# RES™ Technology

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# Surface-Coated Polymers on DES: A Necessary Evil?

Surface-coated polymers enables:

- Modulation of drug release, prevention of boost release
- Surface protection to minimize delivery-associated drug release
- Minimization of cytotoxicity of drugs with small therapeutic window

Issues with surface-coated polymers:

- Polymer webbing, chipping
- Limited mechanical strength
- Pro-inflammatory, associated with delayed healing and increased neointima formation
- Thrombogenic, associated with endothelial dysfunction

# Biodegradable polymers: The next step

## Biostable polymers

- pB-methylacrylate vinyl acetate (Cypher°)
- Triblock styrene (Taxus°)
- Fluoropolymer (Xience°)
- p-vinylpyrrolidone (Biolynx°)

**Biostable monomers can be harmful!**

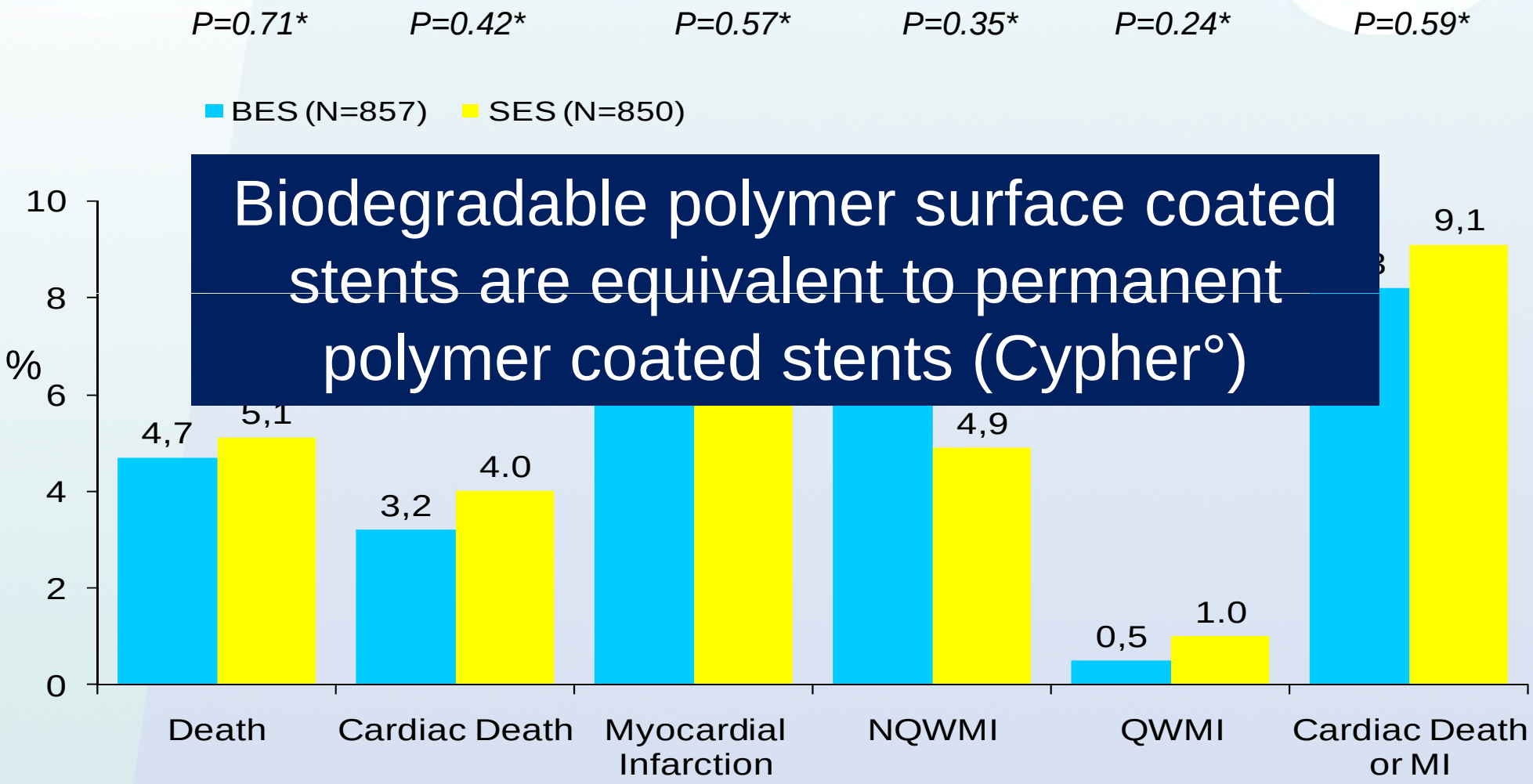
## Biodegradable polymers

- Poly(lactic acid)s and co-polymers >>>lactic acid and glycolic acid
- Poly(tyrosine carbonate)s >>>chemicals, metabolites and oligomers
- Polyanhydrides >>> chemicals
- Poly(orthoesters) >>> chemicals

**Are biodegradable polymers as effective and/or safe?**

# LEADERS Trial: 2-Year Safety Endpoints

*P values for superiority




Biodegradable polymer surface coated stents are equivalent to permanent polymer coated stents (Cypher®)

# Drug coated stent without polymer: Not efficacious?

1. **Drug « coated » stent (polymer free stent):**

- Clinical results with paclitaxel (Deliver, Elutes, Aspect trials) similar to BMS
- Microporous surface: Yukon DES, Translumina:

➢ PF* SES non inferior to Taxus (ISAR-TEST), but late catch-up (Ruef et al.)

➢ Dual-DES non inferior to Cypher or Xience (ISAR-TEST-2), BP° non inferior to Cypher (ISAR-TEST-3 & ISAR-TEST-4)

2. **Non surface coated stent:**

- Reservoir Technology: NEVO™ (Cordis J&J)
- Tubular struts with microholes (Medtronic)

* Polymer Free, ° Biodegradable Polymer

# Polymer free stents: the storybook

## *1. DELIVER trial: PTX polymer free coated stent vs BMS*

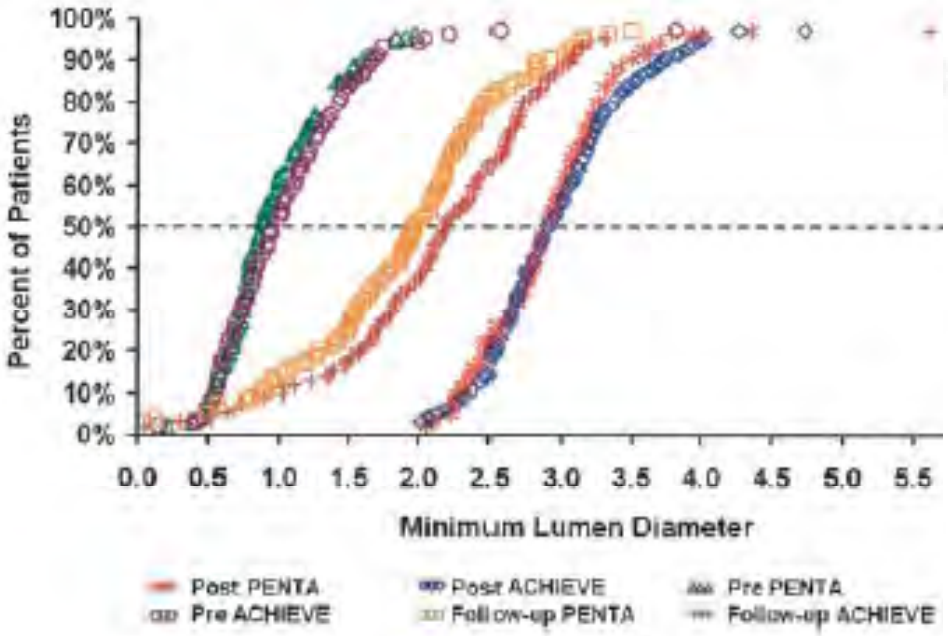



**Figure 2.** In-stent cumulative distribution curve for minimum lumen diameter (MLD).

**TABLE 3. Acute Gain, Late Loss, and Binary Restenosis in the Angiographic Substudy**

| | ACHIEVE (n=228) | ML PENTA (n=214) | *P* |
|---|---|---|---|
| Acute gain, mm | | | |
| In-stent | 1.91±0.51 | 1.91±0.41 | 1.0 |
| Segment | 1.41±0.54 | 1.42±0.48 | 0.8 |
| Late loss, mm | | | |
| In-stent | 0.81±0.60 | 0.98±0.57 | 0.0025 |
| Segment | 0.43±0.57 | 0.56±0.59 | 0.01 |
| Proximal margin | 0.28±0.57 | 0.31±0.57 | 0.6 |
| Distal margin | 0.11±0.49 | 0.18±0.54 | 0.15 |
| Binary restenosis, % | | | |
| In-stent | 14.9 | 20.6 | 0.076 |
| Segment | 16.7 | 22.4 | 0.08 |
| Proximal margin | 4.4 | 5.6 | 0.7 |
| Distal margin | 2.2 | 4.2 | 0.3 |

Lansky A et al Circulation.2004;109:1948-54

# Polymer free stents: the storybook

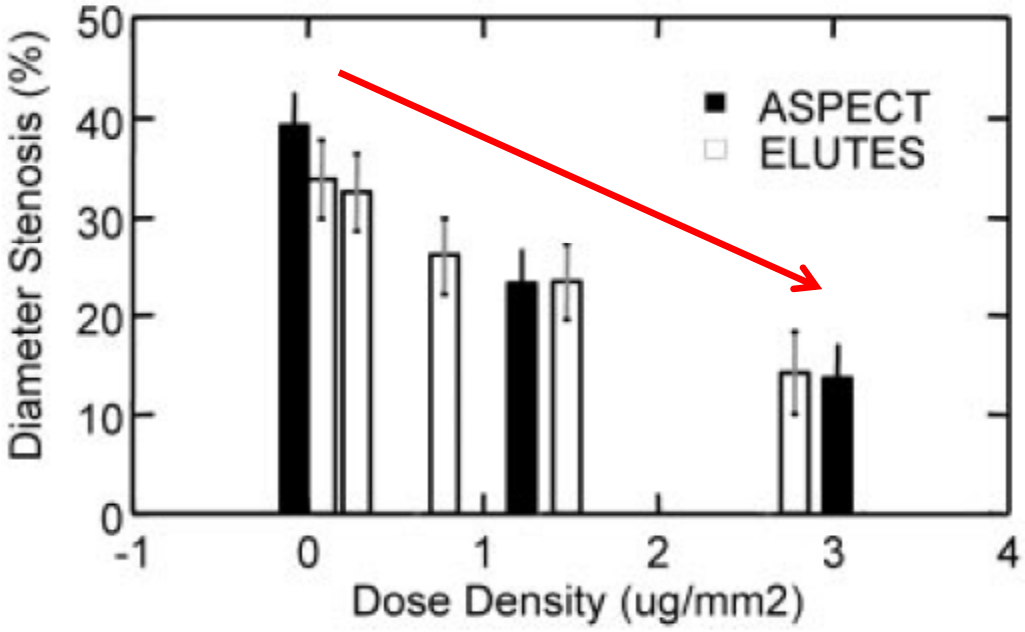
## *2. ELUTES trial: PTX polymer free coated stent dose evaluation study*

**TABLE 3. Cumulative MACE at 12 Months**

| | Paclitaxel Dose Density, μg/mm² | | | | | |
|---|---|---|---|---|---|---|
| | 0 (Control; n=38) | 0.2 (n=37) | 0.7 (n=39) | 1.4 (n=39) | 2.7 (n=37) | *P** |
| Death | 0 | 0 | 0 | 0 | 1 | NS |
| Q-wave MI | 0 | 0 | 0 | 0 | 0 | NS |
| SAT | 1 | 0 | 0 | 0 | 1 | NS |
| Non–Q-wave MI | 0 | 0 | 1 | 0 | 1 | NS |
| Total TLR | 6 | 2 | 2 | 4 | 2 | NS |
| CABG | 1 | 0 | 1 | 0 | 0 | |
| PCI | 5 | 2 | 1 | 4 | 2 | |
| Event-free, % | 82 | 95 | 92 | 90 | 86 | 0.754 |

SAT indicates subacute thrombosis.

**Combined results for%DS from ELUTES and ASPECT as a function of dose density**

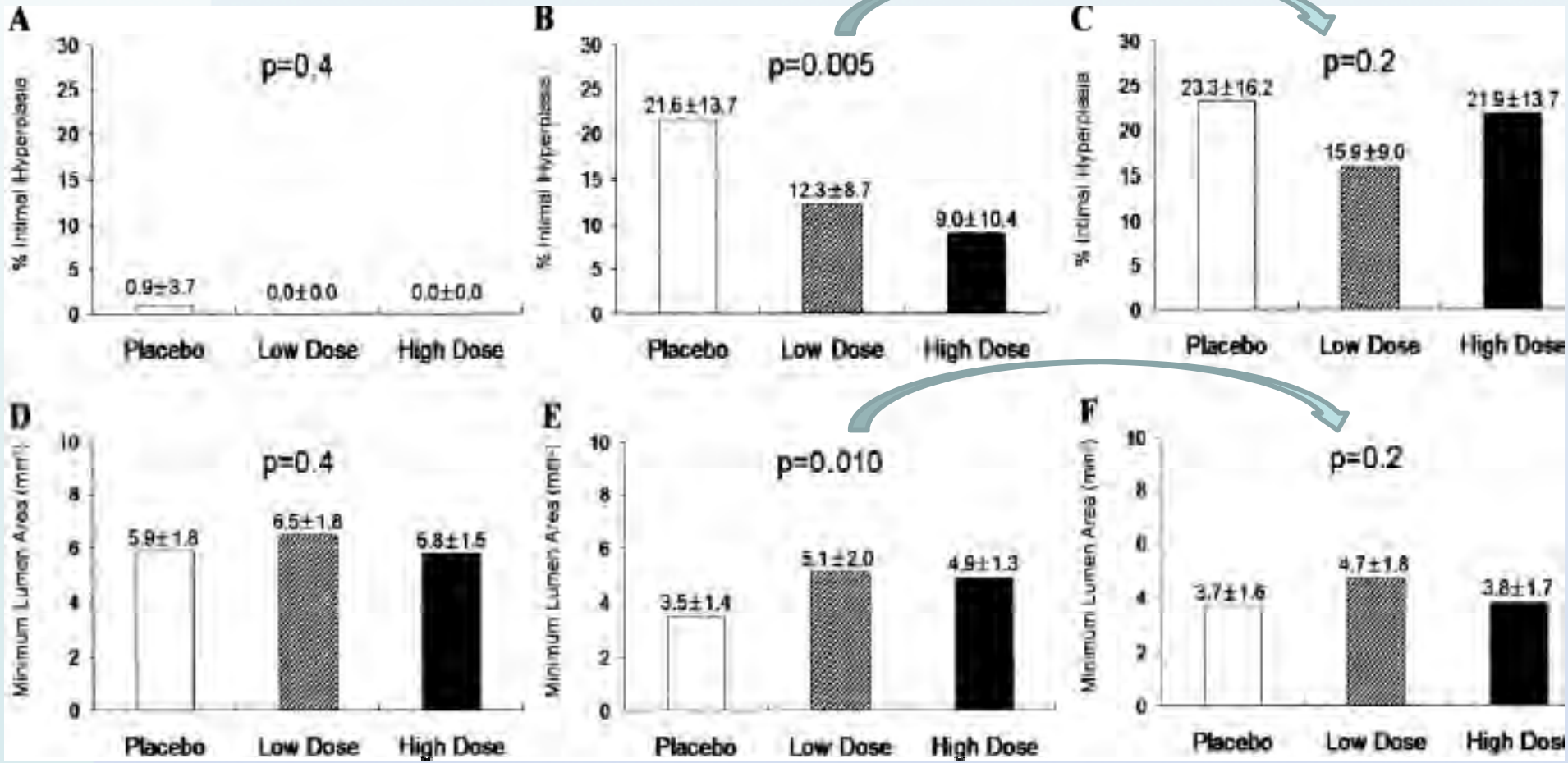



Gershlick A et al Circulation.2004;109: 487-493

# Polymer free stents: the storybook

## *3. ASPECT trial: PTX polymer free coated stent vs BMS*

**Post PCI** **@ 6 months** **@ 24 months**




Park DW et al JACC.2006: 48; 2432-9.

# Non surface coated stent: The solution?

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2. **Non surface coated stent:**

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* Polymer Free, ° Biodegradable Polymer

# What Is Reservoir Technology?

## Surface-Coated Stents

- Polymer coating can crack or peel during stent delivery
- Struts completely covered with polymer → *Potential toxicity*
- Permanent polymer exposure → *potential contributor to VLST*[1]
- Drug is eluted from both vessel-wall and lumen-facing sides of stent.

## NEVO™

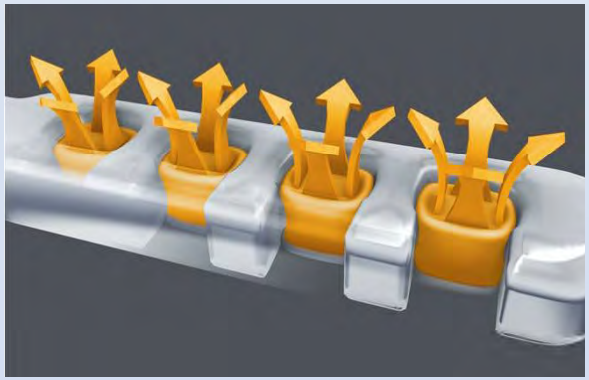
- Polymer is protected within the reservoirs
- No polymer on the surface
- Polymer is bioabsorbed in as little as 90 days
- Controlled drug delivery preferentially to the vessel wall

NEVO will utilize RES technology to deliver sirolimus, the most proven drug

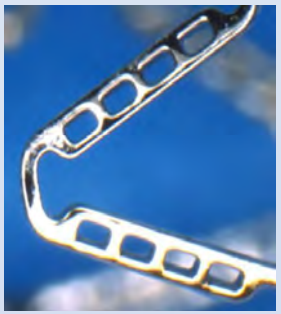
Wessely R. The relationship between stent components and safety: from intervention to long-term prognosis. Cardiac & Vascular Update 2010;2:4-9

# NEVO™: An Innovative Stent Concept Beyond Surface-Coated Stents

| During Implantation | Post-implantation | Long Term |
|---|---|---|
| **Designed to deliver as a BMS** | **Designed for controlled drug delivery** | **Designed to transform to a BMS in ~90 days** |



Day 1

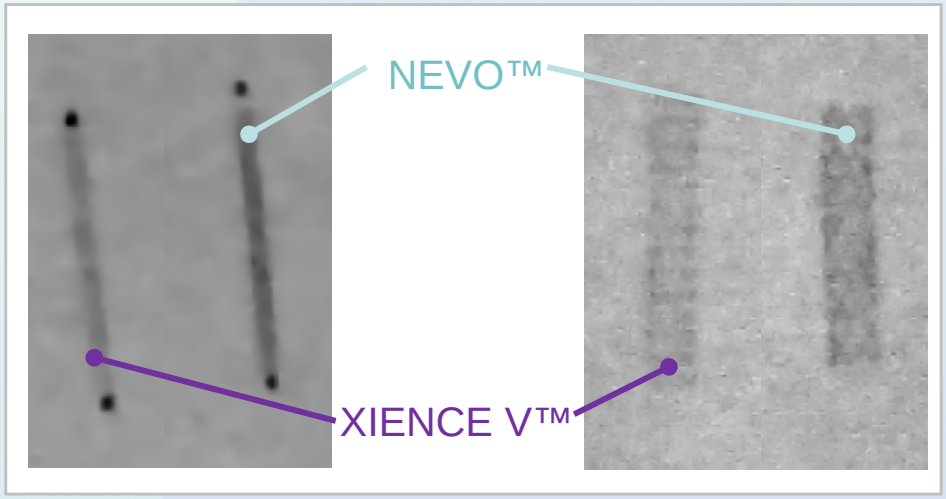


Day 90

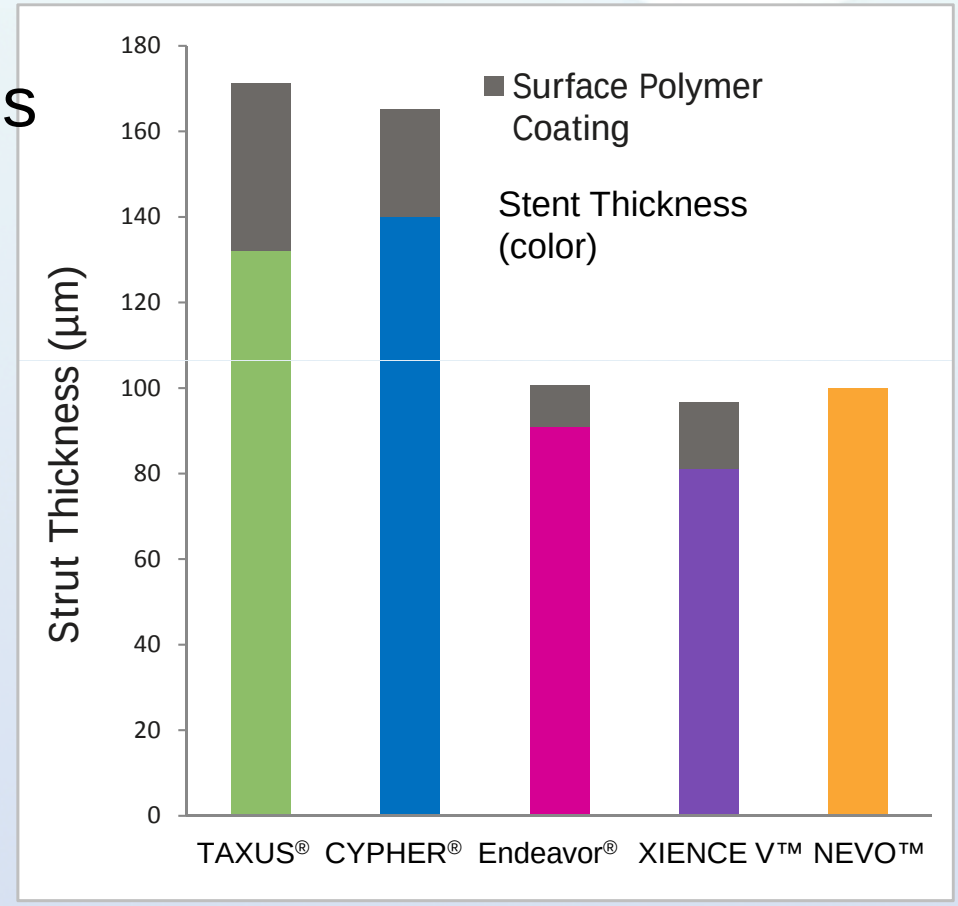
# The NEVO™ Platform: Fluoroscopic Radiopacity and Strut Thickness

## Balanced Performance Features

- Improved radiopacity
- Better radial strength
- Low recoil




**COMPARISON OF RADIOPACITY**

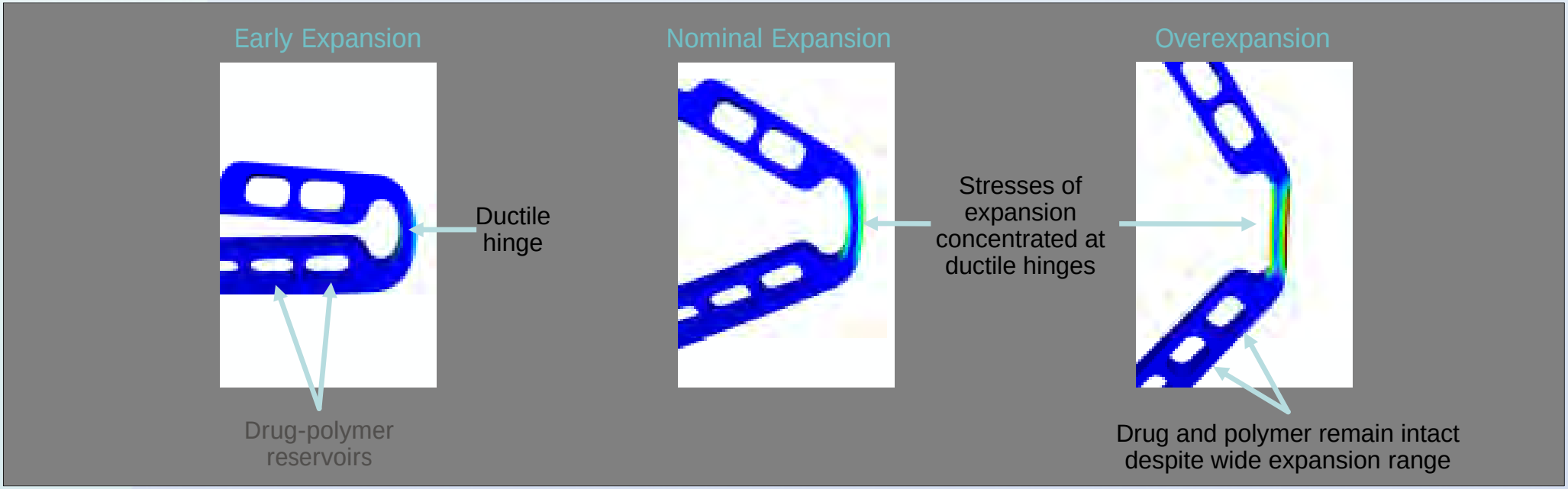



**COMPARISON OF STRUT THICKNESS**

# NEVO™ is Designed to be Highly Fracture Resistant

## NEVO™ incorporates ductile hinges to:

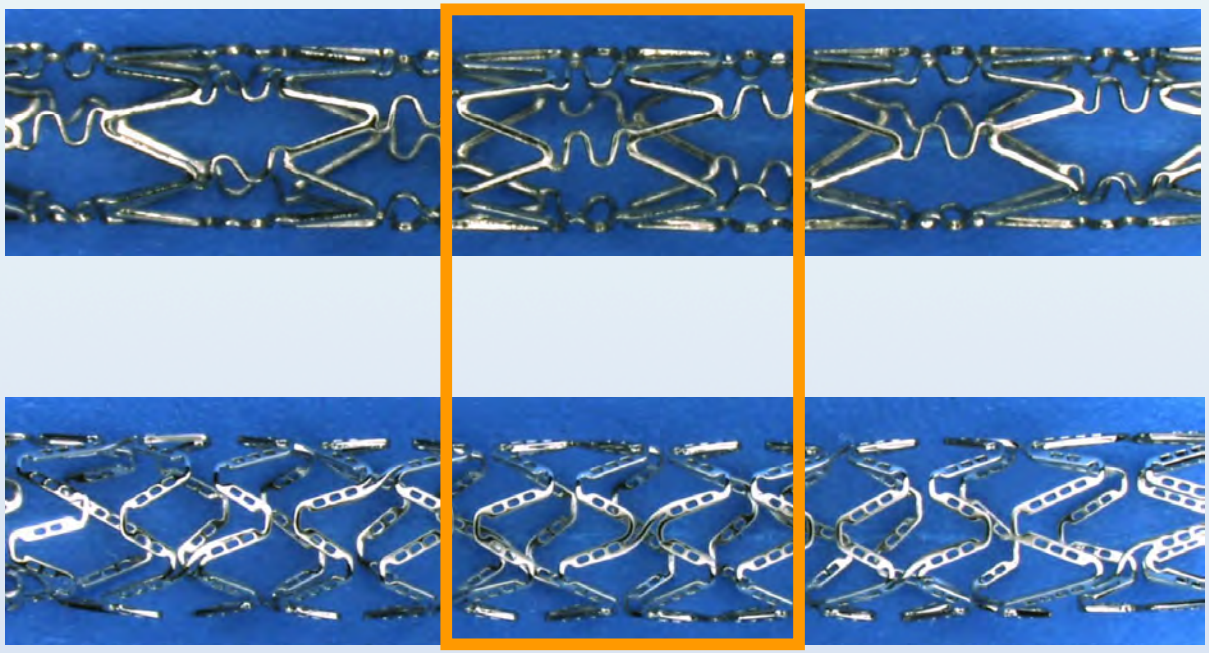
- Absorb expansion forces and pulsatile energy
- Maintain reservoir integrity
- Retain proper orientation of stent against artery wall[1]
- Resist fractures[2]



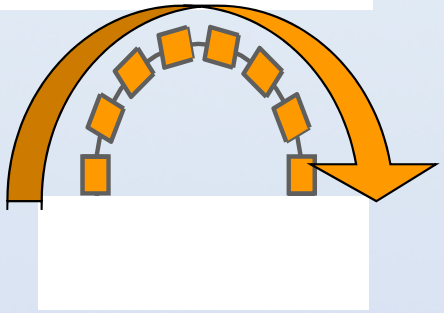

1. Overlapping stents implanted in porcine coronary arteries. Data on file, Cordis Corp.

# NEVO™ Technology
## Flexibility & Conformability

**CYPHER®**



**NEVO™**



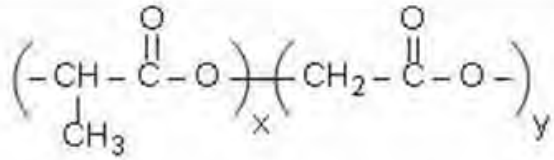


A tighter repeating pattern & open architecture are key design parameters behind NEVO's optimized flexibility & conformability.

# RES Technology utilizes a Fully Bioabsorbable PLGA Polymer


Data taken with NEVO™ stent utilizing RES TECHNOLOGY™

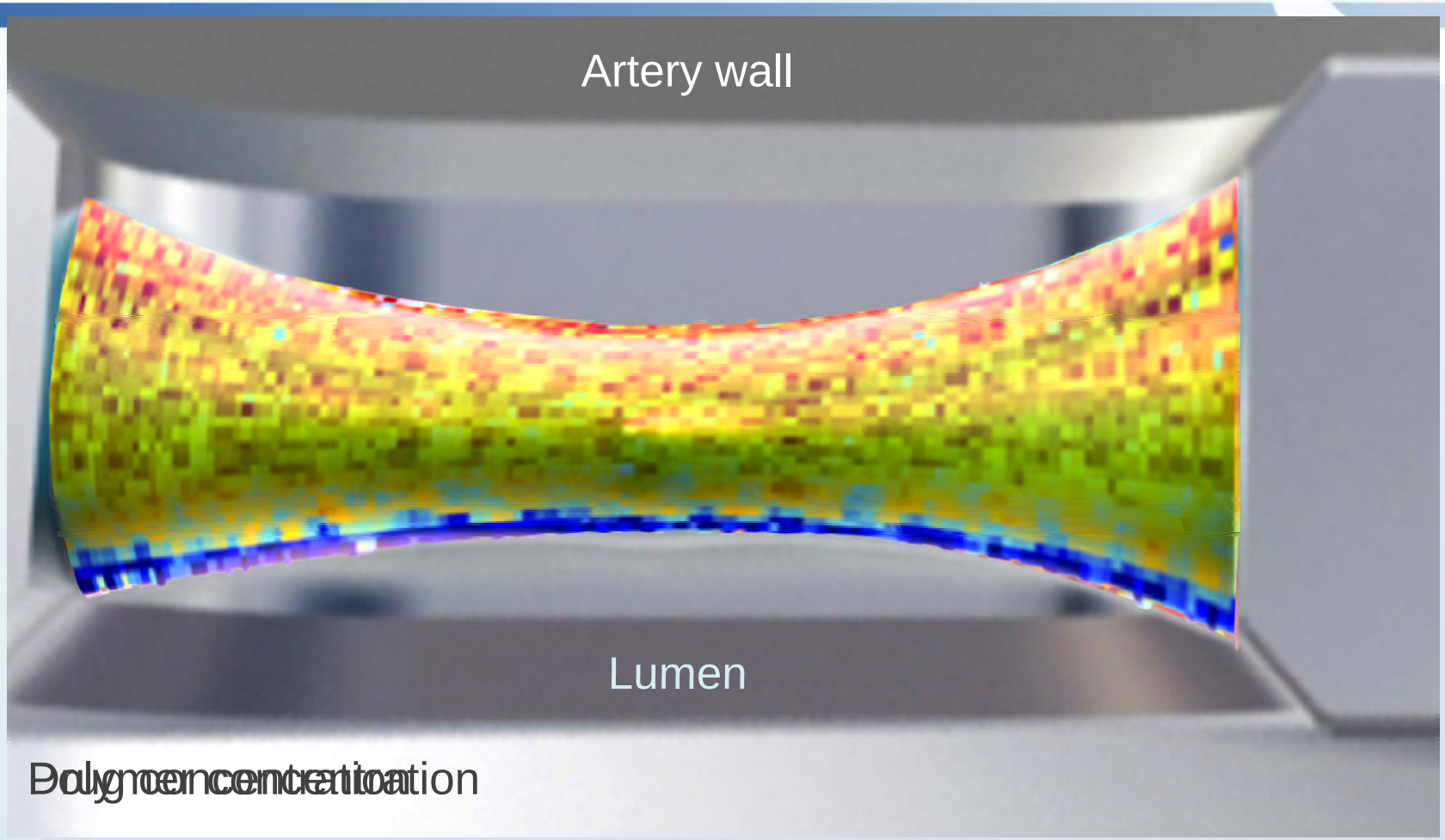
## Fully bioabsorbable PLGA polymer



- Used in a variety of medical applications such as VICRYL™ sutures[1]
- Highly biocompatible
- Fully metabolized bioproducts ($CO_2$ + $H_2O$)
- Designed for complete bioabsorption so that RES TECHNOLOGY™ stents transform into BMS

Falotico R et al. *EuroIntervention.* 2009;5(suppl F):F88-F93.

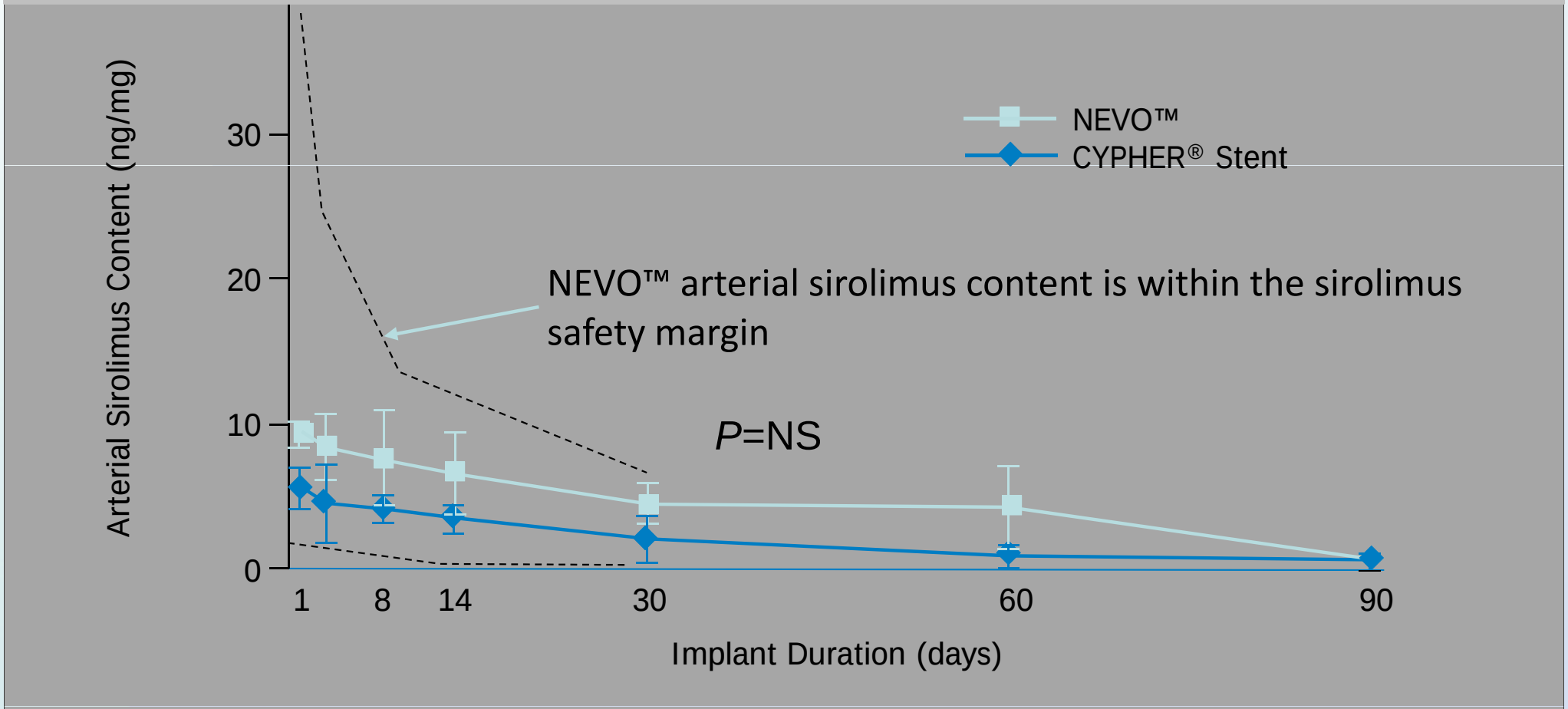
# NEVO™ Reservoirs are Designed for Directional Sirolimus Release to the Artery Wall




Balss, Chisholm, Maryanoff. Internal data on file. Cordis Corp.

# NEVO™ Yields Controlled and Sustained Arterial Sirolimus Levels

## NEVO ELUTION PROFILE ENSURES OPTIMAL SUPPRESSION OF INFLAMMATION AND NEOINTIMAL TISSUE FORMATION




1. Falotico R et al. *EuroIntervention.* 2009;5(suppl F):F88-F93.

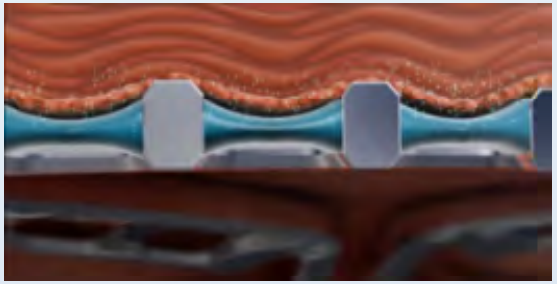
# NEVO™ Sirolimus-Eluting Stent

## CoCr stent platform

- Flexible, conformable, thin struts, maximized vessel coverage, open cell design

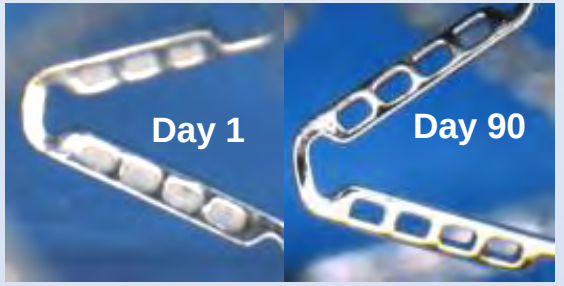
## Reservoir technology

- Drug and polymer recessed within reservoirs in the stent strut - no surface-coating.
- Reduced vessel wall – polymer contact



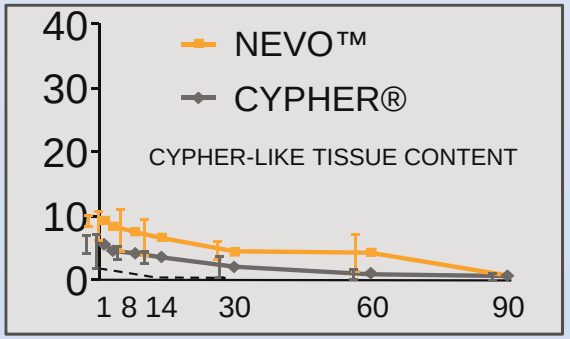
## Bioabsorbable polymer

- Designed for complete bioabsorption in as little as 90 days

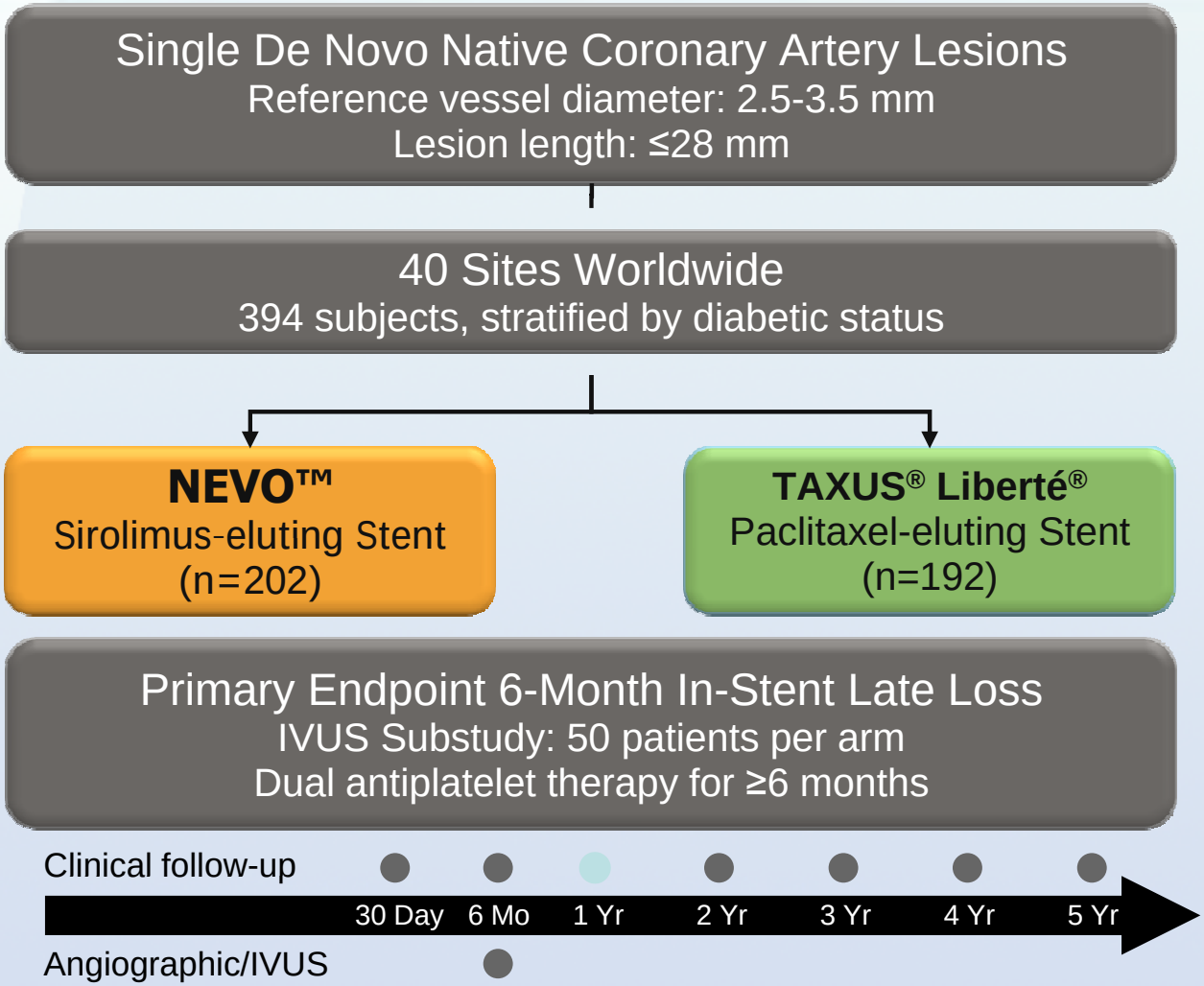



## Proven Sirolimus Evidence

- CYPHER®-like tissue content
- Largest body of evidence with safety data out to 10 years



# NEVO RES-I Study Overview




89.3% Angiographic follow-up; 94.7% 360-day clinical follow-up

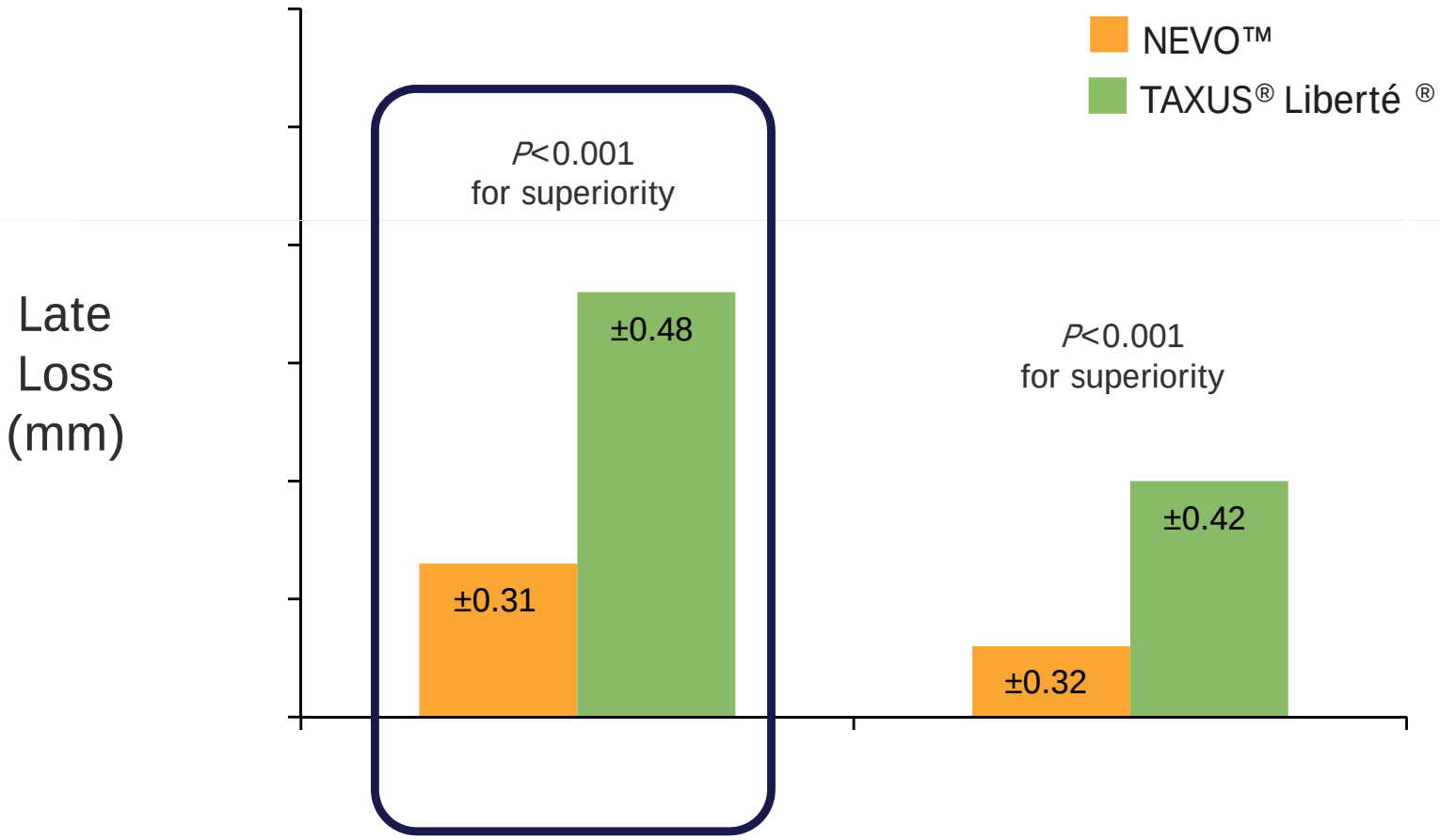
**Principal Investigators**
John Ormiston
Alexandre Abizaid
Christian Spaulding

*TLF = Target Lesion Failure
**IVUS=intravascular ultrasound
.

EuroPCR 2009, oral presentation, Chr. Spaulding

# NEVO RES-I: Primary Endpoint – Late Lumen Loss at 6 Months

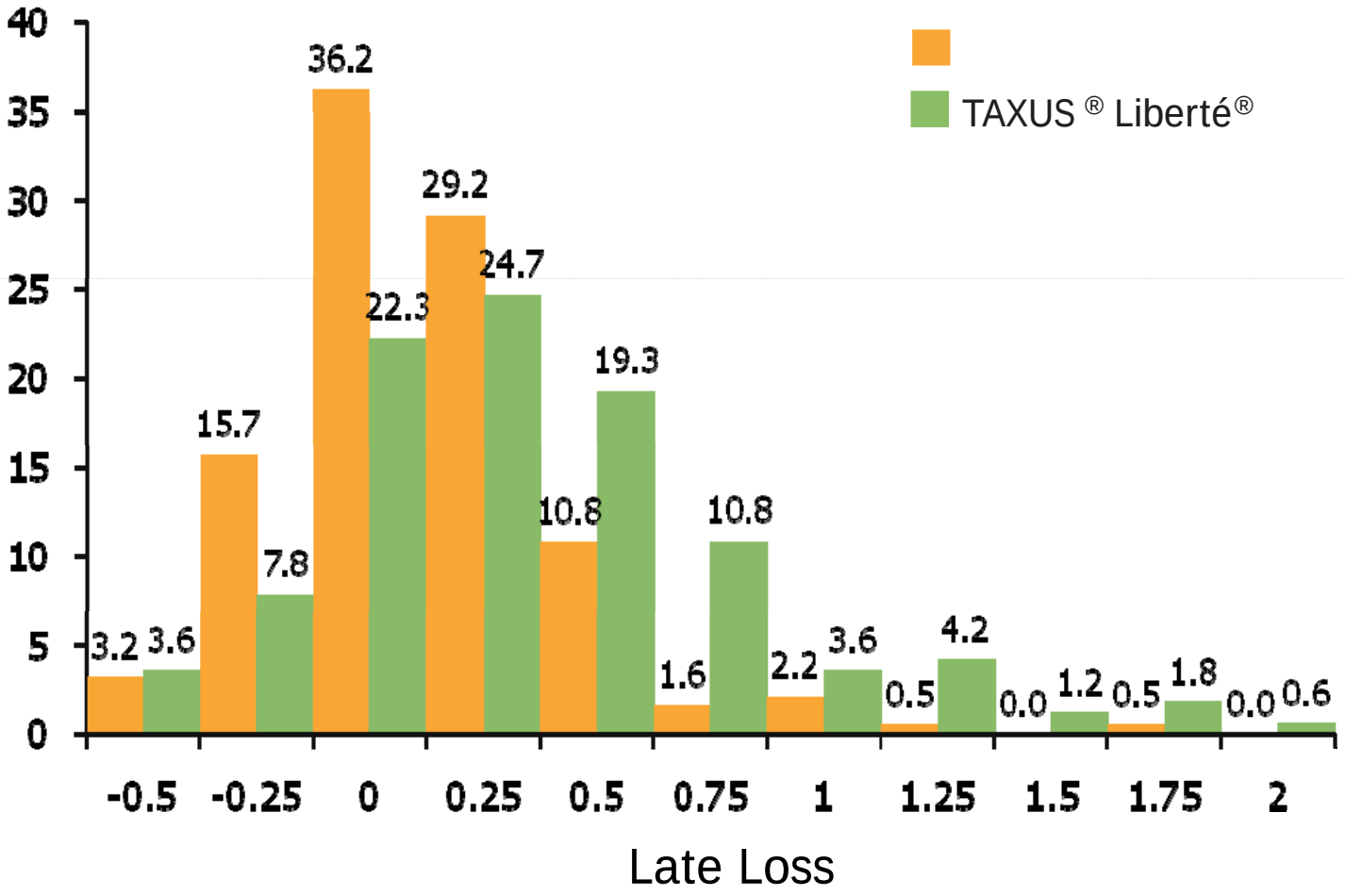
## PRIMARY ENDPOINT: LATE LUMEN LOSS AT 6 MONTHS




TCT 2009, oral presentation, J. Ormiston.

# NEVO RES-I: Distribution of In-Stent Late Loss

## DISTRIBUTION OF IN-STENT LATE LOSS

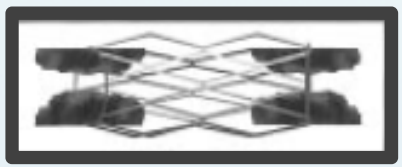


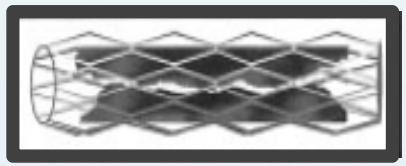

Data reflect completed 6 months follow-up, core lab, and CEC adjudication.
TCT 09, Oral presentation, J. Ormiston

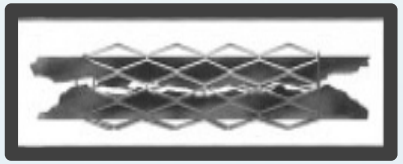
# NEVO RES-I:
# In-Stent Restenosis Pattern at 6 Months

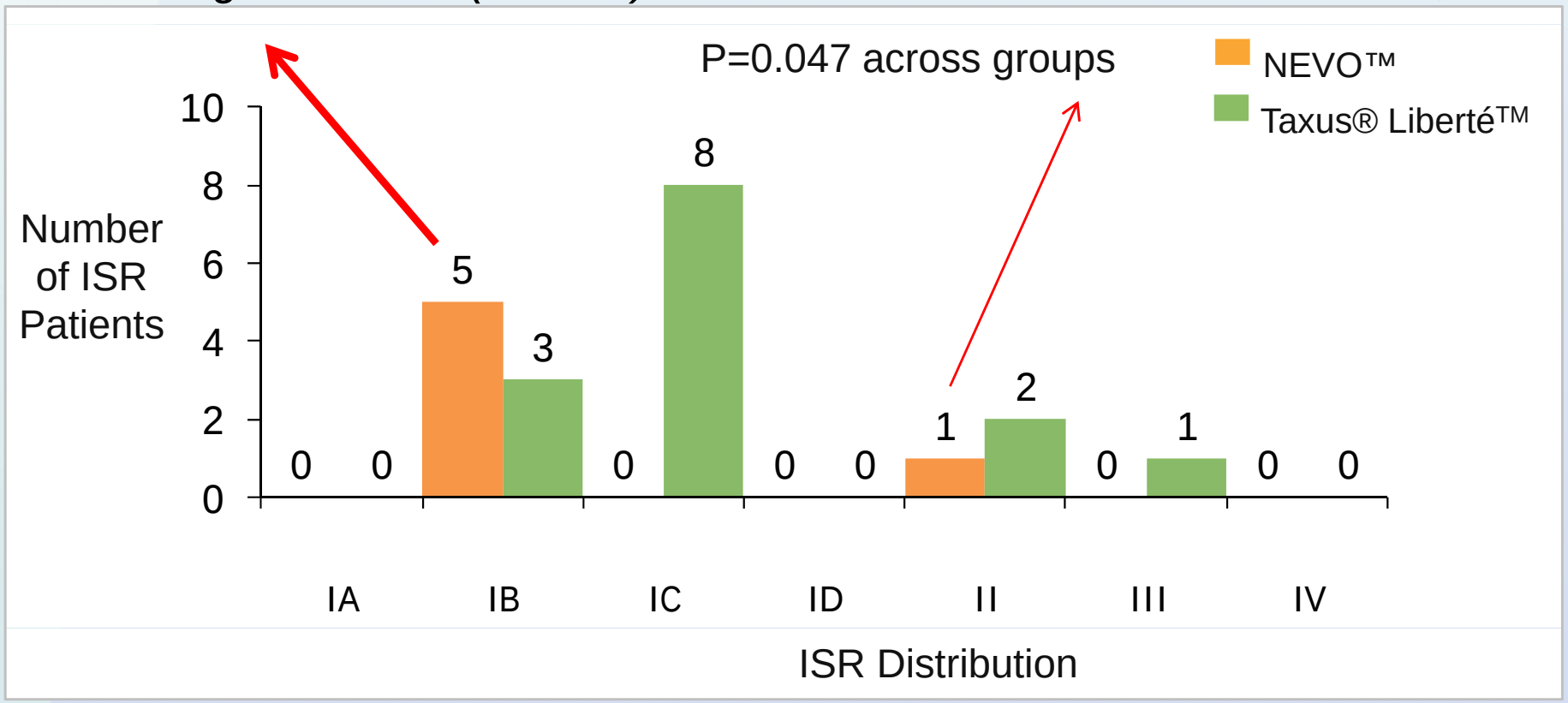

*Type IB: (Focal) < 10 mm at edge*


*Type IC: (Focal) < 10 mm (in-stent)*


*Type ID: Multi-Focal ISR*


*Type II: Diffuse In-stent*

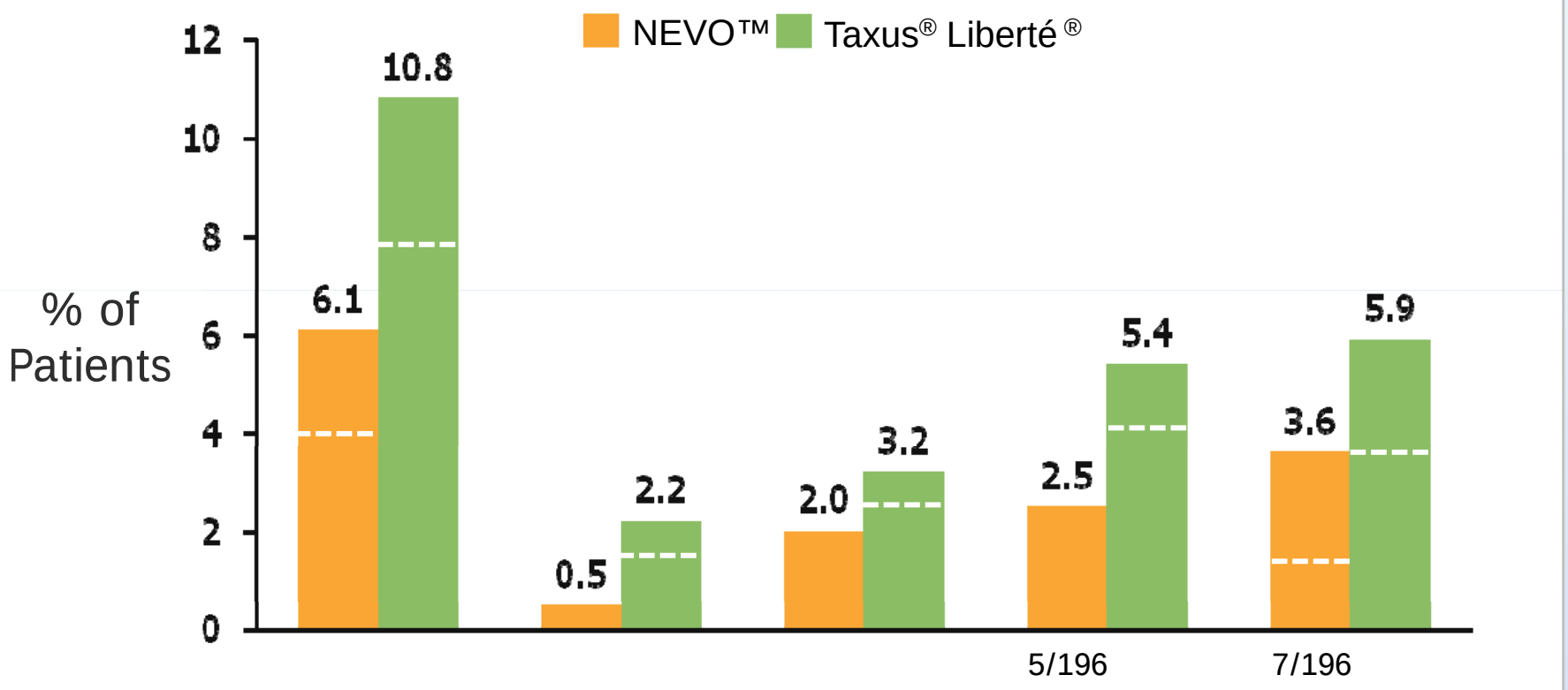

*Type III: Diffuse, Proliferative*




Abizaid A., et al., EuroPCR 2010; Oral Presentation.

# NEVO RES-I: 12-month MACE and Components

12-MONTH MACE AND COMPONENTS

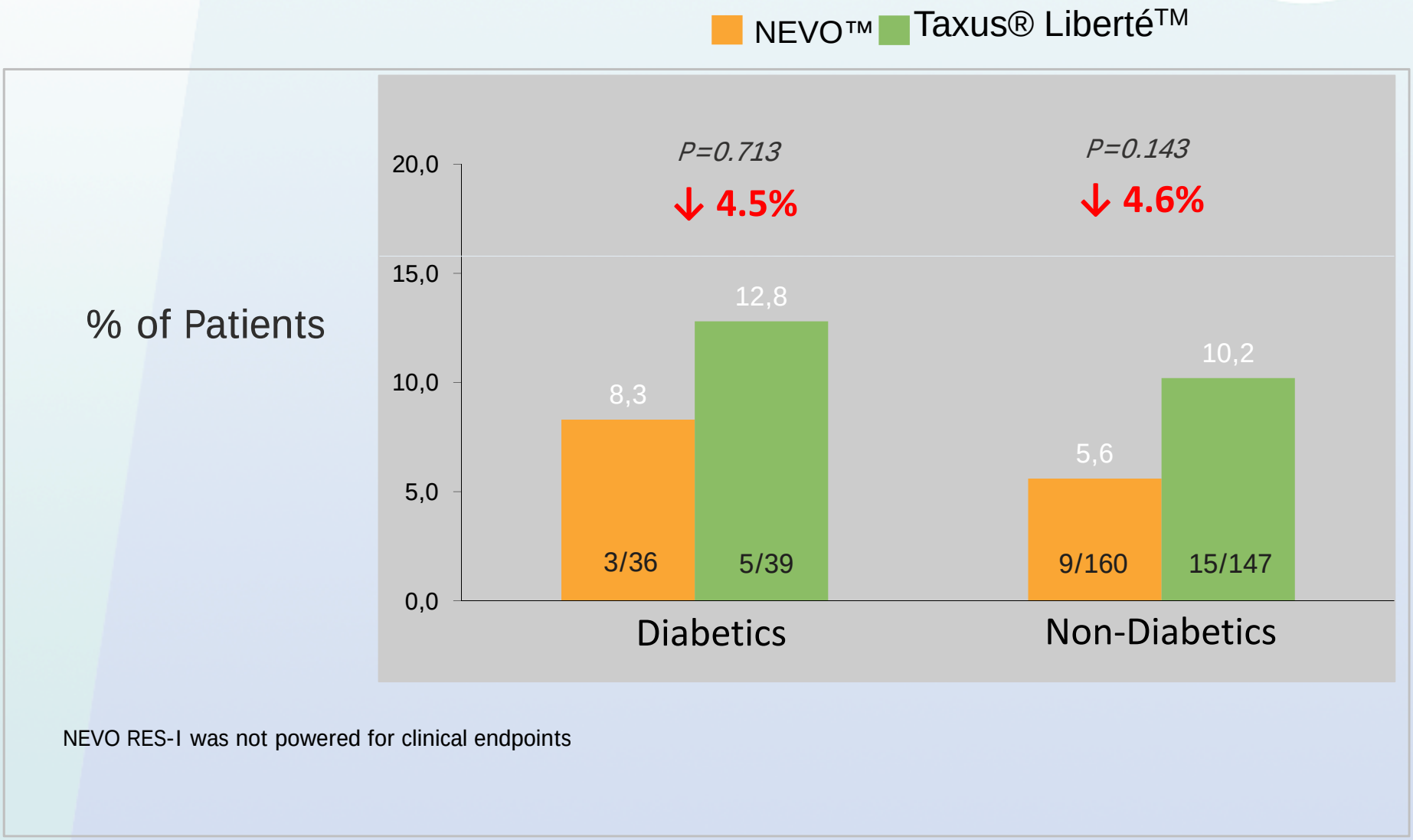



No reports of death or MI between 6 and 12 months in NEVO arm

NEVO RES-I was not powered for clinical endpoints
MACE=Major adverse cardiac events.

Abizaid A., et al., EuroPCR 2010; Oral Presentation.

# NEVO RES-I: Diabetic Subgroup – 12-Mth MACE




NEVO RES-I was not powered for clinical endpoints

Abizaid A., et al., EuroPCR 2010; Oral Presentation.

# NEVO RES-I: ARC Stent Thrombosis Through 12 Months

| | NEVO™ (n=202) | TAXUS® Liberté® (n=192) | *P* Value |
|---|---|---|---|
| Definite | 0 | 0 | -- |
| Probable | 0 | 1 (0.5%) | 0.49 |
| Possible | 0 | 1 (0.5%) | 0.49 |
| Any ARC | 0 | 2 (1.1%) | 0.24 |

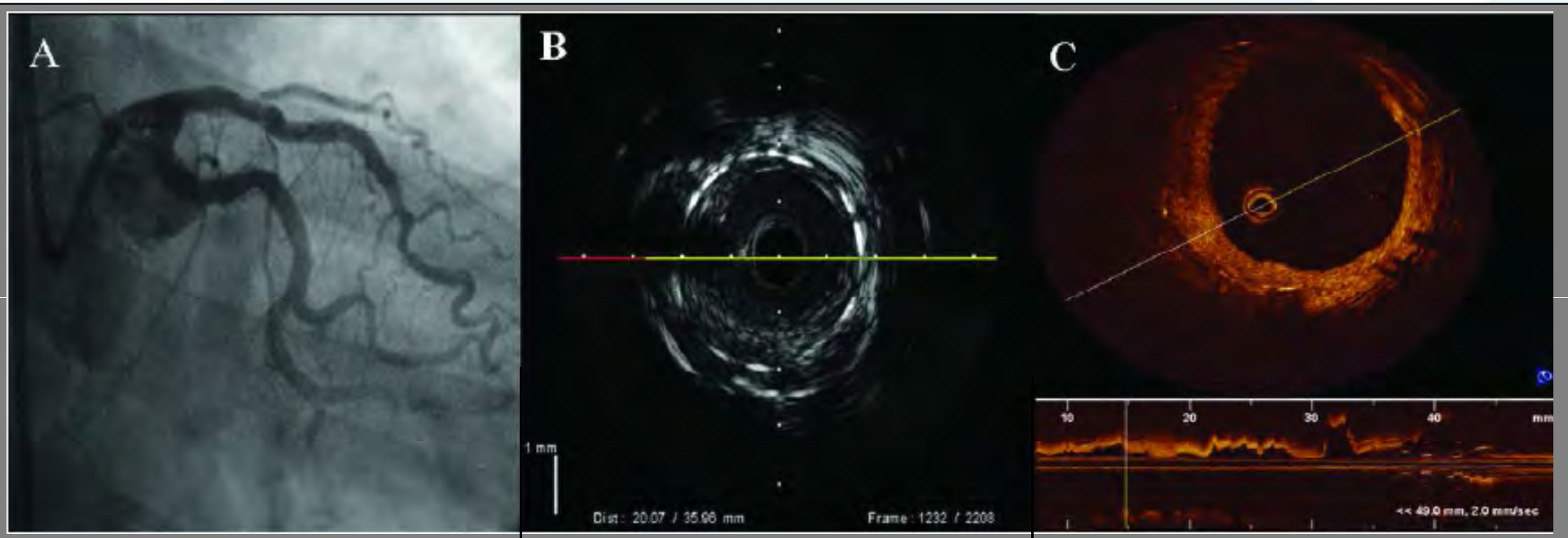
- No reports of early (first 30 days) stent thrombosis in either arm
- 2 reports of late stent thrombosis in TAXUS® Liberté®-treated patients
  - ARC probable stent thrombosis on Day 180
  - ARC possible stent thrombosis on Day 101

Through 12 months, **no cases of stent thrombosis**, regardless of definition, were reported in **NEVO™-treated patients.**

At Day 410, a TAXUS® Liberté® patient had a definite ST 25 days after DAPT was discontinued for elective surgery'

NEVO RES-I was not powered for clinical endpoints.
Abizaid A et al. EuroPCR 2010, oral presentation.

# 9 mths invasive FU: IVUS, and OCT



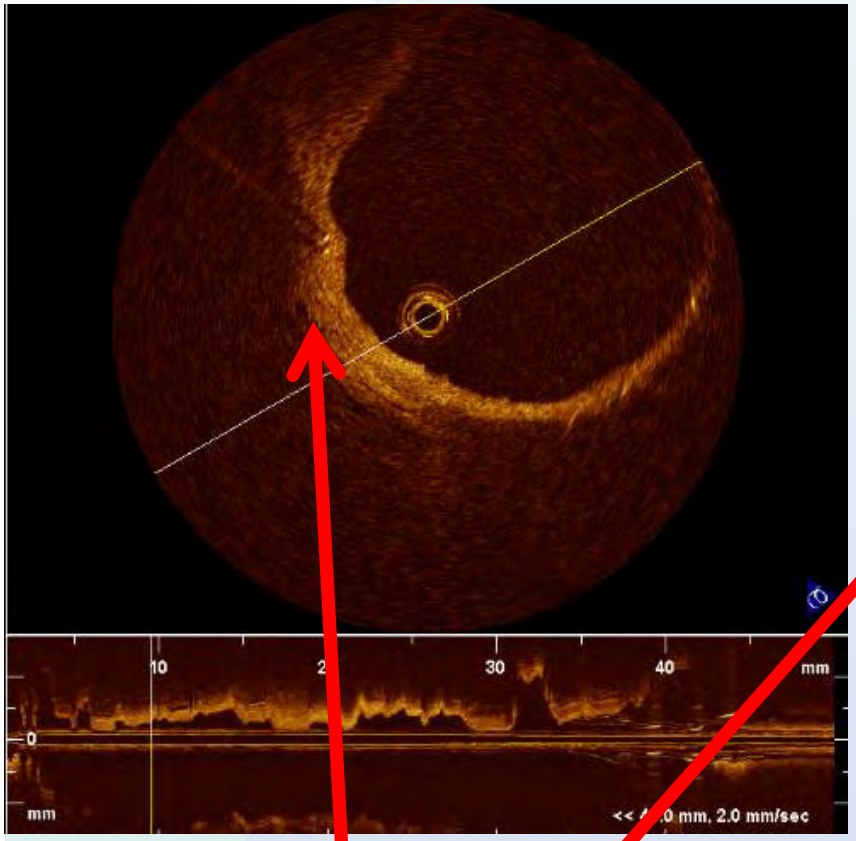

**angiography showing the six-month** result preserved, with no sign of catch-up;

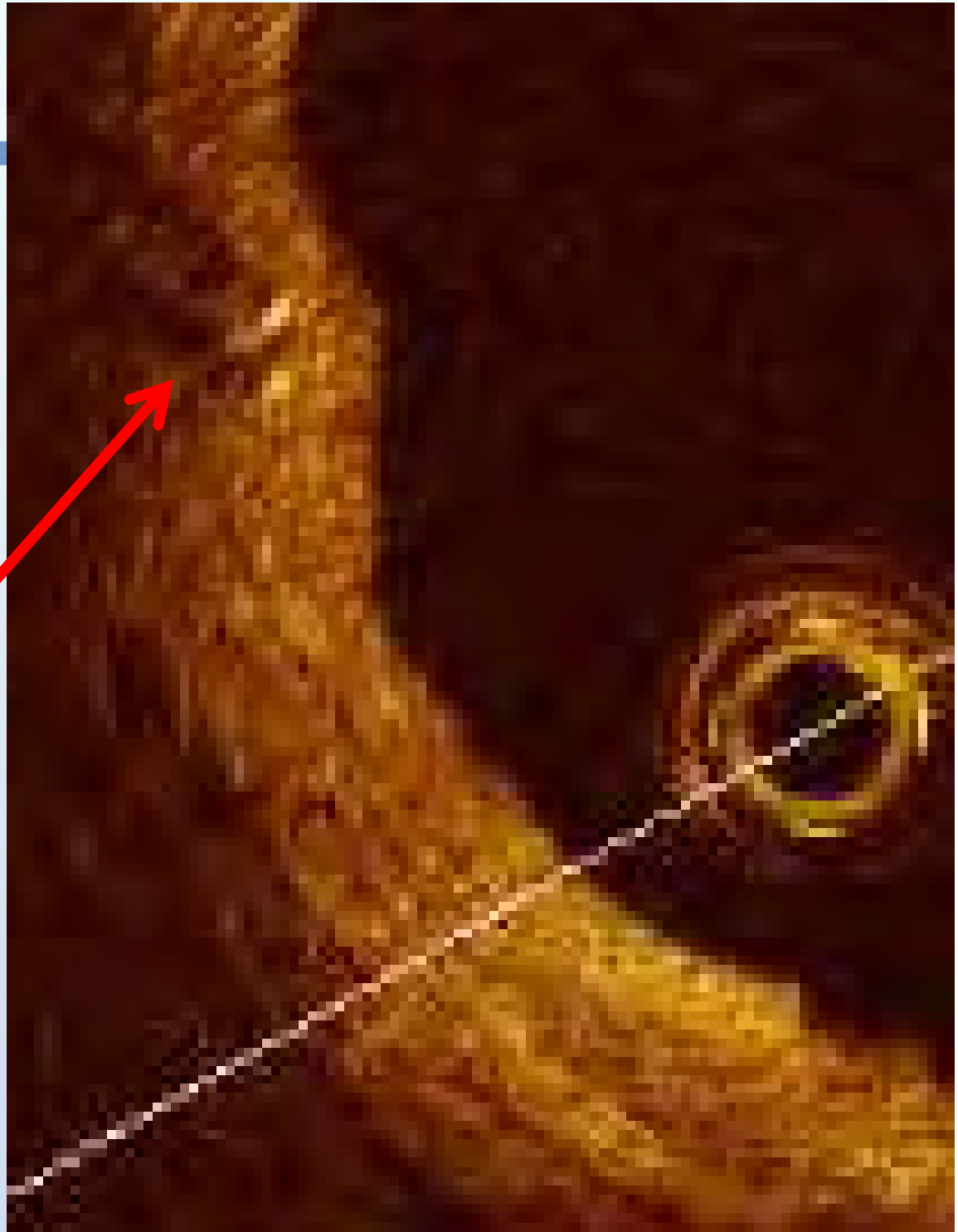
**IVUS examination at 9 months** confirming the excellent angiographic result

**OCT image at 9 months** showing complete strut coverage with “normal-looking” tissue and no occurrence of incomplete strut apposition.

Abizaid A et al. Catheterization and Cardiovascular Interventions, June 2010

# NEVO™ OCT image - 9 months



**Reservoir**

Abizaid A et al. Catheterization and Cardiovascular Interventions, June 2010

# Conclusions

- NEVO™ incorporates novel features: RES TECHNOLOGY™ with sirolimus and a bioabsorbable polymer (absorbtion in ~ 90 days) on an open cell, flexible cobalt chromium platform
- The NEVO-RES I trial demonstrated the superiority of NEVO™ over Taxus® Liberté™ with a highly significant  and clinically meaningful difference in the primary endpoint of in-stent late loss at 6 months.
- While not powered for clinical endpoints, the 12-month rates of death, MI, and revascularization as well as the composite endpoints of TLF, TVF, and MACE numerically favored NEVO™ over Taxus® Liberté™
    - The same magnitude of benefit of the NEVO™ stent over the Taxus® Liberté™ stent was seen in the pre-defined subgroups of diabetes and long lesions.
- No stent thromboses were observed in the NEVO™ group while 2 late thromboses during dual APT therapy occurred in the Taxus® Liberté™ group through 12 months, and a third occurred after 13 months

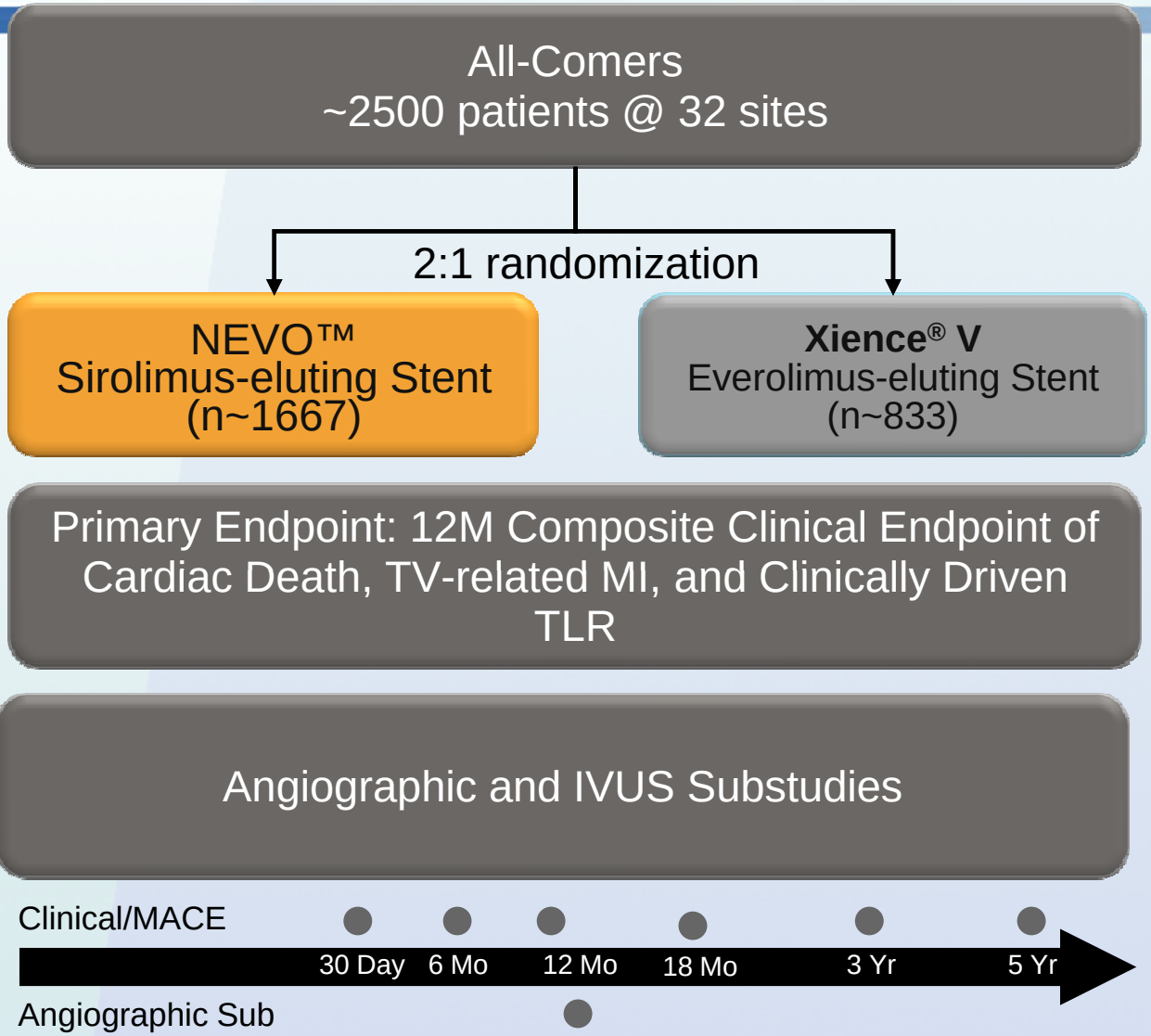
# NEVO™ Clinical Trial Program

**NEVO will be compared against all leading surface-coated DES across a broad spectrum of patients**

| NEVO RES-I | NEVO II | NEVO III | CYNERGY |
|---|---|---|---|
| • 394 patients<br>• Europe, NZ, SA, Australia<br>• Randomized<br>• Angiographic study vs TAXUS® Liberte®<br>• 1º Endpoint: 6-mo in-stent late loss<br>• "On-label" | • 2500 patients<br>• Europe, Israel<br>• Randomized<br>• Clinical outcomes vs Xience V®/Prime<br>• 1º Endpoint: 12-mo TLF<br>• All-comers | • 1600 patients<br>• US<br>• Nonrandomized<br>• Clinical outcomes vs CYPHER® (CYPRESS study)<br>• 1º Endpoint: 12-mo TLF<br>• "Near on-label" | • 14,000 patients<br>• EMEA, LATAM, APAC, CAN<br>• Sequential enrollment of CYPHER® and then NEVO™<br>• Clinical outcomes vs CYPHER®<br>• 1º Endpoint: 12-mo TLF<br>• Patients with STEMI, DM, MVD |

TLF=target lesion failure.
STEMI=ST-elevation myocardial infarction.
DM=diabetes mellitus.
MVD=multivessel disease.

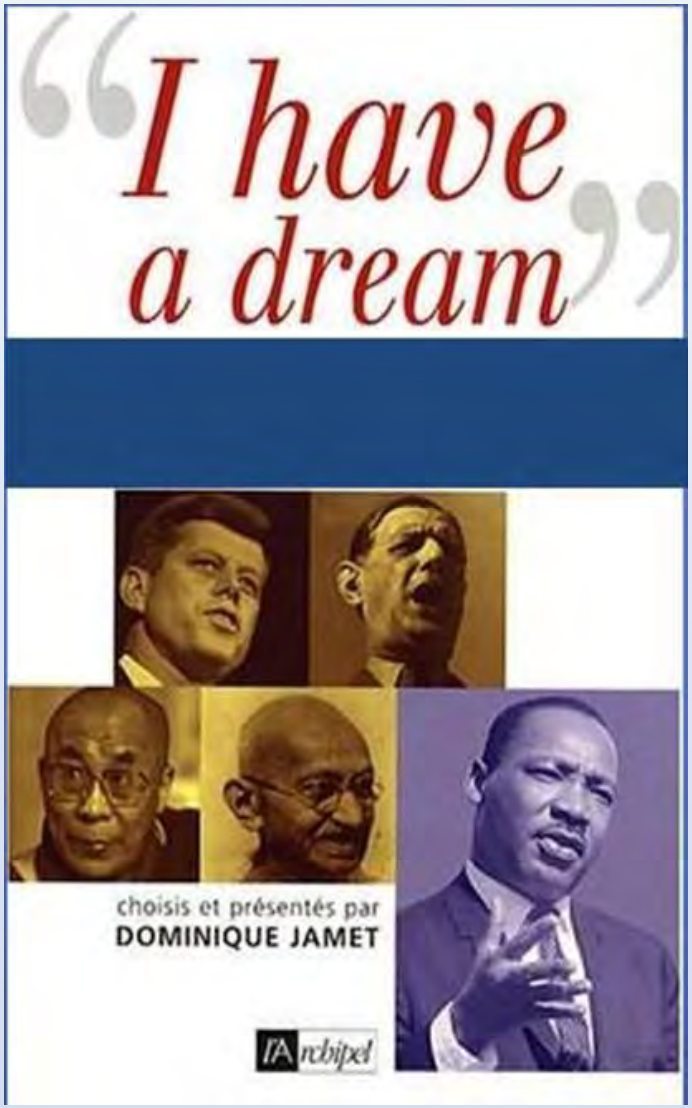
# NEVO-II Study Overview




**Principal Investigators**
Patrick Serruys
Stefan Windecker
Manel Sabaté

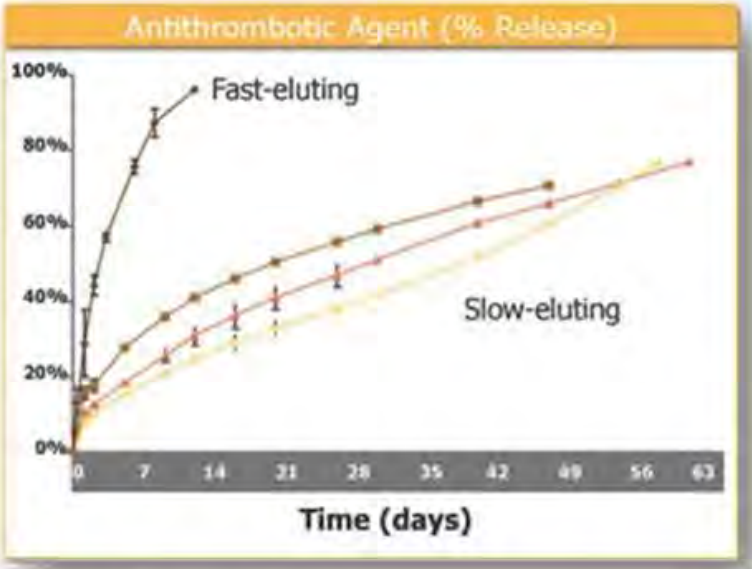
TV=target vessel. MI=myocardial infraction. TLR=target lesion revascularization. IVUS=intravascular ultrasound.

# What will be the next frontier?



# RES Technology Provides a Wide Range of Controlled Drug Delivery Options

**Controlled release kinetics**
Rapid (days) or prolonged (months) drug-elution profiles can be achieved by modifying the reservoir inlay composition[1]




**Directional drug release**
– Towards the lumen or vessel wall[2]

**Multiple drug delivery**
– With independent release kinetics and direction[3]



1. Edelman E et al. *Cardiac & Vascular Update.* 2009;2:7-9.
2. Parker T et al. Release kinetics for a cilostazol eluting stent using RES TECHNOLOGY™. BioInterface 2009 Conference; October 26-28, 2009; San Mateo, CA.
3. Li C et al. Cilostazol and sirolimus dual drug eluting stent based on RES TECHNOLOGY™. Transcatheter Cardiovascular Therapeutics Conference (TCT 2009); September 21-25, 2009; San Francisco, CA.

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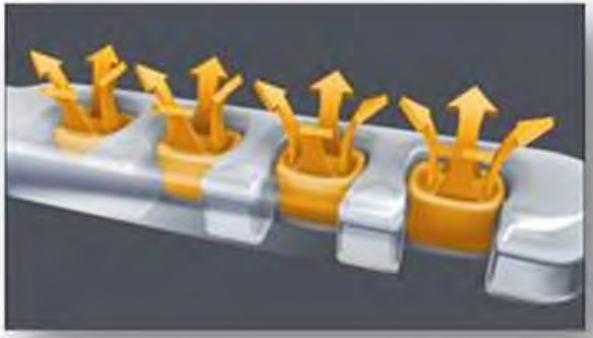
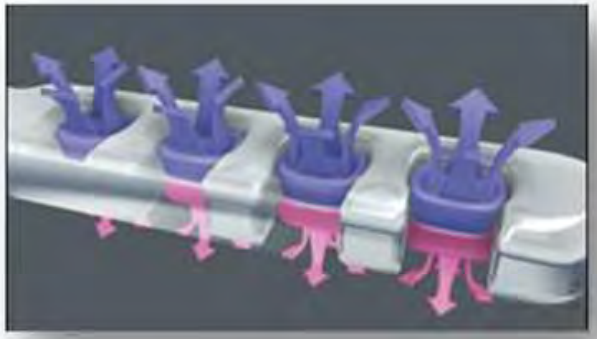
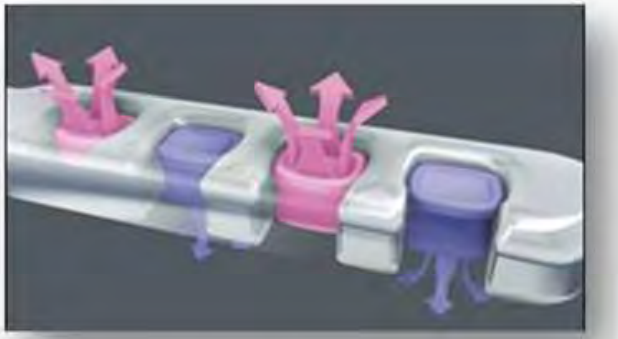
The reservoirs allow for different drug release combinations



Preferential
directional release
(NEVO™)



Dual drug in
single reservoir
bi-directional release
(Future)



Dual drug in
alternate reservoirs
bi-directional release
(Future)

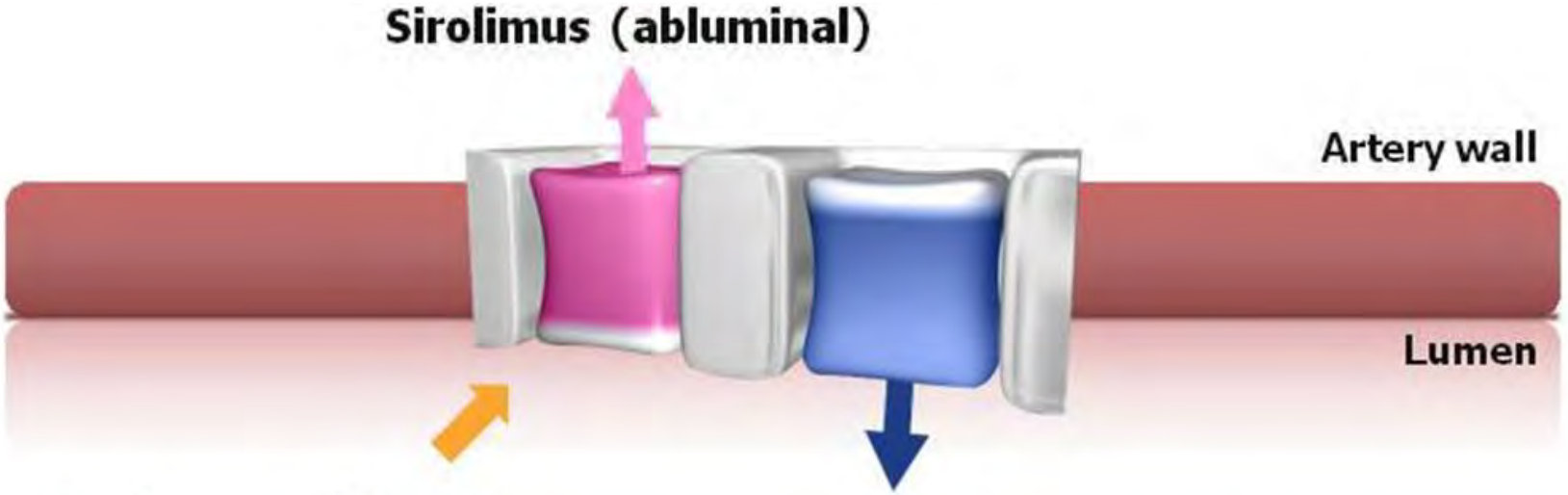
# Therapeutics Programs Utilizing RES TECHNOLOGY™

**Thrombosis**
Reduce stent thrombosis and DAPT dependence

**Acute MI**
Prevent “no-reflow” and reduce infarct size

**Diabetes**
Further reduce restenosis and improve clinical outcomes

# Antithrombotic Stent Strategies




**Surface-modification**

- Low MW heparin
- Nitric oxide
- Endothelial cell promoter

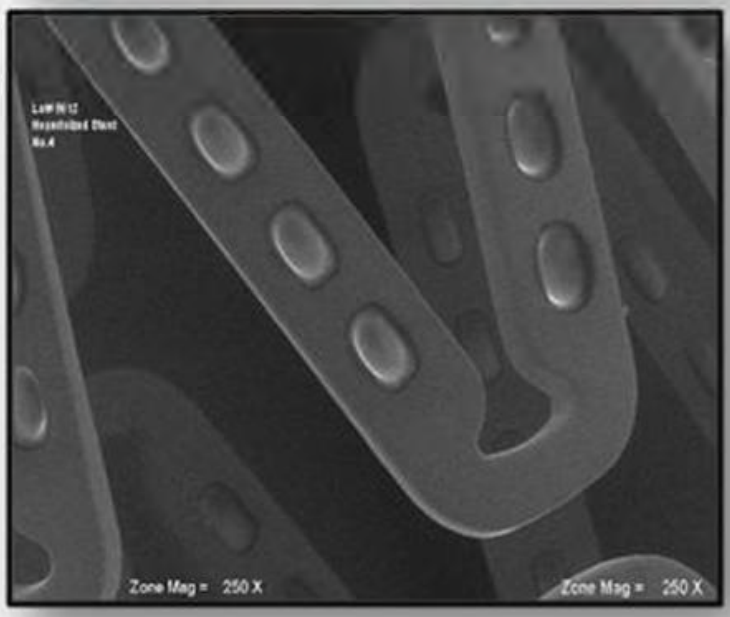
**Antithrombotic (luminal)**

- Factor Xa - thrombin inhibitor
- GP2b/3a inhibitor (tirofiban)
- Direct platelet inhibitor (cilostazol)

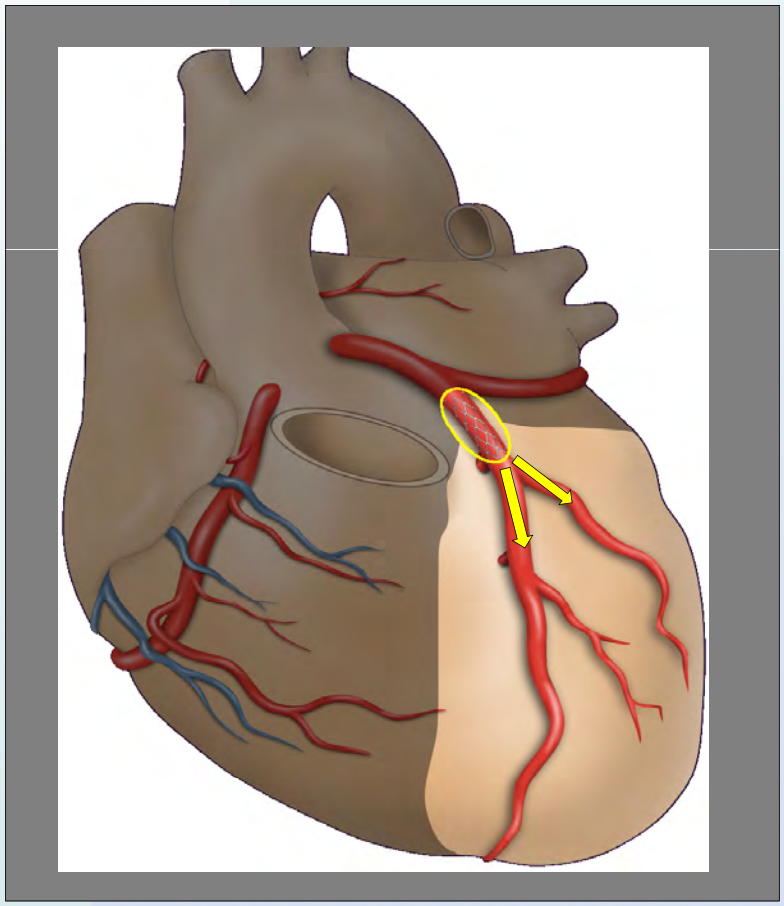
# Sirolimus-eluting Stent with Antithrombotic Surface Modification

**Design Features:**

- Nanolayer of low molecular weight heparin covalently bound to bare metal surface
- Reservoirs loaded with sirolimus
  - Same dose and release kinetics as NEVO™
- Potential to inhibit both early and late stent thrombosis



# RES Technology for Acute Myocardial Infarction



**Objectives:**

- Early reperfusion with a stent
- Elution of a therapeutic agent

-Reduce stent thrombosis

-Prevent no-reflow

-Reduce infarct size

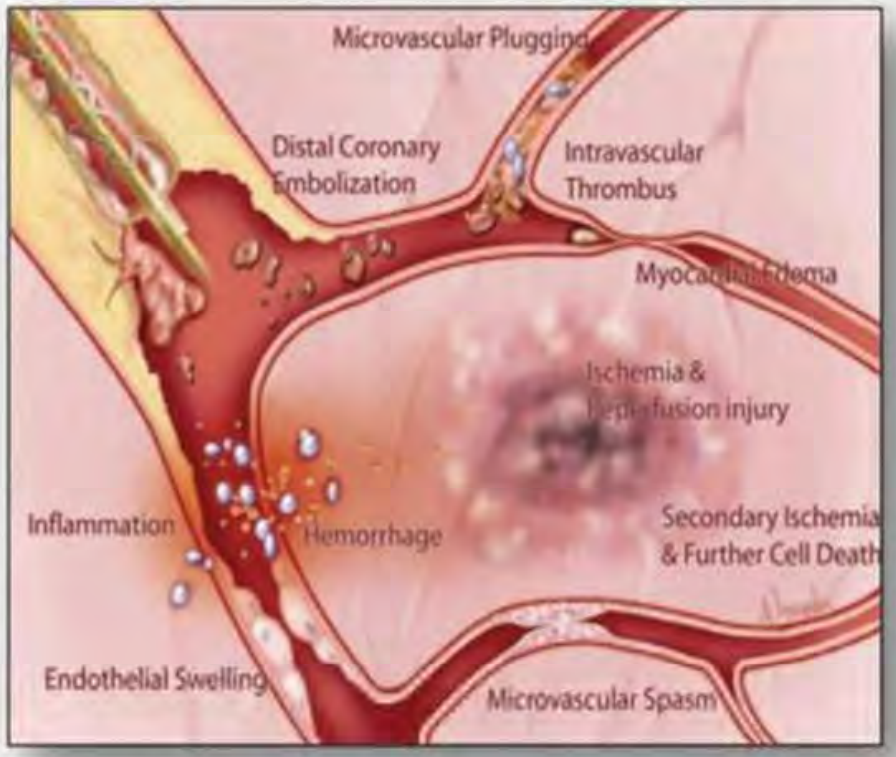
- Reduce clinical events

-Mortality

-LV dysfunction

-CHF

# « No Reflow » Following Coronary Reperfusion




Jaffe, et. al., *Circulation* 2008;117:3152-3156

**Significance**:

- Impairs myocardial perfusion (TIMI III flow)
- Direct association with increased mortality

**Causes**:

- Distal embolization of thrombus
- Interstitial edema & swelling
- Endothelial damage
- Leukocyte plugging
- Vasospasm and constriction

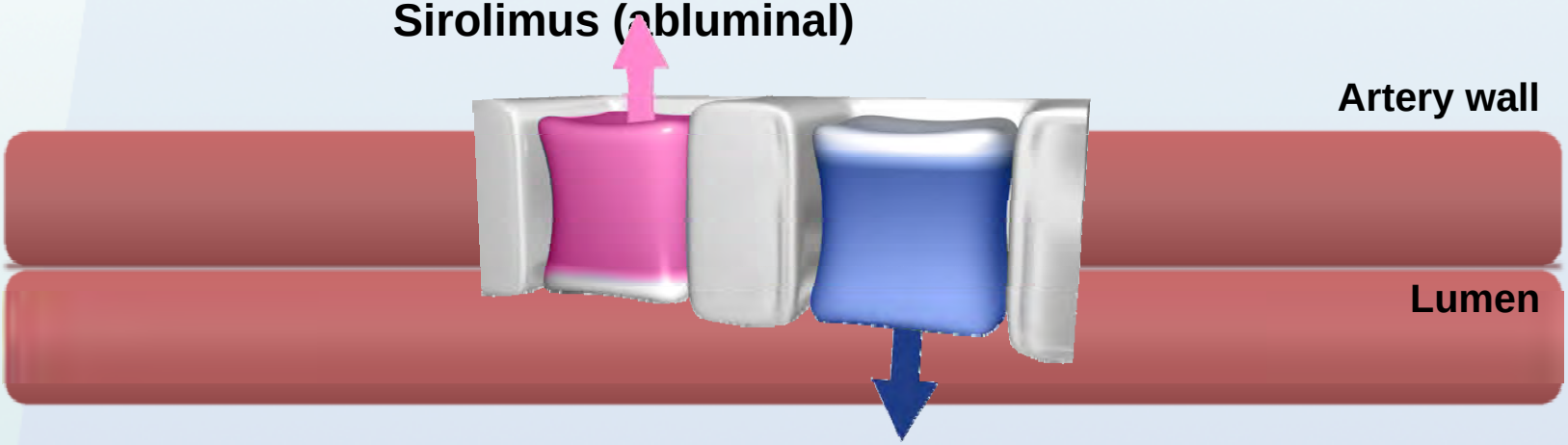
**Treatment strategies**:

- Thrombus aspiration/extraction
- Pharmacologic agents
  - Adenosine
  - Nitric oxide
  - Calcium channel blockers
  - GP2b/3a inhibitors

# Next-Generation Stent for Diabetics

## Objective:

- Address unmet needs of the diabetic patient
- Further reduce neointimal proliferation, TLR, stent thrombosis




**Complementary therapeutic (luminal or abluminal)**

- Antithrombotic
- Antiinflammatory
- Antiproliferative that synergizes with sirolimus

# Summary

- RES TECHNOLOGY™ provides a unique platform for intravascular drug delivery.
- Therapeutic programs in thrombosis, acute MI and diabetes are in progress.
- Promising candidates have been developed that are active in preclinical models.
- These devices have the potential to provide significant clinical benefit over current therapies.
- RES TECHNOLOGY™, beginning with NEVO™, will lead the next revolution in interventional cardiology and transform the treatment of vascular disease.