Should We Expect “Late Catch-up” (Late Restenosis) after DES Treatment ---- Is the Genie out of the Bottle? You have Simply Postponed the Inevitable

Angioplasty Summit 2004
30th April, 2004

Renu Virmani, M.D.
Armed Forces Institute of Pathology,
Washington, DC
What is the problem and why we need Drug-Eluting Stents

- Incidence of in-stent restenosis by angiography - as high as 30 to 40%
- Incidence of clinical symptomatic restenosis is close to 10 to 15%
- Of the 81 patients who died >3 months following stenting, 57 (70%) patients had ISR, and of these 25 patients (40%) died from severe coronary disease elsewhere (with or without thrombus 17 patients) and from non-cardiac death (8 patients).
In-Stent Restenosis and Sudden Coronary Death

Instent Restenosis (ISR) n=57

Sudden coronary death 31 (54%)

ISR Culprit lesion 14 (24%)
- ISR only 11 (19%)
  - + Healed MI 8 (14%)
  - No Healed MI 3 (5%)
- ISR + Late Stent Thrombosis 3 (5%)

ISR + Multivessel Disease 17 (30%)
- Additional Severe CAD 14 (25%)
- Acute Thrombosis in Non-ISR Artery 3 (5%)

Non-Sudden Death 26 (46%)
Non-coronary death in 8

* Post PCI for Instent Restenosis in 5, Post CABG in 5, additional CAD in 5, acute thrombus in 3
Drug-Eluting Stents Comprise a Three-Component System

Ideal Stent design

Drug (lipophylic), binds to tissues better than to blood, Cytostatic, and allows endothelialization while suppressing smooth muscle cell proliferation and migration

Polymer (erodable/non-erodable)

Polymer that does not induce inflammation but allows rapid release followed by slow release of drug over a long period
Polymer Based Drug Delivery

- **Biodegradable**
  - *Polyglycolic acid/polylactic acid copolymer*
  - Polycaprolactone
  - *Polyhydro-butyrate/-valerate copolymer*
  - Polyorthoester
  - Polyethyleneoxide/polybutylene terephthalate copolymer
  - *Copolymeric polylactide*

- **Nonbiodegradable**
  - Polyurethane
  - Poly(dimethyl)-siloxane
  - Polyethylene terephthalate
  - Polyethylene-vinyl acetate copolymer (PEVA)
  - Ethylene vinyl alcohol (EVAL)
  - Ethylene vinyl acetate (EVA)
  - Poly Butyl Methacrylate (PBMA)
  - Phosphorylcholine (PC)
Non-Bioerodable Polymer

28 days

28 days

28 days

90 days

90 days

90 days
Bioerodable Polymer

28 days

90 days
Restenosis Processes and Inhibitors

Normal artery + Stent

Platelet + Fibrin + Coagulation factors

Adhesion molecules + Chemotactic factors

Inflammation

Growth Factors + Cytokines

Contractile → Synthetic Smooth Muscle cells (SMC)

Hirudin/Iloprost
Heparin
Nitric Oxide
IIb/IIIa inhibitors

Corticosteroids
Tranilast
Sirolimus & its derivatives

Sirolimus
Everolimus
ABT578
Cyclosporine
Tacrolimus
Mycophenolic Acid

Radiation
Actinomycin-D

Go

Taxol
Taxane

G1
S
G2
M

Signal transduction

Proteoglycans

SMC Migration (MMPs)

Collagen Type III

Remodeling (Collagen Type I)

Batismastat
Morphologic Changes Observed with Various Drugs Used on Stents in Preclinical Studies Performed in Animals

- Sirolimus
- Paclitaxel
- Actinomycin-D
Lessons From Preclinical Studies of DES

Undesirable Effects of DES

**Impaired Arterial Healing**

- **Efficacy at 28 days but no beneficial effect at 90 and 180 days**

  - Neointimal Area mm$^2$
    - Control
    - Sirolimus

**SIROLIMUS - PIG STUDY**

- **Cypher**
- **Bx Velocity**
- **Neointimal Decrease - 28 days**

**Stent Malapposition**

- **Medial Necrosis**
- **Paclitaxel Induced Inflammation 28 days**

**Hypersensitivity**

- **Reaction to polymer**

**Incomplete Endothelialization**

- **Intimal thickness above stent at 28 days**
- **Actinomycin-D 2.5μg**

**Inc. cell proliferation**

- **Control 180 days**
- **Actinomycin-D 180 days**

**Undesirable Effects of DES**

- Medial Necrosis
- Hypersensitivity
Pathology of Drug Eluting Stents in Humans

A rare glimpse!!
Human Atherectomy specimens Examined from patients who had received QuaDS-QP2 (7-Hexanoyltaxol)-Eluting Stent or TAXUS Stent
QuaDS-QP2 (7-Hexanoyltaxol) Stent

- Registry of 15 patients with ISR
- 6 months: 3 TLR’s, angiographic restenosis 13.3%
- 12 months: Angiographic restenosis in 61.5% (late, late lumen loss)
- In-stent DCA specimens reviewed in 5 pts.
  - $11.2 \pm 1.0$ months post-stenting
- Mechanisms
  - Toxicity of high drug dose
  - Reaction to plastic sleeve

Virmani et al. Circulation 2002; 106
Atherectomy From Patient Treated with QuaDS-QP2 for Recurrent In-Stent Restenosis

Patient 2

“Taxane” a paclitaxel derivative 2400 µg for 13 mm stent length
Virmani et al. Circulation 2002
## Morphometric Assessment of Atherectomy Specimens From Patients Treated with QuaDS-QP2 for Recurrent In-Stent Restenosis at 11 months

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>MLD At 12 months</th>
<th>Restenotic Lesion area (mm²)</th>
<th>α-Actin (%)</th>
<th>Fibrin (%)</th>
<th>CD68 (%)</th>
<th>CD45RO (mm²)</th>
<th>*Ki-67 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/F</td>
<td>0.0</td>
<td>4.94</td>
<td>5.45</td>
<td>16.85</td>
<td>4.01</td>
<td>134.13</td>
<td>0.85</td>
</tr>
<tr>
<td>2</td>
<td>49/M</td>
<td>1.19</td>
<td>7.13</td>
<td>3.90</td>
<td>10.26</td>
<td>0.63</td>
<td>2.10</td>
<td>0.48</td>
</tr>
<tr>
<td>3</td>
<td>67/M</td>
<td>1.59</td>
<td>2.23</td>
<td>3.59</td>
<td>14.46</td>
<td>0.61</td>
<td>0.90</td>
<td>0.41</td>
</tr>
<tr>
<td>4</td>
<td>65/M</td>
<td>0.52</td>
<td>3.74</td>
<td>4.60</td>
<td>3.83</td>
<td>0</td>
<td>4.81</td>
<td>0.61</td>
</tr>
<tr>
<td>Total</td>
<td>–</td>
<td>–</td>
<td>4.51±2.07</td>
<td>4.38±0.82</td>
<td>11.35±1.82</td>
<td>1.31±1.82</td>
<td>35.48±65</td>
<td>0.59±0.19</td>
</tr>
</tbody>
</table>

*Proliferative index in the restenotic area without inflammation. In the two cases with marked inflammation (patients 1 and 2), the proliferative index was 5.2 and 4.7 respectively. [α-Actin= smooth muscle cells, CD68= macrophages, CD45RO= T cells.]

Virmani et al. Circulation 2002
60-year-old man 6 mo post stent deployment

BMS DCA

TAXUS DCA

Increased chronic inflammation & hemosiderin
Is there a problem with Boston Scientific’s TAXUS? (NY Times 23rd April, 2004)

- 27 to 30 patients had adverse events involving the Taxus stent caused by an inability to separate the balloon from the expanded Stent.

- Of these 5 patients had to undergo surgical removal of the device with coronary endarterectomy and bypass surgery.

- A French report from 2 catheterization laboratories (Lyon and Brest) that performed bench tests claim:
  - Paclitaxel coating is sticky and non uniform leading to mechanical difficulties after stent implantation.
  - Paclitaxel local concentration may vary within the stent
  - Manufacturers quality control is questioned

Lynne Peterson, April 2004, Trend’s in Medicine
Patient underwent endarterectomy after a TAXUS stent placement that resulted in a dissection, an Express stent was placed however, the dissection extended and a second Express was placed. While withdrawing the balloon it got stuck at the TAXUS stent and had to be removed surgically.
ACTION STUDY
Actinomycin-D Eluting Stent

- 2.5 and 10 μg/stent
- Increased in-stent and stent edge neointimal growth
- Increased TLR
- Increased MACE
- Trial halted

Patrick W. Serruys, JACC, In Press
<table>
<thead>
<tr>
<th>Restenosis</th>
<th>Age (years)</th>
<th>Area (mm²)</th>
<th>SMCs (%)</th>
<th>MØs (%)</th>
<th>T-cells (mm²)</th>
<th>Fibrin (%)</th>
<th>Ki-67 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt. 1</td>
<td>58</td>
<td>13.28</td>
<td>12.6</td>
<td>0.08</td>
<td>0.08</td>
<td>5.9</td>
<td>0.13</td>
</tr>
<tr>
<td>Pt. 2</td>
<td>63</td>
<td>10.90</td>
<td>18.3</td>
<td>0.10</td>
<td>0.10</td>
<td>1.0</td>
<td>0.43</td>
</tr>
<tr>
<td>Pt. 3</td>
<td>78</td>
<td>2.80</td>
<td>3.8</td>
<td>0.17</td>
<td>0</td>
<td>26.0</td>
<td>0.81</td>
</tr>
<tr>
<td>Pt. 4</td>
<td>-</td>
<td>11.69</td>
<td>1.4</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>0.38</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>9.67±4.69</td>
<td>9.0±7.8</td>
<td>0.09±0.07</td>
<td>7.8±9.7</td>
<td>8.2±12.1</td>
<td>0.44±0.28</td>
</tr>
</tbody>
</table>

* Two patients received actinomycin-D dose 2.5 µg/cm², one 10 µg/cm² and one unknown. At trial mandated 6-months follow-up severe stenosis was found in all 4 patients and underwent DCA.

John Ormiston 2004
Atherectomy From a Patient with In-stent Restenosis in an Actinomycin D Eluting Stent

- Fibrin II
- Ki-67
- α-Actin
- KP-1
- Fibrin II
### AFIP Experience at Autopsy Following Cypher Stent Placement

<table>
<thead>
<tr>
<th>Patient age/Se</th>
<th>Indication</th>
<th>CA</th>
<th>Interval stent to †</th>
<th>Cause of death</th>
<th>Thrombus at stent site</th>
<th>Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>57 F</td>
<td>MI (non-Q)</td>
<td>LAD/LOM &amp; LCx</td>
<td>7 days</td>
<td>AMI</td>
<td>Occlusive</td>
<td>Minimal</td>
</tr>
<tr>
<td>51 M</td>
<td>AP with in-stent restenosis</td>
<td>LCx &amp; distal RCA</td>
<td>10 days</td>
<td>SD -CAD</td>
<td>Minimal</td>
<td>Occasional</td>
</tr>
<tr>
<td>65 M</td>
<td>Recent AMI</td>
<td>LAD prox</td>
<td>38 days</td>
<td>Stroke, stent thrombosis</td>
<td>Occlusive</td>
<td>Absent</td>
</tr>
<tr>
<td>61 M</td>
<td>AMI</td>
<td>LCx/ PD</td>
<td>4 months</td>
<td>SD-CAD</td>
<td>Non-occlusive</td>
<td>Severe</td>
</tr>
<tr>
<td>71 F</td>
<td>Asymptomatic</td>
<td>LAD</td>
<td>16 months</td>
<td>Stroke -AMI</td>
<td>Small thrombus side branch</td>
<td>Occasional giant cells</td>
</tr>
<tr>
<td>58 M</td>
<td>UAP (E-SIRUS)</td>
<td>LCx</td>
<td>18 months</td>
<td>AMI thrombus</td>
<td>Occlusive</td>
<td>Severe</td>
</tr>
<tr>
<td>61 M</td>
<td>Asymptomatic, (FIM )</td>
<td>RCA</td>
<td>4 year (AS+MS, 1 year †)</td>
<td>Plaque rupture-stroke</td>
<td>None</td>
<td>Minimal</td>
</tr>
</tbody>
</table>
October 29, 2003 FDA Advises Physicians of Adverse Events Associated with Cordis CYPHER™ Stents

- CYPHER™ stent approved in April 2003 for patients undergoing PCI, since its approval 450,000 units have been distributed worldwide (>260,000 US and >180,000 Outside US). To date FDA has received 290 reports (>260 US and >25 Outside US) involving subacute (occurring between 24 hours and 30 days post procedure) thrombosis (SAT) associated with CYPHER™ stent. More than 60 reports of SATs were associated with patient death. Also, more than 50 reports, including some deaths, that Cordis considers possible hypersensitivity reactions.

- “We have received numerous reports of adverse events for CYPHER™ stent through MDR system, which is subject to significant under reporting.”

FDA Talk Paper, 2003
37-year old white woman with CAD, hyperlipidemia (total cholesterol 252, HDL 27, triglycerides 442 mg/dl) and cigarette smoker; developed chest pain and had a non-Q wave myocardial infarction 10 days antemortem. Cardiac catheterization: Severe LAD and LCX disease and occluded RCA

Multivessel stenting performed:
- Two ZETA stents placed in mid-RCA 8 days antemortem
- CYPHER stent placed in mid-LCX 7 days antemortem
- CYPHER stent placed in mid-LAD + bifurcation stenting of LD (PC-coated BiodivYsio) 7 days antemortem

Presented to ER on day of expiration with chest pain and ECG evidence of acute anterior MI followed by cardiac arrest.
Cypher™ Stent in Left Circumflex and Left Anterior Descending Coronary Arteries and BiodivYsio Stent in Left Diagonal
Clinical: AMI & Cardiac arrest 7 days post-CYPHER

Pathology:
Patent CYPHER Stent in Mid-LCX

Platelet thrombus + acute inflammation
Adventitia

A. Farb, R. Virmani, AFIP, Washington, DC
Subacute Stent Thrombosis - 7 days

Thrombus

A

B

C

D
Causes of subacute thrombosis - CYPHER?

- Polymer peeling off the stent during deployment
- Under expansion of the stent
- Small stent used in a larger vessel-cracking of polymer
- Drug?
- Inappropriate location chosen for stent - bifurcation, crush technique
65-year old male with CYPHER stent placed post AMI; 33 days later presented with stroke, anticoagulants stopped patient died 38 days post stenting.
61 year-old male with hypertension and hyperlipidemia presented with acute coronary syndrome 4 months before death. Catheterization: 99% stenosis of PDA, CYPHER stent placed 2.5x18 mm. 1 month before death catheterization repeated for positive stress test - No restenosis. Sudden death after complaining of dyspnea and diaphoresis.

**PDA just proximal to CYPHER stent**
IVUS observations in CYPHER

- Incomplete Apposition of Stent
  - RAVEL - DES stents = 10/48 (21%)
  - Uncoated Bx Velocity Stents = 2/47 (4%)
  - SIRIUS - DES stents = 7%
  - Uncoated Bx Velocity = 0%

A 58-year old man was first seen on 12/20/01 with UAP. He was a smoker, non-diabetic, non-hypertensive. Coronary angiography showed:
- 95% narrowing with >20mm long lesion in prox and mid LCX
- 70% mid LAD, and non-critical lesion in prox RCA
- 2 CYPHER™ stents (3.0x18 and 2.5x18 mm) stents implanted following PTCA (2.5 at 12-14 ATM), with overlap. IVUS showed stent well apposed to the wall without mal-apposition.

1/10/02 skin rash- trunk, ankle, and wrist with itching and irritation - interpreted as secondary to ticlopidine and patient switched to clopidogrel. Rash resolved.

- 8 months post-stenting protocol driven angiography and IVUS, no in-stent stenosis nor neointimal formation

6/9/03 patient experienced epigastric CP of >20 min duration with a syncopal episode, recovered. Developed recurrent intermittent CP admitted to CCU on 6/13/03, DX recent non-Q wave MI.
- 6/16/03 angiography, LCX total occlusion (TIMI 1), could not be crossed, LAD 85%, RCA 90%. While attempting to cross RCA patient arrested and could not be resuscitated.
58-WM enrolled in E-SIRUS for UA (Dec 2001) presented 18 month later with CP for 4 d

Pre procedure

Post-Implant

8 months post SRL stent

Long LCx lesion (70% stenosis)

2 CYPHER stents placed in LCx 3x18 mm and 2.5x18 mm, without much overlap

18 months post SRL stent

Giulio Guagliumi, MD
ICUS Analysis, Cardialysis Rotterdam

Baseline 8 Months

Vessel Volume mm³  407  462
Stent Volume mm³  187  194
Plaque behind stent mm³  221  269
Neointimal Volume mm³  0  0.7
% Stent Volume Obstruction mm³  - 1
No overlap

Cardiac rupture secondary to AMI
Proximal Stent

- Medial destruction
- Inflammation
- Foreign body giant cell reaction
All native arteries showed inflammation typical of atherosclerosis. None of the non-stented coronary arteries showed an eosinophilic inflammatory reaction.
Causes of Adventitial, Medial and Intimal Inflammation (↑eosinophils) limited to the area of the Stent:

- Hypersensitivity reaction to drug?
- √ Hypersensitivity reaction to polymer?
- Part of atherosclerosis
- Infection

Adverse side effects to Sirolimus mostly limited to: bone-marrow suppression, hypercholesterolemia and triglyceridemia. Other reported side-effects include hypocalcemia, hyperglycemia, diarrhea, and abnormal liver function tests. Hypersensitivity has been reported in one patient following Sirolimus.
Granulomatous reaction seen in 12.5 and 35% of CYPHER Stents Implanted for 28 and 90 days in Pig Coronary Arteries
Stent Mal-apposition and Plaque Expansion is Related to Hypersensitivity to Cypher™ Stent (polymer) in Selected Patients?

CYPHER™ polymer is non-erodable consisting of co-polymer poly-n-methacrylate (PBMA) and polyethylene-vinyl acetate (PEVA). PBMA a component of bone cement when implanted subcutaneously results in a macrophage and giant cell reaction accompanied by tissue damage and fibrosis. PEVA in rabbit elicits an intense inflammation in 25% of animals subjected to subcutaneous or intramuscular implants.
Clinical History Case 7

- 61-yrs old man received SRL-Eluting Stent (Fast Release) in RCA 4 years prior to death
- Angio and IVUS at 4 months, 1 year, and 2 years showed minimal neointimal growth in mid-stent
- AVR and MVR 1 year prior to death
- Presented with cardiac arrest & suffered severe cerebral damage
- Angio showed widely patent stent and no change in neointimal growth
- Developed brain death and expired

First in Man

pre

RCA FIM SRL-Eluting Stent (Fast Release)  
4-Years Post-Deployment

Post-Mortem Radiographs

RCA FIM SRL-Eluting Stent
(Fast Release)
4-Years Post-Deployment

*Struts in necrotic core

Thin healed neointima

Strut + Polymer (polarized light)

Fibrin

Ca+

Mφ

α-actin
>95% Endothelialized

Uncovered strut at branch ostium

Non-Stented Arteries

Proximal LAD Plaque Rupture

PDA Nodular Calcification
Arterial Healing Following Stainless Steel and Drug Eluting Stent Placement in Animals and Humans

Drug Eluting Stents

Conclusion:

- DES reduce neointima upto 12-24 months - but will the effect be permanent!!!!
- Drug-Eluting Stents only Delay the Inevitable - late clinical results done carefully will fail to show long-term benefit
- May Even in Sensitive Patients Cause Harm by:
  - Thrombosis (early and late)?
  - Inflammation induced by the polymer or through toxic effect of drug resulting in positive remodeling and stent malapposition!!
- Safest, to design better stents and in combination with oral therapy will reduce restenosis until better polymer/drug combination are available!!!
Morphologic Predictors of Poor Outcome in Drug Eluting Stents

- Persistent poor endothelialization
- Excessive thrombus
- Medial necrosis ± stent malapposition
- Excessive inflammation
- Hypersensitivity reaction

"Science is always wrong. It never solves a problem without creating ten more."

*George Bernard Shaw (1856-1950), Irish dramatist and critic*
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• Leslie Keefer
Comparison of 7 days Bare SS Stent Implant to 28 days Sirolimus-Eluting Stent and Bare SS Stent

Bare Stainless Steel (SS) stent at 7 days

Sirolimus-eluting stent at 28 days

Bare SS stent at 28 days
Sirolimus-Eluting Stent Implanted in Human Coronary Artery for 16 Months: Pathologic Findings

Giulio Guagliumi, Andrew Farb, Giuseppe Musumeci
Orazio Valsecchi, Maurizio Tespili, Teresio Motta,
Renu Virmani, M.D.
Sirolimus-Eluting Stent Implanted in Human Coronary Artery for 16 Months: Pathologic Findings

- Well-healed neointima
- Very small thrombus at side branch
- >80% surface endothelialization
- Loose intercellular junctions
- Rare minute platelet aggregates
- Fibrin w/strut embedded in core
- Minimal inflammation

Images:
A. General view of the stent
B. Cross-section view of the stent
C. Magnified view showing giant cells
D. Fibrin II
E. α-actin staining

Legend:
- fp
- Giant cells
- Th
- nc
- * Fibrin w/strut
- ** Minimal inflammation
- α-actin
- Well-healed neointima
- Very small thrombus at side branch