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

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Cochin Hospital, Paris Descartes University
Paris, France
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
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)

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total No. of Events</th>
<th>Cumulative Event Rate at 12 Mo</th>
<th>Cumulative Event Rate at 24 Mo</th>
<th>Hazard Ratio (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel + Aspirin</td>
<td>Aspirin Alone</td>
<td>Clopidogrel + Aspirin</td>
<td>Aspirin Alone</td>
<td></td>
</tr>
<tr>
<td>Primary end point: MI or death from cardiac causes</td>
<td>20</td>
<td>12</td>
<td>0.7</td>
<td>0.5</td>
<td>1.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>20</td>
<td>13</td>
<td>0.5</td>
<td>0.5</td>
<td>1.52</td>
</tr>
<tr>
<td>MI</td>
<td>10</td>
<td>7</td>
<td>0.4</td>
<td>0.3</td>
<td>1.41</td>
</tr>
<tr>
<td>Stroke</td>
<td>9</td>
<td>4</td>
<td>0.3</td>
<td>0.3</td>
<td>2.22</td>
</tr>
<tr>
<td>Silent thrombosis, definite</td>
<td>5</td>
<td>4</td>
<td>0.2</td>
<td>0.1</td>
<td>1.23</td>
</tr>
<tr>
<td>Repeat revascularization</td>
<td>36</td>
<td>26</td>
<td>1.7</td>
<td>1.1</td>
<td>1.37</td>
</tr>
<tr>
<td>MI or death from any cause</td>
<td>27</td>
<td>17</td>
<td>0.8</td>
<td>0.8</td>
<td>1.57</td>
</tr>
<tr>
<td>MI, stroke, or death from any cause</td>
<td>35</td>
<td>20</td>
<td>1.1</td>
<td>1.1</td>
<td>1.73</td>
</tr>
<tr>
<td>MI, stroke, or death from any cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI, stroke, or death from cardiac causes</td>
<td>28</td>
<td>15</td>
<td>1.0</td>
<td>0.8</td>
<td>1.84</td>
</tr>
<tr>
<td>Major bleeding, according to TIMI criteria‡</td>
<td>3</td>
<td>1</td>
<td>0.2</td>
<td>0.1</td>
<td>2.96</td>
</tr>
</tbody>
</table>
SORT OUT III Definite Stent Thrombosis

HR = 2.19 (0.83 – 5.77)
P = 0.13
SORT OUT III All Cause Mortality

HR = 1.61 (1.03 – 2.50)

P = 0.035

END: 4.4%

CYP: 2.7%
SORT OUT III Myocardial Infarction

HR = 2.22 (1.09 – 4.53)

P = 0.029

END: 2.1%

CYP: 0.9%
Endothelialization (%) between struts and above struts in different stent types. SEM analysis, 14 day Rabbit Iliac Arterial Model.

Comparison:
- *P<0.0001
- P=NS

Stent Types:
- SES
- PES
- ZES
- EES
- BMS
NEWER SURFACE-COATED DES CONTINUE TO HAVE LIMITATIONS AFTER 1 YEAR (XIENCE V)

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

Awaiting long-term follow-up from SPIRIT IV/COMPARE
Cumulative Incidence of ARC Def/Prob ST over 4 yrs after DES (CYPHER & TAXUS)

Bern-Rotterdam

Cypher & Taxus Pooled Analyses

5.7% [95% CI] CYPHER & TAXUS (n=8,146)

2.1% (17) CYPHER Stent (n=878)

2.1% (26) TAXUS Stent (n=1401)


2 Wenaweser et al; J Am Coll Cardiol 2008;52:1134-40
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™

Polymer is protected during delivery
Less friction during stent delivery
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™ arterial sirolimus content is within the sirolimus safety margin
NEVO™ Sirolimus-eluting Coronary Stent is an investigational device exclusively for clinical investigations and is not approved for sale in any market.

NEVO is designed to transform to a BMS

![Day 1](image1)
![Day 30](image2)
![Day 60](image3)
![Day 90](image4)

**Fully bioabsorbable PLGA polymer**
- Used in a variety of medical applications such as VICRYL™ sutures¹
- Designed for complete bioabsorption in as little as 90 days
- Highly biocompatible
- Fully metabolized bioproducts (CO₂ + H₂O)
- RES TECHNOLOGY stents transform into a BMS in as little as 90 days

NEVO™ Sirolimus-eluting Coronary Stent is an investigational device exclusively for clinical investigations and is not approved for sale in any market.

### NEVO RES-I Study Overview

<table>
<thead>
<tr>
<th>Single De Novo Native Coronary Artery Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference Vessel Diameter: 2.5-3.5 mm</td>
</tr>
<tr>
<td>Lesion Length: ≤28 mm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>40 Sites Worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe, South America, Australia, and New Zealand</td>
</tr>
<tr>
<td>394 subjects, stratified by diabetic status, and randomized 1:1</td>
</tr>
</tbody>
</table>

#### NEVO Sirolimus-eluting Stent (n=202)

#### TAXUS® Liberté Paclitaxel-eluting Stent (n=192)

### Primary Endpoint 6-Month In-Stent Late Loss

Substudy: IVUS subset (50 patients per arm)
- Dual antiplatelet therapy for ≥6 months

<table>
<thead>
<tr>
<th>Clinical/MACE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Angiographic/IVUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>87% Angiographic follow-up; 95% 180-day clinical follow-up</td>
</tr>
</tbody>
</table>

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

#### Principal Investigators
- John Ormiston
- Alexandre Abizaid
- Christian 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

### In-Stent

- NEVO: 0.13 ± 0.31
- TAXUS Liberté: 0.36 ± 0.48

### In-Segment

- NEVO: 0.05 ± 0.32
- TAXUS Liberté: 0.20 ± 0.42

**P < 0.001** for superiority

TCT 09, Oral presentation, J. Ormiston

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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

**IN-STENT LATE LOSS (mm)**

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.13 ± 0.31</td>
</tr>
<tr>
<td>0.36 ± 0.48</td>
</tr>
</tbody>
</table>

| n=185             |
| n=166             |

**IN-STENT BAR (%)**

<table>
<thead>
<tr>
<th>% VOLUME OBSTRUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 ± 1.1</td>
</tr>
<tr>
<td>7.8 ± 7.8</td>
</tr>
</tbody>
</table>

| n=2/186              |
| n=13/166             |

**% VOLUME OBSTRUCTION**

| 5.82 ± 5.82          |
| 19.45 ± 19.45        |

| n=35                 |
| n=38                 |

**P=0.002**

**P=0.004**

EuroPCR 09, Oral presentation, Chr. Spaulding
NEVO RES-I: 6-Month MACE and Components

6-MONTH MACE AND COMPONENTS

<table>
<thead>
<tr>
<th>Component</th>
<th>NEVO</th>
<th>TAXUS Liberté</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>8/193</td>
<td>13/187</td>
<td>&lt;0.19</td>
</tr>
<tr>
<td>Death</td>
<td>1/193</td>
<td>3/187</td>
<td>0.5</td>
</tr>
<tr>
<td>MI</td>
<td>4/193</td>
<td>5/187</td>
<td>1.6</td>
</tr>
<tr>
<td>Death or MI</td>
<td>5/193</td>
<td>8/187</td>
<td>2.5</td>
</tr>
<tr>
<td>TLR</td>
<td>3/193</td>
<td>6/187</td>
<td>1.5</td>
</tr>
</tbody>
</table>

P=NS for all endpoints

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 (mm)

<table>
<thead>
<tr>
<th></th>
<th>Diabetics</th>
<th>Nondiabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=66</td>
<td>n=286</td>
</tr>
<tr>
<td>NEVO</td>
<td>±0.17</td>
<td>±0.12</td>
</tr>
<tr>
<td></td>
<td>±0.42</td>
<td>±0.27</td>
</tr>
<tr>
<td>TAXUS Liberté</td>
<td>±0.55</td>
<td>±0.46</td>
</tr>
<tr>
<td></td>
<td>P=0.0318</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

EuroPCR 09, Oral presentation, Chr. Spaulding
NEVO RES-I: ARC Stent Thrombosis (ST) Through 6 Months

<table>
<thead>
<tr>
<th></th>
<th>NEVO (n=202)</th>
<th>TAXUS Liberté (n=192)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Probable</td>
<td>0</td>
<td>1 (0.5%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Possible</td>
<td>0</td>
<td>1 (0.5%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Any ARC</td>
<td>0</td>
<td>2 (1.1%)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

- 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™

Pre-procedure

Post-procedure

6 months FU

RAO

LAO

Post NEVO

Excellent conformability

NEVO™ Stent Deployment
(2.5 mm x 22 mm)

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

NEVO™ Sirolimus-eluting Coronary Stent is an investigational device exclusively for clinical investigations and is not approved for sale in any market.
NEVO™-II Study Overview

All-Comers
~2500 patients @ 32 sites

2:1 randomization

NEVO Sirolimus-eluting Stent
(n~1667)

Xience V Everolimus-eluting Stent
(n~833)

Principal Investigators
Patrick Serruys
Stefan Windecker
Manel Sabaté

Primary Endpoint: 12M Composite Clinical Endpoint of Cardiac Death, TV-related MI, and Clinically Driven TLR

Angiographic substudy of near on-label patients:
NEVO: 150 angio/75 IVUS
Xience V: 75 angio/38 IVUS

Clinical/MACE*

30 Day 6 Mo 13 Mo 3 Yr 5 Yr

Angiographic Sub
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

Clinical/MACE*

- 30 Day
- 6 Mo
- 1 Yr
- 2 Yr
- 3 Yr
- 4 Yr
- 5 Yr

Principal Investigators
- Dan Simon
- David Kandzari
NEVO™ Sirolimus-eluting Coronary Stent is an investigational device exclusively for clinical investigations and is not approved for sale in any market.

10,000 patients @ 150 sites from 20 EMEA countries

CYPHER® Sirolimus-eluting Stent (n=4,000)

NEVO™ Sirolimus-eluting Stent (n=6,000)

Primary Endpoint: TLF at 12 months in NEVO™ group

ONLY patients with

- STEMI
- MVD
- Diabetes

ALL patients, including

- STEMI
- MVD
- Diabetes
- Other

Co-Primary Endpoint: Non-inferiority of TLF at 12 months

30 Day  6 Mo  1 Yr  2 Yr

PI : P Urban
RES TECHNOLOGY
Antithrombotic Stent Strategies

Sirolimus (abluminal) - Polymer Cap

Polymer Cap

Vessel Wall

Lumen

SURFACE MODIFICATION
• Heparin
• Nitric oxide
• Endothelial cell promoter

2nd Drug (luminal)

ELUTABLE ANTITHROMBOTIC
• Thrombin inhibitor
• GP2b/3a inhibitor
• Other platelet inhibitors

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


**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

![Graph showing comparison between Control with BMS and Adenosine: 3 mg IC bolus + 0.5 mg on stent.](image)

- Control with BMS
- Adenosine: 3 mg IC bolus + 0.5 mg on stent

- % (Infarct Size/Area of Risk)
- N=12
- P=0.0032

### AMISTAD 2

![Graph showing event-free survival at 180 days and infarct size.](image)

- Pooled Adenosine
- Placebo

- Incident:
  - N=12
  - N=16

- Trend:  $P=0.03$
- Pooled:  $P=0.08$

- Infarct Size (% LV)
- 50 µg/kg/min
- 70 µg/kg/min

- Event-free Survival at 180 Days

- 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
Need references for these two graphs/pieces of data

grogan, 2010-04-09
**RES TECHNOLOGY**

Diabetes and Vascular Dysfunction

<table>
<thead>
<tr>
<th>Problem</th>
<th>Increased neointimal proliferation post-PCI increased thrombosis</th>
</tr>
</thead>
</table>
| Objective | Address unmet need of the diabetic patient  
• Further reduce neointimal proliferation and restenosis  
• Expand treatment options |

**Synergistic therapeutic agent:**

- Antiproliferative
- Anti-inflammatory
- Antithrombotic

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