First Clinical Results and Future Developments of RES Technology
NEVO RES I Trial

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Nevo™
SIROLIMUS-ELUTING
CORONARY STENT

A Few Misconceptions…..

- Late and very late stent thrombosis have virtually dissapeared from my practice because:
  - Prolonged dual antiplatelet therapy has increased safety
  - « Second generation » drug eluting stents are safer

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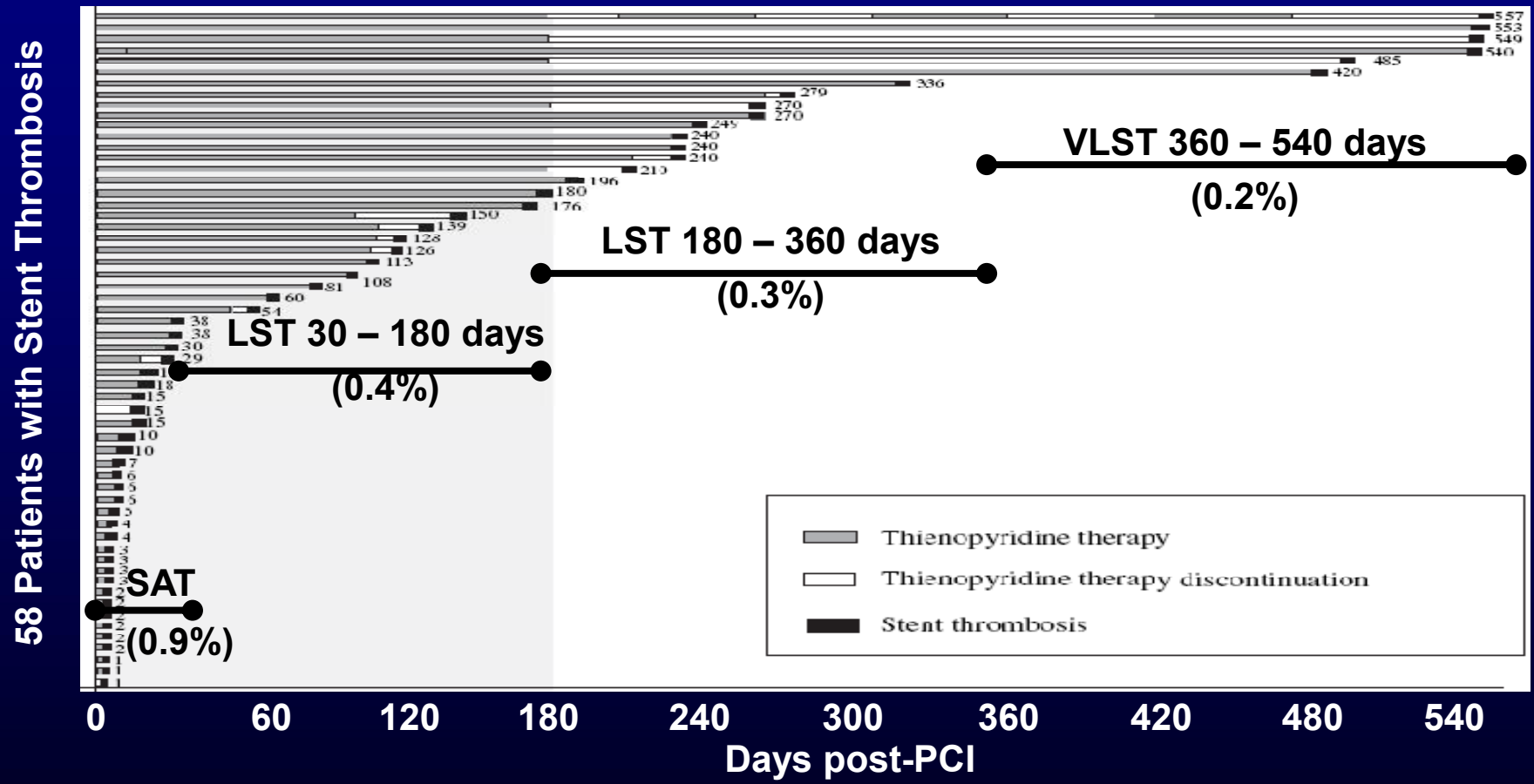
CORONARY STENT

Relationship between discontinuation of thienopyridine therapy and ST



Median time from clopidogrel discontinuation and ST:

- ST within first 6 months: 13.5 days (IQR range, 5.2 to 25.7)

- ST after the first 6 months: 90 days (IQR, 30 to 365 days)

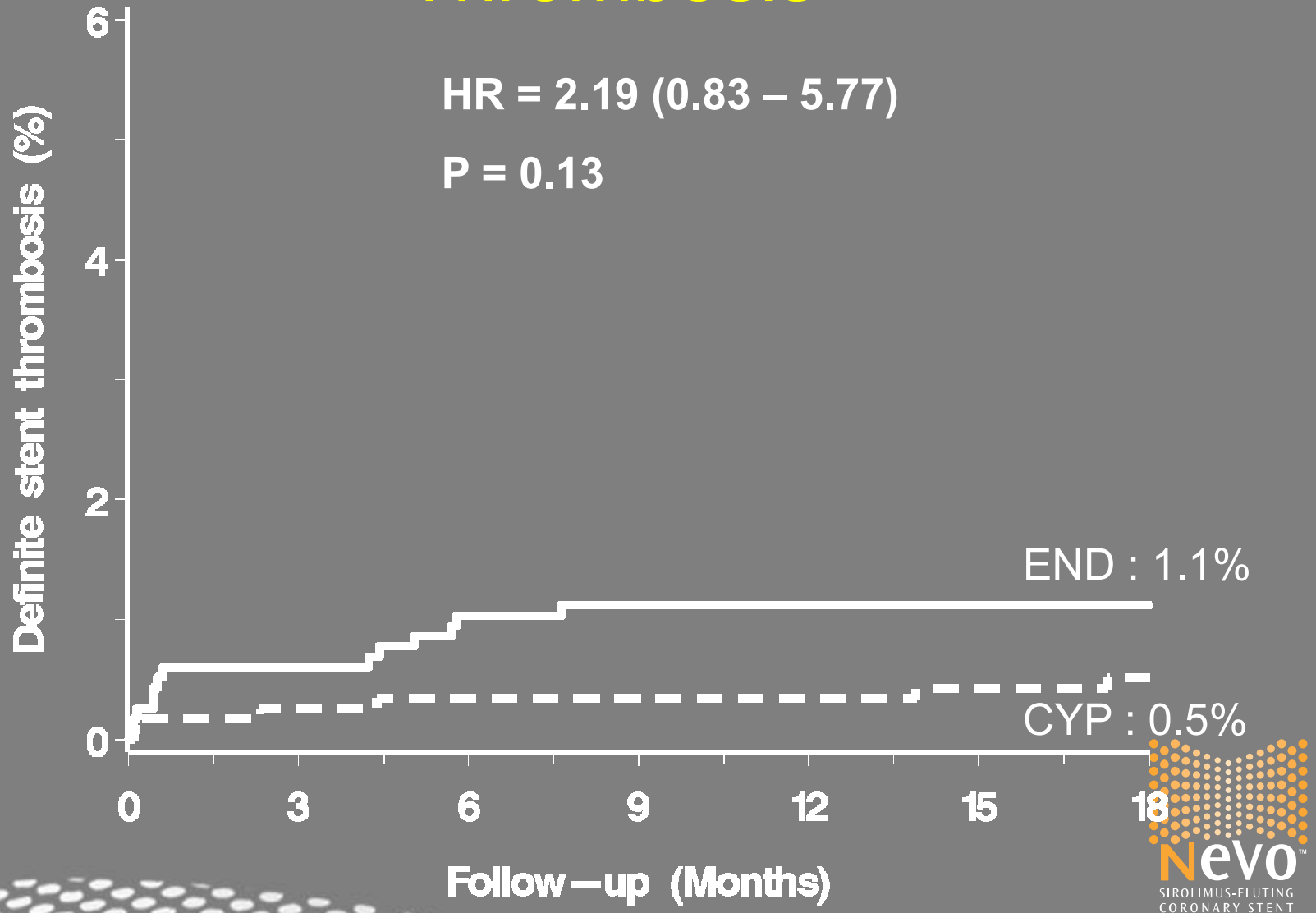
Airoldi, F., et al., Colombo., A., et al., *Circulation* 2007; 116:745-54.

Park S-J et al, N Engl J Med 2010

Table 3. Outcome Rates at 12 Months and 24 Months, According to Treatment Group.*

Outcome	Total No. of Events		Cumulative Event Rate at 12 Mo		Cumulative Event Rate at 24 Mo		Hazard Ratio (95% CI)†	P Value
	Clopidogrel +Aspirin	Aspirin Alone	Clopidogrel +Aspirin	Aspirin Alone	Clopidogrel +Aspirin	Aspirin Alone		
Primary end point: MI or death from cardiac causes	20	12	0.7	0.5	1.8	1.2	1.65 (0.80–3.36)	0.17
Secondary end points								
Death from any cause	20	13	0.5	0.5	1.6	1.4	1.52 (0.75–3.50)	0.24
MI	10	7	0.4	0.3	0.8	0.7	1.41 (0.54–3.71)	0.49
Stroke	9	4	0.3	0.3	1.0	0.3	2.22 (0.68–7.20)	0.19
Stent thrombosis, definite	5	4	0.2	0.1	0.4	0.4	1.23 (0.33–4.58)	0.76
Repeat revascularization	36	26	1.7	1.1	3.1	2.4	1.37 (0.83 2.27)	0.22
MI or death from any cause	27	17	0.8	0.8	2.3	1.7	1.57 (0.85–2.88)	0.15
MI, stroke, or death from any cause	35	20	1.1	1.1	3.2	1.8	1.73 (0.99–3.00)	0.05
MI, stroke, or death from cardiac causes	28	15	1.0	0.8	2.7	1.3	1.84 (0.99–3.45)	0.06
Major bleeding, according to TIMI criteria‡	3	1	0.2	0.1	0.2	0.1	2.96 (0.31–28.46)	0.35

SORT OUT III Definite Stent Thrombosis



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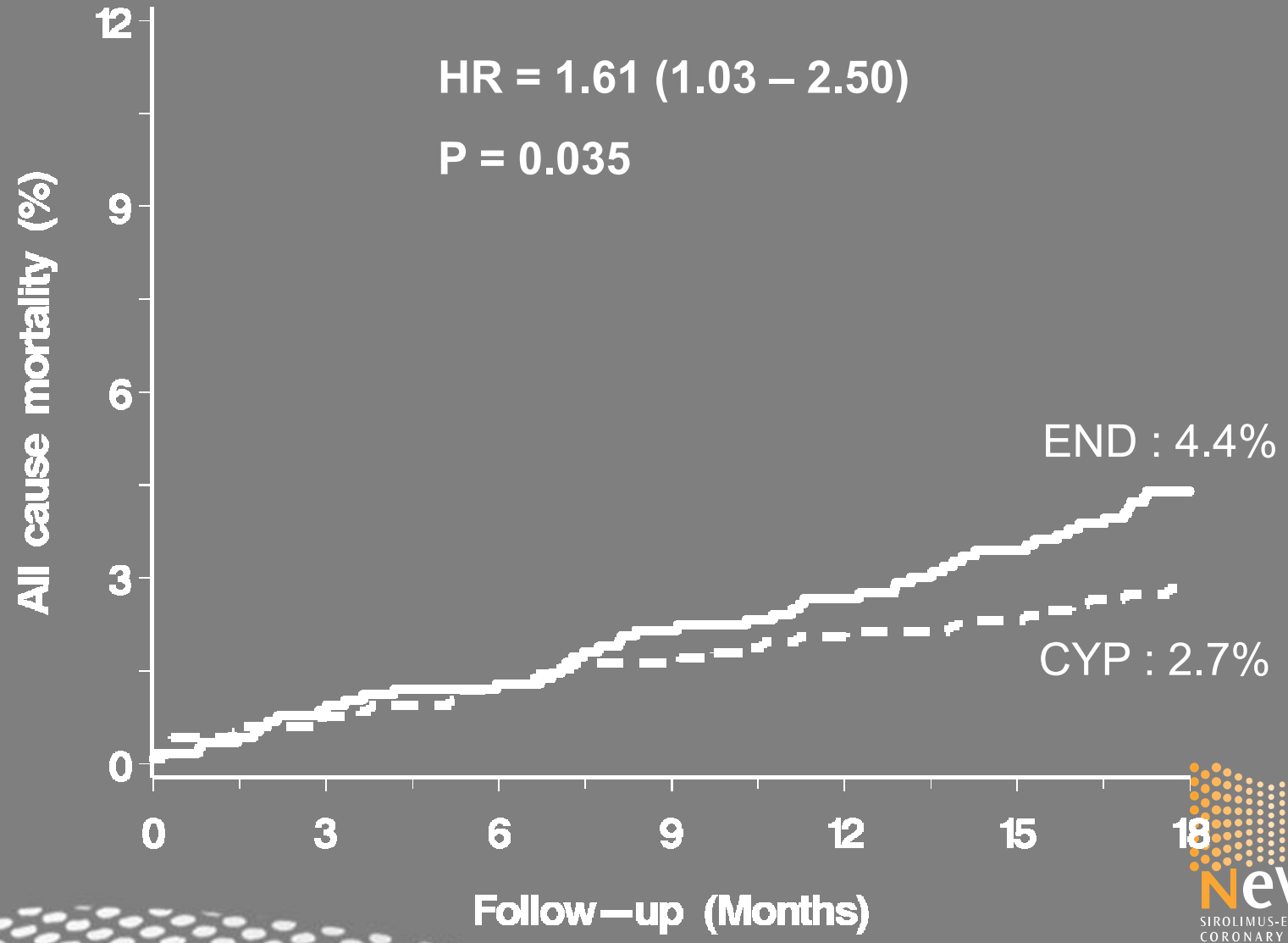
CORONARY STENT

SORT OUT III All Cause Mortality



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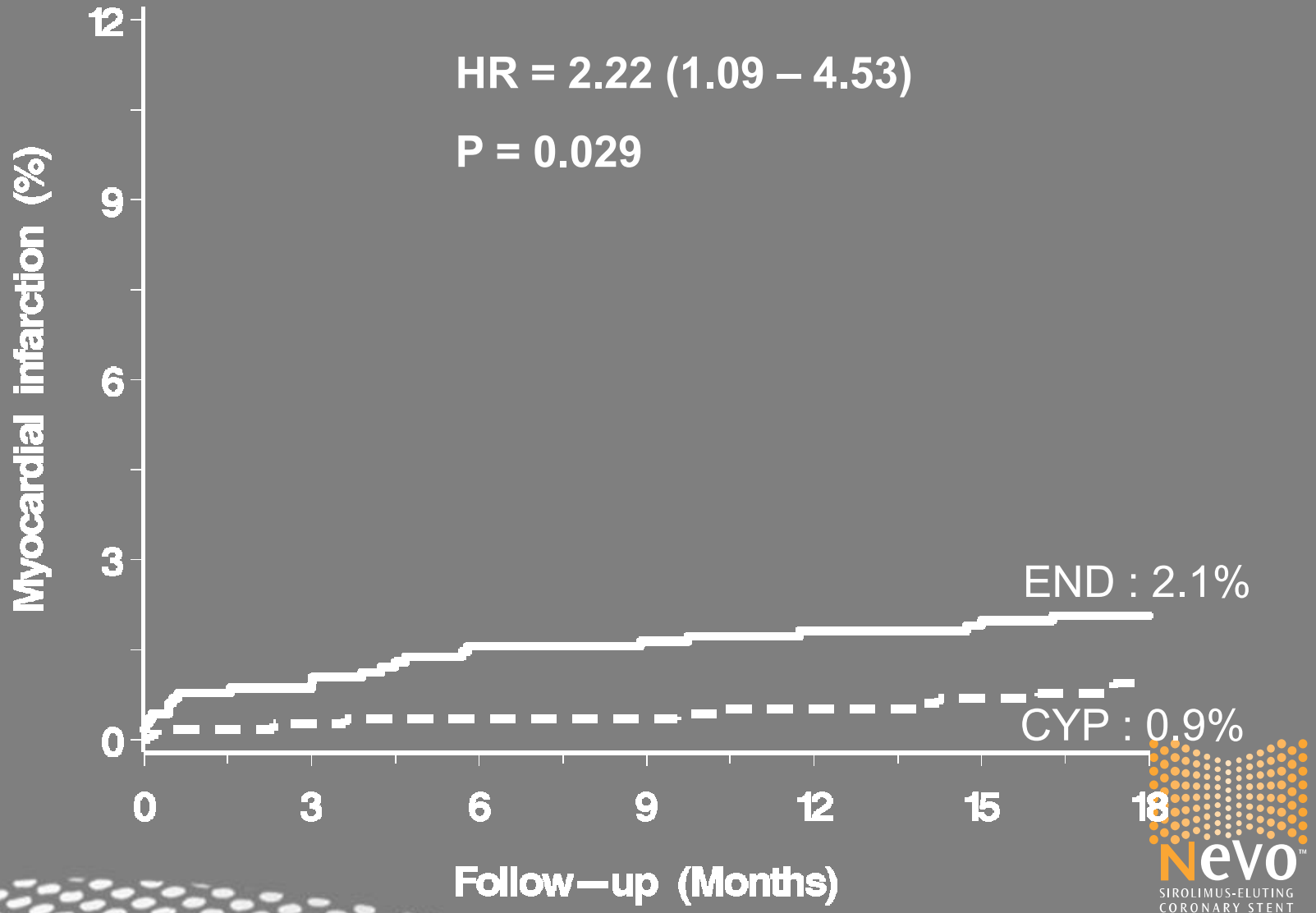
CORONARY STENT

SORT OUT III Myocardial Infarction



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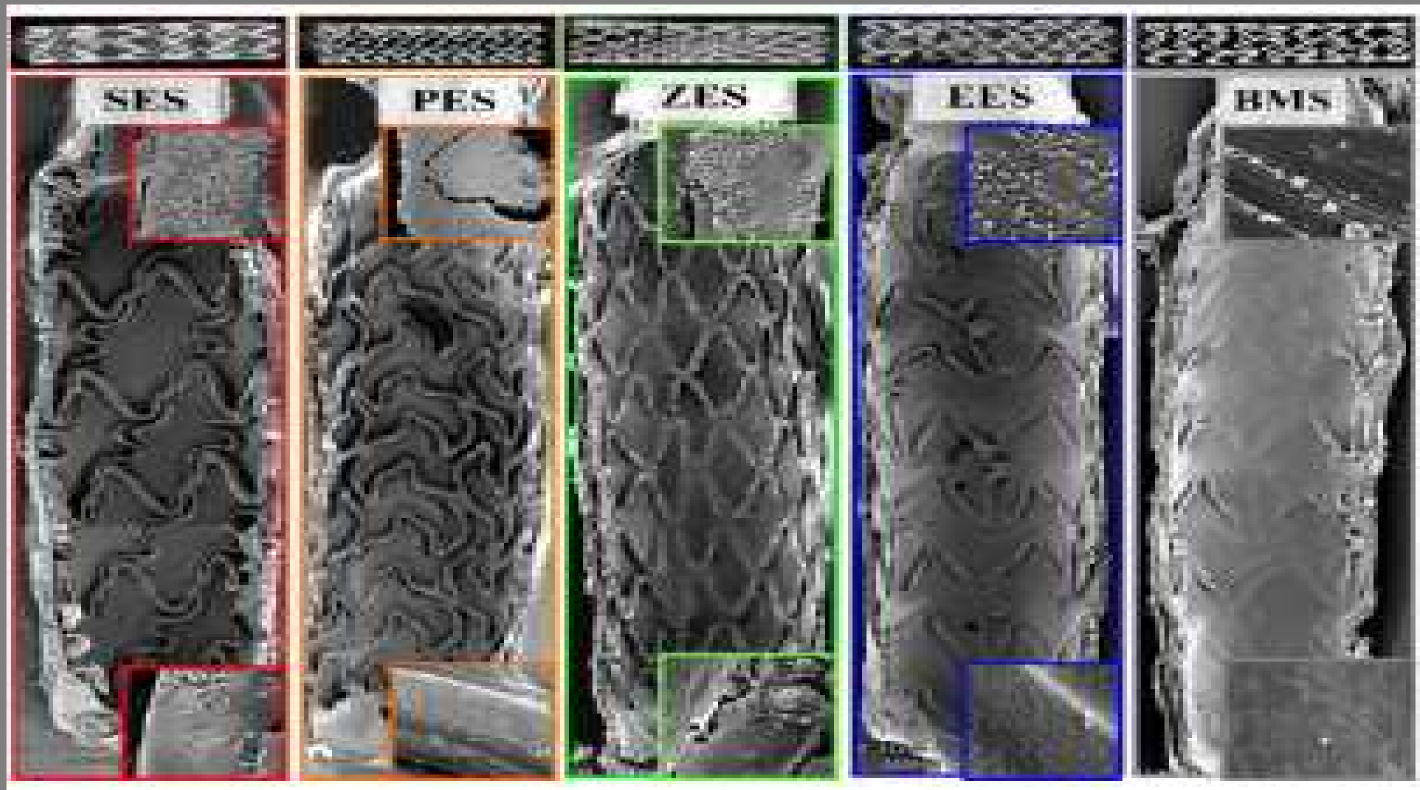
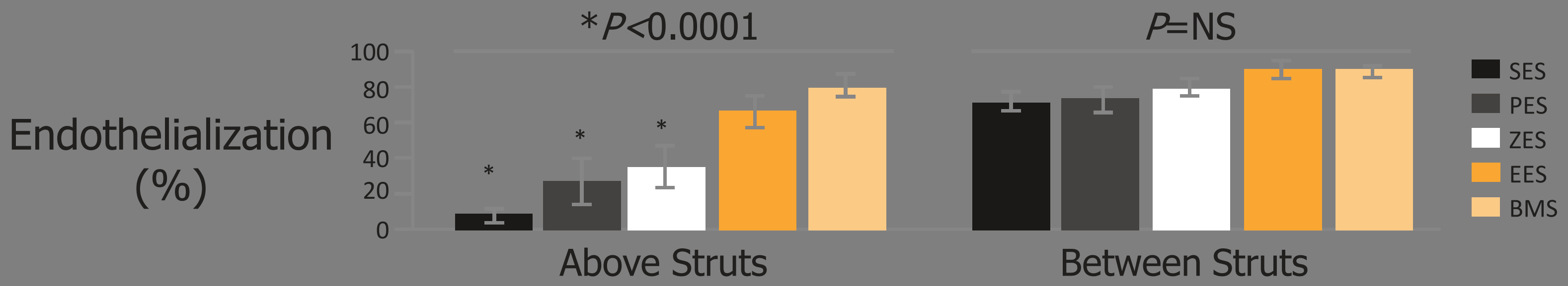
CORONARY STENT

ENDOTHELIALIZATION

Cordis
a Johnson & Johnson company





En taca SEM analysis, 14 day Rabbit Iliac Arterial Model

Nevo™
SIROLIMUS-ELUTING CORONARY STENT
Advanced Safety

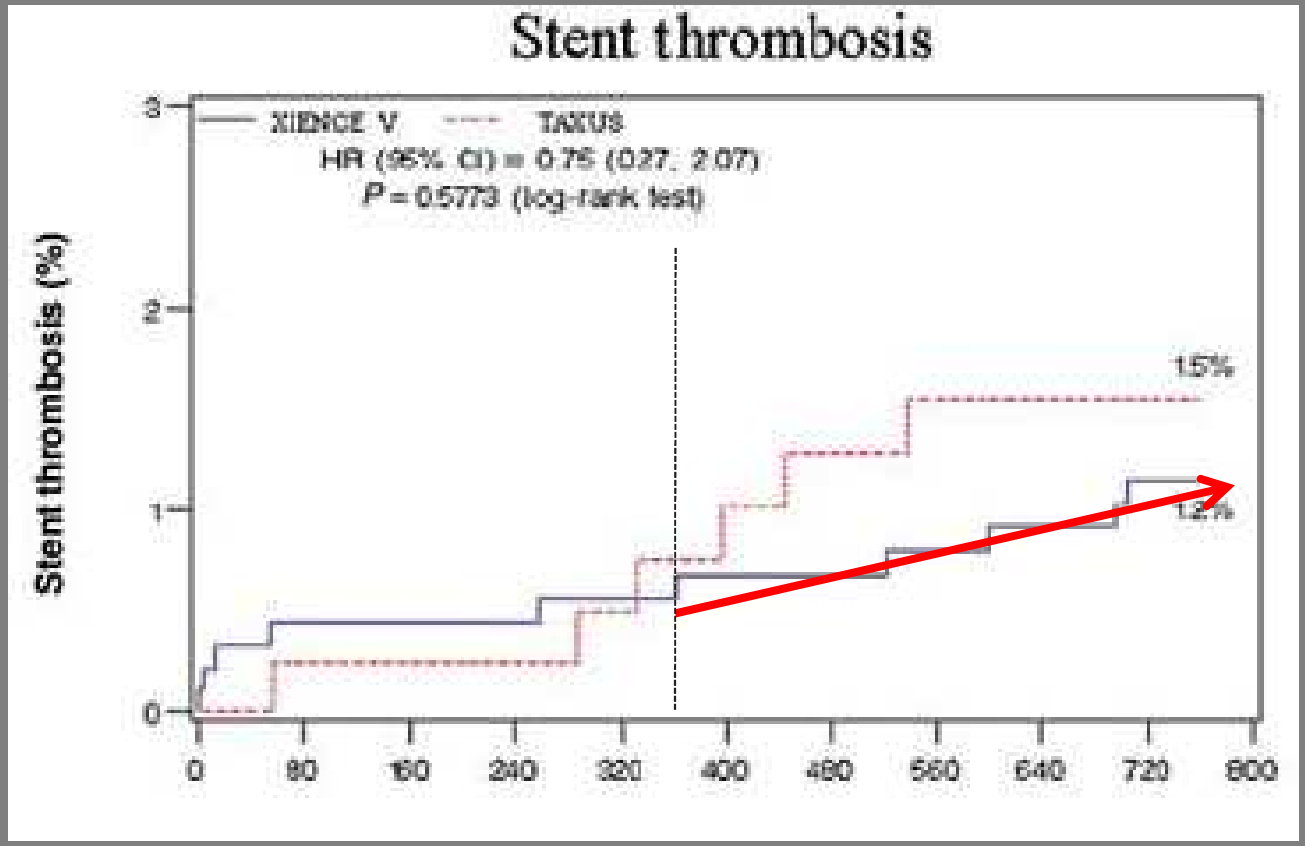
Joner M et al. *J Am Coll Cardiol.* 2008;52(5):333-342.

NEWER SURFACE-COATED DES CONTINUE TO HAVE LIMITATIONS AFTER 1 YEAR (XIENCE V)

Cordis
a Johnson & Johnson company

0.5% VLST (ARC def/prob, or protcol) rate in SPIRIT II/III

Awaiting long-term follow-up from SPIRIT IV/COMPARE



Nevo™
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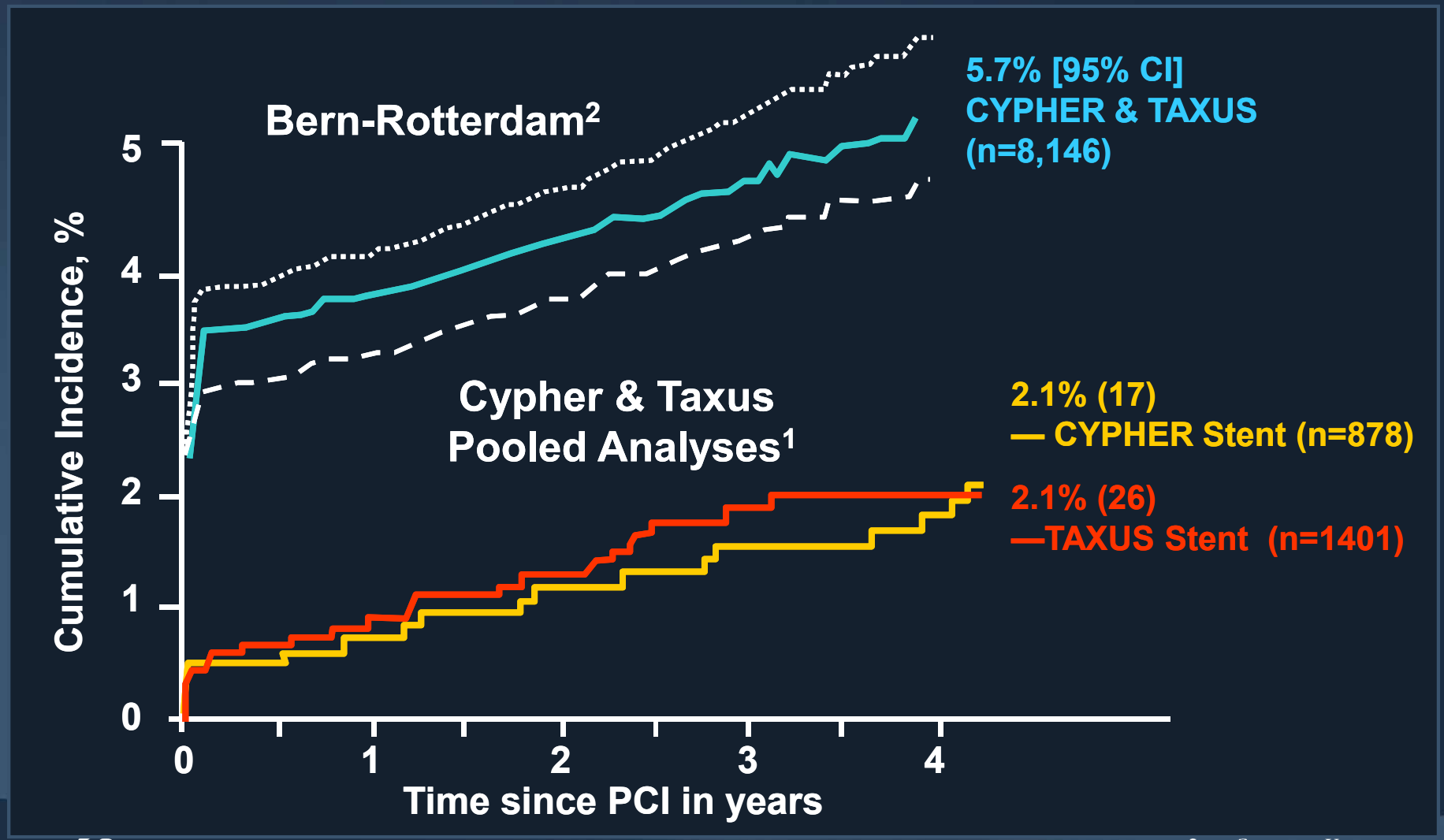
CORONARY STENT

20 YEARS OF INNOVATION
TCT 2008

Cumulative Incidence of ARC Def/Prob ST over 4 yrs after DES (CYPHER & TAXUS)



[1] Mauri et al; N Engl J Med 2007;356:1020-9
[2] Wenaweser et al; J Am Coll Cardiol 2008;52:1134-40

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian
The University Hospital of Columbia and Cornell

NEVO™:
Advancing Safety Beyond Surface-coated Stents

Unique RES TECHNOLOGY™

- No surface polymer coating
- Controlled drug delivery
- Bioabsorbable polymer, fully absorbed in as little as 90 days

Advanced Deliverability

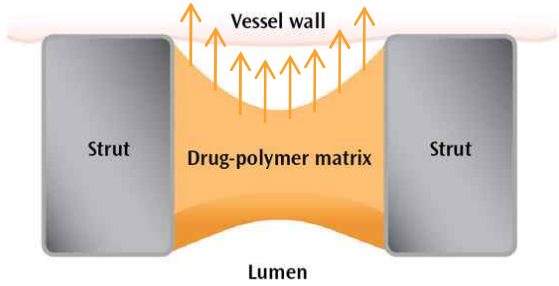
- Optimized CoCr stent design
- Advanced delivery system

Proven Sirolimus Evidence

- CYPHER®-like tissue content
- Largest body of evidence up to 7 years

NEVO™ is Designed to Deliver as a BMS

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



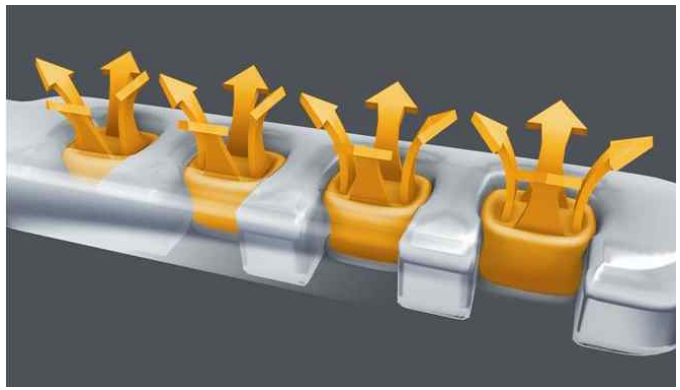
Cross-section of reservoir

Polymer is protected during delivery
Less friction during stent delivery

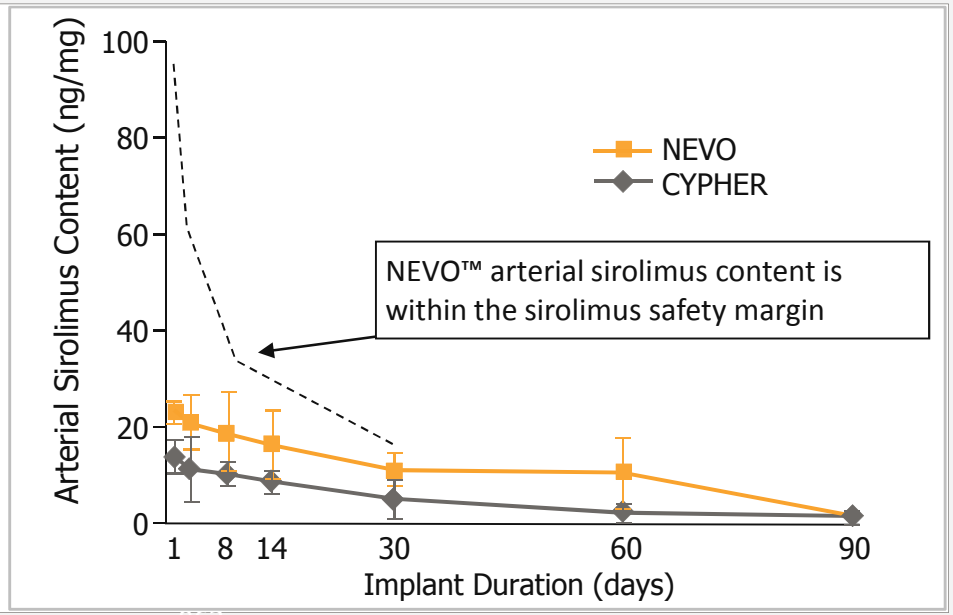
Designed to Deliver as a BMS

NEVO™ Delivers Sirolimus Directly to the Vessel Wall

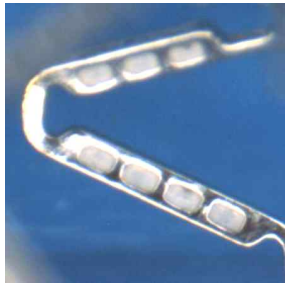
NEVO™ provides controlled preferential delivery of sirolimus to the vessel wall



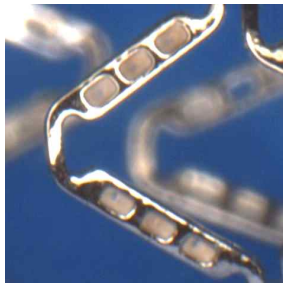
NEVO™ achieves sirolimus content in tissue similar to CYPHER



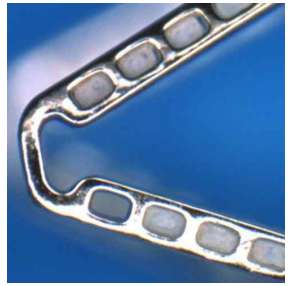
NEVO is designed to transform to a BMS



Day 1



Day 30

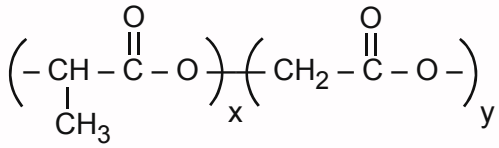


Day 60

Day 90

DES → **BMS**

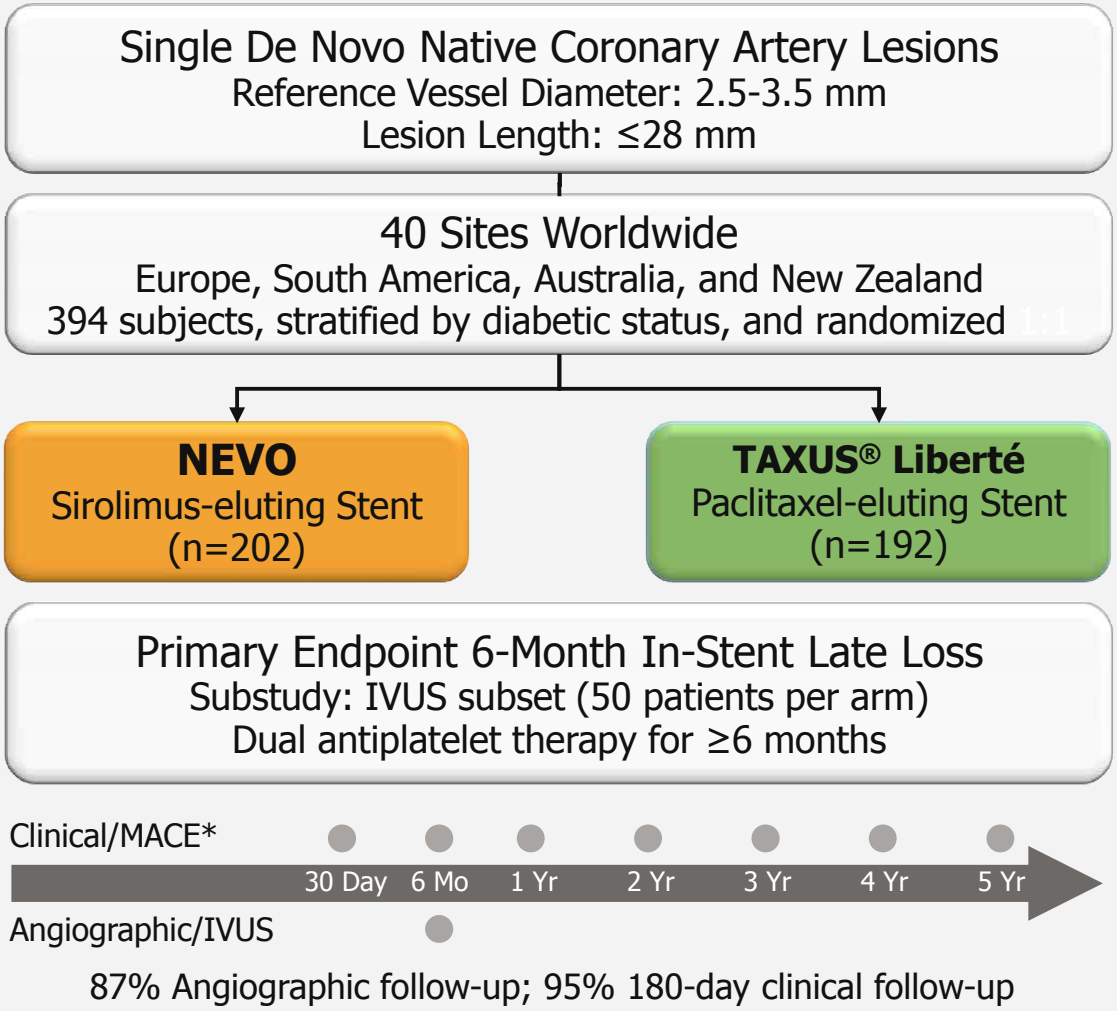
Fully bioabsorbable PLGA polymer



- Used in a variety of medical applications such as VICRYL™ sutures[1]
- Designed for complete bioabsorption in as little as 90 days
- Highly biocompatible
- Fully metabolized bioproducts (CO_2 + H_2O)
- RES TECHNOLOGY stents transform 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 RES-I Study Overview



87% Angiographic follow-up; 95% 180-day clinical follow-up

Principal Investigators
John Ormiston
Alexandre Abizaid
Christian Spaulding

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

NEVO RES-I: Objective and Methods

Objective

To demonstrate noninferiority (and, if positive, superiority) of NEVO™ to TAXUS Liberté for the primary endpoint of angiographic in-stent late loss at 6 months

Major inclusion criteria

- Single de novo lesions in native coronary arteries
- Lesion length ≤28 mm
- 2.5 mm to 3.5 mm in diameter

Major exclusion criteria

- Acute myocardial infarction
- Unprotected left main stem lesions
- Ostial lesions
- Bifurcation lesions with side branch vessel diameter >2.0mm

DAPT Recommendation

Dual antiplatelet drug treatment recommended for a minimum of 6 months with 12 months recommended for all patients at low risk of bleeding

EuroPCR 09, 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

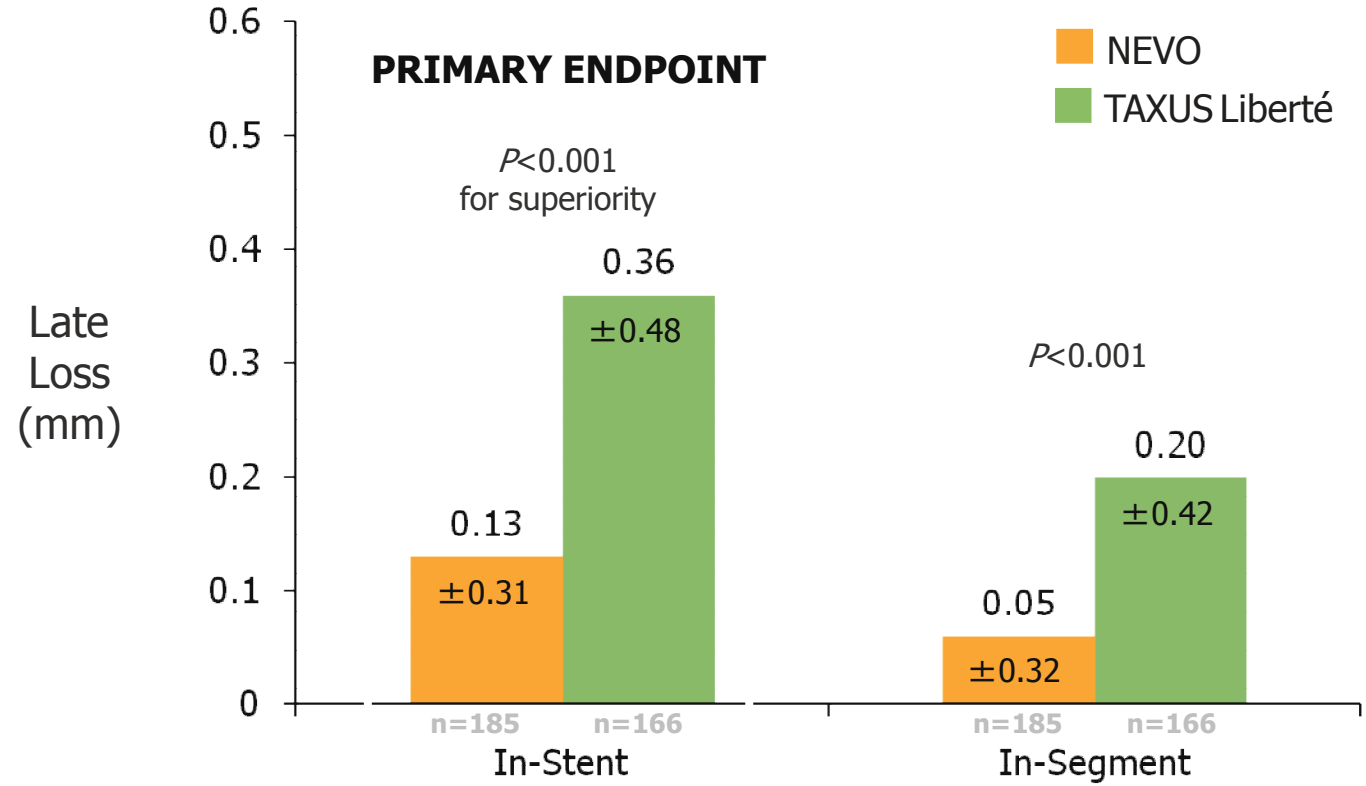
Pre-specified subgroup analyses

- Diabetes and no diabetes
- Reference vessel diameter
- Lesion length ≤ versus ≥20 mm

EuroPCR 09, Oral presentation, Chr. Spaulding

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

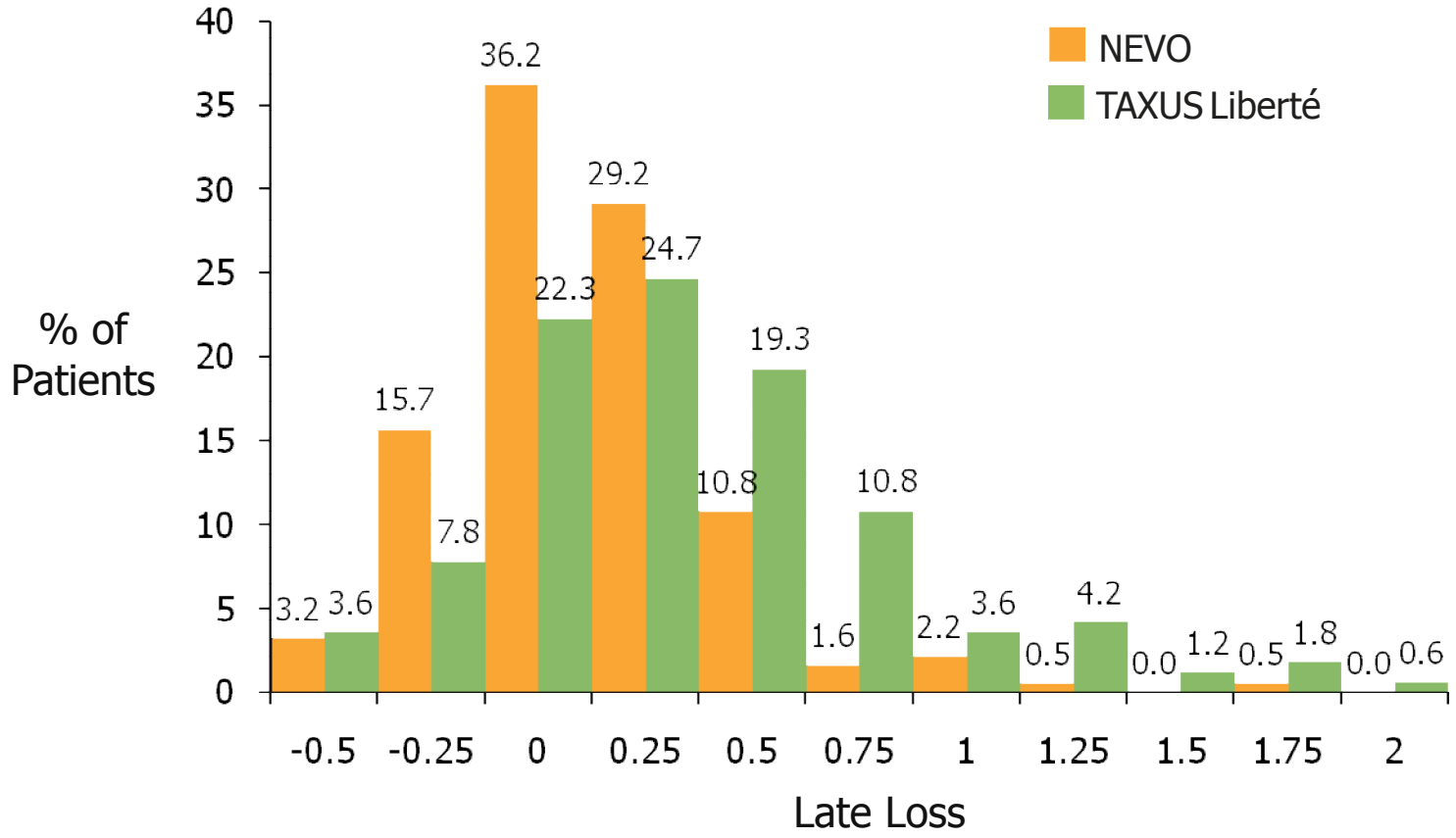
PRIMARY ENDPOINT: LATE LUMEN LOSS AT 6 MONTHS



TCT 09, Oral presentation, J. Ormiston

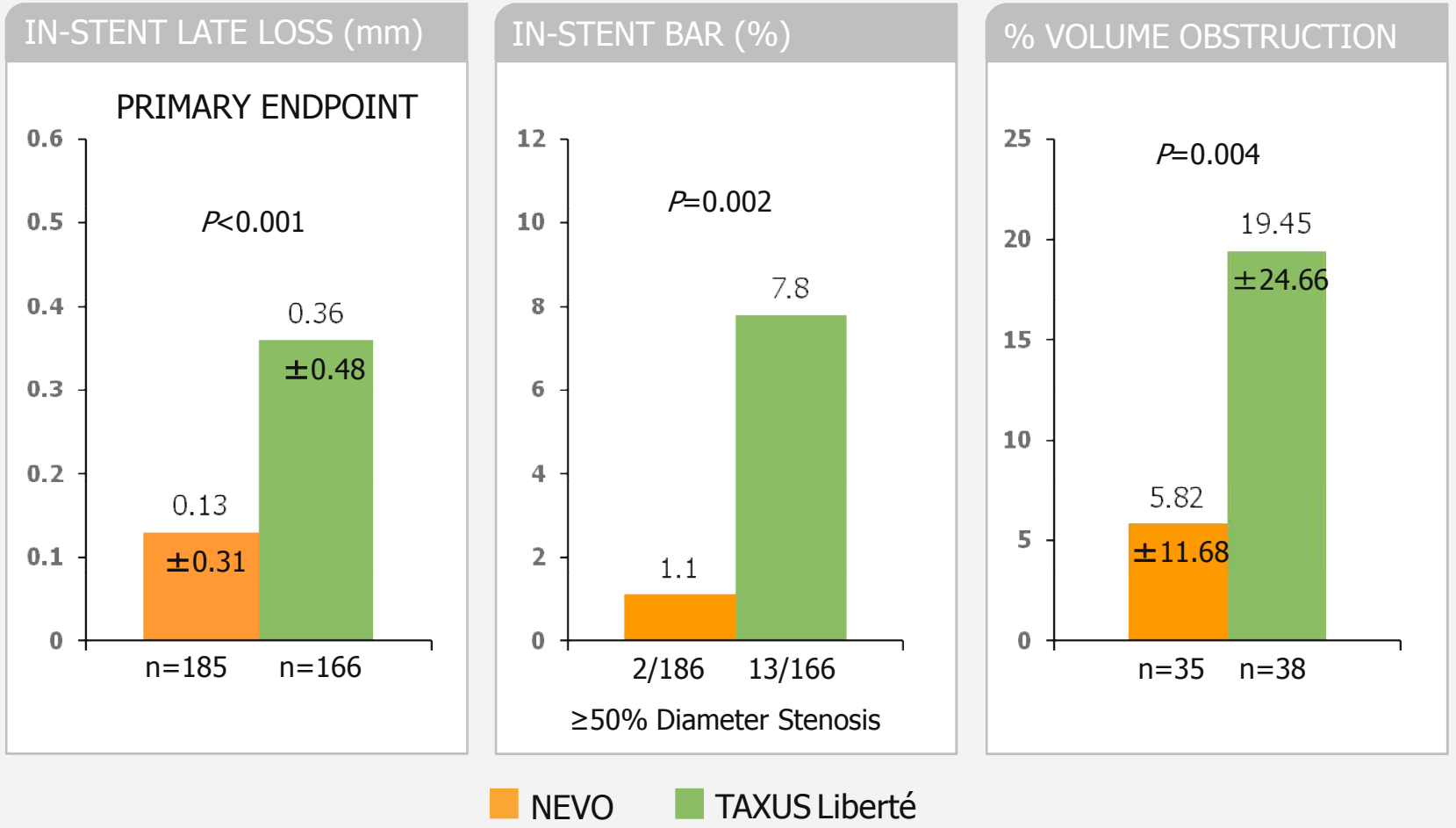
NEVO RES-I: Distribution of In-Stent Late Loss

DISTRIBUTION OF IN-STENT LATE LOSS



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

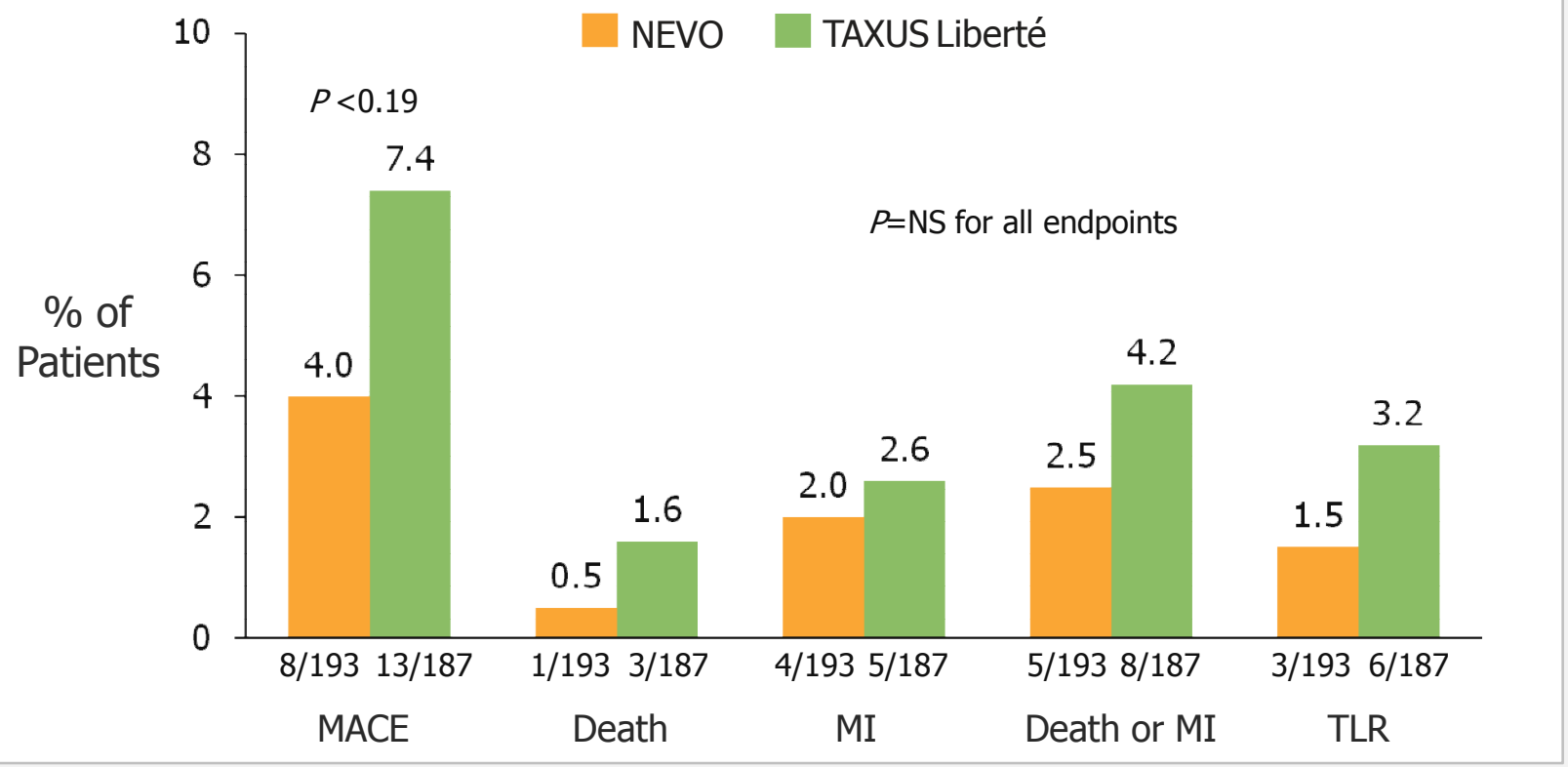
NEVO RES-I: 6-Month In-Stent Late Loss, In-Stent Bar, and IVUS-defined % Volume Obstruction



EuroPCR 09, Oral presentation, Chr. Spaulding

NEVO RES-I: 6-Month MACE and Components

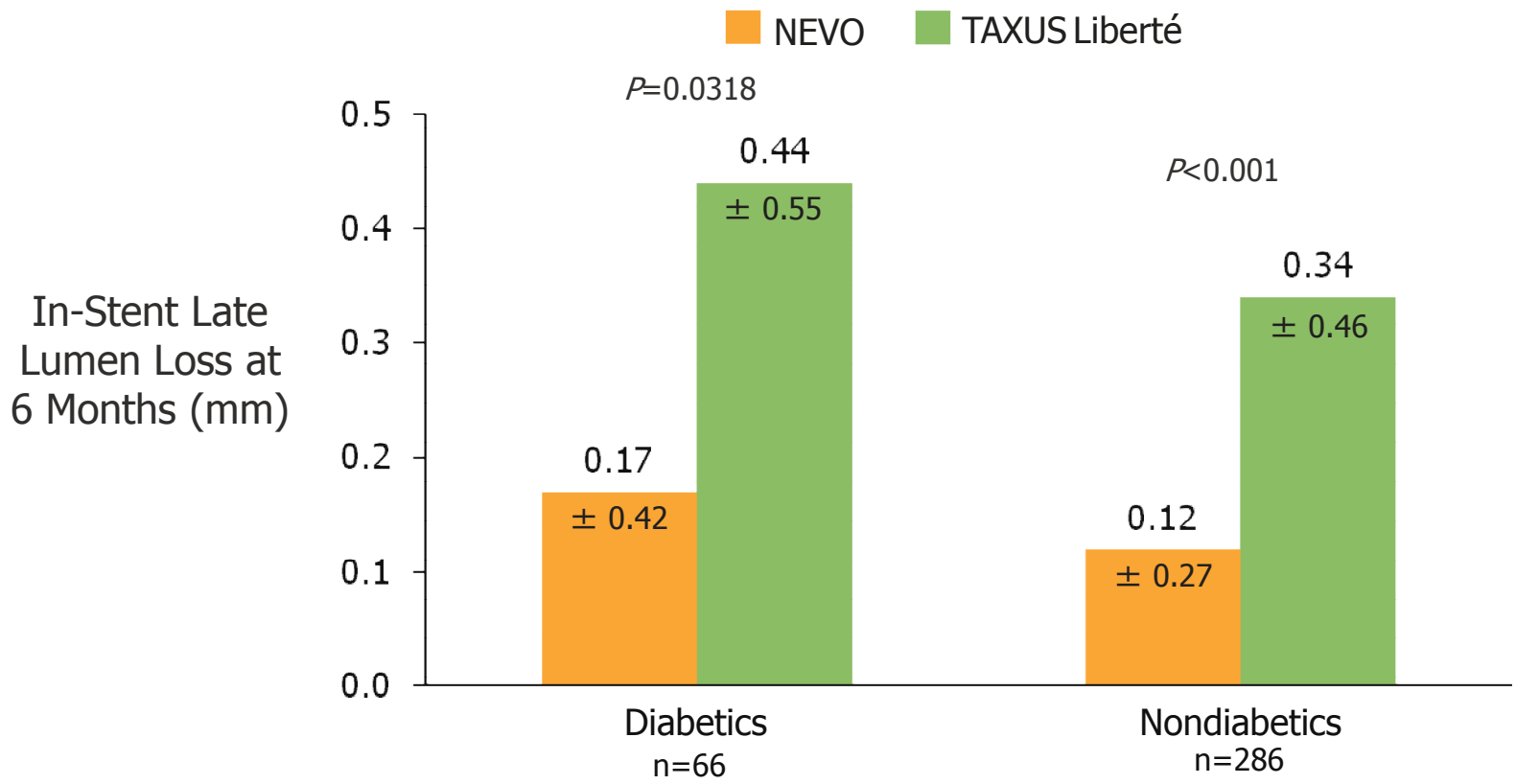
6-MONTH MACE AND COMPONENTS



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

NEVO RES-I: Diabetic Subgroup Analysis – In-Stent Late Loss at 6 Months

IN-STENT LATE LUMEN LOSS AT 6 MONTHS



EuroPCR 09, Oral presentation, Chr. Spaulding

NEVO RES-I: ARC Stent Thrombosis (ST) Through 6 Months

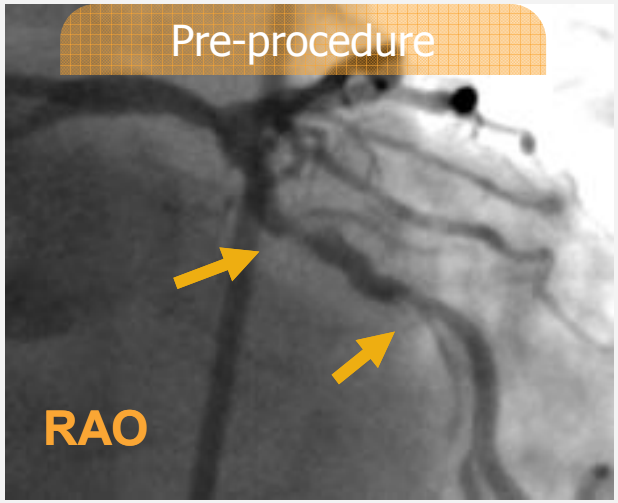
	NEVO (n=202)	**TAXUS Liberté** (n=192)	***P* Value**
Definite	0	0	--
Probable	0	1 (0.5%)	0.49
Possible	0	1 (0.5%)	0.49
Any ARC	0	2 (1.1%)	0.24

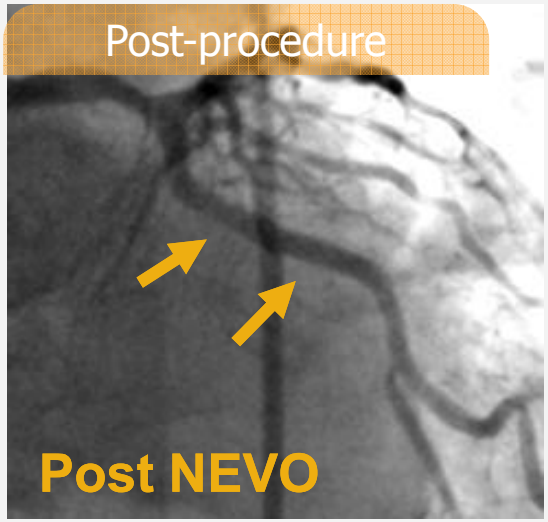
- No reports of early (first 30 days) stent thrombosis in either arm
- 2 reports of late stent thrombosis in TAXUS Liberté-treated patients
  - ARC probable stent thrombosis on day 180
  - ARC possible stent thrombosis on day 101

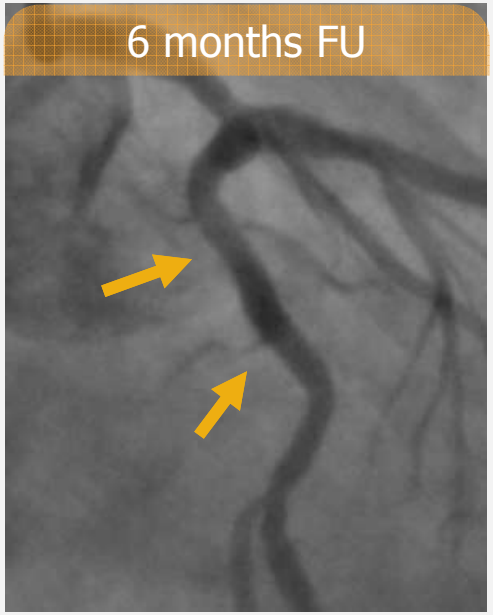
Through 6 months, no cases of stent thrombosis, regardless of definition, were reported in NEVO-treated patients

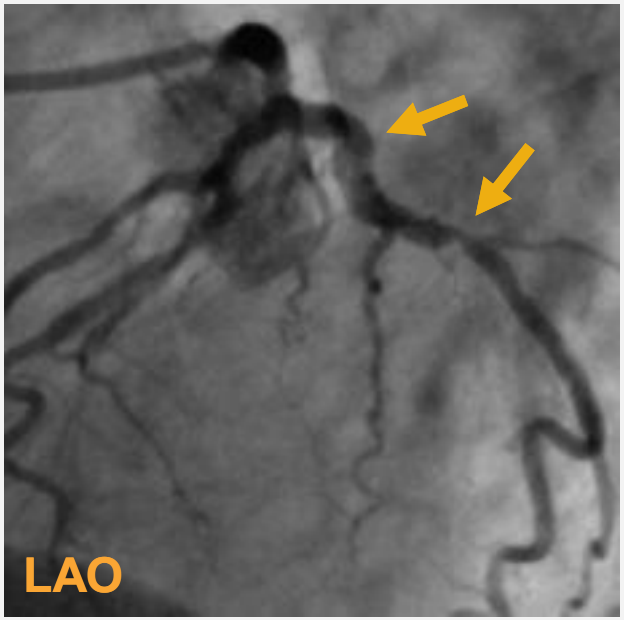
EuroPCR 09, Oral presentation, Chr. Spaulding

First Patient Enrolled- Angiogram with NEVO™





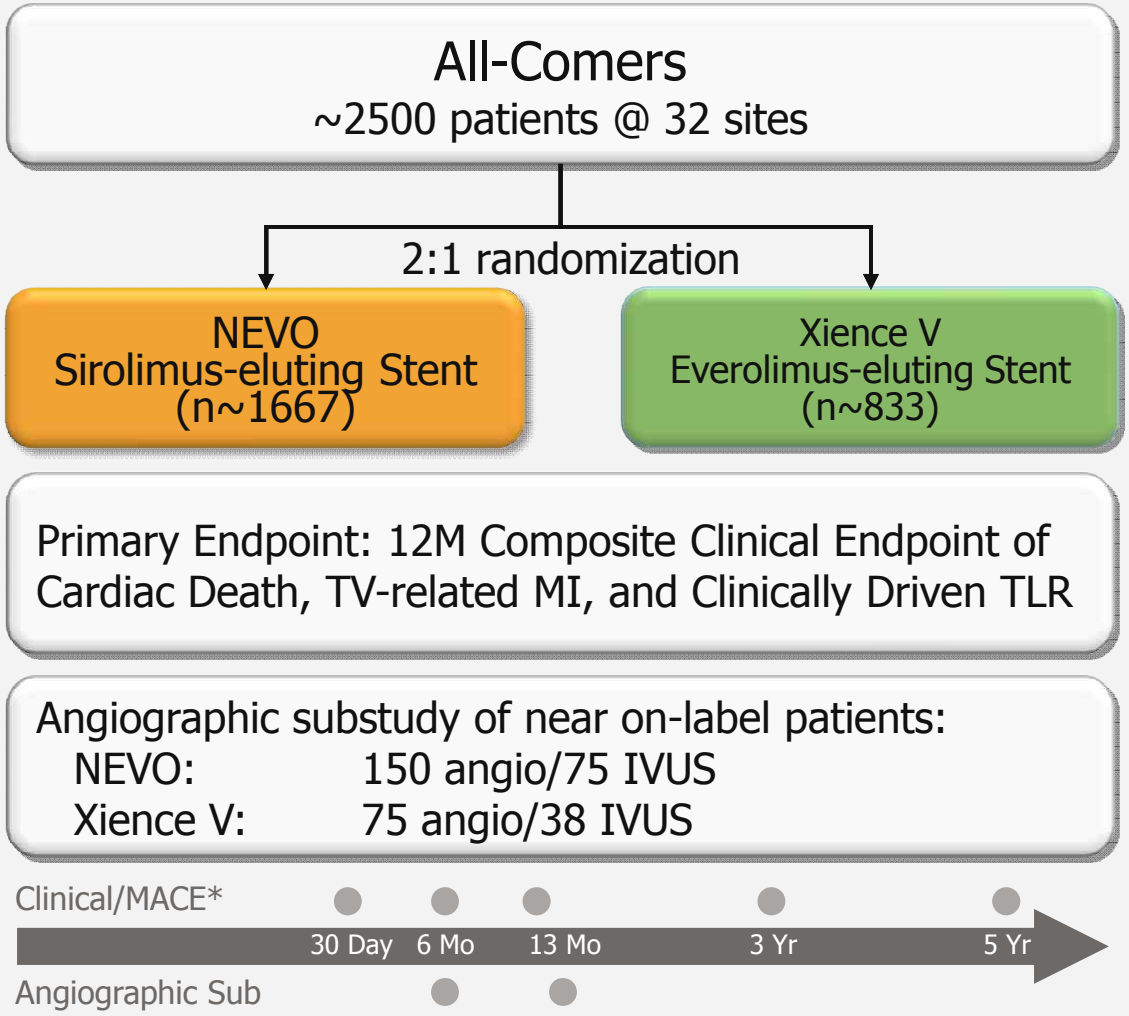




NEVO™ Stent Deployment
(2.5 mm x 22 mm)

Images courtesy of:
John Ormiston, MD
NEVO RES-I:
March 19, 2008,
Auckland, NZ

NEVO™-II Study Overview



Principal Investigators
Patrick Serruys
Stefan Windecker
Manel Sabaté

NEVO™-III US IDE Nonrandomized Trial

Up to 2 lesions in up to 2 vessels
Lesion length: ≤34 mm
Reference vessel diameter: 2.25 - 3.5 mm

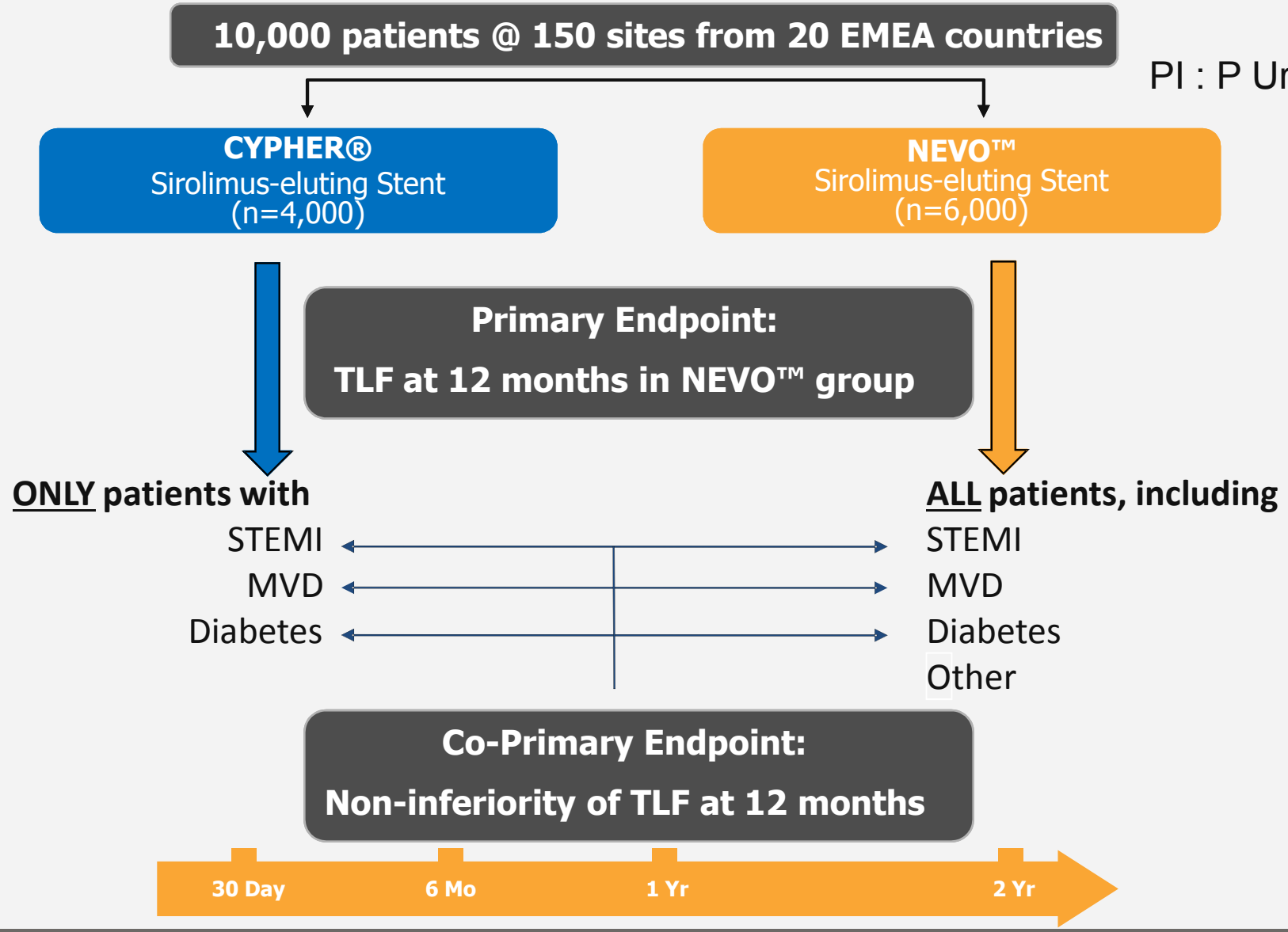
1300 patients @ ~100 sites in US and Canada

NEVO
Sirolimus-eluting Stent
(n=1300)

Primary Endpoint 6-Month In-Stent Late Loss
Dual antiplatelet therapy for ≥6 months but recommend 12 months in patients at low risk of bleeding

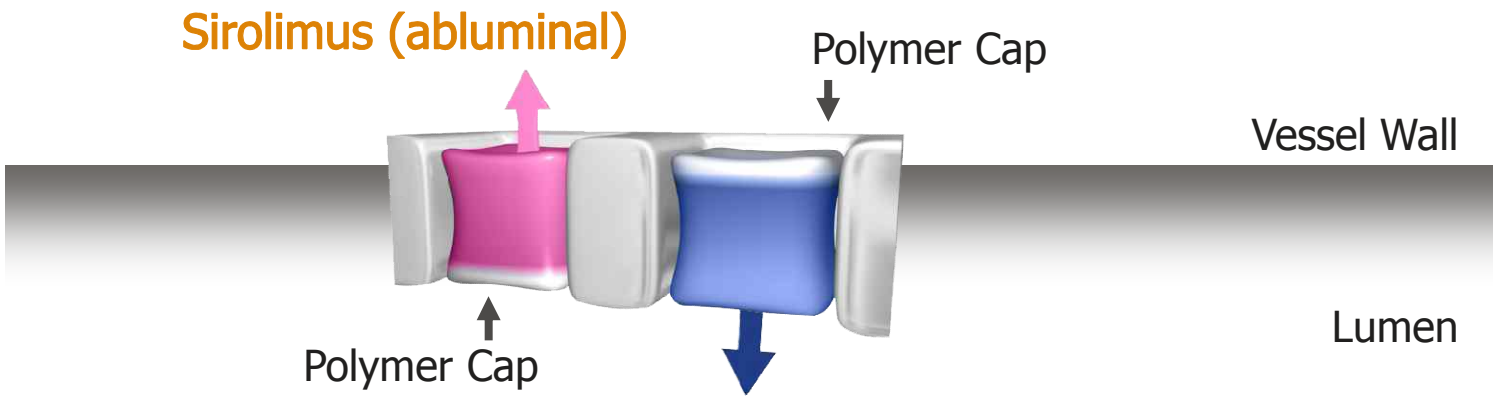
Principal Investigators
Dan Simon
David Kandzari

CYNERGY- The CYPHER and NEVO Clinical REGISTRY



RES TECHNOLOGY

Antithrombotic Stent Strategies



2nd Drug (luminal)

SURFACE MODIFICATION

- Heparin
- Nitric oxide
- Endothelial cell promoter

ELUTABLE ANTITHROMBOTIC

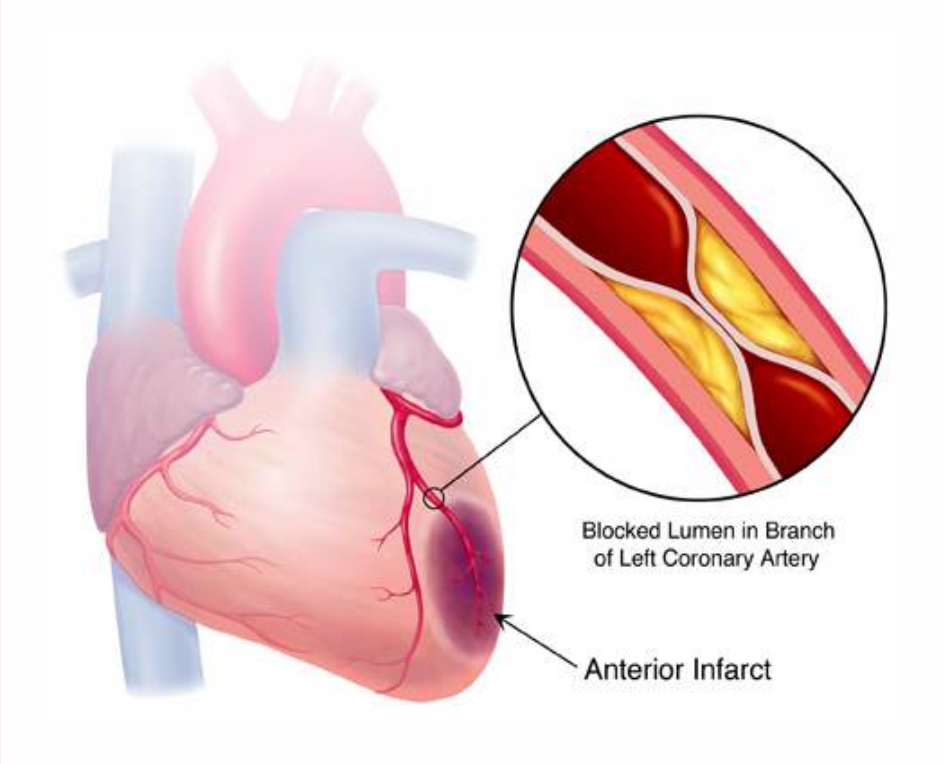
- Thrombin inhibitor
- GP2b/3a inhibitor
- Other platelet inhibitors

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

RES TECHNOLOGY
Acute Myocardial Infarction

Objectives

- Rapid reperfusion of ischemic myocardium with a stent
- Elution of a therapeutic agent downstream to reduce infarct size
  - Prevent "no-reflow"
  - Prevent reperfusion injury
  - Reduce stent thrombosis
- Reduce mortality, prevent LV dysfunction and CHF



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

gr2

RES TECHNOLOGY

Acute Myocardial Infarction

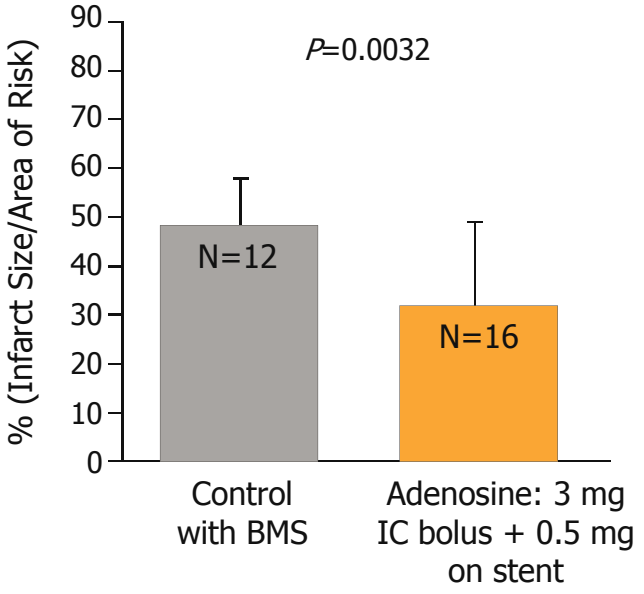
Preclinical Study

Adenosine + stent reduces infarct size compared with adenosine alone

Clinical Study

Adenosine infusion may reduce infarct size in humans

ADENOSINE STUDY



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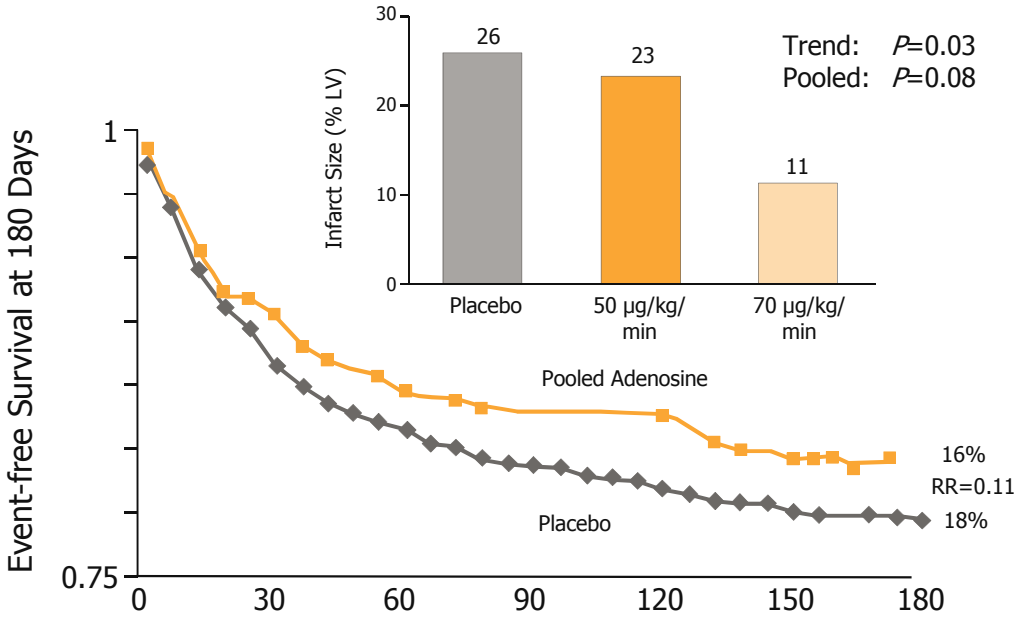


- Patients with anterior wall MI reperfused within 6 hours
- Intravenous adenosine infusion for 3 hours (50 or 70 µg/kg/min)
- Significant reduction in infarct size at 70 µg/kg/min dose
- Improved survival at 6 months if treated within 3 hours

Slide 30

gr2 Need references for these two graphs/pieces of data
grogan, 2010-04-09

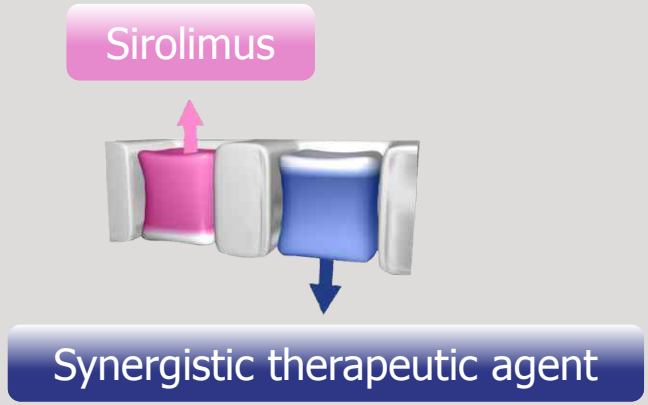
RES TECHNOLOGY

Diabetes and Vascular Dysfunction

Diabetes Mellitus (Type 2)	
Problem	Increased neointimal proliferation post-PCI increased thrombosis
Objective	Address unmet need of the diabetic patient • Further reduce neointimal proliferation and restenosis • Expand treatment options

Synergistic therapeutic agent:

- Antiproliferative
- Anti-inflammatory
- Antithrombotic



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

NEVO RES-I: Conclusions

- NEVO™ was superior to the Taxus® Liberté® stent for the angiographic primary endpoint of in-stent late loss
  - Superiority was also observed in the predefined subgroups of diabetes, vessel diameter, and lesion length
  - More uniform tissue response was observed with NEVO™
- No ARC stent thromboses with NEVO™
  - 2 reports of late thromboses with Taxus Liberté (1 probably, 1 possible)
- While not powered for clinical endpoints, the rates of death, MI, and revascularization, as well as the composite endpoints of TLF, TVF, and MACE, all favored NEVO™ over Taxus Liberté
- On-going clinical program: NEVO II, III, Cynergy

EuroPCR 09, Oral presentation, Chr. Spaulding`

RES TECHNOLOGY™ Will Greatly Expand the Scope and Potential of Drug-eluting Stents

- NEVO utilizing RES TECHNOLOGY™
  - Allows transformation to bare metal stent in as little as 90 days
    - Significantly reduces tissue-to-polymer ratio
    - Effectively controls drug release kinetics
    - Reduces the potential for late stent thrombosis
    - Leads to better vascular compatibility
- RES TECHNOLOGY™ offers great versatility in unique drug delivery
  - Elutes single or multiple drugs independently with a directional release
  - Independent release kinetics and long or short release duration
  - Potential to modify bare metal surface for therapeutic benefit
- Programs are underway to investigate the potential of this technology in the areas of acute MI, diabetes, and thrombosis