Intérêts de la technologie réservoirs NEVO RES-1

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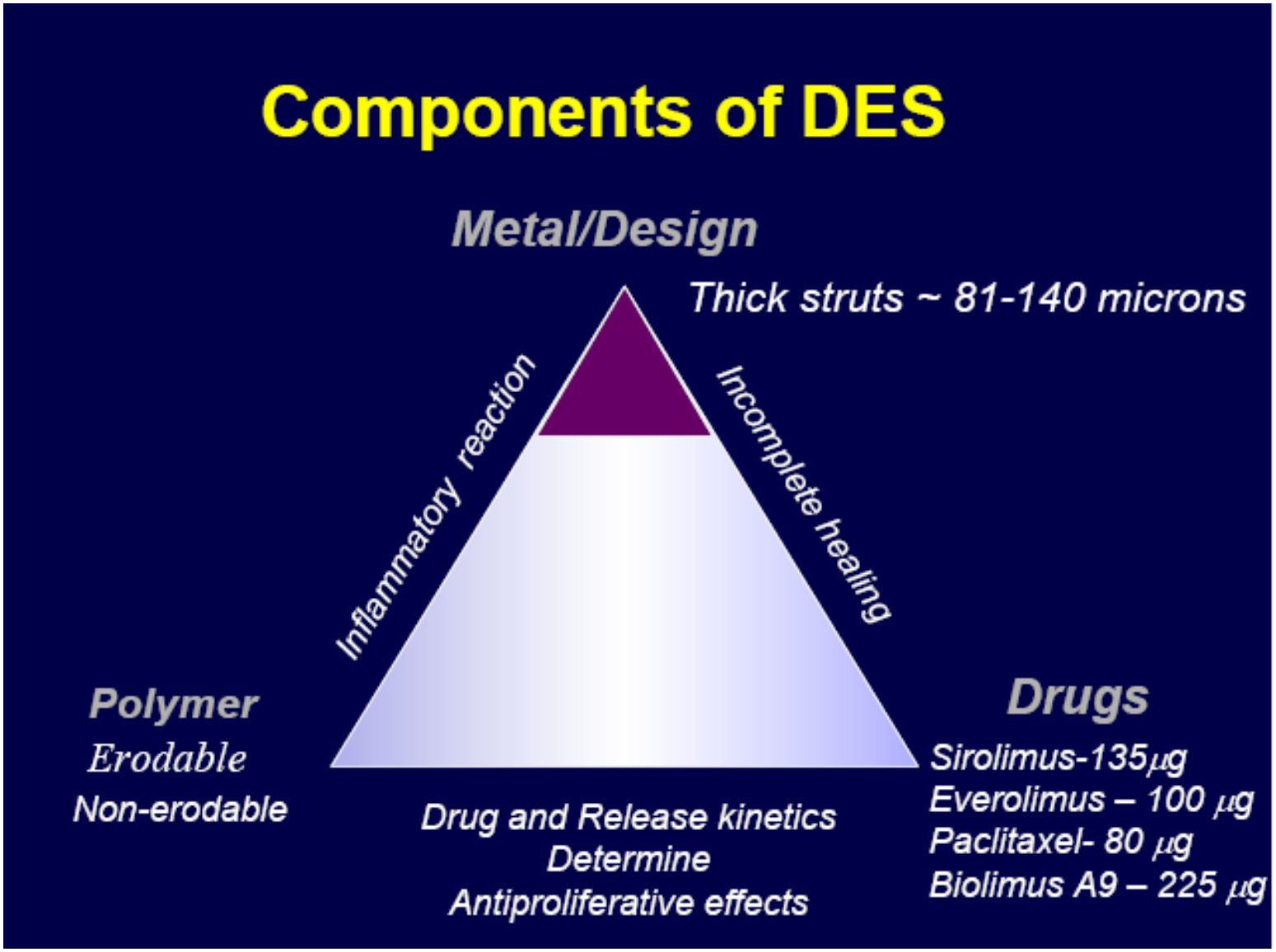
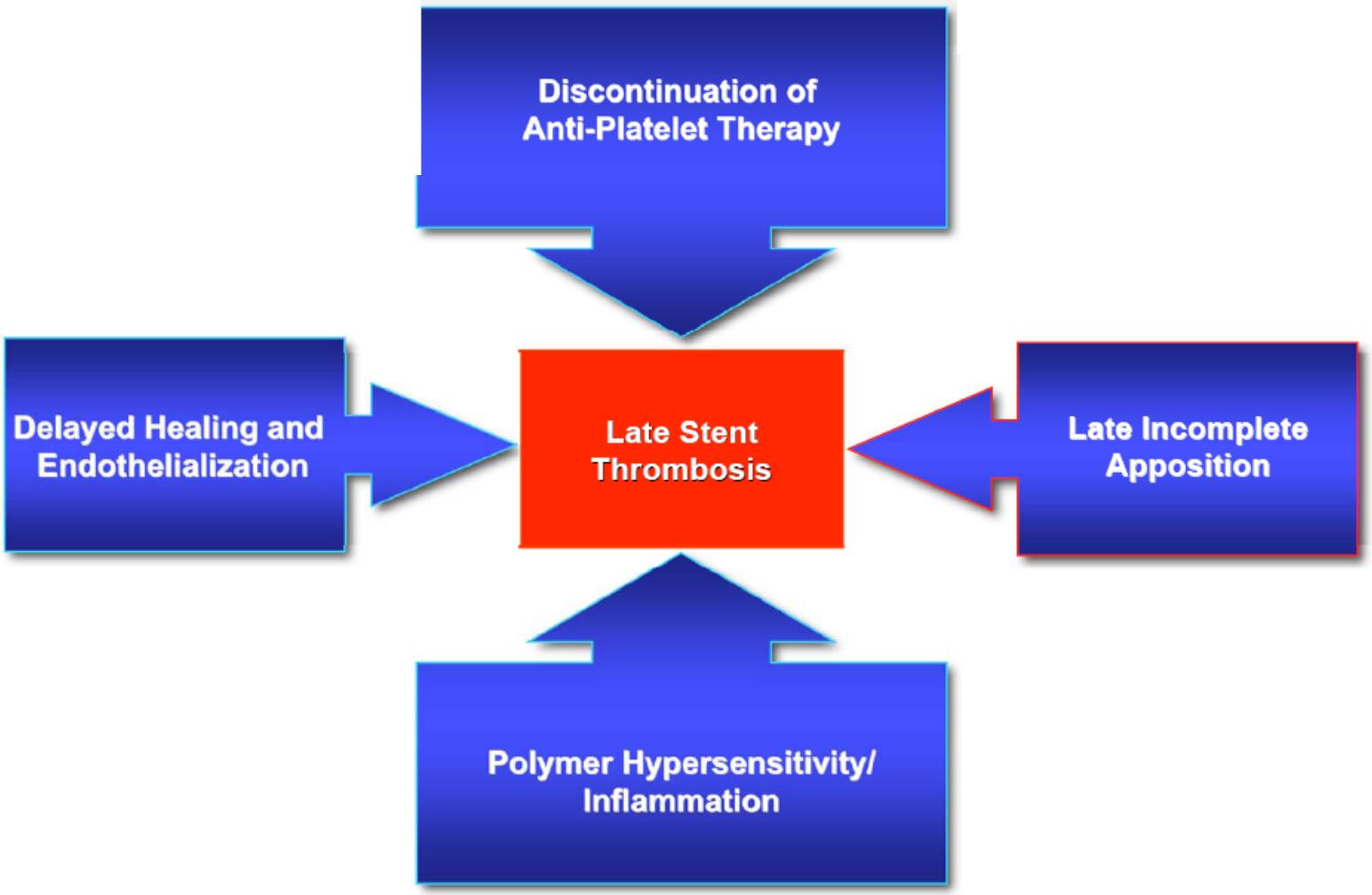
Components of DES

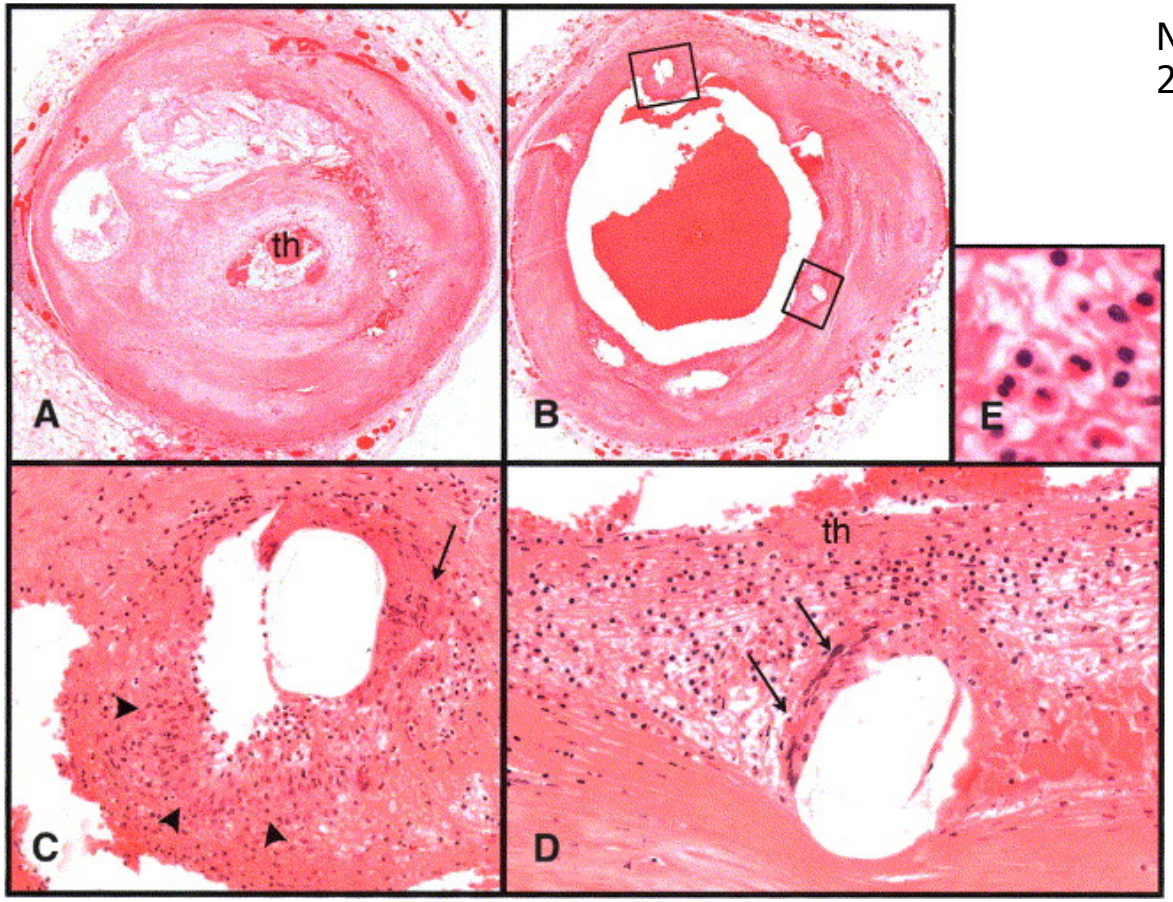


Late Stent Thrombosis
Factors to Consider



Thrombogénicité du polymère

4 pts: Thromboses (avec décès) 4 à 18 mois après stent actif: infiltrat inflammatoire+++ macrophages , cell géantes, éosinophiles



Nebeker,JACC, 2006,47:175-181

400 autopsies avec stents nus:
jamais de réactions avec hyperéosinophiles

What is the IDEAL DRUG ELUTING POLYMER!

- **Inert Polymer that is completely biocompatible**
  - ***note: important to distinguish between "short" and "long term" biocompatibility. Most if not all biocompatible polymers may cause some foreign body reactions months or years later***
- **Ability to control drug release at desired rate over a prescribed time period**
  - **note: *cytotoxic drugs may have more stringent release requirements than cytostatic agents***
- **Good adhesion to stent struts & high flexibility**
  - ***no acute or late cracking or peeling!***
- **High drug carrying capacity (I.e. "carrying efficiency")**
  - ***low polymer "dose" critical to minimize chronic inflammatory response***

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

Middleton JC and Tipton AJ. Biomaterials 2000;21:2335

Synthetic Biodegradable Polymers

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

Bioabsorbable Polymers for Drug Delivery

- Material properties of ideal Polymer are a delicate balance between mechanical, thermal, and viscoelastic factors.
- The earliest and the most commonly used bioabsorbable materials include polyglycolic acid (PGA), poly lactic acid (PLA). PGA-PLA copolymers and poly(ortho esters). Numerous others have been developed.
- Kulkarni et al. introduced the concept of bioabsorbable materials in 1960s, animal models have contributed to the success. Rabbit has been the standard for in vivo measurements of biocompatibility, but rats, dogs, sheep, and pigs have been utilized to varying degrees.

Degradation Speed in Various Biodegredable Polymers

Material	Degradation Period
Polylactic 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

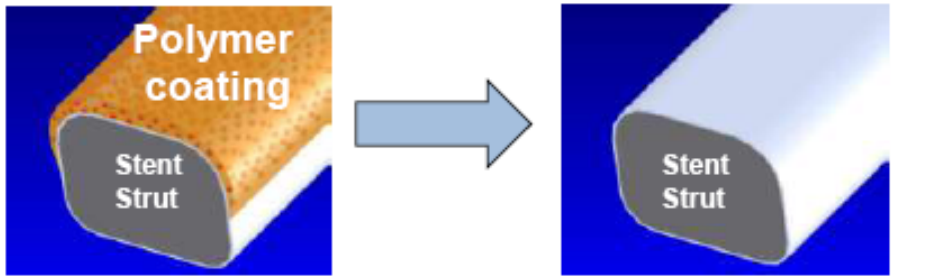
Biodegradable Polymer Coatings

Polylactide Acid (PLA)
-Biosensors
-Terumo
-Devax
-Xtent

Polylactide-co-glycolic acid (PLGA)
-Conor/Cordis
-Boston Scientifc

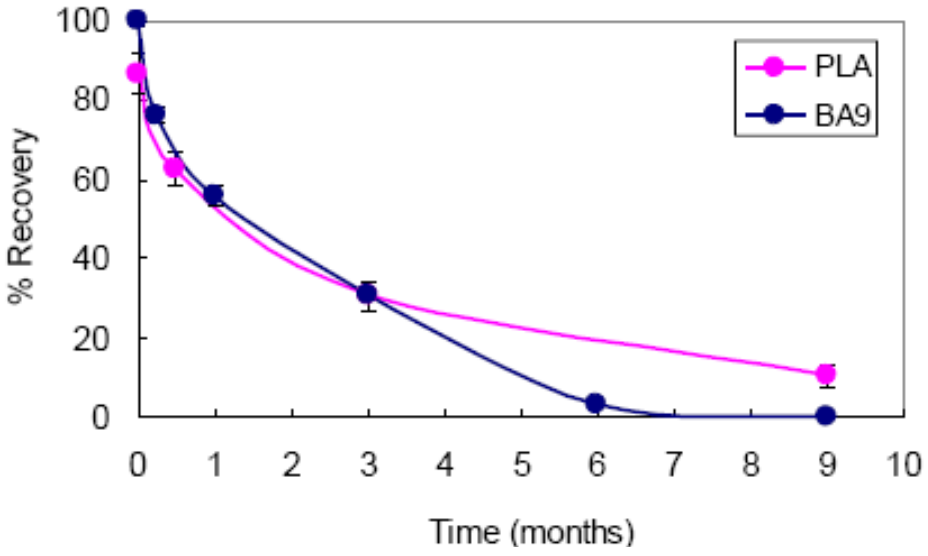
Poly-L-lactide Acid (PLLA)
-Biotronik

Heparinized polymer blend of PLLA, PLGA, polyvinyl pyrrolidine
-Sahajanand



Stent with biodegradable coating abluminal only

After release of biodegradable coating



Degradation

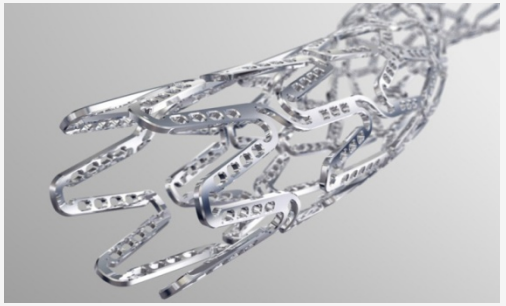
- The degradation-absorption mechanism is the result of many interrelated factors, including:
  - The chemical stability of the polymer backbone
  - The presence of catalysts
  - Additives
  - Impurities or plasticizers
  - Geometry of the device
  - Location of the device
- *Factors which accelerate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

Middleton JC and Tipton AJ. Biomaterials 2000;21:2335

NEVO™ Sirolimus-Eluting Stent : Cordis' 1st RES TECHNOLOGY™ Stent

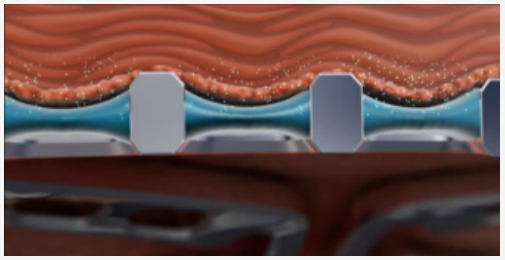
CoCr stent platform

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



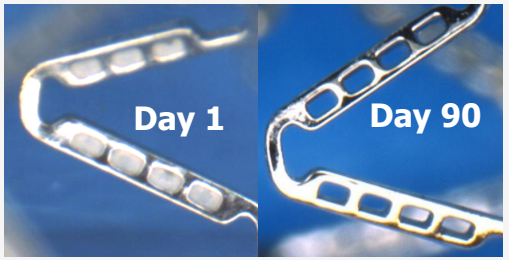
Reservoir technology

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



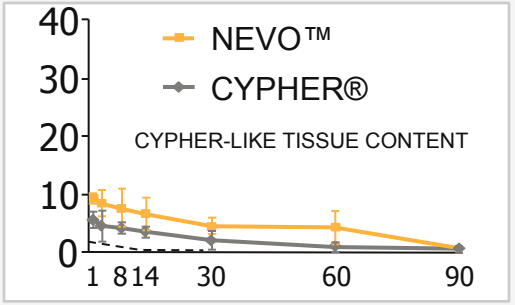
Bioabsorbable polymer

- Designed for complete bioabsorption in as little as 90 days



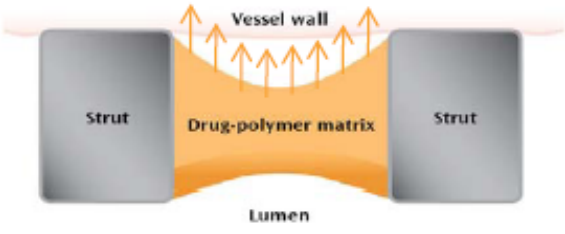
Proven Sirolimus Evidence

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



Designed for controlled drug delivery

Drug-polymer matrix is recessed into the reservoirs →
No polymer on the surface of NEVO™



Cross-section of reservoir

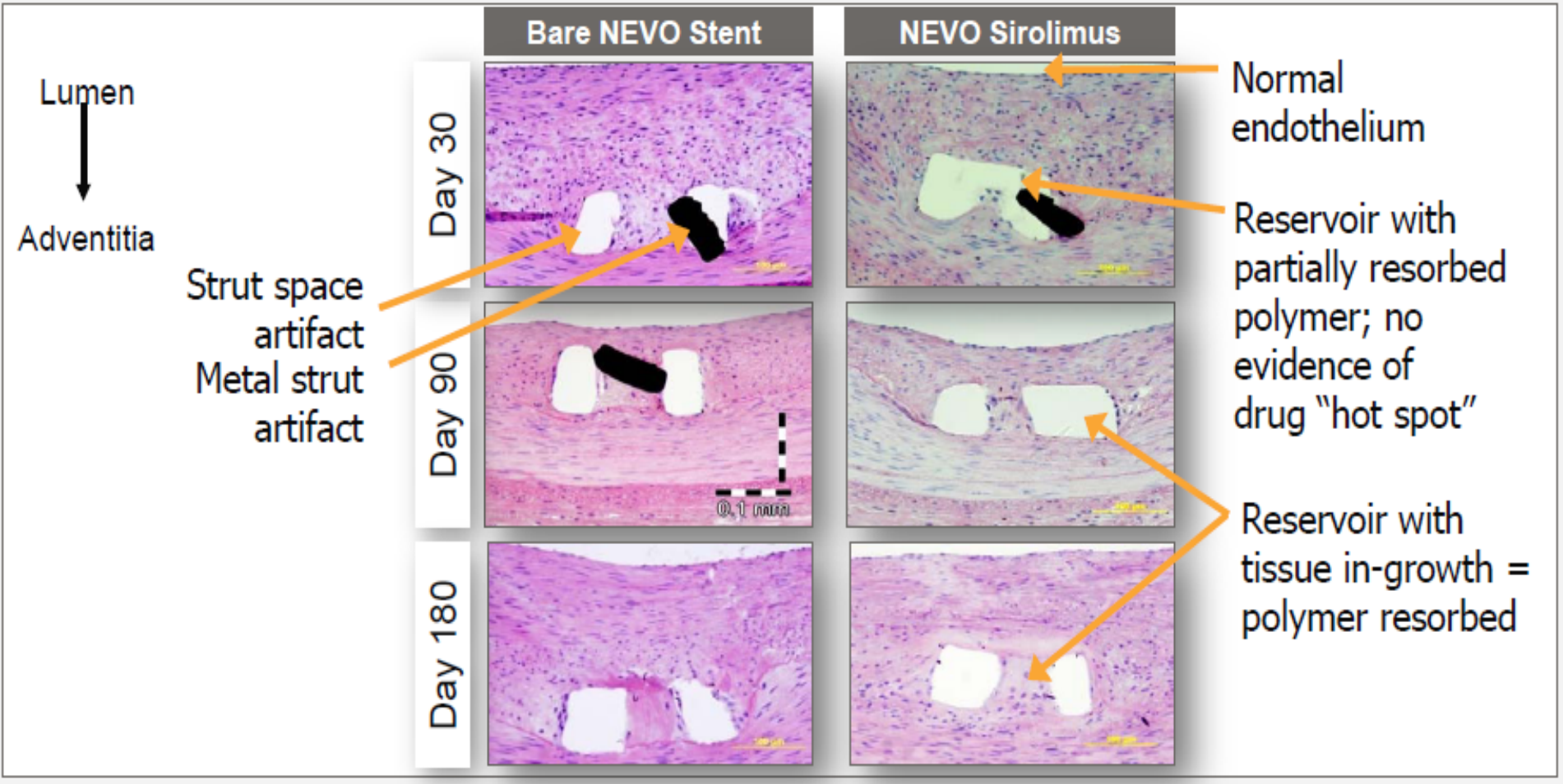
NEVO™ is Designed to Transform to a BMS

Fully bioabsorbable PLGA polymer[1]

- Used in a variety of medical applications such as VICRYL™ sutures
- Designed for complete bioabsorption in as little as 90 days
- Biocompatible
- Fully metabolized bioproducts (CO_2 + H_2O)
- NEVO™ transforms into a BMS in as little as 90 days

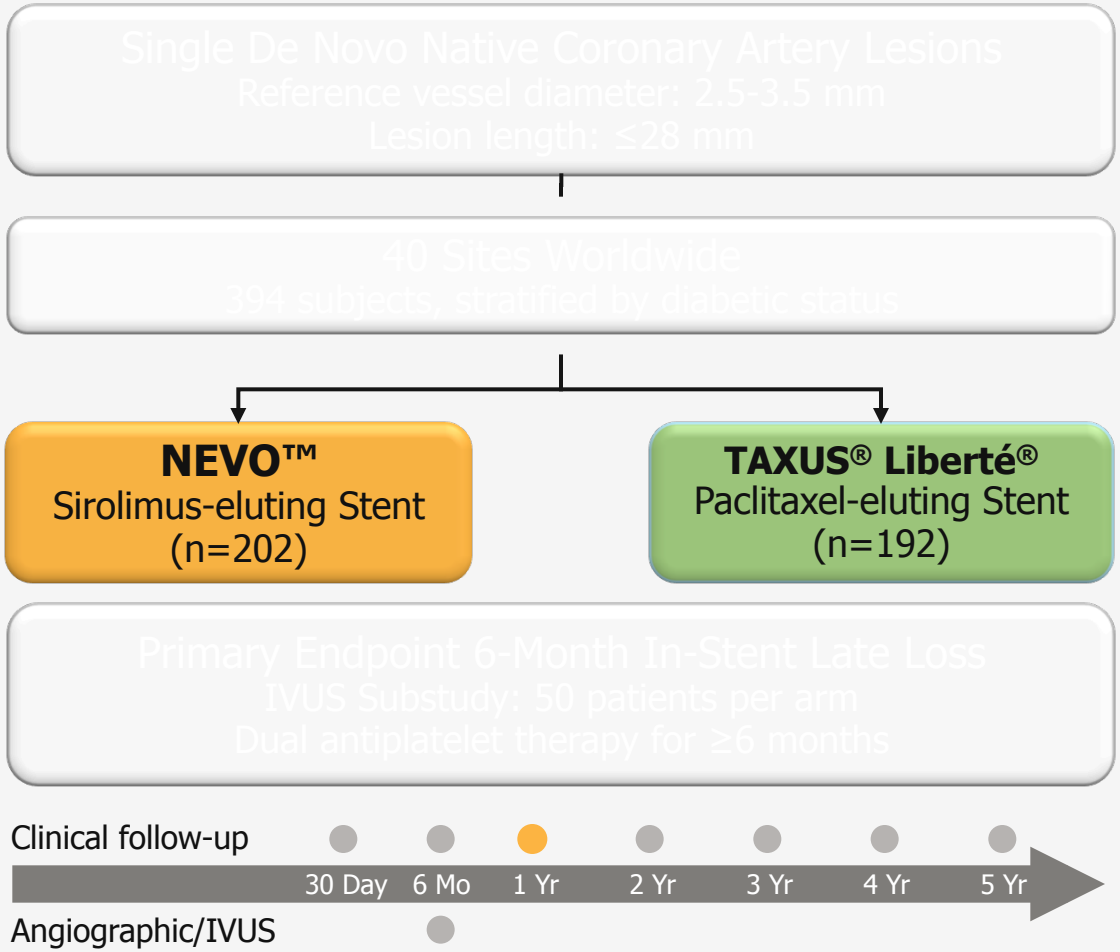
1. Robert Falotico et al. "NEVO™: a new generation of sirolimus-eluting coronary stent"; EuroIntervention 5 (Supplement F) (2009) F88-F93

NEVO™ Vascular Healing Comparable to BMS



Study data from AP-057

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: Key Endpoints

Primary endpoint

Angiographic in-stent late loss at 6 months

Secondary endpoints

- In-stent / In-segment binary restenosis, % diameter stenosis, and MLD
- Device, lesion, and procedure success
- Stent thrombosis (ARC and "Protocol" definition), including follow-up to 5 years
- TLF/TVF/MACE and individual components, including follow-up to 5 years
- Stent malapposition and % volume obstruction (IVUS)
- Quality of life at baseline, 30 days, 6 months, and 1 year

Pre-specified subgroup analyses

- Diabetes and no diabetes
- Lesion length ≤ versus >20 mm

EuroPCR 09, Oral presentation, Chr. Spaulding

NEVO RES-I: Baseline Patient Characteristics

	NEVO™ (n=202)	TAXUS® Liberté® (n=192)	*P* Value
Mean age (yrs)	62.95	64.37	0.16
Men (%)	78.22	74.48	0.41
BMI (kg/m^2)	27.76	27.54	0.61
Prior PCI (%)	33.66	25.00	0.06
Prior CABG (%)	1.49	2.08	0.72
Prior MI (%)	32.18	26.04	0.19
Hypertension (%)	67.33	68.23	0.91
Hyperlipidemia (%)	74.75	75.00	1.00
Diabetes mellitus (%) – Diet-controlled only (%) – Oral medication (%) – Insulin (%)	17.82 0.99 11.39 5.45	20.31 2.60 12.50 5.21	0.61 0.27 0.76 1.00
Current smoker (%)	27.23	22.40	0.30
Peripheral vascular disease (%)	5.94	5.73	1.00

BMI=body mass index. CAGB=coronary artery bypass graft. PCI=percutaneous coronary intervention. MI=myocardial infarction.
EuroPCR 2009, oral presentation, Chr. Spaulding.

Note: Products using RES TECHNOLOGY™ are under development and are not approved or available for sale in any market.

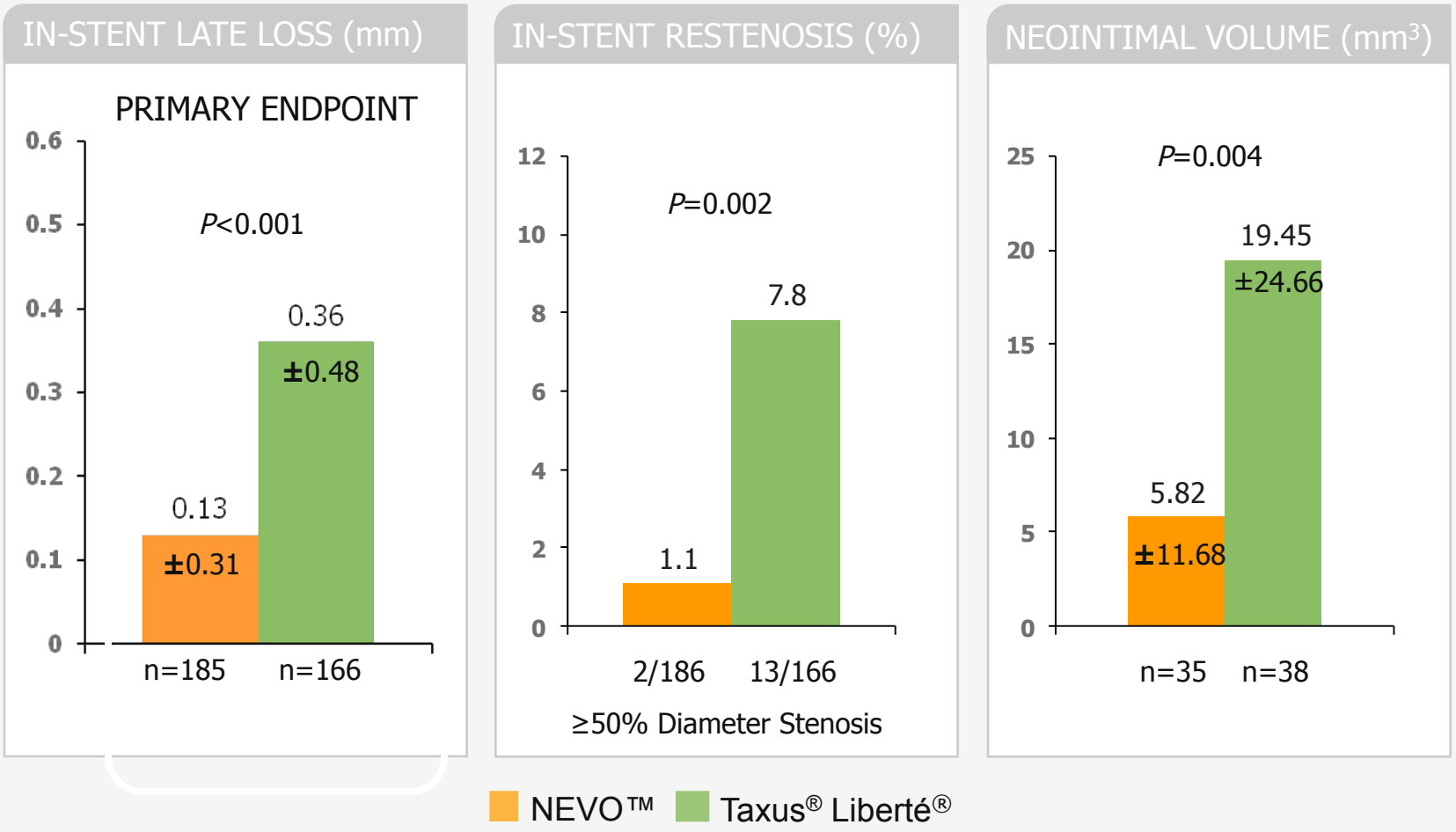
NEVO RES-I: Baseline Lesion Characteristics

		NEVO™ (n=202)	TAXUS® Liberté® (n=192)	*P* Value
Reference vessel diameter (mm)		2.64 ± 0.41	2.68 ± 0.43	0.37
MLD (mm)		0.66 ± 0.29	0.68 ± 0.30	0.52
% Stenosis		74.8 ± 10.2	74.6 ± 9.8	0.85
Lesion length (mm)		13.8 ± 6.6	13.7 ± 6.1	0.84
Diffuse lesions (>20 mm %)		17.8	16.7	0.79
Vessel location (%)	LAD RCX RCA	45.0 27.2 27.7	46.9 22.9 30.2	0.60
ACC/AHA lesion class (%)	A B1 B2 C	11.4 30.7 31.7 26.2	9.9 26.0 39.1 25.0	0.50
Calcification (%)	Mild Moderate Severe	77.7 14.9 7.4	70.8 21.9 7.3	0.15

MLD=minimal stenotic diameter. ACC/AHA=American College of Cardiology/American Heart Association

EuroPCR 2009, oral presentation, Chr. Spaulding.

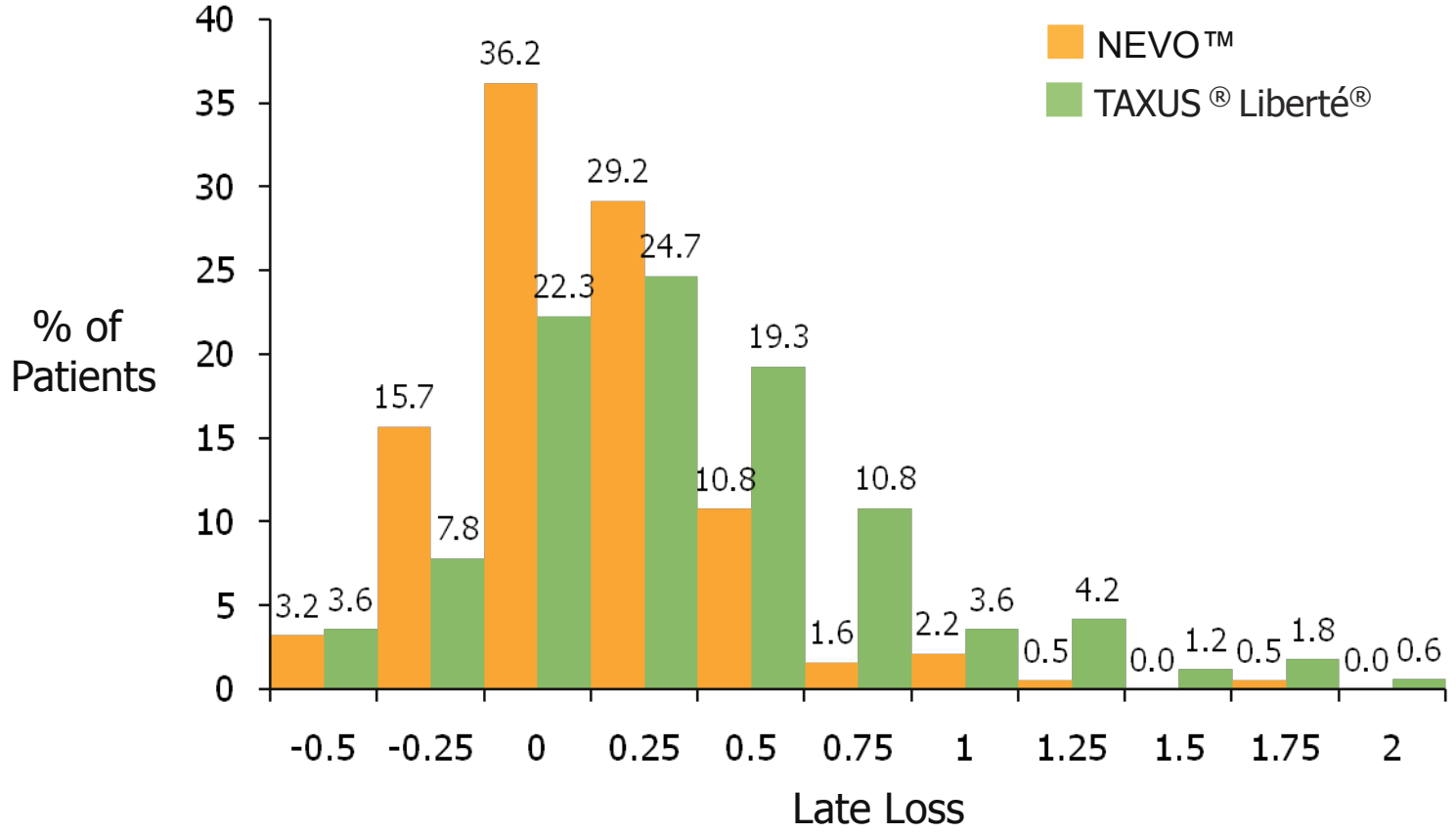
NEVO RES-I: 6-Month In-Stent Late Loss, In-Stent BAR, and IVUS-defined Neointimal Volume



EuroPCR 09, Oral presentation, Chr. Spaulding

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

DISTRIBUTION OF IN-STENT LATE LOSS



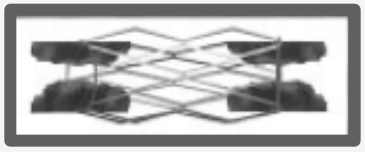
Data reflect completed 6 months follow-up, core lab, and CEC adjudication.
TCT 09, Oral presentation, J. Ormiston

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

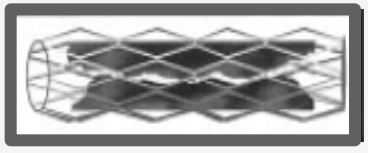
Type IB: (Focal) < 10 mm at edge

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

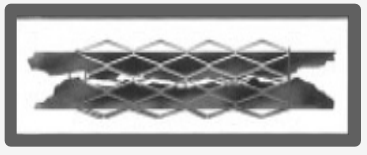
Type ID: Multi-Focal ISR

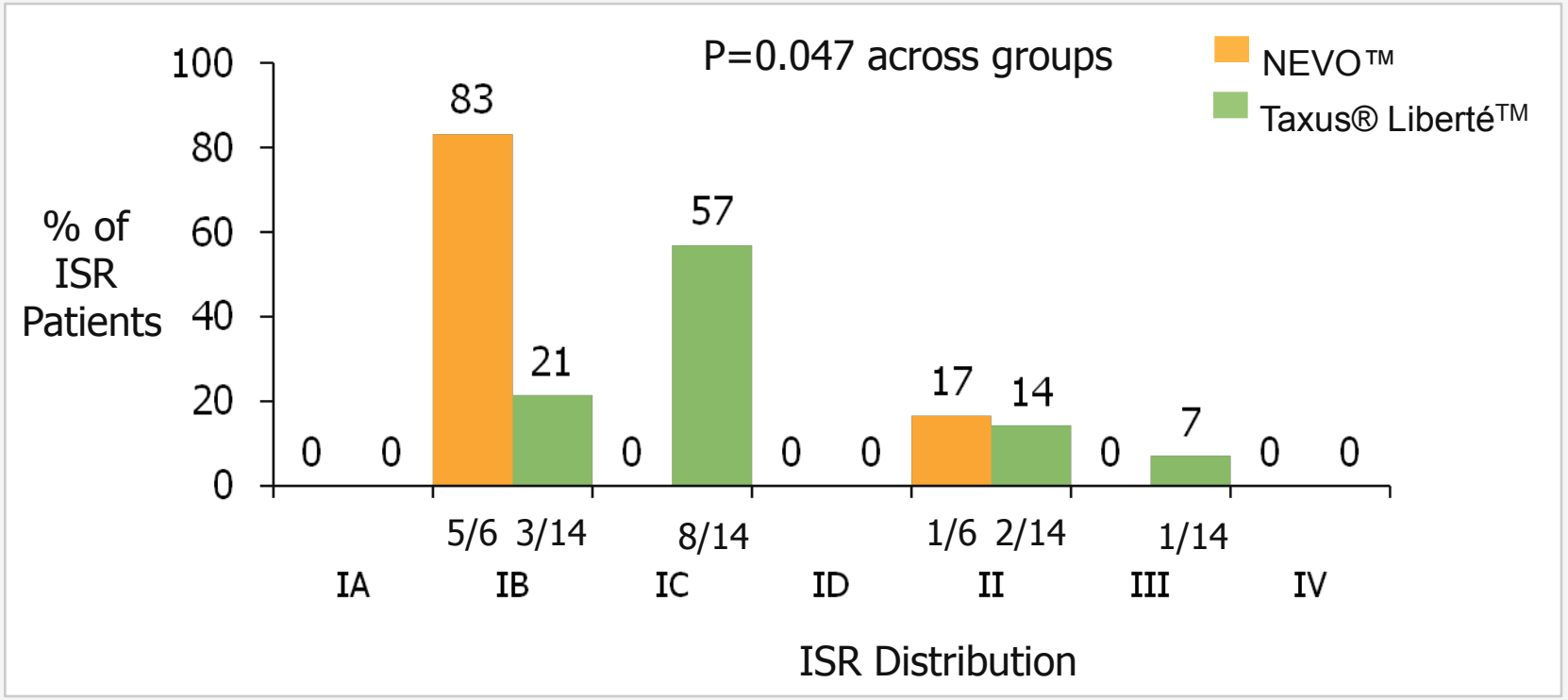


Type II: Diffuse In-stent



Type III: Diffuse, Proliferative



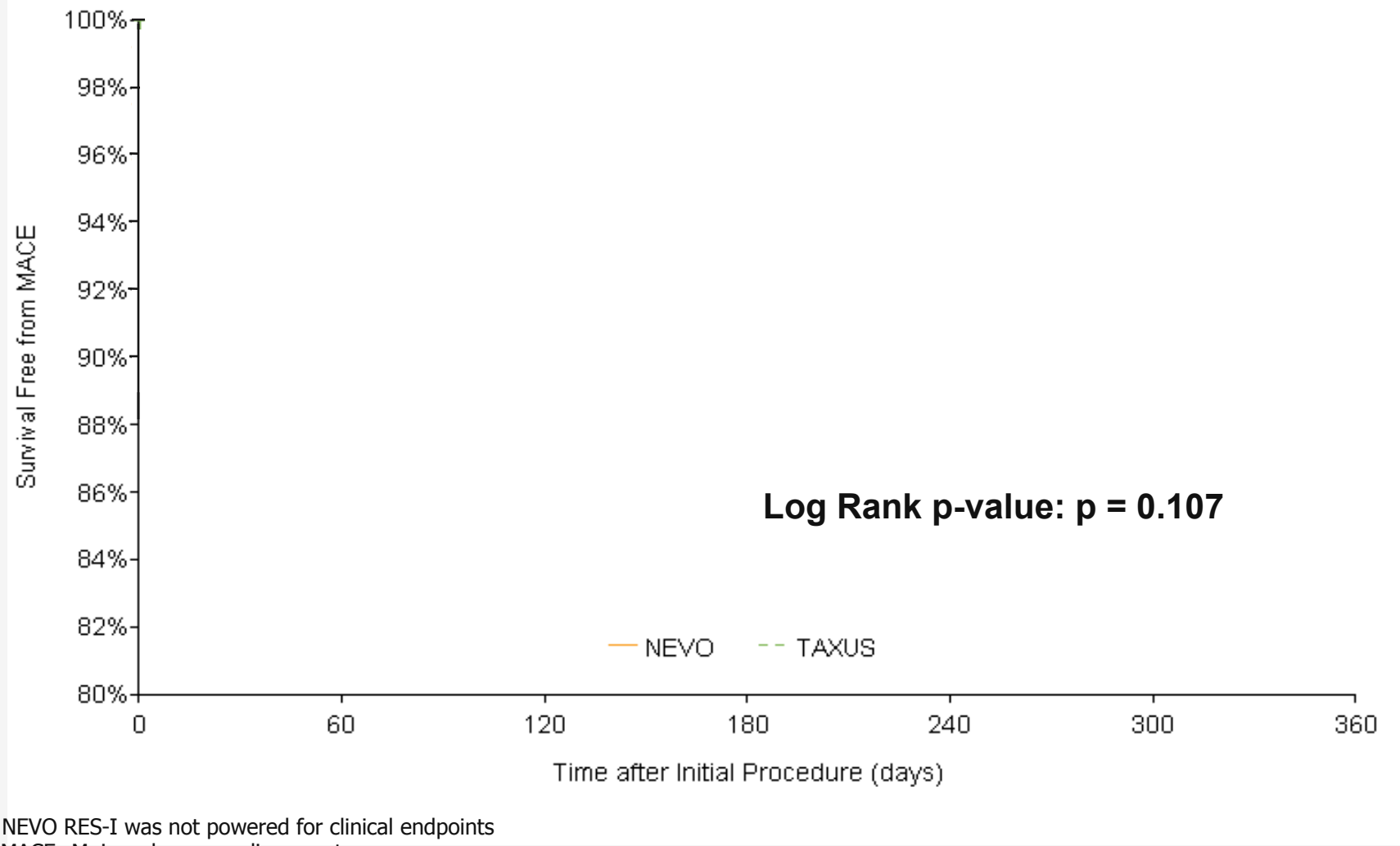


Abizaid A., et al., EuroPCR 2010; Oral Presentation.

NEVO RES-I:
12-Month Outcomes

Cordis®
a Johnson & Johnson company

NEVO RES-I: 12-month MACE-Free Survival

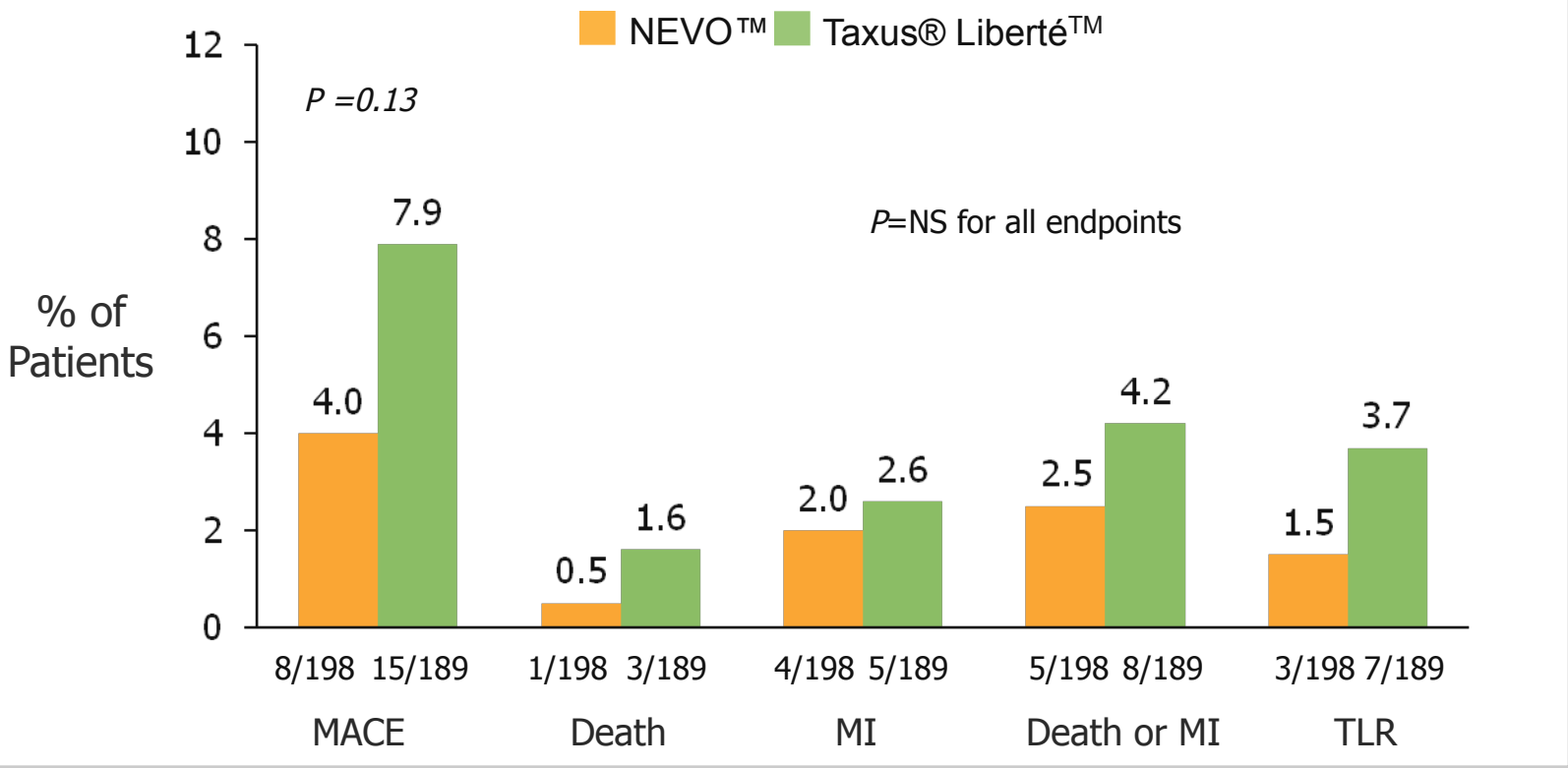


NEVO RES-I was not powered for clinical endpoints
MACE=Major adverse cardiac events.
Absolute Differences (%) are based on Kaplan Meier Estimates

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

NEVO RES-I: 6-Month MACE and Components

6-MONTH MACE AND COMPONENTS

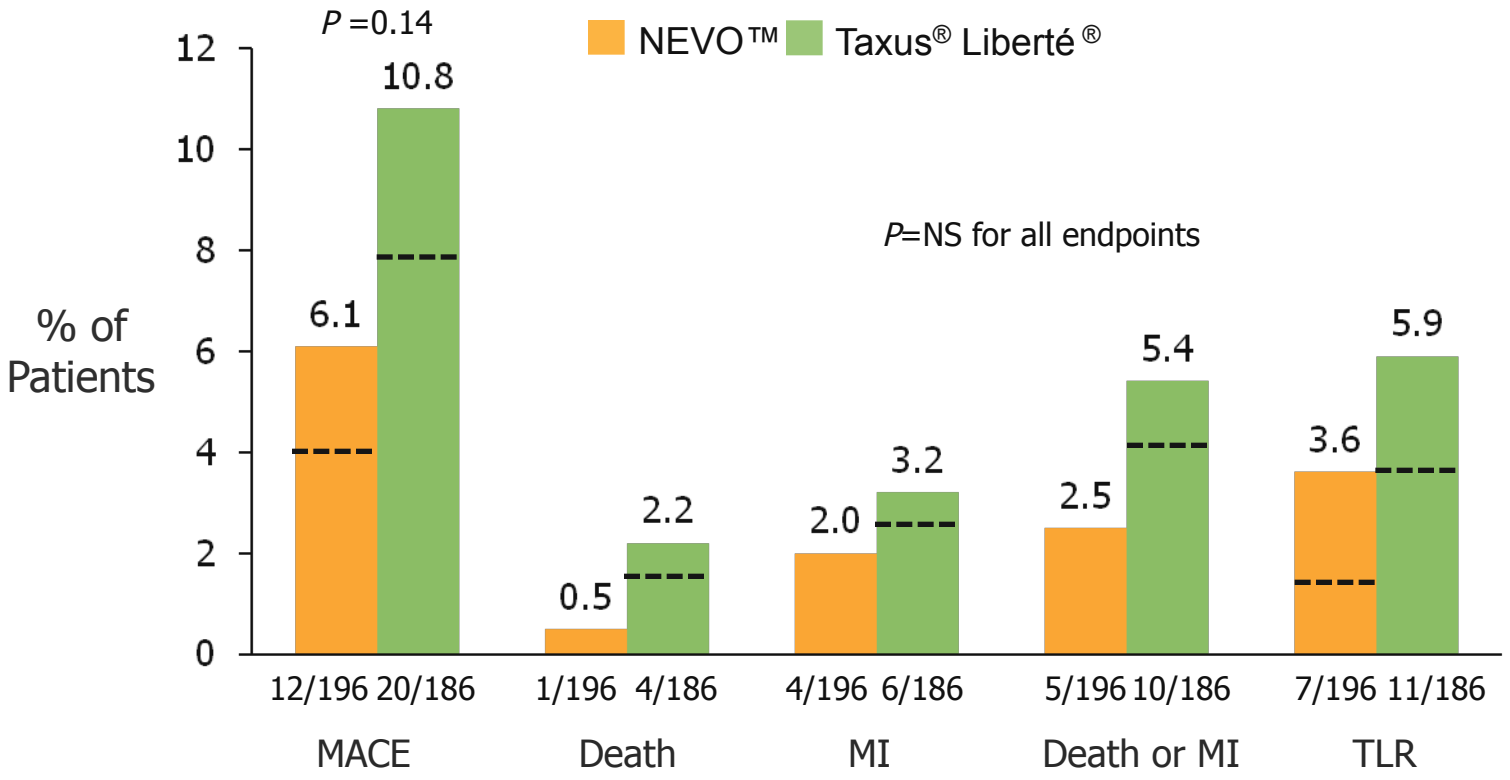


NEVO RES-I was not powered for clinical endpoints

MACE=Major adverse cardiac events.
EuroPCR 09, Oral presentation, Chr. Spaulding

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

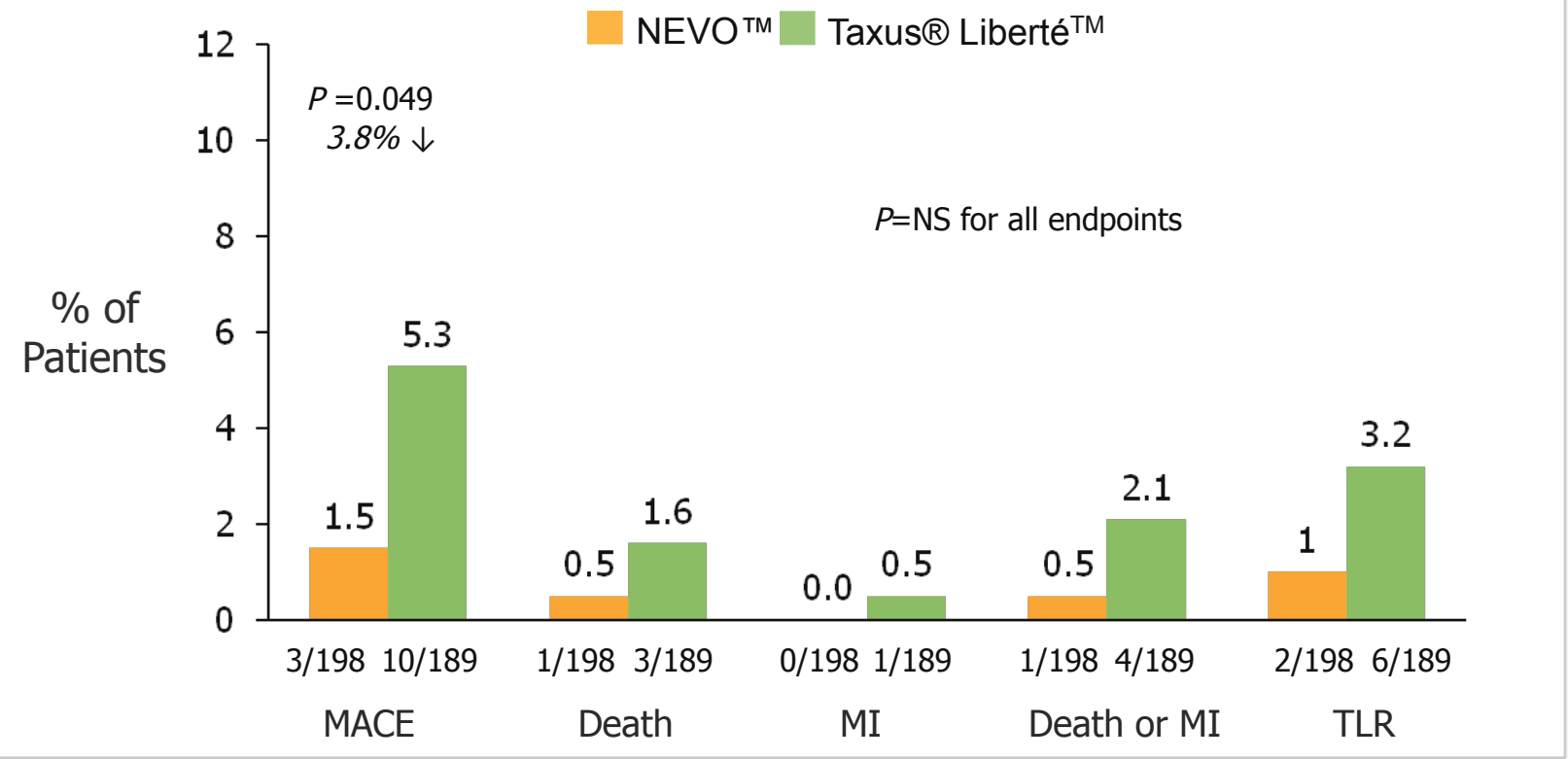
NEVO RES-I was not powered for clinical endpoints

MACE=Major adverse cardiac events.

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

NEVO RES-I:
6-Month Out-of-Hospital MACE and Components

6-MONTH MACE AND COMPONENTS



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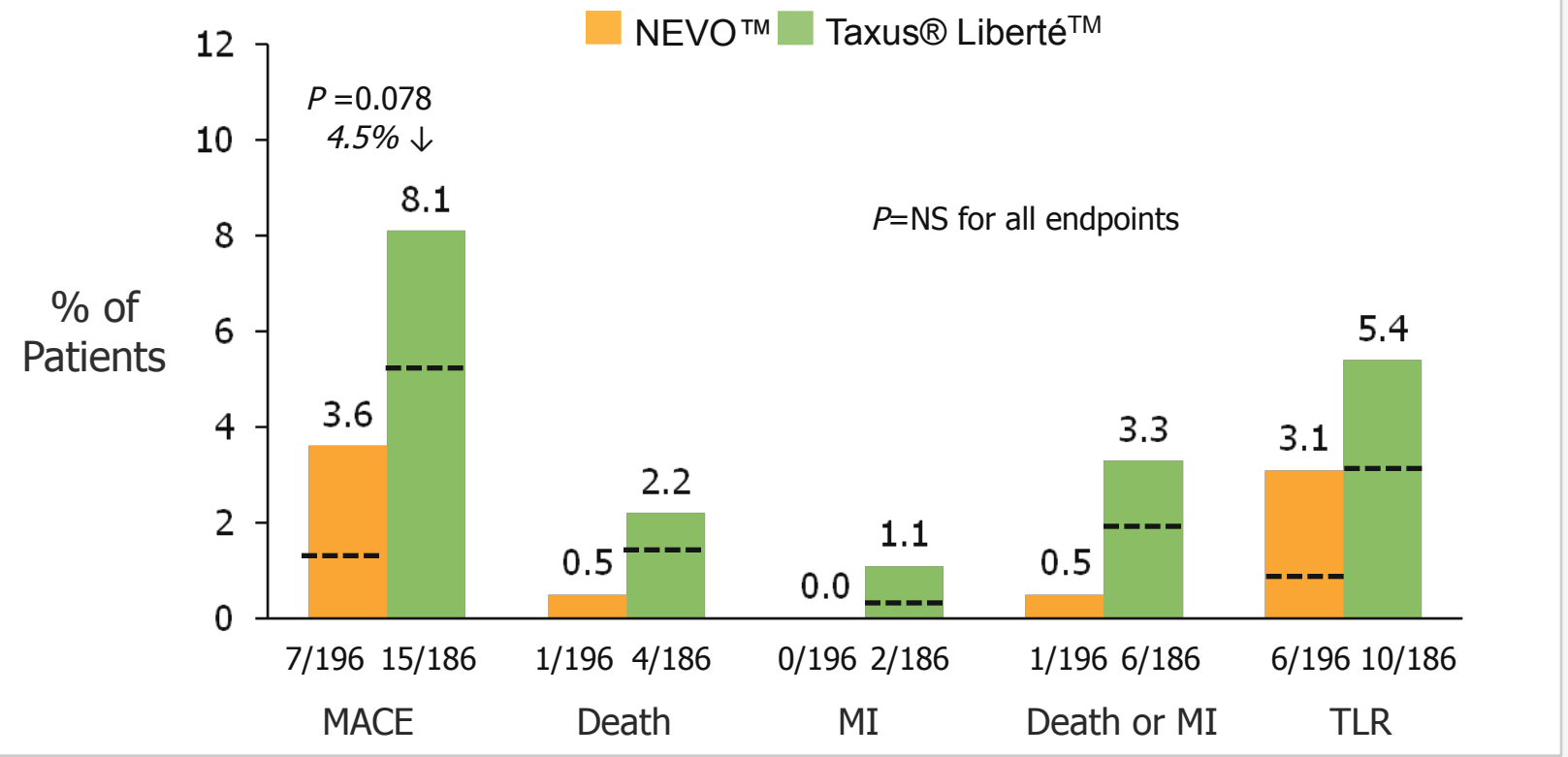
EuroPCR 09, Oral presentation, Chr. Spaulding

NEVO RES-I:
12-Month Out-of-Hospital MACE and Components

12-MONTH MACE AND COMPONENTS

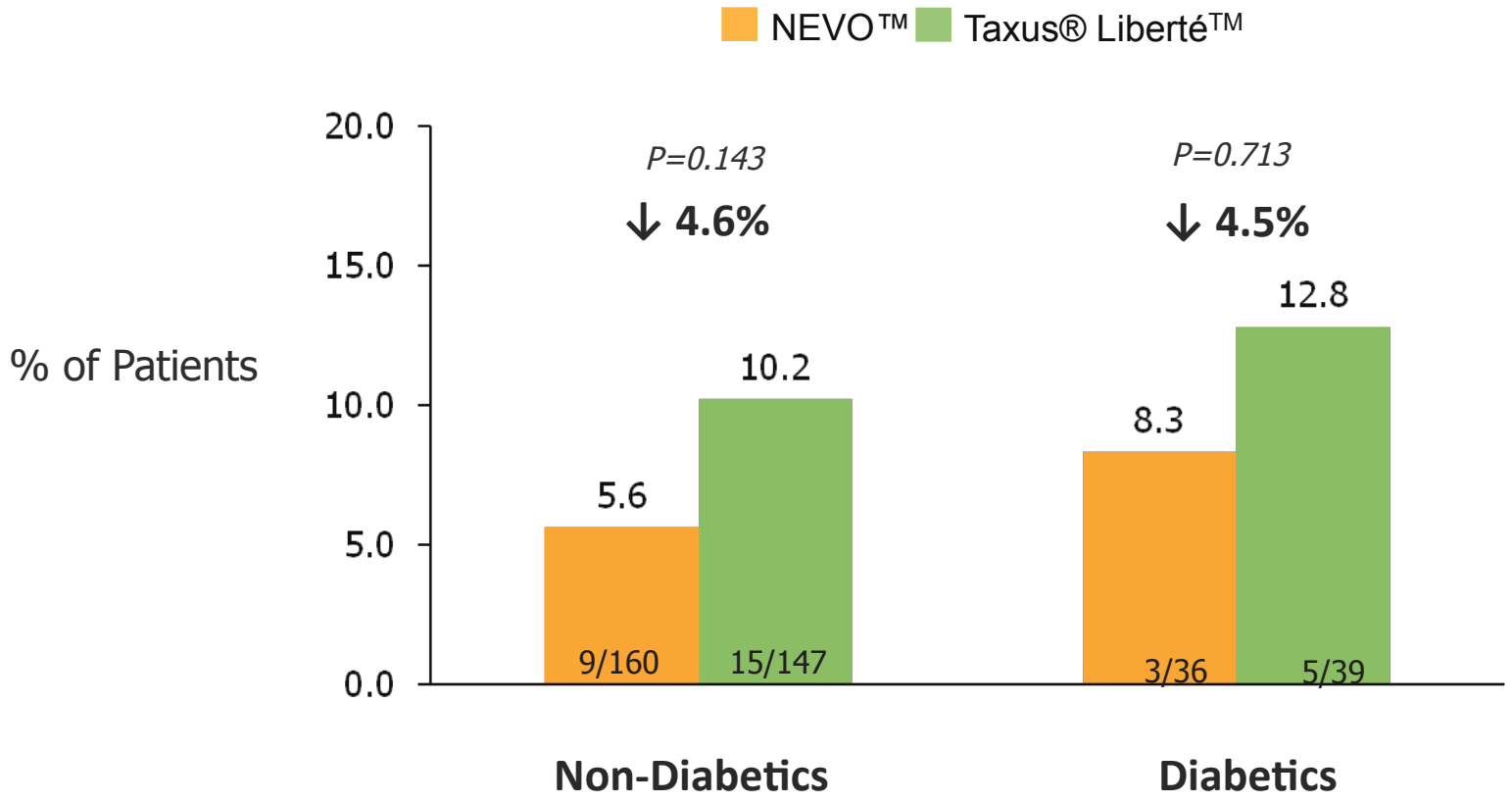


NEVO RES-I was not powered for clinical endpoints

MACE=Major adverse cardiac events.
EuroPCR 09, Oral presentation, Chr. Spaulding

NEVO RES-I: Diabetic Subgroup Analysis – 12-Month MACE

12-Month MACE

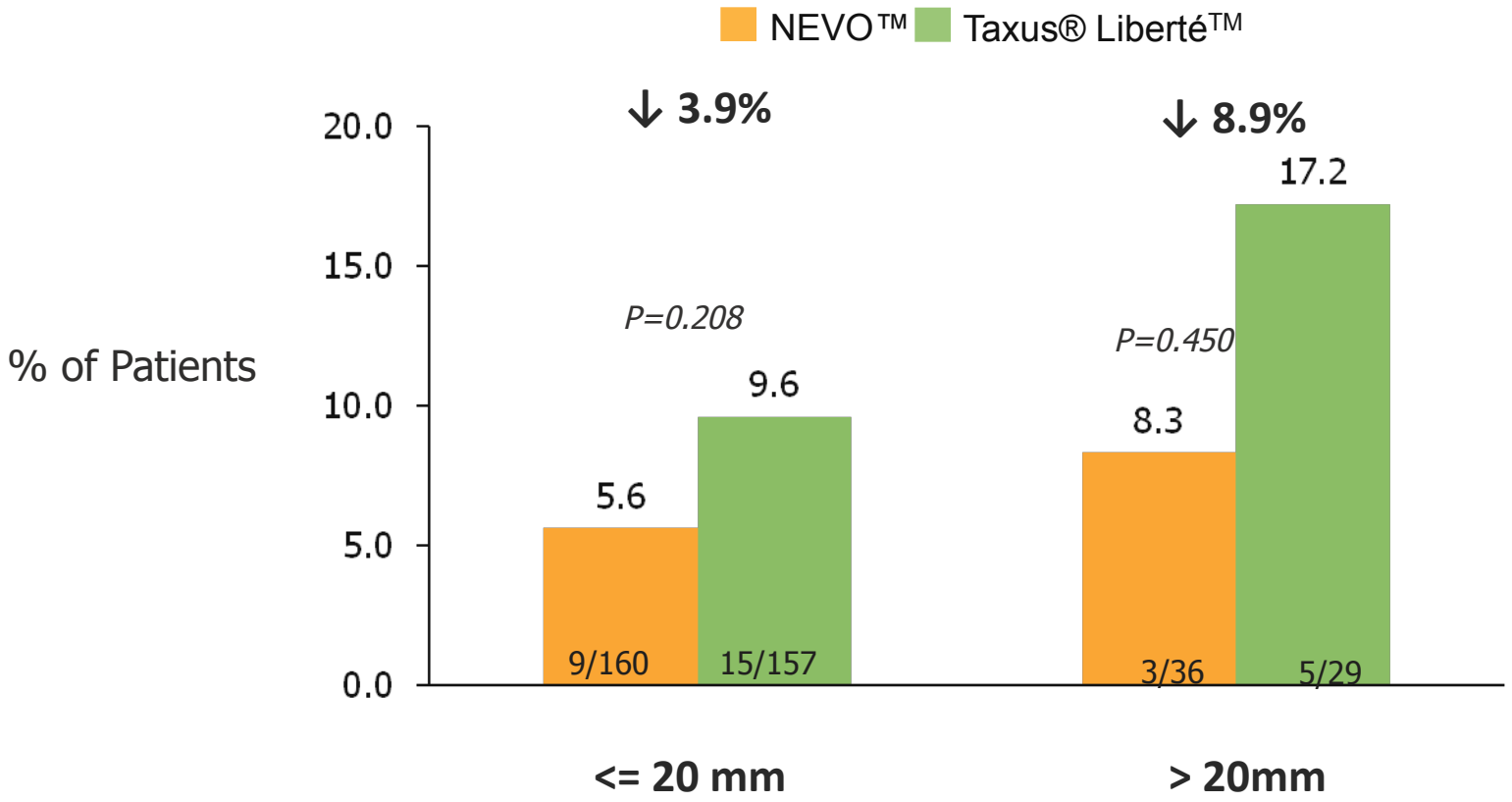


NEVO RES-I was not powered for clinical endpoints

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

NEVO RES-I: Lesion Length Analysis – 12-Month MACE

12-Month 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

no cases of stent thrombosis
NEVO™-treated patients.

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

NEVO RES-I: Conclusions

- The NEVO™ stent demonstrated superiority over the Taxus® Liberté™ stent 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

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

CONCLUSION

- La nature du polymère est un composant essentiel de l'efficacité et de la tolérance des stents actifs
- Un polymère biodégradable offre à priori l'avantage de réduire les inconvénients potentiels d'un polymère persistant
- La technologie réservoir combinée au sirolimus permet d'obtenir d'excellents résultats angiographiques et cliniques
- Le bénéfice à long terme notamment en terme de thrombose reste à confirmer par le suivi à long terme