

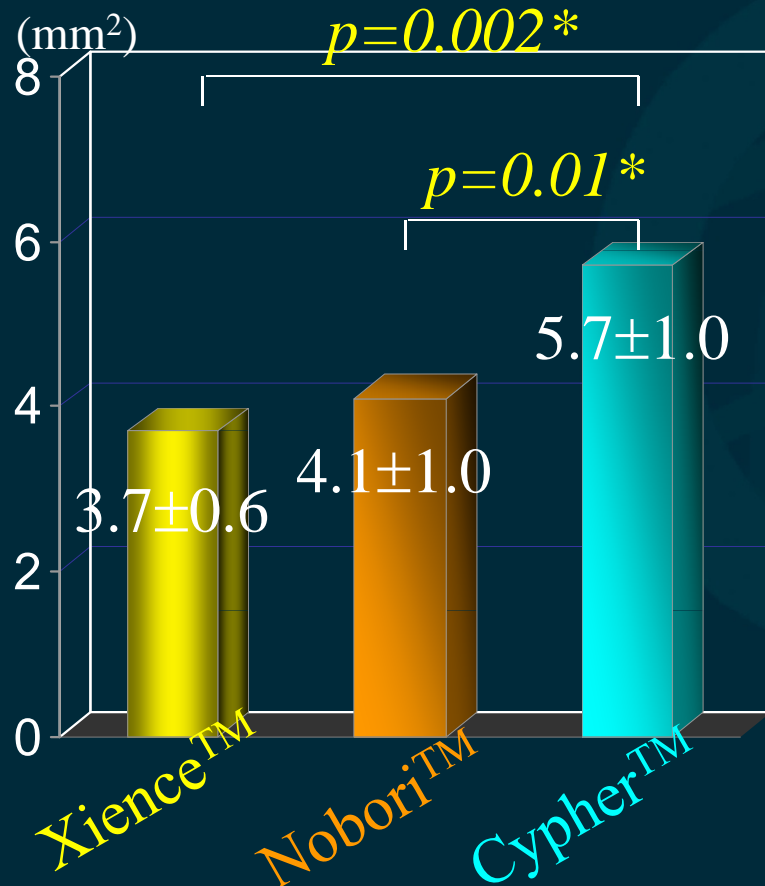
3-month group: OCT Analysis Status



Follow-up OCT Results @ 3 months

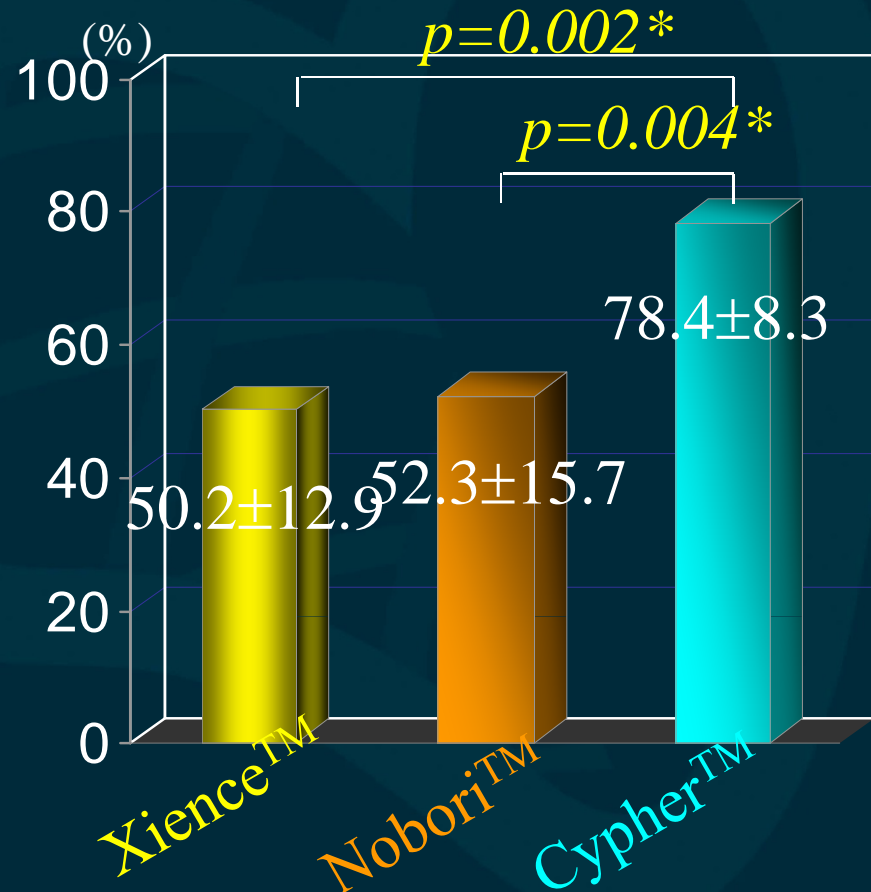
~ Neointima proliferation ~

Average Neointimal Area



Average %Neointimal Area

(NIA /Stent area)

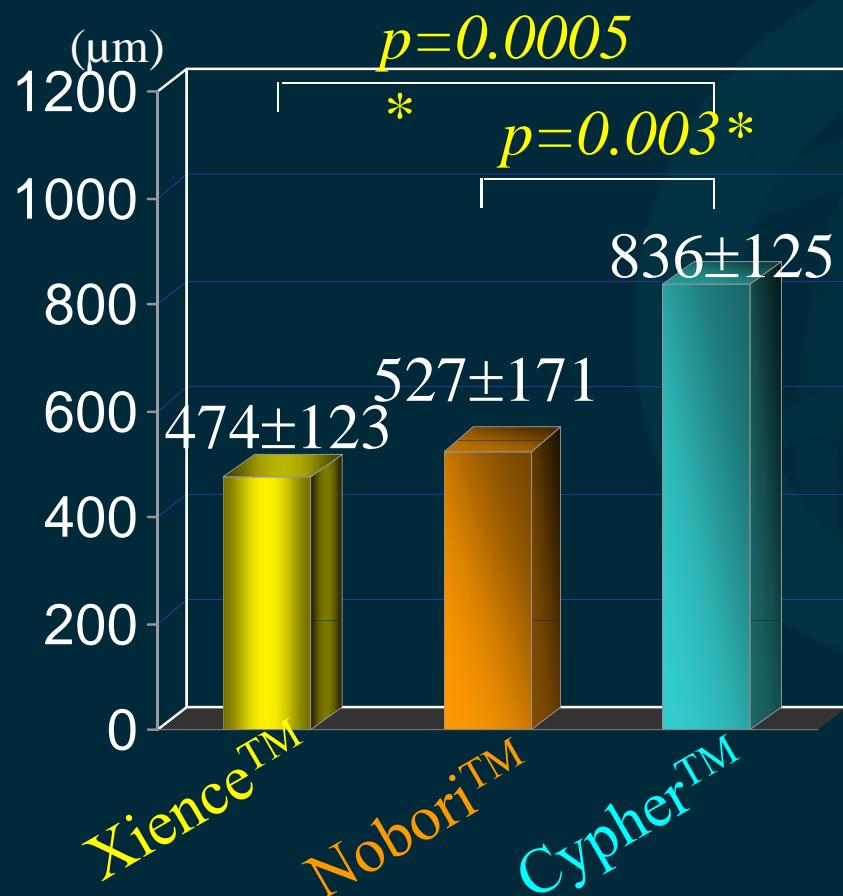


* Bonferoni/Dunn test

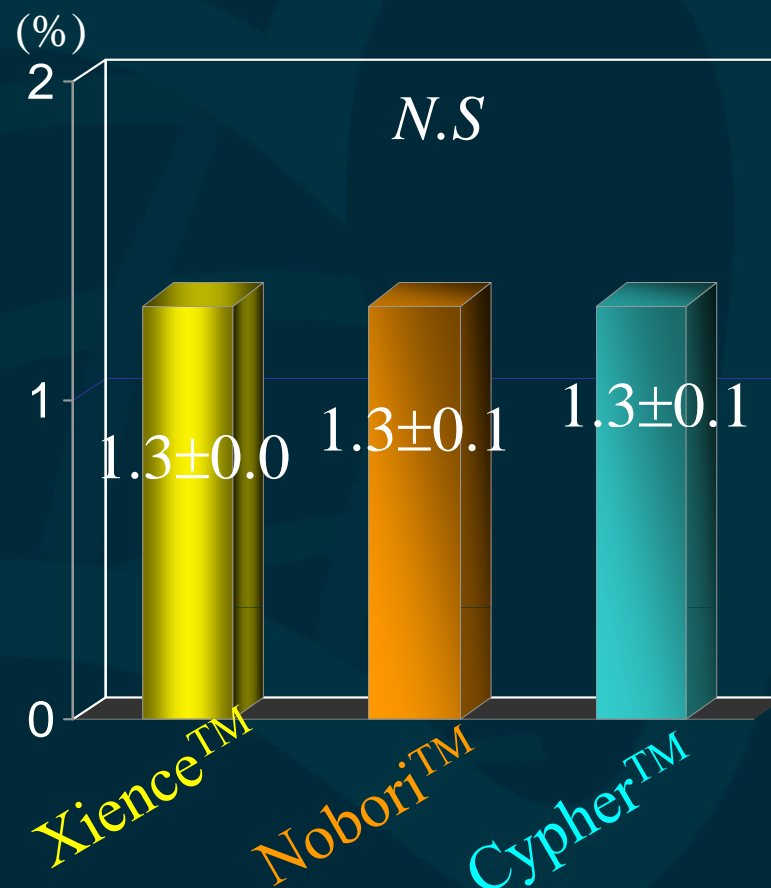
Follow-up OCT Results @ 3months

~ Neointima proliferation ~

Average Neointima Thickness



Neointimal Unevenness Score

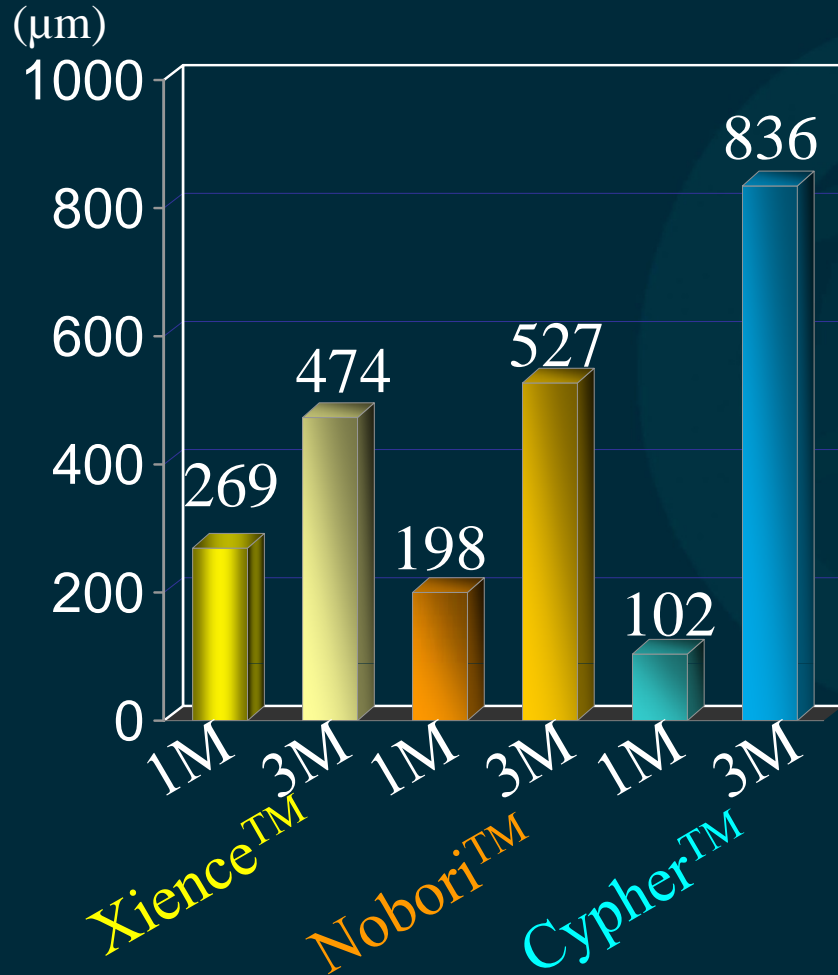


* Bonferoni/Dunn test

1- and 3-month OCT Results

~ Neointima proliferation ~

Average neointima thickness



Neointimal Unevenness Score



*Results from Histologic Analysis will
be coming soon...*

Summary

- Improvements of DES technology allow us to treat more complex patients
- Although we intuitively feel that DES with biodegradable polymer would be favorable, it is still not clear that those are clinically better than DESs with good durable polymers