# Renovascular diseases: current recommendations

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BNS 2024

SEMMELWEIS
EGYETEM 1769

# Case presentation: A 60-year-old female with resistant hypertension and worsening renal function (2016)

Past medical history: endometrioid adenocc. (PT2aN0M0), hysterectomy (2012), postop. irradiation (last treatment: 04/2013).

Urologic evaluation revealed right-sided, grade III hydronephrosis (2013).

- Renal scintigraphy: 24% l.d. and 76% l.s. isotope activity.
- eGFR: 45 ml/min/1.73m$^2$
- A double J catheter insertion was planned, but the intervention was not successful.
- Considering her overall fine and afebrile condition, transrenal drain was not inserted.

2016: urologic control

- The right kidney had extremely thin parenchyma
- Renal scintigraphy: 0% l.d. and 100% l.s. isotope activity.
- eGFR: 38 ml/min/1.73m$^2$

# Case presentation: A 60-year-old female with resistant hypertension and worsening renal function (2016)

Nephrology outpatient unit

System review: Afebrile. She had no loss of consciousness. No cough or dyspnea. No chest or abdominal pain. Appetite maintained, weight stable (75 kg). No nausea or vomiting. Passes stool regularly, stool is not bloody or black. No need of laxatives. No dysuria or urgency, no visible blood in urine. Minimal leg swelling.
Home BP: 120-140 mmHg SBP (according to diary).

Medications: perindopril/indapamide 1*5/1.25mg, nebivolol 1*2.5mg, rilmenidine 1*1mg, doxazosine 1*4mg, furosemide occasionally
CAVE: CCBs (profound leg swelling)

Laboratory:
wbc/hgb/plt: 4.4/115/228 Na/K:137/4.8 creat/BUN:132/6.9
Urine: SG:1005, pH:7,0, protein:neg, sediment:neg.

Status: RR: 161/95 repeatedly 175/92 mmHg, pulse rate 60-62/min, reg.

# Case presentation: A 60-year-old female with resistant hypertension and worsening renal function (2016)

Hospitalization

She arrives at the hospital for the revision of her blood pressure control. In the past weeks she often measured SBP over 200 mmHg, accompanied by headache. GP changed her antihypertensive treatment, without therapeutic success.

Dg.: Resistant hypertension

Endocrine tests:
TSH: 1.195 mU/L,
Renin: 4.01(H) ng/mL/hour; Aldosterone: 6.2 ng/dl
Cortisol = 447.0 nmol/l
Metanephrine 75.1 (64 - 302 mcg/24h), Normetanephrine 244 (162 - 527 mcg/24h)

ABPM after changing treatment (ACE-inhibitor dose elevated): 24-hour average 130/70 mmHg, daily average 128/69 mmHg, nighttime average 131/70 mmHg, pulse 68/min, diurnal index -2/-1 %

# Case presentation: A 60-year-old female with resistant hypertension and worsening renal function (2016)

PROBLEM: eGFR : 38 ->23 ->15 ml/min/1.73m2

What to think of? Renal artery stenosis

Drug therapy modified: ~~Perindopril /indapamide~~, nebivolol 1*2.5mg, rilmenidine 1*1mg, doxazosine 2*4mg, furosemide 1*40mg, spironolactone 1*25mg, isosorbide mononitrate 1*40mg
eGFR: 17 -> 20 -> 34 ml/min/1.73m2

MRI angiography
The right kidney exhibits hydronephrosis, the renal pelvis is wide, the cortex is 5 mm thin. Kidney size is 131x97 mm, and the kidney compresses the inferior vena cava slightly. The right-sided renal artery receives contrast material sparsely. The ureter is diffusely wider (16mm), and curvaceous, the uretero-vesical junction was not visible.

The left kidney has normal size and structure, and the thickness of the parenchyma is maintained. The lower pole of the kidney contains a 5 mm cortical cyst. The uptake of contrast material is regular. Hydronephrosis cannot be detected. The left renal artery contains a 5 mm long, severe stenosis immediately after its origin. Polar renal artery cannot be identified. Venous outflow is regular.

# Case presentation: A 60-year-old female with resistant hypertension and worsening renal function (2016)

## Conservative treatment vs. intervention ?

No significant difference

- in blood pressure (EMMA 1998, DRASTIC 2000)
- in renal function (STAR 2009, ASTRAL 2009)
- in left ventricular mass index (RASCAD 2012)
- in all-cause mortality / CV events /dialysis (NITER 2005)
- in adverse fatal /non-fatal CV /renal events (CORAL 2014)

Conservative treatment applied without radiologic / surgical intervention

eGFR: 43 – 41 – 40 – 45 – 44 – 43 – 46 ml/min/1.73m$^2$ (2017-2023)
Office blood pressure: 115/70 mmHg (2023.10)

# Renal artery stenosis / atherosclerotic renovascular disease

## Questions

- When to think of renal artery stenosis ? Only in case of red flags present ?
- Which imaging method to choose ?
- What to do with RAS-inhibition ?
- When to apply radiologic intervention ?

## Answer sources


- Hicks et al.: Atherosclerotic renovascular disease: A KDIGO (Kidney Disease: Improving Global Outcomes) controversies conference. AJKD 79:289-301, 2021
- Bhalla et al.: Revascularization for renovascular disease: a scientific statement from the American Heart Association. Hypertension 79:e128-e143, 2022
- Sarafidis et al.: Atherosclerotic renovascular disease: a clinical practice document by the European Renal Best Practice (ERBP) board of European Renal Associaton (ERA) and the Working Group Hypertension and the Kidney of the European Society of Hypertension (ESH). NDT 38:2835-2850, 2023

# When to think of renal artery stenosis / atherosclerotic renovascular disease?

## Hypertension

Prevalence:

- 1% in mild hypertension, 14-24% in severe or resistant hypertension (ERA/ESH)
- 0.1-5% in all hypertensives (AHA)
- 20% in hypertension + diabetes (KDIGO)

Second most common cause of secondary hypertension. No race differences.

Red flags: sudden onset, grade III hypertension, resistant hypertension

## Atherosclerosis

Prevalence:

- 12-45 % in patients with PAD, 5-30 % in patients with CAD (ERA/ESH, KDIGO)
- 14-40 % in patients with PAD (AHA)

# When to think of renal artery stenosis / atherosclerotic renovascular disease (ARVD)?

## Heart failure

Prevalence:

- < 5% in normal echocardiography (KDIGO)
- 48%  in patients referred for CABG (KDIGO)
- 54 %  in patients with HF and < 40% EF, 68% in patients with HF + CKD (ERA/ESH, KDIGO, AHA)

Red flags: flash pulmonary edema, repeated hospitalization for decompensation with preserved LV function on echocardiography

## Chronic kidney disease

5-22% in patients with >50 yrs + advanced CKD, 11-22% in dialyzed population (KDIGO, ERA/ESH, AHA)

Red flags: atrophic kidney, size difference > 1.5 cm between kidneys, unexplained rapid AKI, eGFR decline > 30% after ACEI/ARB treatment initiation

**ARVD is a common disease, and the presence of certain clinical phenotypes (red flags) should prompt investigation**

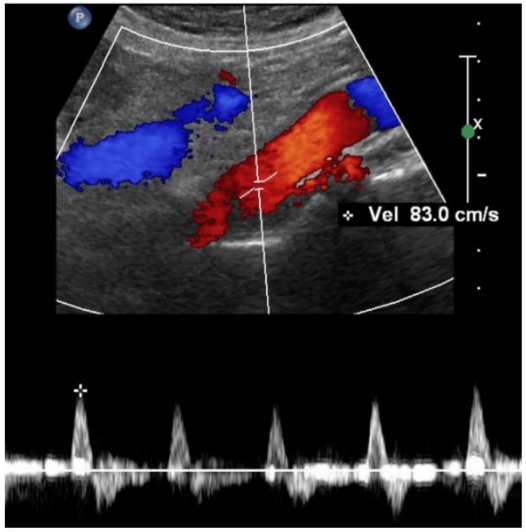
# How to investigate patients with potential renal artery stenosis / ARVD ?

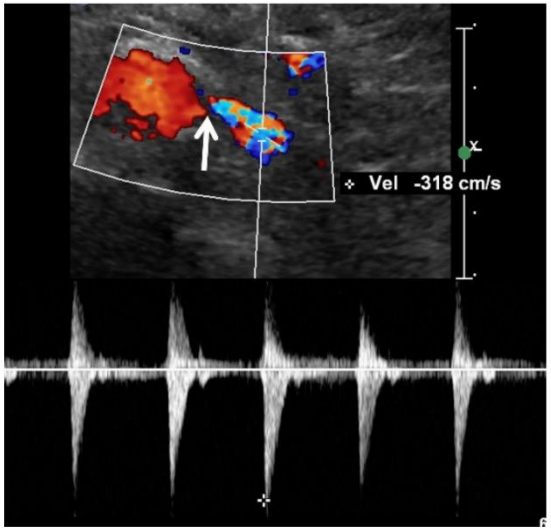
## Duplex US

91-100 % sensitivity, 82-91% specificity

Pros: inexpensive, noninvasive, provides data about kidney viability

Cons: requires expert radiologist, limited by high BMI, time-consuming




*Park BK, J. Clin Med., 2022*

Peak systolic velocity > 200 cm/s (95% sensitivity for >50% stenosis)

Renal-to-aorta PSV > 3.5 (92% sensitivity for > 60% stenosis)

Renal resistive index < 0.8 - possible viability of renal parenchyma

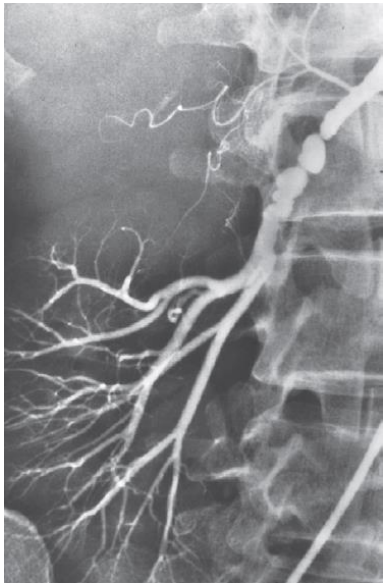
# How to investigate patients with potential renal artery stenosis / ARVD ?

## Multidetector CT angiography

64-96 (90-96) % sensitivity, 90-92 % specificity

Pros: rapid acquisition, allows detection of accessory renal arteries

Cons: radiation, requires iodinated contrast



*Hicks CW, AJKD, 2021*

Risk of contrast nephropathy ~ 5% even in CKD IV.

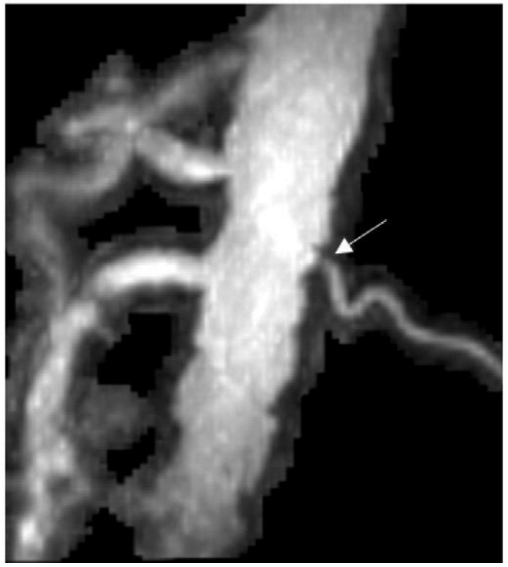
# How to investigate patients with potential renal artery stenosis / ARVD ?

## MR angiography

94-97 % sensitivity, 85-93 % specificity

Pros: no radiation / iodinated contrast needed

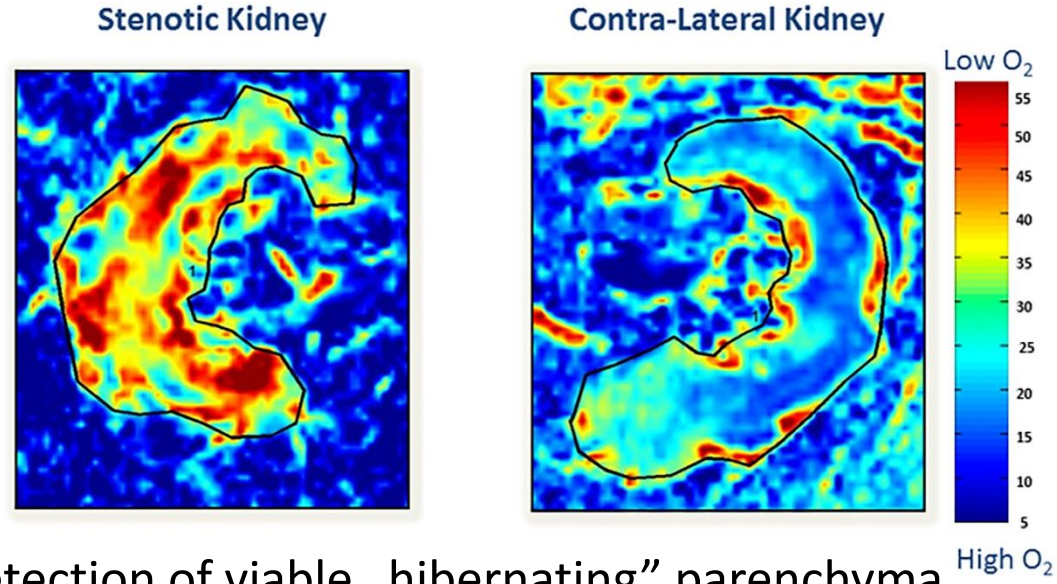
Cons: long acquisition time, may overestimate stenosis



*Hicks CW, AJKD, 2021*

Risk of nephrogenic systemic fibrosis is < 0.07% in CKD IV-V.

## BOLD-MRI




*Hermann SM, Endocrinol Metab Clin North Am, 2019*

Detection of viable „hibernating" parenchyma

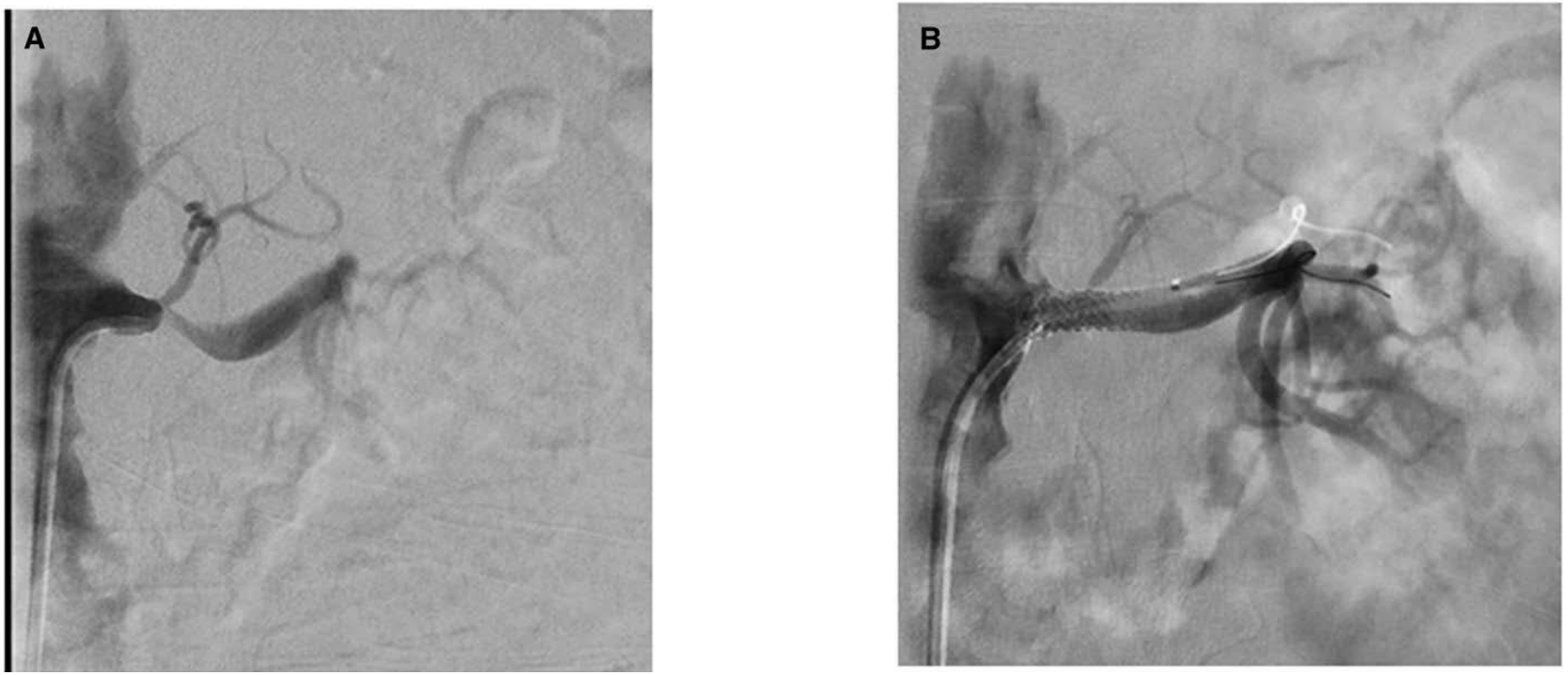
# How to investigate patients with potential renal artery stenosis / ARVD ?

## Catheter angiography

100 % sensitivity, 100 % specificity

Pros: gold standard, can evaluate and treat in the same setting, enables measurement of pre- and postintervention gradients

Cons: invasive, requires iodinated contrast ($CO_2$ can be sustituted)




*Bhalla V, Hypertension, 2022*

# Renal artery stenosis and RAS inhibition

With regards to antihipertensive classes, ACEIs and ARBs are considered first-line options, as observational studies suggest that these agents can reduce mortality risk in patients with ARVD. … In cases of bilateral RAS or RAS in solitary kidneys, ACEIs and ARBs should generally be avoided and the patient evaluated directly for revascularization *(ERA/ESH)*

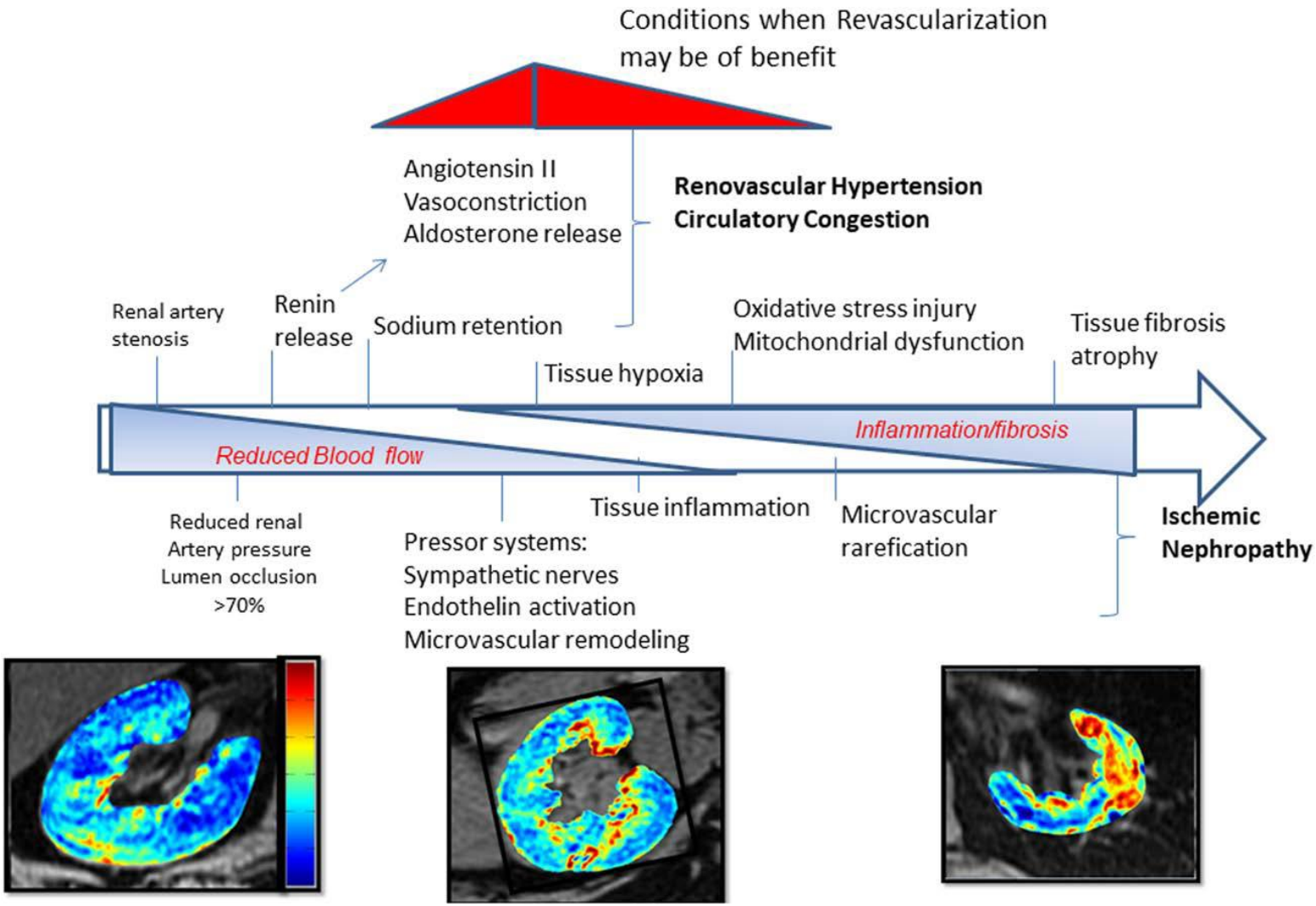
It is recommended that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers be continued until an increase in serum creatinine level of 30%-50% is noted. *(KDIGO)*

# Major limitations of previous RCTs

- Non-standardized inclusion criteria
- Inclusion of patients with mild / asymptomatic RAS, mild hypertension or advanced CKD
- Exclusion of patients with clinical presentation suggestive of critical RAS (recurrent flash pulmonary oedema, resistant hypertension, progressive renal function decline)
- Great variability between and within study protocols in imaging techniques of RAS diagnosis and evaluation, often resulting in overestimation of the degree of stenosis
- Enrolment delays
- Protocol revisions during the trial
- High crossover rates between treatment arms
- Low event rates of major outcomes

*(ERA/ESH)*

# When to apply radiologic intervention - the therapeutic window




*(AHA)*

# When to apply radiologic intervention – KDIGO 2021

## Definite indications

- Acute pulmonary edema or acute decompensations of heart failure and high-grade RAS
- Progressive CKD in high-grade (>75%) RAS (bilateral or solitary kidney)
- AKI due to acute renal artery occlusion or high-grade RAS
- ACEi or ARB intolerance in high-grade RAS
- Kidney transplant with RAS (symptomatic or asymptomatic)

## Possible indications

- Chronic heart failure and high-grade RAS
- Coexistence of progressive CKD and uncontrolled hypertension
- Asymptomatic high-grade RAS (either bilateral or supplying solitary kidney) with viable renal parenchyma (to prevent atrophy)
- New (<3 mo) dialysis patient with nonfunctioning but possibly viable kidney

## Nonindications

- Moderate to severe hypertension alone
- Asymptomatic unilateral or bilateral (<75%) RAS

# When to apply radiologic intervention – KDIGO 2021

Favorable features

- Timing of kidney function deterioration < 6 months
- Urine protein-to-creatinine ratio < 20 mg/mmol (<200 mg/g)
- Distict cortex on ultrasound, presence of corticomedullary differentiation
- Renal resistive index < 0.8
- Renal artery length > 8 cm

# When to apply radiologic intervention – AHA 2022

- High-risk clinical syndromes
  - Rapidly progressive hypertension
  - Rapidly declining estimated glomerular filtration rate
  - Flash pulmonary edema
- Bilateral renal artery stenosis with progressive loss of renal functional mass
- Fibromuscular dysplasia with hypertension
- Single native kidney renal artery stenosis
- Special populations:
  - Renal allograft: transplant renal artery stenosis with or without CNIs
  - Episodic, circulatory congestion with bilateral atherosclerotic renovascular disease
  - Progressive loss of glomerular filtration rate with occlusive atherosclerotic renovascular disease and no other kidney disease (ischemic nephropathy)
  - Aortic disease with renovascular protection as part of endovascular repair
  - Left-ventricular assist device
  - Radiation-induced renovascular disease with clinical syndromes
  - Other diseases: eg, Takayasu arteritis, extrinsic vascular compression
  - Pediatric patients with mid aortic syndrome or fibromuscular variants

# When to apply radiologic intervention – AHA 2022

Favorable features

- Absence of proteinuria
- Recent onset or exacerbation of hypertension (< 1 year)
- Identifiable activation of renin-angiotensin system

  hyperreninemia

  lateralization of renal vein renin
- Younger age
- Radiologic evidence of progressive renal artery occlusion
- Angiotensin-dependent glomerular filtration rate

# When to apply radiologic intervention – ESH/ERA 2023

## Strong indications

High-grade ( > 70%) RAS in association with one of the following criteria:

- Resistant hypertension
- New-onset or recently uncontrolled hypertension
- Acute pulmonary oedema or acute decompensated HF
- Rapid decline of eGFR (bilateral stenosis or solitary kidney)
- ACEI or ARB intolerance ( ≥30% eGFR reduction)
- Renal replacement treatment (with possibly viable renal parenchyma) if stenosis detected < 3 months after renal replacement treatment or if uncontrolled hypertension with multiple (five or more) antihypertensive agents
- AKI due to acute renal artery occlusion or high-grade stenosis
- Kidney transplant with RAS

## Moderately strong indications

High-grade ( > 70%) RAS in association with one of the following criteria:

- Chronic HF
- Asymptomatic but either bilateral or supplying a solitary kidney with viable renal parenchyma (non-atrophic kidney, distinct renal cortex)

# What to focus on in future studies – ESH/ERA 2023

## Intervention

**When** - Studies establishing the optimal timeline of revascularization to avoid delay-related ineffectiveness

**Whom** - Studies identifying predictors of PTRA benefit

**How** - Studies testing the impact of functional non-invasive imaging, such as BOLD MRI, to identify patients more likely to benefit from revascularization

**Subject populations** - RCTs enrolling patients with haemodynamically significant ARVD and high-risk clinical presentations, with true renovascular hypertension rather than patients with primary hypertension and incidental RAS through a wider and more systematic use of the translesional pressure gradient. Studies examining the efficacy of PTRA on moderate versus advanced CKD

**Additional therapies** - Studies evaluating the efficacy of PTRA in combination with novel therapeutic strategies (e.g. targeting inflammation-related pathways, mesenchymal stem cells or angiogenic/growth factors)

## Conservative treatment

Studies including patients on newer agents as standard therapy (sacubitril-valsartan, SGLT2 inhibitors)

Thank you for the attention!