Does Renal Artery Distal Protection Have a Role in Renal Artery Stenting?

Evolving Clinical Science

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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
  - Reperfusion Injury
  - Contrast Nephropathy
  - Atheroemboli
Atheroembolization

- Material impacts in small arteries, arterioles and glomeruli

- Intimal thickening and formation of giant cells

- Distal micro-infaracts and ischemic atrophy

- Becomes clinically evident 1 day to 2 months post-procedure

From Schrier, 7th ed.

FIG. 70-11. Light microscopy illustrates the needle-shaped clefts of atheroemboli in a renal arteriole. Foreign-body giant cells (arrows) surround the cholesterol clefts.
RAS + EPD = Improved/Stabilized GFR
Aorto-renal Endartectomy Specimen

Hiromoto, JVS June ‘05
>100 µm fragments released from ex-vivo renal arteries angioplasty with stent placement

- Are atheroembolic events clinical relevant?
- If so, how is renal injury assessed?
- In what patient group?
- At what time point?
- What is the right device?
83 arteries treated in 63 consecutive pts. All patients had baseline CRI with a documented decline in renal function over the preceding 6 mos.

All patients had an identical “primary filter passage” technique and primary renal stenting.

All patients had a minimum 6 mos. follow up.
The severity of the pre-intervention CRI was classified using the Kidney Disease Outcome Quality Initiative (K-DOQI)

<table>
<thead>
<tr>
<th>eGFR</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>K-DOQI 3A</td>
<td>41-59 ml/min</td>
</tr>
<tr>
<td>K-DOQI 3B</td>
<td>30-40 ml/min</td>
</tr>
<tr>
<td>K-DOQI 4</td>
<td>15-29 ml/min</td>
</tr>
</tbody>
</table>

44 patients (70%) were hypertensive pre-intervention
Study Design

- The primary study measures were sCr at day 1 and 6 mos. post-stenting.
- The day 1 sCr: detect any acute-procedure related deterioration in renal function.
- The 6 month sCr: measure renal function at a sufficient interval post-stenting to assess any sub-acute effects from atheromatous embolization.
Alterations in Scr at 6 mos. were classified as follows:

<table>
<thead>
<tr>
<th>Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>SCr &gt;20% below baseline</td>
</tr>
<tr>
<td>Progressive</td>
<td>SCr &gt;20% after baseline</td>
</tr>
<tr>
<td>deterioration</td>
<td></td>
</tr>
<tr>
<td>Stabilized</td>
<td>SCr within 20% of baseline</td>
</tr>
</tbody>
</table>

After Harden, Lancet 2000
## RESULTS at 6 months

### Level of pre-intervention CRI

<table>
<thead>
<tr>
<th></th>
<th>K-DOQI 3A</th>
<th>K-DOQI 3B</th>
<th>K-DOQI 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Improved</strong></td>
<td>12(52%)</td>
<td>8(32%)</td>
<td>5(33%)</td>
<td>25(40%)</td>
</tr>
<tr>
<td><strong>Stabilized</strong></td>
<td>11(48%)</td>
<td>15(60%)</td>
<td>10(67%)</td>
<td>36(57%)</td>
</tr>
<tr>
<td><strong>Unchanged decline</strong></td>
<td>0(0%)</td>
<td>2(8%)</td>
<td>0(0%)</td>
<td>2(3%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>23</td>
<td>25</td>
<td>15</td>
<td>63</td>
</tr>
</tbody>
</table>

97% of patients had renal function improved or stabilized at 6 mos.
Regression Lines

Inverse Serum Creatinine (umol/l) \(^{-1}\)

Time relative to Intervention (Months)
Filter Contents

Macroscopic embolic contents present in 38/63 filters (60%)

<table>
<thead>
<tr>
<th>Filter contents</th>
<th>Improved</th>
<th>Stabilized or Unchanged</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>20</td>
<td>18</td>
<td>38 (60%)</td>
</tr>
<tr>
<td>Negative</td>
<td>5</td>
<td>20</td>
<td>25 (40%)</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>38</td>
<td>63 (100%)</td>
</tr>
</tbody>
</table>

Patients with positive filter contents had significantly improved outcome (p = 0.01)
Primary Aims of the RESIST Study:

1. Determine whether embolic protection with the **AngioGuard XP Short Tip** device during stent implant ± **ReoPro** 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?
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
<table>
<thead>
<tr>
<th>ReoPro Infusion</th>
<th>- -</th>
<th>- +</th>
<th>+ -</th>
<th>+ +</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=28</td>
<td>n=22</td>
<td>n=25</td>
<td>n=25</td>
<td></td>
</tr>
</tbody>
</table>
AngioGuard™ Short-Tip: RESIST Trial
RESIST Trial: Effect on Platelet Activation

Soluble CD40 Ligand: Baseline, Post and 24 hr Post
% Patients with Platelet-Rich Thrombus and/or Visible Atheroma in Filter
RESIST Trial: Percent Change in eGFR at 1 mo.
# Potential Renal Biomarkers

<table>
<thead>
<tr>
<th>NEPHRON-SEGMENT</th>
<th>ABNORMAL FUNCT, MECHANISM TESTED</th>
<th>MARKER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLOMERULUS</strong></td>
<td>GFR</td>
<td>Serum Creatinine, Creatinine Clearance, Serum Cystatin C, Serum β-2-microglobulin, Serum Retinol-binding protein</td>
</tr>
<tr>
<td></td>
<td>Basem. Membr. integrity</td>
<td>Collagen IV</td>
</tr>
<tr>
<td><strong>PROXIMAL TUBULE</strong></td>
<td>Substance release</td>
<td>Urine α-Glutathione S-Transferase (α-GST), Human Kidney Injury Molecule-1, Neutrophil Gelatinase-associated lipocalin</td>
</tr>
<tr>
<td></td>
<td>Substance absorption</td>
<td>Urine β-2-microglobulin</td>
</tr>
<tr>
<td><strong>DISTAL TUBULE</strong></td>
<td>Substance release</td>
<td>π-Glutathione S-Transferase (π-GST), H-Fatty Acid-Binding Protein</td>
</tr>
<tr>
<td><strong>COLLECTING DUCT</strong></td>
<td>Papillary Function</td>
<td>Renal Papillary Antigen-1 (RPA-1)</td>
</tr>
</tbody>
</table>
KIM-1
Kidney Injury Molecule

γGT

Alk Phos

T-Protein

Kidney Int. 2002
62(1):237-44
Length of stent-EPD system

• The current combined length of the filter-balloon-stent systems are between 30 and 35mm

• The main renal artery is ~40mm long in adults but early branching occurs in 20-30% of cases

Courtesy of M.Jaff and A.Holden
Landing Zones & Filter Lengths
VIVA III Trial: FiberNet EPD
CONCLUSIONS

• Protected renal artery stenting with a distal filter is technically feasible…most of the time
• Embolic protection appears to impact renal preservation in pts. with IN…RCTs are needed
• The potential role of platelet activation in the pathophysiology of atheroembolization and progressive renal dysfunction requires further study
• Renal-specific markers of injury are needed
• A renal-specific EDP system is needed