Renal Stent Trials: ASPIRE II, RESIST & CORAL Trials

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The Challenges of Renal Stenting:

- No U.S. FDA approved clinical indication
- Angiographic indication only: Failed/suboptimal PTA

This fact reflects:

- Diverse population w/ variety of indications (HTN, renal insufficiency, cardiac disturbances)
- Difficult 'hard' surrogate end-points
Improved Morbidity/Mortality

Renal function preservation
CHF/Angina Control
Improved BP control

Surrogate End-points
U.S. Renal PMA Stent Trials

- Palmaz, (Cordis J&J): ASPIRE I Pilot Trial (Completed)
- Palmaz, (Cordis J&J): ASPIRE II (Completed, in press)
- Genesis, (Cordis J&J): GREAT Trial (completed) and RESIST Trial (in progress)
- Herculink, (Guidant): HERMES Trial (Completed, not published)
- Herculink Plus, (Guidant): -----------------------------------
- AVE Bridge Stent (Medtronic): SOAR Trial (completed, not published)
- IntraStent, (eV3): ---------------------------------------------
- Abbott: ---------------------------------------------------------
- Express stent, (Boston Scientific): Renaissance Trial (Enrollment complete, results pending)
ASPIRE 2 Study Design

- **Design:** Prospective, non-randomized study of 208 patients at 23 US sites
- **Primary endpoint:** 9 mo. restenosis of the PALMAZ stent after failed PTRA
- **Secondary endpoints:**
  - MACE
    - Device or procedure related death
    - Procedure related Q-wave MI
    - Target lesion revascularization
    - Embolic events (defined as causing end-organ damage or loss of renal function)
  - Effect on control of blood pressure
  - Effect on renal function
    - As defined by a rise in serum creatinine

Rocha-Singh, et al. JACC ’05, in press
<table>
<thead>
<tr>
<th>Metric</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion Success (% DS &lt; 50%)</td>
<td>99.6% (251/252)</td>
</tr>
<tr>
<td>Acute Procedure Success (%DS &lt;30% &amp; gradient &lt;5mmHg)</td>
<td>80.2% (182/227)</td>
</tr>
<tr>
<td>Primary Patency (QA/duplex ultrasound @ 9 mo.)</td>
<td>81.0% (149/184)</td>
</tr>
<tr>
<td>9-Month Restenosis Rate (by duplex ultrasound &amp; angiography)</td>
<td>17.4% (32/184)</td>
</tr>
<tr>
<td>Target Lesion Free at 270 days (K-M Estimate, Lesion Based)</td>
<td>96.7%</td>
</tr>
<tr>
<td>Target Lesion Free at 720 days (K-M Estimate, Lesion Based)</td>
<td>85.9%</td>
</tr>
</tbody>
</table>

Rocha-Singh, et al. JACC ’05, in press
## Effect on Hypertension: Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Visit</th>
<th>N</th>
<th>Mean ± SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>208</td>
<td>167.6 ± 25.2</td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>202</td>
<td>147.6 ± 22.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1 month</td>
<td>196</td>
<td>151.5 ± 24.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6 month</td>
<td>182</td>
<td>149.2 ± 22.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>9 month</td>
<td>178</td>
<td>149.5 ± 23.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>24 month</td>
<td>158</td>
<td>149.3 ± 25.3</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Rocha-Singh, et al. JACC ’05, in press
### Effect on Hypertension: Diastolic Blood Pressure

<table>
<thead>
<tr>
<th>Visit</th>
<th>N</th>
<th>Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>208</td>
<td>81.53 ± 13.1</td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>202</td>
<td>70.88 ± 12.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1 month</td>
<td>196</td>
<td>75.25 ± 11.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6 month</td>
<td>182</td>
<td>76.85 ± 11.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>9 month</td>
<td>178</td>
<td>77.34 ± 12.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>24 month</td>
<td>158</td>
<td>76.87 ± 11.9</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Rocha-Singh, et al. JACC ’05, in press
### Effect on Renal Function

**Serum Creatinine**

Patients with **Abnormal** Renal Function Only  
*(Baseline creatinine > 1.5 mg/dl)*

<table>
<thead>
<tr>
<th>Visit</th>
<th>N</th>
<th>Mean±SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>74</td>
<td>1.94±0.39</td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>64</td>
<td>1.89±0.72</td>
<td>0.64</td>
</tr>
<tr>
<td>6 month</td>
<td>60</td>
<td>1.98±0.66</td>
<td>0.49</td>
</tr>
<tr>
<td>9 month</td>
<td>63</td>
<td>1.87±0.58</td>
<td>0.53</td>
</tr>
<tr>
<td>24 month</td>
<td>53</td>
<td>1.93±0.71</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Rocha-Singh, et al. JACC ’05, in press
• 17% restenosis rate is comparable to rates in literature
  – Extremely favorable compared to PTRA alone
  – Comparable to surgical revascularization

• Blood Pressure response showed significant reductions in blood pressure at 9 and 24 months
  – Systolic:
    • 18.1 point improvement at 9 mo. (10.8% decrease)
    • 18.3 point improvement at 24 mo. (10.9% decrease)
  – Diastolic:
    • 4.2 point improvement at 9 mo. (5.1% decrease)
    • 4.7 point improvement at 24 mo. (5.7% decrease)

Rocha-Singh, et al. JACC ’05, in press
• No significant changes in serum creatinine levels at 9-month follow-up
  - No change in subset who were abnormal at baseline
  - No significant change when all patients are considered

• BP/Antihypertensive medication response showed 45% of patients were cured or improved at both 9- and 24-month marks

  55% of patients experienced no BP improvement
Outcomes Of Renal Revascularization In Chronic Azotemic Renovascular Disease

**Improved GFR**
- 25 - 30%
- Restoration of Blood Flow
- Reversible Parenchymal Injury

**Stable GFR**
- 45 - 50%
- No Further Loss of Blood Flow
- Stable Tissue Fibrosis

**Deterioration of GFR**
- 20 - 25%
- Progressive Parenchymal Injury
- Concurrent Diseases
- Atheroemboli
- Reperfusion Injury
### Renal Stent Related Complications: ASPIRE II

<table>
<thead>
<tr>
<th>Major Adverse Events – 9 mos.</th>
<th>10.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent Thrombosis</td>
<td>1.8%</td>
</tr>
<tr>
<td>Significant Embolic Event</td>
<td>5.3%</td>
</tr>
<tr>
<td>Target Lesion Revascularization</td>
<td>4.8%</td>
</tr>
<tr>
<td>Access Site Complication</td>
<td>4.8%</td>
</tr>
<tr>
<td>Worsening Renal Function</td>
<td>3.8%</td>
</tr>
<tr>
<td>Complication Requiring Surgery</td>
<td>2.1%</td>
</tr>
<tr>
<td>Complication Requiring Nephrectomy</td>
<td>0.0%</td>
</tr>
<tr>
<td>30-day Mortality</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Rosenfield ‘00
Material impacts in small arteries, arterioles and glomeruli

- Intimal thickening and formation of giant cells
- Distal micro-infarcts and ischemic atrophy

- Becomes clinically evident 1 day to 2 months after the procedure

From Schrier, 7th ed.
• Retrospective review of patients prior to and with embolic protection
  – 20 before, and 37 after
• Mean follow up 1 year

JVS 2003; 38:962-968.
Commercially Available
DP Technology

PercuSurge™

FilterWire EX™
RESIST Trial

A Prospective Randomized Multicenter Study Comparing the Safety & Efficacy of Renal Artery Stenting with & without the use of a Distal Protection Device (Angioguard) and with & without the use of Reopro.

- Multi-center, prospective, randomized, feasibility Trial
- 100 patients stented with PALMAZ® GENESIS® Stent
- 50 patients randomized to stent + ANGIOGUARD™ and 50 patients to stent alone
- 50 patients randomized to receive Reopro
- Patient follow-up at 1 and 6 months
- Enrollment at 66 patients to date
Primary Aims of the RESIST Study:

1. Determine whether embolic protection with the **Angioguard XP Short Tip** device during stent implant results in:
   
a. Retrieval of atheroembolic material...amount
   b. Improved renal function at 1 month post-procedure
   c. Evidence of decreased injury in the kidney(s)
   d. Is it safe?
Primary Aims of RESIST Study

2. Determine whether the inhibition with ReoPro results in:

   a. Improved renal function 1 month post-procedure.
   b. Decreases evidence of injury in the kidney(s)
   c. Is it safe?
RESIST Follow-up:

1 month visit:
   a. Blood pressure assessment
   b. Creatinine assessment with BMP
   c. Renal function assessment with DTPA scan to assess GFR and Iohexal clearance
   d. Hypertensive medication assessment

6 month visit:
   a. Blood pressure assessment
   b. Creatinine assessment with BMP
   c. Hypertensive medication assessment
Strategies to Avoid Distal Embolization

- **Patient selection: ‘High risk’ cohort**
  - Elderly
  - Renal dysfunction, bilateral disease
  - Diseased aorta

- **Active Protection: Technical Points**
  - Atraumatic catheter intubation: Use ‘No touch’
  - Choice of the device:
    - Small french diagnostic and guiding catheters
    - 0.014” guide wires, balloons, short stents...
    - Coronary devices & techniques

=> **Passive Protection: DP Devices**
AngioGuard-XP Wire
CORAL is designed to test a **singular** hypothesis:

Does ‘best medical therapy’ combined with stenting of hemodynamically-significant renal artery stenoses in patients with systolic hypertension reduce the incidence of adverse cardiovascular and renal events compared with ‘best medical therapy’ alone.
Prospective, multicenter, two armed, randomized, un-blinded trial

**Interventions:**

1. **Optimal Medical Therapy**
   - All receive Candesartan, Angiotensin Receptor Blocker
   - LDL, BP and HbA1c to guideline

2. **OMT plus Stent Revascularization**
   - AngioGuard embolic protection
   - Genesis balloon expandable stent
Randomization and Follow-up

Randomization of All Angiographically Eligible Patients
- Performed in angiography lab immediately after diagnostic angiogram confirms eligibility

1080 Patients
- Medical Therapy: 540 Patients
- Stent + Medical Therapy: 540 Patients

Follow-up
- 1st Year of Follow-up
  - q 2 Weeks up to 2 Months for BP Control
  - q 3 Months Physician Office Visits
  - Monthly Coordinator Phone Contact
- 2nd Year through End of Study Follow-up
  - Semi-annual + Annual Physician Office Visits
  - Quarterly Research Coordinator Visits
  - Monthly Coordinator Phone Contacts
Primary Outcome:

- Survival free from a composite of clinically important Cardiovascular and Renal Adverse Events: Hard End-points
  - Cardiovascular or Renal Death
  - Stroke
  - Myocardial Infarction
  - Hospitalization from CHF
  - Progressive Renal Insufficiency
    - Doubling of Cr from baseline, persisting on 2 core lab draws separated by 60 days
  - Renal Replacement Therapy (HD)

Adjudicated by an independent CEC
Why is "State-of the-art" intervention critical?

- Comparison should be best vs best
- Interventional committee will continue to review "best" interventional care
- Results should be relevant in 2010 and beyond

Why is Optimal Medical Therapy critical?

- If stenting wins, it wins against the best.
- If blood pressure or renal function benefits emerge, it isn’t because of poor medical therapy!
  - OMT needs to be balanced for effect of stenting to be evaluable.
- *Every* patient in this trial will be treated well.
# Optimal Medical Therapy

## Required Therapies

<table>
<thead>
<tr>
<th>Required Therapies</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP to target</td>
<td>Compliance</td>
</tr>
<tr>
<td>• ARB (Candesartan) based</td>
<td>• Candesartan</td>
</tr>
<tr>
<td>• &lt;140/90</td>
<td>• BP Quarterly</td>
</tr>
<tr>
<td>• &lt;130/80 with DM</td>
<td>• LDL annually</td>
</tr>
<tr>
<td>LDL to goal</td>
<td>• HbA1c annually</td>
</tr>
<tr>
<td>• Currently &lt;100 mg/dl</td>
<td>• Document smoking status and education</td>
</tr>
<tr>
<td>Diabetes Management</td>
<td>• Smoking Cessation</td>
</tr>
<tr>
<td>• HbA1c to target, &lt;7</td>
<td></td>
</tr>
<tr>
<td>Smoking Cessation</td>
<td></td>
</tr>
</tbody>
</table>
### Secondary Endpoints

- **All Cause Mortality**

- **Subgroup Interactions:**
  - Men vs Women
  - African American vs non-African American
  - Diabetes vs non-Diabetes Mellitus
  - Global vs Partial Renal Ischemia

- **Longitudinal Kidney Function** \((1/\text{Cr})\)

- **Systolic Blood Pressure**

- **Durability of Renal Artery Patency**

- **Renal Resistive Index:** Preservation of Microvascular Renal Function

- **Correlation between Stenosis Severity and Kidney Function** \((1/\text{Cr})\)

- **Quality of Life**

- **Cost Effectiveness**
**Points of Emphasis:**

1. Enrollment decision based on *clinical*, not anatomic criteria.
2. If patients with severe stenoses or global ischemia are excluded, no inference can be made.
3. As a federally funded project, inclusion of women and minorities is critical for generalizability.
• Clinical indications for medical v. percutaneous intervention will be better defined
• Angiographic v. Duplex doppler restenosis rates will be known
• Impact of medical therapy v. renal intervention on ‘hard end-points’ (death, MI/CVA, BP control & ESRD) will be determined