Renal Artery Stenosis:
New View on a Difficult Clinical Problem

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Potential causes of renal artery stenosis

- **Atherosclerosis**
- **Fibromuscular dysplasia**
  - Medial (string-of-beads appearance)
  - Nonmedial (unifocal or tubular lesions)
- **Arteritis**
  - Takayasu arteritis
  - Polyarteritis nodosa
  - Kawasaki disease
- **Rare diseases (mostly reported in children)**
  - Familial diseases: type 1 neurofibromatosis, tuberous sclerosis, pseudoxanthoma elasticum, vascular Ehlers–Danlos syndrome, Alagille syndrome, Marfan syndrome, Williams syndrome, Turner syndrome
  - Idiopathic mid-aortic syndrome
- **Miscellaneous causes**
  - Renal artery spasms induced by sympathomimetic agent or ergot alkaloid abuse
  - Segmental arterial mediolysis
  - Extrinsic compression

Plouin P. et al. Nat Rev Nephrol 2011; 6, 151-159
Atherosclerotic renovascular hypertension

After angioplasty

after stent implantation

The "string-of-beads" feature in medial fibromuscular dysplasia

Plouin P. et al., Orphanet J. Rare Dis. 2007, 2: 28
Stenosios of the transplanted kidney, before and after successful angioplasty
Endovasular aortic grafts as a cause of renal obstruction

Unadjusted hazard ratios, with 95% confidence intervals, for atherosclerotic renovascular disease (ARVD) by calendar year, with 1992 as reference category

Kalra P. et al., Kidney Int., 2010; 77, 37–43
Frequency of atherosclerotic renovascular hypertension in patients during arteriography of aorta, peripheral artery or coronaryography.
Frequency of renal artery stenosis in patients with high risk renovascular hypertension

- CAG; consecutive subjects [4,20-27]
- Suspected renovascular hypertension [10,12-16]
- CAG and suspected renovascular disease [32-34]
- CAG and hypertension [28-31]
- DM with hypertension [17-19]
- Peripheral vascular disease [8,37-46]
- Abdominal aortic aneurysm [8,40,44]
- End-stage renal failure [48]
- Congestive heart failure [36]

CAG, coronary angiography

Pooled prevalence rate (%)
Correlation between severity of coronary heart disease and frequency of renal artery stenosis

- 1-vessel disease (n = 2248) - 5.5%
- 2-vessel disease (n = 2008) - 9.7%
- 3-vessel disease (n = 2400) - 15.1%

*P < 0.0001*

Prevalence of RAS among patients with other forms of atherosclerosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>RAS prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>10%</td>
</tr>
<tr>
<td>Carotid artery disease</td>
<td>19%</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>6%-40%</td>
</tr>
<tr>
<td>MI</td>
<td>12%</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>20%-38%</td>
</tr>
<tr>
<td>Iliac and lower extremity occlusive disease</td>
<td>21%-49%</td>
</tr>
</tbody>
</table>
1. What are the differences in the pathogenesis of hypertension in patients with unilateral or bilateral renal artery stenosis?

2. What is the critical degree of renal artery stenosis considered as a hemodynamically important in the pathogenesis of renovascular hypertension?

3. What are the most important clinical symptoms and diagnostic tests in patients with renovascular hypertension?

4. How to treat renovascular hypertension?
What you should remember after this lecture

1. What are the differences in the pathogenesis of hypertension in patients with unilateral or bilateral renal artery stenosis?

2. What is the critical degree of renal artery stenosis considered as a hemodynamically important in the pathogenesis of renovascular hypertension?

3. What are the most important clinical symptoms and diagnostic tests in patients with renovascular hypertension?

4. How to treat renovascular hypertension?
Angiotensin II dependent hypertension

UNILATERAL RENAL ARTERY STENOSIS

Reduced renal perfusion

\[ \uparrow \text{Renin-angiotensin system (RAS)} \]
\[ \uparrow \text{Renin} \]
\[ \uparrow \text{Angiotensin II} \]
\[ \uparrow \text{Aldosterone} \]

Angiotensin II–dependent hypertension

Increased renal perfusion

\[ \text{Increased } \text{Na}^+ \text{ excretion (pressure natriuresis)} \]

\[ \text{Suppressed RAS} \]

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

Lateraled features, e.g., renin levels in renal veins, captopril-enhanced renography
Volume dependent hypertension

BILATERAL RENAL ARTERY STENOSIS

Bilateral

Stenosis of solitary kidney

Reduced renal perfusion

↑ Renin-angiotensin system (RAS)
↑ Renin
↑ Angiotensin II
↑ Aldosterone

Impaired Na⁺ and water excretion

Inhibit RAS

Volume expansion

Normal or low angiotensin II

Increased arterial pressure

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
What you should remember after this lecture

1. What are the differences in the pathogenesis of hypertension in patients with unilateral or bilateral renal artery stenosis?

2. What is the critical degree of renal artery stenosis considered as a hemodynamically important in the pathogenesis of renovascular hypertension?

3. What are the most important clinical symptoms and diagnostic tests in patients with renovascular hypertension?

4. How to treat renovascular hypertension?
Clinical classification of renal artery stenosis

Grade I: Renal artery stenosis present, but no clinical manifestations (normal blood pressure and normal renal function).
Grade II: Renal artery stenosis present, but patients have medically controlled hypertension and normal renal function.
Grade III: Renal artery stenosis present and patients have evidence of abnormal renal function, medically refractory hypertension, or evidence of volume overload.

Renal blood flow with canine renal artery constriction

Goldblatt et al., 1934
Decrease of blood pressure (A) and blood flow (B) along stenoted artery in experimental conditions

Data indicate that 70-80% stenosis can show hemodynamically detectable changes

Hemodynamic consequences of renal artery stenosis

What you should remember after this lecture

1. What are the differences in the pathogenesis of hypertension in patients with unilateral or bilateral renal artery stenosis?

2. What is the critical degree of renal artery stenosis considered as a hemodynamically important in the pathogenesis of renovascular hypertension?

3. What are the most important clinical symptoms and diagnostic tests in patients with renovascular hypertension?

4. How to treat renovascular hypertension?
Clinical criteria for pursuing the initial diagnosis of renovascular disease

Clinical findings associated with renovascular disease
Onset hypertension before age of 30 years old
Accelerated, resistant, malignant hypertension
Deterioration of renal function in response to angiotensin-converting enzyme inhibitors or angiotensin-receptor blocker
New onset of hypertension after 50 years of age (suggestive of atherosclerotic renal artery stenosis)
Asymmetric kidneys with more than 1.5 cm of difference in the size and otherwise unexplained loss of kidney function
Sudden unexplained pulmonary edema

Serum creatinine concentration increased on four occasions in association with angiotensin converting enzyme inhibition, leading to dialysis, then remained stable despite patient taking angiotensin converting enzyme inhibitor after dilation and stenting of right renal artery.

Renal arteriogram showing occlusion of left renal artery (left) and tight stenosis of right renal artery before (arrowed) and after stenting (right)
Serum creatinine concentration increased on four occasions in association with angiotensin converting enzyme inhibition, leading to dialysis, then remained stable despite patient taking angiotensin converting enzyme inhibitor after dilation and stenting of right renal artery.

Sensitivity and specificity of different diagnostic procedures in patients with RAS

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scyntygraphy after Captopril</td>
<td>81</td>
<td>78</td>
</tr>
<tr>
<td>Doppler ultrasonography</td>
<td>90</td>
<td>89</td>
</tr>
<tr>
<td>Magnetic resonance angiography</td>
<td>87</td>
<td>99</td>
</tr>
<tr>
<td>Spiral computed tomography</td>
<td>90-100</td>
<td>90-98</td>
</tr>
<tr>
<td>Intra arterial angiography</td>
<td>97-100</td>
<td>100</td>
</tr>
</tbody>
</table>
Scintigram obtained with Tc-99m MAG3 in patient with left renal artery stenosis before (a) and after administration of captopril (b)
Scintigram obtained with Tc-99m MAG3 inpatient with right renal artery stenosis before(a) and after administration of captopril(b)

*(Sequential images obtained at 2-minute intervals)*

(a. before administration of captopril  b. after administration of captopril)
High peak systolic velocity of 3.36 m/s is obtained within in the stenosis. The green color indicates high blood flow velocity with turbulences near the stenosis. Low mean resistive index (RI=47) of the right kidney is an indirect sign of significant stenosis.

Krumme B. and Donauer J. Kidney Int. 2006: 70:1543-7
How to diagnose NSCL / GS:
Measuring renal resistance index (RI)

- Segmental renal artery
- $RI = (1 - (V_{\text{min}} / V_{\text{max}})) \times 100$
Mean (±SEM) change in MAP and the number of antihypertensive drugs taken after the correction of RAS, according to resistance index values before revascularization.
Mean changes in creatinine clearance after the correction of RAS, according to resistance index values before revascularization.
Univariate odds ratio for a worsening of renal function after correction of RAS, with 95% confidence intervals associated with various factors before revascularization.
Blood pressure and renal function response after revascularization based on resistive index by duplex ultrasound

<table>
<thead>
<tr>
<th>Reference</th>
<th>Definition of outcome</th>
<th>RI</th>
<th>BP outcome</th>
<th>RF outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santos et al. [14]</td>
<td>No benefit (NB), improvement (I) or cure (C) of BP</td>
<td>&gt;0.8</td>
<td>5% improvement</td>
<td>No difference of RF in either group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.8</td>
<td>70% improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.5% cure</td>
<td></td>
</tr>
<tr>
<td>Radermacher et al. [13]</td>
<td>Mean arterial BP: ↓ by 10% after RV RF: worsening of CrCl by 10% after RV</td>
<td>&gt;0.8</td>
<td>3% improvement</td>
<td>80% RF worsening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.8</td>
<td>94% improvement</td>
<td>3% RF worsening</td>
</tr>
<tr>
<td>Zeller et al. [16]</td>
<td>Mean arterial BP: ↓ by 5 mmHg after RV RF:↓ Scr by 10% at 6 months after RV</td>
<td>&gt;0.8</td>
<td>Improvement of BP is similar in all groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.7–0.8</td>
<td>80% improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.8</td>
<td>Improvement of Scr is similar in all groups</td>
<td></td>
</tr>
<tr>
<td>Garcia-Criado et al. [15]</td>
<td>Diastolic BP: ↓ by 15% after RV RF:↓ Scr by 20% after RV</td>
<td>&gt;0.8</td>
<td>50% improvement</td>
<td>29% improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.8</td>
<td>85% improvement</td>
<td>45% improvement</td>
</tr>
</tbody>
</table>

• High-resolution 3D gadolinium MRA of the renal arteries using integrated parallel acquisition techniques (iPAT).

• Within 23 s, a data set with a voxel size of 0.8x0.8x0.9 mm spatial resolution was acquired on a high performance imaging system (Magnetom Sonata, Siemens, Erlangen, iPAT factor 2).

• Note that even this high-grade stenosis can be visualized in the in-plane view (A) as well as in orthogonal cuts of the vessel cross-section (B).

• This three-dimensional multiplanar assessment allows a reduction in the overall misinterpretation of the degree of stenosis.

Schoenberg et al. Nephrol Dial Transplant 2003; 18: 1252-1256
Computed tomography angiogram of atherosclerotic renal artery stenosis of the left kidney
Multi phase MRI vs digital substraction angiography

Schoenberg S. et al., 2002
An example of **IVUS** examination directly after PTRA (a) and in follow-up (b)

The principle of BOLD - MRI
Blood Oxygen-Level-Dependent Magnetic Resonance Imaging

The ratio of oxyhemoglobin (diamagnetic) to deoxyhemoglobin (diamagnetic) is proportional to the partial pressure of oxygen (pO2) of blood.

L. Hofmann et al. Kid Int 2006; 70: 144-150
M. Uder et al. Nephrologe 2009; 4:26-32
BOLD - MRI for the assessment of renal oxygenation in humans: Acute effect of nephrotoxic Xenobiotics

- The magnetic effect of different oxygen level is leading to signal attenuation on T2*-weighted MRI-images.
- BOLD-signal estimated by transverse relaxation rate $R_2^*$ (1/T2) can be considered as a sensitive indicator tissue (pO2).

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L. Hofmann et al. Kidney Int 2006; 70: 144-150
Blood-oxygen-level-dependent (BOLD) magnetic resonance (MRI) of kidneys

Figure 5 | Blood-oxygen-level-dependent (BOLD) magnetic resonance (MR) images with parametric maps depicting R2* levels that correspond to tissue levels of deoxyhemoglobin in axial images of the kidneys. Both of these kidneys had high-grade renal arterial stenosis with velocities > 400 cm/s. Serum creatinine was > 3.6 mg/dl, although the patient was treated with angiotensin receptor blockers and diuretics. The larger kidney (right panel, left kidney) has well-preserved cortical oxygenation (blue zone) and a normal corticomedullary oxygen gradient. The smaller kidney (left panels) is developing overt cortical hypoxia with rising R2* levels and expanding zone of medullary hypoxia (inner red zone). These functional imaging tools may assist in defining kidneys that are ‘at risk’ from critical vascular occlusion, yet remain ‘salvageable’ from the point of view of restoring renal blood flow (see text).
Diagnostic procedure in patients with suspected renal artery stenosis

• The past:
  – Captopril test
  – Captoprilu renogram

• The present time:
  – Colour Doppler Sonography (CDS)
  – Computed Tomography Angiography (CTA)
  – Magnetic Resonance Tomography Angiography (MRA)

• The future
  – BOLD- Magnetic Resonance Imaging (MRI)
What you should remember after this lecture

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4. How to treat renovascular hypertension?
Blood pressure changes after removing of clip in experimental renovascular hypertension.

Brown J.J. et al., Lancet, 1976, 1, 1219-1221
Generalized atherosclerosis

- Hypertension (systemic)
- Renal artery stenosis
- Intrarenal atheroembolism

Renal tissue hypoxia

- ↑ Local renin synthesis
- ↑ Local Ang II production

↑ ROS
↑ PDGF-B
↑ TGF-β

glomerulosclerosis
↑ Interstitial fibrosis

vascular rarefaction in interstitium

↓ GFR

Factors favoring medical therapy and surveillance of renal artery stenosis

Controlled blood pressure with stable renal function.
Stable renal artery stenosis without progression on surveillance studies (e.g., serial duplex ultrasound).
Advanced age and/or limited life expectancy.
Extensive comorbidities that make revascularization too risky.
High risk or previous experience with atheroembolic disease.
Other concomitant renal parenchymal diseases that cause progressive renal dysfunction (e.g., diabetic nephropathy).

CV events are more frequent than ESRD in patients with atherosclerotic RAS

- Of 164 patients with RAS > 50% followed-up for 7.1 yr, 33 died from CV disease and 2 progressed to ESRD.
- Compared to the normal Swedish population, risk ratios for overall mortality and CV mortality were 3.3 and 5.7.
- Overall risk ratio for mortality in patients with RAS was higher than that of patients hospitalized for unstable angina and similar to that of patients with colon cancer.

Johansson et al., J Hypertens. 1999;17:1743
Rates of adverse cardiovascular events among Medicare patients in the United States

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence among patients with RAS (events per 1000 patient years)</th>
<th>Incidence in the general population (events per 1000 patient years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic heart disease</td>
<td>303.9</td>
<td>73.5</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>258.6</td>
<td>52.2</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>194.5</td>
<td>56.3</td>
</tr>
<tr>
<td>Cerebrovascular accident or Transient ischemic attack</td>
<td>175.5</td>
<td>52.9</td>
</tr>
<tr>
<td>Death</td>
<td>166.3</td>
<td>63.3</td>
</tr>
</tbody>
</table>
Factors favoring medical therapy and revascularization for renal artery stenosis

Progressive decline in GFR during treatment of hypertension. Failure to achieve adequate blood pressure control with optimal medical therapy. Rapid or recurrent decline in the GFR in association with a reduction in systemic pressure. Decline in GFR during therapy with ACE inhibitors or ARBs. Recurrent congestive heart failure in a patient in whom the adequacy of left ventricular failure does not explain the cause.

Prospective, randomised clinical trials comparing medical therapy with angioplasty (with or without stents)

<table>
<thead>
<tr>
<th>Location</th>
<th>EMMA France</th>
<th>SNRASC CG UK</th>
<th>DRASTIC The Netherlands</th>
<th>ASTRAL UK/Aust/NZ</th>
<th>STAR The Netherlands</th>
<th>NITER Italy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Pts (Intervent./Med Rx)</td>
<td>23/26</td>
<td>25/30</td>
<td>56/60</td>
<td>403/403</td>
<td>64/74</td>
<td>28/24</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>59.4</td>
<td>61.1</td>
<td>59.9</td>
<td>70.5</td>
<td>66.5</td>
<td>72.0</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>48.5</td>
<td>39.3</td>
<td>63.5</td>
</tr>
<tr>
<td>ASPVD (%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>40.5</td>
<td>40.0</td>
<td>46.2</td>
</tr>
<tr>
<td>Creatinine baseline (mg/dl)</td>
<td>1.2</td>
<td>1.8</td>
<td>1.3</td>
<td>2.0</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Bilat (%)</td>
<td>0</td>
<td>50.9</td>
<td>22.6</td>
<td>53.5</td>
<td>47.9</td>
<td>51.5</td>
</tr>
<tr>
<td>ACE/ARB at F/U (%)</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
<td>45</td>
<td>57</td>
<td>61</td>
</tr>
<tr>
<td>Crossover (%)</td>
<td>26.9</td>
<td>6.2</td>
<td>44</td>
<td>3.2</td>
<td>1.3</td>
<td>0</td>
</tr>
<tr>
<td>F/U mean (months)</td>
<td>6</td>
<td>12</td>
<td>12</td>
<td>33.6</td>
<td>24</td>
<td>43</td>
</tr>
</tbody>
</table>

Comment: Entry criteria
- ‘Unilateral only’
- ‘Resistant HTN’
- ‘Resistant HTN’
- ‘Uncertainty of benefit’
- ‘Renal insufficiency’
- ‘Resistant HTN/CRI’

Serum creatinine concentration at the end of follow-up in patients treated with percutaneous intervention or medical therapy only

<table>
<thead>
<tr>
<th>Source</th>
<th>Serum creatinine at end of follow-up</th>
<th>Weighted mean difference (95% CI)</th>
<th>Mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRASC</td>
<td></td>
<td>-0.16 (-0.63, -0.31)</td>
<td>1.9 (0.9)</td>
</tr>
<tr>
<td>ASTRAL</td>
<td></td>
<td>-0.21 (-0.42, 0.00)</td>
<td>2.2 (1.4)</td>
</tr>
<tr>
<td>NITER</td>
<td></td>
<td>-0.08 (-0.37, 0.53)</td>
<td>1.9 (0.9)</td>
</tr>
<tr>
<td>STAR</td>
<td></td>
<td>-0.10 (-0.37, 0.17)</td>
<td>1.8 (0.8)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>-0.14 (-0.29, 0.01)</td>
<td>1.9 (0.9)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2 = 0\%$
Test for overall effect: $P = 0.06$

Clinical outcomes of renal artery revascularization for atherosclerotic renal artery disease

**Serum creatinine concentration**

<table>
<thead>
<tr>
<th>Fall $\geq 1.0$ mg/dl</th>
<th>Same ($\Delta &lt; 1.0$ mg/dl)</th>
<th>Rise $\geq 1.0$ mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n=83$ (27.3%)</td>
<td>$n=160$ (52.6%)</td>
<td>$n=61$ (20.1%)</td>
</tr>
</tbody>
</table>

Progression of CKD after successful revascularisation

Figure 3 | Kaplan-Meier plots of freedom from requiring renal replacement therapy for 550 patients with variable pretreatment levels of estimated glomerular filtration rate (GFR) after technically successful renal artery angioplasty and stenting.
Renal angiograms (a, b) and serial serum creatinine values (c) during a 6-week time period obtained for a 62-years old diabetic patients with morbid obesity

Causes of treatment failure: cholesterol emobolism
Figure 1 | Angiographic images before and after renal artery stenting. (a) Guidewire placement beyond a high-grade proximal stenosis. (b) Stent deployed with filter-wire embolic protection device (EPD), shown after removal in (c). Embolic debris is visible in the distal section of the EPD.
ASTRAL Trial protocol

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
Mean stenosis = 76% (20-100%)
ASTRAL - Systolic and diastolic blood pressure in patients with renal artery stenosis treated with revascularization or medical therapy alone

A Systolic Blood Pressure

B Diastolic Blood Pressure

Number of Patients
Revascularization Medical therapy

ASTRAL - Renal function in patients with renal-artery stenosis treated with revascularization or medical therapy alone

A  Reciprocal of Serum Creatinine

B  Serum Creatinine

ASTRAL - Kaplan–Meier curves for the time to the first renal events

A First Renal Event

No. at Risk
Revascularization | 403 | 315 | 236 | 157 | 99 | 39
Medical therapy   | 403 | 319 | 233 | 145 | 84 | 37

Years since Randomization

ASTRAL - Kaplan–Meier curves for the time to the first cardiovascular events

B  First Cardiovascular Event

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Revascularization</td>
</tr>
<tr>
<td>0</td>
<td>403</td>
</tr>
<tr>
<td>1</td>
<td>278</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
</tr>
<tr>
<td>3</td>
<td>133</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
</tr>
</tbody>
</table>

Medical therapy: 51%
Revascularization: 49%

ASTRAL
Kaplan–Meier curves for overall survival

![Graph showing Kaplan-Meier survival curves for overall survival. The graph compares the survival rates between Revascularization and Medical therapy over different years since randomization. The number of patients at risk for each group at different time points is shown in the table below.

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>Revascularization</th>
<th>Medical therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>403</td>
<td>403</td>
</tr>
<tr>
<td>1</td>
<td>337</td>
<td>332</td>
</tr>
<tr>
<td>2</td>
<td>257</td>
<td>248</td>
</tr>
<tr>
<td>3</td>
<td>178</td>
<td>165</td>
</tr>
<tr>
<td>4</td>
<td>109</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>40</td>
</tr>
</tbody>
</table>

Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function – STAR Trial

140 patients with creatinine clearance less than 80 mL/min per 1.73 m² and ARAS of 50% or greater

## STAR-Trial - Participant characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Medication Group (n = 76)</th>
<th>Stent Group (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>67 (9)</td>
<td>66 (8)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>45 (59)</td>
<td>43 (67)</td>
</tr>
<tr>
<td>Vascular history, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any vascular disease</td>
<td>59 (78)</td>
<td>54 (84)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18 (31)</td>
<td>16 (30)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>18 (31)</td>
<td>15 (28)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7 (12)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>9 (15)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>30 (51)</td>
<td>26 (48)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>32 (54)</td>
<td>23 (43)</td>
</tr>
<tr>
<td>Current or past smoking</td>
<td>52 (68)</td>
<td>46 (72)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>15 (20)</td>
<td>20 (31)</td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean serum creatinine level (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>μmol/L</td>
<td>145 (51)</td>
<td>154 (60)</td>
</tr>
<tr>
<td>mg/dL</td>
<td>1.6 (0.58)</td>
<td>1.7 (0.68)</td>
</tr>
<tr>
<td>Mean estimated creatinine clearance (SD), mL/min per 1.73 m²</td>
<td>46 (16)</td>
<td>45 (15)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>73 (96)</td>
<td>63 (98)</td>
</tr>
<tr>
<td>Mean systolic blood pressure (SD), mm Hg</td>
<td>163 (26)</td>
<td>160 (25)</td>
</tr>
<tr>
<td>Mean diastolic blood pressure (SD), mm Hg</td>
<td>82 (12)</td>
<td>83 (13)</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of drug categories (SD)</td>
<td>2.9 (1.0)</td>
<td>2.8 (1.0)</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>23 (30)</td>
<td>21 (33)</td>
</tr>
<tr>
<td>Angiotensin II–receptor antagonists</td>
<td>18 (24)</td>
<td>17 (27)</td>
</tr>
</tbody>
</table>
### STAR-Trial - Primary and secondary endpoints

<table>
<thead>
<tr>
<th>End Point</th>
<th>Medication Group (n = 74)*</th>
<th>Stent Group (n = 62)*</th>
<th>Crude Hazard Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point, n (%)‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral or bilateral stenosis</td>
<td>16 (22)</td>
<td>10 (16)</td>
<td>0.73 (0.33–1.61)</td>
</tr>
<tr>
<td>Unilateral stenosis only</td>
<td>8 (20)</td>
<td>3 (9)</td>
<td>0.48 (0.13–1.81)</td>
</tr>
<tr>
<td>Bilateral stenosis only</td>
<td>8 (23)</td>
<td>7 (22)</td>
<td>0.95 (0.34–2.61)</td>
</tr>
<tr>
<td><strong>Secondary end points, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy-refractory hypertension</td>
<td>3 (4)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Malignant hypertension</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1 (1)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Cardiovascular morbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>3 (4)</td>
<td>1 (2)</td>
<td>0.39 (0.04–3.71)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3 (4)</td>
<td>3 (5)</td>
<td>1.16 (0.23–5.73)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>7 (9)</td>
<td>4 (6)</td>
<td>0.67 (0.20–2.28)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1 (1)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall deaths</td>
<td>6 (8)</td>
<td>5 (8)</td>
<td>0.99 (0.30–3.24)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>4 (5)</td>
<td>2 (3)</td>
<td>0.59 (0.11–3.25)</td>
</tr>
<tr>
<td>Periprocedural mortality§</td>
<td>0</td>
<td>2 (3)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Primary end point or death, n (%)</strong></td>
<td>22 (30)</td>
<td>15 (24)</td>
<td>0.81 (0.42–1.56)</td>
</tr>
</tbody>
</table>

**Primary end-point:** worsening of kidney function, defined as a 20% or greater decrease of eGFR

STAR-Trial

Survival curves for the primary end point during 2 years of follow-up

Survival curves for the primary end point plus death during 2 years of follow-up

STAR- Conclusions

• In this randomized trial, medical treatment of renal artery stenosis was compared with medical treatment plus stenting

• Patients who underwent stenting experienced no clear benefits, and several experienced complications, including 2 procedure-related deaths

• In this sample, stenting of stenosed renal arteries provided no clear benefit and caused harm, suggesting that patients with renal artery stenosis should be treated with medical therapy alone

Indications for renal revascularization—the landscape after the ASTRAL study

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Keywords: angioplasty; ischaemic nephropathy; renal artery stenosis; renovascular hypertension

Atherosclerotic renovascular disease (ARVD) is a common clinical condition. Fourteen percent of patients with refractory arterial hypertension over 70 years [1] and 12–16% of those with chronic kidney disease (CKD) starting renal replacement therapy have renal artery stenosis (RAS) [2,3]. ARVD is frequently associated both with arterial hypertension and CKD. As ARVD is a progressive disease, deterioration of kidney excretory function with potential CKD stage 5 necessitating renal replacement therapy is also expected. During the last 50 years ARVD was treated mainly by surgical revascularization [7]. In 1978 endovascular therapy was implemented for kidney revascularization [8]. Initially, it was balloon angioplasty and more recently balloon angioplasty with stent insertion [9]. Stent insertion in atherosclerotic RAS has improved the procedural efficacy of endovascular therapy up to 98%, overcoming the problem of elastic recoil or artery dissection and reduced the risk of re-stenosis (defined as over 50%) within 6–9 months from 26 to 17% [10]. Currently, there is no evidence suggesting that drug-eluting stents will further reduce the risk of renal artery re-stenosis. The alternative method to renal angioplasty with stent insertion is angio-plasty with intravascular brachytherapy [11]. The direct
PTA/OP in patients with atherosclerotic RAS

PRO

• Refractory hypertension
• Unilateral RAS of the single kidney or bilateral RAS
• Normal kidney size
• Acute kidney injury after ACEIs or ABRs
• Hypertension induced pulmonary oedema
• RAS with RI < 0,8
• Expected longer survival time
PTA/OP in patients with atherosclerotic RAS

- Normotension + normal renal function + contralateral renal artery without stenosis
- Expected short survival time

**CAVE:** Patients > 65 years with atherosclerotic RAS has 50% possibility to death within 2 years

- RAS with RI > 0.8 or with negative Captopril scintigraphy
- RAS with high grade chronic renal insufficiency (Ccreat < 30 ml/min) and kidney size < 8.0 cm)
Diagnostic work up of patients with suspected renal artery stenosis

Clinical signs:
- Severe hypertension and/or
- Progressive renal failure
- Unexplained lung edema

Laboratory examinations:
- Serum-creatinine (eGFR)
- Potassium
- Cholesterol

Imaging techniques:
- Colour Doppler sonography
- CT-angiography
- MR-angiography

Evaluation of blood pressure:
- Office blood pressure
- 24h-measurements
- antihypertensive drugs

No stenosis or Stenosis ≤ 75%
Medical Treatment

Stenosis > 75%
PTA/Stent

Difficult to treat hypertension:
- ≥ 4 antihypertensive drugs
- BP > 140/90mmHg in 24h
and / or
Rapid increase of creatinine in the last 6 months
Although no final conclusions can be drawn from ASTRAL because of some limitations in its design (patients with a strong indication for intervention were excluded from randomization) and lack of statistical power, intervention is at present not recommended in atherosclerotic renal artery stenosis if renal function has remained stable over the past 6–12 months and if hypertension can be controlled by an acceptable medical regimen (*Class III, Level B*). Suitable medical regimens can include RAS blockers, except in bilateral renal artery stenosis or in unilateral artery stenosis with evidence of functional importance by ultrasound examinations or scintigraphy.

2013 ESH/ESC Guidelines for the management of arterial hypertension

*The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)*

Mancia G. et al., *J. Hypertens.* 2013, 31:1281–1357
Future directions

- **CORAL** (Cardiovascular Outcome in Renal Atherosclerotic Lesions)
- Randomisation: Renal artery stenting plus optimal medical therapy vs optimal medical therapy alone
- Primary end-point: combination of cardiovascular or renal death, stroke, myocardial infarction, hospitalisation for congestive heart failure, doubling of serum creatinine, and need for renal replacement therapy
- Anticipated enrollment: 1080 patients in USA
- **Recruitment was initiated in 2005, end of enrollment - 2009, first results – 2011**
- **Study is NOT completed now!!! (2013)**

www.coralclinicaltrial.org
Thank you very much for your attention!

Andrzej Wiecek

Katowice/Poland
Trends in revascularisation in USA (angioplasty in patients with atherosclerotic RAS)

Kalra P et al., Kidney Int., 2010; 77, 37–43