Eluting stents

The beginning of the end and the end of the beginning

Patrick Washington Serruys, MD, PhD
Professor of medicine at the Erasmus University (EMC)
Head of the department of interventional cardiology at the Thoraxcenter

James B. Herrick lecture
Chicago
When I learned that I would receive this prestigious award...

I went to read James Bryan Herrick’s old papers (difficult to obtain from the university library)

I became fascinated by the actuality of a paper written almost a century ago in the Transactions of the association of American Physicians: “Concerning thrombosis of the coronary arteries”

I was also charmed by the fact that he earned his Bachelor of Arts degree before getting his medical education.

I felt some sympathy for this great man...having myself studied philosophy before getting engaged in medicine.
The Title of my talk may seem cryptic…but was inspired by a quotation of Sir Winston Churchill, in a speech in November 1942 in an early, but critical phase of the World War II: “Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.”

I’ll try to convince you that we have seen the beginning of the end of a surgical era in coronary revascularization and that we are perhaps going to see the end of the first generation of drug-eluting stent and the beginning of the second and third generation of drug-eluting stent.
Overview of this lecture

Part I
The rosy prophecy and the beginning of the end

Part II
The DES journey from the rosy prophecy to harsh reality

Part III
Perspective and future expectations
Overview of this lecture

Part I
The rosy prophecy and the beginning of the end

Part II
The DES journey from the rosy prophecy to harsh reality

Part III
Perspective and future expectations
FIM: FIRST IN MAN

Rapamycin experience:

15 patients (Sao Paulo, E. Sousa); fast release
4 months follow-up → No restenosis, no TVR*

15 patients (Sao Paulo, E. Sousa); slow release
4 months follow-up → No restenosis*, no TVR*

15 patients (Rotterdam, PW. Serruys); slow release
6 months follow-up → No restenosis, no TVR

Don’t wake me up, don’t pinch me, let me keep dreaming
Andreas Gruentzig’s Lecture, ESC Sep, 2000 Amsterdam

My rosy prophecy

ARTS2: Eluting STENT
ARTS2: CABG (95%)

ARTS: CABG (90%)

CABRI: CABG (91%)
CABRI: PTCA (59%)

ARTS II: 200?
CABRI: 1994
ARTS: 1999

CABRI: 1994
ARTS: 1999

ARTS I — the rapamycin eluting stent; ARTS II — the rosy prophecy
P. W. Serruys

Eur Heart J. 2002;23:757-759

Freedom from Death / MI / CABG / Re-PTCA

Days

P. W. Serruys
This is the last governmental report of Sweden on use of

1. coronary angiography (Cor.ai),
2. bypass surgery (CABG)
3. percutaneous coronary intervention (PCI)

The beginning of the end…
During debates my friend-surgeons usually misquote me by telling the audience that I once said:

“Surgical coronary revascularization will disappear”

What I really said was the following:

“The question is not whether surgical coronary revascularization will disappear but when?”
**ARTS II - Study design**

- **Primary endpoint:** Major adverse cardiac and cerebrovascular events (MACCE) free survival at 1 year.
- **Same inclusion / exclusion criteria as in ARTS I**
- **Same MACCE definition as in ARTS I**

Serruys PW et al; EuroInterv 2005; 1: 147-56
ARTS II - MACCE up to 1 year

**Event free Survival (%)**

- ARTS II
- ARTS I CABG
- ARTS I PCI

P (log rank) = 0.46 between ARTS II and ARTS I-CABG

Serruys PW et al; EuroInterv 2005; 1: 147-56
ARTS II - MACCE up to 1 year

The rosy prophecy came true !!!

**The Rosy period**

Serruys PW et al; EuroInterv 2005; 1: 147-56

Event free Survival (%) vs Time (Days)

- ARTS II
- ARTS I CABG
- ARTS I PCI

P (log rank) = 0.46 between ARTS II and ARTS I-CABG

89.5%
88.5%
73.7%
### ARTS II (recruitment completed in November 2003) 3-year follow-up

#### Hierarchical MACCE at 3 years

<table>
<thead>
<tr>
<th>Event</th>
<th>Cypher (%)</th>
<th>BMS (%)</th>
<th>CABG (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3.1</td>
<td>4.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Death/MI</td>
<td>6.6</td>
<td>10.5</td>
<td>8.8</td>
</tr>
<tr>
<td>Death/CVA/MI</td>
<td>8.4</td>
<td>13.3</td>
<td>11.0</td>
</tr>
<tr>
<td>Revascularisation</td>
<td>11.3</td>
<td>21.4</td>
<td>5.1</td>
</tr>
<tr>
<td>MACCE</td>
<td>19.8</td>
<td>34.7</td>
<td>16.1</td>
</tr>
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</table>

Preview of non-adjudicated events, to be presented at ACC
ARTS II (recruitment completed in November 2003) 3-year follow-up

Hierarchical MACCE at 3 years

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<tr>
<td>MACCE</td>
<td>19.8</td>
<td><em>34.7</em></td>
<td>16.1</td>
</tr>
</tbody>
</table>

Δ 3.7%

In November 2003 we started to design the next randomized trial...
Design of a new generation of randomized trial comparing percutaneous revascularization with DES and surgery for main stem and 3 vessel disease

- Rotterdam Draft rationale
- Frankfurt Group
  - Feasibility
  - Innovative design
- Noordwijk group
  1st Protocol
- FDA meeting
- EuroPCR Steering committee (Paris)
- US Investigator orientation (Chicago)
- European Investigator orientation (Munich & Leipzig)

2003
- Nov
- Dec

2004
- Jan
- Feb
- Mar
- Apr
- May
- Jun
- Jul
- Aug
- Sep

**concept** Syntax Chronology **realization**
Statement made by Friedrich Mohr, professor of surgery in Leipzig during the Frankfurt kick-off meeting on February 21\textsuperscript{st} 2004

“\textbf{I fully disagree! These trials represent biased patient selection and it does not reflect the current practice in surgery!}”

Therefore we need to study all-comers!
Trials studied highly selected patients

Patients Undergoing Angiography

- Clinical Criteria: 100%
  - 76% do not meet clinical inclusion/exclusion criteria

- Surgeon & Interventional Cardiologist Agreement: 24%
  - 18% physicians cannot agree amenable to either revascularization approach

- Patient Consent: 6%
  - 2% patients will not agree to participate

Randomized: GABI, EAST, RITA, ERACI, CABRI, BARI, MAAS-II, AWESOME, ERACI-II, SoS, ARTS-I

Percentages based on original pt. pool.
Syntax Overall Study Goal

For patients with 3VD or LM disease

1) to define the patient to be treated by CABG
2) to define the patients to be treated by PCI

all comers study  
*instead of* highly selected patient population

consensus physician agreement (surgeon & cardiologist)  
*instead of* inclusion & exclusion criteria

nested registry to define patient characteristics and outcomes  
of patients amenable only to either CABG or PCI
**Heart Team (surgeon and interventionalist)**

All Patients with 3VD/LM amenable for one treatment approach or amenable for both treatments options.

2894 pts enrolled, 1653 pts randomized.

**SYNTAX: Study Design**

Two Registry Arms:
- **CABG**: 2750 captured (750 followed)
- **PCI**: All captured and followed

Randomized Arm: $N=1800$ (1:1)

- **TAXUS** vs **CABG**
  - reasonable doubt
  - follow-up: 30d, 6m, 1-5 yrs
  - **Goal**: to define the most appropriate treatment through randomized trial methods

**Goal**: to profile larger pool of non randomizable patients and their subsequent outcomes

Consensus exists that only one treatment option (CABG vs PCI) is appropriate.
FREEDOM: Study Design

Diabetes Mellitus with 2-3VD

Randomized Arm
N=2400 (1:1)

- DES vs CABG
- follow-up: 30d, 6m, 1-5 yrs
- Goal: to define the most appropriate treatment for diabetic patients through randomized trial methods

Two Registry Arms
N=2000

- CABG
  - All captured and followed
  - consensus exists that only one treatment option (CABG vs PCI) is appropriate
  - Goal: to compare outcomes with randomized group

- PCI
  - All captured and followed

surgeon and interventionalist

amenable for both treatments options

amenable for one treatment approach

460 pts enrolled
COMBAT Randomized Trial

COMparison of Bypass surgery and Angioplasty using sirolimus eluting stent in patients with left main coronary artery disease

**Left main disease with or without MVD**

- Randomized Arm
  - **N=1730 (1:1)**
  - PCI with Cypher **vs** CABG

- Three Registry Arms
  - **N=1000**
  - CABG: All captured and followed
  - PCI: All captured and followed

Primary Endpoint: 2-year death, MI and stroke

Secondary Endpoint: 6-month QCA; 2-year, 5-year TLR, MACE
Are their still cases with left main lesion that we could not technically treat with PCI?

• Patient: 66 years old pt with no previous medical history

• Coronary Risk Factors: Smoking

• Admitted to a peripheral hospital because of acute heart failure and evidence of semi-recent anterior MI (LDH ↑)

• Medication: aspirin 100mg, clopidogrel 75mg, atorvastatine 40mg, ramipril, carvedilol, furosemide, heparine iv
### SYNTAX SCORE

<table>
<thead>
<tr>
<th>Lesion 1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Segment 1 (1x5)</td>
<td>5</td>
</tr>
<tr>
<td>Age of total occlusion unknown</td>
<td>1</td>
</tr>
<tr>
<td>Bridging</td>
<td>1</td>
</tr>
<tr>
<td>First Segment Visualized (seg 2)</td>
<td>0</td>
</tr>
<tr>
<td>+ side branches&lt;1.5mm</td>
<td>1</td>
</tr>
<tr>
<td>Length &gt;20</td>
<td>1</td>
</tr>
</tbody>
</table>

**Sub total lesion 1 Score** 9

---

<table>
<thead>
<tr>
<th>Lesion 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Segment 5 (5x2)</td>
<td>10</td>
</tr>
<tr>
<td>Segment 11 (1.5x2)</td>
<td>3</td>
</tr>
<tr>
<td>Trifurcation <em>(2 diseased seg. Involved)</em></td>
<td>4</td>
</tr>
<tr>
<td>Severe Tortuosity</td>
<td>2</td>
</tr>
<tr>
<td><strong>Sub total lesion 2 Score</strong></td>
<td><strong>19</strong></td>
</tr>
</tbody>
</table>

## SYNTAX SCORE

<table>
<thead>
<tr>
<th>Lesion 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Segment 7 (2.5x2)</td>
<td></td>
</tr>
<tr>
<td><strong>Sub total lesion 3 Score</strong></td>
<td><strong>5</strong></td>
</tr>
<tr>
<td>Lesion 4</td>
<td></td>
</tr>
<tr>
<td>Segment 7 (2.5x2)</td>
<td><strong>1</strong></td>
</tr>
<tr>
<td>Severe Tortuosity</td>
<td><strong>2</strong></td>
</tr>
<tr>
<td><strong>Sub total lesion 4 Score</strong></td>
<td><strong>3</strong></td>
</tr>
</tbody>
</table>

**Total Syntax Score:** 36

---

Left Venticulogram
<table>
<thead>
<tr>
<th>Cardiac-related factors</th>
<th>Operation-related factors</th>
<th>Total EuroScore = 9</th>
<th>Logistic Euroscore = 11.42%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina</td>
<td>Yes</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>LV function</td>
<td>No</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Recent MI</td>
<td>Yes</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>No</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emergency</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Surgery on thoracic aorta</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Post infarct septal rupture</td>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>
Surgery or PCI?
The surgeon asked us to treat the patient percutaneously... and we did it, but with the hemodynamic support of percutaneous left ventricular assist device.

Removes oxygenated blood from the left atrium via a transseptal cannula into the femoral artery.
Simultaneous triple-balloon dilatation in the LM during one of the phase of the treatment
Hemodynamic support by the left ventricular assist device during occlusion of the left main stem coronary artery

Mean pressure was 79 mmHg
LV during gradual TANDEMHEART™ Function

Opening aortic valve  Aortic valve remaining closed

TANDEMHEART™ off  TANDEMHEART™ on
Final result

LCX mid
3.0 x 12 mm

Left main- LCX ostium
3.5 x 20 mm

LAD mid
3.0 x 16 mm

LAD ostium
3.5 x 16 mm

Intermediate ostium
2.5 x 12 mm

Total stent number: 5
Total stent length: 76 mm
Follow-up Angiogram (at 9 months)

RSO View

Spider View
Overview of this lecture

Part I
The rosy prophecy and the beginning of the end

Part II
The DES journey from the rosy prophecy to harsh reality

Part III
Perspective and future expectations
Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy

Eugène P McFadden, Eugenio Stabile, Evelyn Regar, Edouard Cheneau, Andrew T L Ong, Timothy Kinnaird, William O Suddath, Neil J Weissman, Rebecca Torguson, Kenneth M Kent, August D Pichard, Lowell F Satler, Ron Waksman, Patrick W Serruys
Incidence of Late Stent Thrombosis
Drug-Eluting Stents

The Black period

<table>
<thead>
<tr>
<th>Study</th>
<th>Total ST (%)</th>
<th>Late ST (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ong</td>
<td>1.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Iakovou</td>
<td>1.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Rodriguez</td>
<td>3.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Kuchulakanti</td>
<td>1.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Park</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Urban</td>
<td>0.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Wenaweser</td>
<td>0.9</td>
<td>0.2</td>
</tr>
</tbody>
</table>

N=2,006      N=2,229      N=225      N=2,974      N=594     N=13,437    N=3,376
ESC firestorm: Issue #1 very late stent thrombosis with drug-eluting stents

Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session 1, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year’s meeting.

“Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is unknown,” said Yusuf. “I’ve a feeling the data we’re seeing today is only the tip of the iceberg. We need to encourage more public access to the data.”

Presenter, Edoardo Camenzind (Geneva, Switzerland) was more guarded. He noted that patients implanted with a DES carry a higher risk of stent thrombosis. In his presentation he outlined an observational study that compared mortality after PCI using a DES in his experience at three centers in France. He was also concerned about the potential for DES to cause late oncologic events. “We need to think about this,” he said.

Obtaining this data from the manufacturer,” said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). “The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed,” he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

“There’s no beneficial influence on mortality – PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest pain. It’s not re-stenosis that kills but the thousands of lesions you can’t see. Stable...
Angiographic DES Stent Thrombosis: Bern - Rotterdam Cohort Study: N = 8146 pts (Lancet in-press)

Cumulative probability of stent thrombosis (%)

Early ST
91 pts (60%)

Late ST
61 pts (40%)

Days after stenting 30 365 730 1095
Cumulative incidence (%) 1.2 1.7 2.3 2.9
Patients at risk (n) 8146 7002 5339 2841 971

Between 30 days to 3 years:
Slope = 0.6% / year
Incidence density 1.3 / 100 patient years
In-hospital death and MI in stent thrombosis patients

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>9</td>
<td>68</td>
</tr>
<tr>
<td>Late</td>
<td>5</td>
<td>72</td>
</tr>
<tr>
<td>Overall</td>
<td>7</td>
<td>70</td>
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Trading Restenosis for Thrombosis? New Questions about Drug-Eluting Stents

Miriam Shuchman, M.D.

In September, at the World Cardiology Congress in Barcelona, Donald Baim, a cardiologist who is the new chief medical and scientific officer of Boston Scientific, was talking to a reporter when he mentioned disturbing new findings regarding the risk of late thrombosis associated with drug-eluting coronary stents. The revelation fueled a newly ignited controversy. Lauded as a means of preventing restenosis, drug-eluting stents have been implanted in nearly 6 million patients worldwide since they were introduced 3 years ago. The Food and Drug Administration (FDA) responded to the controversy by issuing a statement that drug-eluting stents are “safe and effective when used for the FDA-approved indications,” which involve discrete and relatively short lesions (up to 28 mm in the case of one approved stent and up to 30 mm in the other in relatively small, native blood vessels (2.5 to 3.5 or 3.75 mm in diameter), but drug-eluting stents are also widely used on an off-label basis for longer lesions, larger vessels, and multivessel lesions. The FDA plans to discuss questions about the safety of drug-eluting stents at an open meeting of its Cardiovascular & Endovascular Devices Advisory Panel on December 7 and 8, 2006, to be attended by physicians, scientists, and the two leaders — and fierce rivals — in the $5.5 billion stent industry, Boston Scientific and Johnson & Johnson.

In approving drug-eluting stents, the FDA obliged manufacturers to track all subjects in their pivotal clinical trials for 5 years, and it was Boston Scientific’s review of the data on its paclitaxel-eluting Taxus stent to which Baim was alluding. Four years of data on nearly 8900 patients randomly assigned to receive the Taxus stent or a bare-metal stent showed that the risk of thrombus formation more than 6 months after stent placement was significantly higher in the Taxus group. The difference in risk increased by about 0.2% per year, so that 3 years after stent placement, patients with the Taxus stent had a risk that was about 9.5% higher than that of their counterparts with the bare-metal stent. In early August, the FDA met with Boston Scientific to review these findings.

Concerned about the risks of myocardial infarction and death associated with stent thrombosis, the FDA also met with Johnson & Johnson to discuss that company’s data. Dennis Donohoe, vice president of clinical and regulatory affairs at Cordis Corporation, the division that makes Johnson &
ESC firestorm: Issue #2 death at...

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Presenter, Edoardo Camenzind (Geneva, Switzerland).

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MACE rates individual data-studied data
HCR and Cardialysis vs. Camenzind

<table>
<thead>
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<th></th>
<th>Control</th>
<th>Cypher</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Death</td>
<td>6.3%</td>
<td>1.6%</td>
<td>0.40</td>
</tr>
<tr>
<td>MI</td>
<td>4.7%</td>
<td>3.3%</td>
<td>0.13</td>
</tr>
<tr>
<td>Q-MI</td>
<td>5.1%</td>
<td>2.1%</td>
<td>0.26</td>
</tr>
<tr>
<td>Death total and all MI</td>
<td>0.13</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>Death total and Q-MI</td>
<td>0.26</td>
<td>0.03</td>
<td>0.06</td>
</tr>
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Although not completely correct from a methodological point of view, the Camenzind’s report at ESC became a wake up call for everybody (device industry, PI’s, CRO’s and FDA)

RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS

N = 1748

Independent physician-directed meta-analysis versus
Independent physician-assessed patient level meta-analysis
Fortunately, prior to ESC the people listed on this slide met in Washington (March 2006) and in Dublin (June 2006) to re-define the clinical endpoints of coronary stent trials and created the...

**Academic Research Consortium (ARC)**

**ARC Co-Chairs**

- Don Cutlip, MD, Harvard and HCRI
- Patrick Serruys, MD PhD, Thoraxcenter, Rotterdam and Cardialysis

**Other Participants**

- Interventional Cardiologists
- Representatives from FDA
- Academic CROs (Cardialysis, HCRI, DCRI, CRF)
- Representatives from major stent manufacturers
ARC Proposed Standard Definitions for stent thrombosis

- **Definite/Confirmed**
  - Acute coronary syndrome AND
  - [Angiographic confirmation of thrombus or occlusion OR Pathologic confirmation of acute thrombosis]

- **Probable**
  - Unexplained death within 30 days
  - Target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion

- **Possible**
  - Unexplained death after 30 days

**NOTE:** Patients who have a TLR prior to a thrombosis are included by this set of definitions, as opposed to the “Per Protocol” definition.
**Rationale for ARC Definitions* for DES Endpoints**

**Concerns**
- Variability in definitions of key clinical endpoints across DES Trials
- Inappropriate comparisons and conclusions based on different definitions
- Potential to bias results by choosing definitions most favorable to those conducting analyses

**Objectives**
- Standardization of definitions
- Consensus on the new standard
- Consistency for reporting
- Transparency of data

*Previously referred to as the “Dublin Definition”*
ARC: The New Standard

- FDA requirement for December 2006 Panel Meeting
- Endorsed by British Cardiovascular Intervention Society (BCIS)

“BCIS believes these agreed definitions should be used in all future reports of the data, and that events should be independently adjudicated in all trials and registries.”
Freedom From Thrombosis: 0 – 1,440 Days
All Patients: ARC Total

Pooled data from the RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS Trials

LR p=0.8959
**Thrombosis from Day 0**

**Incidence Analysis: ARC Total**

<table>
<thead>
<tr>
<th></th>
<th>SES (N=878 Patients)</th>
<th>BMS (N=870 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARC Definition Stent Thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent thrombosis (0 – 30 days)</td>
<td>0.5% (4/877)</td>
<td>0.3% (3/870)</td>
</tr>
<tr>
<td>Stent thrombosis (0 - 1 year)</td>
<td>0.7% (6/871)</td>
<td>1.6% (14/864)</td>
</tr>
<tr>
<td>Stent thrombosis (0 - 4 years)</td>
<td>3.5% (29/832)</td>
<td>3.4% (28/825)</td>
</tr>
</tbody>
</table>

NOTE: Of the 57 subjects with stent thrombosis during 0-4 years, 10 underwent an intervening TLR prior to the thrombosis. However, only 1 of those 10 received any DES (SES) during TLR.
Percentage of Bare Metal Stents (BMS) ISR Cases Presentation

9.5% of BMS In-Stent Restenosis Cases Presented as an MI

10% of BMS In-Stent Restenosis Cases Presented as an MI


Restenosis with BMS is NOT just a nuisance: It has potentially severe consequences

1186 consecutive cases of clinical episodes of bare metal ISR

Hospitalized for UA* or MI = 36% (425/1186)

MI = 9.5% (112/1186)
Death = 0.7% (8/1186)

Hypothesis: By preventing 100 restenoses per 1,000 patients (clinical restenosis reduced from 20% → 10%)
DES could prevent ~10 restenosis-related MIs (9.5% of 100 prevented restenoses)
A 10 per 1,000 case reduction of restenosis-related MIs would be sufficient to offset a 5 per 1,000 case increase in VLST-related MI, to lead to the similar late death and MI rates for DES and the bare metal stent control

*Hospitalized before coronary angiography.
ISR = in-stent restenosis; UA = unstable angina.
# Impact of TLR on Stent Thrombosis Rate

Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS Trials.

<table>
<thead>
<tr>
<th>ARC Any</th>
<th>CYPHER® Stent</th>
<th>BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary ST</td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Late</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Very Late</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>0</td>
</tr>
</tbody>
</table>

- Independent and meticulous adjudication using the new ARC definition of 4 double-blind randomized trials on drug-eluting stent (DES) involving 1,748 patients shows:
  - no significant difference in the rate of thrombosis was demonstrated between the CYPHER® Stent and BMS out to 4 years, although mechanisms of primary stent thrombosis vs. stent thrombosis post TLR may be different.
What are my options?

Option A: There is a new problem
Use of DES results in more late thromboses than BMS

Option B: There is no new problem
The rate of early and late thrombosis (definite, probable, possible, ARC criteria) is similar to that of BMS

Option C: There is a problem. Early and late thrombosis should be abolished

What are my expectations?
1st endpoint: Death, MI
2nd endpoint: stent thrombosis

ASA/Prasugrel
ASA/Clopidogrel

6-12 mts  3 years

Late stent thrombosis

Going to Pharma

1st endpoint: stent thrombosis
2nd endpoint: Death, MI

“Revolution”
“Trias HR”
“Protect”

Costar
Genous

“Fight” between 1st gen DES
“Fight” between DES and non-DES

Durable polymer

3 years

Late stent thrombosis

New development

New coating (absorbable coating, no coating)
Absorbable metallic or polymeric platform
New Biological target (thrombosis, inflammation)
New drug (no cytostatic or cytotoxic)

New technique of elution (dual elution)
Pro Healing approach (EPC capture)
Pro Healing approach + Sirolimus or Paclitaxel
1st endpoint: Death, MI
2nd endpoint: stent thrombosis

6-12 mts ← 3 years

ASA/Prasugrel
ASA/Clopidogrel

RT

Late stent thrombosis

Costar ← Durable polymer
Genous ← Taxus
Endeavor ← Cypher

“Revolution”
“Trias HR”
“Protect”

3 years ← 3 years

“Fight” between 1st gen DES
“Fight” between DES and non-DES

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ASA/Clopidogrel

6-12 mts ↔ 3 years

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**Genous** ↔ Taxus

**Endeavor** ↔ **Cypher**

3 years ↔ 3 years

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Pro Healing approach + Sirolimus or Paclitaxel
Survey of the next generation of drug-eluting stents: meaningful advances or more of the same?

1. New coating (absorbable coating, no coating)
2. Absorbable metallic or polymeric platform
3. New Biological target (thrombosis, inflammation)
4. New drug (less cytostatic or cytotoxic)
5. New technique of elution (reservoir, dual elution)
6. Pro Healing approach (EPC capture)
7. Pro Healing approach + Sirolimus or Paclitaxel
Survey of the next generation of drug-eluting stents: meaningful advances or more of the same?

1. New coating (absorbable coating, no coating)

Problems with the polymer
- Inflammatory response
- Increased thrombogenicity
- Non-homogenous drug distribution
- Flaking, peeling, webbing, bonding
Hydroxyapatite Coating

Closely resembling biological apatite

Hydroxyapatite (bone!) is natural to the human body

Biocompatible, bioactive and bioresorbable

* Electro-Chemical Deposition

Heparin is coupled with Poly L-Lactide to create a heparinized polymer which will serve as a reservoir for another drug.

Monomer of PLA

Heparin molecule

DCC / DMAP

Formamide / DMF

PLA conjugate Heparin
Heparin is coupled with Poly L-Lactide to create a heparinized polymer which will serve as a reservoir for another drug.
Both therapeutic agents elute simultaneously. Heparin will give effect almost for 50 days and Sirolimus for 60 days.
BI OABSORBABLE METAL STENT in Magnesium

Light Microscopy

Scanning Electron Microscopy

Continuous immersion test of stents in 0.9% NaCl; 37°C; pH 7.0
BI OABSORBABLE Poly-L Lactide Stent Eluting Everolimus

Bioabsorbable DES system

ML VI SI ON® SDS
Polymeric Coating
Eluting Everolimus

BVS stent
Guidant
Today, we can non-invasively diagnose stenosis with MSCT (64, ultrafast) and...Assess non-invasively the long-term result of non-radio opaque absorbable stent
Today, we can non-invasively diagnose stenosis with MSCT (64, ultrafast) and...Assess non-invasively the long-term result of non radio opaque absorbable stent.
New Biological target, New drug, Dual elution

Sirolimus, Biolimus A9
Everolimus, Zotarolimus

Cytostatic agent
Cell cycle arrested

G₀ phase
Cell works but is not actively replicating

G₁ phase
Cell enlarges and makes new proteins

S phase
DNA replication

G₂ phase
Preparation for division

M phase
Cell division (mitosis)

Checkpoint:
Point at which cell commits to completing the cell cycle

Cytotoxic agent
Cell dies

Tacrolimus
Pimecrolimus

Paclitaxel
2 Drugs with 2 Different Targets: Pimecrolimus-Paclitaxel
Isoflavone-Sirolimus
Dexamethazone-Zotarolimus

Sirolimus, Biolimus A9
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Cell dies

Tacrolimus
Pimecrolimus

Paclitaxel
Scanning Electron Microscopy: 14-day

XIENCE

CYPHER

TAXUS

ENDEAVOR

Courtesy of R Virmani
Morphometric Measurement of Extent of Endothelialization at 14 and 28 days in the Rabbit

- Taxus Liberte
- Cypher
- Xience V
- Endeavor

Rapid re-endothelialization associated with Xience™ V
Immunocytochemistry of the endothelial layer shows a fully functional endothelium in the high dose group, as illustrated by the presence of E-NOS expression and the absence of vWF expression (the brown colored product on the endothelium (arrow)).
Conor Dual Drug Stent

Paclitaxel
Pimecrolimus
Genistein

- Genistein is a potential isoflavone which possesses dose dependent anti-platelet and anti-proliferative properties.
- Genistein inhibits collagen-induced platelet aggregation which is responsible for primary thrombosis.

Sirolimus

- Sirolimus is a naturally occurring Antibiotic drug.
- Wyeth-Ayerst Laboratories discovered its potent Immunosuppressive activity.
- Sirolimus prevent neointimal hyperplasia by inhibiting inflammatory response and cell proliferation.

- Approved by FDA for prevention of blood clots (Nov. 2000).
Five Layers of Genistein-Sirolimus Eluting Stent

- No Drug - Top layer (Protective layer E)
- Genistein (Top layer D)
- Genistein + Sirolimus (Middle layer C)
- Genistein↓ + Sirolimus↑ (Middle layer B)
- Genistein (Base layer A)

Total Drug Dose: 2.51 µg/mm² (112 µg Genistein and 76 µg Sirolimus content on 16 mm stent)

Unique Biodegradable Heparinized Polymers Blend includes-Poly L-Lactide, 50/50 Poly DL-Lactide-co-Glycolide and Polyvinyl Pyrrolidone
Elution Profile for Genistein-Sirolimus Eluting Stent

- **Initial high dose of Genistein for 2 days** to prevent platelet aggregation. (Top layer D)
- **Concurrent release of Genistein and Sirolimus from Layer C between 3 to 9 days** will target primary thrombus formation and intimal cell proliferation.
- **Slow release of Genistein and Sirolimus (Layer B)** between 10 to 49 days to prevent mainly cell proliferation.
- **Finally slow release of Genistein (Layer A)** from 50 to 89 days will prevent late thrombosis up to 3 months.

![Cumulative Drug Release from Genistein-Sirolimus stent](chart.png)

% drug release profile for 16-mm long Genistein-Sirolimus eluting stent.
**ENDOTHELIAL PROGENITOR CELL CAPTURE**

**EPC Capture Coating Technology**

*Human progenitor cell with CD34 Cell Surface Antigen*

**CD34 Antibody Layer**

**Intermideate Layer**

**Stent Adhering Bottom Layer**

**Stent Surface**

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*Endothelial Progenitor Cell Capture by Stents Coated With Antibody Against CD34*

The HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) Registry

- Aoki, MD,* Patrick W. Serruys, MD, PhD, FACC,* Helen van Beekeno, MD, PhD,* Andor T. L. Ong, MBBS, FRACM,* Eugene F. McFadden, MRCPath, MD, FRCP, FACC,* Georgios Simos, PhD,* Willem J. van der Giessen, MD, PhD,* Evert R. Raper, MD, PhD,*
- Yun J. de Feyter, MD, PhD, FACC,* H. Richard Davis, MSc,* Stephen Rowland, PhD,*
- Michael J. E. Knez, MD, PhD

Rottterdam, the Netherlands; Fort Lauderdale, Florida; and Toronto, Canada
EPC Capture Coating

HUVEC Cells attaching to AB Coated glass plate
Bare metal coated stents with monoclonal antibody against CD34 capturing Endothelial Progenitor Cell to accelerate the Healing Process are in clinical trial!
Correlation in-stent late luminal loss and circulating EPC titer at 6 months FU

- Low EPC (< 6,5 /100 µl)
- Normal EPC (> 6,5 /100 µl)

$R = 0.727$
ENDOTHELIAL PROGENITOR CELL CAPTURE

DES COMBO with EPC Technology

**EPC capture coating with Sirolimus Eluting Stent**

**Sirolimus Eluting Stent**
(Cypher Select)

3-Day Porcine Implants
Virmani/Leon unpublished data 2006
ENDOTHELIAL PROGENITOR CELL CAPTURE

DES COMBO with EPC Technology

**EPC capture coating with Sirolimus Eluting Stent**  

**Sirolimus Eluting Stent (Cypher Select)**

14-Day Porcine Implants

Virmani/Leon unpublished data 2006
Conclusions

- Following the 2 pioneers of DES (Cypher and TAXUS), various types of new designed coated stents will emerge and become available in a few years time.
- Although these conventional DESs have produced promising outcomes, their remarkable effectiveness is not yet established for all anatomic subsets.
- Besides, there are several caveats and concerns about conventional DESs (late thrombosis, hypersensitivity, abnormal vasomotion, etc).
- Abolition of neointimal hyperplasia is no longer the ultimate goal. Development of more biocompatible and bioabsorbable stent facilitating adequate endothelialization, is expected in the near future.
High dose tacrolimus at 90 and 180 days shows a complete healing response without inflammation or a late catch-up. The polymer control also shows good healing at both 90 and 180 days. There is some inflammation in the polymer group, but only deep in the adventitia without neointimal involvement.
PCI in the UK continues to increase at a rate of about 17% per annum,
no real change in surgical revascularisation, which has not increased
since about 1997.
The ratio between PCI and CABG in 2004 was 2.5 and in 2005 is 3.1.

The British Cardiovascular Intervention Society (BCIS)
Ludman PCI vs CABG Audit in the UK 2004
The beginning of the end and... the end of the beginning

In the Netherlands !!!
Overview of this lecture

Part I

The rosy prophecy and the beginning of the end

Part II

The DES journey from the rosy prophecy to harsh reality

Part III

Perspective and future expectations