Renovascular Hypertension and Ischemic Nephropathy: 2018

2nd International Renal Conference
Brugge, Belgium
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Mayo Clinic
Rochester, MN
Disclosures

Site PI: CORAL Trial
NHLBI / NIDDK
Mayo Center for Regenerative Medicine
DSMB: Sentien Biopharmaceuticals

Section Editor: UpToDate
TCT Appropriate Use: Renal Artery Stent

• Renal Revascularization: MAJOR Pendulum Swings

Editorial Comment

Open Renal Arteries Are Better Than Closed Renal Arteries

Christopher J. White, MD
Department of Cardiology,
Ochsner Clinic,
New Orleans, Louisiana

Stents Do Not Improve RAS Outcomes

Optimal medical therapy prevented adverse events just as well in patients with CKD or hypertension

BY ARRIE KANAN
EAST LANSING—Renal artery stenting provided no additional benefit beyond optimal medical therapy for preventing adverse renal and cardiovascular events in patients with renal artery stenosis and end-stage kidney disease, compared with optimal medical therapy alone, according to the Cardiovascular Outcomes in Renal Arteries (CORAL) trial, presented by Christopher J. Cooper, MD, at the American Heart Association Scientific Sessions 2014 and published online ahead of print in the New England Journal of Medicine. In a commentary accompanying the study, both authors and other researchers advocate for the restriction of renal artery stenting to high-risk patients.

"Our data indicate that renal artery stenting should not be used for the treatment of renovascular disease in the absence of high-risk features," Dr. Cooper said. "We hope this CORAL study will diminish the enthusiasm that I feel many interventionalists have" for stenting, he added, based on data from the REST and other recent clinical trials of renal artery stenting in patients with end-stage kidney disease.
Renovascular Disease: 2018

• The State of the Vessel

• The Condition of the Kidney
Issues in Renovascular Disease

Prototype of Secondary Hypertension
- Potentially treatable with revascularization

- USA: Estimated 60 million hypertensives
  1-3% with RVH: >600,000

Approximately: 85% Atherosclerotic disease
14% Fibromuscular disease
1% Other

Progressive Disorder: ?increasing prevalence?
“The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review”
de Mast Q, Beutler JJ: J. Hypertens. 27:1333, 2009

N=40 Studies: 15,879 patients

“50% luminal” narrowing: Pooled Prevalence rates

- “Suspected Renovascular HTN” 14.1%
- Coronary Angiography: 10.5%
  With HTN: 17.8%
- Peripheral vascular disease: 25.3%
- AAA: 33.1%
- ESRD: 40.8%
- Congestive Heart Failure: 54.1%
Spectrum of Renovascular Disease Manifestations: 2018

- Asymptomatic “Incidental RAS”
- Renovascular Hypertension
- Accelerated CV Disease
  - Congestive Heart failure
  - Stroke
- Ischemic Nephropathy

Textor
Human Renovascular Disease 2018

- Renovascular Hypertension:
  - Renin release
  - can be managed medically

- "Adaptation" to reduced blood flow
  - without tissue hypoxia
  - minimal structural damage

- Advancing disease: adequate blood flow for tissue oxygenation?

- Progressive injury - recoverable?
66 y.o. woman
Progressive HTN
Creatinine 1.1 mg/dL
GFR: 47 ml/min

US velocity: 355 cm/s

RBF: Right: 142 ml/min GFR: 16 ml/min
Left: 273 ml/min: GFR: 31 ml/min

Medications: Lisinopril 40 mg
Amlodipine 5 mg
indapamide 1.25 mg

BP: 136 / 82 mm Hg
Creatinine 1.2 mg/dL
Management of Renovascular Hypertension and Ischemic Nephropathy

Hypertension + Reduced GFR

Initiate Therapy: Antihypertensive Medications
Lifestyle, Risk Factor and Dyslipidemia Management

Suspicion of Renovascular Disease
?Age, Associated Vascular Disease
?Diminishing GFR / Proteinuria
?Clinical Features / abrupt onset (see Text)

Non-Invasive Imaging: RAS present
? Comorbid Disease Risk
? Indications for Revascularization
- Circulatory Congestion
- Deteriorating Kidney Function
- ACE Inhibitor
- Advanced renal failure
- Bilateral High-grade RAS
- Solitary Functioning Kidney
- Uncontrolled Hypertension

Stable Renal Function
Excellent Blood Pressure

High-Risk Clinical Syndromes?

Optimize Antihypertensive and Medical Therapy

Repeat Assessment: 3-6 months
? Significant Disease Progression?

Significant Disease Progression?
Renovascular Hypertension due to arterial occlusive lesions

- Fibromuscular dysplasia
- Atherosclerotic disease
- Renal artery embolism
- Dissection / thrombosis
- Post-traumatic injury
- Aortic stent graft occlusion
Aortic Endovascular procedures: a new form of iatrogenic RAS:

Induced RAS
Increases mortality in AAA disease
Problem: Severity of stenoses is overestimated!
Hemodynamic Effects of Arterial Stenosis

Flow (%) vs. Stenosis (%)

Flow (%)

Stenosis (%)

82%
Consequences of Renal Arterial Stenosis

**Angiotensinogen** → **Renin** → **Angiotensin I** → **ACE** → **Angiotensin II**

**Vascular effects**
- Hypertrophy
- Remodeling
- Endothelin release
- Prostaglandins
- Oxidative Stress

**Sympathetic nerve system activation**

**Myocardial effects**
- LV hypertrophy
- Myocyte growth
- LV remodeling

**Renal sodium retention**

**Aldosterone secretion**

**Vasomotor effects**
Unilateral Renal Artery Stenosis

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Reduced renal perfusion

- \( \uparrow \) renin-angiotensin system (RAS)
- \( \uparrow \) renin
- \( \uparrow \) angiotensin II
- \( \uparrow \) aldosterone

\[ \text{Angiotensin II dependent hypertension} \]

Increased renal perfusion

- \( \downarrow \) Supressed RAS
- \( \downarrow \) Increased Na\(^+\) excretion (pressure natriuresis)

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**Effect of blockade of RAS**
- Reduced arterial pressure
- Enhanced lateralization of diagnostic tests
- Glomerular filtration rate (GFR) in stenotic kidney may fall

**Diagnostic tests**
- Plasma renin activity elevated
- Lateralized features, e.g. renin levels in renal veins, captopril-enhanced renography
Clinical Features: Renovascular Hypertension

- Activated Renin-angiotensin-aldosterone system
- Paroxysmal symptoms: adrenergic activation
- Abnormal Circadian Rhythm
- Accelerated Target organ damage
  - Left Ventricular Hypertrophy
  - Microvascular disease
- Renal injury: fibrosis/ ischemia
Medial Fibroplasia

- Early Onset  (Mean age: 33 years)
- Female predominance: progresses with smoking
- Amenable to balloon dilation
Table 2. Results of Percutaneous Transluminal Angioplasty of the Renal Arteries in Patients with Fibromuscular Renovascular Disease and Hypertension.*

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Technical Success Rate</th>
<th>Effect on Blood Pressure</th>
<th>Months of Follow-up</th>
<th>Complication Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>%</td>
<td></td>
<td>mean (range)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>%</td>
<td>Cured</td>
<td>Improved</td>
<td>Unimproved</td>
</tr>
<tr>
<td>Sos et al.⁵⁷</td>
<td>1983</td>
<td>31</td>
<td>87</td>
<td>59</td>
<td>34</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16 (4–40)</td>
<td>6</td>
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<tr>
<td>Baert et al.⁵⁸</td>
<td>1990</td>
<td>22</td>
<td>83</td>
<td>58</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26 (6–72)</td>
<td>NR</td>
</tr>
<tr>
<td>Tegtmeyer et al.⁵⁹</td>
<td>1991</td>
<td>66</td>
<td>100</td>
<td>39</td>
<td>59</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39 (1–121)</td>
<td>13</td>
</tr>
<tr>
<td>Bonelli et al.⁶⁰</td>
<td>1995</td>
<td>105</td>
<td>89</td>
<td>22</td>
<td>63</td>
<td>15</td>
</tr>
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<td></td>
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<td></td>
<td>43 (0–168)</td>
<td>11 (major)</td>
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<tr>
<td>Jensen et al.⁶¹</td>
<td>1995</td>
<td>30</td>
<td>97</td>
<td>39</td>
<td>47</td>
<td>14</td>
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<td></td>
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<td></td>
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<td></td>
<td>12 (NR)</td>
<td>3 (major)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 (minor)</td>
</tr>
<tr>
<td>Davidson et al.⁶²</td>
<td>1996</td>
<td>23</td>
<td>100</td>
<td>52</td>
<td>22</td>
<td>26</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>13</td>
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<tr>
<td>Klow et al.⁶³</td>
<td>1998</td>
<td>49</td>
<td>98</td>
<td>26</td>
<td>44</td>
<td>30</td>
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<td></td>
<td></td>
<td></td>
<td>9 (1–96)</td>
<td>0</td>
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<tr>
<td>Birrer et al.⁶⁴</td>
<td>2002</td>
<td>27</td>
<td>100</td>
<td>74↑</td>
<td>26</td>
<td>10 (NR)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>7.4</td>
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<tr>
<td>Surowiec et al.⁶⁵</td>
<td>2003</td>
<td>14</td>
<td>95</td>
<td>79↑</td>
<td>21</td>
<td>NR</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28.5</td>
</tr>
<tr>
<td>de Fraissinette et al.⁶⁶</td>
<td>2003</td>
<td>70</td>
<td>94</td>
<td>14</td>
<td>74</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39 (1–204)</td>
<td>11</td>
</tr>
</tbody>
</table>

* NR denotes not reported.
† The percentage shown is the total for cured and improved.
Medical Therapy of Renovascular Disease

- ACE / ARB as part of Regimen
- Stability of GFR
- Potassium Adequacy of BP Control
- Calcium Channel Blockade
- Multiple Drug Regimens
- CV Risk: Statins, Aspirin, Smoking
Dispelling the myth: the use of renin–angiotensin blockade in atheromatous renovascular disease

Constantina Chrysochou¹, Robert N. Foley², James F. Young¹, Kaivan Khavandi¹, Ching M. Cheung¹ and Philip A. Kalra¹

¹Renal department, Salford Royal Hospital, Manchester Academic Health Science Centre, The University of Manchester, Salford, UK and ²Chronic Disease Research Group, School of Medicine, University of Minnesota—Twin Cities, Minneapolis, MN, USA

N=621 ARVD registry patients
-Prospective: 357/378 tolerated RAB (92%)
-54/78 (78%) of Bilateral ARVD

Multivariate time-adjusted analysis:
HR for Death 0.61 (0.40-0.91) p=.02

Prospective RCTs in Renovascular Disease

- **BP Rx:** Webster, et.al: 1998
  Plouin, et.al: 1998
  Van Jaarsveld, et.al: 2000

- **Renal Function:** ASTRAL: 2009
  STAR: 2009

- **Cardiovascular Outcomes:** Cooper, et. al. CORAL 2014
Revascularization versus Medical Therapy for Renal-Artery Stenosis

The ASTRAL Investigators*

Patients were eligible to participate if they had substantial anatomical atherosclerotic stenosis in at least one renal artery that was considered potentially suitable for endovascular revascularization and if the patient's doctor was uncertain that the patient would definitely have a worthwhile clinical benefit from revascularization, taking into account the available evidence. Patients required surgical revascularization or had a high nonatheromatous cardiovascular risk. Patients who had undergone previous revascularization were excluded.

CONCLUSIONS
We found substantial risks but no evidence of a worthwhile clinical benefit from revascularization in patients with atherosclerotic renovascular disease. (Current Controlled Trials number, ISRCTN59586944.)
Kiss My Astral: One Seriously Flawed Study of Renal Stenting After Another

Christopher J. White, MD
Editor-in-Chief, Catheterization and Cardiovascular Interventions

PERIPHERAL VASCULAR DISEASE

Original Studies

The Benefit of Renal Artery Stenting in Patients with Atheromatous Renovascular Disease and Advanced Chronic Kidney Disease

Philip A. Kalra, MD, FRCR, Constantina Chrysochou, MBChB, MRCR,
Darren Green, MBChB, MRCR, Ching M. Cheung, MBChB, MRCR, Kavian Khavandi, MBChB, MRCP,
Sebastian Sixt, MD, Aljoscha Rastan, MD, and Thomas Zeller, MD
Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

Christopher J. Cooper, M.D., Timothy P. Murphy, M.D., Donald E. Cutlip, M.D., Kenneth Jamerson, M.D., William Henrich, M.D., Diane M. Reid, M.D., David J. Cohen, M.D., Alan H. Matsumoto, M.D., Michael Steffes, M.D., Michael R. Jaff, D.O., Martin R. Prince, M.D., Ph.D., Eldrin F. Lewis, M.D., Katherine R. Tuttle, M.D., Joseph I. Shapiro, M.D., M.P.H., John H. Rundback, M.D., Joseph M. Massaro, Ph.D., Ralph B. D'Agostino, Sr., Ph.D., and Lance D. Dworkin, M.D., for the CORAL Investigators*
New Onset Clinical Events after Dx of Atherosclerotic Renovascular Disease

Events / 1000 pt years

N=1,085,250 medicare claims
N=5875 newly identified RAS

Baseline:
- BP: reasonably controlled
- eGFR preserved
- Degree of stenosis overestimated
  <20% above 80%

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stenting plus Medical Therapy (N=459)</th>
<th>Medical Therapy Only (N=472)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>69.3±9.4</td>
<td>69.0±9.0</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>51.0</td>
<td>48.9</td>
</tr>
<tr>
<td>Race (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Other</td>
<td>93.0</td>
<td>93.0</td>
</tr>
<tr>
<td>Body-mass index†</td>
<td>28.2±5.3</td>
<td>28.7±5.7</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>149.9±23.2</td>
<td>150.4±23.0</td>
</tr>
<tr>
<td>Blood pressure at target level (%)§</td>
<td>29.2</td>
<td>25.3</td>
</tr>
<tr>
<td>Estimated GFR (ml/min/1.73 m²)¶</td>
<td>58.0±23.4</td>
<td>57.4±21.7</td>
</tr>
<tr>
<td>Stage ≥3 chronic kidney disease (%)</td>
<td>49.6</td>
<td>50.4</td>
</tr>
<tr>
<td>Method of identification of stenosis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>68.4</td>
<td>68.6</td>
</tr>
<tr>
<td>Duplex ultrasonography</td>
<td>25.5</td>
<td>24.2</td>
</tr>
<tr>
<td>Computed tomographic angiography</td>
<td>4.4</td>
<td>5.3</td>
</tr>
<tr>
<td>Magnetic resonance angiography</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Medical history and risk factors (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>32.4</td>
<td>34.3</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>26.5</td>
<td>30.2</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>12.0</td>
<td>15.1</td>
</tr>
<tr>
<td>Smoking in past yr</td>
<td>28.0</td>
<td>32.2</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>89.4</td>
<td>90.0</td>
</tr>
<tr>
<td>Angiographic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Stenosis, as assessed by core laboratory</td>
<td>67.3±11.4</td>
<td>66.9±11.9</td>
</tr>
<tr>
<td>% Stenosis, as assessed by investigator</td>
<td>72.5±14.6</td>
<td>74.3±13.1</td>
</tr>
<tr>
<td>Global ischemia (%)</td>
<td>20.0</td>
<td>16.2</td>
</tr>
<tr>
<td>Bilateral disease (%)</td>
<td>22.0</td>
<td>18.1</td>
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</table>
### Table 2. Clinical End Points. *

<table>
<thead>
<tr>
<th>End Point</th>
<th>Stenting plus Medical Therapy (N=459)</th>
<th>Medical Therapy Only (N=472)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point: death from cardiovascular or renal causes, stroke, myocardial infarction</td>
<td>161 (35.1)</td>
<td>169 (35.8)</td>
<td>0.94 (0.76–1.17)</td>
<td>0.58</td>
</tr>
<tr>
<td>CCI</td>
<td>20 (4.4)</td>
<td>20 (4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>12 (2.6)</td>
<td>16 (3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major adverse events</td>
<td>30 (6.5)</td>
<td>27 (5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>27 (5.9)</td>
<td>26 (5.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>68 (14.8)</td>
<td>77 (16.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4 (0.9)</td>
<td>3 (0.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Figure 2. Kaplan–Meier Curves for the Primary Outcome.*

Survival curves are truncated at 5 years owing to instability of the curves because few participants remained in the study after 5 years.
Utilization of Endovascular Renal Artery Stenting in Medicare Beneficiaries

Modified from Murphy, Am. J. Roentg. 2004
Medicare (CMS review) 2007  Textor JASN 2008
Limitations of Clinical Trials: Atherosclerotic Renal Artery Stenosis

- **Patient Selection**
  - excluded most severe cases: CHF
  - progressive renal dysfunction usually excluded
  - included minor lesions

- **Outcome Measurement**
  - wide variation in definition of BP goals / achieved levels / renal function
  - circulatory congestion / volume control / drugs
  - crossovers from medical to interventional arms
  - short duration of follow-up
Human Renovascular Disease 2018

- Renovascular Hypertension:
  - Renin release
  - can be managed medically

- “Adaptation” to reduced blood flow
  - without tissue hypoxia
  - minimal structural damage

- Advancing disease: progressive injury
  - recoverable?
Arterial Pressure Measured Sequentially Before and After Placement of Silver Clip

**Aortic coarctation**

Carotid (n=5) (n=9)

Iliac (n=6)

Time relative to coarctation (days)

Weeks

**P<0.01**

Textor, Smith-Powell,: Journal of Hypertension, Vol 6, 1988

CP1071019-1
“Ischemic nephropathy”? : Definition

1. “Hemodynamically significant” main renal artery disease
2. Loss of function (GFR) due to vascular insufficiency
3. ?”ischemia”
Atherosclerotic Renal Artery Stenosis reduces kidney volume and blood flow
Renal Circulation is preferential to the Cortex

Figure from Brenner: The Kidney, 2012
Medullary oxygenation is related both to blood flow to oxygen consumption from active solute transport

Furosemide
Protocol evaluation of blood flow, GFR and tissue oxygenation using Blood Oxygen Level Dependent (BOLD) MR in Atherosclerotic Renovascular Disease:

**Sodium Diet: 150 mEq  Rx: ACE/ARB /diuretics**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
</table>
| -Urinary Sodium | -BOLD MR: 3 Tesla  
1) Baseline  
2) After loop diuretic: furosemide-suppressible oxygen consumption (FSOC) | -Renal vein determinations  
-renin  
-isoprostanes  
-TGF Beta |
| -microalbumin  
-creatinine  
-iothalamate GFR | | |
| Isoprostanexcretion | MDCT: Regional blood flow and volume: medulla / cortex |
| TGF Beta: urine/blood | Transjugular Renal Biopsy |
### MDCT: volumes and flow reduced in Stenotic kidneys

<table>
<thead>
<tr>
<th></th>
<th>Ess HTN: n=28</th>
<th>Stenotic Kidney n=14</th>
<th>Contralateral n=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney volume (ml)</td>
<td>144±6</td>
<td>119±10 *</td>
<td>155±14</td>
</tr>
<tr>
<td>Renal Blood flow (ml/min)</td>
<td>405±29</td>
<td>270±42 *</td>
<td>383±49</td>
</tr>
<tr>
<td>Cortex perfusion (ml/cc tissue)</td>
<td>3.5±0.2</td>
<td>2.7±0.3 *</td>
<td>2.9±0.3</td>
</tr>
<tr>
<td>Medullary perfusion (ml/cc)</td>
<td>1.5±0.1</td>
<td>1.2±0.1 #</td>
<td>1.2±0.1 #</td>
</tr>
<tr>
<td>Cortical volume (ml)</td>
<td>96±6</td>
<td>80±8 *</td>
<td>112±12</td>
</tr>
<tr>
<td>Medullary volume (ml)</td>
<td>48±3</td>
<td>39±5</td>
<td>44±6</td>
</tr>
</tbody>
</table>

* p<.05 vs Contralateral  # p<.05 vs EH

Preserved Oxygenation Despite Reduced Blood Flow in Poststenotic Kidneys in Human Atherosclerotic Renal Artery Stenosis

Monika L. Gloviczki, James F. Glockner, Lilach O. Lerman, Michael A. McKusick, Sanjay Misra, Joseph P. Grande, Stephen C. Textor
Renovascular Disease and Tissue Oxygenation

Reduced perfusion / Preserved oxygenation

Tissue Oxygenation

Renal Blood Flow

Normal Cortical Oxygenation

50% 100%

Textor
Many patients can be treated with medical Therapy with no loss of renal function

**Figure 1.** Renal Function in Patients with Renal-Artery Stenosis Treated with Revascularization or Medical Therapy Alone.

Shown are mean values for the reciprocal of the serum creatinine level (Panel A) and for the serum creatinine level (Panel B). The second measures for both values were performed 1 to 3 months after baseline; the third measures were performed 6 to 8 months after baseline. The I bars indicate 95% confidence intervals.
“Prospective Study of Atherosclerotic Disease Progression in the Renal Artery”


Total Occlusion: 9/295 arteries (3%)

Renal Artery Stenosis

Critical perfusion pressure

Renal hypoperfusion

Intermediate

Reversible changes

Irreversible changes

Modifying factors

? age

? rate of change

? other disease

Nephrosclerosis

Diabetes

End-stage renal disease
Face Validity: Internet Truths

- “Blood circulation is one of the most important functions in the body. It supplies oxygen to the brain and other organs.

- It’s what makes our bodies work.”
Adaptation of kidney oxygenation to reduced blood flow

Induction of inflammatory and fibrogenic pathways

Reduced perfusion / preserved oxygenation

Tissue hypoxia
Severe Renal hypoperfusion with near total occlusion
Kidney

Blood Oxygen Level-Dependent Magnetic Resonance Imaging Identifies Cortical Hypoxia in Severe Renovascular Disease

Monika L. Gloviczki, James F. Glockner, John A. Crane, Michael A. McKusick, Sanjay Misra, Joseph P. Grande, Lilach O. Lerman, Stephen C. Textor

Hypertension: 58: 1066, 2011
Renovascular Disease and Tissue Oxygenation

Reduced perfusion / Preserved oxygenation

Tissue hypoxia

Normal Cortical Oxygenation

Tissue Oxygenation

Renal Blood Flow

100%

50%

100%

Reduced perfusion / Preserved oxygenation

Textor
Transition from hemodynamic to inflammatory injury

Progression over time

- Critical Renal Artery Stenosis: reduced blood flow and perfusion
- Inflammatory injury And Fibrosis
Tissue Oxygenation

Induction of inflammatory and fibrogenic pathways: Revascularization fails to recover kidney function

Prospective Trials
Observational Reports

Severe
Moderate

Reduced perfusion / preserved oxygenation
Normal cortical oxygenation

Tissue hypoxia

Renal Blood Flow

Cortical Oxygenation

50% 100%
High-Risk Clinical Presentations in Atherosclerotic Renovascular Disease: Prognosis and Response to Renal Artery Revascularization

James Ritchie, MB ChB, Darren Green, PhD, Constantina Chrysochou, PhD, Nicholas Chalmers, MB ChB, Robert N. Foley, MD, and Philip A. Kalra, MD

Pulmonary Edema

Rapidly declining GFR + Refractory HTN

p<.01

p<.04

Progressive rise in creatinine in a woman with previous renal artery occlusion.
High-Grade Renal Artery Stenosis To Solitary Functioning Kidney
Removal of ARB with recovery of GFR

Post-Stent: BP and Creatinine Stable
No further episodes CHF
“Appropriate Use” : Indications for Renal Revascularization:

- Resistant Hypertension: Failure of Medical Therapy
  Need for ACE Inhibition / with Angiotensin Dependent GFR

- Progressive Renal Insufficiency: Salvageable Kidneys
  Recent rise in serum Creatinine
  Loss in GFR during BP Rx: e.g. ACE / ARB / Other
  Evidence of Diastolic blood flow: Resistive Index

- Recurrent Circulatory Congestion: “Flash Pulmonary Edema”

Textor 2018
Human Renovascular Disease 2018

- Renovascular Hypertension:
  - Renin release
  - can be managed medically

- “Adaptation” to reduced blood flow
  - without tissue hypoxia
  - minimal structural damage

- Advancing disease: adequate blood flow for tissue oxygenation?

- progressive injury - recoverable?
Critical Renal Artery Stenosis

Reduced Renal Blood Flow

"Ischemic Nephropathy"

Vascular rarefication

Oxidative Stress Injury

Inflammatory cell infiltration

Fibrosis / Atubular Glomeruli / Glomerulosclerosis

Irreversible Kidney Injury

Potential Therapeutic Targets

Renal artery revascularization

RAAS Blockade

Angiogenesis:
- EPC/ MSC infusion
- angiogenic peptides/stimulation

Targeted Mitochondrial Protection

Immunomodulation:
- anti-T cell therapy
- cytokine modulation
- Cell-based therapy
  -- EPC
  -- MSC

1. Progressive Renal injury in ARVD:  
   - hemodynamic versus inflammatory injury

2. Repair / Regeneration after kidney injury:  
   macrophages and mesenchymal stromal/stem cells  
   - angiogenesis  
   - immunomodulation
Adipose Tissue-Derived Mesenchymal Stem Cells Improve Revascularization Outcomes to Restore Renal Function in Swine Atherosclerotic Renal Artery Stenosis

Alfonso Eirin, MD¹, Xiang-Yang Zhu, MD, PhD¹, James D. Krier¹, Hui Tang, MD, PhD¹, Kyra L. Jordan¹, Joseph P. Grande, MD, PhD¹,², Amir Lerman, MD³; Stephen C. Textor, MD¹, Lilach O. Lerman, MD, PhD¹,³
Schematic View of Protocol for adipose-derived h-MSC administration For Human Atherosclerotic Renal Artery Stenosis
Intra-arterial MSC increase cortical perfusion in human ARVD

Cortical blood flow

Medullary blood flow

Renal blood flow

$P = 0.02$

$NS$

$P = 0.01$

Textor 2017
Fractional Hypoxia (>30%) fell from 12.1% to 6.8% After 3 months (p=.03)
Spectrum of Renovascular Disease Manifestations: 2018

- Asymptomatic "Incidental RAS"
- Renovascular Hypertension
- Accelerated CV Disease
  - Congestive Heart failure
  - Stroke
- Ischemic Nephropathy

Textor
Human Renovascular Disease 2018

• Renovascular Hypertension:
  - Renin release
  - can be managed medically

• "Adaptation" to reduced blood flow
  - without tissue hypoxia
  - minimal structural damage

• Advancing disease: adequate blood flow for tissue oxygenation?

• progressive injury - ? recoverable?
First pants, THEN your shoes
Renovascular Disease: 2018

• The State of the Vessel

• The Condition of the Kidney
1. Epidemiology and Manifestations of ARVD:

2. Progressive Renal injury in ARVD:
   - hemodynamic versus inflammatory injury

3. Repair / Regeneration after kidney injury:
   - macrophages and mesenchymal stromal/stem cells
Kidney Oxygenation

Hyperoxia

- Toxic Free radical Generation
- Mitochondrial respiration

Hypoxia

- Inflammatory
- Fibrogenic
- Tubular injury
Disclosures

Site PI:  CORAL Trial
NHLBI / NIDDK
Stealth Peptides
Mayo Center for Regenerative Medicine

Section Editor: UpToDate
Systolic blood pressure (mm Hg)

- **2KHT**
- **Sacrificed**
- **Stop captopril**
- **CP1073437-1**

**2KHT + Captopril (100 mg/kg/day)**

**Sham (n=5)**

2KHT + Captopril=8

* P<0.05 from sham
° P<0.05 from 2KHT + captopril
Deforrest: AJC, 1982
Bilateral Renal Artery Stenosis

- Bilateral
- Stenosis of solitary kidney

Reduced renal perfusion

- renin-angiotensin system (RAS)
- renin
- angiotensin II
- aldosterone

Increased arterial pressure

- Normal or low angiotensin II

Effect of blockade of RAS

- Reduced arterial pressure only after volume depletion
- May lower GFR

Diagnostic tests

- Plasma renin activity normal or low
- Lateralized features: none
69 y.o. with recent CVA and BP 180/110

F/U Creatinine 1.2 mg/dL
BP: 120 / 60
Ramipril / metoprolol
Clinical Issues: 69 y.o. after CVA Bilateral RAS

• Am I at risk for needing dialysis?
• What will happen if I depend upon medical therapy?
• What will happen if I have a stent?
• What to do?
AR Question: ACE/ARB use in most patients with renovascular disease:

A. Should be avoided to preserve filtration pressure in the post-stenotic kidney

B. Is associated with lower rates of AKI

C. Is associated with increased mortality

D. Is associated with irreversible fibrosis

E. Can be used safely after revascularization
Use of Renin-Angiotensin Inhibitors in People with Renal Artery Stenosis

Kaleigh L. Evans,* Katherine R. Tuttle,† David A. Folt,* Taylor Dawson,* Steven T. Haller,* Pamela S. Brewster,* Wencan He,* Kenneth Jamerson,* Lance D. Dworkin,§ Donald E. Cutlip,‖ Timothy P. Murphy,§ Ralph B. D’Agostino Sr.,§ William Henrich,** and Christopher J. Cooper*
Renovascular RCT’s had lower mortality than registry / observational cohorts

U.S. Medicare 2 year mortality Between ages 65-67 without RAS*

Figure 1.2 Nephrons and the collecting duct system. Shown are short-looped and long-looped nephrons, together with:

1. Renal corpuscle
2. Proximal convoluted tubule
3. Proximal straight tubule
4. Descending thin limb
5. Ascending thin limb
6. Distal straight tubule (thick ascending limb)
7. Macula densa
8. Distal convoluted tubule
9. Connecting tubule
10. Cortical collecting duct
11. Outer medullary collecting duct
12. Inner medullary collecting duct

Figure 1.4 Microvasculature of the kidney. Afferent arterioles supply the glomeruli and efferent arterioles leave the glomeruli and divide into the descending vasa recta, which, together with...
“Moderate ARAS”

US velocity = 300 cm/s sGFR = 38
Adaptation of kidney oxygenation to reduced blood flow

Tissue Oxygenation

Induction of inflammatory and Fibrogenic pathways

Tissue hypoxia

Reduced perfusion / Preserved oxygenation

Renal Blood Flow

100%
Cumulative Rates of Progressive Renal Insufficiency in CORAL

F/U 43 mos 14.8-16.3%

Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

Christopher J. Cooper, M.D., Timothy P. Murphy, M.D., Donald E. Cutlip, M.D., Kenneth Jamerson, M.D., William Henrich, M.D., Diane M. Reid, M.D., David J. Cohen, M.D., Alan H. Matsumoto, M.D., Michael Steffer, M.D., Michael F. Jaff, D.O., Martin R. Prince, M.D., Ph.D., Eldrin F. Lewis, M.D., Katherine R. Tuttle, M.D., Joseph I. Shapiro, M.D., M.P.H., John H. Rundback, M.D., Joseph M. Massaro, Ph.D., Ralph B. D'Agostino, Sr., Ph.D., and Lance D. Dworkin, M.D., for the CORAL Investigators®
Worsening Hypertension and Rising Creatinine

64 y.o. Solitary functioning kidney
Blood Pressure and Creatinine after PTRA in 64 y.o. with RAS in Solitary Functioning Kidney

Data from Textor and Wilcox, Semin. Nephrol. 20:489, 2000
Worsening Hypertension and Rising Creatinine

64 y.o. Solitary functioning kidney
Creatinine in Azotemic Patients with RAS

Fall $\geq$ 1.0 mg/dL
n=83 (27.3%)

Same ($\Delta <$ 1.0 mg/dL)
n=160 (52.6%)

Rise $\geq$ 1.0 mg/dL
n=61 (20.1%)

Preop LFU

<table>
<thead>
<tr>
<th>Complications of Renal Artery Stenting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minor:</strong></td>
</tr>
<tr>
<td>Groin Hematoma</td>
</tr>
<tr>
<td><strong>Major:</strong></td>
</tr>
<tr>
<td>Renal Failure</td>
</tr>
<tr>
<td>Segmental Infarction</td>
</tr>
<tr>
<td>Perinephric Hematoma</td>
</tr>
<tr>
<td>Renal artery thrombosis/occlusion</td>
</tr>
<tr>
<td>Stent misplacement</td>
</tr>
<tr>
<td>Other: proteinuria/ sepsis</td>
</tr>
<tr>
<td>cholesterol embolism,</td>
</tr>
<tr>
<td>iliac artery dissection</td>
</tr>
</tbody>
</table>

**Overall:** 9% Major Events

Meta-analysis: n=14 reports, n=678 patients
Severe Renal hypoperfusion with near total occlusion
Microvascular rarefaction in Experimental Renal Artery Stenosis

Figure 1. Representative three-dimensional reconstruction of the renal microvascular architecture (using microcomputed tomophy) and renal morphology (trichrome staining) showing opposing changes in microvascular architecture in early atherosclerosis compared with chronic ischemia (top). Scale bar (trichrome): 25 μm.

Microvascular rarefaction in particular is accompanied by severe renal fibrosis (bottom). MV, microvascular.

Lerman and Chade, 2008
Kidney

Blood Oxygen Level-Dependent Magnetic Resonance Imaging Identifies Cortical Hypoxia in Severe Renovascular Disease

Monika L. Gloviczki, James F. Glockner, John A. Crane, Michael A. McKusick, Sanjay Misra, Joseph P. Grande, Lilach O. Lerman, Stephen C. Textor

Hypertension: 58: 1066, 2011
Normal

Moderate RAS

Severe RAS

Textor and Lerman, JASN 2015
Tissue Oxygenation

- Induction of inflammatory and fibrogenic pathways: Revascularization fails to recover kidney function

Prospective Trials
Observational Reports

Severe
Moderate

Renal Blood Flow

- Normal Cortical Oxygenation
- Reduced perfusion / preserved oxygenation

Tissue hypoxia

50%
100%
High-Risk Clinical Presentations in Atherosclerotic Renovascular Disease: Prognosis and Response to Renal Artery Revascularization

James Ritchie, MB ChB, Darren Green, PhD, Constantina Chrysochou, PhD, Nicholas Chalmers, MB ChB, Robert N. Foley, MD, and Philip A. Kalra, MD

Change in creatinine clearance (mL/min)

Resistance index <80

Resistance index ≥80

No. with follow-up data

<table>
<thead>
<tr>
<th>Resistance index &lt;80</th>
<th>96</th>
<th>96</th>
<th>95</th>
<th>83</th>
<th>73</th>
<th>59</th>
<th>43</th>
<th>34</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance index ≥80</td>
<td>35</td>
<td>35</td>
<td>33</td>
<td>31</td>
<td>26</td>
<td>21</td>
<td>16</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

Radermacher, NEJM 2001
Relationship Between Changes in Slope Values of Reciprocal Serum Creatinine Plot vs Time Before and After PTRA

Post-angioplasty slope variation (mg/dL/days)

Slope preangioplasty (mg/dL/days)

Responders

Non-responders

Muray: AJKD, 2002
Removal of ARB with progressive rise in creatinine in a woman with previous renal artery occlusion.

Post-Stent: BP and Creatinine Stable No further episodes CHF ARB with recovery of GFR.
High-Grade Renal Artery Stenosis To Solitary Functioning Kidney
Removal of ARB with recovery of GFR

Post-Stent: BP and Creatinine Stable
No further episodes CHF
“Pearls”: Indications for Renal Revascularization:

• Resistant Hypertension: Failure of Medical Therapy
  Need for ACE Inhibition / with All
  Dependent GFR

• Progressive Renal Insufficiency: Salvageable Kidneys
  Recent rise in serum Creatinine
  Loss in GFR during BP Rx: e.g. ACE / ARB / Other
  Evidence of Diastolic blood flow: Resistive Index

• Recurrent Circulatory Congestion: “Flash Pulmonary Edema”
Management of Renovascular Hypertension and Ischemic Nephropathy

Hypertension + Reduced GFR

Initiate Therapy: Antihypertensive Medications
Lifestyle, Risk Factor and Dyslipidemia Management

Suspicion of Renovascular Disease
? Age, Associated Vascular Disease
? Diminishing GFR / Proteinuria
? Clinical Features / abrupt onset (see Text)

Non-Invasive Imaging:
? RAS present
? Comorbid Disease Risk
? Indications for Revascularization
- Circulatory Congestion
- Deteriorating Kidney Function
  - ACE Inhibitor
  - Advanced renal failure
- Bilateral High-grade RAS
- Solitary Functioning Kidney
- Uncontrolled Hypertension

Stable Renal Function
Excellent Blood Pressure

Optimize Antihypertensive and Medical Therapy

Repeat Assessment: 3-6 months

? Role of Age / Expected Longevity

High-Risk Clinical Syndromes?
Renovascular Hypertension and Ischemic Nephropathy 2017

- Prevalence / Associated Disease
- Pathophysiology / Clinical manifestations
- Medical Rx: role of ACE / ARB
- Prospective Trials: low risk groups
- High-risk subsets
- Revascularization 2017: pros and cons
Interactive mechanisms underlying Hypertension and kidney injury in atherosclerotic RAS

**Tissue Underperfusion**
- activation of RAAS
- altered endothelial function
  - endothelin
  - NO, Prostaglandins
- Sympathoadrenergic activation
- Cytokine release / Inflammation
  - NF-KB, TNF, TGF-Beta, PAI-1, IL-1
- Impaired tubular function
- Apoptosis / necrosis

**Recurrent Local Ischemia**
- ATP depletion
- Tubulointerstitial injury
- Microvascular damage
- Immune activation
- Vascular remodeling
- Interstitial fibrosis
- RAAS activation
- Sympathoadrenergic activation
- Endothelin
- Disturbances of Oxidative stress
- Oxidized LDL

Textor, JASN: 2008
Survival and ACEi in RVH

Cumulative survival

ACEi

No ACEi

Months

Three Studies comparing Medical Rx and PTRA (with or without stents):

Webster, et. al 1998, J.Human Hyper.
- N=55
- Unilateral = 27
- Run-In Med. Rx
- Random Zero BP
- No ACE inhibitors
- No difference in BP, renal Function, survival; ?Crossover?

Plouin, et. al. 1998: Hypertension
- N=49
- All Unilateral
- Multicenter, ABPM at 6 mos
- No ACE inhibitors
- No difference in BP, slightly Fewer meds in PTRA group, More complications: Crossover in Med Rx: 7/26 (27%)

Van Jaarsveld 2000: NEJM
- N=106
- Unilateral
- Multicenter, Office and Automated BP
- Lateralization studies (scan, Renal vein renin)
- No Difference in BP at 12 mos
- Crossover in Med Rx: 22/50 (44%)
Critical Renal Artery Stenosis

Reduced Renal Blood Flow

“Ischemic Nephropathy”

Vascular rarefication

Oxidative Stress Injury

Inflammatory cell infiltration

Fibrosis / Atubular Glomeruli / Glomerulosclerosis

Irreversible Kidney Injury

Potential Therapeutic Targets

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RAAS Blockade

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- Cell-based therapy
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