A Randomized Multicenter Clinical Trial of Renal Artery Stenting in Preventing Cardiovascular and Renal Events: Results of the CORAL Study

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on behalf of the CORAL Investigators
Disclosures

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- Pfizer
- Cordis

Study drugs provided by:

- Astra Zeneca
- Pfizer
Background

- Atherosclerotic renal artery stenosis is a common problem in the elderly.
- Despite several randomized trials, the utility of revascularization for prevention of major adverse renal and cardiovascular events is controversial.
Methods

- Open label, randomized, international, multicenter controlled clinical trial

- All received Medical Therapy:
  - BP, Diabetes and Lipids to goal, with participants provided free:
    - Candesartan ± hydrochlorothiazide (Atacand ®)
    - Atorvastatin + Amlodipine (Caduet ®)
  - Anti-platelet therapy
Inclusion Criteria

Clinical Syndrome:
- Hypertension ≥2 anti-hypertensive medications, OR
- Renal dysfunction defined as Stage 3 or greater CKD

-AND-

Atherosclerotic Renal Artery Stenosis:
- Angiographic: ≥ 60% and < 100%, OR
- Duplex: systolic velocity of >300 cm/sec, OR
- Core lab approved MRA, OR
- Core lab approved CTA
Primary Endpoint

- Composite of major cardiovascular or renal events:
  - Cardiovascular or Renal Death
  - Stroke
  - Myocardial Infarction
  - Heart Failure Hospitalization
  - Progressive Renal Insufficiency
  - Permanent Renal Replacement Therapy
Primary endpoint analyzed as time to the first primary endpoint event on an intent-to-treat basis.

- 16 participants excluded from a single site where scientific integrity issues of consent and eligibility were noted, and the data was administratively withdrawn.

Sample size selected to provide 90% power to test hypothesis that stenting reduced the incidence of the primary endpoint by 25%.
Screening and Enrollment

Screened Patients (N=5322)

Not Randomized (N=4375)

Randomized (N=947)

Patient Refusal (N=801)
Physician Preference (N=210)
Anatomic Exclusion (N=1866)
Clinical Exclusion (N=628)
Other Reasons (N=870)

Stent Plus Medical Therapy (N=467)
- Received Stent (N=434, 94.6%)
- Not Attempted (N=9, 1.9%)
- False + Non-Invasive Study (N=13, 2.8%)
- Failed Stent (N=3, 0.9%)

Excluded for Scientific Integrity (N=8)

Included in Primary Analysis (N=459)

Medical Therapy Only (N=480)
- Cross Over to Stent before Endpoint (N=12, 2.5%)

Excluded for Scientific Integrity (N=8)

Included in Primary Analysis (N=472)
Baseline Characteristics

- No significant differences in clinical and angiography characteristics
- Approximately 20% global ischemia
- Stenosis severity similar to FDA approval trials 1-3


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stent + Medical (N = 459)</th>
<th>Medical (N = 472)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.3 ± 9.4</td>
<td>69.0 ± 9.0</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>51.0</td>
<td>48.9</td>
</tr>
<tr>
<td>White race (%)</td>
<td>91.5</td>
<td>90.9</td>
</tr>
<tr>
<td>Black race (%)</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.2 ± 5.3</td>
<td>28.7 ± 5.7</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>149 ± 23.2</td>
<td>150.4 ± 23.0</td>
</tr>
<tr>
<td>Estimate GFR (ml/minute)</td>
<td>58.0 ± 23.4</td>
<td>57.4 ± 21.7</td>
</tr>
<tr>
<td>Medical history and risk factors (%)</td>
<td></td>
<td></td>
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<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 year</td>
<td>28.0</td>
<td>32.2</td>
</tr>
<tr>
<td>Angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% stenosis (core lab)</td>
<td>67.3 ± 11.4</td>
<td>66.9 ± 11.9</td>
</tr>
<tr>
<td>% stenosis (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>
Stenosis reduced to: 16±8% (p<0.001)

- Stents per vessel 1.04±0.20
- Embolic protection device, per vessel 124/543 (22.8%)

Procedural Angiographic complications

- Dissection 11/495 (2.2%)
- Branch vessel occlusion 6/495 (1.2%)
- Angiographic distal embolization 6/495 (1.2%)
- Wire perforation 1/495 (0.2%)
- Vessel rupture 1/495 (0.2%)
- Pseudoaneurysm 1/495 (0.2%)
Results: Peri-Procedural Clinical Complications

- No participant required dialysis within 30-days of randomization.
- 1/459 (0.2%) in Stent + Medical Therapy initiated dialysis between 30 and 90-days after randomization.
- 1 stroke resulting in death, day of randomization, Medical Therapy Only group.
Stent + Medical Therapy: 35.1%, 3-years
Medical Therapy: 35.8%, 3-years
HR 0.94 [0.76-1.17], p = 0.58
Results: Secondary Endpoints

CV + Renal Death
- P=ns

Stroke
- P=ns

Myocardial Infarction
- P=ns

Heart Failure
- P=ns

Progressive Renal Insufficiency
- P=ns

Renal Replacement
- P=ns
## Results: Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Stent N (%)</th>
<th>Medical Therapy N (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>161/459 (35)</td>
<td>169/472 (36)</td>
<td>0.94 (0.76, 1.17)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Creatinine</strong></td>
<td></td>
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<tr>
<td>&gt; 1.6 (mg/dl)</td>
<td>43/84 (51)</td>
<td>34/87 (39)</td>
<td>1.35 (0.86, 2.11)</td>
<td>0.80</td>
</tr>
<tr>
<td>≤ 1.6 (mg/dl)</td>
<td>112/352 (32)</td>
<td>128/367 (35)</td>
<td>0.87 (0.67, 1.12)</td>
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<tr>
<td><strong>MDRD eGFR</strong></td>
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</tr>
<tr>
<td>≥ 45 (ml/min/1.73 m^2)</td>
<td>91/288 (32)</td>
<td>105/311 (34)</td>
<td>0.93 (0.70, 1.23)</td>
<td>0.17</td>
</tr>
<tr>
<td>&lt; 45 (ml/min/1.73 m^2)</td>
<td>64/148 (43)</td>
<td>57/143 (40)</td>
<td>0.98 (0.68, 1.40)</td>
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<tr>
<td><strong>Diabetes</strong></td>
<td></td>
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<tr>
<td>Yes</td>
<td>69/148 (47)</td>
<td>66/162 (41)</td>
<td>1.15 (0.82, 1.61)</td>
<td>0.64</td>
</tr>
<tr>
<td>No</td>
<td>92/309 (30)</td>
<td>103/310 (33)</td>
<td>0.84 (0.64, 1.12)</td>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
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<tr>
<td>Male</td>
<td>75/234 (32)</td>
<td>78/231 (34)</td>
<td>0.89 (0.65, 1.22)</td>
<td>0.32</td>
</tr>
<tr>
<td>Female</td>
<td>86/225 (38)</td>
<td>91/241 (38)</td>
<td>0.99 (0.74, 1.33)</td>
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<tr>
<td><strong>Global Ischemia</strong></td>
<td></td>
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<tr>
<td>Yes</td>
<td>39/89 (44)</td>
<td>20/51 (39)</td>
<td>1.07 (0.62, 1.83)</td>
<td>0.62</td>
</tr>
<tr>
<td>No</td>
<td>119/356 (33)</td>
<td>106/264 (39)</td>
<td>0.78 (0.60, 1.01)</td>
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<tr>
<td><strong>Race</strong></td>
<td></td>
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<tr>
<td>African American</td>
<td>11/29 (33)</td>
<td>10/30 (33)</td>
<td>1.01 (0.42, 2.43)</td>
<td>0.55</td>
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<tr>
<td>Other</td>
<td>126/356 (35)</td>
<td>136/357 (38)</td>
<td>0.88 (0.69, 1.13)</td>
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<tr>
<td><strong>Baseline SBP</strong></td>
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<td></td>
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<tr>
<td>&gt; 160 (mmHg)</td>
<td>66/148 (45)</td>
<td>58/139 (42)</td>
<td>1.02 (0.71, 1.45)</td>
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<tr>
<td>≤ 160 (mmHg)</td>
<td>95/309 (31)</td>
<td>108/328 (33)</td>
<td>0.90 (0.68, 1.18)</td>
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<tr>
<td><strong>Age</strong></td>
<td></td>
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<tr>
<td>&gt; 70 (years)</td>
<td>91/226 (40)</td>
<td>94/220 (43)</td>
<td>0.87 (0.65, 1.16)</td>
<td>0.56</td>
</tr>
<tr>
<td>≤ 70 (years)</td>
<td>70/233 (30)</td>
<td>75/252 (30)</td>
<td>1.00 (0.72, 1.39)</td>
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<tr>
<td><strong>US Sites</strong></td>
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<tr>
<td>Yes</td>
<td>137/385 (36)</td>
<td>146/387 (38)</td>
<td>0.90 (0.71, 1.14)</td>
<td>0.38</td>
</tr>
<tr>
<td>No</td>
<td>27/74(32)</td>
<td>23/85(27)</td>
<td>1.22 (0.69, 2.16)</td>
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<tr>
<td><strong>Site Reported Max Stenosis</strong></td>
<td></td>
<td></td>
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<tr>
<td>&gt; 80%</td>
<td>77/198 (39)</td>
<td>64/166 (39)</td>
<td>0.93 (0.67, 1.30)</td>
<td>0.66</td>
</tr>
<tr>
<td>≤ 80%</td>
<td>77/231 (33)</td>
<td>79/208 (38)</td>
<td>0.84 (0.61, 1.14)</td>
<td></td>
</tr>
</tbody>
</table>
Results: Systolic Blood Pressure

P = 0.03
Conclusion

- Renal artery stenting did not confer a benefit to the prevention of clinical events when added to comprehensive, multi-factorial medical therapy in people with atherosclerotic renal artery stenosis and hypertension or chronic kidney disease.

Now available at: www.NEJM.org
Acknowledgements