Update in PCI - What’s New and Where are We Going?

Breakthroughs 2008 and beyond

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Disclosures

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Research Grants: Cordis, Boston Sci

Consultant: Conor

Equity: MediVas, FlowMedica
“A good conversation touches on everything but dwells on nothing”

--- Oscar Wilde
Transcatheter Valve Therapy

Aortic Stenosis

First Generation Devices

Cribier-Edwards
391 patients

CoreValve
154 patients
tAVR: Vancouver Experiences

AV Area and Gradients

Aortic valve area (cm²) vs. Aortic valve mean gradient (mmHg)

- **Base line** (n=50)
- **Valve implanted** (n=43)
- **Pre discharge** (n=42)
- **1 month** (n=38)
- **6 month** (n=27)
- **12 month** (n=16)

- **Aortic valve area (cm²)**
- **Aortic valve mean gradient (mmHg)**

Statistical significance:
- P<0.001
- P=0.15
- P=0.88

**AV Area and Gradients**

**tAVR**: Vancouver Experiences

**Aortic valve area (cm²)**

**Aortic valve mean gradient (mmHg)**

**Courtesy of J. Webb**
tAVR: Vancouver Experiences

Symptom Status

![Symptom Status Graph]

% in each NYHA class

- NYHA I
- NYHA II
- NYHA III
- NYHA IV

Base line (n=37)
1 month (n=37)
6 month (n=35)
1 year (n=17)

- (n=37)
- (n=37)
- (n=35)
- (n=17)

P<0.0001
p=0.59

Symptom Status Graph

COLUMBIA UNIVERSITY MEDICAL CENTER

Courtesy of J. Webb
PARTNER US, Randomized Trials
Total = 600 Patient Pivotal Trial

High Risk Symptomatic Critical Aortic Stenosis

“operable”?

1ry endpoint = mortality @ 1 yr

Medical Management Superiority, n=250
1:1 Randomization

Best Medical Tx SAPIEN THV

Surgical AVR Non-inferiority, n=350
1:1 Randomization

Surgical AVR SAPIEN THV
Percutaneous Mitral Repair Approaches

- **Coronary sinus annuloplasty**
  - Edwards Monarc
  - Cardiac Dimensions Carillon
  - Viacor Shape Changing Rods
  - St. Jude Annulus Reshaping

- **Direct annuloplasty**
  - Mitralign Suture-Based Plication
  - Guided Delivery Anchor-Cinch Plication
  - QuantumCor RF Annulus Remodeling
  - MiCardia variable size ring

- **Leaflet repair**
  - EValve Mitraclip
  - Edwards Mobius stitch

- **Chamber + annular remodeling**
  - Myocor iCoapsys
  - Ample PS3
Edwards MONARC System

12F guiding catheter
9F delivery system

59 pts have been treated

Distal Anchor
Proximal Anchor
Bridge

12F guiding catheter at implant
9F delivery system at ~4-6 weeks
In a pre-clinical model, “a relatively small (1 cm, 20%) plication of the posterior annulus can normalize the S-L dimension and eliminate Ischemic MR” *

* Tibayan et al., Circ. 2003;108:II-128-133
MR Reduction
[Pre vs. 24 hours Post]

Pre 3+

Post 2+

Independent Core Assessment, Brad Munt, MD
PISA method

Siegburg/Stanford
Standard balloon catheter with a paclitaxel coating applied to surface of balloon (dip-coated), 3 µg / mm²

Cellular uptake of paclitaxel in vessel facilitated by the hydrophilic drug carrier Ultravist 370

Ultravist may provide emulsifying activity and solubility for taxol

Contrast agents appear to “coat” vessel lining; thus may facilitate cellular uptake of associated drugs
Drug Eluting Balloons
Paclitaxel Pharmacokinetics

Typically, 10% drug remains on the balloon

10% - 20% of the drug is found in the vessel wall after 5 minutes

1% - 2% of the drug remains in the vessel wall after 24 hours
## Drug Eluting Paclitaxel Balloon Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>THUNDER (Tepe)</th>
<th>Ricke Study</th>
<th>Scheller (NEJM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peripheral SFA</td>
<td>Peripheral SFA</td>
<td>Coronary ISR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 m FU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Taxol</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>n = 54</td>
<td>N = 48</td>
<td>N = 42</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>2.8 ± 1.9</td>
<td>4.1 ± 1.4</td>
<td>n.a.</td>
</tr>
<tr>
<td>LL (mm) in segment</td>
<td>1.7 ± 1.8</td>
<td>0.4 ± 1.2</td>
<td>n.a.</td>
</tr>
<tr>
<td>Binary restenosis</td>
<td>39%</td>
<td>15%</td>
<td>n.a.</td>
</tr>
<tr>
<td>TLR</td>
<td>28%</td>
<td>6%</td>
<td>33%</td>
</tr>
<tr>
<td>Rutherford decrease</td>
<td>1.5 ± 1.5</td>
<td>2.3 ± 1.8</td>
<td>0.8 ± 1.1</td>
</tr>
</tbody>
</table>
BreakDOWNs in PVD
Treatments: 2007

• Reimbursement 2007 - 2008
  ▪ Asymptomatic Carotid stents were NOT reimbursed

Continued turf wars!

For carotid stenting, CMS currently reimburses treatment of patients at high risk for carotid endarterectomy, provided they meet one of the following conditions:
1. They have symptomatic carotid artery stenosis (>70%)
2. They are participating in an IDE clinical trial and are symptomatic (>50% stenosis) or asymptomatic (>80% stenosis), or
3. They are participating in an FDA-mandated post-approval study and are being treated according to the approved device indications.

▪ If your patient is NOT high risk, by very strict criteria, and they strongly desire stents, you can not help them. Insurance mandates CEA!
• FDA closes biliary stent approval pathway for SFA and renal stents
  ▪ Forces physicians and industry to conduct appropriate clinical trials
  ▪ Objective Performance Criteria (OPC ie single arm comparison to a control data sets) embraced for various peripheral device trials
# RESILIENT Trial Interim Results (Intent to Treat)
## 12 Month Results

<table>
<thead>
<tr>
<th>Measure</th>
<th>PTA Patients</th>
<th>LifeStent Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Limb ABI (mmHg), ( \mu \pm S.D. ) (#)</td>
<td>0.9 ± 0.2 (31)</td>
<td>0.9 ± 0.2 (61)</td>
</tr>
<tr>
<td>Freedom from Re-Intervention, %</td>
<td>44.1%</td>
<td>81.5%</td>
</tr>
</tbody>
</table>

## Stent Fracture

<table>
<thead>
<tr>
<th>Measure</th>
<th>12-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Stented Subjects</td>
<td>81</td>
</tr>
<tr>
<td>No. of Implanted Stents</td>
<td>136</td>
</tr>
<tr>
<td>No. of Fracture Stents</td>
<td>5*</td>
</tr>
<tr>
<td>Fracture Rate (per evaluable stents)</td>
<td>3.7%</td>
</tr>
</tbody>
</table>

*No clinical symptoms, all treated vessels patent at last follow-up

Katzen et al 2007
ABSOLUTE TRIAL
Nitinol Stents vs. POBA for SFA Disease
2 Year Follow-up

Figure 1. Freedom from restenosis (>50%) in 98 patients with chronic limb ischemia and femoropopliteal obstructions randomized to primary stent implantation (Stent) vs balloon angioplasty with optional stenting (PTA).

Figure 2. Freedom from target vessel revascularization (TVR) in 98 patients with chronic limb ischemia and femoropopliteal obstructions randomized to primary stent implantation (Stent) vs balloon angioplasty with optional stenting (PTA).

Targeted Renal Delivery to Prevent Contrast Induced Nephropathy
Proof of Principle: IV followed by IR Fenoldopam Vs placebo infusion in “at risk” patients

Glomerular Filtration Rate: Fenoldopam

IV FEN increased GFR by 4.9% from baseline (p<0.05).

IR FEN increased GFR by 23.6% (p=0.0007 compared to IV FEN)

At 2 hours following discontinuation of FEN, GFR remained increased by 25.1%, while it decreased by 14% in the control group.

* p < 0.05, fenoldopam vs. placebo

Percentages indicate change from baseline to 2-hours post Rx

- Fenoldopam, n = 22
- Placebo, n = 11
Device training is available

4 CPT (Physician) Codes Apply*

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>75625</td>
<td>Aortography: performance + interpretation</td>
</tr>
<tr>
<td>36245</td>
<td>Selective catheter placement, arterial system</td>
</tr>
<tr>
<td>37202</td>
<td>Transcatheter therapy; infusion of vasoconstrictive agent</td>
</tr>
<tr>
<td>75896</td>
<td>Transcatheter therapy, infusion, any method, radiological supervision and interpretation</td>
</tr>
</tbody>
</table>

Contact Info:  [www.flowmedica.com](http://www.flowmedica.com)
Intravascular Ultrasound in the Drug-Eluting Stent Era

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New York, New York; and Washington, DC

Intravascular ultrasound (IVUS) has become an indispensable part of all drug-eluting stent (DES) studies; findings must be put into context with the IVUS findings in bare metal stents. Unfortunately, there is not yet a complete picture of either the Cypher (Cordis, Miami, Florida) or the Taxus (Boston Scientific, Maple Grove, Minnesota) stent (the two U.S. Food and Drug Administration-approved devices). Intimal hyperplasia volume in DES is reduced to <15% of stent volume, but stent underexpansion continues to be a consistent finding in DES failures (restenosis and thrombosis). The utility of IVUS to assure adequate stent expansion may be more important whenever there are clinical risk factors for DES failure. (J Am Coll Cardiol 2006;48:421–9) © 2006 by the American College of Cardiology Foundation

In the bare-metal stent (BMS) era serial (post-intervention and follow-up) intravascular ultrasound (IVUS) was crucial to understanding how stents worked and why they failed. Chronic stent recoil was rare, and late lumen loss
Importance of Complete Strut Apposition

TLR

SATs

Restenosis

Drug Delivery

44% TLR reduction with complete stent apposition
CRUISE Study, 2003

78% of SATs involved incomplete stent apposition
Chenau, et al, 2003

DES restenosis with incomplete stent strut apposition
Takebayashi, 2004

Complete stent apposition facilitates uniform drug delivery
Hwang, 2001
ANTIPLATELET AGENTS: The Next Generation
6 Month Outcomes post-DES: The Scripps Clinic Experience

*On clopidogrel at 30 day & 6-month FU or reached an endpoint on clopidogrel by 6-month FU

The RECLOSE Study: 6 Month Outcomes After DES Implantation Stratified By Post-Plavix ADP-mediated Platelet Reactivity

Overall (n=804)  Responders (n=699)  Non-Responders (n=105)

Cardiac Death: 2.4% 1.4% 8.6%
p<0.001

Stent Thrombosis: 3.1% 2.4% 8.6%
p<0.001

Cardiac Death and ST: 3.5% 2.7% 10.5%
p<0.001

Non-responders defined as >70% aggregation by LTA 12 hours after 600-mg plavix load

Limitations of Clopidogrel

• Slow onset of inhibitory effect
  – Need to preload before angiography, preferably at least 4 hours prior to PCI for greatest benefit

• Slow offset
  – Guidelines recommend waiting at least 5-7 days for surgery (benefit of POC testing)

• Variable response among individuals
  – Increase incidence of out-of-hospital ischemic events/stent thrombosis among non-responders
  – ? increased incidence of peri-procedural MI?
Making Clopidogrel Better: A Next Generation Thienopyridine

Ticlopidine (1st generation)

Clopidogrel (2nd generation)

Prasugrel (CS-747) (LY640315) (3rd generation)

Prasugrel is not approved by the US Food and Drug Administration.
TRITON TIMI-38 Study Design

**ACS (STEMI or UA/NSTEMI) & Planned PCI**

**ASA**

N = 13,600

**Double-blind**

**CLOPIDOGREL**
300 mg LD/75 mg MD

**PRASUGREL**
60 mg LD/10 mg MD

Median duration of therapy = 12 months

1° endpoint: CV death, MI, Stroke

2° endpoints: CV death, MI, Stroke, Rehosp-Recurrence Ischemia

CV death, MI, UTVR

Stent Thrombosis (ARC definite/prob.)

Safety endpoints: TIMI major bleeds, Life-threatening bleeds

Key Substudies: Pharmacokinetic, Genomic

Primary Endpoint CV Death, MI, Stroke

- **Prasugrel**
  - HR 0.80
  - P = 0.0003
  - NNT = 46

- **Clopidogrel**
  - 12.1 (781)
  - 9.9 (643)
  - HR 0.81 (0.73-0.90)
  - P = 0.0004
  - NNT = 46

Stent Thrombosis (ARC Definite + Probable)

Any Stent at Index PCI
N= 12,844

Days

Endpoint (%)

0 30 60 90 180 270 360 450

Prasugrel

HR 0.48
P <0.0001
NNT= 77

Clopidogrel

2.4 (142)

Cangrelor Cangrelor: Intravenous Administration

- Intravenous P2Y12 Inhibitor
- Plasma half-life 3-5 minutes
- Full recovery of platelet function <60 minutes

Data on file, The Medicines Company
Potential Advantages/Roles For Cangrelor

- Eliminates need for pre-loading (can begin infusion at time of PCI after diagnostic angiogram)

- May reduce peri-procedural MI without increased bleeding?
  - (more potent P2y12 inhibition, less variability, short-acting, not via gpIIbIIla receptor)

- Bridge for patients on clopidogrel who need surgery?
Drug delivery stents that provide temporary scaffolding, are compatible with cardiac MRI, and that *Disappear after* drug treatment of some or all of the vessel!