Renal Artery Stenting

“We are unable to predict patients who will benefit from RAS“

MEET 2008

Thomas Ischinger MD FACC FESC
Heart Center Bogenhausen
Munich, Germany
Disclosure Statement of Financial Interest

I DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

MEET 2008
Effects of renal artery stenosis on blood pressure and the heart: Pathophysiology

Renin-Angiotensin-Aldosterone-System

regulates: Fluid volume, blood pressure, cardiovascular function

Angiotensinogen

<table>
<thead>
<tr>
<th>Angiotensin I</th>
<th>Angiotensin II</th>
<th>Aldosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin</td>
<td>Angiotensin Converting Enzyme</td>
<td>Sodium/Water-Retention</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>Bloodpressure</td>
<td></td>
</tr>
</tbody>
</table>

Stenosis

Negative Feedback

Isch meet 08
Association of renal artery stenosis and heart failure

Risk factors:
- hypertension, nicotin, diabetes, FA, HLP, age, gender

Atherosclerosis,
renal artery stenosis

Activated RAAS,
renal dysfunction

Hypertension,
increased LV-mass,
syst. and diast. dysfunction

Acute heart failure,
pulmonary edema,
cardiac arrhythmia,
angina pectoris

Chronic heart failure,
chronic renal insufficiency
G.Zie, female, 55y

Post reocclusion after 1.RAS of right renal artery. Silent at szinti.

Medication:
Nebivolol 5mg,
Ramipiril 30mg,
Valsartan 240mg, HCT 20mg, Lercarnidipin 20mg, Moxonidin 0.3mg, Torasemid 20mg

Therapy:
Recanalization + 2. stenting of renal artery
Renal artery stenting, illustrative case

• Malignant hypertension in 54 year old female with Angina as initially leading symptom
• Stenting of right renal ostial stenosis
• Reocclusion
• Recanalization & restenting
• Reocclusion
• Further therapies & medications
RAS occluded

RAS recan / restented

RAS reoccluded

RAS, illustrative case

angiographies

isch05
Reoccluded renal stent
**History:** H.S. 61 J / S/P bypass Surgery, multiple PTCA+stent, ACS with bei hypertensive crisis, pulm. edema, CCU, acute coronary angio. No coronary restenosis, high grade prox. RAS right (Angio + Duplex). Left 50%. **Tx:** PTA right RAS, cutting bal., stent. 1 year FU: no antihypertensive medication (110/90)
Renal artery stenting: Background & Facts

- Atherosclerotic disease of renal arteries is common
  - > 7% over age 65, > 10% with chr renal disease, >30% of older pts with CHF
  - in cardiac cath pts a >70% RAS was present in:
    - 7% of pts w severe atherosclerosis, in 9% w hypertension, in 16% with renal dysfunction, in 22% w pulmonary edema
- RAS > 50% is independ. predictor of all cause mortality (30-50%)
- RAS may lead to renovasc.hypertx & and loss of renal function
- RAS is considered an avoidable cause of renal failure
- RAS >60% DS progress to occlusion in 5% of pts/year
- RA stenting is Tx of choice, yet is associated with hazards
- Selection of pts who may (predictably?) benefit is warranted

Buller JACC 2004, White Circ 2006
What are the benefits we wish to expect from RA stenting?

- Long term patency of the RA...and thereby
- ...sustained improvement in BP control
- Improvement in renal functional parameters
- Slowing of deterioration of renal function (delay of end stage renal failure)
- Decrease of cardiac destabilisation syndromes
- Decrease of all cause mortality (cardiac, cerebrovascular events)
Renal artery stenting: outcome reporting I

Definition of failure & benefit
(benefit = cure or improvement)

- **Anatomic success:** < 30% DS by QCA, MLD > 2mm
- **Hemodynamic success:**
  translesional P gradient < 20mmHg,
  PSV < 180cm/s, RAR (renal/aortic ratio) < 3
- **Clinical success:**
  - cardiovascular events (MI, stroke, UA, flash pulm. edema)
  - hypertension > 120 days post tx (cure: dP<90, sP<140 w/o drugs, improvement: on drugs, failure: no change)
  - renal function:
    absolute value of creatinine („binary outcome“) & slope of functional decline (5xCrea pre during 3 mos / 5x Crea post Tx for 3mos, starting 1 week post tx)

_AHA Guidelines for Reporting Renal Artery Revascularization, Circulation 2002; 106:1572_
Breakpoint analysis of GFR

Benefit = improvement or stabilization of slope alpha2 post intervention


Isch meet 08
Renal artery stenting: Outcome reporting II

- **Patency or restenosis (>50% DS):** primary or assisted primary patency, secondary patency (after reocclusion) (@ 3-6 mos..?)

- **Complications:** (within 30 days)
  - Major Clinical Adverse Events (MaCE), systemic and local: additional procedure, prolonged LOS, transfusion, surgical revision, death, MI, stroke, renal failure
  
  - Minor Clinical Adverse Events (MiCE): no prolonged LOS, hematoma, transient rise in Crea

_AHA Guidelines for Reporting Renal Artery Revascularization, Circulation 2002; 106:1572_
Is there any evidence that RAS works?

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Study</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plouin</td>
<td>1998</td>
<td>58</td>
<td>R med vs bal</td>
<td>BP ns</td>
</tr>
<tr>
<td>Webster</td>
<td>1998</td>
<td>55</td>
<td>R med vs bal</td>
<td>BP/RF ns</td>
</tr>
<tr>
<td>Jaarsveld</td>
<td>2000</td>
<td>106</td>
<td>R med vs bal</td>
<td>BP/RF ns</td>
</tr>
<tr>
<td>Nordmann</td>
<td>2003</td>
<td>219</td>
<td>med vs bal meta</td>
<td>BP red sign.</td>
</tr>
<tr>
<td>De Ven</td>
<td>1999</td>
<td>84</td>
<td>R stent vs bal</td>
<td>Patency x 4, no BP/renF</td>
</tr>
<tr>
<td>Soulez</td>
<td>2003</td>
<td>74</td>
<td>NR</td>
<td>BP red in 50%</td>
</tr>
<tr>
<td>Zeller</td>
<td>2003</td>
<td>215</td>
<td>NR</td>
<td>BP red in 76%, crea red in 52%</td>
</tr>
<tr>
<td>ASTRAL</td>
<td>2008</td>
<td>806</td>
<td>R med vs stent</td>
<td>BP/RF/events ns</td>
</tr>
<tr>
<td>CORAL</td>
<td>2008</td>
<td></td>
<td>R med vs stent+med</td>
<td>ongoing</td>
</tr>
</tbody>
</table>

BP = blood pressure, RF = renal function, red = reduction, ns = non significant, NR = non randomized
The ASTRAL study  
(Angioplasty and STenting for Renal Artery Lesions)

- Pts: n=806, with > 60% renal stenosis, average crea 2.0, 33% diabetes, 50% CAD  
- Randomization: stenting vs medical tx  
- Successful stenting in 88%  
- Complications in 3%  
- **RESULTS @ 1 year:**  
  no differences between tx:  
  - rise of crea in both groups by 0.2  
  - similar event rates, renal and cardio/cerebrovascular  
  - arterial pressure reduction similar in both groups

ACC i2 summit, Chicago, April 2008
Unexpected deterioration of renal function by RA stenting: 

**RESIST study**

N=100

Zur Anzeige wird der QuickTime™ Dekompressor „TIFF (Unkomprimiert)“ benötigt.
Complications

• Renal Complications (total 6-10%):
  - Deterioration of renal function (1-10%) (embolism, contrast induced nephropathy)
  - renal artery dissection (< 2-3%)
  - aortic dissection (< 1%)
  - renal artery perforation (< 1%)
  - dislocation/embolization of stent (< 1%)

• Access complications (3-4%):
  - bleeding, transfusion, surgical revision, false aneurysm (compression)
Renal stenting: Have expectations come true? current knowledge and guesses

• Anatomical success (stenosis reduction): almost always
• Improvement of BP? Probably in some patients, but durable?
• Improvement in renal function? Sometimes
• Slowing of renal functional loss? Probably sometimes
• Delay of end stage renal failure? Unknown
• Saving lives by preventing cardiovascular events? Unknown

Isch meet 2008
Selection of patients who have *may* benefit from RAS - clinical parameters

- **High prevalence in**: atherosclerotic vascular disease in multiple vascular territories > 60% DS (CAD, supraaortic, PAD), Heart F
- **Proven renal hypertension** (more likely: absence of fam hx, resistant Hytx, reduction of renal function post ACE, > 1.5cm diff in kidney size, younger age)
- **Bilateral stenoses** (significant)
- **Single kidney**
- **Resistant Hypertension**
- **Elevated Serum-Crea**
- **Pulm. flash edema**
- **Kidney length > 90 mm**

Przewlocki 2007, Bates 2008
Evidence for no/low predictability?

- Even after **most stringent** patient selection for „significant“ renal artery stenosis = \( DS > 70\% \), hypertension and/or Crea elevation:
  - Some improvement in hypertension in 50%-75% (8% cure, 42% improved)
  - No/some improvement in Crea clearance (0-52%)
  - No clinical parameters to reliably predict „successful“ outcome (-high Crea, low LV predict RF, -female, high BP, preserved parenchym predict BP)
  - No angiographic predictor
  - with current selection criteria (clinical, functional & anatomic criteria): clinical success in < 2/3 of pts


Isch meet 2008
Why is there no predictable cure of hypertension by stenting of significant Atheromatous Renal Artery Stenosis (ARAS)?

- Because ARAS is not the (target)disease to treat?
- Because ARAS is not so much the cause of hypertension but rather the consequence of the atheromatous process for which hypertension is the major contributor..
- ...And patients with ARAS tend to have generalized atherosclerotic disease in coronary, cerebral and peripheral circulation

Beevers, J Human Hypertension 2007

Isch meet 2008
But: BP improvement by Stenting despite RI > 0.8 = severe nephrosclerosis*

From Zeller Circ 2003

*improvement in renal function (Crea) with RI > 0.7
Is lack of predictability of therapeutic benefit the nail in the coffin of RA stenting?

- No, because measureable benefit in > 50% of selected pts may outweigh „useless“ procedures - yet: complications must be avoided/minimized (*is likely with experience / selection*)
- No, because there is evidence, that refined (functional) selection criteria or criteria that reflect function, improve likelihood of clinical benefit
- No, because restenosis / low patency rates may interfere with longer term improvement, thus concealing benefit ..
- Yes, if intense medical treatment is equally effective in avoiding renal failure, cardiovascular events and decreasing hypertension as a patent renal artery...

Isch meet 08
Can we better identify predictors for „benefit“ or predictors for „failure“?

• Definitely NOT, if we rely on angiography as gold (and only) standard for assessing hemodynamic significance of RAS
• May be some, if we use improved functional criteria....
• Therefore next step: improved selection process...?
Poor correlation between renal angiography and hemodynamic parameters

Relationship between angiographic stenosis and RFFR
Excellent correlation between renal FFR & baseline PG

Relationship between basal pressure gradient (BPG) and RFR

Correlation coefficient = 0.87

Subramanian, Catheter Cardiovasc Interv 2005
**Next step:**
Avoid Overestimation of stenosis significance by degree & function = avoid wrong Tx targets

<table>
<thead>
<tr>
<th>parameter</th>
<th>Current / revised value</th>
<th>Diagnostic accuracy</th>
<th>False positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAR</td>
<td>&gt; 3.5 / &gt; 3.80</td>
<td>79%</td>
<td>15%</td>
</tr>
<tr>
<td>EDV (cm/s)</td>
<td>&gt; 90 / &gt; 75</td>
<td>77%</td>
<td>11%</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>&lt; 2 / &lt; 1.75</td>
<td>77%</td>
<td>15%</td>
</tr>
<tr>
<td>DS (%)</td>
<td>&gt; 50 / &gt; 65%</td>
<td>60%</td>
<td>38%</td>
</tr>
<tr>
<td>PSV (cm/s)</td>
<td>&gt; 180 / &gt; 320</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>Pd/Pa</td>
<td>&lt; 90 accepted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RI bi/unilat</td>
<td>0.75(0.65)</td>
<td>Evaluation of 66% / 60%</td>
<td>stenosis &amp; tissue</td>
</tr>
<tr>
<td>Kidney Length</td>
<td>&gt; 90 mm</td>
<td>70%</td>
<td></td>
</tr>
</tbody>
</table>

**But:** Lack of Correlation Between Renal Translesional Pressure Gradients and Treatment Response After Renal Artery Stent Placement$^{40}$

<table>
<thead>
<tr>
<th></th>
<th>Peak, mm Hg</th>
<th>Mean, mm Hg</th>
<th>Hyperemic, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>28.6 ±26</td>
<td>10.6 ±13.8</td>
<td>15.5 ±17.9</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>30.7 ±26.9</td>
<td>9.5 ±8.1</td>
<td>18.9 ±10.9</td>
</tr>
<tr>
<td>$P$</td>
<td>0.88</td>
<td>0.85</td>
<td>0.64</td>
</tr>
</tbody>
</table>

White Circ 2006
We only need to reliably answer 2 questions...:

• 1.- Is degree of stenosis significant enough to trigger RENIN release and cause renal hypertension?

• 2.- Does cure of stenosis cure kidney... and decrease RENIN?
Is that possible by identifying predictors for „benefit“ or predictors for „failure“?

- Definitely NOT, if we rely on angiography as gold (and only) standard for assessing hemodynamic significance of RAS
- Yes, some, if we use improved functional criteria (in combination with few clinical criteria), but still not reliably
- Complications, albeit rare, can not predictably be avoided, therefore must also influence pt selection by risk/benefit assessment

- Prediction of failure is certainly not reliable enough to deny renal artery stenting to patients who may progress to loss of kidney and worse cardiovascular event prognosis
Incidence of RAS at cardiac catheterization

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Patients, n</th>
<th>Any RAS, %</th>
<th>RAS 50%, %</th>
<th>Bilateral, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqel et al\textsuperscript{14}</td>
<td>90</td>
<td>NR</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>Weber-Mzell et al\textsuperscript{15}</td>
<td>177</td>
<td>25</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Rihal et al\textsuperscript{16}</td>
<td>297</td>
<td>34</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Vetrovec et al\textsuperscript{17}</td>
<td>116</td>
<td>29</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>Harding et al\textsuperscript{18}</td>
<td>1302</td>
<td>30</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>Jean et al\textsuperscript{19}</td>
<td>196</td>
<td>33</td>
<td>18</td>
<td>NR</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>2178</td>
<td>30.2±3.6</td>
<td>19±6</td>
<td>17.4±14.2</td>
</tr>
</tbody>
</table>

RAS indicates renal artery stenosis; NR, not reported.

White, Circ 2006
# Causes of Increased Prevalence of Renal Artery Stenosis

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of hypertension $\leq 30$ years or $\geq 55$ years</td>
</tr>
<tr>
<td>Malignant, accelerated, or resistant hypertension</td>
</tr>
<tr>
<td>Unexplained renal dysfunction</td>
</tr>
<tr>
<td>Development of azotemia with an ACE inhibitor or ARB medication</td>
</tr>
<tr>
<td>Unexplained size discrepancy of $\geq 1.5$ cm between kidneys</td>
</tr>
<tr>
<td>Cardiac disturbance syndrome (flash pulmonary edema)</td>
</tr>
<tr>
<td>Peripheral arterial disease (abdominal aortic aneurysm or ABI $&lt;0.9$)</td>
</tr>
<tr>
<td>Multivessel ($\geq 2$) coronary artery disease</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; and ABI, ankle brachial index.

White, Circ 2006
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Patients, n</th>
<th>Death, %</th>
<th>Dialysis, %</th>
<th>Major Complications, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocha-Singh et al&lt;sup&gt;62&lt;/sup&gt;</td>
<td>180</td>
<td>0.6</td>
<td>0</td>
<td>2.6</td>
</tr>
<tr>
<td>Tuttle et al&lt;sup&gt;59&lt;/sup&gt;</td>
<td>148</td>
<td>0</td>
<td>0</td>
<td>4.1</td>
</tr>
<tr>
<td>White et al&lt;sup&gt;63&lt;/sup&gt;</td>
<td>133</td>
<td>0</td>
<td>0</td>
<td>0.75</td>
</tr>
<tr>
<td>Burket et al&lt;sup&gt;60&lt;/sup&gt;</td>
<td>171</td>
<td>0</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Dorros et al&lt;sup&gt;61&lt;/sup&gt;</td>
<td>163</td>
<td>0.6</td>
<td>0</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>795</strong></td>
<td><strong>&lt;1%</strong></td>
<td><strong>&lt;1%</strong></td>
<td><strong>2.0%</strong></td>
</tr>
</tbody>
</table>

Major complications include death, myocardial infarction, emergency surgery, need for dialysis, or blood transfusion.
RAS facts and uncertainty

• Facts:
  – High prevalence of renal artery stenosis in vascular patients
  – RAS marker of CV risk
  – Renovascular HTN present in 5%

• Questions:
  – Does PTRA or stenting improve BP?
  – Is renal function preserved after RA stenting?
  – Does RA stenting lower CV events?
ACC/AHA Guidelines 2006
INDICATIONS FOR RENAL REVASCULARIZATION

• Hypertension
  – Class IIa (Level of evidence: B)
• Preservation of Renal Function
  – Class IIa (Level of evidence: B) – RAS and CKD with b/l RAS or RAS to a solitary functioning kidney.
  – Class IIb (Level of evidence: C) – RAS and CRI and u/l RAS
• CHF and Unstable Angina
  – Class I (Level of evidence: B) – unexplained pulmonary edema
  – Class IIa (Level of evidence: B) – RAS and unstable angina

NO LEVEL 1/A DATA – multiple RCT’s or meta-analyses to support any renal intervention
Renal Trials to date

• Evaluating Stenting:
  – Van de Ven – RCT, restenosis: stenting 14%, PTRA 48%
  – ASPIRE 2 – salvage stenting better than OPC
  – GREAT Trial – Renal DES
  – RENAISSANCE Trial

• Evaluating BP response:
  – Webster – PTRA only beneficial for bilateral disease
  – EMMA – PTRA no better than medical therapy
  – DRASTIC – PTRA no better than medical therapy