An Update on Angioplasty and Coronary Stents

Raymond D. Magorien, MD
Director, Cardiac Catheterization Lab
The Ohio State University, Columbus, Ohio

Objectives
- Outline the history and development of coronary angiography, coronary angioplasty, coronary stenting
- Discuss In-Stent-Restenosis and the impact it has on our patients and the medical community
- Discuss the data behind Drug Eluting Stents
- Discuss Stent Thrombosis and it's impact on current standard of care
- Discuss future concepts in the cardiac catheterization laboratory

Introduction
- Richard M. Ross Heart Hospital
  - The Ohio State University, Columbus, OH
  - Universal Bed Concept
- 90 bed hospital
  - 60 more beds open in 9/08
  - Cardiology
  - Cardiothoracic Surgery
  - Vascular Surgery

Introduction
- Cath Lab Volumes 12 Month 24 Month
  - Diagnostic 5,345 10,506
  - Interventional 1,903 3,939
### Risks of Cardiac Catheterization

- **Diagnostic Catheterization:** 1/1000 chance of the following:
  - Death
  - Stroke
  - Loss of Limb
  - Myocardial Infarction
  - Major Bleed (1/500)

### History of Angioplasty

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>3000 B.C.</td>
<td>Egyptians perform bladder catheterizations using metal pipes.</td>
</tr>
<tr>
<td>400 B.C.</td>
<td>Hollow reed catheters used in cadavers to study the function of cardiac valves.</td>
</tr>
<tr>
<td>1711</td>
<td>Hales conducts the first cardiac cath on a horse using brass pipes, a glass tube and a goose trachea.</td>
</tr>
<tr>
<td>1844</td>
<td>Bernard uses catheters to record intracardiac pressures and coins the term “cardiac catheterization.”</td>
</tr>
<tr>
<td>1929</td>
<td>First documented human cardiac catheterization is performed by Dr. Werner Forssmann in Eberswald, Germany...on himself.</td>
</tr>
<tr>
<td>1941</td>
<td>Cardiac output measured by Cournand and Richards, first use of cardiac cath as diagnostic tool.</td>
</tr>
<tr>
<td>1956</td>
<td>Forssmann, Cournand and Richards share the Nobel Prize.</td>
</tr>
<tr>
<td>1958</td>
<td>Mason Sones performs first diagnostic coronary angiogram at the Cleveland Clinic...by accident.</td>
</tr>
<tr>
<td>1964</td>
<td>Transluminal Angioplasty, the concept of &quot;remodeling the artery&quot;, is introduced by Charles Dotter</td>
</tr>
</tbody>
</table>
History of Angioplasty

1967: Judkins technique introduced.

1974: Gruentzig performs the first human angioplasty...in a lower extremity.

1976: Gruentzig presents results of animal studies at AHA meeting.

1977: First human coronary balloon angioplasty performed intraoperatively by Gruentzig, Myler and Hanna in San Francisco.

1977: Gruentzig performs first cath lab PTCA on awake patient in Zurich.

1982: Over-the-wire coaxial balloon systems introduced, brachial guiding catheters and steerable guide wires are developed.

1985: Gruentzig dies in plane crash.

1986: Coronary atherectomy devices are introduced.

1987-1993: Lasers, rotational atherectomy, IVUS and stents introduced into practice.

1994: Palmaz-Schatz stent is approved by the FDA for use in U.S.

1997: Over one million angioplasties performed.

1997: Over one million angioplasties performed.
### History of Angioplasty

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>Two million angioplasties and stents performed.</td>
</tr>
<tr>
<td>2003</td>
<td>First drug-eluting stent (Cypher-J&amp;J, Cordis) approved by FDA.</td>
</tr>
<tr>
<td>2004</td>
<td>Taxus (Boston Sci.) approved by FDA.</td>
</tr>
<tr>
<td>2006</td>
<td>European Bioabsorbable Stent: First in Man</td>
</tr>
<tr>
<td>2007</td>
<td>2nd Generation DES introduced to Market in Europe</td>
</tr>
<tr>
<td>2006</td>
<td>EPC (Endothelial Progenitor Cell) Coated Antibody Stent Introduced: First in Man</td>
</tr>
</tbody>
</table>

### Data and Clinical Practice

- **1980’s**: Plain Old Balloon Angioplasty (“POBA”) led to restenosis in 15-60% of patients
- **1990’s**: Bare metal coronary stents significantly reduced overall target vessel revascularization.
- Two important studies in the August 1994 issue of NEJM looked at BMS vs. angioplasty alone

Fischman DL et al. NEJM August 15, 1994 (331): 496-501
Serruys PW et al. NEJM August 25, 1994 (331): 489-495
BENESTENT Trial (1994)

- 520 Patients w/ stable angina and a single coronary lesion
  - 262 Stent vs 258 PTCA ("POBA")
  - PEP: Death, CVA, MI, CABG, repeat PCI
  - Follow-up 7 months
  - Primary Angiographic Endpoint: MLD 7 months
  - Pt’s treated w/ ASA & Dipyridamole for 6 months
  - Stent patients received Warfarin 3 months

BENESTENT Trial Findings

- Favoring PTCA
  - Decreased primary endpoint (20% v 30%, P=0.02)
  - Driven by less repeat PCI (13% v 23%, P=0.005)
  - Larger Lumen Diameter at 7 months (2.0 vs 2.5mm, P<0.001)
  - Less Restenosis of >50% (22% vs 32%, p=0.02)
  - Less blood transfusions, peripheral vascular complications (13.5% vs 3.1%, P<0.001)
  - Shorter hospitalizations (8.5 vs 3.1 days, P<0.001)
  - Non Significant difference in death, myocardial infarction

STRESS Study 1994

- 420 patients with symptomatic coronary disease
  - 207 Stent vs 203 PTCA
  - PEP: Angiographic evidence of >50% restenosis on follow-up angiogram at 6 months
  - Clinical Endpoints: Death, MI, CABG, repeat revascularization (in-hospital and 6 months)
  - ASA, Dipyridamole started before procedure
  - Warfarin and dipyridamole for 1 month, ASA indefinitely
STRESS Study Findings

- Favoring Stents
  - Higher procedural success (96% vs 89%, p=0.011)
  - Larger post procedural (1.7mm vs 1.2mm, p=0.001) and 6-month lumen diameters (1.7mm vs 1.5mm, p=0.007)
  - Lower restenosis at 6 months (31.2 vs 42.6%, p=0.046)
  - Less target lesion revascularization (10.2 vs 15.4%, p=0.06)

STRESS Study Findings

“Trend” Towards improved Survival

BMS Update 2002

- Meta-analysis of 29 randomized trials comparing BMS to PTCA up until 6/2002
- Important things to remember:
  - Every study included patients with stable angina
  - Very few of the studies included patients with unstable angina (varied definitions)
  - None of the studies included NSTEMI/STEMI patients

Conclusions

- No Difference between Stenting and PTCA in terms of Death and Myocardial Infarction
- Stenting reduced restenosis rates and recurrent PCI
**Replacing One Problem for Another: ISRS?**

- By 1999, Stenting comprised 85% of Percutaneous Coronary Interventions
- However;
  - Increased risk of subacute thrombosis in the stented segment (3.7% of all procedures)
  - Replacement of atherosclerotic coronary disease with the iatrogenic in-stent neointimal hyperplasia

**Restenosis after Bare Metal Stents**

**Scope of the Problem**

- PCI worldwide 2005:
  - 2.4 million
  - ~ 50% performed in United States
- Angiographic restenosis: 600,000/yr
- Clinical events: 300,000/yr
- Recurrent clinical events: 120,000/yr
- Ultimate bypass surgery: 100,000/yr

---

**Clinical Restenosis after Bare Metal Stenting: Multicenter Perspective**

Balloon angioplasty ~30 to 40% Restenosis

**Economic Burden of Restenosis in U.S.**

1 million PCI procedures in US during 2004

>70% of PCIs used bare metal stents (conservative)

Estimated TVR frequency (Centers for Medicine & Medicaid Services population) 14.4% in the BMS era

Mean cost for each TVR event $11,913

Est. annual economic burden in the US ~$1.2 billion
Is Restenosis a Benign Entity?
1186 Cases of single lesion Bare Metal In-Stent-Restenosis at the Cleveland Clinic

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>64.1%</td>
<td>Effort Angina</td>
</tr>
<tr>
<td>26.4%</td>
<td>Unstable Angina</td>
</tr>
<tr>
<td>9.5%</td>
<td>Acute MI</td>
</tr>
<tr>
<td>7.3%</td>
<td>NSTEMI</td>
</tr>
<tr>
<td>2.2%</td>
<td>STEMI</td>
</tr>
</tbody>
</table>

1006 cases (8.9%) totally occluded

TREATMENT
8 (0.7%) Procedural Deaths

Drug Eluting Stents: A New Solution First Generation 2003

Drug eluting stents promised to reduce the number of repeat revascularization procedures (ISR) by inhibiting neointimal proliferation (AKA “delayed healing”)

- **Cypher (J&J, Cordis)**: Sirolimus (Rapamycin) coated stent. Cytostatic with anti-inflammatory and antiproliferative properties.
- **Taxus (Boston Scientific)** Paclitaxel (derived from the Pacific yew tree, Taxus brevifolia) coated stent. Lipophilic, inhibits cellular division, motility, activation, secretory processes and signal transduction.

An Update on Angioplasty and Coronary Stents

Ernest L. Mazzaferri Jr, MD, FACC
Director, Regional STEMI Program
The Richard M. Ross Heart Hospital
The Ohio State University, Columbus, Ohio

The First Available DES

**TAXUS**
Paclitaxel | Polyolefin derivative | Express²
---|---|---
Drug | Polymer | Stent

**Cypher**
Sirolimus | PEVA + PBMA blend | BX Velocity
DES: A Transforming Technology

Pre Post 4 Months
12 months 24 months 48 months

Taxus Data: 3 Randomized Trials 2003-2004
Percent of Angiographic Restenosis at 6-9 Months

<table>
<thead>
<tr>
<th></th>
<th>Bare Metal Stents</th>
<th>Drug-eluting Stents</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAXUS-II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Trials</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0 5 10 15 20 25

Percent

* Led to US FDA approval of Taxus DES in 2004

Cypher Data: 4 Randomized Trials 2002-2004
Percent Angiographic Restenosis at 6-9 Months

<table>
<thead>
<tr>
<th></th>
<th>Bare Metal Stent</th>
<th>Drug-eluting Stents</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVEL (2002)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-SIRIUS (2003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Trials</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0 10 20 30 40 50 60

* Led to US FDA approval of Cypher DES in 2003

DES Overtakes Market...

- On the basis of SIRIUS/TAXUS IV, drug-eluting stents were approved for use in previously untreated coronary lesions of less than 30 mm in length and a reference-vessel diameter of 2.50 to 3.75 mm.
- Over time, the use of drug-eluting stents has been expanded to all types of patients, including those with more complicated coronary lesions and in acute settings.

✓ AKA: “Off-Label” Stenting
Real World Data: RESEARCH Registry 2004

1 year TVR

1 year MACE

P<0.001

P=0.008

JAMA 2005: Increased Stent Thrombosis for DES?

Stent Thrombosis
Subacute Thrombosis
Late Thrombosis

Personal Injury Lawyers

• ? What To Do? If you, or a loved one, received an implanted heart stent as part of an angioplasty procedure anytime since 2003 and have suffered a heart attack or other heart complication, it may make sense to investigate your situation further.

November 2006 ‘Millions face Risk from Drug Eluting Stents’

“Millions of Americans could be walking around with tiny time bombs in their hearts.”
Update on Drug Eluting Stents

Definition of Stent Thrombosis

Acute ➞ within 24 hours
Subacute ➞ 2 to 30 days
Late ➞ 30 days to 1 yr
Very Late ➞ more than 1 yr

New Concept: “Delayed Healing in DES”
Cypher Stents from Different Coronary Arteries in the Same Patient

2007: Data from 9 Randomized Trials

4-Year Clinical Follow-up

- Stent Thrombosis
- Myocardial Infarction
- Cardiac Death

Percentage

Bare Metal Stent  Cypher Stent  Taxus Stent  Bare Metal Stent

P=NS  P=NS  P=NS
2003-2007: Survival, Randomized Trials

- 4,958 patients
- Follow-up 1-5 years


2003-2007: Death & MI, Randomized Trials

- 4,958 patients
- Follow-up 1-5 years


2000-2007 Observational Study
Duke University: "Real World" Evaluation 3165 BMS, 1501 DES
24 month outcomes; Clopidogrel status at 6 months

- BMS - Clopidogrel
- BMS + Clopidogrel
- DES - Clopidogrel
- DES - Clopidogrel

P=0.02
P=NS
P=0.03
P=NS

Eisenstein E et al. JAMA 2007;297:159-168

2000-2007 Observational Study
Duke University: "Real World" Evaluation 3165 BMS, 1501 DES
24 month outcomes; Clopidogrel status at 12 months

- BMS - Clopidogrel
- BMS + Clopidogrel
- DES - Clopidogrel
- DES - Clopidogrel

P=0.004
P=NS
P<0.001
P=NS

Eisenstein E et al. JAMA 2007;297:159-168
February 2007
AHA/ACC/SCAI/ADA Science Advisory Panel
Anti-platelet Therapy Update

- **After Drug Eluting Stent Placement:**
  - The Advisory stresses the importance of *12 months of dual antiplatelet (ASA and Plavix)* therapy, longer if tolerated
  - Educating the patient and healthcare providers about the hazards of premature discontinuation of dual antiplatelet therapy
  - The Advisory recommends *postponing elective surgery for 1 year*, and if surgery cannot be deferred, considering the continuation of ASA during the perioperative period in high risk patients

Drug Eluting Stents in 2008
“The Second Generation”

- Medtronic Endeavor Stent
- Guidant Xience Stent
- Boston Scientific Promeus Stent
- Boston Scientific Liberte Drug Coated Stent
- Cordis J&J Elite Stent

2007: U.S. DES Penetration Analysis

<table>
<thead>
<tr>
<th>BSC</th>
<th>Jan: 71%</th>
<th>Feb: 69%</th>
<th>Mar: 67%</th>
<th>Apr: 65%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>76%</td>
<td>74%</td>
<td>72%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>78%</td>
<td>76%</td>
<td>74%</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>68%</td>
<td>66%</td>
<td>64%</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>58%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>70%</td>
<td>68%</td>
<td>66%</td>
<td>64%</td>
<td>62%</td>
<td>60%</td>
<td>58%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Future Stent Concepts

- The ideal stent would have “advanced healing” of the endothelium without neointimal hyperplasia
  - This potentially would allow for minimal antiplatelet therapy after stent placement
- Medtronic Bioabsorbable Stent
  - First in Man Trial Enrolling in European Centers
  - Preliminary Data
Future Stent Concepts

- Orbus Neich Endothelial Progenitor Cell (EPC) covered stents
  - First in Man Trial Enrolling in Scandinavian Centers
  - Preliminary Data

Future Stent Concepts

- Orbus Neich Endothelial Progenitor Cell (EPC) covered stents
  - First in Man Trial Enrolling in Scandinavian Centers
  - Preliminary Data

FREEDOM Trial (NHLBI)

FUTURE REVASCULARIZATION EVALUATION IN PATIENTS WITH DIABETES MELLITUS:
OPTIMAL MANAGEMENT OF MULTIVESSEL DISEASE

Eligibility: DM patients with MV-CAD eligible for stent or surgery
Excluding: Patients with acute STEMI, cardiogenic shock

N=2400 at 100 centers from NA, SA, EU, Rand. 1:1

- MV DES stenting (Cypher or TAXUS) and abciximab
- CABG with or without cardiopulmonary bypass

Primary Endpoint: 3-year death, MI, stroke
Secondary Endpoints: 12-month MACCE, 3-year Quality of Life
PI: Valentin Fuster

Ongoing Trials: SYNTAX

De novo disease acceptable for revascularization

- Left main disease (minimum 710) and/or 3-vessel disease
- Randomize 1800
- PCI Registry
- TAXUS PCI
- CABG Registry
- CABG

Primary NI endpoint – 1 year MACCE
All cause death, MI, cerebrovascular events, repeat revascularization

PIs: Patrick Serruys and Frederick Mohr

Conclusions

- Restenosis Rates: PTCA>BMS>DES
- Death/MI: PTCA>BMS=DES
- Plavix Duration (ASA indefinite):
  - PTCA approx 30d
  - BMS 30d
  - DES 12 months, longer if tolerated
- If patients can tolerate long-term dual anti-platelet therapy, outcomes appear best with DES