When is Revascularization Considered in Renal Artery Stenosis?

William A. Gray MD
Director of Endovascular Services
Associate Professor of Clinical Medicine
Columbia University Medical Center
The Cardiovascular Research Foundation
Renovascular disease: incidence

- <1% in general, but more in selected populations:
  - Iliofemoral arterial disease: 30%-40%
  - Carotid disease: 20%-30%
  - Coronary artery disease: 20%-30%
  - Congestive heart failure: 30%
  - ESRD: 20%

- 80% atherosclerotic/20% fibromuscular dysplasia

- In general, the severity of associated atherosclerotic disease correlates with renal artery stenosis severity
Renovascular disease: pathophysiology

Hypertension

- Renal parenchymal hypoperfusion with activation of the renin-angiotensin-aldosterone system
  - Vasoconstriction
  - Aldosterone-mediated volume expansion
  - Endothelial dysfunction (chronic changes)
- Modulated by contralateral kidney naturesis and ipsilateral capsular collaterals

Renal insufficiency

- Ipsilateral chronic hypoperfusion and progressive “ischemic nephropathy”
- Contralateral hypertensive arteriolar nephrosclerosis
- Continuous cholesterol/atheromatous embolization?
Renal Artery Stenosis is a Progressive Problem

- Review of 5 angiographic trials
- Progression in 49%
- Progression to occlusion in 14%

RAS Progression

RAS progression according to time between studies (N = 1189)

Risk of atrophy in kidneys with atherosclerotic renal artery stenosis

- 122 patients with at least one renal artery stenosis/204 kidneys followed for a mean of 33 months

- Patients followed with Renal Artery Duplex Ultrasonography performed every six months
Risk of atrophy in kidneys with atherosclerotic renal artery stenosis

Renal Atrophy According to Baseline Renal Artery Disease

![Graph showing cumulative incidence of renal atrophy over time]

- Baseline Disease Class
  - >= 60% stenosis
  - < 60% stenosis
  - Normal

Cumulative incidence of renal atrophy, %

- $P = 0.009$ (log rank test)

Number of kidneys observed:

- Time, months:
  - 0, 6, 12, 18, 24

- Number of kidneys:
  - >= 60% stenosis: 99, 87, 59, 36, 36
  - < 60% stenosis: 62, 56, 43, 32, 22
  - Normal: 43, 42, 37, 31, 29

Kidney International 1998;53:735-42
Loss Of Renal Function

Disease progression is associated with a decline in renal function.


Serum Creatinine (µmol/L)

<table>
<thead>
<tr>
<th>Stenosis at Follow-up</th>
<th>Serum Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>97 ± 44</td>
</tr>
<tr>
<td>&gt; 75%</td>
<td>141 ± 114</td>
</tr>
</tbody>
</table>

\[ P = 0.01 \]
Renal artery stenosis is an independent predictor of mortality


<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS</td>
<td>2.9 (1.7 - 7.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVEF</td>
<td>1.7 (1.2 - 2.2)</td>
<td>0.0002</td>
</tr>
<tr>
<td>CRI</td>
<td>1.3 (1.1 - 1.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>CHF</td>
<td>2.4 (1.3 - 4.1)</td>
<td>0.0021</td>
</tr>
</tbody>
</table>
In unilateral disease, ACEI and ARB’s are safe and effective

Beta-blockers are also effective

Medications usually effective in controlling hypertension associated with RAS

However, renal size and GFR continue to decrease even with good hypertensive control

Compared with surgery, long-term mortality with medical therapy is worse
Renovascular disease: percutaneous Rx

Angioplasty

- Limited by suboptimal acute (<80%) and long-term success rates (restenosis 20%-25%)

  - ~100 patients randomized to either medical therapy or renal angioplasty
  - Results: ½ medical patients crossed-over to angioplasty, and an overall reduction in antihypertensive medication in angioplasty group was observed
  - Intention-to-treat analysis: no difference in Rx

Conclusions not supported by the data generated
Intervene in the Appropriate Scenario

- Dialysis-Dependent Renal Failure
- Chronic Renal Insufficiency
- Refractory/Resistant Hypertension
- Cardiac Disturbance Syndrome
- Need for Use of ACEI/ARB
- Unilateral Renal Artery Stenosis
Does renal stenting preserve renal function?

- Observational study of stenting in patients with:
  - Chronic renal insufficiency (Cr ≥ 1.5 ≤ 4.0 mg/dL)
  - Global renal ischemia (≥ 70% stenosis)
    - Bilateral RAS
    - Unilateral RAS with solitary kidney
- Renal function
  - regression lines of 1/SCreat over time

 Watson et al: Circulation 2000;102:1671
Renal stenting: effect on renal function

“improvement”

“stabilization”

“slowing of deterioration”

Linear regression plots of 1/Scr

Watson et al; Circulation 2000;102:1671
Renal stenting: effect on renal function

Delta slope of 1/Screat before and after renal artery stent deployment (N=25)

Watson et al; Circulation 2000;102:1671
### Table 1. Characteristics of Included Studies Comparing the Effects of Medical Therapy with Balloon Angioplasty for the Treatment of Hypertension with Renal Artery Stenosis

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Number of Patients</th>
<th>Bilateral Stenosis Number (%)</th>
<th>Follow-up (months)</th>
<th>Run-In Period</th>
<th>Primary Outcome</th>
<th>Crossover from Medical Therapy to Angioplasty Number (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRASTIC (12)</td>
<td>56</td>
<td>50</td>
<td>24 (23)</td>
<td>12</td>
<td>Office blood pressure</td>
<td>22 (44)</td>
<td>3-month analysis before, 12-month analysis after crossover</td>
</tr>
<tr>
<td>EMMA (14)</td>
<td>23</td>
<td>26</td>
<td>0</td>
<td>6</td>
<td>24-hour ambulatory blood pressure</td>
<td>7 (27)</td>
<td>Endpoints documented before crossover in medical therapy group</td>
</tr>
<tr>
<td>SNRASCG (13)</td>
<td>25</td>
<td>30</td>
<td>28 (51)</td>
<td>6</td>
<td>Office blood pressure</td>
<td>0</td>
<td>Results of patients with unilateral and bilateral renal artery stenosis were reported separately</td>
</tr>
</tbody>
</table>

DRASTIC = Dutch Renal Artery Stenosis Intervention Cooperative trial; EMMA = Esaï Multicentrique Medicaments vs Angioplastie trial; SNRASCG = Scottish and Newcastle Renal Artery Stenosis Collaborative Group trial.
Meta-Analysis: PTRA vs Medicine in Hypertension and RAS

Mean Difference (95% Confidence Interval), in mm Hg

Systolic Blood Pressure
DRASTIC (12)
EMMA (14)
SNRASCG (13)

Diastolic Blood Pressure
DRASTIC
EMMA
SNRASCG

Weighted Mean Difference

Favors Balloon Angioplasty

Favors Medical Therapy

Am J Med 2003;114:44-50
Data-supported facts about renal therapy

- Is superior to balloon-angioplasty
- Is safer than surgery
- Can achieve clinical goals in *certain* individual patients
  - Improve control of HTN
  - Preserve renal function
  - Control of cardiac disturbance syndromes (CHF/Angina)
Predictors of effectiveness of renal stenting for hypertension

- MAP > 110 and/or the presence of bilateral renal artery stenosis (1)
- Low renal vascular resistance (2)

Renal artery stenting vs. angioplasty

Study has shown stenting (n=40) superior to angioplasty (n=15) due to late deterioration of the angioplasty results, especially in patients with baseline azotemia.

Age and its relationship to renal artery stenting

Compared to patients <75 (n=80), patients >75 years (n=19) still have a significant antihypertensive effect after stenting, and no significant difference in renal deterioration or progression to dialysis.

Patients with solitary kidney and renal stenting

- A recent small (n=26) study in this patient subset demonstrated improvement in renal function, as assessed by stabilized creatinine levels in 62% of patients stented, but continued renal deterioration in 38% of those treated.
- Best predictor of improvement was baseline creatinine levels—conclusion: intervene early in these patients.

Renal artery stenting and embolic protection

- A small study using Percusurge as the embolic protection device in 32 procedures demonstrated feasibility and safety. Total occlusion time averaged 6.55 minutes.
- At ~6 month follow-up no deterioration in renal function was noted, and improvement in hypertension was noted.
- “Debris was returned in all cases”

Renovascular disease: percutaneous Rx

Large series

- 363 renal stenting procedures analyzed
- 100% procedural success, no deaths or surgery
- Median 16 month follow-up:
  - 70% had reductions in BP regardless of baseline renal function
    - SBP decreased 164 mmHg to 142 mmHg p<0.001
  - In patients with baseline renal insufficiency, 73% improved or stabilized and 27% continued deterioration
    - Post-procedural azotemia 12%, persistent in only 2%
- 10% mortality, predicted by CAD and azotemia
- Restenosis low and predicted by vessel size <4.5mm

Renal artery stenting: Conclusions

- Good acute and long-term success rates
- Complication rates improved and low
  - Hemorrhage, embolism, renal failure
  - Mortality <1%
- Efficacy
  - Improved hypertension in 2/3 (cure 10%)
  - Stabilized or improved renal function in 2/3
  - Improved CHF and coronary ischemia control
UK MULTI-CENTRE TRIAL IN
ATHEROSCLEROTIC RENOVASCULAR DISEASE

ASTRAL
Angioplasty and STent for Renal Artery Lesions
ASTRAL Trial Schema

Diagnosis of ARVD
(Unilateral or Bilateral)
Revascularisation not contraindicated

Uncertain whether to revascularise
Randomisation

Revascularisation
with angioplasty and/or stent
(and medical treatment)

No revascularisation
Medical Treatment only
ASTRAL Trial

- No baseline differences between groups in:
  - Blood pressure
  - Renal function
  - Angiography
  - Medical treatment
Procedural safety

- 24 patients experienced an immediate post-op complication
  - Revascularisation = 23 / 308 (7%)
  - Medical = 1 / 18 (6%)
Mean change in SCr
Mean change in systolic BP

Months from Randomisation

Revascularisation
Medical Management

Mean Change in Systolic BP

Revascularisation: 384 330 315 274 216 137 83
Medical: 388 341 327 290 211 127 81

Treatment Difference

COLUMBIA UNIVERSITY MEDICAL CENTER
Time to first MI, stroke, vascular death or hospitalization for angina, fluid overload or heart failure

HR = 0.90, 95% CI = 0.66 to 1.15

At risk:
- Revasc: 403
- Medical: 403

Years from Randomisation

<table>
<thead>
<tr>
<th>Years</th>
<th>Revasc</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>403</td>
<td>403</td>
</tr>
<tr>
<td>1</td>
<td>246</td>
<td>251</td>
</tr>
<tr>
<td>2</td>
<td>159</td>
<td>158</td>
</tr>
<tr>
<td>3</td>
<td>104</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>50</td>
</tr>
</tbody>
</table>

HR = 0.90, 95% CI = 0.66 to 1.15
Mortality

HR = 0.92, 95% CI = 0.68 to 1.26

Revasc
Revasc
Medical
Medical

No. Patients
403
403

No. Obs.
79
81

No. Events
82.2
77.8

Exp.

0
1
2
3
4

Years from Randomisation

% Event Free

2P = 0.6

At risk:

Revasc
403
286
195
127
72

Medical
403
284
194
123
67
Summary

- Currently no evidence of a benefit for revascularisation on renal function in the ARVD patients entered into ASTRAL: those in whom clinicians ‘uncertain’ of whether to revascularize

- Also no evidence of differences between the arms for any of the secondary endpoints (i.e. blood pressure, major events)

- No evidence of differences in treatment effect across the various subgroups

- Longer follow-up is needed

- Plan to update meta-analysis published in NDT in 2003 to include ASTRAL and other trials
Critique

- The indications for the patients entered into this study are unclear:
  - ? Hypertension
    - If so, was it resistant?
  - Renal insufficiency
  - The presence of a renal stenosis without clinical indication?
- Severity of stenosis
  - Method of measurement?
  - Physiologic testing?
- Complication rate excessive
Renovascular disease: therapeutic paradigm

- Evaluate probability of RAS based on risk factors

- Recommend therapy based on:
  - Age
  - Adequacy of blood pressure control
  - Renal function/size
  - Bilateral disease or solitary kidney
  - Associated conditions (CHF, CAD)
  - Atherosclerotic vs. fibromuscular origin
  - Decreasing procedural morbidity
  - ?drug-eluting stents change paradigm?
Atherosclerotic Renal Artery Stenosis

- **Incidence**
  - General Population: 0.1%
  - Hypertension: 4.0%

- **Prevalence in an autopsy series**
  - 27%
  - In patients > 70 years, 62
Atherosclerotic Renal Artery Stenosis

Incidence of RAS in Patients with Peripheral Vascular Disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>% (Total No. of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dustan (1964)</td>
<td>37 (149)</td>
</tr>
<tr>
<td>Olin (1990)</td>
<td>39 (189)</td>
</tr>
<tr>
<td>Wilms (1990)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>Choudri (1990)</td>
<td>59 (100)</td>
</tr>
<tr>
<td>Swartbol (1992)</td>
<td>49 (100)</td>
</tr>
<tr>
<td>Missouris (1994)</td>
<td>45 (127)</td>
</tr>
</tbody>
</table>

Scoble JE. In Renal Vascular Disease 1996:143-9
## Prevalence of bilateral renal artery stenosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Stenotic Arteries, N</th>
<th>Bilateral, N (%)</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holley, 1964</td>
<td>159</td>
<td>105 (66)</td>
<td>Autopsy</td>
</tr>
<tr>
<td>Wollenweiber, 1968</td>
<td>109</td>
<td>67 (61)</td>
<td>Angio</td>
</tr>
<tr>
<td>Dean, 1981</td>
<td>41</td>
<td>14 (34)</td>
<td>Angio</td>
</tr>
<tr>
<td>Tollefson, 1991</td>
<td>48</td>
<td>14 (29)</td>
<td>Angio</td>
</tr>
<tr>
<td>Harding, 1992</td>
<td>192</td>
<td>52 (27)</td>
<td>Angio</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>549</strong></td>
<td><strong>252 (46)</strong></td>
<td></td>
</tr>
</tbody>
</table>
Renal artery stenosis: coronary artery disease and mortality

- 3987 patients underwent coronary arteriography followed by abdominal aortography
- Significant RAS defined as >75%
- Patients followed for 4 years prospectively
- 4.8% of patients with RAS
  - 0.8% with bilateral RAS

Renal Artery Stenosis, Coronary Artery Disease, and Mortality

Four Year Survival

RAS | No RAS
--- | ---

Percent

p<0.001

Renal Artery Stenosis, Coronary Artery Disease, and Mortality

Four Year Survival

What Does The Future Hold?

- Trial to (finally) demonstrate impact of renal artery intervention on survival, major cardiovascular events, hypertension, and (potentially) renal function
- Role of Embolic Protection Devices in renal artery intervention
- Benefit of Drug-Eluting Stents in renal artery intervention
The CORAL Trial
Cardiovascular Outcomes of Renal Artery Lesions
Prospective, Randomized Trial of Patients with RAS and HTN: Stent and Med Rx vs Med Rx Alone

Primary Endpoint Events

- Cardiovascular death
  - Any within 30 days of randomization
  - CV death ≥ 31 days
- Myocardial infarction
- Hospitalization for congestive heart failure
  - ≥ 30 days post randomization
- Stroke

- Uncontrollable hypertension
  - > 200 systolic and or >120 diastolic mm Hg
  - all tolerable medications
- Progressive renal insufficiency
  - decrease in iohexol-determined GFR of ≥ 33%
  - Persists 14 days
- Need for renal replacement therapy
  - ≥ 31 days post randomization
Renal artery stenting: therapeutic targets

- Effective therapy for stenting in the appropriate clinical scenario
  - Truly refractory/resistant HTN with RAS
  - Renal insufficiency with ischemia to functioning renal mass
  - Cardiac disturbance syndromes with ischemia to functioning renal mass
# Renal Artery Stenosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>0.1%</td>
</tr>
<tr>
<td>Hypertensive population</td>
<td>4.0%</td>
</tr>
<tr>
<td>HTN &amp; suspected CAD</td>
<td>10 - 20%</td>
</tr>
<tr>
<td>Malignant HTN</td>
<td>20 - 30%</td>
</tr>
<tr>
<td>Malignant HTN &amp; renal insufficiency</td>
<td>30 - 40%</td>
</tr>
<tr>
<td>HTN and PAD</td>
<td>44%</td>
</tr>
</tbody>
</table>
Incidence of Unsuspected RAS

- 196 consecutive patients referred for coronary angiography for suspected CAD underwent (drive-by) renal angiography.


- 22% (1 in 5) of the patients with CAD had significant (> 50%) renal artery stenosis.
The Consequences: Renovascular Hypertension

- Cardiovascular
- Renal
Natural History of Renal Artery Disease

- Trend in untreated or medically treated renal artery stenoses for progression of stenosis (to occlusion) and loss of renal function.
Natural history of renal artery stenosis

- 84 pts & 139 renal arteries not treated with revascularization followed for 13 months
- Progression at two years in 42%
- Progression to occlusion in 11%

Criteria For Renal Stenting

- Which lesions, if any, should be treated?
  - Solitary $\geq 70\%$ stenosis.
  - Bilateral $\geq 70\%$ stenoses.
  - Unilateral $\geq 70\%$ stenosis.
Can stenting renal artery stenosis improve or stabilize renal function?

- Renal stent deployment in patients with:
  - Chronic renal insufficiency (Cr $\geq$ 1.5 mg/dL).
  - Global renal ischemia ($\geq$ 70% stenosis).
    - Bilateral RAS.
    - Unilateral RAS with solitary kidney.
- Renal function assessed with slopes or regression lines for the reciprocal of serum creatinine over time.

## Stent Complications

<table>
<thead>
<tr>
<th>Renal Stents</th>
<th>Number</th>
<th>Death</th>
<th>Dialysis</th>
<th>Major Comp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blum</td>
<td>74</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Harjai</td>
<td>88</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tuttle</td>
<td>148</td>
<td>0</td>
<td>0</td>
<td>4.10</td>
</tr>
<tr>
<td>Rocha-Singh</td>
<td>180</td>
<td>0.6</td>
<td>0</td>
<td>2.60</td>
</tr>
<tr>
<td>Burket</td>
<td>171</td>
<td>0</td>
<td>0.7</td>
<td>0.70</td>
</tr>
<tr>
<td>White</td>
<td>133</td>
<td>0</td>
<td>0</td>
<td>0.75</td>
</tr>
<tr>
<td>Dorros</td>
<td>163</td>
<td>0.6</td>
<td>0</td>
<td>1.80</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>957</strong></td>
<td><strong>&lt; 1%</strong></td>
<td><strong>&lt; 1%</strong></td>
<td><strong>1.4%</strong></td>
</tr>
</tbody>
</table>
Renal Artery Duplex Ultrasonography

Courtesy of M.Jaff
Renal MRA-high quality
Renal Artery Stenosis and Intervention

Shifting Trends

- Increasing prevalence
- Heightened awareness
- Increasing detection
  MRA, Duplex, CTA
- Explosive growth in procedure volume
## Renal Stenting Trends

**Charges submitted to Medicare**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PTA only</td>
<td>3780</td>
<td>3840</td>
<td>4380</td>
</tr>
<tr>
<td>Stent only</td>
<td>1220</td>
<td>2400</td>
<td>5740</td>
</tr>
<tr>
<td>Both</td>
<td>2660</td>
<td>5160</td>
<td>8400</td>
</tr>
<tr>
<td>Renal Bypass</td>
<td>4040</td>
<td></td>
<td>2260</td>
</tr>
</tbody>
</table>

**Changes over 5 years:**

- Renal Intervention: +242%
- Renal Stenting: +364%
- Renal Bypass Surg: -45%

*Extrapolated from 5% file data*

**IS THIS CHANGE JUSTIFIED???
Renal Artery Stenosis

Truth and Consequences

- Progressive disease
- Tremendous cost to society of ESRD
  - US hemodialysis program - >$25 billion/year by 2010
- Lost wages
- Effect on quality of life
Screening and Management of RAS

Confounding Issues

• Absence of disease-specific symptoms
  – progression is silent
• Pathophysiologic effect on kidney poorly understood
• Cause & effect relationship between lesion and clinical syndromes (e.g. HTN, CHF, azotemia) is unclear
  – Difficult to predict which patients will derive benefit, or to what degree
• Literature reflects variable results from RAR
• Conflicting opinions about who should be screened/treated
Renal Artery Stenosis
What we don’t know…

Whether individual patients will benefit
What are the predictors of response to revascularization
Pathophysiology to explain decline in renal function
Mechanism and relative contribution of RAS to deterioration in renal function

Knowledge base in RAS lags far behind that for CAD

What have we learned from trials and experience?
Renal anioplasty (with bail-out stent) vs. primary stenting

<table>
<thead>
<tr>
<th></th>
<th>POBA (n=42)</th>
<th>STENT (n=43)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1° success (&lt;50% residual)</strong></td>
<td>24 (57%)</td>
<td>37 (88%)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td><strong>6 mo patency</strong></td>
<td>12 (29%)</td>
<td>30 (75%)</td>
<td></td>
</tr>
<tr>
<td><strong>Restenosis</strong></td>
<td>48%</td>
<td>14%</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td><strong>Crossover</strong></td>
<td>12 (29%)</td>
<td>(5 acute)</td>
<td></td>
</tr>
</tbody>
</table>

van de Ven et al, Lancet 1999 Jan 23;353:282-6
## Renal Stenting: Technical Success

<table>
<thead>
<tr>
<th>Study series</th>
<th>Year of publication</th>
<th>Study period</th>
<th>No. of Arteries</th>
<th>Stent type</th>
<th>Ostial lesion (%)</th>
<th>Success definition</th>
<th>Technical success (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>van de Ven [9]</td>
<td>1999</td>
<td>93 - 97</td>
<td>52</td>
<td>Palmaz</td>
<td>100</td>
<td>RS* &lt; 50%</td>
<td>90</td>
</tr>
<tr>
<td>Henry [21]</td>
<td>1999</td>
<td>NA</td>
<td>104</td>
<td>AVE</td>
<td>77</td>
<td>RS &lt; 20%</td>
<td>99</td>
</tr>
<tr>
<td>Rocha-Singh [12]</td>
<td>1999</td>
<td>93 - 95</td>
<td>180</td>
<td>Palmaz</td>
<td>43</td>
<td>#PG &lt; 5mmHg</td>
<td>98</td>
</tr>
<tr>
<td>Tuttle [22]</td>
<td>1998</td>
<td>91 - 96</td>
<td>148</td>
<td>Palmaz</td>
<td>100</td>
<td>RS &lt; 30%</td>
<td>98</td>
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<tr>
<td>Dorros [23]</td>
<td>1998</td>
<td>90 - 95</td>
<td>202</td>
<td>Palmaz</td>
<td>NA</td>
<td>RS &lt; 50%</td>
<td>99</td>
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<tr>
<td>Harden [17]</td>
<td>1997</td>
<td>92 - 95</td>
<td>32</td>
<td>Palmaz</td>
<td>75</td>
<td>RS &lt; 10%</td>
<td>100</td>
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<tr>
<td>Blum [8]</td>
<td>1997</td>
<td>89 - 96</td>
<td>74</td>
<td>Palmaz</td>
<td>100</td>
<td>RS &lt; 50%</td>
<td>100</td>
</tr>
<tr>
<td>Henry [26]</td>
<td>1996</td>
<td>90 - 94</td>
<td>64</td>
<td>Palmaz</td>
<td>53</td>
<td>RS &lt; 20%</td>
<td>100</td>
</tr>
<tr>
<td>Iannone [27]</td>
<td>1996</td>
<td>92 - 93</td>
<td>83</td>
<td>Palmaz</td>
<td>78</td>
<td>RS &lt; 30%</td>
<td>99</td>
</tr>
<tr>
<td>Hennequin [28]</td>
<td>1994</td>
<td>87 - 91</td>
<td>21</td>
<td>Wallstent</td>
<td>33</td>
<td>NA</td>
<td>100</td>
</tr>
<tr>
<td>Rees [29]</td>
<td>1994</td>
<td>88 - 92</td>
<td>296</td>
<td>Palmaz</td>
<td>100</td>
<td>RS &lt; 30%</td>
<td>98</td>
</tr>
</tbody>
</table>

* RS=residual stenosis  
# PG=pressure gradient

~98%
### Table 2. Restenosis Rate of Renal Stents

<table>
<thead>
<tr>
<th>Study series</th>
<th>No. of Arteries</th>
<th>Arteries evaluated (% original total arteries)</th>
<th>Ostial lesion (%)</th>
<th>Stent type</th>
<th>Method of evaluation</th>
<th>Average time to evaluation (month)</th>
<th>Restenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>van de Ven, 1999</td>
<td>52</td>
<td>50 (95%)</td>
<td>100</td>
<td>Palmaz</td>
<td>angio*</td>
<td>6</td>
<td>21%</td>
</tr>
<tr>
<td>Rocha-Singh, 1999</td>
<td>180</td>
<td>158 (88%)</td>
<td>43</td>
<td>Palmaz</td>
<td>duplex + angio</td>
<td>13</td>
<td>12%</td>
</tr>
<tr>
<td>Tuttle, 1998</td>
<td>148</td>
<td>49 (33%)</td>
<td>100</td>
<td>Palmaz</td>
<td>angio</td>
<td>8</td>
<td>14%</td>
</tr>
<tr>
<td>Rundback, 1998</td>
<td>54</td>
<td>28 (52%)</td>
<td>NA</td>
<td>Palmaz</td>
<td>angio* + spiral CT</td>
<td>12</td>
<td>26%</td>
</tr>
<tr>
<td>White, 1997</td>
<td>133</td>
<td>80 (60%)</td>
<td>81</td>
<td>Palmaz</td>
<td>angio*</td>
<td>9</td>
<td>19%</td>
</tr>
<tr>
<td>Harden, 1997</td>
<td>32</td>
<td>24 (75%)</td>
<td>75</td>
<td>Palmaz</td>
<td>angio*</td>
<td>6</td>
<td>12%</td>
</tr>
<tr>
<td>Blum, 1997</td>
<td>74</td>
<td>74 (100%)</td>
<td>100</td>
<td>Palmaz</td>
<td>angio*</td>
<td>24</td>
<td>11%</td>
</tr>
<tr>
<td>Henry, 1996</td>
<td>64</td>
<td>54 (84%)</td>
<td>53</td>
<td>Palmaz</td>
<td>angio*</td>
<td>14</td>
<td>9%</td>
</tr>
<tr>
<td>Iannone, 1996</td>
<td>83</td>
<td>69 (85%)</td>
<td>78</td>
<td>Palmaz</td>
<td>duplex</td>
<td>11</td>
<td>14%</td>
</tr>
<tr>
<td>Dorros, 1995 [30]</td>
<td>92</td>
<td>56 (61%)</td>
<td>100</td>
<td>Palmaz</td>
<td>angio*</td>
<td>7</td>
<td>25%</td>
</tr>
<tr>
<td>Hennequin, 1994</td>
<td>21</td>
<td>20 (95%)</td>
<td>33</td>
<td>Wallstent</td>
<td>angio*</td>
<td>29</td>
<td>20%</td>
</tr>
<tr>
<td>Rees, 1994</td>
<td>296</td>
<td>150 (51%)</td>
<td>100</td>
<td>Palmaz</td>
<td>angio*</td>
<td>7</td>
<td>33%</td>
</tr>
</tbody>
</table>

**weighted average** 10  

**~20%**
Renal artery stenosis in 2008

Possible targets of stenting

- HTN
- Renal Preservation
- Cardiac Disturbance Syndromes
- Mortality (?)
Treatment Effect: Hypertension

- 72 y.o. male h/o of Inf MI, now unstable angina
- Cath: critical 3V CAD with LVEF 40%
- Cr 1.1
- BP 170-230/80-90 on 5 anti-hypertensive meds
Treatment Effect: Hypertension

- Post-stent
- Uneventful CABG
- Asymptomatic at 3 year f/up; Cr 1.0
- SBP 140-160 on 3 Anti-HTN meds
## Stent Effect on Hypertension: ASPIRE 2 Trial

<table>
<thead>
<tr>
<th>Visit</th>
<th>N</th>
<th>Systolic Pressure 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>
Progression to occlusion increases with severity of stenosis

Initial Angiogram

Percent

<50% 5.1
50–75% 10
75–99% 39

Implications of renal stenosis

Progressive loss of renal mass

- Duplex q6 months on 122 pts, 204 kidneys
- Renal atrophy (loss of 1cm length)
- mean f/up 33 months

<table>
<thead>
<tr>
<th>Duplex finding</th>
<th>Renal Atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>5.5%</td>
</tr>
<tr>
<td>&lt;60%</td>
<td>11.7%</td>
</tr>
<tr>
<td>&gt;60%</td>
<td>20.8%</td>
</tr>
</tbody>
</table>

- Other factors correlated with renal atrophy:
  - elevated Creatinine
  - SBP>180
  - PSV>400cm/sec, EDV<5cm/sec

Renal artery stenosis

Progression and timing of intervention

- Progression is unpredictable in the individual patient
  - Occurs in significant percentage of patients, who stand to suffer consequences

- Waiting until progression is measurable by atrophy or notable decline in renal function may be too late for RAR to have desired impact
• 72 year old male
• Acute anuric renal failure immediately post CABG
• Failure to thrive
• Immediate urine production
• Creatinine down to 3.5
• 7 year follow-up: creatinine=4.2
Effect On Renal Function: ASPIRE 2 Trial

<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>207</td>
<td>1.36±0.52</td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>187</td>
<td>1.35±0.62</td>
<td>0.74</td>
</tr>
<tr>
<td>6 month</td>
<td>174</td>
<td>1.41±0.61</td>
<td>0.03</td>
</tr>
<tr>
<td>9 month</td>
<td>173</td>
<td>1.40±0.61</td>
<td>0.31</td>
</tr>
<tr>
<td>24 month</td>
<td>153</td>
<td>1.46±0.81</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Uncertainties in renal disease therapy

- How to predict the effect of RAR on control of HTN, renal function, and mortality in a given patient with RAS?

- What represents a “significant” percent stenosis or gradient?

- How does acute and long-term success vary based on factors like vessel diameter, resistive index in distal vascular bed, DM?

- What is the true rate of complications from PTRA and stenting, and what is the causality (atheroemboli, contrast, other)?

- Will distal embolic protection improve outcomes?
Renal Stenting

Gaps in our knowledge base

Is this significant?

Gradient 20
peak/11mean
(5 french catheter)
Renal Artery Stenting vs Medical Therapy

# Randomized Trials:

Columbia University Medical Center
The Cardiovascular Research Foundation
PTRA vs. Medical Rx for HTN

van Jaarsveld et. al, NEJM, April 2000, 342:1007

- 106 patients, randomized to PTRA vs. meds
- % diam stenosis >50
- Creatinine <2.4
- Outcomes: BP, meds, renal function, patency at 3 and 12 months
## PTRA vs. Medical Rx for HTN

**van Jaarsveld et al, NEJM, 4/2000, 342:1007**

106 patients, randomized to PTRA vs. meds

<table>
<thead>
<tr>
<th></th>
<th>PTRA</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>179 ---</td>
<td>169</td>
</tr>
<tr>
<td></td>
<td>180 ---</td>
<td>176</td>
</tr>
<tr>
<td>Mean</td>
<td>104</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>103</td>
<td>101</td>
</tr>
<tr>
<td>Meds</td>
<td>2.5</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>(p&lt;.001)</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

**Conclusion:** “For treatment of HTN and RAS, angioplasty has little advantage over drug therapy.”
PTRA vs. Medical Rx for HTN

van Jaarsveld et. al, NEJM, April 2000, 342:1007

**PTRA group**
- only 2/56 received stent (54/56 had POBA)

**Medical group**
- 22/50 (44%) crossed to PTRA
- 8/50 (16%) developed renal artery occlusion
- 6/50 (12%) had >50% increase in creat (vs. 4% in PTRA group)
van Jaarsveld et al, NEJM, April 2000, 342:1007

ISSUES

- grossly underpowered
- average 2 interventions/site
- Optimal revasc. strategy (ie. stenting) not employed
- Many occlusions and crossovers in medical group
EDITORIAL COMMENT

“Renal Artery Stenosis: ‘Fortuitous Diagnosis’, Problematic Therapy”
-Weinrauch and D’Elia

“…studies (to date do) not address the consequences of RAS in a population.”
Renal Artery Stenting
Need for Large-scale Randomized Trial

Weinrauch and D’Elia

“Experience has demonstrated that less than half of patients undergoing (renal revascularization) benefit with respect to HTN control or rescue of an ischemic organ”

“Review of the literature found a high incidence of CV death with no evidence for prolongation of life after RAR”
Renal Artery Stenting

Need for Large-scale Randomized Trial

Weinrauch and D’Elia

“The only benefit that should be accepted as a reason for revascularization…is one that can be measured.”

“In the absence of randomized controlled studies, clinicians would do well to…pursue long-term follow-up of this cohort to determine the significance of RAS with respect to specific heart and kidney disease outcomes…”
Renal Artery Stenosis
Defining the Future

- Trial to demonstrate impact of renal artery intervention on survival, major cardiovascular events, hypertension, and renal function
- Improve case selection - multivariate models to establish predictors of success or failure
- Role of Embolic Protection Devices
- Anti-restenosis therapies
  - DES
• **Hypothesis**: Medical therapy with stenting of hemodynamically significant, angiographically documented, renal artery stenoses in subjects with systolic hypertension reduces the incidence of adverse cardiovascular and renal events compared with medical therapy alone.
Population:
- 1080 patients with atherosclerotic RAS
- Up to 85 US sites

Inclusion Criteria
- Systolic hypertension
  - ≥155 mm Hg
  - on ≥2 antihypertensive medication
- ≥1 renal artery stenosis
  - ≥60% with a 20 mm Hg systolic pressure gradient
  - ≥80% no pressure gradient required.
• **Optimal Medical Therapy (OMT)**
  - All receive ARB (Candesartan)
  - LDL, BP and HbA1c to guideline

• **OMT plus Stent Revascularization**
  - Angioguard embolic protection
  - Genesis balloon expandable stent
Survival free from Cardiovascular and Renal Adverse Events

- Cardiovascular or Renal Death
- Stroke
- Myocardial Infarction
- Hospitalization from CHF
- Progressive Renal Insufficiency
- Renal Replacement Therapy
## RAR- Effect on Renal Function

<table>
<thead>
<tr>
<th>Study series</th>
<th>No. of patients</th>
<th>Improved (%)</th>
<th>Stable (%)</th>
<th>Deteriorated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>van de Ven, 1999</td>
<td>42</td>
<td>12%</td>
<td>62%</td>
<td>26%</td>
</tr>
<tr>
<td>Rocha-Singh, 1999</td>
<td>150</td>
<td>22%</td>
<td>70%</td>
<td>8%</td>
</tr>
<tr>
<td>Tuttle, 1998</td>
<td>129</td>
<td>15%</td>
<td>81%</td>
<td>4%</td>
</tr>
<tr>
<td>Dorros, 1998</td>
<td>163</td>
<td>18%</td>
<td>48%</td>
<td>34%</td>
</tr>
<tr>
<td>Rundback, 1998</td>
<td>45</td>
<td>20%</td>
<td>47%</td>
<td>33%</td>
</tr>
<tr>
<td>Harden, 1997</td>
<td>32</td>
<td>34%</td>
<td>38%</td>
<td>28%</td>
</tr>
<tr>
<td><strong>Weighted Average</strong></td>
<td><strong>19%</strong></td>
<td><strong>62%</strong></td>
<td><strong>19%</strong></td>
<td></td>
</tr>
</tbody>
</table>