“Epidemiology, Diagnosis and Management of Renovascular Disease”

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KDIGO Controversies
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February, 2020
Disclosures

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

Section Editor: UpToDate
Renovascular Hypertension due to arterial occlusive lesions

- Fibromuscular dysplasia
- Atherosclerotic disease
- Renal artery embolism
- Dissection / thrombosis
- Post-traumatic injury
- Aortic stent graft occlusion
Spectrum of Renovascular Disease Manifestations:

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

Note: This peripheral vascular disease threatens the kidney.
Renovascular Hypertension and Ischemic Nephropathy 2020

- Prevalence / Associated Disease
- Pathophysiology / Clinical manifestations
- Medical Rx: role of ACE / ARB
- Prospective Trials: low risk groups
- High-risk subsets
- Renal Revascularization 2020:
Renal Artery Stents: The Current Clinical Narrative

• 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 WAYNE KURZAR

DALLAS—Renal artery stenting conferred an additional benefit beyond optimal drug therapy for preventing adverse renal and cardiovascular events in patients with renal artery stenosis (RAS) and chronic kidney disease (CKD) or hypertension, data from a randomized controlled trial showed. The results finding that renal artery stenting improves cardiovascular outcomes in renal arteriographic lesions were presented by Christopher J. Cucchiara, MD, at the American Heart Association Scientific Sessions 2013 and published online ahead of print in the New England Journal of Medicine, support those from other recent clinical trials of renal stenting.

The randomized controlled trial, CORDIAL (Coronary and Renal Evaluation of the Effect of Intracoronary Stenting and Abciximab therapy on long-term outcomes), evaluated the effectiveness and safety of renal artery stenting compared with medical therapy alone in patients with RAS and chronic kidney disease (CKD). The trial included 154 patients with RAS and CKD, with a mean follow-up of 4 years. The primary endpoint was the composite of death, myocardial infarction (MI), stroke, and hospitalization for heart failure. The trial showed that renal artery stenting was associated with a significant reduction in the primary endpoint compared with medical therapy alone (5.4% vs. 17.4%, respectively; p = 0.01).

The results of the CORDIAL trial suggest that renal artery stenting may be an effective treatment option for patients with RAS and CKD, particularly those at higher risk for adverse cardiovascular events. However, the results also highlight the need for further research to better understand the long-term benefits and risks of renal artery stenting in this population.
“Face Validity” Paradox: Internet Truth

• “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.”

Vital Proteins: Natural Whole Nutrition Blog

“The kidney needs blood”.

S C Textor
"The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review"

demast 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:
  - With HTN: 17.8%
- Peripheral vascular disease: 25.3%
- AAA: 33.1%
- ESRD: 40.8%
- Congestive Heart Failure: 54.1%

(Population estimate: 6.8%)

Trial results assure many individuals with ARVD will be exposed to reduced renal blood flows for prolonged time periods.
Diagnosis of Renovascular Disease

• Imaging: non-invasive
  • Renal artery duplex ultrasound
  • CT angiography
  • MR angiography

• Angiography
  • Translesional gradients / Functional Flow reserve

• Functional measures
  • Hormonal activation: renin-angiotensin system
  • Blood Oxygen Level Dependent (BOLD) MR
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
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
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*
Baseline:
- BP: reasonably controlled
- eGFR preserved
- Degree of stenosis
  - overestimated on site
  - fewer than 20% above 80%

**Table 1. Baseline Characteristics of the Study Population, According to Treatment Group.**

<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 (mm Hg)</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±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>
</tr>
</tbody>
</table>
Primary End-Point: CORAL

Table 2. Clinical End Points.4

<table>
<thead>
<tr>
<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>161 (35.1)</td>
<td>169 (35.8)</td>
<td>0.94 (0.76–1.17)</td>
<td>0.58</td>
</tr>
<tr>
<td>20 (4.4)</td>
<td>20 (4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 (2.6)</td>
<td>16 (3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 (6.5)</td>
<td>27 (5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27 (5.9)</td>
<td>26 (5.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>68 (14.8)</td>
<td>77 (16.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (0.9)</td>
<td>3 (0.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio with stenting, 0.94 (95% CI, 0.76–1.17), P=0.58 by log-rank test.

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

Trial results released during Period of increased use of Renal revascularization
ABPM: Average Fall 14/6 mmHg
BP Meds: fell from 4.0 to 3.6
No Change in GFR

Courand, et.al: Hypertension, 74: 1516, 2019
"Ischemic nephropathy":

1. "Hemodynamically significant" main renal artery disease
2. Loss of function (GFR) due to vascular insufficiency
3. "ischemia"

Note: "ischemic nephropathy ≠ "renal artery stenosis"
New Onset Clinical Events after Dx of Atherosclerotic Renovascular Disease


N=1,085,250 medicare claims
N=5875 newly identified RAS
Renovascular Disease and Tissue Oxygenation

- Reduced perfusion / Preserved oxygenation
- Tissue hypoxia
- Normal cortical oxygenation

Renal Blood Flow

Textor
Case: 74 y.o. Male: Referred for:
1. Hypertension management
2. Advice re: ?renal transplant?

Hx: 20+ years: moderate hypertension
Longstanding smoker
AAA: aortobifemoral bypass 12 y. ago

Hospitalized: 1 year ago: “TIA” left weakness
BP 210/150 mm Hg

2 mos. Ago: Hospitalized: 230 /140 mmHg
Encephalopathy:
Creatinine from 1.3 mg to 2.5 mg/dL
74 y.o. Male: Medical Regimen:

Valsartan (Diovan) 320 mg
Carvedilol (CoReg) 25 mg bid
Furosemide (Lasix) 80 / 40 mg
Clonidine 0.3 mg QID

minoxidil 2.5 mg bid
Darbopoeitin weekly
Aliskiren (Tekturna) 150 mg

Exam: 174 / 71 mm Hg  P: 72
s/p AAA repair
No carotid bruits 1+ edema

Lab: Hgb 11.7 g/dL Creatinine: 3.8 mg/dL
K+: 5.1  Na+: 138 mEq/L  HCO3: 29 mEq/L
Attending Rounds: A Patient with Accelerated Hypertension and an Atrophic Kidney

Stephen C. Testor
Creatinine mg/dL

<table>
<thead>
<tr>
<th>Time</th>
<th>Creatinine mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year ago</td>
<td>0.5</td>
</tr>
<tr>
<td>1 month ago</td>
<td>2</td>
</tr>
<tr>
<td>Admission</td>
<td>230/125</td>
</tr>
<tr>
<td>3 days</td>
<td>170/82</td>
</tr>
</tbody>
</table>

**Progressive Hypertension**

**Loss of Renal Function**

**Complex Regimen**

- Aliskiren (Tekturna) 150 mg
- Valsartan (Diovan) 320 mg
- Carvedilol (CoReg) 25 mg bid
- Furosemide (Lasix) 80 / 40 mg
- minoxidil 2.5 mg bid
- Clonidine 0.3 mg QID

When is the damage irreversible?

How should this be evaluated?

- imaging
- lab evaluation

When to undertake renal revascularization?
Blood Oxygen Level Dependent (BOLD) MR imaging
74 y.o. male: Bilateral RAS and CKD

Axial Maps of R2* reflect tissue levels of deoxyhemoglobin

Figure 4. | Axial image slices from blood oxygen level–dependent MR for right and left kidneys. Left panel depicts the R2* map (reflecting the level of deoxyhemoglobin) of the right kidney, showing a hypoxic cortical zone and widespread areas of elevated deoxyhemoglobin in the medullary segments (red). Right panel depicts the R2* map in the left kidney, with a lower (blue) cortical zone and more gradual development of deeper medullary areas of hypoxia. This near-normal appearance of the corticomedullary oxygen gradient with the human kidney appeared despite reduced blood flow from renovascular occlusive disease (in the text).

Prognosis: Major Predictors of Renovascular Disease Outcomes: 74 y.o male

- **Size/GFR**
  - Normal kidney size on left/
    - recent creatinine below 1.5 mg/dL

- **Proteinuria**
  - none

- **Evident tissue hypoxia: ?functional (FSOC)**
  - Elevated Cortical and Fraction > 30 sec-1
  - Both fall after furosemide

- **Rapidity of onset and change**
  - Months?
    - @ 12-18 months
  - Years?
  - Decades?
Recovery of Renal Function after stent revascularization:

Encephalopathy
230/125

TIA
240/125

Renal Artery Stent

Creatinine mg/dL

0 0.5 1 1.5 2 2.5 3 3.5 4

1 year ago
1 month ago
admission
3 days
1 week
3 mos
1 year

170/82

Aliskiren (Tekturna) 150 mg
Valsartan (Diovan) 320 mg
Carvedilol (CoReg) 25 mg bid
Furosemide (Lasix) 80 / 40 mg
minoxidil 2.5 mg bid
Clonidine 0.3 mg QID

CJASN: Jan. 2014
Renovascular Disease 2020: Transition from hemodynamic to inflammatory injury
Critical Renal Artery Stenosis

- Reduced Renal Blood Flow
- Vascular rarefication
- Oxidative Stress Injury
- Inflammatory cell infiltration
- Fibrosis / Atubular Glomeruli / Glomerulosclerosis
- Irreversible Kidney Injury

"Ischemic Nephropathy"

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

Injury pathways and targets in Atherosclerotic Renovascular Disease

JASN 26: 2074, 2015

Paradigm Shifts in Atherosclerotic Renovascular Disease: Where Are We Now?

Stephen C. Textor and Lilach O. Lerman
Management of Renovascular Disease: Enthusiasm for renal revascularization

- Nephrectomy: Pressor kidney (1938)
- PTRA +/- Stent 1980’s-90s
- Surgical bypass (1960’s)
- RAAS Blockade 1980’s-90s
- Small HTN Trials (-) 1995-2000
- ASTRAL: 2009
- CORAL: 2014
- Hypertension 2019: “True Resistant Hypertension” by ABPM: France
- Observational Series: High Risk Subsets UK

Textor and Taler, Hypertension 2019 (modified)
Mortality and Renal Replacement Therapy after Renal Artery Stent Placement for Atherosclerotic Renovascular Disease

Sanjay Misra, MD, Ankaj Khosla, MD, Jake Allred, MS, William S. Harmsen, MS, Stephen C. Textor, MD, and Michael A. McKusick, MD

Predictors: Death
--CKD stage
--DM
--Carotid disease
--Proteinuria
--Statin (-)

Predictors: Renal Replacement Therapy
--CKD stage
--Proteinuria
--Smoker
--ACEI (-)
--CCB (+)

N=1052 patients
1996-2009
F/U: 37% died
10.6% RRT

Renovascular Hypertension and Ischemic Nephropathy 2020

- Prevalence / Associated Disease
- Pathophysiology / Clinical manifestations
- Medical Rx: role of ACE / ARB
- Prospective Trials: low risk groups
- High-risk subsets
- Renal Revascularization 2020: Competing risk
  - ?Adjunctive therapy
IS RENOVASCULAR DISEASE “LOST” OR BECOMING AN “ORPHAN DISEASE”?

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