Approach to Secondary Hypertension

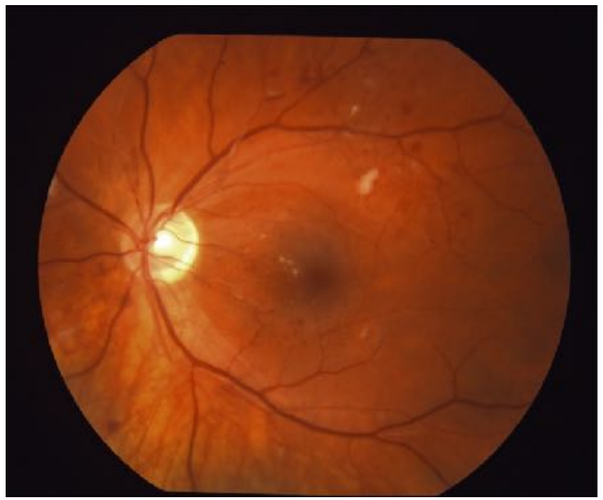
Col. Prof. Bancha Satirapoj, MD
Division of Nephrology
Department of Medicine
Phramongkutklao Hospital and College of Medicine

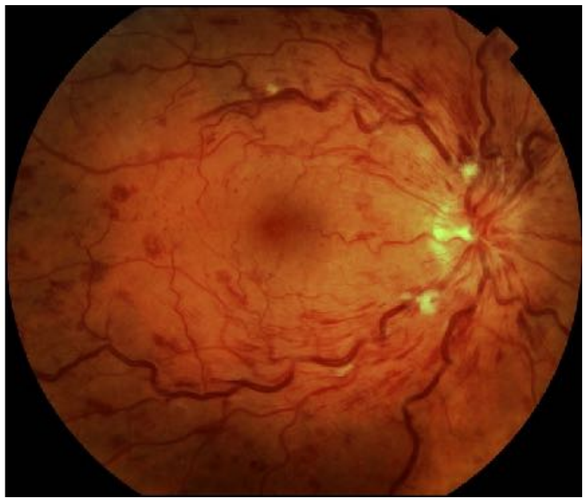
Disclosure information

- **Prof. Bancha Satirapoj, M.D.**
- **Scientific Advisor/Honoraria:**
  - **Astra Zeneca, Abbott Laboratories, Boehringer Ingelheim, Celltrion Healthcare, Fresenius Kabi, LG Life Sciences, Janssen-Cilag, Menarini, MSD, Novo Nordisk, Osotspa Taisho, Sanofi Aventis, Servier, Viatris and Zuellig Pharma**
- **DISCLAIMER**
  - **This presentation is intended for educational purpose for HCPs only. It may contain new science data which is currently not in approved package insert information and is not intended for off-label promotion.**

Case 1

- A 60-year-old man with T2DM, hypertension, and a history of ischemic limb presented with uncontrolled blood pressure (180/110 mmHg) and a progressive rise in creatinine from 1.5 to 3.0 mg/dL over six weeks.
- Current treatment includes: Losartan 100 mg/day, chlorthalidone 12.5 mg/day, amlodipine 10 mg/day, metoprolol 100 mg/day, atorvastatin 40 mg/day, and aspirin 81 mg/day.
- How to approach in this patients?





ESC European Society of Cardiology

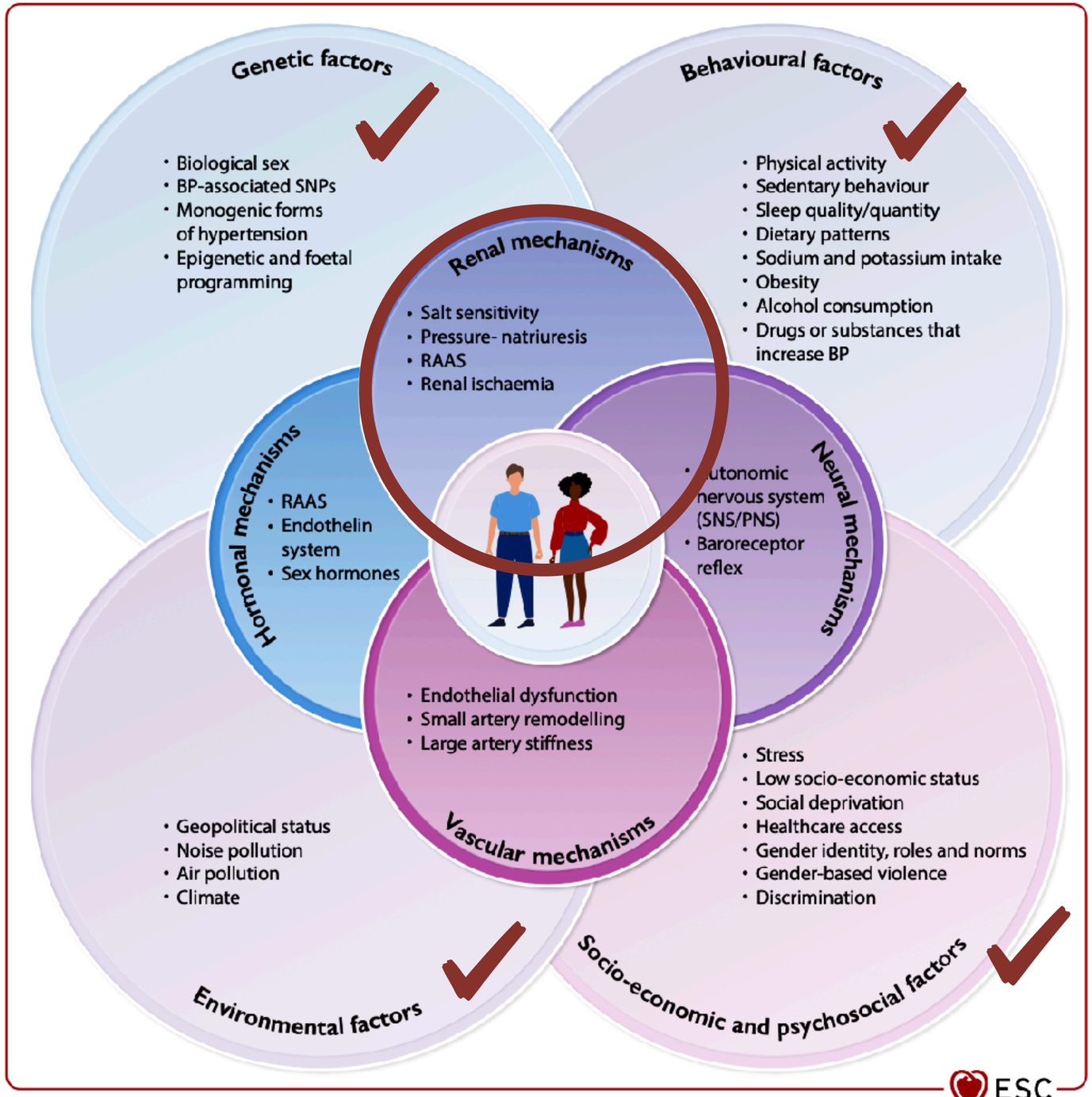
European Heart Journal (2024) **00**, 1–107
https://doi.org/10.1093/eurheartj/ehae178

ESC GUIDELINES

2024 ESC Guidelines for the management of elevated blood pressure and hypertension

Developed by the task force on the management of elevated blood pressure and hypertension of the European Society of Cardiology (ESC) and *endorsed by the European Society of Endocrinology (ESE) and the European Stroke Organisation (ESO)*

McEvoy JW, et al.Eur Heart J. 2024;45(38):3912-4018.

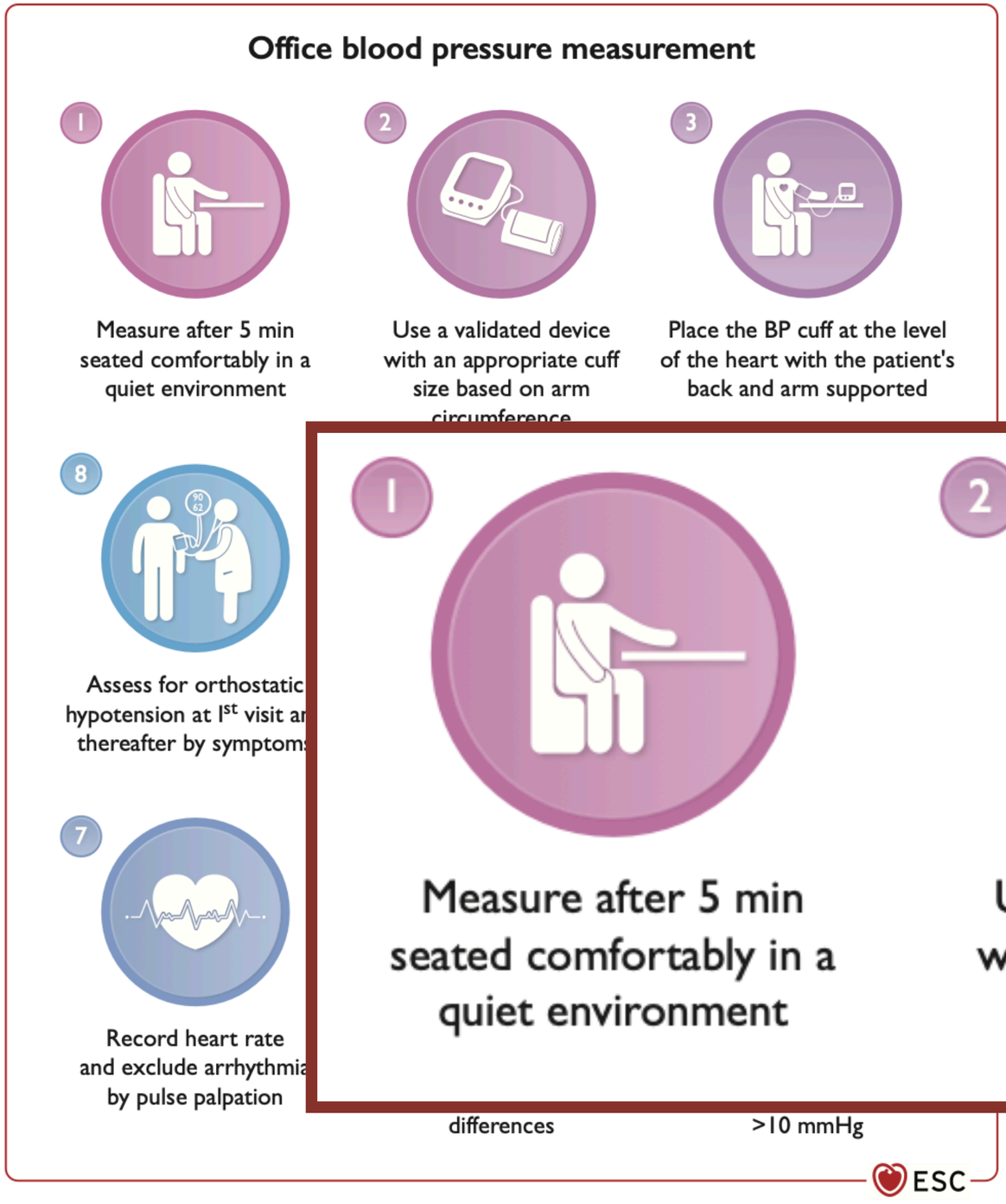


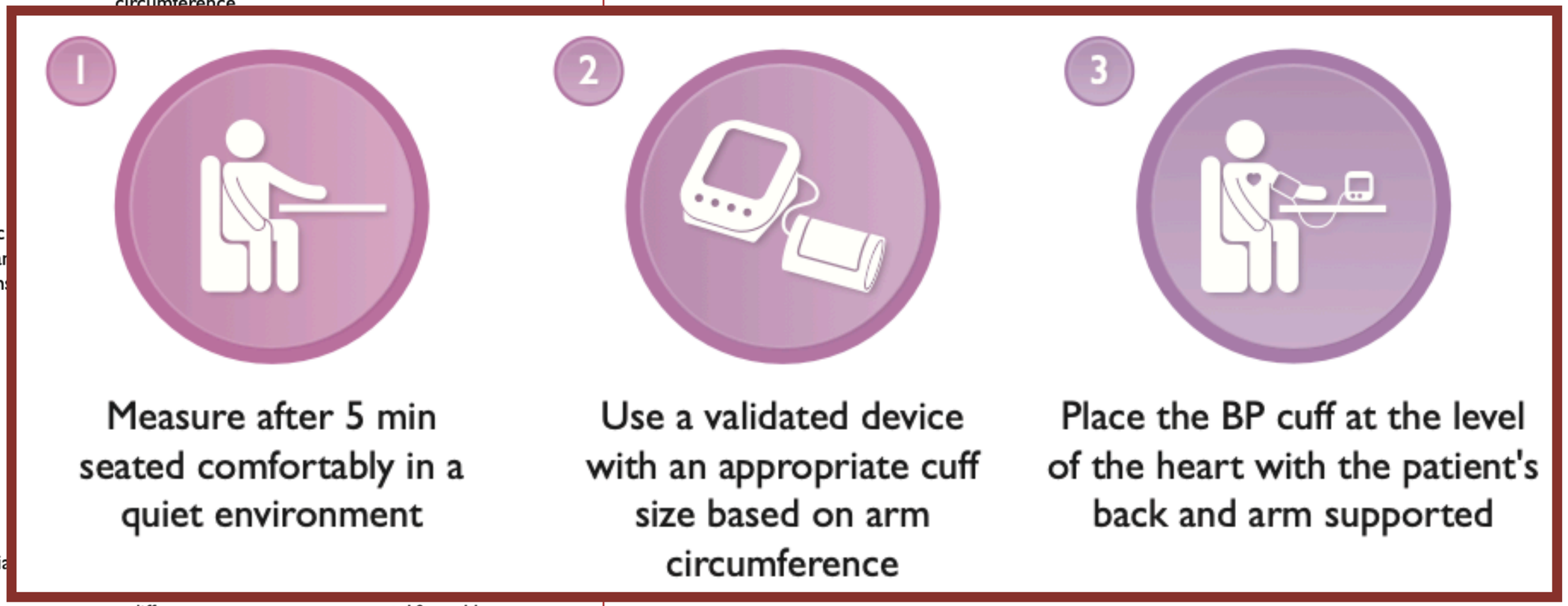
Pathophysiology of elevated BP and hypertension

- Salt sensitivity
- Pressure natriuresis
- RAAS
- Renal ischemia

McEvoy JW, et al.Eur Heart J. 2024;45(38):3912-4018.

Summary of office blood pressure measurement





McEvoy JW, et al.Eur Heart J. 2024;45(38):3912-4018.

Summary of office blood pressure measurement

4

Measure BP three times (1–2 min apart) and average the last 2 readings

5

Obtain further measurements if the readings differ by >10 mmHg

6

Measure BP in both arms at the 1st visit to detect between arm differences

McEvoy JW, et al. Eur Heart J. 2024 Aug 30:ehae178.

Summary of office blood pressure measurement

7

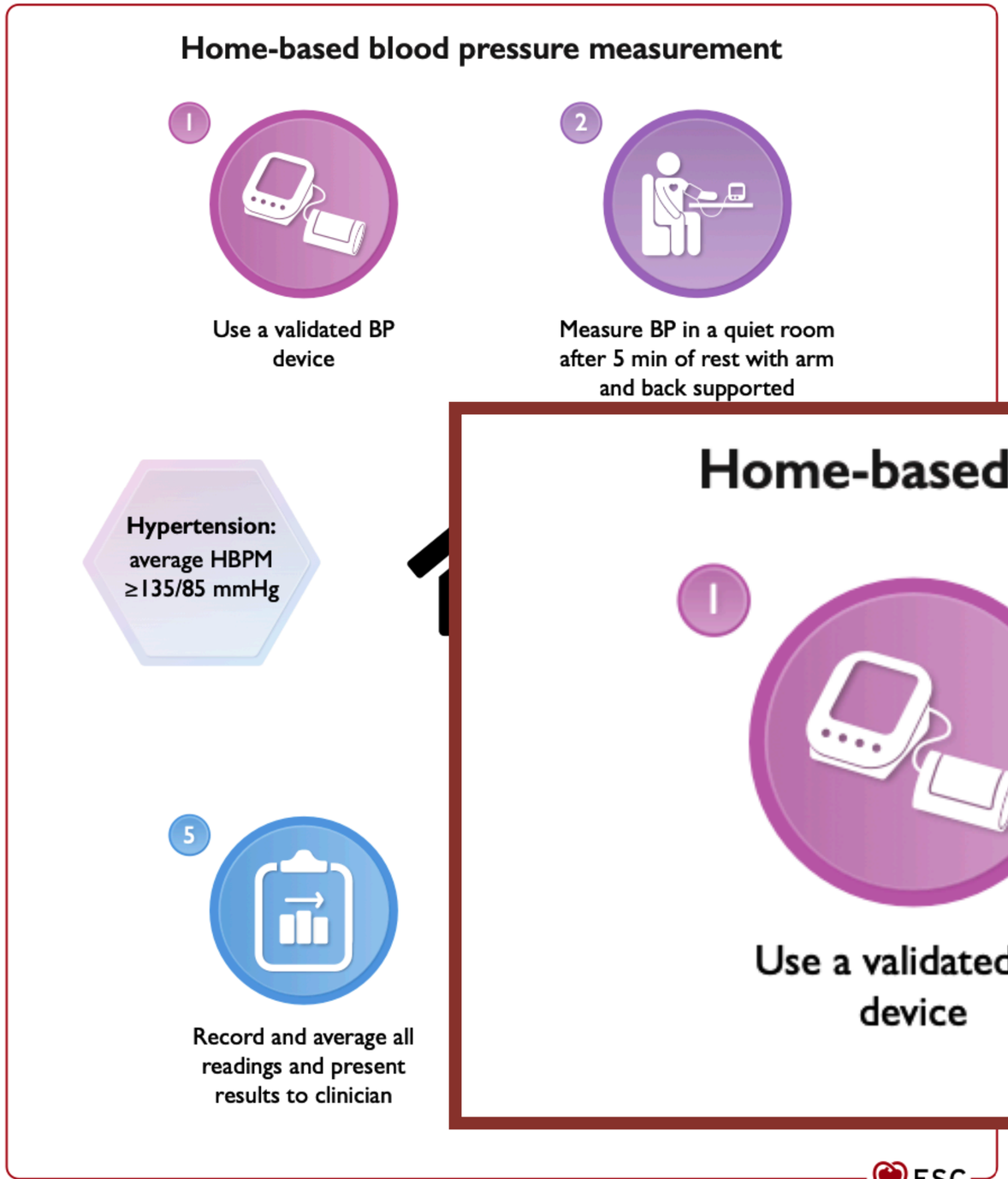
Record heart rate and exclude arrhythmia by pulse palpation

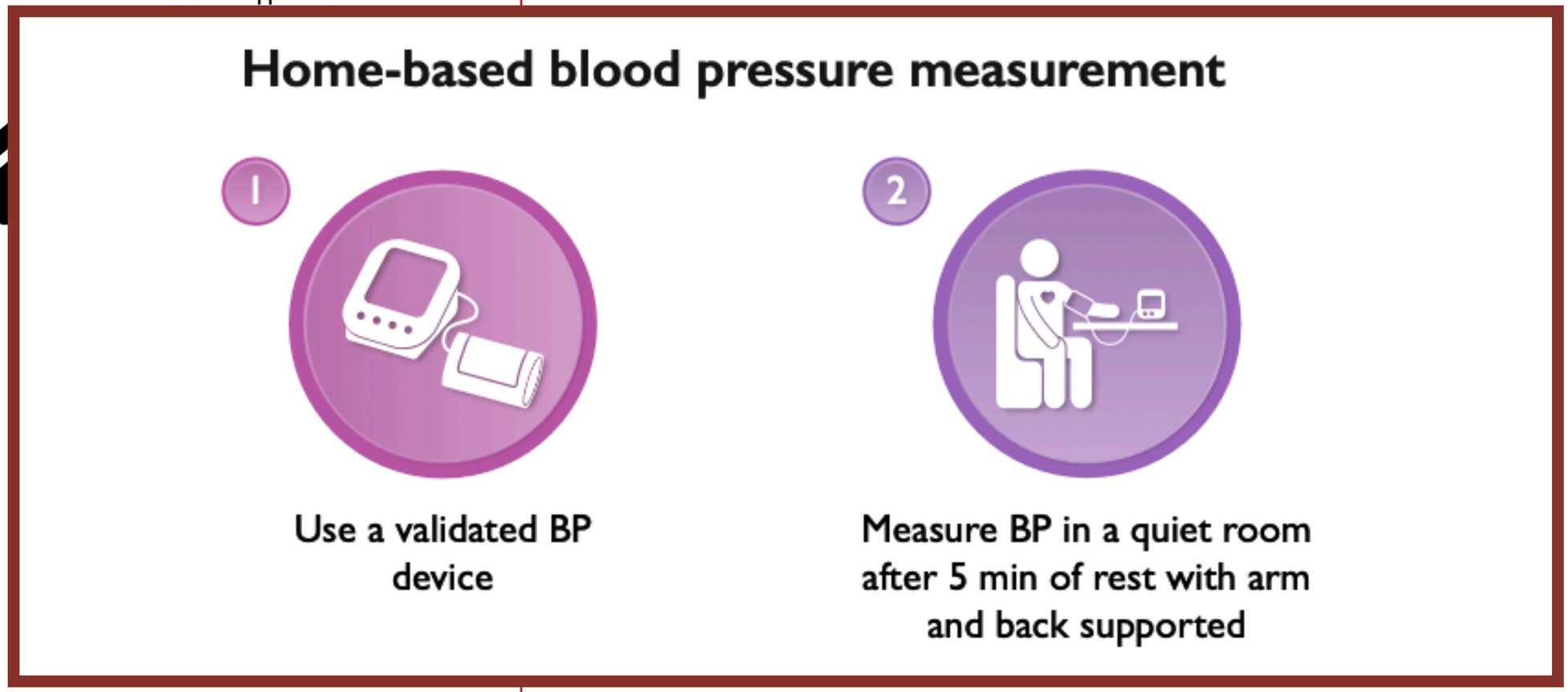
8

Assess for orthostatic hypotension at Ist visit and thereafter by symptoms

McEvoy JW, et al. Eur Heart J. 2024 Aug 30:ehae178.

Summary of home blood pressure measurement





McEvoy JW, et al.Eur Heart J. 2024;45(38):3912-4018.

Summary of home blood pressure measurement

3

Obtain two readings on each occasion, 1–2 min apart

4

Obtain readings twice a day (morning[a] and evening) for at least 3 and ideally 7 days

5

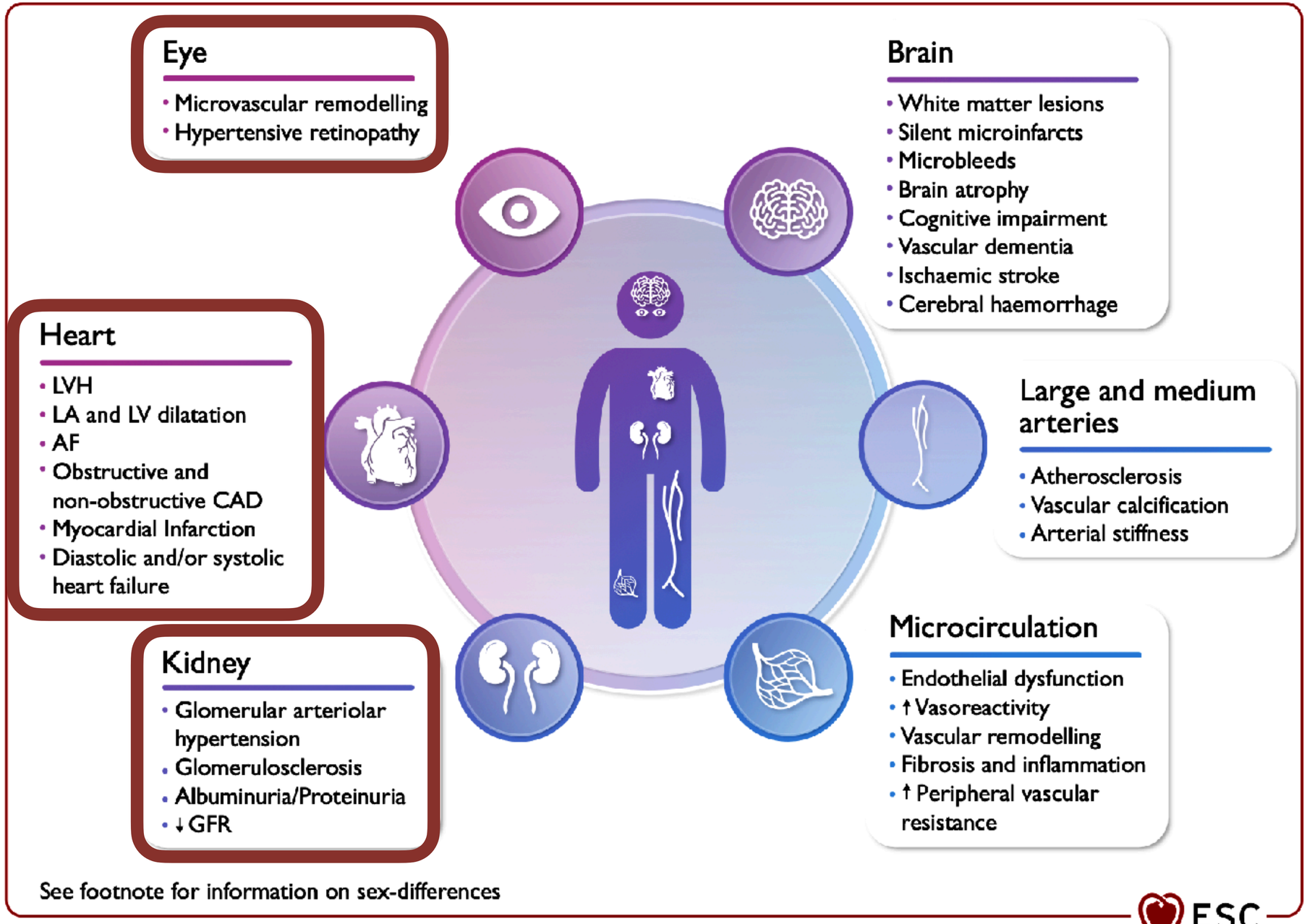
Record and average all readings and present results to clinician

McEvoy JW, et al. Eur Heart J. 2024 Aug 30:ehae178.

Comparison of office, home, and ambulatory BP measurement thresholds for elevated BP and hypertension

	Office BP (mmHg)[a]	Home BP (mmHg)	24 h ABPM (mmHg)
Reference			
Non-elevated BP	<120/70	<120/70	<115/65
Elevated BP	120/70–<140/90	120/70–<135/85	115/65–<130/80
Hypertension	≥140/90	≥135/85	≥130/80

McEvoy JW, et al.Eur Heart J. 2024;45(38):3912-4018.



Persistently elevated BP and hypertension lead to hypertension-mediated organ damage and cardiovascular disease

McEvoy JW, et al.Eur Heart J. 2024;45(38):3912-4018.

Key information to be collected in medical history

	History and symptoms suggesting secondary hypertension
	All causes:
1	BP > 160/100 mmHg in young adults (<40 years), BP > 180/110 mmHg irrespective of age.
2	Sudden development of hypertension or rapidly worsening BP.
3	Resistant hypertension.
4	Hypertensive emergency.

McEvoy JW, et al. Eur Heart J. 2024;45(38):3912-4018.

Conditions	Prevalence in Resistant Hypertension, %	Diagnostic Tests
Obstructive sleep apnea[34]	60-70	Polysomnography
Primary aldosteronism [35-38]	7-20	Serum aldosterone, plasma renin activity
Renal artery stenosis [34,43]	2-24	Duplex Doppler ultrasonography, computed tomographic angiography, or magnetic resonance angiography
Renal parenchymal disease [34]	1-2	Serum creatinine
Drug-induced or heavy alcohol use[9,34]	2-4	History taking
Thyroid disorders[34]	<1	Thyrotropin, free thyroxine

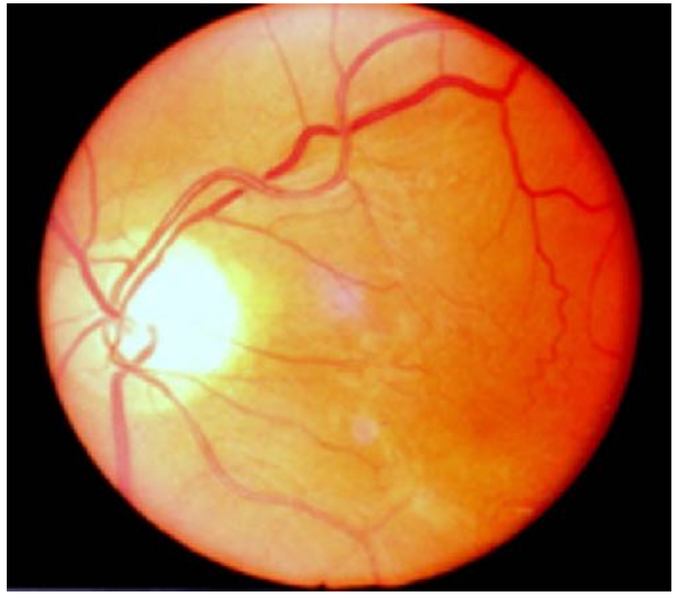
Vongpatanasin W, et al. JAMA. 2014;311:2216–2224.

Key steps in physical examination

Anthropometric measures
Weight and height for BMI calculation.
Waist circumference.
Signs of HMOD or established CVD
Neurological examination and cognitive status (based on clinical suspicion).[211]
Palpation and auscultation of heart and carotid arteries.
Auscultation of abdominal aorta, iliac, and femoral arteries.
Palpation of peripheral arteries.
Comparison of BP in both arms (at least once).

McEvoy JW, et al. Eur Heart J. 2024;45(38):3912-4018.

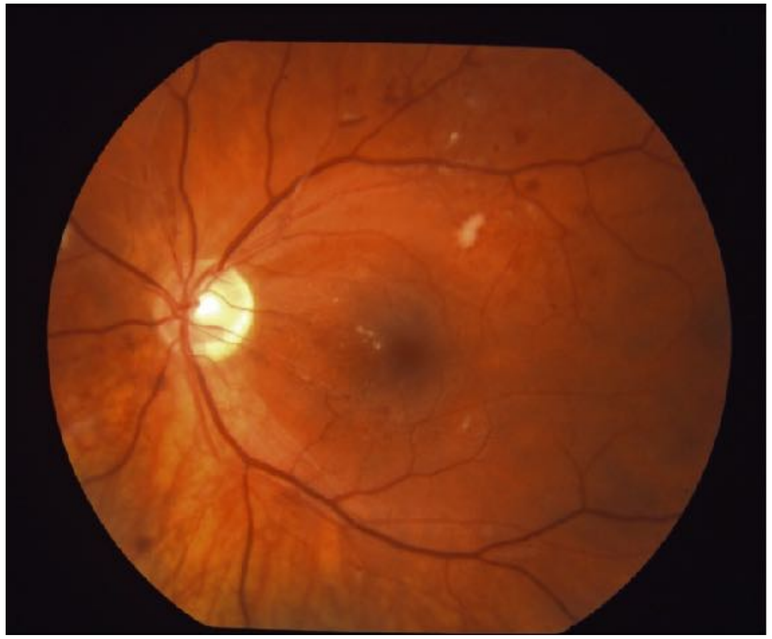
Keith-Wagener-Barker Classification

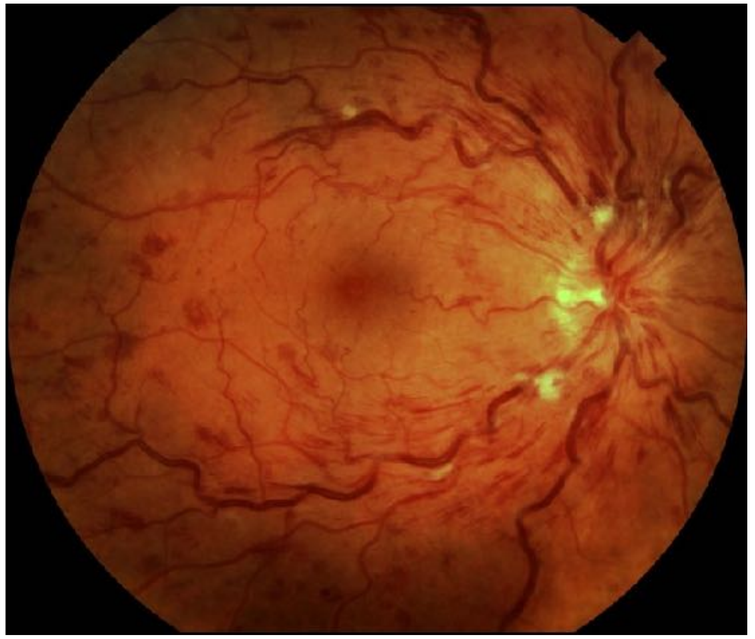


- Grade 1
  - Mild narrowing of the arterioles
  - “Copper Wire”
- Grade 2
  - Moderate narrowing -Copper wire and AV nicking
- Associated with long standing essential hypertension

Keith-Wagener-Barker Classification

- Grade 3
- Severe hemorrhage, cotton wool spots, hard exudates

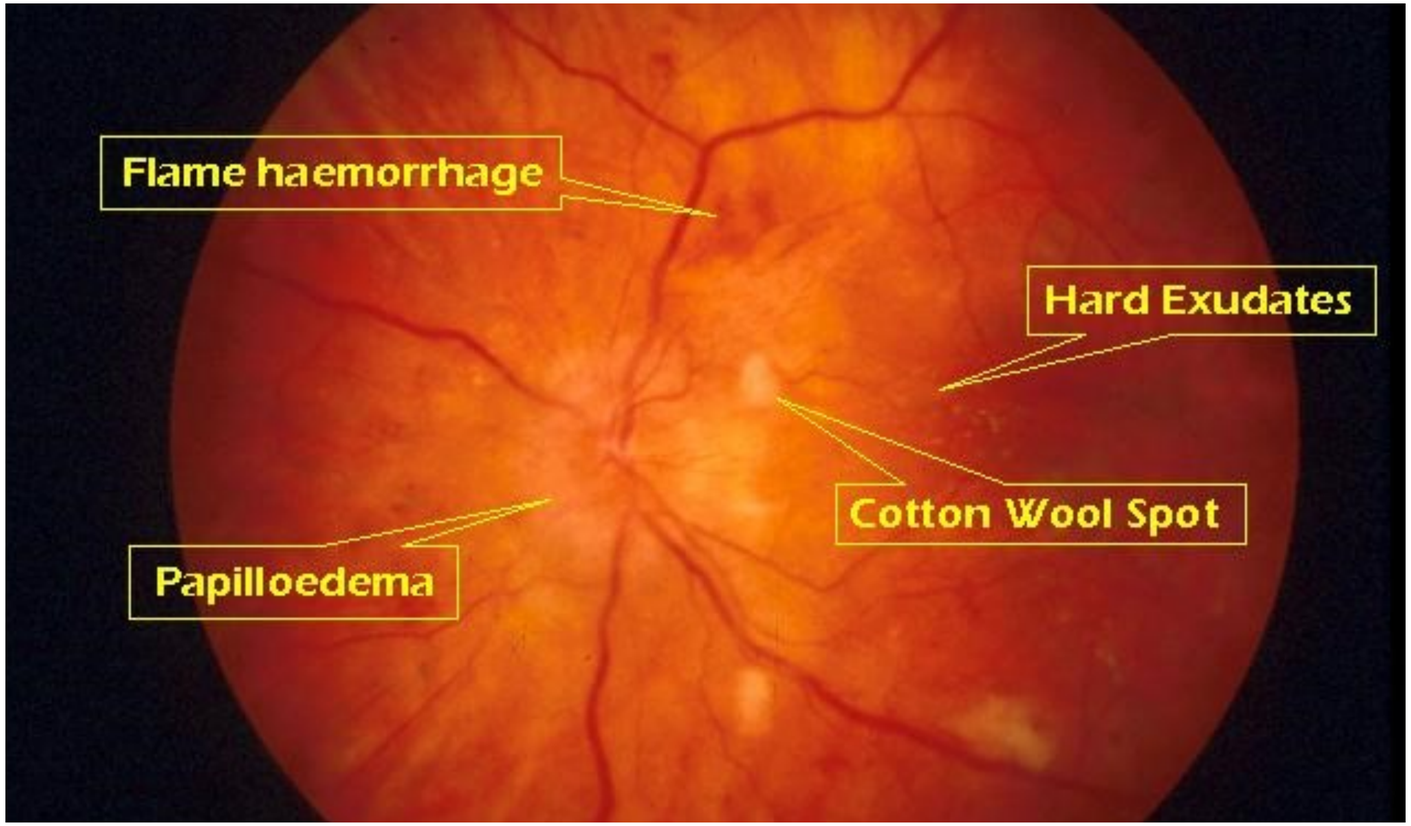




Accelerated hypertension

Keith-Wagener-Barker Classification

- **Grade 4: Grade 3 + Papilledema**



Malignant hypertension

Grade 3 and 4 highly correlated with progression to end organ damage and decreased survival

Key steps in physical examination

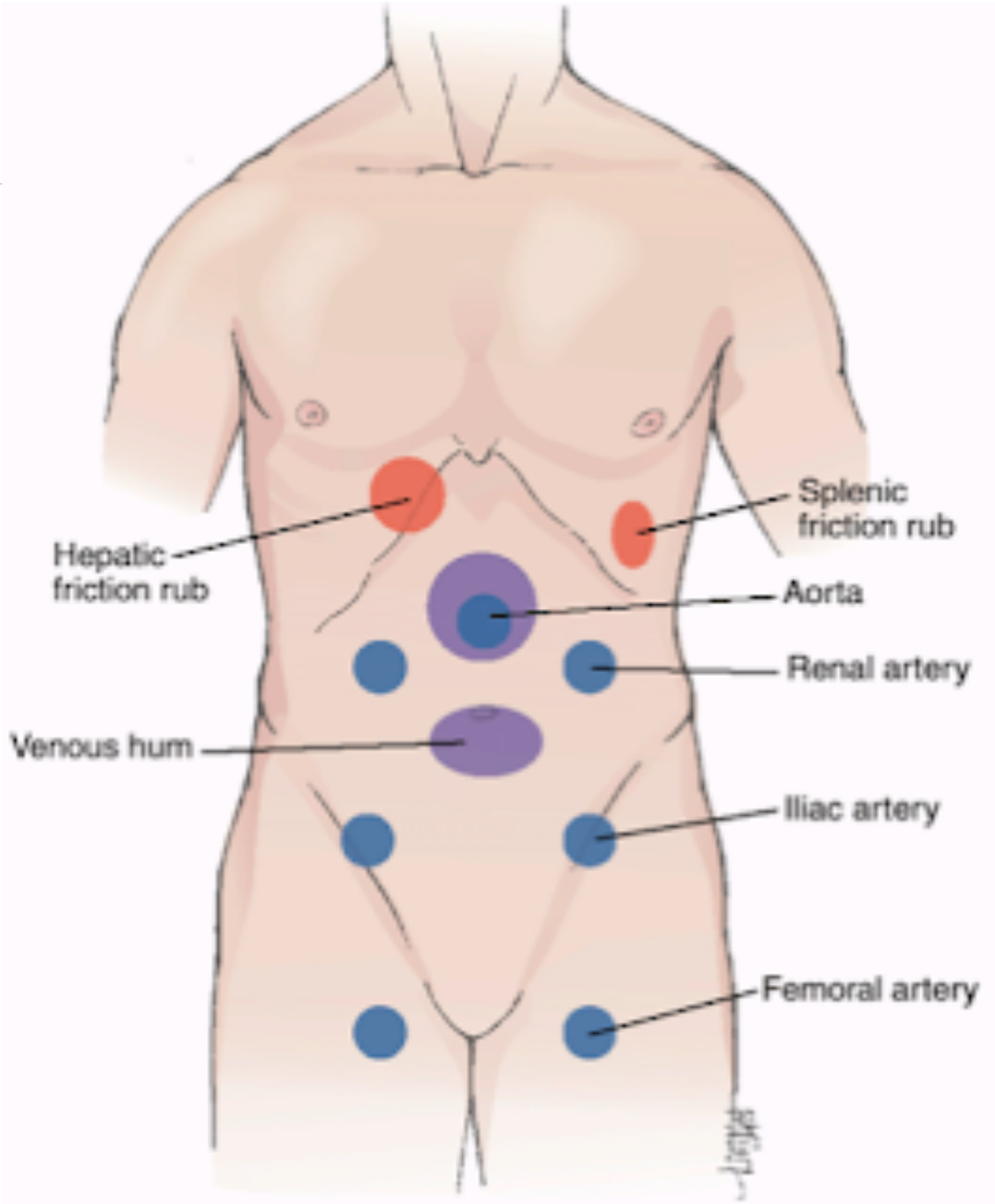
Signs of secondary hypertension
Skin inspection: cafe-au-lait patches of neurofibromatosis (phaeochromocytoma/paraganglioma).
Kidney palpation for signs of renal enlargement (polycystic kidney disease).
Auscultation of heart and renal arteries for murmurs or bruits indicative of aortic coarctation, or renovascular hypertension.
Comparison of radial with femoral pulse, inter-arm BP difference in young individuals with aortic coarctation (aortic murmur may also be heard).
Signs of Cushing's disease or acromegaly.
Signs of thyroid or parathyroid disease.
Neck circumference of >40 cm in men, >35 cm in women (OSAS).

Renal bruits (RAS)

McEvoy JW, et al. Eur Heart J. 2024;45(38):3912-4018.

Abdominal bruits

- Patient in a supine position
- Auscultate
  - Epigastrium
  - All four quadrants



Drugs or substances that may increase blood pressure

Contraceptive drugs	Oral contraceptive pills cause hypertension in 5% of women, especially compounds containing at least 50 μg of oestrogen and 1–4 mg of progestin;[212,213] this hypertension is usually mild, but severe hypertension occurs rarely (up to 20% of contraceptive-induced hypertension cases in older studies).[214] The combined hormonal contraceptive vaginal ring has a minor effect.[215] Post-menopausal hormonal replacement therapy has no pressor effect.[216]
Sympathomimetics	Weight loss drugs, e.g. phenylpropanolamine and sibutramine. Nasal decongestants, e.g. phenylephrine hydrochloride and naphazoline hydrochloride. Drugs used for attention deficiency and hyperactivity disorder, e.g. methylphenidate. Stimulant drugs, e.g. amphetamine, cocaine, and ecstasy; these substances usually cause acute hypertension. Herbal remedies, e.g. ephedra/ma huang.
Non-steroidal anti-inflammatory drugs	Chronic use raises BP by around 5 mmHg, especially indomethacin, naproxen, piroxicam and ibuprofen.[217] They also diminish the effectiveness of some BP-lowering drug classes, especially RAS blockers. Selective cyclooxygenase-2 inhibitors also increase BP.[217,218]
Paracetamol (acetaminophen)	Chronic use at high doses (4 g/day) raises BP by around 5 mmHg.[219,220]
Corticosteroids	Increase BP in a dose-dependent manner.
Immunosuppressive medications	Cyclosporin A induces hypertension in >50% of treated patients. Tacrolimus has a smaller effect on BP; rapamycin and mycophenolate have no effect on BP.
Anti-angiogenic cancer therapies	Vascular endothelial growth factor inhibitors (e.g. bevacizumab, sorafenib, sunitinib, pazopanib) increase BP in most patients and induce hypertension in 20%–90% of patients. Tyrosine kinase inhibitors (e.g. ibrutinib, acalabrutinib) increase BP in up to 72% of patients. About 1% of all patients develop a hypertensive emergency.
Other anticancer drugs	Fluoropyrimidines, cisplatin, abiraterone, bicalutamide, enzalutamide, cyclosporine, tacrolimus.[221]
Triptans	Induce vasoconstriction; conflicting data on BP elevation and risk of CVD events.
Antidepressant drugs	Antidepressant drugs (i.e. venlafaxine and monoamine oxidase inhibitors) increase BP in a dose-dependent manner, probably via noradrenergic stimulation.
Other psychiatric drugs	Clozapine, carbamazepine, lithium.
Liquorice	Increases BP via its mineralocorticoid-like activity (inhibition of the enzyme 11β-hydroxysteroid dehydrogenase 2). Regular use of 50–200 g/day liquorice induces a dose-dependent increase in systolic BP (3–14 mmHg).[222]
Others	Anabolic steroids (testosterone, growth hormone), erythropoietin—often used as doping drugs. Highly active anti-retroviral therapy, through weight gain. Commercially available caffeinated drinks acutely increase systolic BP by around 4 mmHg.[223]
Sodium-containing medications	Effervescent, dispersible, and soluble drugs. Regular use of effervescent paracetamol 3 g/day is associated with a 4 mmHg increase in systolic BP[224] and CVD,[225] compared with non-effervescent paracetamol.

McEvoy JW, et al. Eur Heart J. 2024;45(38):3912-4018.

Prevalence of atherosclerotic RAS in risk groups: a systematic literature review

- **N = 40 studies: 15,879 patients. Prevalence of patients with “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%
ESKD	40.8%?
Congestive heart failure	54.1%?

de Mast Q, Beutler JJ: T. J Hypertens. 2009: 27:1333-1340.

Renovascular hypertension

- Multiple CVD risk factors (atherosclerosis)
- Multisite/generalized atherosclerosis (atherosclerosis)
- Reduced eGFR and/or presence of albuminuria and/or markedly elevated renin concentration
- Acute worsening renal function (decreased eGFR) after administration of ACE inhibitors or ARBs (both)
- Unexplained small kidney or size discrepancy between kidneys of >1.5 cm (both)
- Sudden, unexplained pulmonary edema

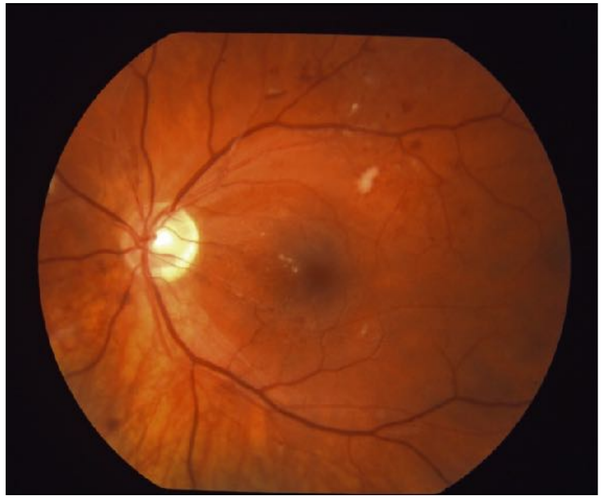
McEvoy JW, et al. Eur Heart J. 2024;45(38):3912-4018.

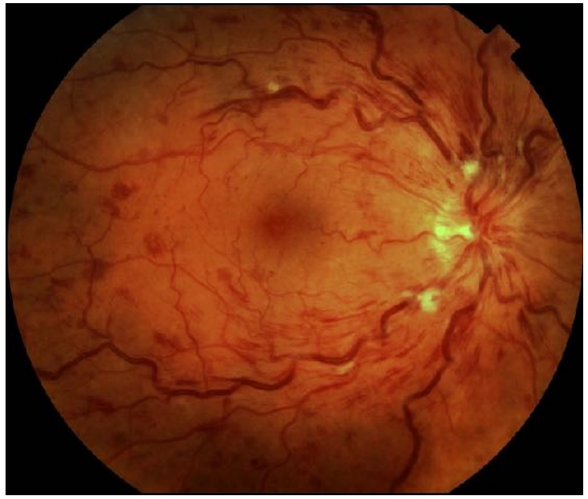
Problem List

- HT emergency with retinal hemorrhage and kidney injury
- Established CV disease: Previous PAD
  - DDX atherosclerosis renal artery stenosis

Case 1

- A 60-year-old man with T2DM, hypertension, and a history of ischemic limb presented with uncontrolled blood pressure (180/110 mmHg) and a progressive rise in creatinine from 1.5 to 3.0 mg/dL over six weeks.
- Current treatment includes: Losartan 100 mg/day, chlorthalidone 12.5 mg/day, amlodipine 10 mg/day, metoprolol 100 mg/day, atorvastatin 40 mg/day, and aspirin 81 mg/day.
- What is the further investigation?





Routine tests recommended in the initial work-up of a patient with elevated BP or hypertension

	Routine test	Clinical utility
1	Fasting blood glucose (and HbA1c if fasting blood glucose is elevated)	Assessing CVD risk and comorbidities
2	Serum lipids: total cholesterol, LDL cholesterol, HDL and non-HDL cholesterol, triglycerides	Assessing CVD risk
3	Blood sodium and potassium, haemoglobin and/or haematocrit, calcium, and TSH	Screening secondary hypertension (primary aldosteronism, Cushing's disease, polycythaemia, hyperparathyroidism, and hyperthyroidism)
4	Blood creatinine and eGFR; urinalysis and urinary albumin-to-creatinine ratio	Assessing CVD risk and HMOD Guiding treatment choice Screening secondary hypertension (renoparenchymal and renovascular)
5	12-lead ECG	Assessing HMOD (left atrial enlargement, left ventricular hypertrophy) Assessing irregular pulse and other comorbidities (AF, previous acute myocardial infarction)

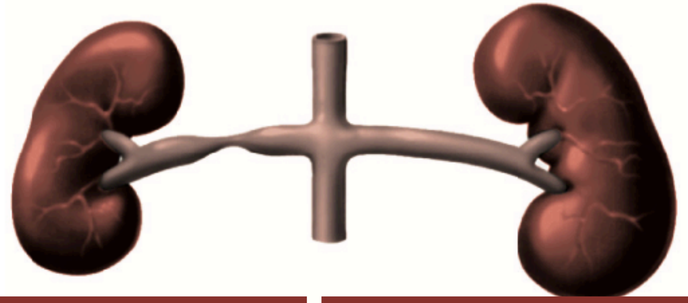
McEvoy JW, et al.Eur Heart J. 2024;45(38):3912-4018.

Recommendation	Class[a]	Level[b]
It is recommended to measure serum creatinine, eGFR, and urine ACR in all patients with hypertension.[170,273]	I	A
If moderate-to-severe CKD is diagnosed, it is recommended to repeat measurements of serum creatinine, eGFR, and urine ACR at least annually.[276]	I	C
Renal ultrasound and Doppler examination should be considered in hypertensive patients with CKD to assess kidney structure and determine causes of CKD and to exclude renoparenchymal and renovascular hypertension.[276,277] CT or magnetic resonance renal angiography are alternative testing options.	IIa	C

Recommendations for assessing renal hypertension-mediated organ damage

McEvoy JW, et al.Eur Heart J. 2024;45(38):3912-4018.

UNILATERAL RENAL ARTERY STENOSIS



Reduced renal perfusion

↓

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

↓

Angiotensin II–dependent hypertension

Increased renal perfusion

↓ ↓

Suppressed RAS

Increased Na^+ excretion (pressure natriuresis)

Effect of blockade of RAS

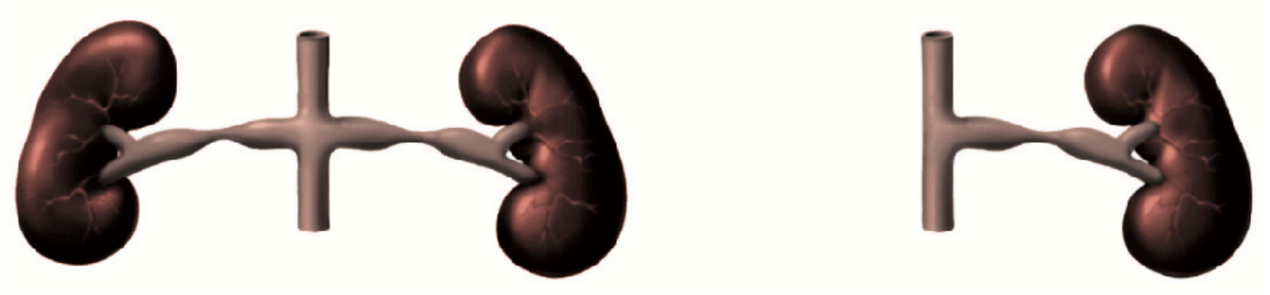
Reduced arterial pressure
Enhanced lateralization of diagnostic tests
Glomerular filtration rate (GFR) in stenotic kidney may fall

Diagnostic tests

Plasma renin activity elevated
Lateralized features, e.g., renin levels in renal veins, captopril-enhanced renography

Brenner and Rector's: the kidney, Philadelphia, 11th Edition

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

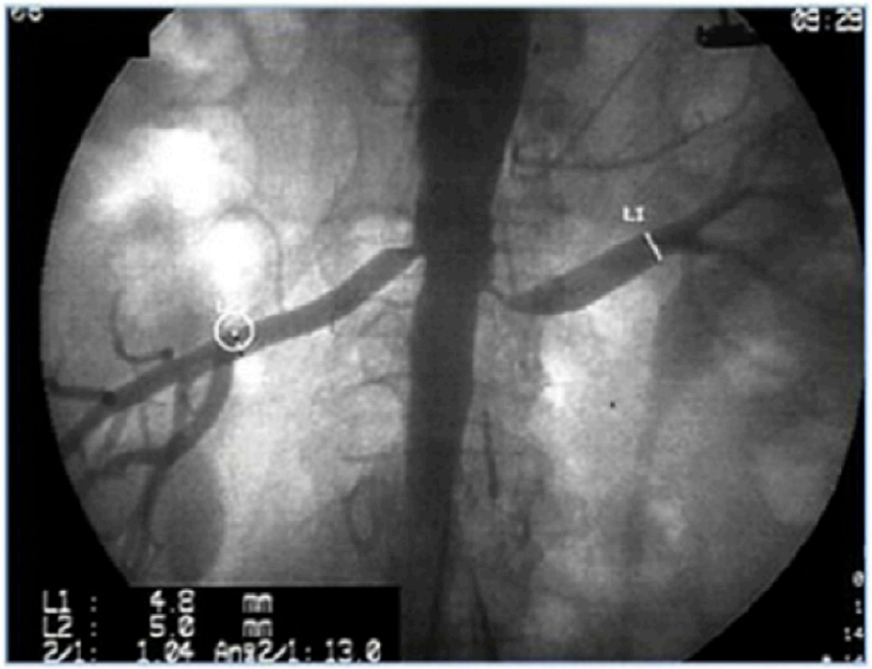
Diagnostic tests

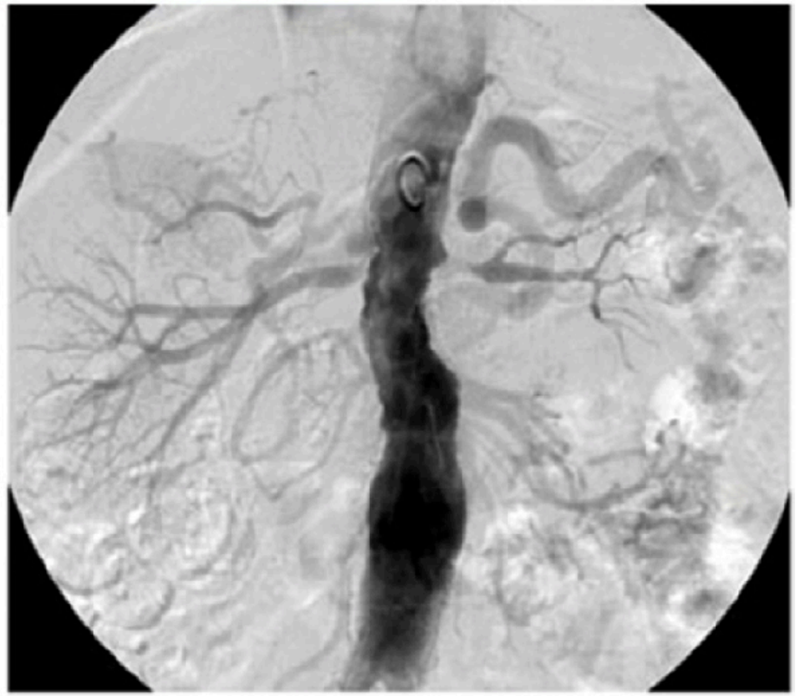
Plasma renin activity normal or low

Lateralized features: none

Brenner and Rector's: the kidney, Philadelphia, 11th Edition

Spectrum of renovascular disease





Asymptomatic
"Incidental RAS"

Renovascular
Hypertension

Accelerated CV Disease
Congestive Heart failure
Stroke

Ischemic Nephropathy

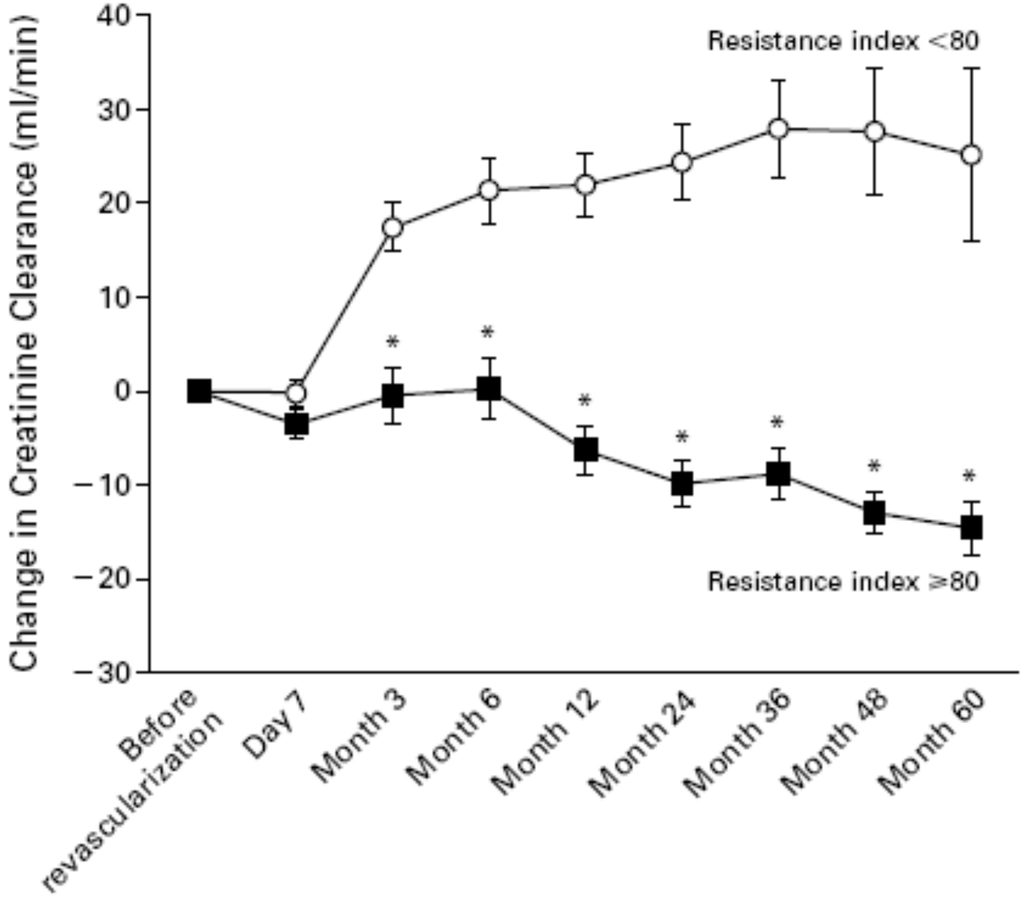
Herrmann SM, et al. Endocrinol Metab Clin North Am. 2019; 48(4):765-778.

Diagnose Atherosclerotic Renovascular Disease

Imaging Modality	Sensitivity	Specificity	Strengths
Duplex ultrasound	91%-100%	82%-91%	Inexpensive, noninvasive, provides waveform and velocity data, provides data about kidney viability (resistive index)
Multidetector CTA	64%-96%	90%-92%	Rapid multiplanar acquisition, allows detection of accessory renal arteries
MRA	94%-97%	85%-93%	No radiation or iodinated contrast required
Catheter angiography	100%	100%	Gold standard of renal artery evaluation, enables measurement of pre- and postintervention gradients, can evaluate and treat in same setting

Hicks CW, et al. Atherosclerotic Renovascular Disease: A KDIGO Controversies Conference. Am J Kidney Dis. 2022; 79(2):289-301.

Outcome after revascularization by renal resistance index



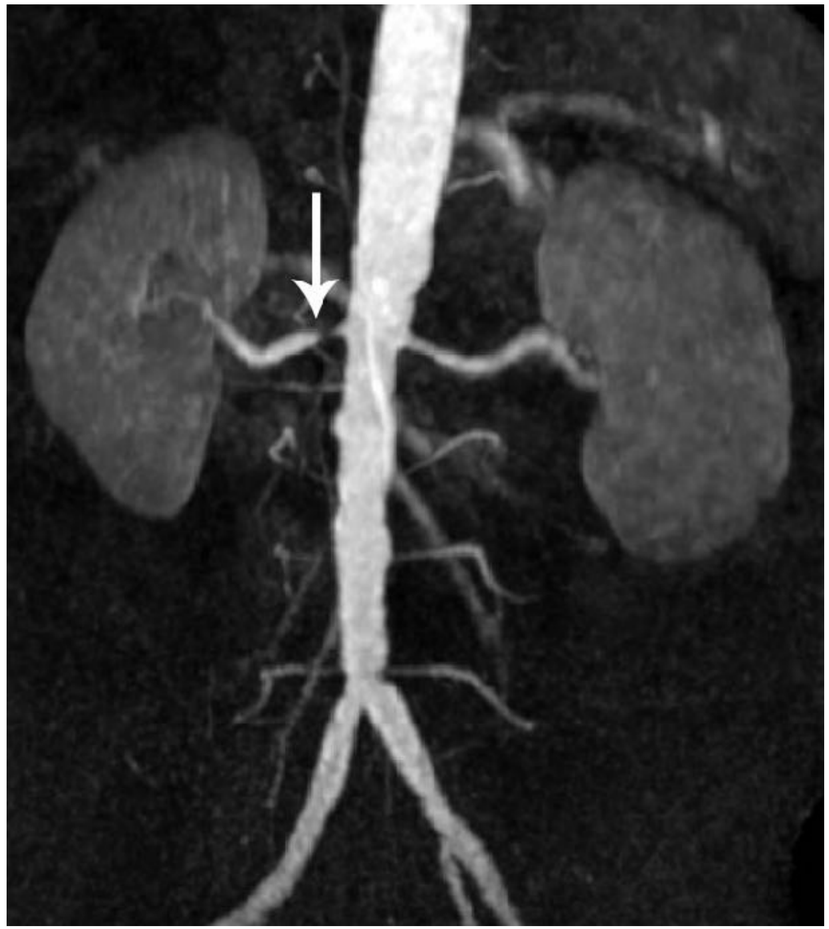
No. with Follow-up Data									
Resistance index <80	96	96	95	83	73	59	43	34	21
Resistance index ≥80	35	35	33	31	26	21	16	8	5

High resistive index reflects intrinsic parenchymal and small vessel disease in the kidney that does not improve after revascularization.

Radermacher J, et al. N Engl J Med 2001: 344:410-417.

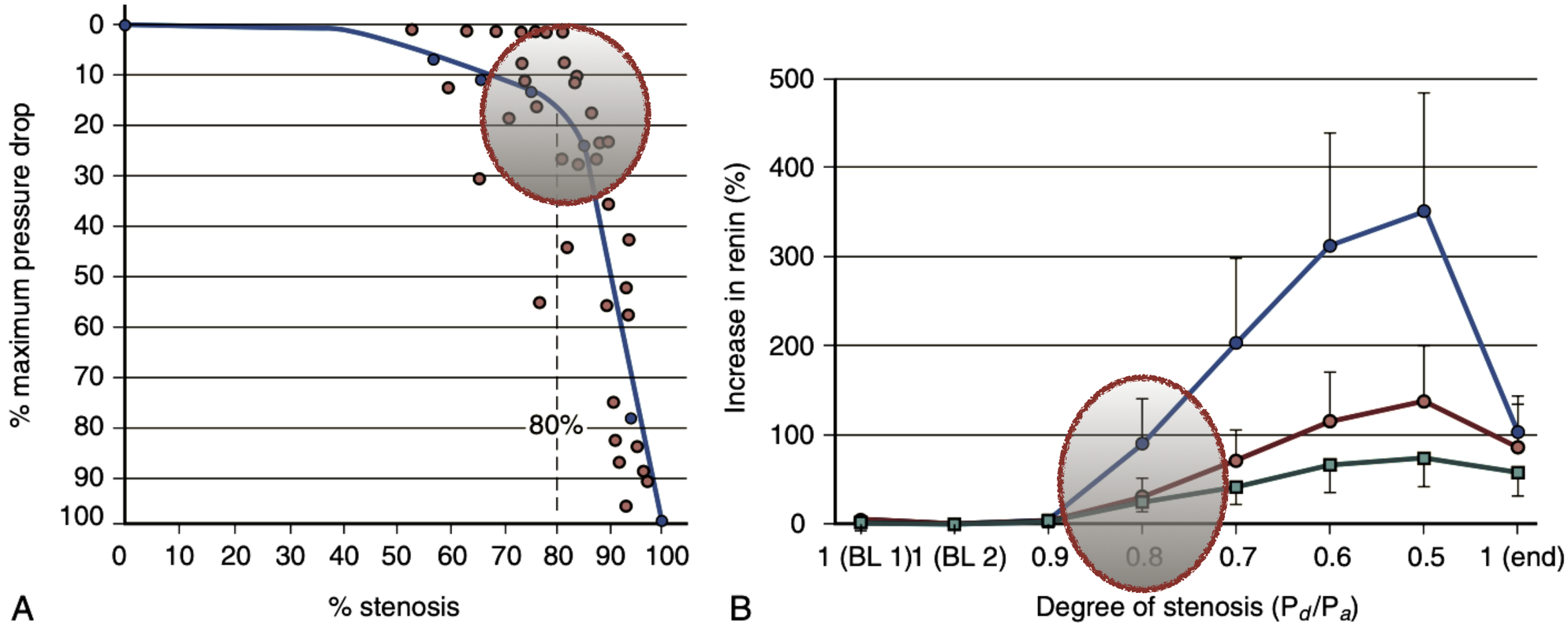
Atherosclerosis RAS

- 90% of renal artery stenosis
- Usually involves the ostium and proximal third of the main renal artery
- Increased prevalence with age, DM, aortoiliac occlusive disease, CAD, HT



Safian RD, et al.N Engl J Med, 2001:344;431-442

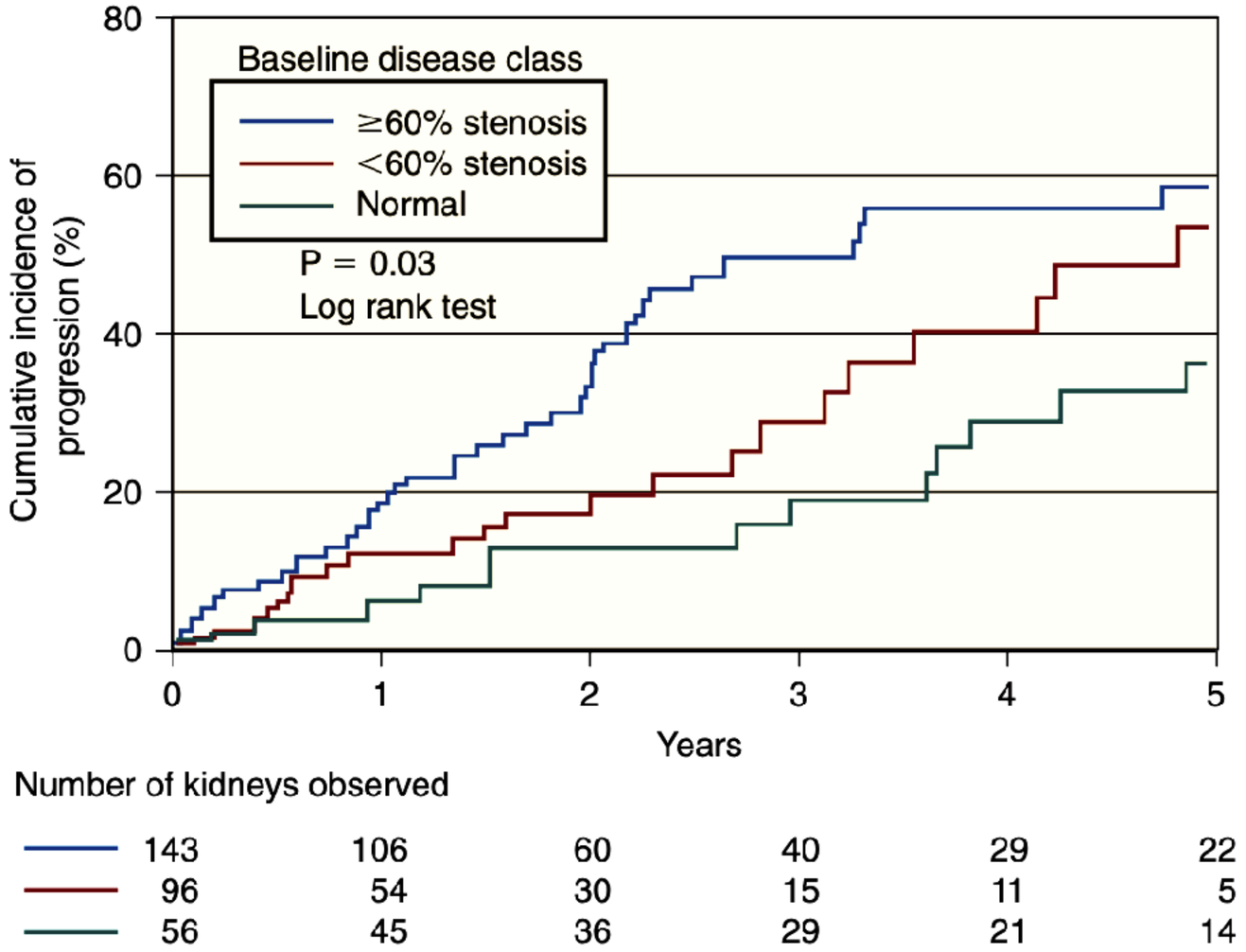
Significant renal artery stenosis



Measured fall in arterial pressure and blood flow across stenotic lesion induced in experimental animals. The degree of stenosis was determined using latex casts after completion of the experiment. These data indicate that critical lesions require 70% to 80% luminal obstruction before hemodynamic effects can be detected. Studies from human subjects with translesional pressure gradients indicate that aortic-renal pressure gradient of 10% to 20% is necessary to detect renin release

Brenner and Rector's: the kidney, Philadelphia, 10th Edition

Atherosclerotic disease progression in the renal artery

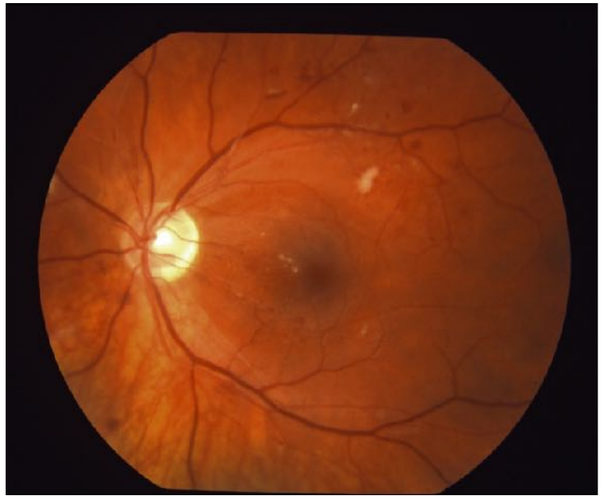


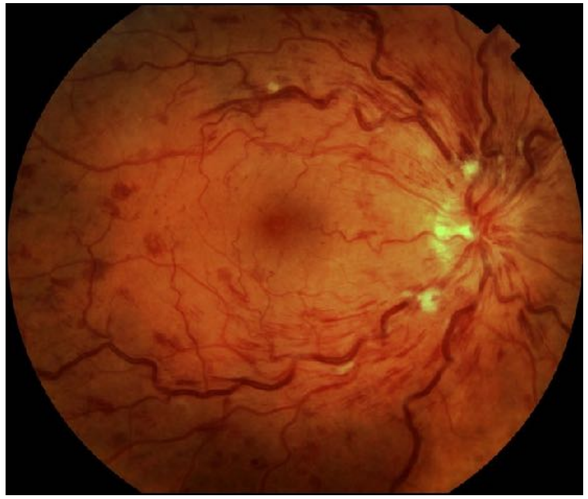
The risk of renal artery disease progression is highest among individuals with preexisting high-grade stenosis

Modified from Caps MT, et al: Circulation. 1998: 98:2866-2872.

Case 1

- A 60-year-old man with T2DM, hypertension, and a history of ischemic limb presented with uncontrolled blood pressure (180/110 mmHg) and a progressive rise in creatinine from 1.5 to 3.0 mg/dL over six weeks.
- Current treatment includes: Losartan 100 mg/day, chlorthalidone 12.5 mg/day, amlodipine 10 mg/day, metoprolol 100 mg/day, atorvastatin 40 mg/day, and aspirin 81 mg/day.
- What is the definite treatment?





Hypertensive emergencies requiring immediate BP-lowering

Clinical presentation	Timing and BP target	First-line treatment
Malignant hypertension with or without acute renal failure	Several hours Reduce MAP by 20–25%	Labetalol[a] Nicardipine
Hypertensive encephalopathy	Immediately reduce MAP by 20–25%	Labetalol[a] Nicardipine
Acute coronary event	Immediate reduce SBP to <140 mmHg	Nitroglycerine Labetalol[a]
Acute cardiogenic pulmonary edema	Immediately reduce SBP to <140 mmHg	Nitroprusside or nitroglycerine (with loop diuretic)
Acute aortic dissection	Immediately reduce SBP to <120 mmHg and heart rate to <60 bpm	Esmolol AND nitroprusside or nitroglycerine or nicardipine
Eclampsia and severe preeclampsia/HELLP	Immediately reduce SBP to <160 mmHg and DBP to <105 mmHg	Labetalol[a] or nicardipine and magnesium sulphate

Mancia G, et al. J Hypertens. 2023; 41(12):1874-2071.

Year Study	2009 ASTRAL[43]	2009 STAR[44]	2014 CORAL[53]
Cohort	Hypertension	Hypertension and CKD	Hypertension and/or CKD
Entry BP	No BP threshold required	BP <140/90 mm Hg and stable for 1 month and eGFR <80 mL/min	SBP >155 mm Hg on two or more medications or eGFR <60 mL/min
Stenosis	>50% by MRA, CTA, angiography	>50% by MRA, CTA, or angiography	>60% by MRA, CTA, angiography, DUS
Excluded	Clinician certain patient would benefit from stent or require stent within 6 months	Malignant hypertension Pulmonary edema with bilateral RAS Intolerance to ACEI/ARBs as evidenced by >20% drop in CrCl	Entry creatinine >4 mg/dl Kidney Length <7 cm
% Stenosis	75.5 mean %	NA	67.3%/66.2%
CKD	Mean creatinine 2.0 mg/dl	Mean creatinine 1.7 mg/dl	Mean eGFR 58 mL/min
% Bilateral	53.5%	47.9%	22%
Subjects per arm (N/N)	403/403	76/64	459/472
F/u	33.6 months	24 months	43 months
Treatment	Stent	Stent	Stent
Medical treatment	At discretion of sites BP control with or without ACEI or ARB No specified target BP	BP target <140/90 mm Hg ACEI/ARB last resort ASA Statin Smoking cessation counseling	BP target <140/90 mm Hg 130/80 mm Hg for DM and CKD ACE/ARB first-line ASA Statin goal LDL <70 mg/dl, HbA_{1c} <7.0% for DM Smoking cessation counseling
End-point	Rate of progression of CKD based on reciprocal creatinine over time	≥20% decrease in CrCl	Composite cardiovascular and renal events
Outcome	No significant difference	No significant difference	No significant difference

ASTRAL Investigators. N Engl J Med. 2009;361:1953–1962. Cooper C, et al. New Engl J Med. 2014;370:13–22. Bax L, et al. Ann Int Med. 2009;150:840–848.

Meta-Analysis of Revascularization Versus Medical Therapy for Atherosclerotic Renal Artery Stenosis

Irbaz B. Riaz, MBBS[a], Muhammad Husnain, MBBS[a,*], Haris Riaz, MBBS[b], Majid Asawaeer, MD[c], Jawad Bilal, MBBS[a], Anil Pandit, MD[d], Ranjith Shetty, MD[e], and Kwan S. Lee, MD[e]

Study	Mean Age* (Years)	Patients Enrolled*	DBP (mm Hg)	CC (ml/min)	ARAS (% Stenosis)	Primary Outcome Measures	Duration of follow-up (Months)
Plouin et al	59.2 vs. 59.5	49 (23 vs. 26)	≥95	≥50	—	↓SBP	6
Jaarsveld et al	61 vs. 59	106 (56 vs. 50)	≥95	—	—	Renal function	12
Bax et al	66 vs. 67	140 (64 vs. 76)	—	<80	≥50	Renal function	1, 3, 24
Webster et al	59.4 vs. 62.6	135 (55 25 vs. 30)	≥95	—	—	↓SBP	1, 3, 6 and every 6 there after
ASTRAL Investigators	70 vs. 71	806 (403 vs. 403)	—	—	—	Renal function	60
CORAL study	69.3 vs. 69.	947 (459 vs. 472)	—	—	≥60	Clinical end points†	43 (median)

PTRA and PTRAS are not superior to medical therapy alone with respect to all-cause mortality, nonfatal MI, and stroke

Riaz IB, et al.. Am J Cardiol. 2014;114(7):1116-23.

Use of PTRA in atherosclerotic RAS: a systematic review and meta-analysis

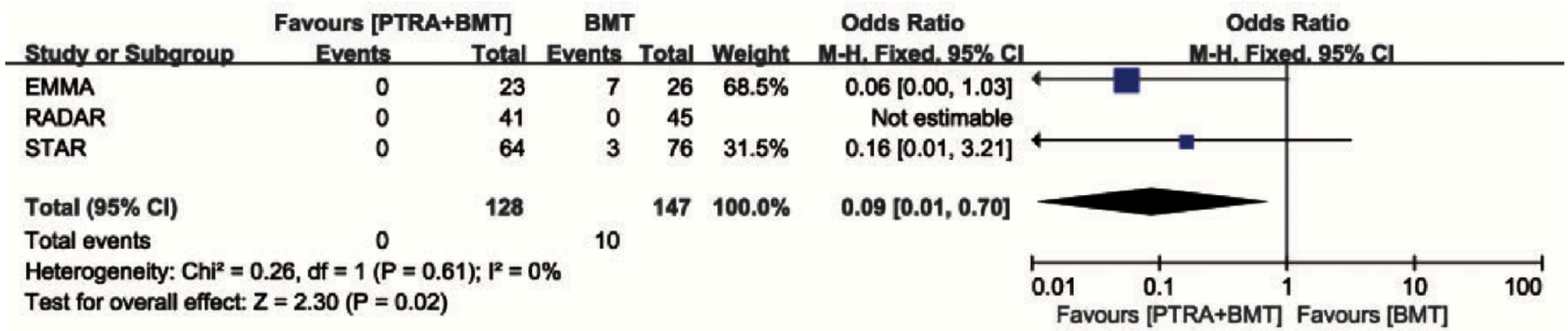
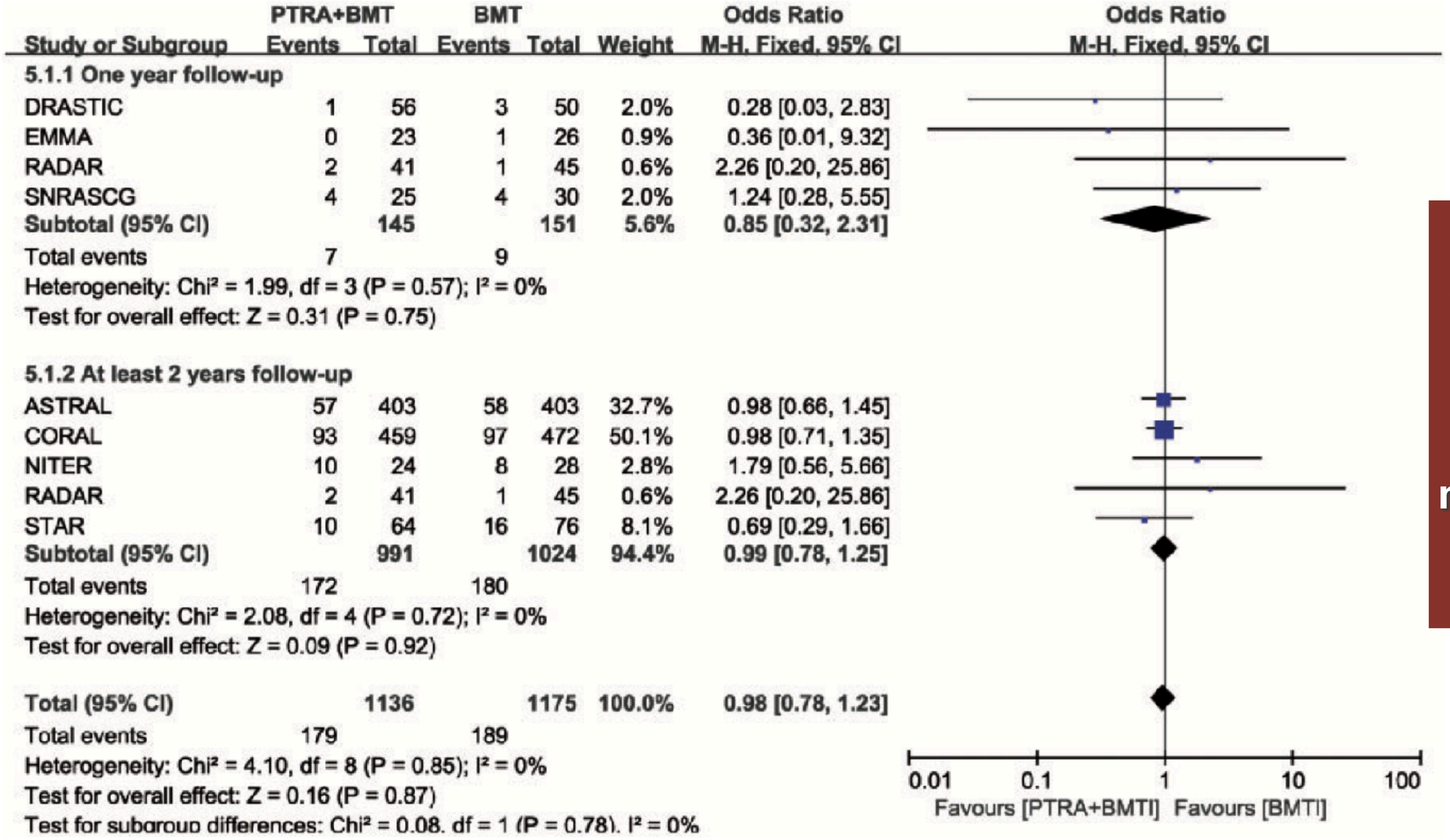


Figure 3. Refractory hypertension within 2 years of follow-up
PTRA, percutaneous transluminal renal angioplasty; BMT, best medical therapy; M-H, Mantel–Haenszel; CI, confidence interval.

Medical treatment plus PTRA group, the incidence of refractory hypertension was significantly lower compared with that in the medical alone group

Chen Y, et al. J Int Med Res. 2021;49(1):300060520983585.



There were no significant differences in the rates of stroke, renal events, cardiac events, cardiac mortality, and all-cause mortality between the two groups.

Figure 5. Renal events in 1 year and with at least 2 years of follow-up
PTRA, percutaneous transluminal renal angioplasty; BMT, best medical therapy; M-H, Mantel -Haenszel; CI, confidence interval.

Chen Y, et al. J Int Med Res. 2021;49(1):300060520983585.

Recommendations for managing hypertension in patients with renovascular hypertension

Recommendations	Class[a]	Level[b]
Renal artery angioplasty is not recommended in patients without confirmed haemodynamically significant renal artery stenosis.[c] 938,939	III	A

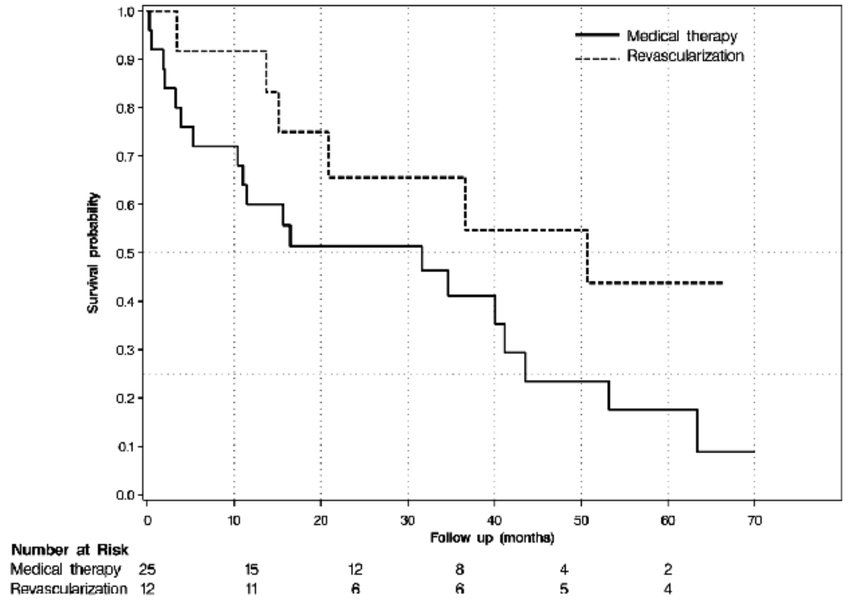
McEvoy JW, et al. Eur Heart J. 2024;45(38):3912-4018.

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

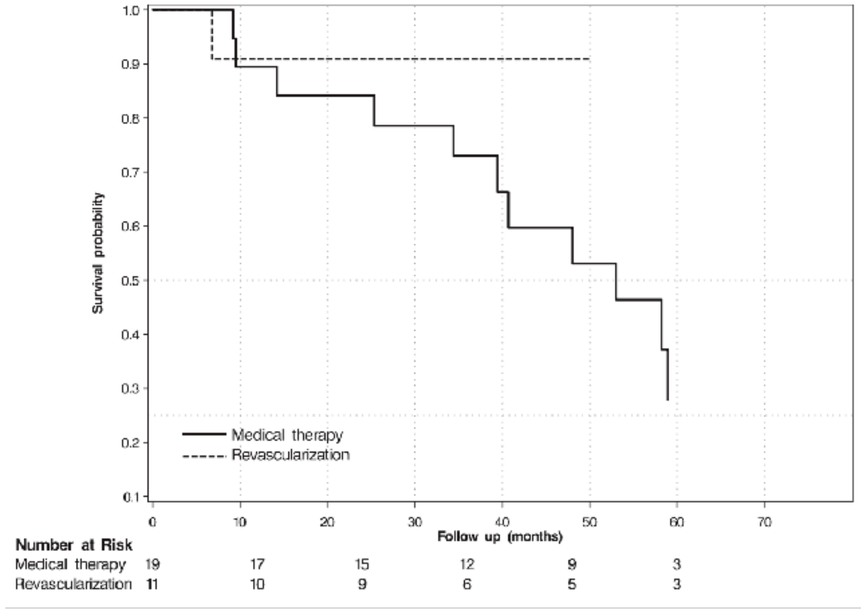
James Ritchie, MB ChB,[1] Darren Green, PhD,[1] Constantina Chrysochou, PhD,[1]

- **Prospective cohort study in 467 patients with renal artery stenosis >50%, managed according to clinical presentation/ flash pulmonary edema (7.8%), refractory hypertension (24.3%), or rapidly declining kidney function (9.7%) compared to low-risk presentation with none of these phenotypes (49%)**

Flash pulmonary edema



Refractory HT and GFR decline



Ritchie J, et al. Am J Kidney Dis. 2014;63(2):186-197.

Recommendations for managing hypertension in patients with renovascular hypertension

Recommendations	Class[a]	Level[b]
Renal artery angioplasty and stenting may be considered in patients with haemodynamically significant, atherosclerotic, renal artery stenosis (stenosis of 70%–99%, or 50%–69% with post-stenotic dilatation and/or significant trans-stenotic pressure gradient) with:	IIb	C
1 Recurrent heart failure, unstable angina, or sudden onset flash pulmonary oedema despite maximally tolerated medical therapy;		
2 Resistant hypertension;		
3 Hypertension with unexplained unilaterally small kidney or CKD;		
4 Bilateral renal artery stenosis or unilateral renal artery stenosis in a solitary viable kidney.[942,943]		

McEvoy JW, et al. Eur Heart J. 2024;45(38):3912-4018.

Case 2

- A 40-year-old woman presented with headache, neck pain, uncontrolled BP 190/100 mmHg and tinnitus for 10 weeks
- History of ischemic stroke
- Current treatment includes: Valsartan 160 mg/day, thiazide 12.5 mg/day, amlodipine 10 mg/day, atorvastatin 40 mg/day, and aspirin 81 mg/day.

- How to approach in this patients?

Definition of resistant hypertension

- **Hypertension is defined as resistant when a treatment strategy including appropriate lifestyle measures and treatment with maximum or maximally tolerated doses of a diuretic (thiazide or thiazide-like), a RAS blocker, and a CCB fail to lower office BP values to <140/90 mmHg**

- **These uncontrolled BP values must be confirmed by out-of-office BP measurements (HBPM or ABPM for relevant BP thresholds)**

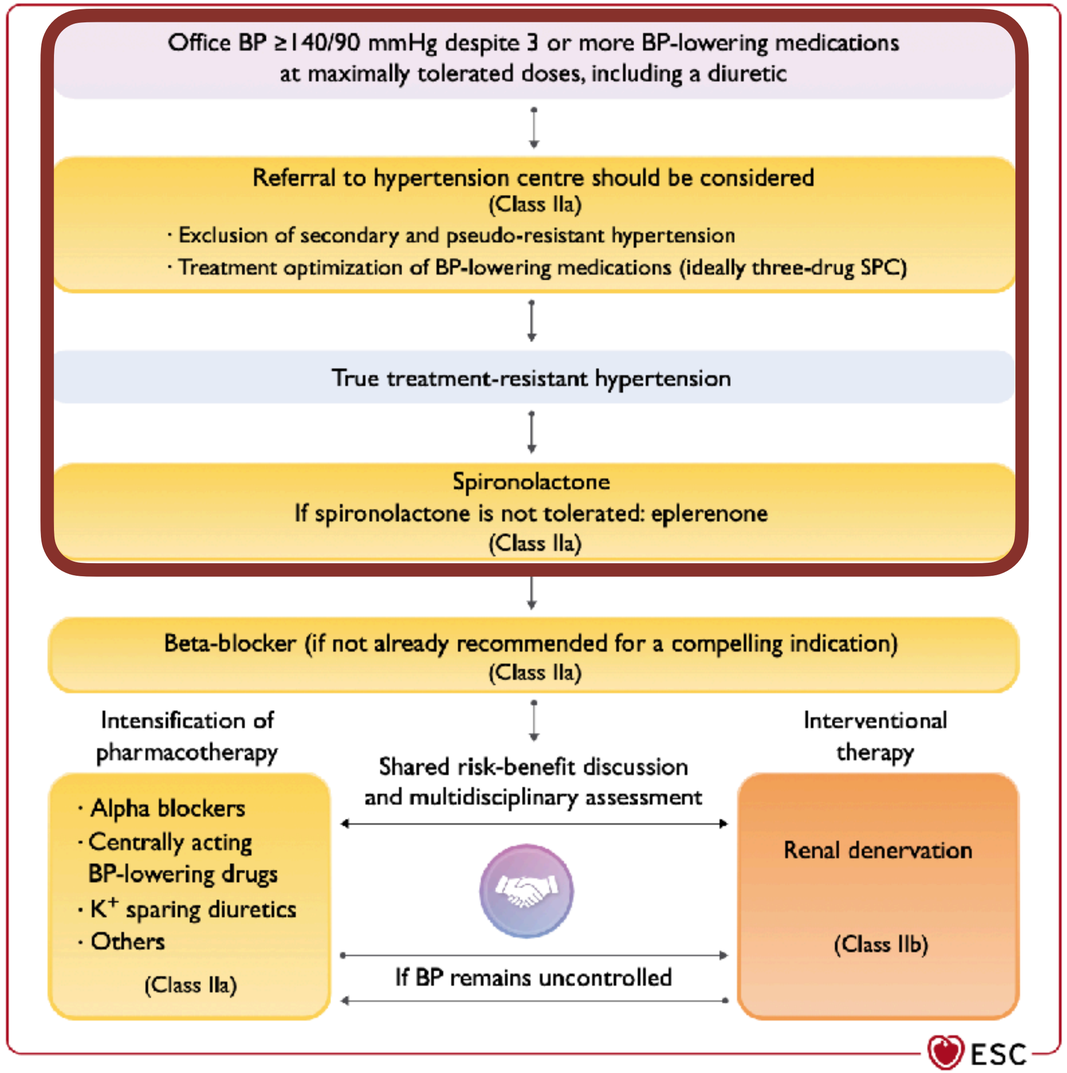
McEvoy JW, et al. Eur Heart J. 2024;45(38):3912-4018.

Causes of resistant hypertension

1. Behavioural factors
2. Overweight/obesity
3. Physical inactivity
4. Excess daily dietary sodium
5. Excess habitual alcohol consumption
6. Use of drugs or substances that may increase BP
7. Undetected secondary hypertension

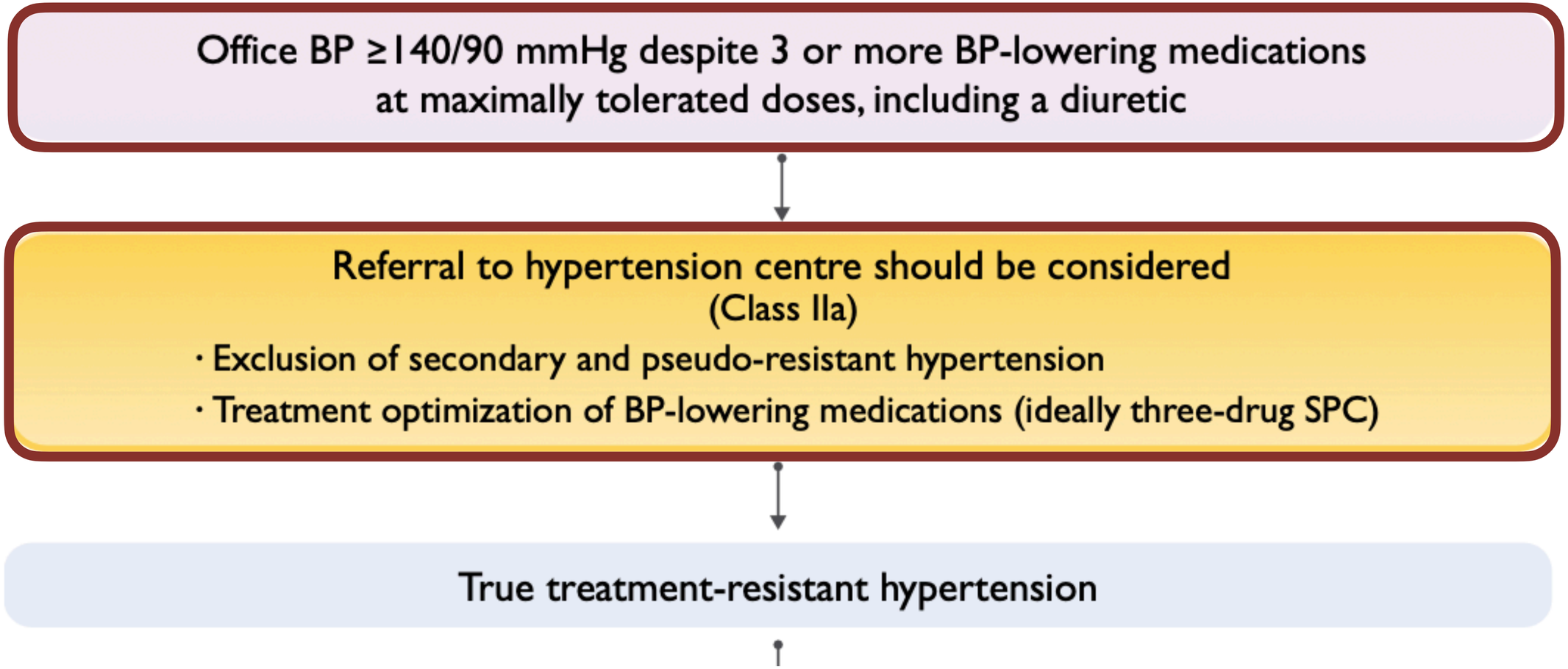
McEvoy JW, et al. Eur Heart J. 2024;45(38):3912-4018.

Management of resistant hypertension



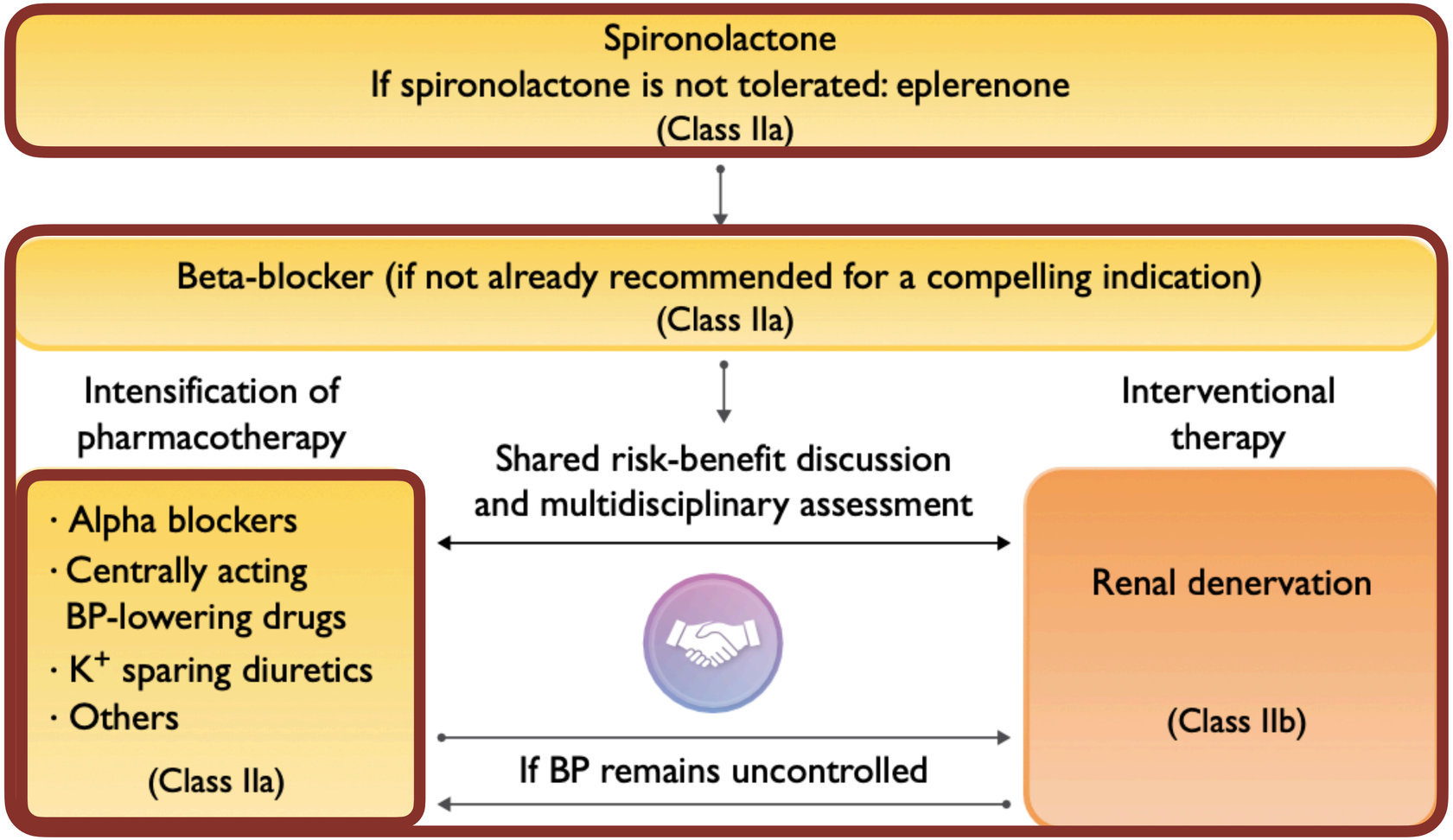
McEvoy JW, et al. Eur Heart J. 2024 Aug 30:ehae178.

Management of resistant hypertension



McEvoy JW, et al. Eur Heart J. 2024 Aug 30:ehae178.

Management of resistant hypertension



McEvoy JW, et al. Eur Heart J. 2024 Aug 30:ehae178.

Clinical manifestations of fibromuscular dysplasia

Common symptoms

- Headache 57 percent
- Pulsatile tinnitus 33 percent
- Neck pain 27 percent
- Flank pain 17 percent

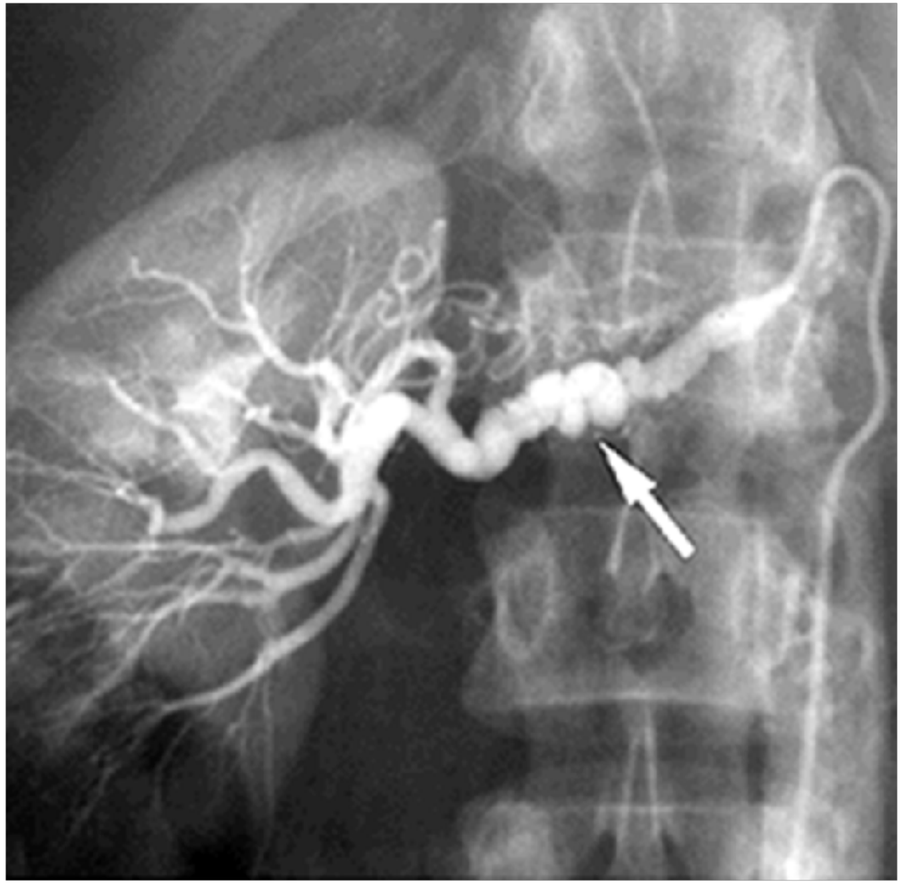
Common signs

- Hypertension 67 percent
- Cervical bruit 25 percent
- Abdominal bruit 11 percent
- TIA 10 percent
- Stroke 8 percent

Kim ES, et al. J Am Coll Cardiol 2013; 62:2026.

Fibromuscular dysplasia (FMD)

- Women 15-50 years
- Mid-portion of the vessel or at the first arterial bifurcation
- United States Registry: 447 patients:
- 75-80% in renal arteries
- 75% in extracranial cerebrovascular disease



Beaded appearance of right renal artery

Olin JW, et al. Circulation 2012; 125:3182.

Causes of renovascular hypertension

Atherosclerotic renal artery stenosis
Fibromuscular disease
Medial fibroplasia
Perimedial fibroplasia
Intimal fibroplasia
Medial hyperplasia
Extrinsic fibrous band

Herrmann SM, et al. Am J Hypertens. 2018; 31(2):139-149.

Recommendations for managing hypertension in patients with renovascular hypertension

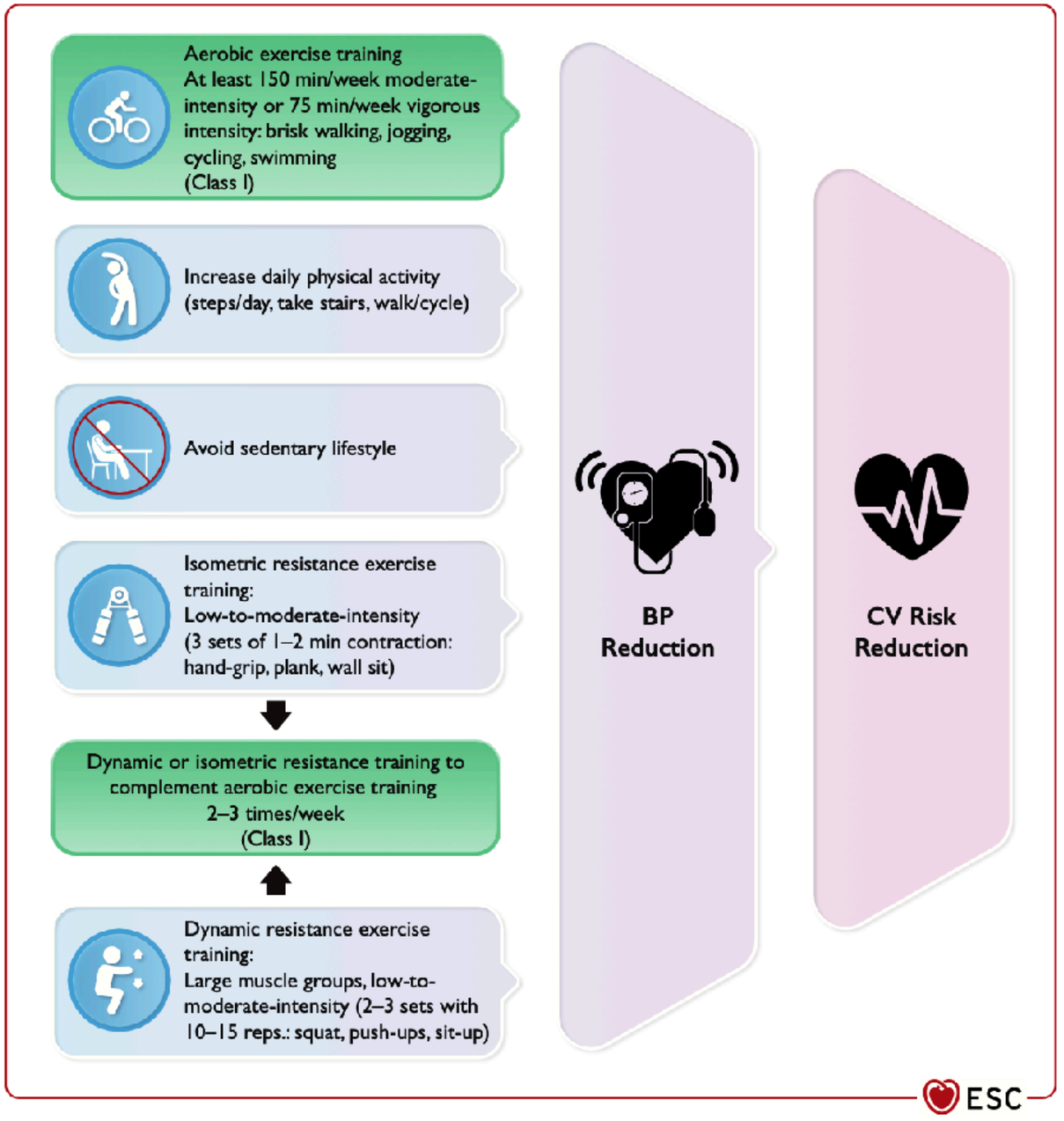
Recommendations	Class[a]	Level[b]
Renal artery angioplasty without stenting should be considered for patients with hypertension and haemodynamically significant renal artery stenosis due to fibromuscular dysplasia.[941]	IIa	C

McEvoy JW, et al. Eur Heart J. 2024;45(38):3912-4018.

	Atherosclerotic RAS	FMD
Age, y	Older age	Mean, 52 y (5–97 y)
Sex	More common in men	90% women (US registry)
Risk factors/associations	Diabetes, HTN, hyperlipidemia	Turner syndrome, Ehler-Danlos
Site of lesions	Typically involves the ostium and proximal one-third of the renal artery	Usually middle or distal segments
Typical angiographic findings	Proximal stenosis	String-of-beads appearance (multifocal) or band-like focal stenosis
Extrarenal lesions/manifestations	Atherosclerosis in other vascular beds	Headache, pulsatile tinnitus
Progression	Yes	No

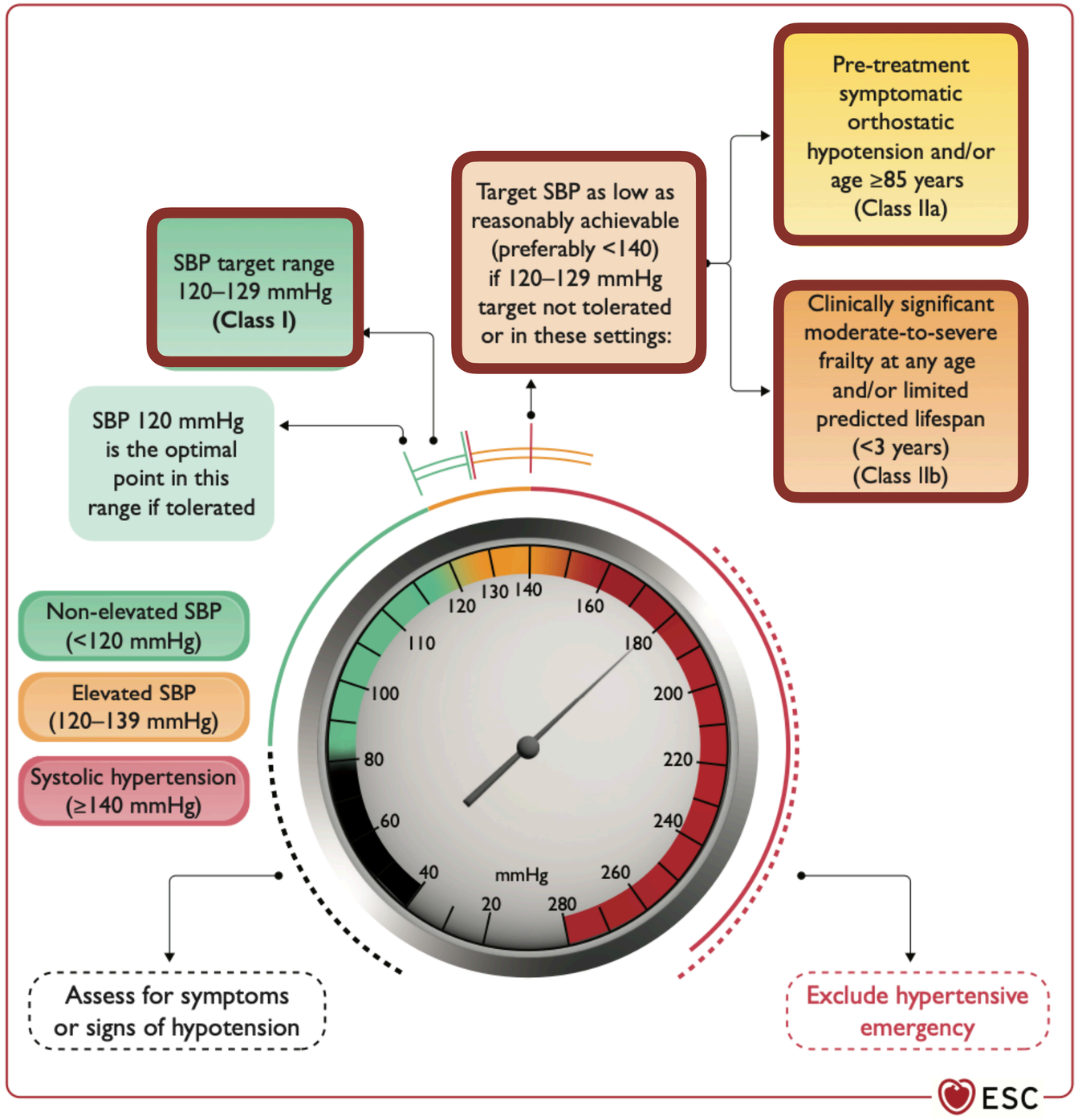
Differences between atherosclerotic RAS and FMD

Koratala A, et al. Hypertension. 2021; 77(4):1022-1028.



McEvoy JW, et al.Eur Heart J. 2024;45(38):3912-4018.

Practical algorithm for pharmacological blood pressure lowering



Recommendations	Class[a]	Level[b]
To reduce CVD risk, it is recommended that treated systolic BP values in most adults be targeted to 120–129 mmHg, provided the treatment is well tolerated.[22,122,131,523,541]	I	A
In cases where BP-lowering treatment is poorly tolerated and achieving a systolic of 120–129 mmHg is not possible, it is recommended to target a systolic BP level that is 'as low as reasonably achievable' (ALARA principle).[22,122,131,523,541]	I	A

Recommendation	Class[a]	Level[b]
Once BP is controlled and stable under BP-lowering therapy, at least a yearly follow-up for BP and other CVD risk factors should be considered.	IIa	C

McEvoy JW, et al.Eur Heart J. 2024;45(38):3912-4018.

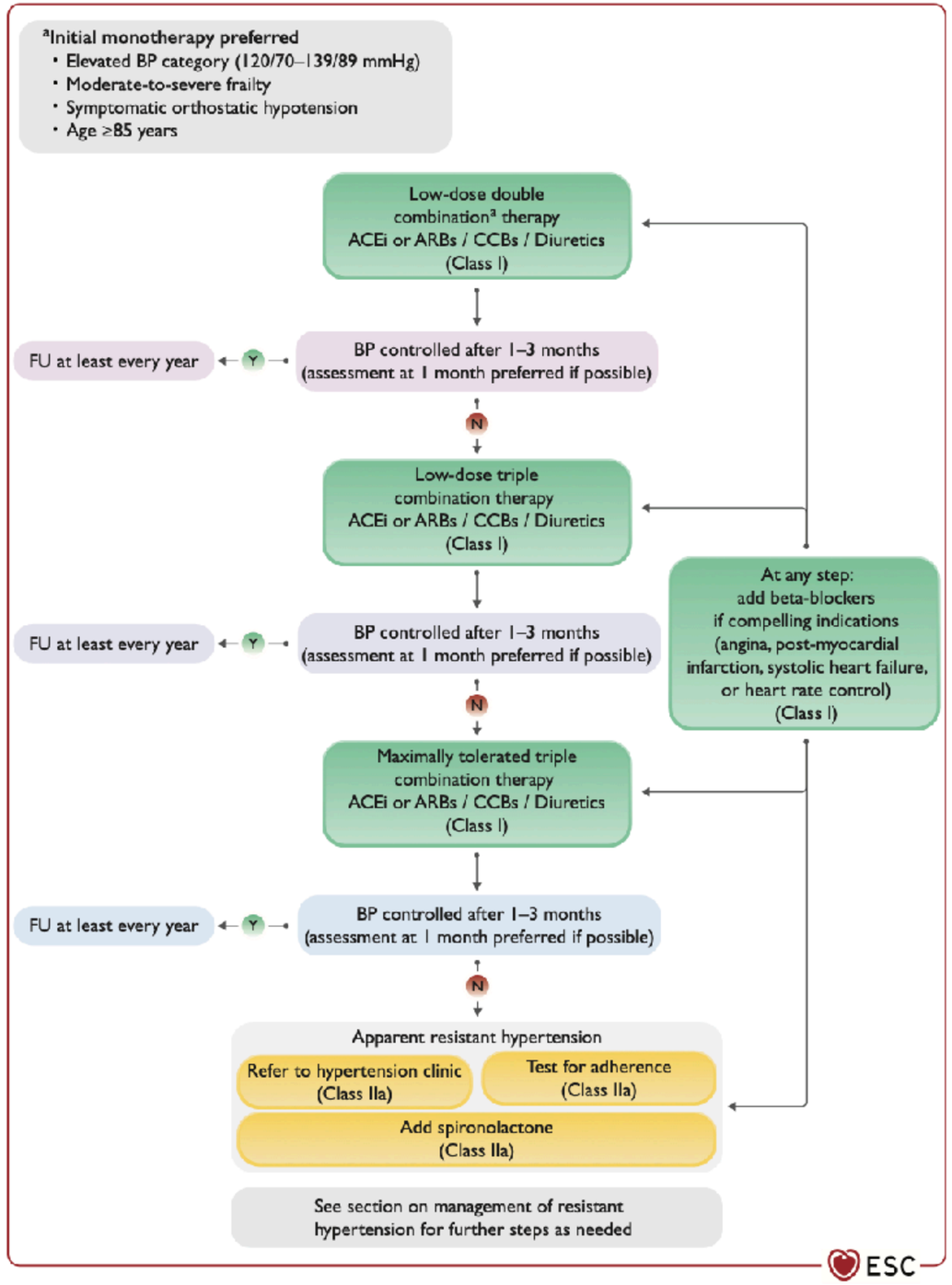
Recommendations for pharmacological treatment of hypertension

Recommendations	Class[a]	Level[b]
Among all BP-lowering drugs, ACE inhibitors, ARBs, dihydropyridine CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated the most effective reduction of BP and CVD events, and are therefore recommended as first-line treatments to lower	I	A

ACEIs, ARBs, CCBs and diuretics

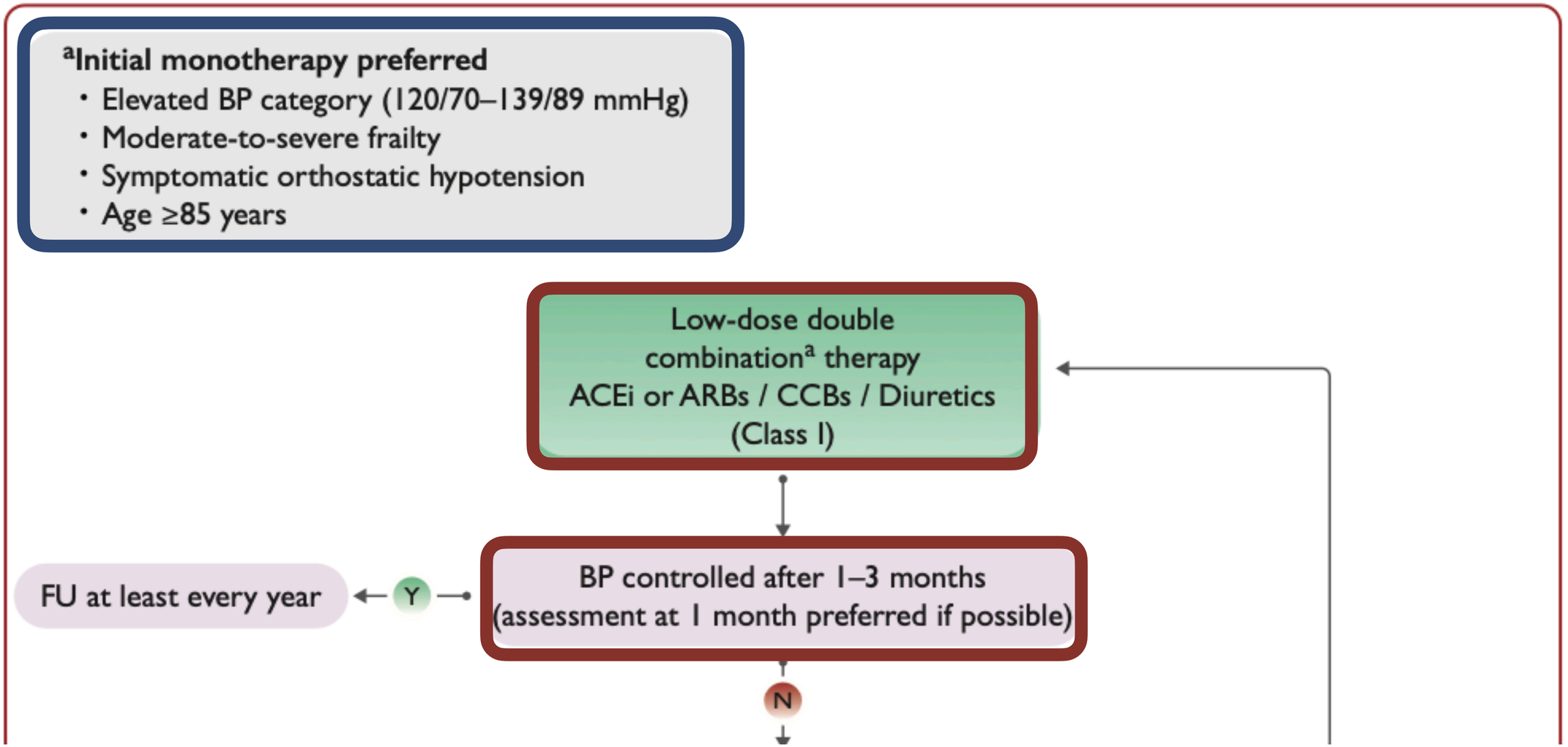
McEvoy JW, et al.Eur Heart J. 2024;45(38):3912-4018.

Practical algorithm for pharmacological blood pressure lowering



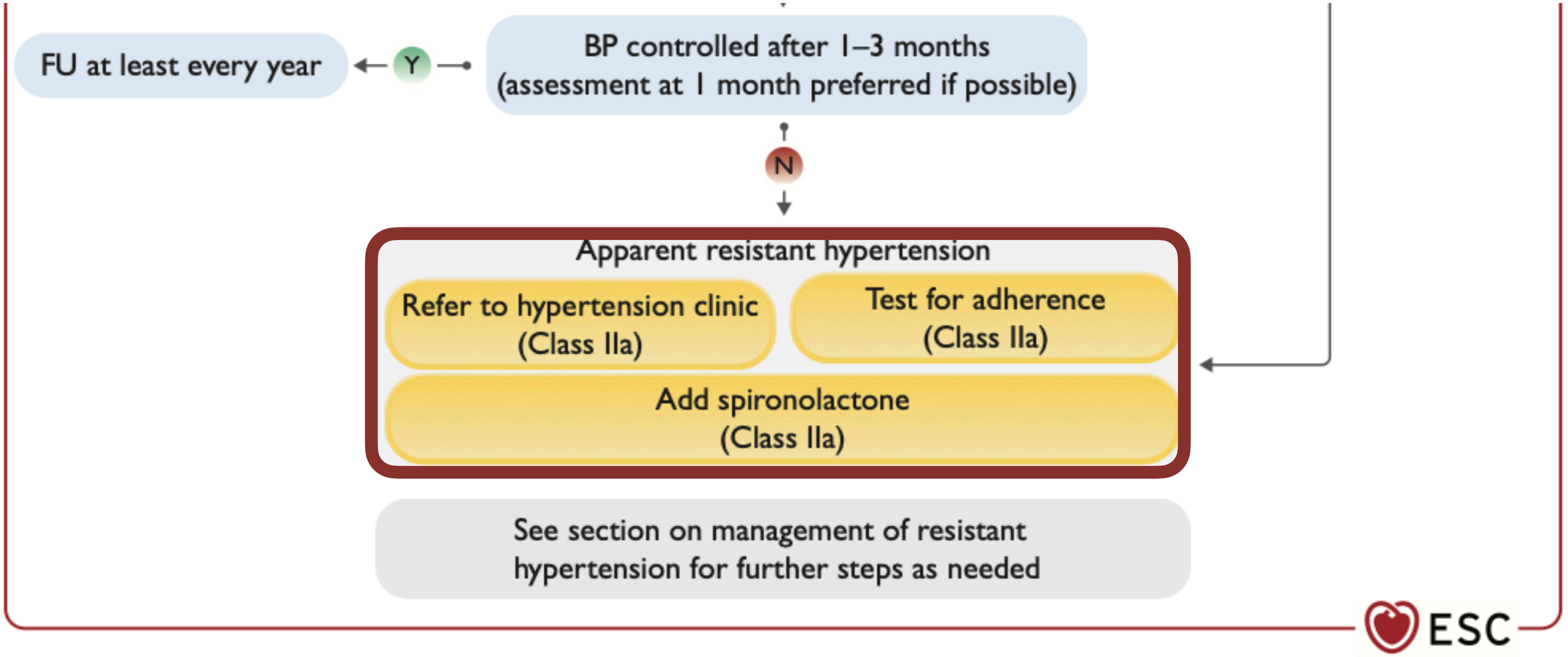
McEvoy JW, et al.Eur Heart J. 2024;45(38):3912-4018.

Practical algorithm for pharmacological blood pressure lowering



McEvoy JW, et al.Eur Heart J. 2024;45(38):3912-4018.

Practical algorithm for pharmacological blood pressure lowering



McEvoy JW, et al.Eur Heart J. 2024;45(38):3912-4018.

Causes of renovascular hypertension

Renal trauma
Arterial dissection
Segmental renal infarction
Page kidney (perirenal fibrosis)
Aortic dissection
Arterial embolus
Aortic endograft occluding the renal artery
Miscellaneous:
Hypercoagulable state with renal infarction (e.g., Lupus anticoagulate)
Autoimmune diseases (e.g., Takayasu's arteritis, Polyarteritis nodosa))
Malignancy encircling the renal artery (e.g., Renal cell carcinoma, pheochromocytoma)

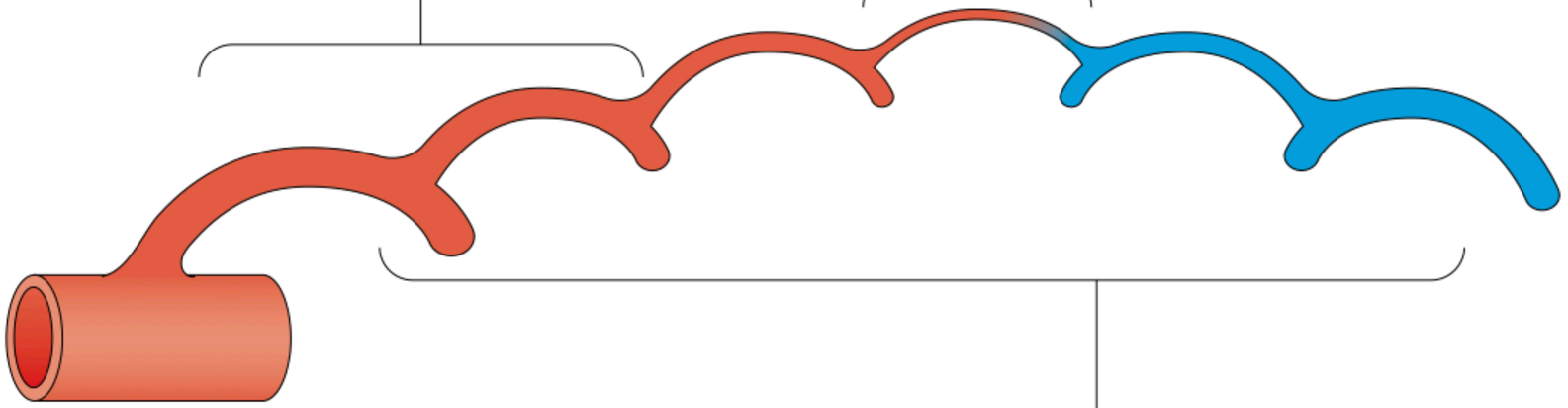
Herrmann SM, et al. Am J Hypertens. 2018; 31(2):139-149.

a

Medium vessel vasculitis
- Polyarteritis nodosa
- Kawasaki disease

Immune complex small vessel vasculitis
- Cryoglobulinaemic vasculitis
- IgA vasculitis (Henoch–Schönlein purpura)
- Hypocomplementemic urticarial vasculitis (Anti-C1q vasculitis)

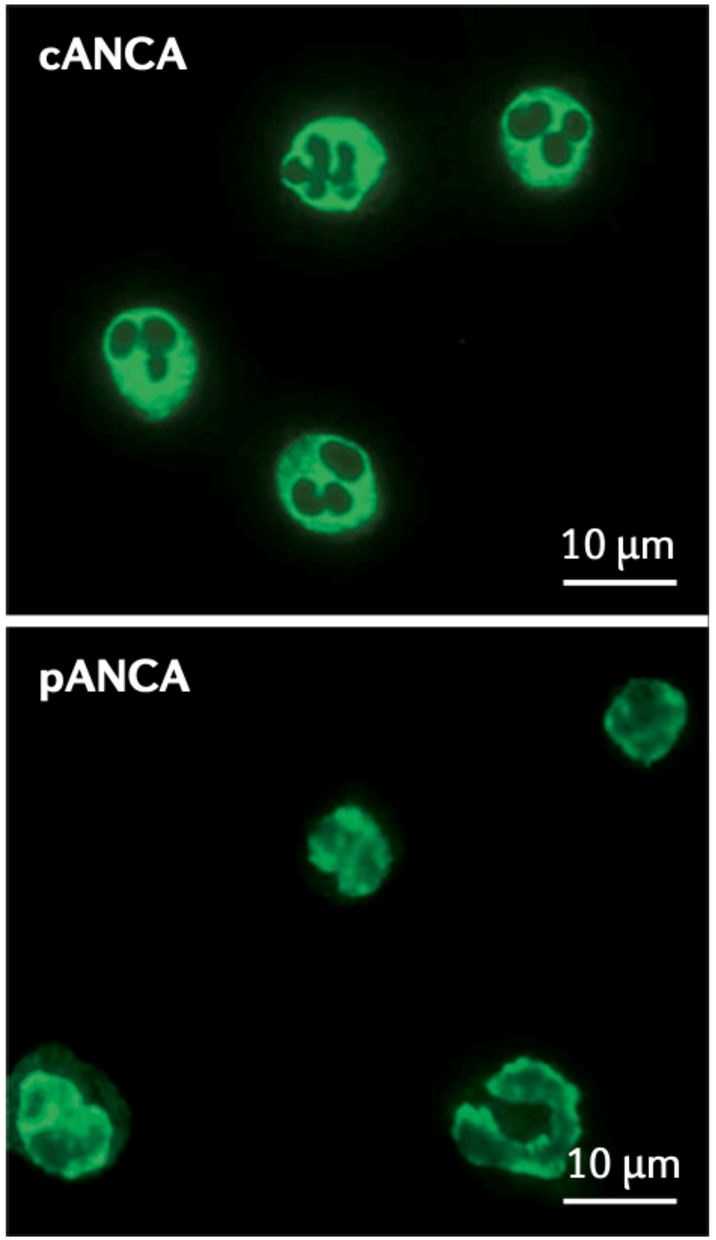
Anti-GBM disease



Large vessel vasculitis
- Takayasu arteritis
- Giant cell arteritis

ANCA-associated small vessel vasculitis
- Microscopic polyangiitis
- Granulomatosis with polyangiitis
- Eosinophilic granulomatosis with polyangiitis

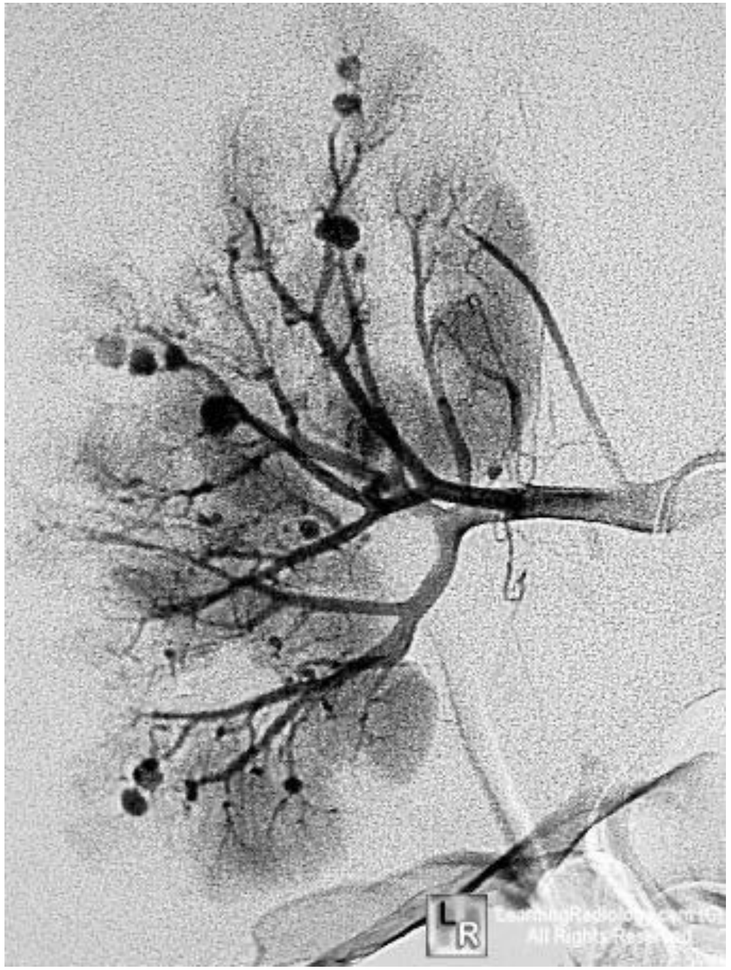
b



Kitching AR, et al. Nat Rev Dis Primers. 2020; 6(1):71.

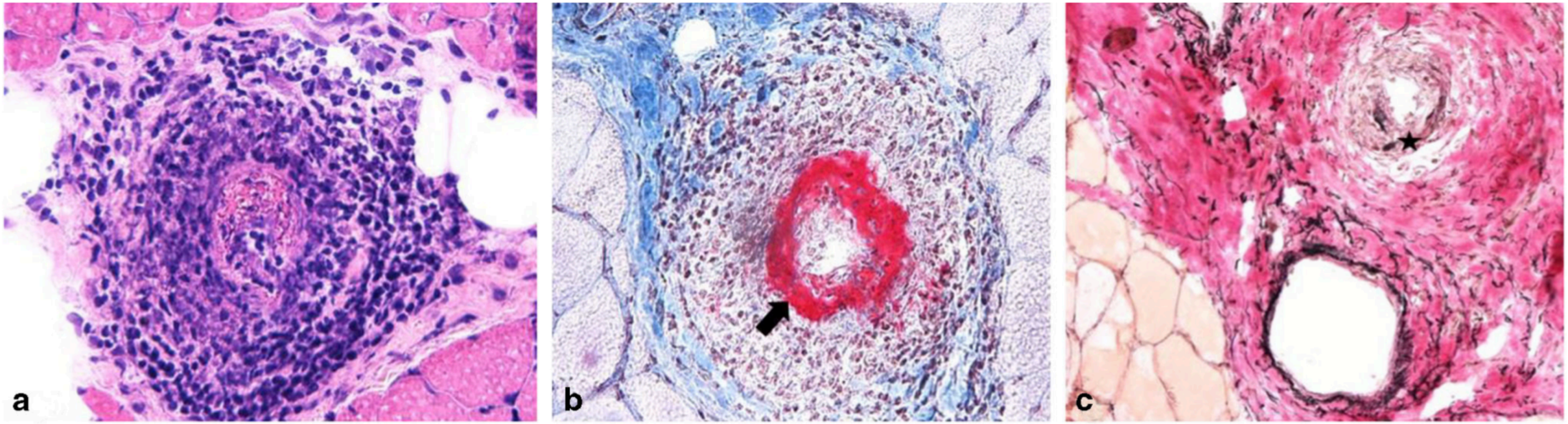
Polyarteritis nodosa (PAN)

- Systemic necrotizing inflammation of medium/small-sized muscular arteries
- Associated with hepatitis B antigenemia
- Abdominal pain, anorexia and weight loss, jaundice, hematemesis, melena
- Peripheral neuropathy
- Tender subcutaneous nodules
- Gangrene of fingers and toes
- Painless hematuria
- Necrotizing major renal artery with aneurysm formation 85%, renal infraction, renovascular HT without glomerulonephritis



Hočevar A, et al. Curr Rheumatol Rep. 2021; 23(3):14.

Medium-vessel vasculitis. Inflammatory cell infiltrate (a) with associated fibrinoid necrosis (b) and elastic fibers destruction (c)



Hočevar A, et al. Curr Rheumatol Rep. 2021; 23(3):14.

ACR 1990 classification criteria [70]	Japanese diagnostic criteria [71]
• Weight loss ≥4 kg • Livedo reticularis • Testicular pain/ tenderness • Myalgias, weakness, or leg tenderness • Mononeuropathy or polyneuropathy • Diastolic blood pressure>90 mmHg • Elevated blood urea nitrogen or creatinine • Hepatitis B virus • Arteriographic abnormality • Neutrophils in a biopsy of small-/medium-sized artery Presence of ≥3 items: 82.2% sensitivity and 86.6% specificity	• Fever or weight loss ≥4 kg • Gastrointestinal involvement • Urine protein <2+ • Mononeuropathy multiplex • Negative anti-MPO/pANCA • Angiographic/CTA/MRA abnormality • Granulocytes or mixed leukocyte infiltrates in wall of medium or small artery Presence of ≥4 items: 92.3% sensitivity; 91.7% specificity

Hočevar A, et al. Curr Rheumatol Rep. 2021; 23(3):14.
Lightfoot RW Jr, et al. Arthritis Rheum. 1990;33(8):1088e93. Yamamoto S, et al. Rheumatol Int. 2020;40(8):1223-7.

EULAR recommendations for the management of primary medium vessel vasculitis

- Treatment of idiopathic generalized PAN is guided by disease severity
  - Prednisone is usually used at doses of 1 mg/kg/day with subsequent tapering
  - Severe cases based on the combination of glucocorticoids and cyclophosphamide

We recommend a combination of cyclophosphamide (IV or oral) and glucocorticoids for remission induction of generalized primary small and median vessel vasculitis (1B for PAN)

Mukhtyar C, et al. Ann Rheum Dis 2009;68(3):310–317.

Case 3

- A 40-year-old woman presented with chronic headache, recurrent gross hematuria and UTI and BP180/100 mmHg for 20 weeks
- No abdominal bruit, both renal mass with soft consistency and no tenderness and no edema

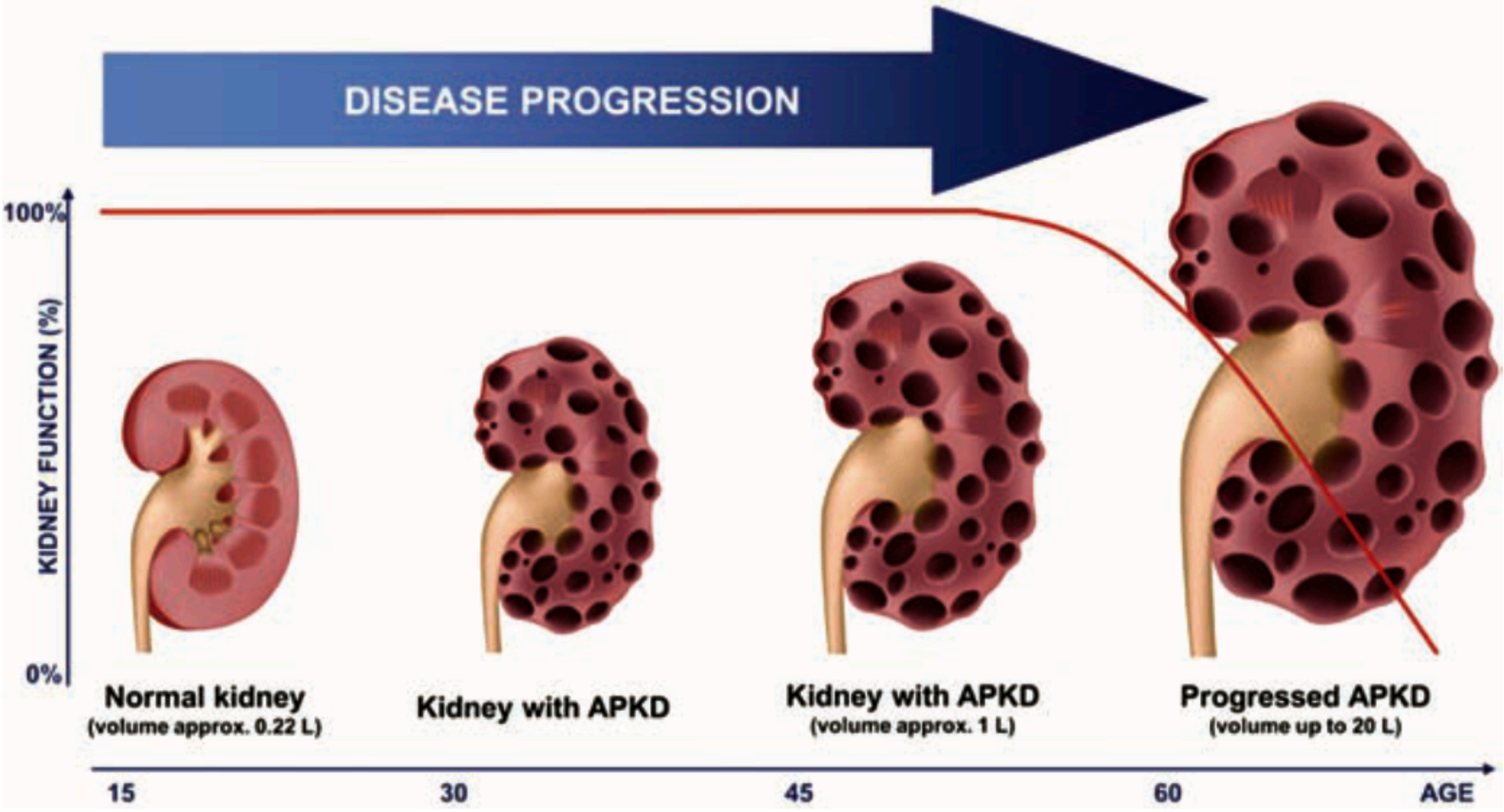
- How to approach in this patients ?

Key steps in physical examination

Signs of secondary hypertension
Skin inspection: cafe-au-lait patches of neurofibromatosis (phaeochromocytoma/paraganglioma).
Kidney palpation for signs of renal enlargement (polycystic kidney disease).
Auscultation of heart and renal arteries for murmurs or bruits indicative of aortic coarctation, or renovascular hypertension.
Comparison of radial with fe individuals with aortic coarctation (aortic murmur may also be heard).
Signs of Cushing's disease or acromegaly.
Signs of thyroid or parathyroid disease.
Neck circumference of >40 cm in men, >35 cm in women (OSAS).

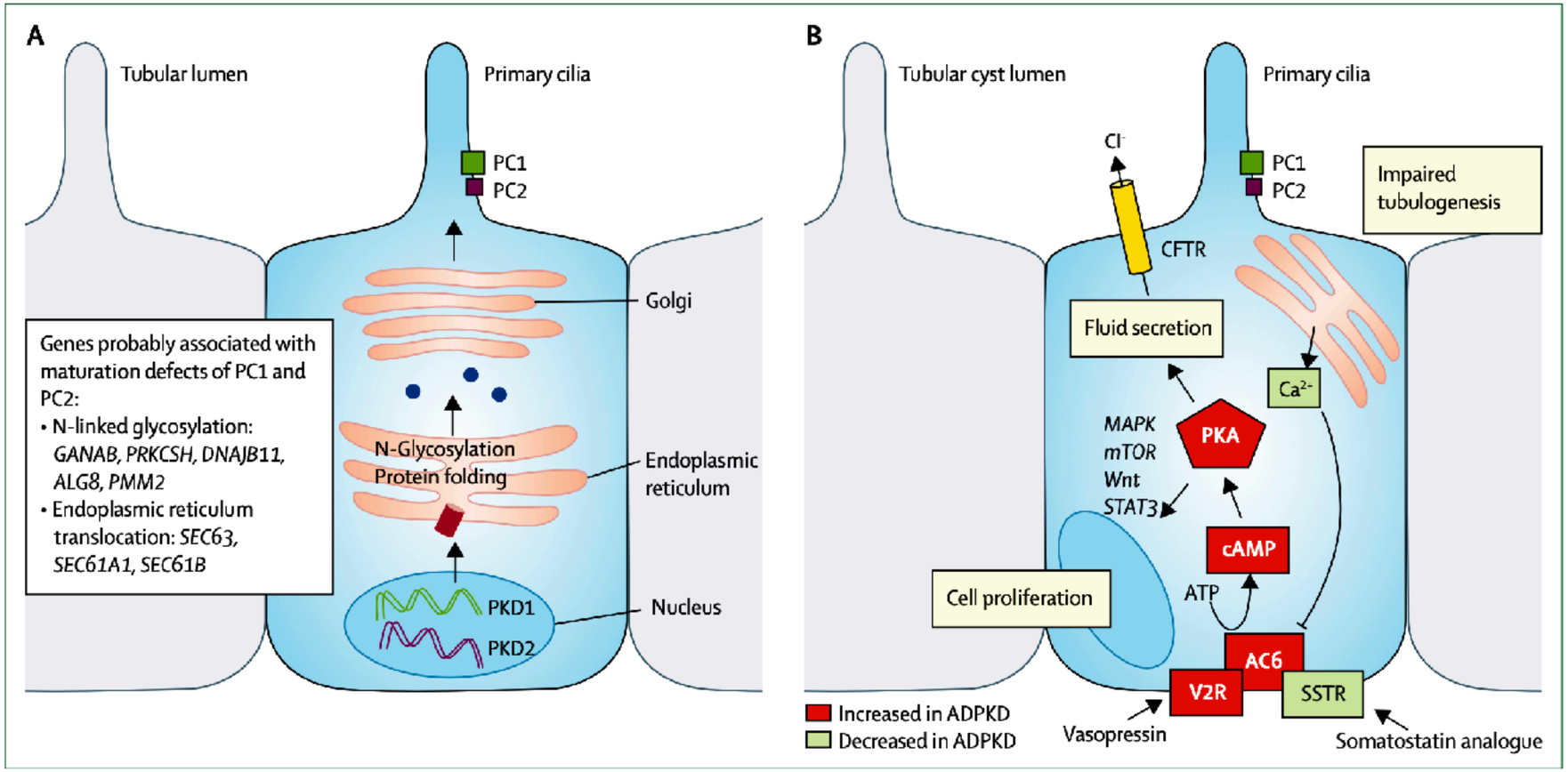
Renal enlargement (PKD)

McEvoy JW, et al. Eur Heart J. 2024;45(38):3912-4018.



Patel SJ, Sadowski CK. JAAPA. 2023 Jun 1;36(6):11-16.

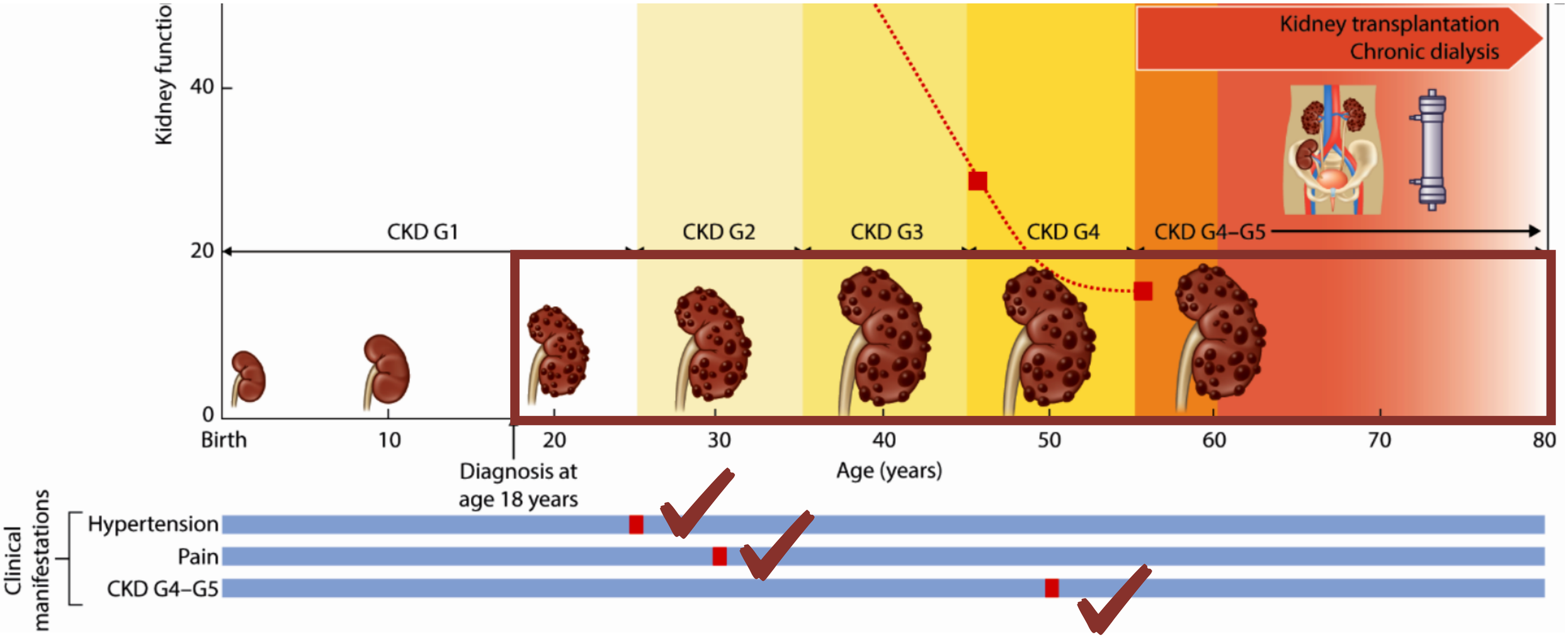
Cystogenesis mechanisms in ADPKD



Maturation and processing of PC1 and PC2 in tubular epithelial cells

High intracellular titres in cAMP result in the subsequent activation of PKA

Cornec-Le Gall E, et al. Lancet. 2019; 393(10174):919-935.



KDIGO 2023 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION, MANAGEMENT, AND TREATMENT OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD): Draft 2023

Renal manifestations in ADPKD

Manifestation	Prevalence	Comments
Renal		
Urinary concentration defect[a]	Up to 60% of children	Earliest manifestation of mild polyuria is often undetected
Hypertension[a]	• 50–70% of patients prior to GFR decline • Average age of onset is 30 years • At least 20–40% of children	Screen children with family history of ADPKD from 5 years of age, then at 3-year intervals if negative for hypertension
ESRD[a]	**PKD1 age 56-68 yr PKD2 age 78 yr**	Mean age of onset of 56 years (truncating *PKD1* mutations), 68 years (non-truncating *PKD1* mutations) or 78 years (*PKD2* mutations)
Proteinuria (>300 mg/day)	Associated with GFR decline	Prognostic marker of ADPKD
Abdominal or flank pain	>60% of adult patients	• Acute or chronic • Multiple causes
Nephrolithiasis	20–35% of adult patients	Uric acid and/or calcium oxalate stones
Cyst haemorrhage and/or gross haematuria	Up to 60% of adult patients	Most haemorrhages resolve within 2–7 days without intervention
Urinary tract infection[a]	30–50% of adult patients	More common in women than in men
Renal cell carcinoma	**<1% of adults patients**	Risk not increased compared with the general population, but patients can present with systemic symptoms of cancer

Bergmann C, et a. Nat Rev Dis Primers. 2018; 4(1):50.

Extrarenal manifestations in ADPKD

Extrarenal		
Polycystic liver disease	>80% of patients by 30 years of age	Include liver imaging in initial visit; further follow-up dependent on result of imaging
ICA	• 8% of all adult patients • 21% of adult patients with a family history of ICA	Screen if family history of subarachnoid haemorrhage or ICA, personal history of intracranial haemorrhage, individuals working in high-risk professions and before major elective surgery (including before transplantation)
Arachnoid cysts	8% of adult patients	Possible increased risk of spontaneous subdural haematoma
Mitral valve prolapse or bicuspid aortic valve	Up to 25% of adult patients	Screen when there is a heart murmur or symptoms
Idiopathic dilated cardiomyopathy or left ventricular non-compaction	Rare	Screen when there is a family history of these conditions
Pericardial effusion	Up to 35% of adult patients	Screen if symptoms of pericardial effusion are present
Pancreatic cysts	10% of adult patients	No screening needed
Diverticulosis	Up to 50% of patients with ESRD	Increased risk of diverticulum perforation following renal transplantation
Bronchiectasis	Up to 35–40% of adult patients	Mild; no screening needed
Congenital hepatic fibrosis[a]	Rare (on the basis of case reports)	No screening needed
Seminal vesicle cysts	Up to 40% of men	No correlation to semen abnormalities
Male infertility	Associated with ADPKD	Abnormal semen parameters reported

Bergmann C, et a. Nat Rev Dis Primers. 2018; 4(1):50.

Problem list

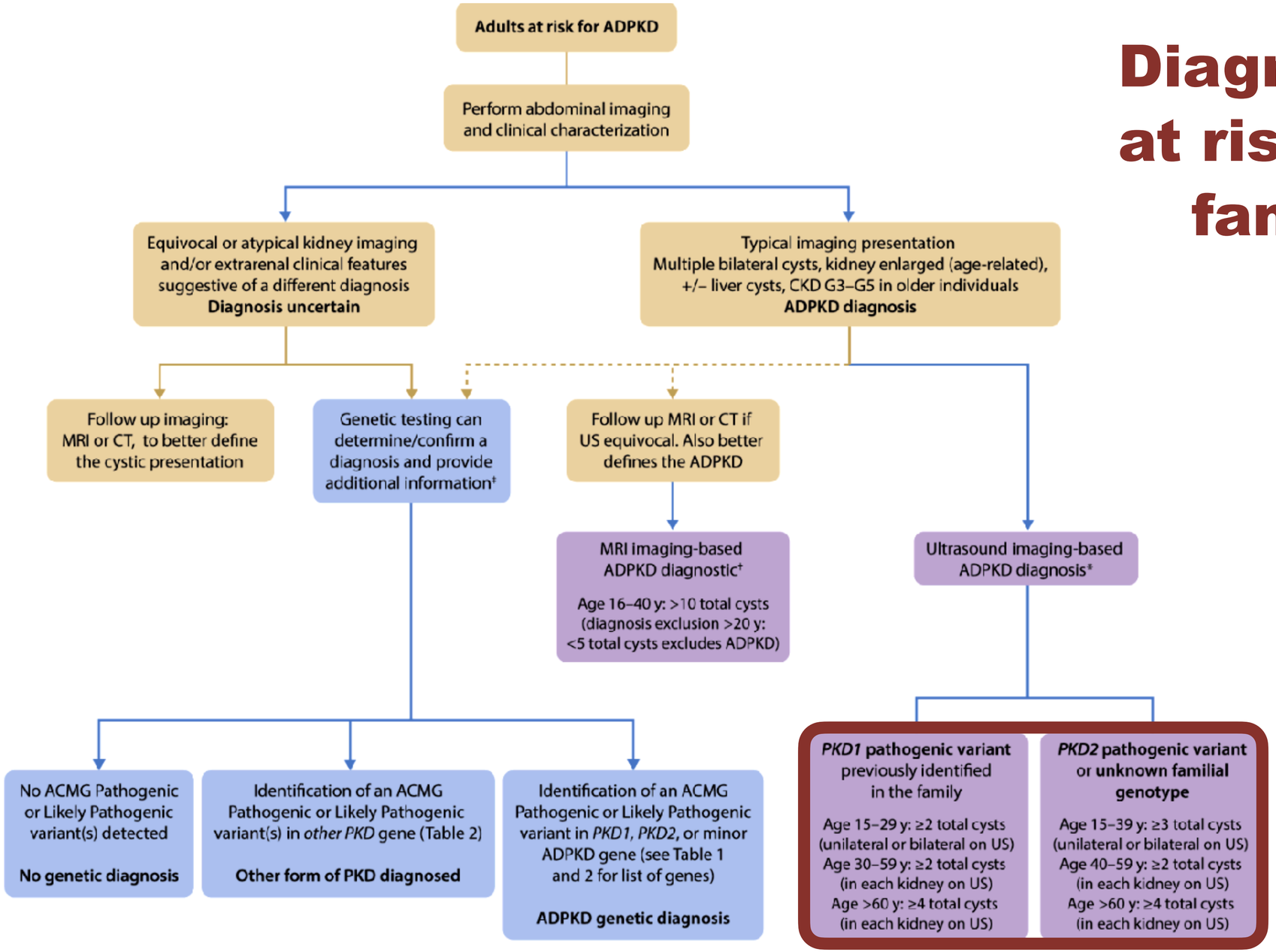
- **Uncontrolled hypertension, chronic headache, recurrent gross hematuria, UTI and both renal mass**

Case 3

- A 40-year-old woman presented with chronic headache, recurrent gross hematuria and UTI and BP180/100 mmHg for 20 weeks
- No abdominal bruit, both renal mass with soft consistency and no tenderness and no edema

- What is the further investigation ?

Diagnosis algorithm in at risk adults (positive family history) for ADPKD)



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Diagnosis algorithm in at risk adults (positive family history) for ADPKD

PKD1 pathogenic variant previously identified in the family	*PKD2* pathogenic variant or unknown familial genotype
Age 15–29 y: ≥2 total cysts (unilateral or bilateral on US)	Age 15–39 y: ≥3 total cysts (unilateral or bilateral on US)
Age 30–59 y: ≥2 total cysts (in each kidney on US)	Age 40–59 y: ≥2 total cysts (in each kidney on US)
Age >60 y: ≥4 total cysts (in each kidney on US)	Age >60 y: ≥4 total cysts (in each kidney on US)

Pei Y, et al. J Am Soc Nephrol 2009; 20: 205-212.

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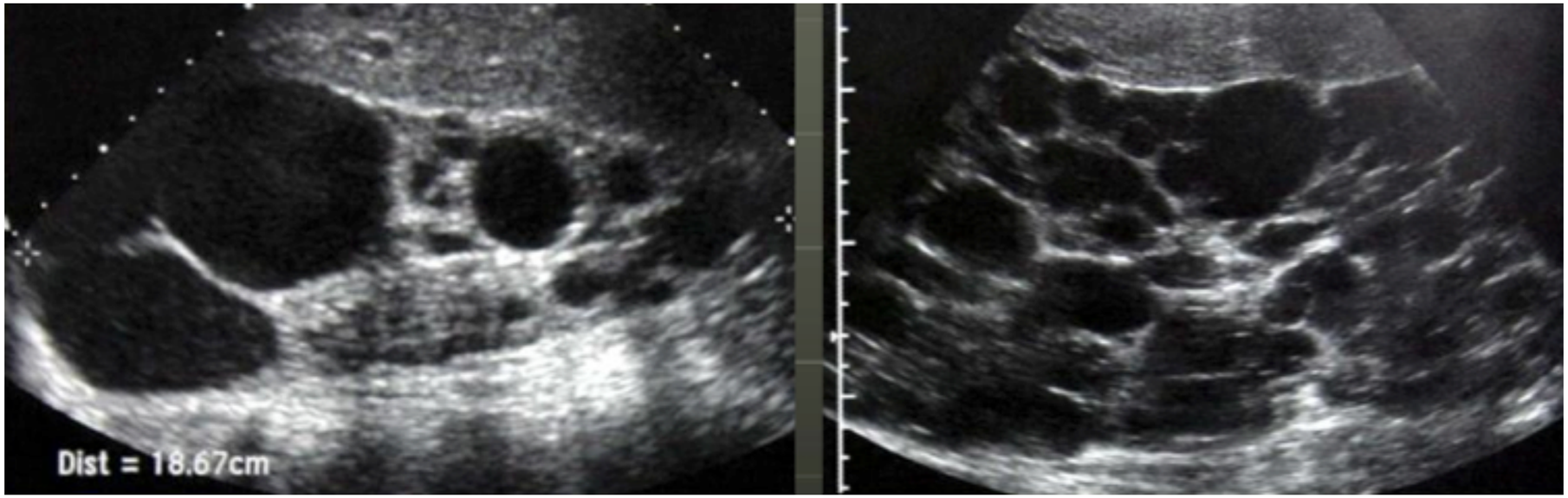
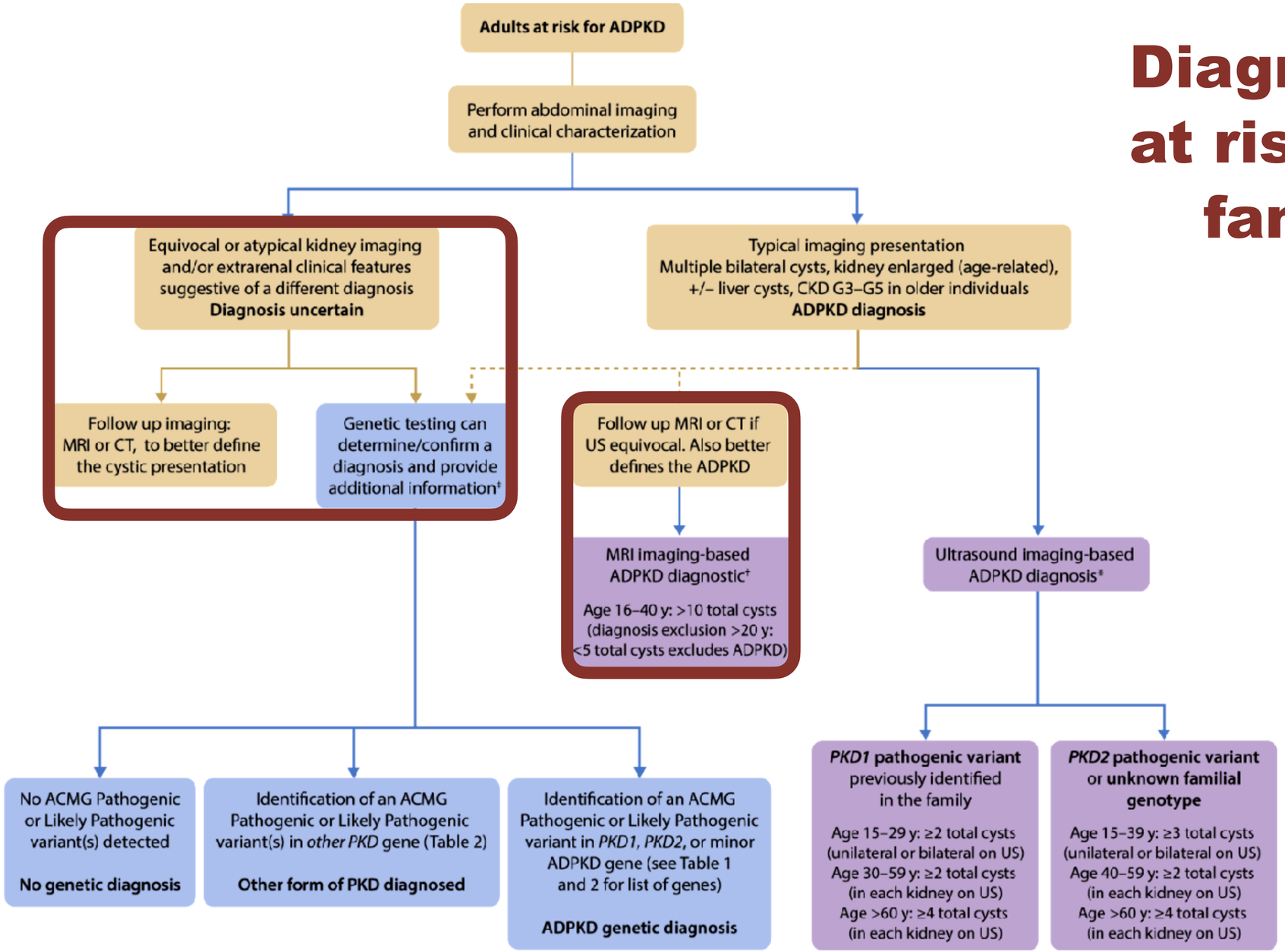
Autosomal dominant polycystic kidney disease

- Both kidneys have enlarged size
- Innumerable varying in size anechoic cystic lesions occupy in both kidneys, and some anechogenic cysts in liver



Diagnosis algorithm in at risk adults (positive family history) for ADPKD)



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MRI criteria for ages 16-40 years in people with a positive family history

>10 cysts total	Sufficient for diagnosis (PPV and sensitivity = 100)
<5 cysts total	Sufficient for exclusion (NPV and specificity = 100)

Pei Y, et al. J Am Soc Nephrol 2015; 26: 746-753.
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Diagnosis of ADPKD

Recommendation	Evidence
When making an initial diagnosis of ADPKD in an adult at risk, we recommend first using abdominal imaging by ultrasound. Follow-up magnetic resonance imaging (MRI) or computed tomography (CT) imaging may clarify the diagnosis and can provide prognostic information through MIC classification (1B).	**1B**

Genetic testing is particularly informative for people with an equivocal diagnosis based on kidney imaging and in the setting of a negative or unknown family history

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Genetic testing can clarify the diagnosis and aid prognosis

Situation
Limited number of cysts
Variable disease severity in a family
Atypical imaging, including asymmetric or unilateral disease

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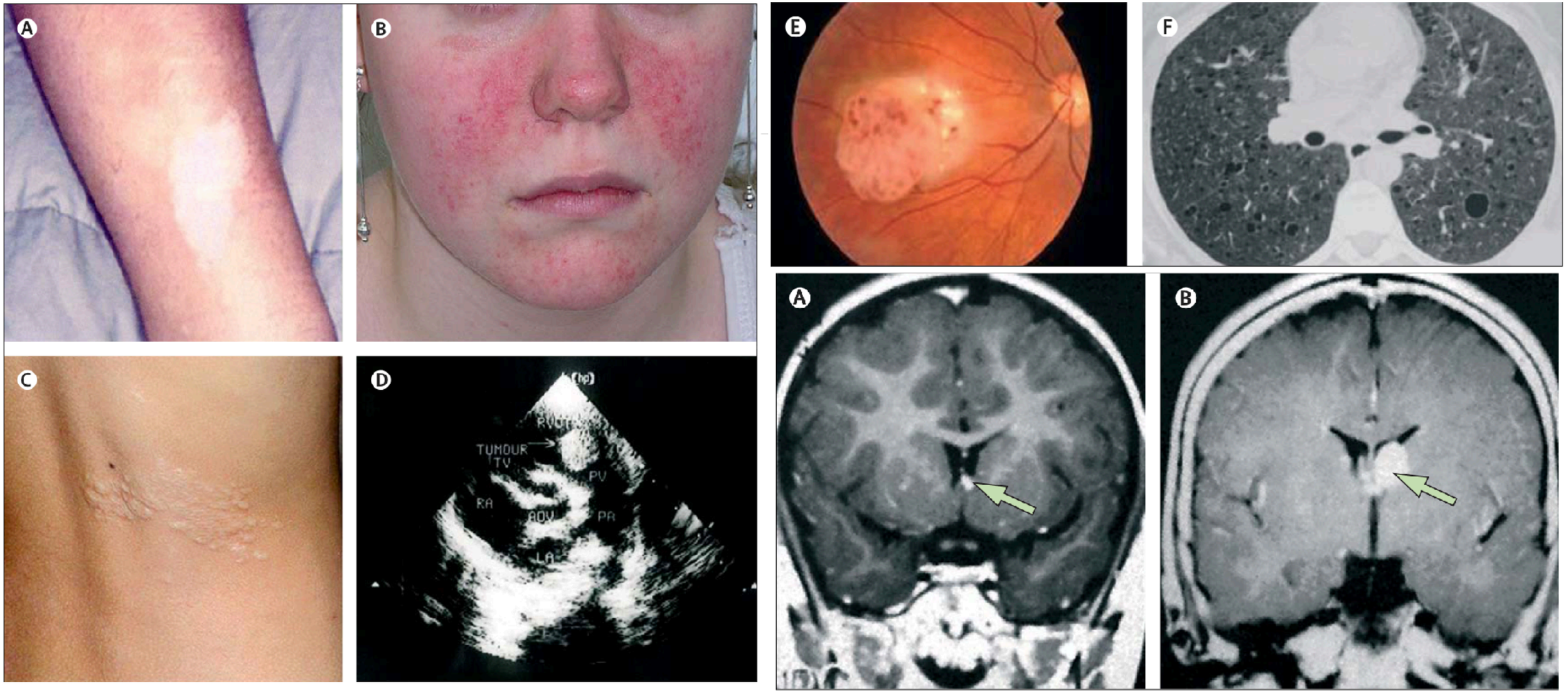
Syndromic forms of PKD

Tuberous sclerosis	Multiple and bilateral angiomyolipomas and renal cysts; kidney function usually preserved; possible evolution to ESKD, either by destruction of the renal parenchyma by multiple angiomyolipomas or following nephrectomies for haemorrhagic angiomyolipomas; if there is contiguous gene deletion of *TSC2* and *PKD1*, severe PKD with evolution to ESKD occurs before age 30 years
Von Hippel-Lindau disease	Bilateral renal cysts, renal cell carcinoma
HANAC syndrome or *COL4A1*-related disease	Bilateral renal cysts occasionally reported; patients can develop renal insufficiency after about age 50–60 years
Oro-facial-digital syndrome type 1	X-linked, embryonically lethal in boys, PKD in women

Cornec-Le Gall E, et al. Lancet. 2019; 393(10174):919-935.



Hypomelanotic macules (A). Facial angiofibromas (B). Shagreen patch (C). Hyperechoic rhabdomyoma detected by echocardiography (D). Retinal hamartoma (E). Lymphangiomyomatosis (F)

Curatolo P, et al. Lancet. 2008; 372(9639):657.

Autosomal dominant tuberous sclerosis complex

- Multiple kidney cysts
- Renal angiomyolipomas
- Facial angiofibromas
- Hypomelanotic macules
- Retinal nodular hamartomas

Major Criteria	Minor Criteria
Hypomelanotic macules (≥3; at least 5 mm diameter)	"Confetti" skin lesions
Angiofibroma (≥3) or fibrous cephalic plaque	Dental enamel pits (≥3)
Ungual fibromas (≥2)	Intraoral fibromas (≥2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Multiple cortical tubers and/or radial migration lines	Nonrenal hamartomas
Subependymal nodule (≥2)	Sclerotic bone lesions
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
LAM*	
Angiomyolipomas (≥2)*	

Definite TSC: 2 major features or 1 major feature with 2 minor features.
Possible TSC: either 1 major feature or ≥2 minor features.

Northrup H, et al Pediatr Neurol. 2021; 123:50-66.

Organ System or Specialty Area	Recommendations
Genetics	Obtain three-generation family history to assess for additional family members at risk of TSC. Offer genetic testing for family counseling or when TSC diagnosis is in question but cannot be clinically confirmed.
Brain	Obtain MRI of the brain to assess for the presence of tubers, SEN, migrational defects, and SEGA. During infancy, educate parents to recognize infantile spasms and focal seizures, even if none have occurred at the time of first diagnosis. Obtain baseline routine EEG while awake and asleep. If abnormal, especially if features of TAND are also present, follow-up with 8- to 24-h video-EEG to assess for seizure activity.
TAND	Perform comprehensive assessment for all levels of potential TAND manifestations (see Fig of TAND umbrella for details of levels). Refer as appropriate to suitable professionals to initiate evidence-based interventions based on the TAND profile of above-identified needs. Provide parent/caregiver education and training about TAND to ensure families know what to look out for in emerging TAND manifestations (e.g. autism spectrum disorder, language disorders, attention-deficit/hyperactivity disorder, anxiety disorders). Provide psychological and social support to families around diagnosis, coming to terms with the diagnosis of TSC and TAND, and ensure strategies are in place to support caregiver well-being.
Kidney	Obtain MRI of the abdomen to assess for the presence of angiomyolipomas and renal cysts. Screen for hypertension by obtaining an accurate blood pressure. Evaluate renal function by determination of GFR.
Lung	Inquire about tobacco exposure, connective tissue disease manifestations, signs of chyle leak, and pulmonary manifestations of dyspnea, cough, and spontaneous pneumothorax in all adult patients with TSC. Perform baseline chest CT in all females, and symptomatic males, starting at age 18 years or older. Perform baseline PFTs and 6MWT in patients with evidence of cystic lung disease consistent with LAM on the screening chest CT.
Skin	Perform a detailed clinical dermatologic inspection/examination.
Teeth	Perform a detailed clinical dental inspection/examination.
Heart	Consider fetal echocardiography to detect individuals with high risk of heart failure after delivery when rhabdomyomas are identified via prenatal ultrasound. Obtain an echocardiography in pediatric patients, especially if younger than age three years. Obtain an electrocardiography at all ages to assess for underlying conduction defects.
Eye	Perform a complete ophthalmologic evaluation, including dilated fundoscopy, to assess for retinal findings (astrocytic hamartoma and achromic patch) and visual field deficits.

Organ System or Specialty Area	Recommendations
Genetics	Obtain three-generation family history to assess for additional family members at risk of TSC. Offer genetic testing for family counseling or when TSC diagnosis is in question but cannot be clinically confirmed.
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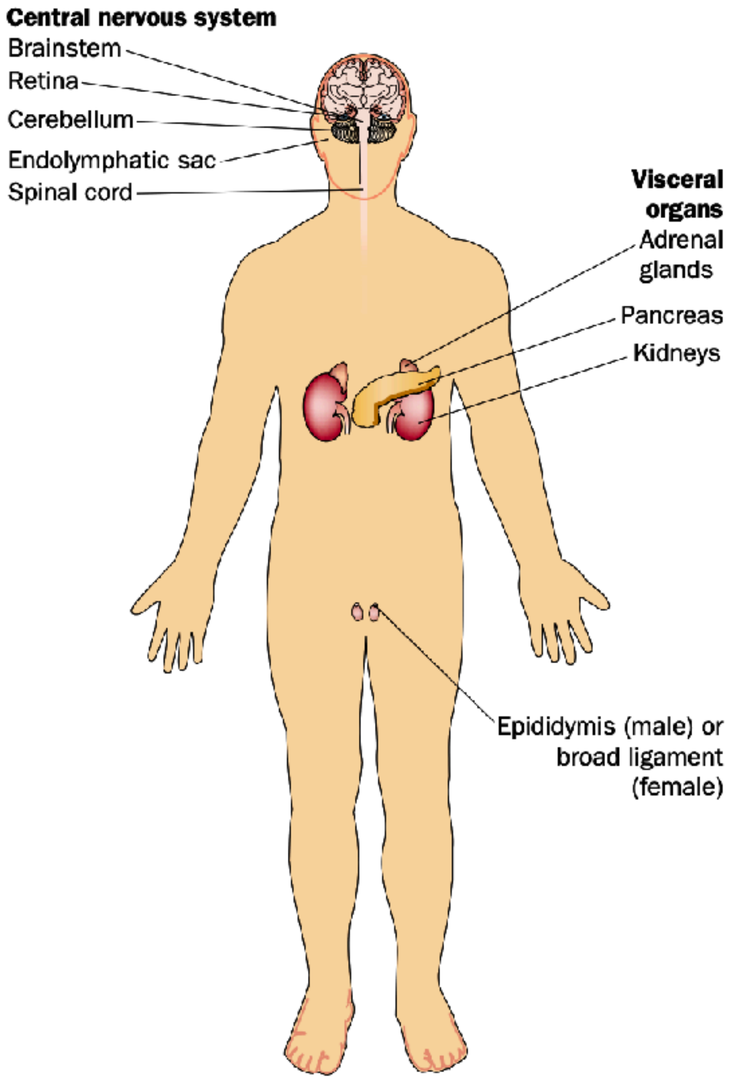
TAND	Perform comprehensive assessment for all levels of potential TAND manifestations (see Fig of TAND umbrella for details of levels). Refer as appropriate to suitable professionals to initiate evidence-based interventions based on the TAND profile of above-identified needs. Provide parent/caregiver education and training about TAND to ensure families know what to look out for in emerging TAND manifestations (e.g. autism spectrum disorder, language disorders, attention-deficit/hyperactivity disorder, anxiety disorders).
Kidney	❖ Obtain MRI of the abdomen to assess for the presence of angiomyolipomas and renal cysts ❖ Screen for hypertension by obtaining an accurate blood pressure ❖ Evaluate renal function by determination of GFR
Lung	
Skin	Perform a detailed clinical dermatologic inspection/examination.
Teeth	Perform a detailed clinical dental inspection/examination.
Heart	Consider fetal echocardiography to detect individuals with high risk of heart failure after delivery when rhabdomyomas are identified via prenatal ultrasound. Obtain an echocardiography in pediatric patients, especially if younger than age three years. Obtain an electrocardiography at all ages to assess for underlying conduction defects.
Eye	Perform a complete ophthalmologic evaluation, including dilated fundoscopy, to assess for retinal findings (astrocytic hamartoma and achromic patch) and visual field deficits.

Northrup H, et al Pediatr Neurol. 2021; 123:50-66.

von Hippel-Lindau disease

- Heritable multisystem cancer syndrome
- Germline mutation of the VHL tumour suppressor gene on the short arm of chromosome 3.
- Kidney cysts
- Retinal hemangiomas
- Clear cell carcinomas of the kidney
- Cerebellar and spinal hemangioblastomas
- Pheochromocytoma
- Endocrine pancreatic tumors



Lonser RR, et al. Lancet. 2003; 361(9374):2059-67.

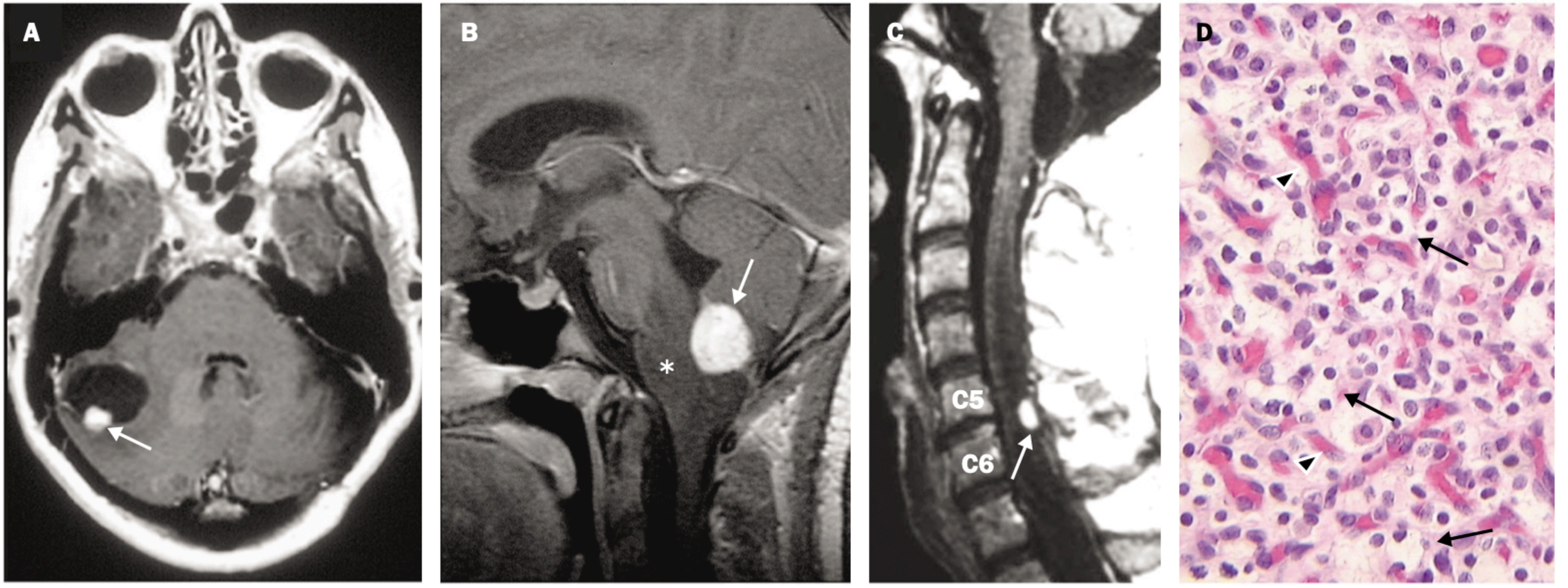


Figure 3: **MRI and histological features of CNS haemangioblastomas**

(A) Axial T1-weighted contrast-enhanced MRI of a cerebellar haemangioblastoma (arrow) with an associated cyst (homogeneous associated dark region) in a 40-year-old woman. (B) Mid-sagittal T1-weighted postcontrast MRI of medullary haemangioblastoma (arrow) with associated brainstem oedema (asterisk) in a 12-year-old girl. (C) Mid-sagittal postcontrast T1-weighted MRI of the spinal cord of a 50-year-old man. The haemangioblastoma is located in the posterior portion of the spinal cord at C5 and C6 (arrow), and is associated with a large syrinx (dark intraspinal region extending rostral and caudal to the lesion). (D) Haematoxylin and eosin staining of a haemangioblastoma showing the lipid-laden stromal cells (arrows) distributed within a capillary network (arrowheads).

Lonser RR, et al. Lancet. 2003; 361(9374):2059-67.

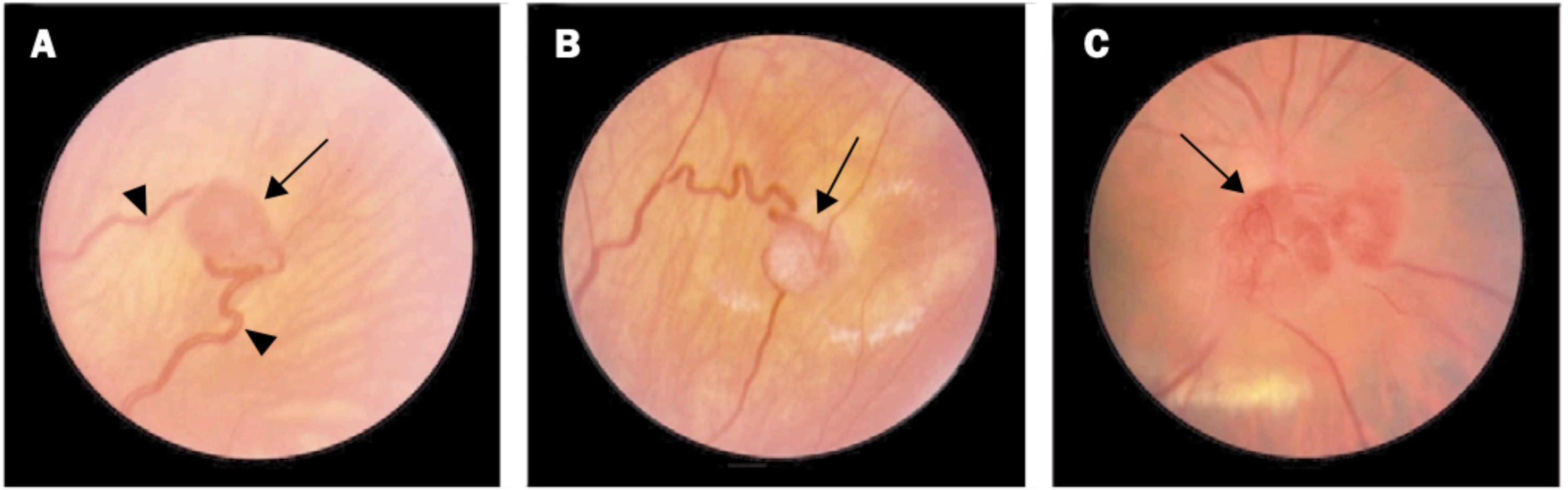


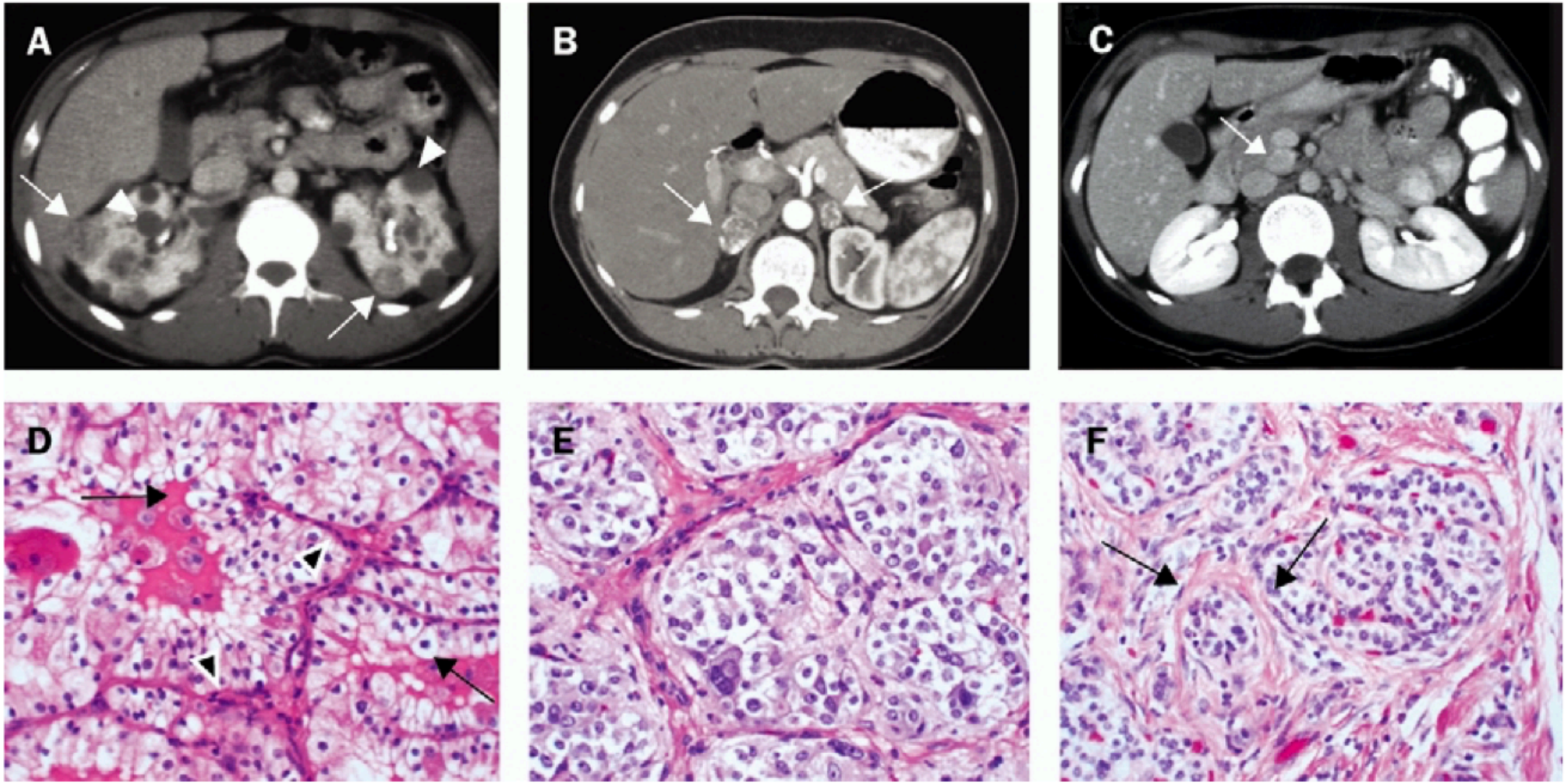
Figure 4: **Ophthalmoscopic view of retinal haemangioblastomas**
(A) Peripheral retinal haemangioblastoma (arrow) with an enlarged vessel (arrowheads) in a 22-year-old woman. (B) Peripheral retinal haemangioblastoma (arrow) with fibrous changes, and hard exudates and retinal oedema in the surrounding region in a 24-year-old man. (C) Retinal haemangioblastoma (arrow) on the optic nerve head with yellow retinal hard exudates below it in a 32-year-old man.

Lonser RR, et al. Lancet. 2003; 361(9374):2059-67.

Bilateral multifocal renal cell carcinoma

Bilateral phaeochromocytomas

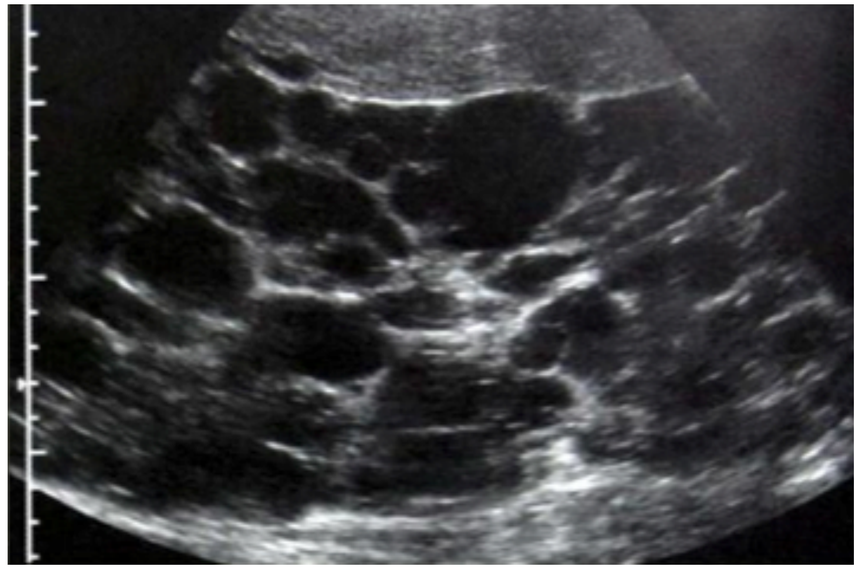
Pancreatic neuroendocrine tumour



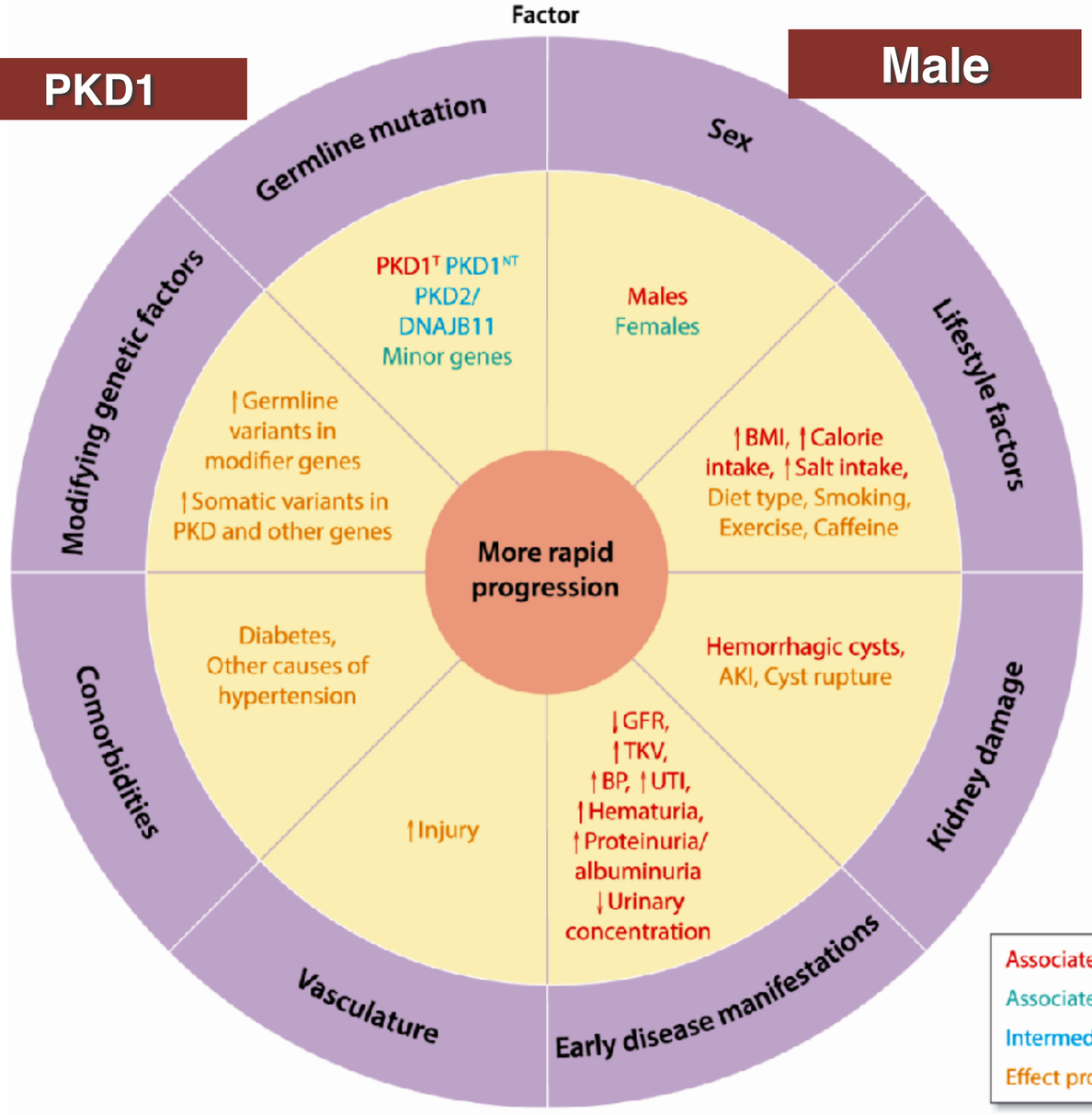
Lonser RR, et al. Lancet. 2003; 361(9374):2059-67.

Case 3

- A 40-year-old woman presented with chronic headache, recurrent gross hematuria and UTI and BP180/100 mmHg for 20 weeks
- No abdominal bruit, both renal mass with soft consistency and no tenderness and no edema
- What is the definite treatment?



Factors associated with the rate of disease progression in ADPKD



- ↓ GFR
- ↑ TKV
- ↑ BP
- ↑ UTI
- Hematuria
- Proteinuria
- ↓ Urine concentration

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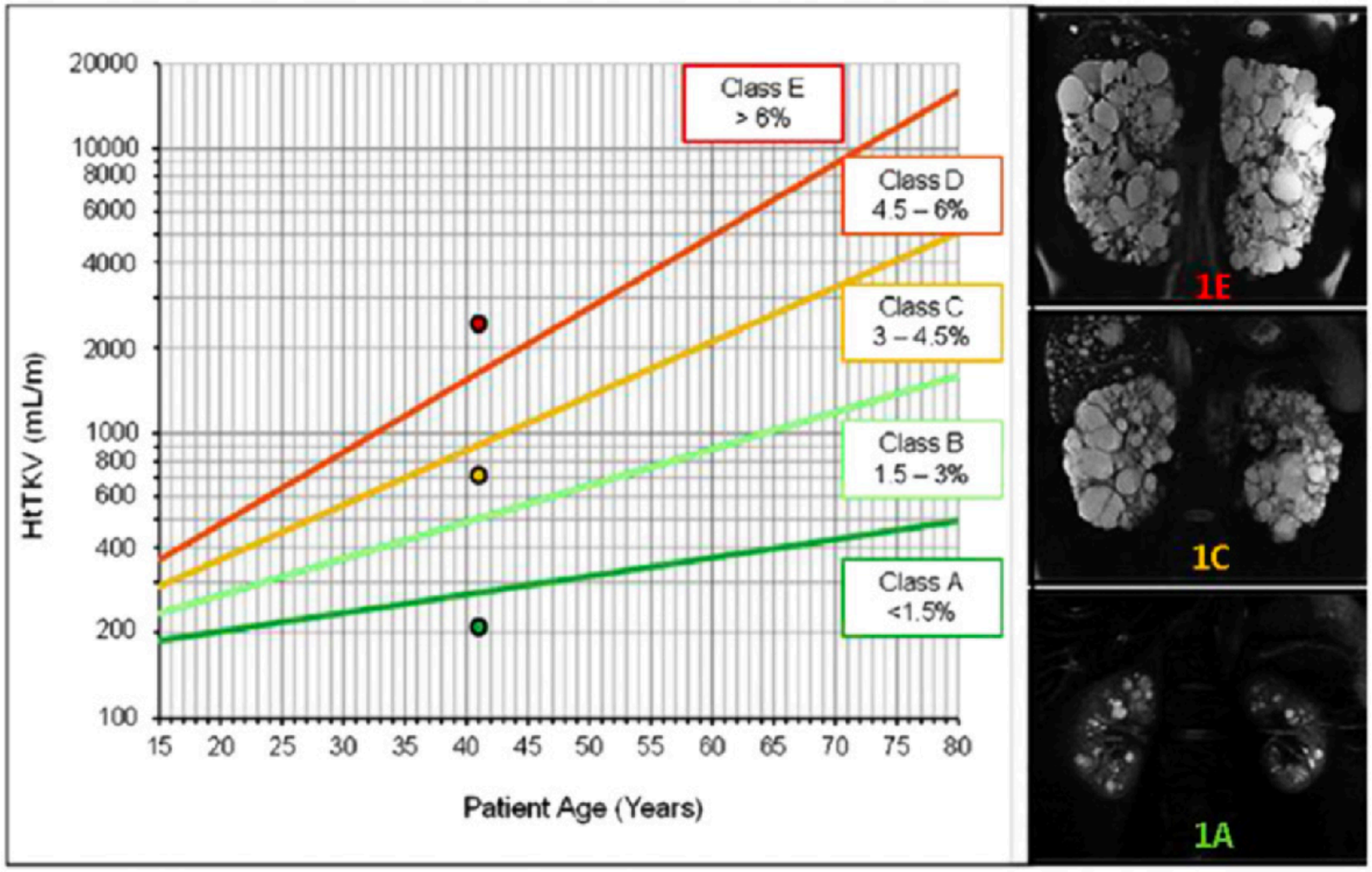
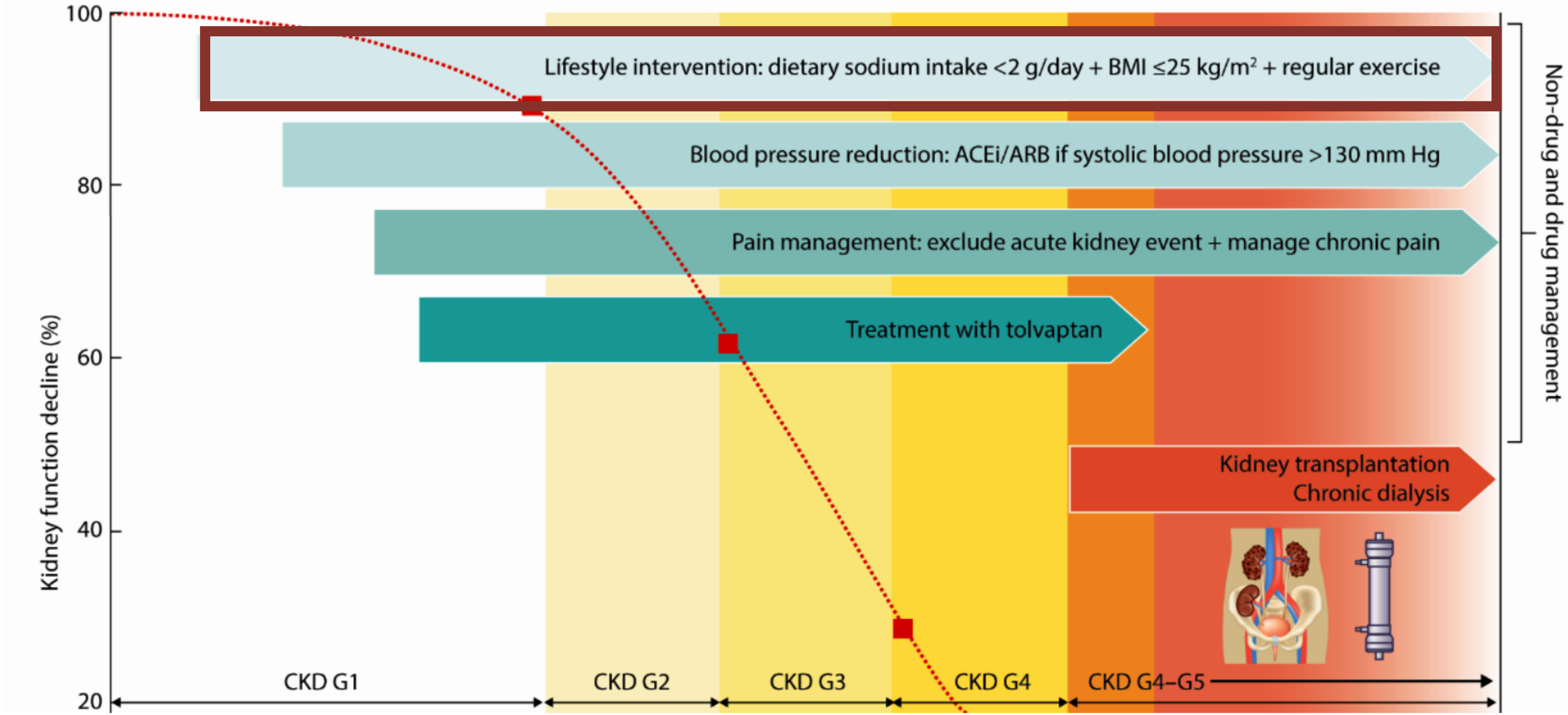
Mayo imaging classification provides a simple tool for the identification of patients with rapidly progressive ADPKD



annual htTKV growth rates

Chebib FT, et al. J Am Soc Nephrol 2018: 29: 2458–2470.



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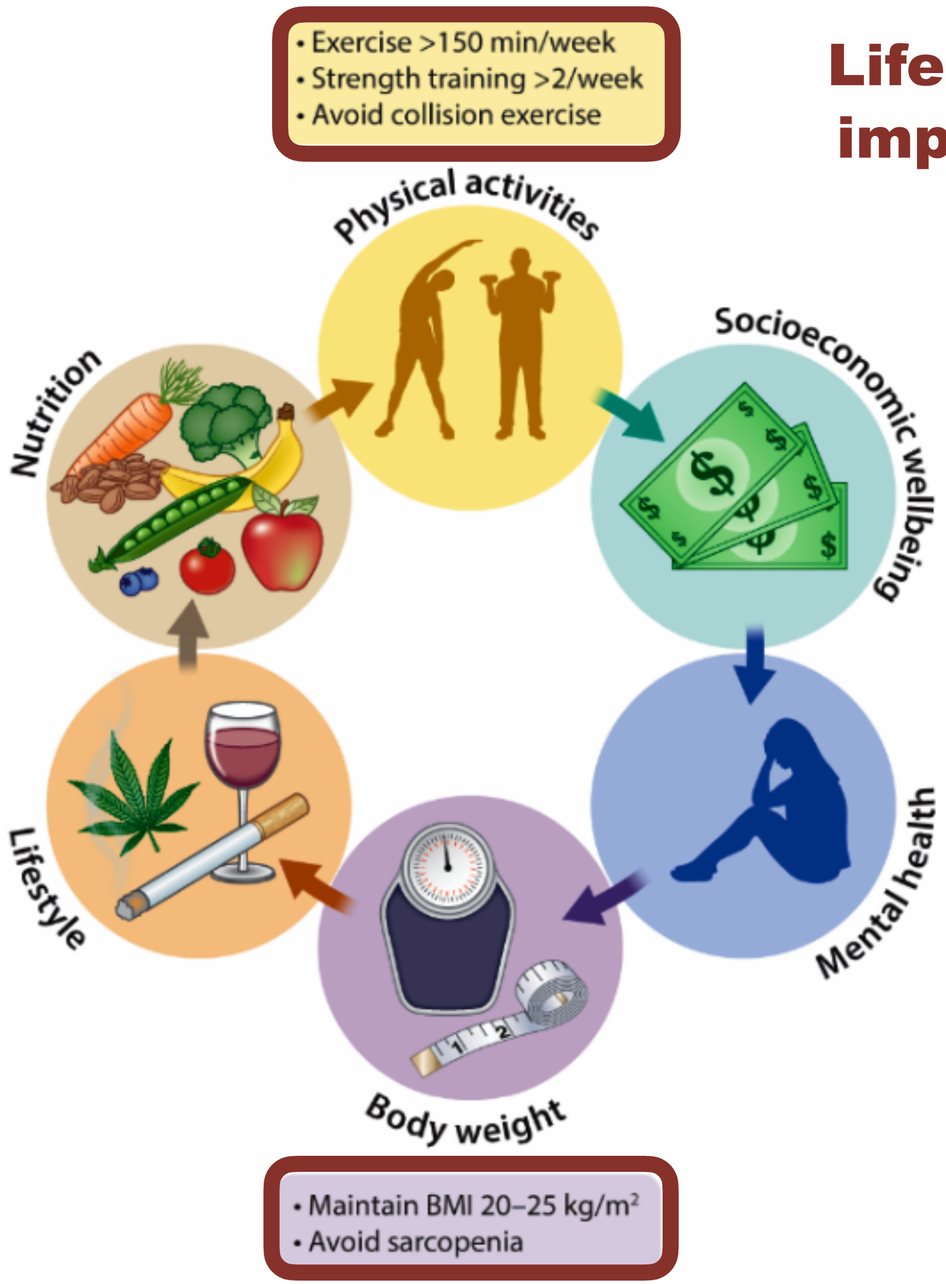
Lifestyle and psychosocial care for improved outcomes in people with ADPKD



- Exercise >150 min/week
- Strength training >2/week
- Avoid collision exercise

- Water ≥2 l/day
- Sodium <2 g/day, salt <5 g/day
- Protein 0.8–1 g/kg/day
- Calories 25–35 kcal/kg/day
- Fat <30% of daily energy intake
- Fiber 25–38 g/day
- Caffeine <400 mg/day

- Avoid tobacco products
- Limit alcohol intake: ≤2 drinks/d (M), ≤1 drink/d (F)
- Counsel patients about the use of cannabis products
- Avoid recreational drugs and nephrotoxins

- Maintain BMI 20–25 kg/m²
- Avoid sarcopenia

- Look for solutions for:
  - Social discrimination
  - Financial burden

- Seek professional support for:
  - Anxiety and depression
  - Genetic guilt
  - Chronic pain
  - Body image and sexual dysfunction

Potential benefits

- ↓Kidney cyst growth
- ↓Kidney function loss
- ↓Blood pressure
- ↓Cardiovascular events
- ↓Early mortality
- ↑General health status
- ↑Quality of life

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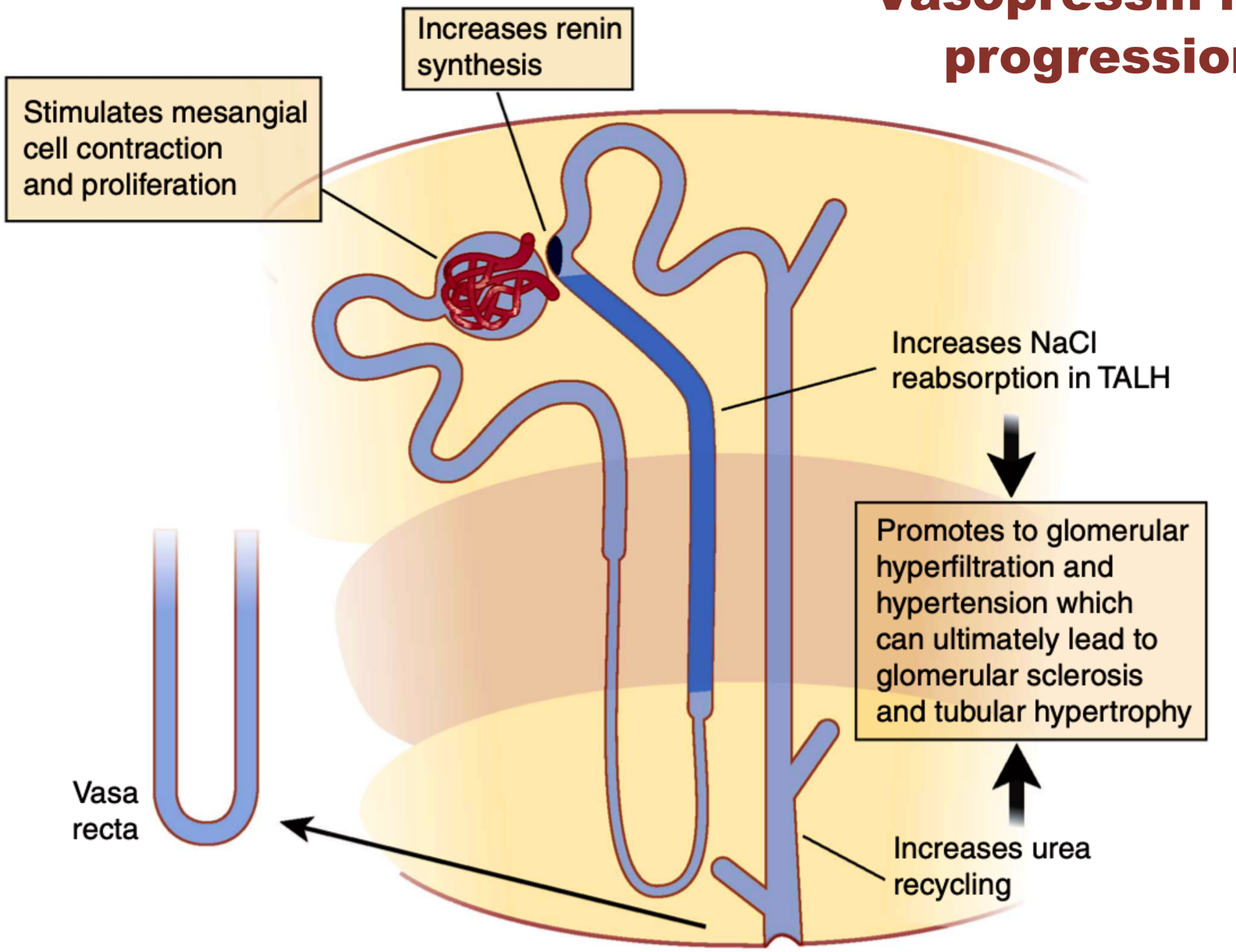
Vasopressin may adversely affect the progression of established renal diseases



In PKD, increased water intake slows renal cyst growth in animals via direct vasopressin suppression,

PKD may benefit from 3 to 4 l of urine output each day, a level of excretion that is likely to be safe.

Wang CJ, et al. Kidney Int. 2013 Jul;84(1):45-53.

Water intake in the absence of tolvaptan

Recommendation	Evidence
We suggest adapting water intake, spread throughout the day, to achieve at least 2 liters of urine per day in people with ADPKD and an eGFR ≥30 ml/min per 1.73 m2 without contraindications to excreting a solute load	2D

People with CKD G4-G5 (eGFR <30 ml/min per 1.73 m2) or who have a clinical contraindication to high water intake should drink to thirst and/or follow individualized clinical advice.

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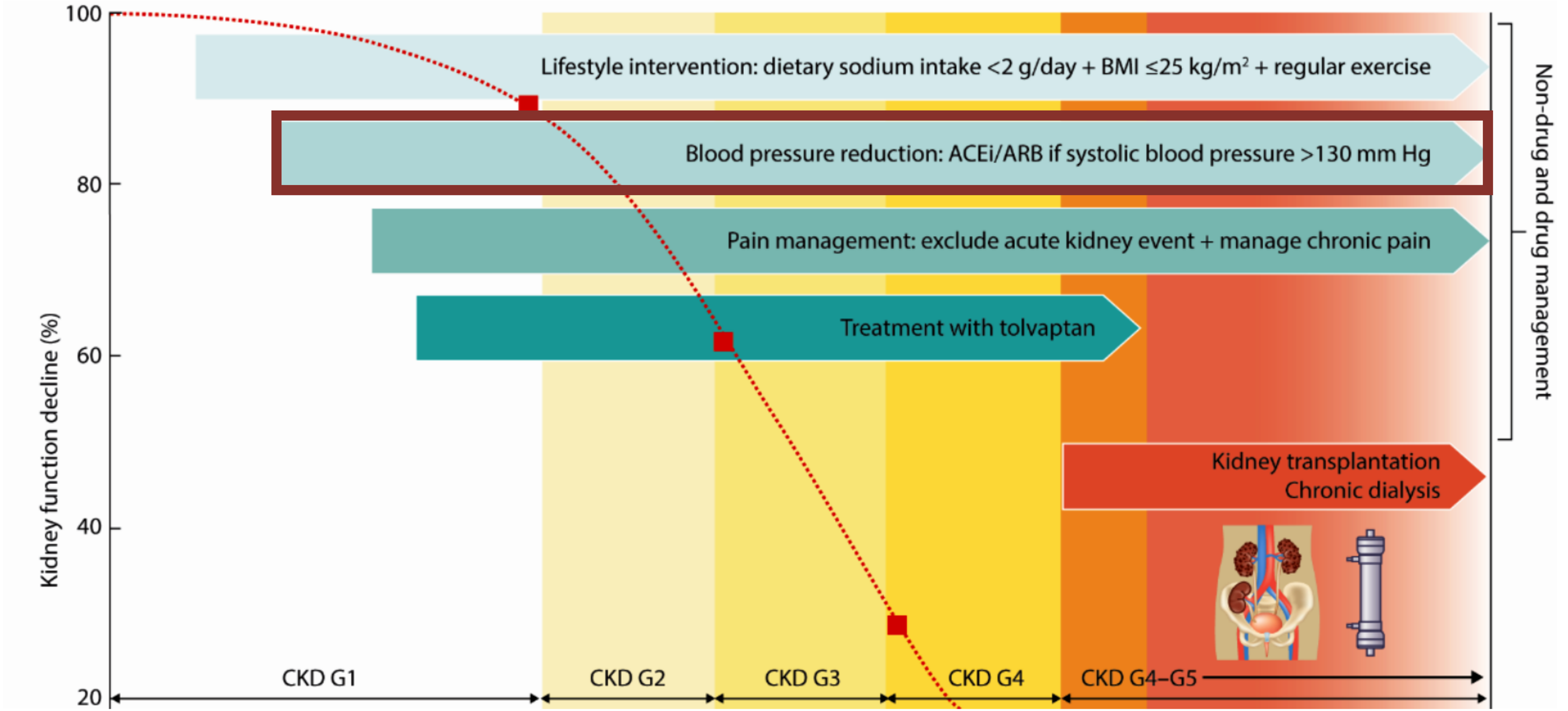

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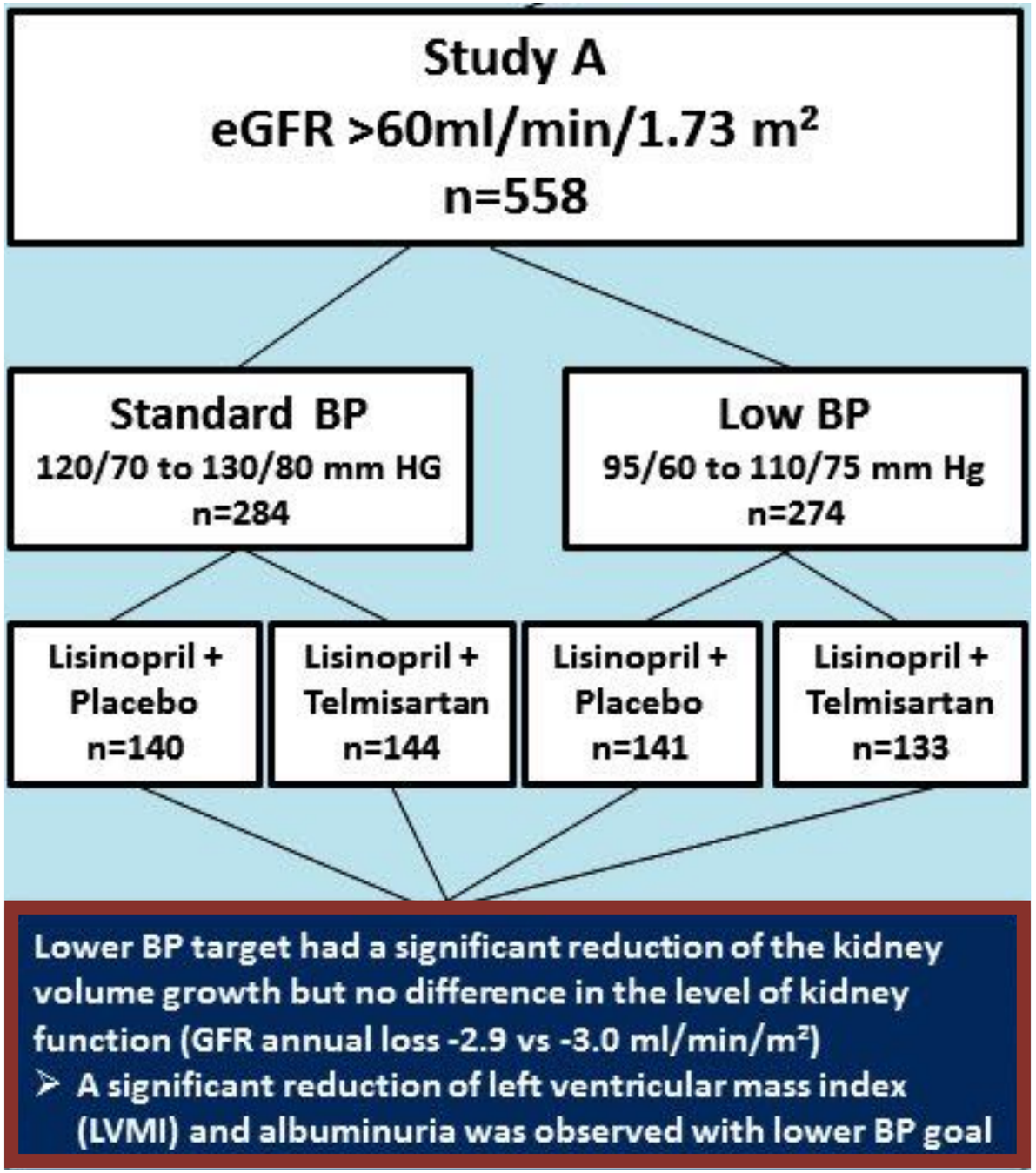
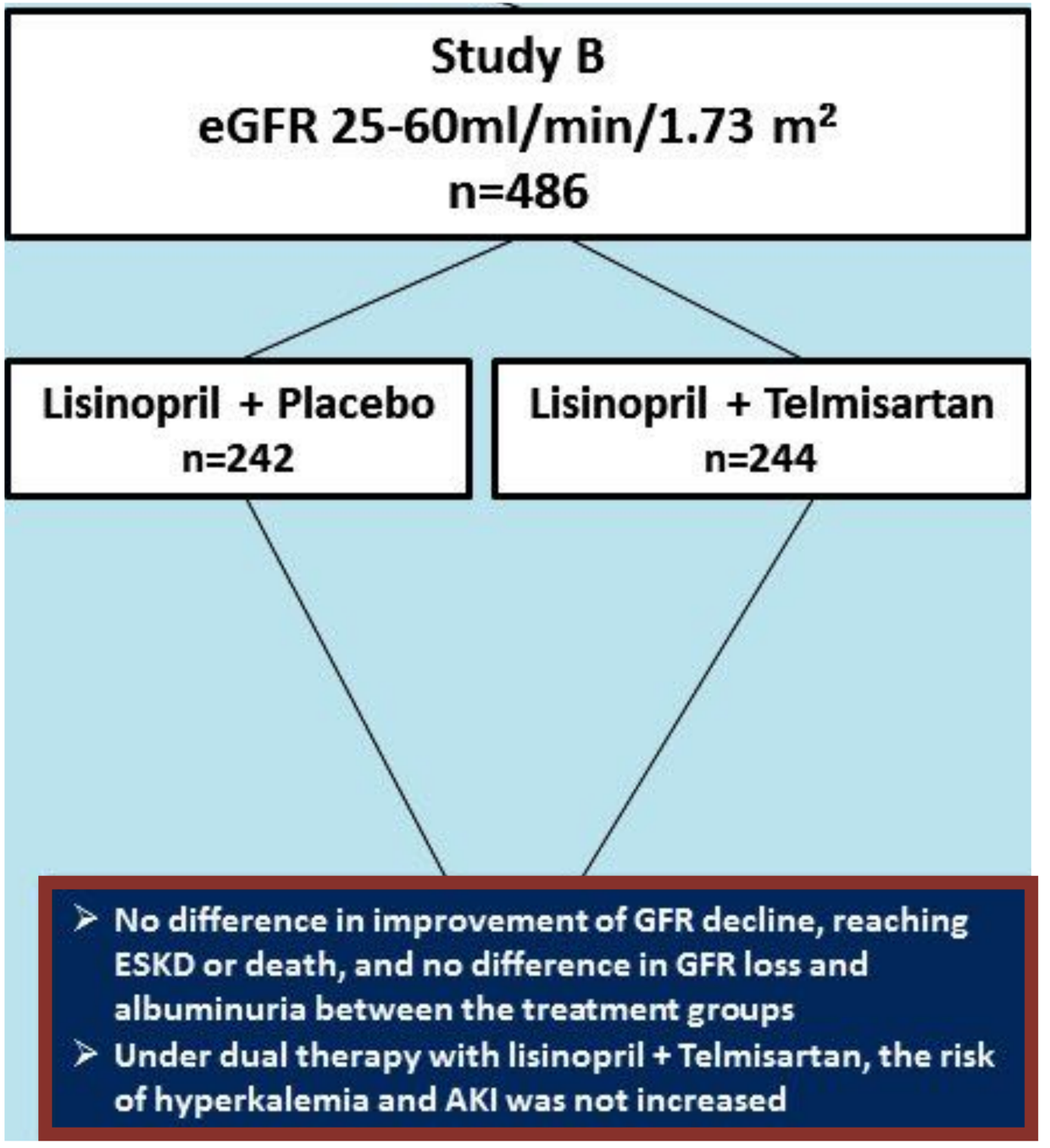

Study A
eGFR >60ml/min/1.73 m²
n=558
Standard BP
120/70 to 130/80 mm HG
n=284
Low BP
95/60 to 110/75 mm Hg
n=274
Lisinopril + Placebo
n=140
Lisinopril + Telmisartan
n=144
Lisinopril + Placebo
n=141
Lisinopril + Telmisartan
n=133
Lower BP target had a significant reduction of the kidney volume growth but no difference in the level of kidney function (GFR annual loss -2.9 vs -3.0 ml/min/m²)
A significant reduction of left ventricular mass index (LVMI) and albuminuria was observed with lower BP goal


Study B
eGFR 25-60ml/min/1.73 m²
n=486
Lisinopril + Placebo
n=242
Lisinopril + Telmisartan
n=244
No difference in improvement of GFR decline, reaching ESKD or death, and no difference in GFR loss and albuminuria between the treatment groups
Under dual therapy with lisinopril + Telmisartan, the risk of hyperkalemia and AKI was not increased

Management of high BP in people with ADPKD

Non-pharmacologic interventions	Medical management
• Reduce dietary sodium including minimizing processed foods • Optimize body weight with a healthy diet and regular exercise • Optimize pain management, including sympathetic renal nerve inhibition, if appropriate	• Inhibition of RAS provides the cornerstone of BP management and includes the use of an ACEi or ARB • Optimize BP control with addition of diuretic therapy to RAS blockade, if needed

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Management of high BP in people with ADPKD

Recommendation	Evidence
For people with ADPKD aged 18–49 years with CKD G1-G2 and high BP (>130/85 mm Hg), we recommend a target BP ≤110/75 mm Hg as measured by HBPM	1D
For people with ADPKD ≥50 years of age and/or with more advanced CKD (CKD G3-G5), we suggest a target mean SBP <120 mmHg, if tolerated, using standardized office BP measurement	2B
For people with ADPKD and high BP, we recommend using RASi as first-line treatment to achieve the recommended target BP (1C).	1C

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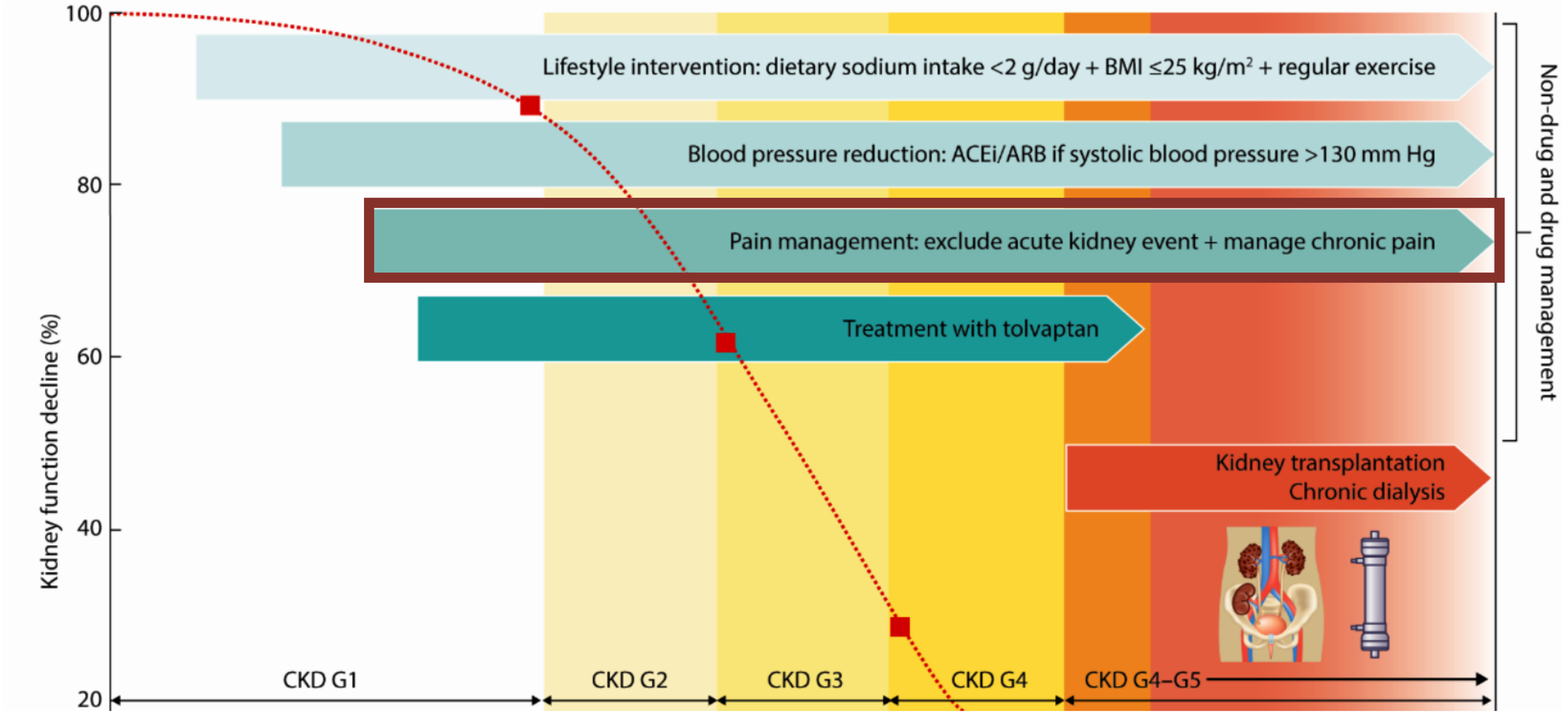

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Potential indications for native kidney nephrectomy in people with ADPKD receiving a kidney transplant

- Recurrent and/or severe kidney infection
- Symptomatic nephrolithiasis
- Recurrent and/or severe kidney cyst bleeding
- Intractable pain
- Suspicion of kidney cancer
- Insufficient space for insertion of a kidney graft
- Ventral hernia in the setting of massively enlarged kidneys
- Severe symptoms related to massively enlarged kidneys*

Recommendation: We suggest unilateral rather than bilateral native kidney nephrectomy in people with ADPKD, when appropriate (*2D*).

Recommendation: We suggest that kidney transplant candidates with ADPKD who require native kidney nephrectomy undergo the procedure at the time of or after, but not before, transplantation, whenever possible (2C).

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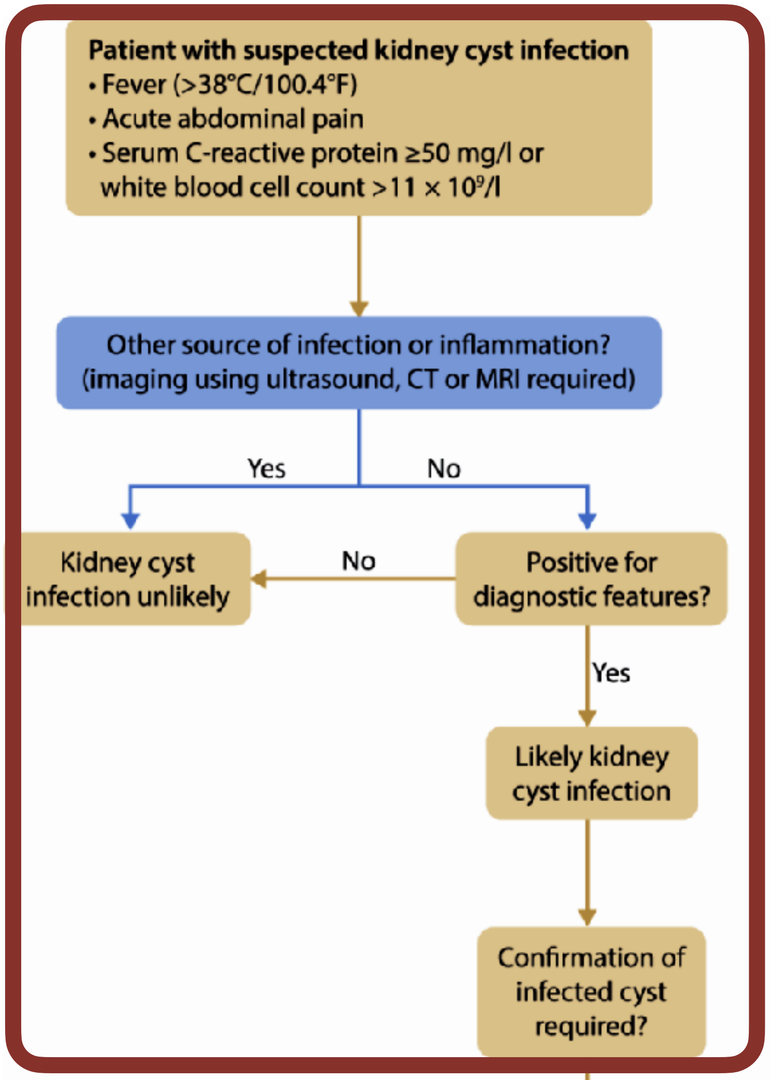
Diagnostic algorithm for infected kidney cyst



Diagnostic features
Diagnostic features are considered positive in the presence of ≥2 items in ≥2 categories:

Clinical factors
1. Acute pain or tenderness in kidney area
2. Symptoms of urinary tract infection
3. Recent instrumentation of urinary tract
4. Immune compromised patient (including patients on dialysis)

Microbiology
5. Positive urine and/or blood culture
6. Positive cyst fluid culture

Imaging
7. Imaging (ultrasounds, CT, or MRI) before and after onset of symptoms demonstrating a new complex cyst
8. Intracystic gas (ultrasound, CT, or MRI)
9. Pericystic inflammation of a cyst (CT or MRI)
10. Fluid-fluid levels in a cyst (MRI)
11. Thickened cyst wall (CT or MRI)
12. Contrast enhancement in the lining of cyst walls (CT or MRI)
13. Diffusion weighted imaging showing increased cyst density compared to normal cysts
14. Single-photon emission CT with Ga67 abnormal uptake by a cyst
15. 111indium-white blood cell scan showing accumulation in a cyst

Treatment
16. Clinical response to antibiotic treatment

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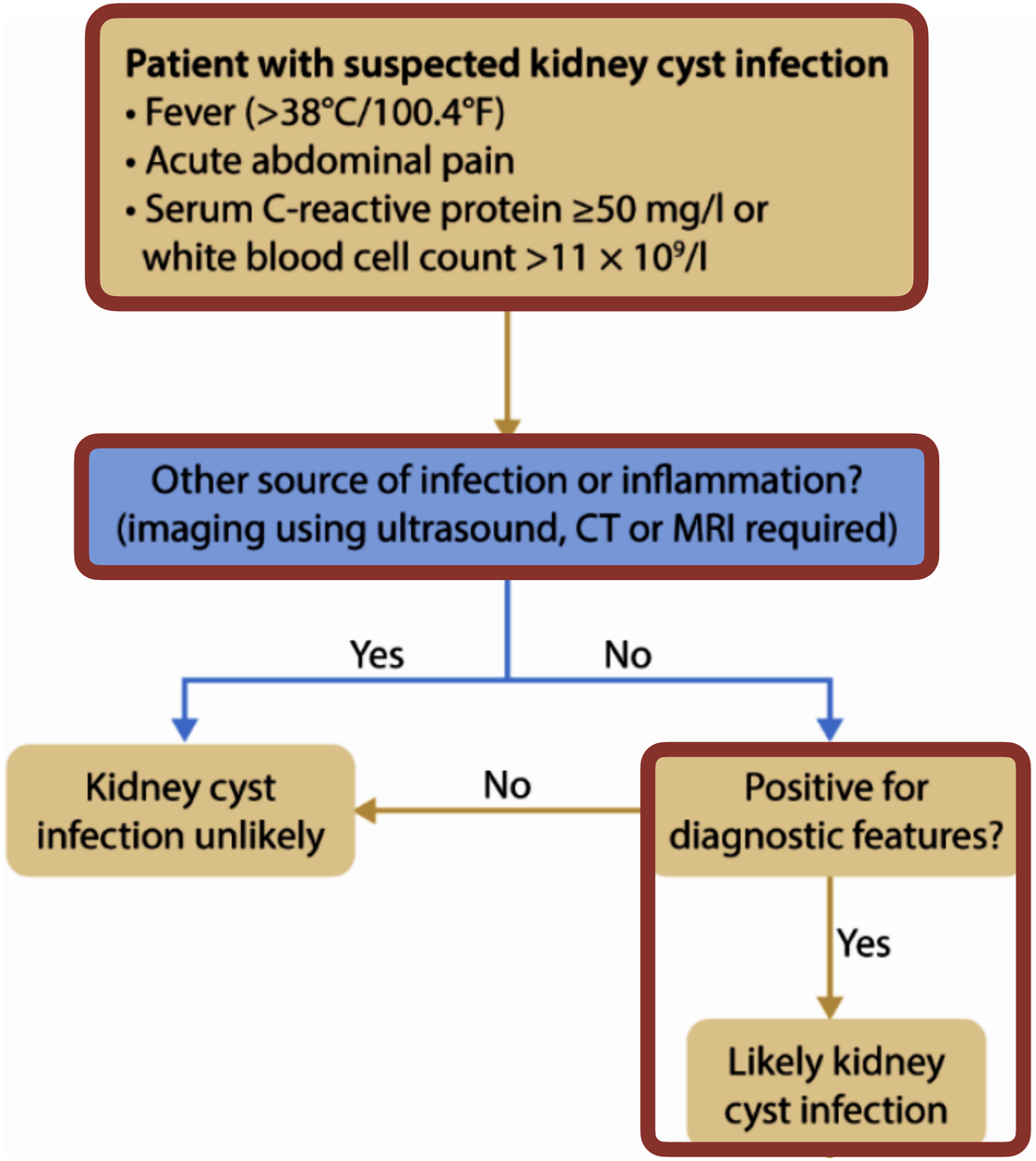
Diagnostic algorithm for infected kidney cyst



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Microbiology

5. Positive urine and/or blood culture
6. Positive cyst fluid culture

Imaging

7. Imaging (ultrasounds, CT, or MRI) before and after onset of symptoms demonstrating a new complex cyst
8. Intracystic gas (ultrasound, CT, or MRI)
9. Pericystic inflammation of a cyst (CT or MRI)
10. Fluid-fluid levels in a cyst (MRI)
11. Thickened cyst wall (CT or MRI)
12. Contrast enhancement in the lining of cyst walls (CT or MRI)
13. Diffusion weighted imaging showing increased cyst density compared to normal cysts
14. Single-photon emission CT with Ga67 abnormal uptake by a cyst
15. 111indium-white blood cell scan showing accumulation in a cyst

Diagnostic algorithm for infected kidney cyst

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UTIs in people with ADPKD

Recommendation	Evidence
In people with ADPKD and kidney cyst infection, we suggest treatment with 4–6 weeks of antibiotic therapy rather than a shorter course.	2D

A lipid-soluble antibiotic (e.g., fluoroquinolones, trimethoprim-sulfamethoxazole) should be used to treat kidney cyst infection in ADPKD, if possible.

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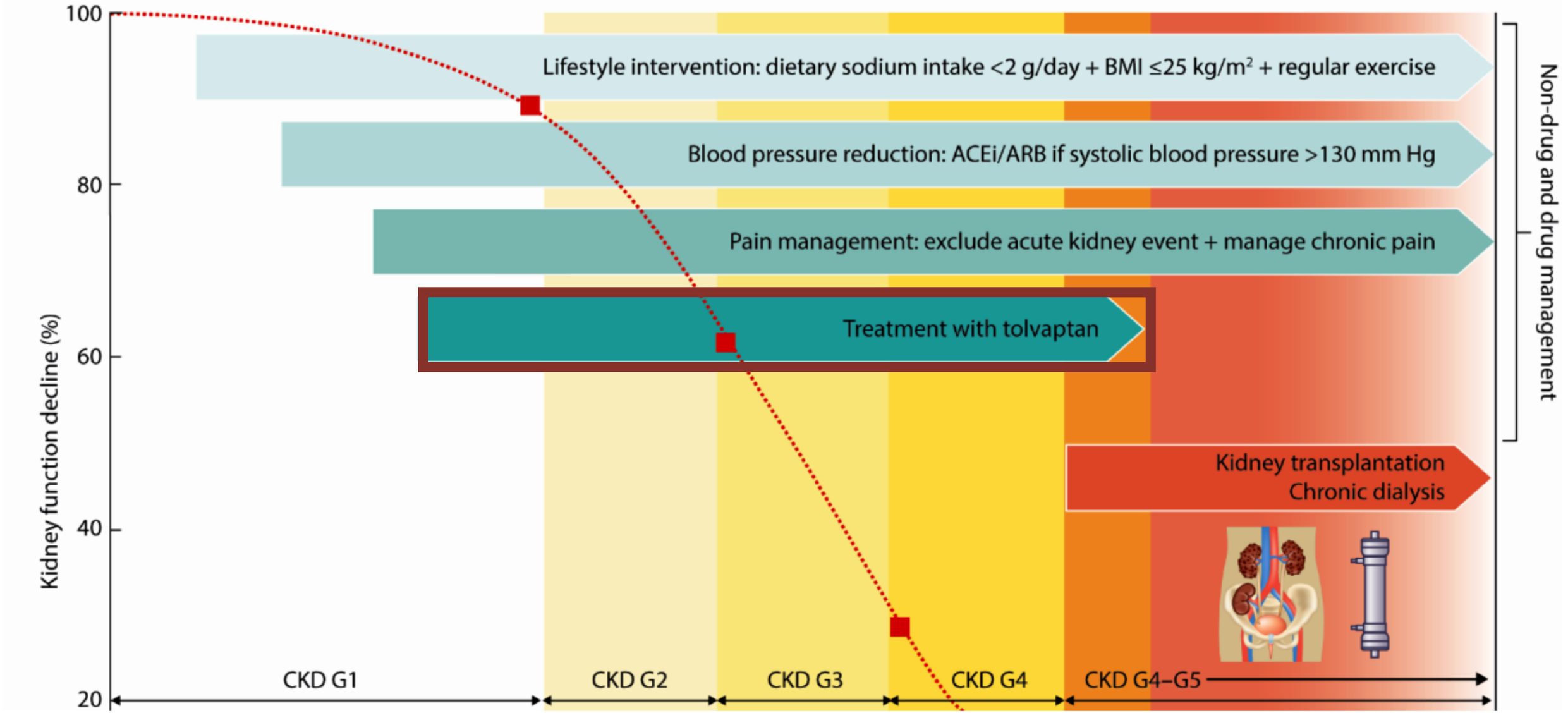
Intracyst antibiotic diffusion in patients with ADPKD

Reference	No. of Patients	Cyst Location	Antibiotic	Intracystic Antibiotic Diffusion
Telenti *et al.* (7)	3	Liver	Ciprofloxacin	Good Concentration ratio cyst/serum 2.3 to 4.4
	1		Chloramphenicol	Good Concentration ratio cyst/serum 1.1
Bennett *et al.* (17)	10	Kidney	Amoxicillin	Poor on day 1/good on day 6
			Aminoside	Poor
			Clindamycin	Good
			Metronidazole	Good
			Bactrim	Good
			Vancomycin	Good
Elzinga *et al.* (18)	7	Kidney	Ciprofloxacin (oral)	Good Concentration ratio cyst/serum 2.5
Hiyama *et al.* (12)	1	Kidney	Ampicillin	Poor Concentration ratio cyst/serum <0.4
			Levofloxacin	Good Concentration ratio cyst/serum 0.96
Elzinga *et al.* (19)	8	Kidney	Trimethoprim	Good Concentration ratio cyst/serum >8
			Sulfamethoxazole	Poor Concentration ratio cyst/serum 0.1 to 0.7
Schwab *et al.* (20)	1	Kidney	Trimethoprim	Good Concentration ratio cyst/serum 1.6 to 23.0
			Sulfamethoxazole	Poor Concentration ratio cyst/serum 0.07 to 0.70
Schwab *et al.* (21)	1	Kidney	Clindamycin	Good Concentration ratio cyst/serum 2.4 to 8.7
			Gentamycin	Poor Concentration ratio cyst/serum 0.18 to 0.34

- Ciprofloxacin
- Cotrimoxazole
- Chloramphenicol
- Clindamycin
- Levofloxacin
- Metronidazole
- Vancomycin

Clin J Am Soc Nephrol 4: 1183-1189, 2009 .



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TEMPO 3:4	CKD G1–G2

Study population
n=1445
18 to 50 years old
TKV >750 ml in CKD

Dose of tolvaptan
120 mg/d (55%), 90 mg/d (21%), 60 mg/d (24%)

Main results
- Primary endpoint: reduced rate of increase in TKV: 2.8%/year in tolvaptan group vs. 5.5%/year in placebo
- Secondary endpoint: slower decline in kidney function (reciprocal of the serum creatinine level, –2.61 [mg/ml]/year vs. –3.81 [mg/ml]/year, P <0.001); lower rates of worsening kidney function (2 vs. 5 events per 100 person-years, P <0. 001) and kidney pain (5 vs. 7 events per 100 person-years of follow-up; P=0.007).

Adverse effects
Tolvaptan associated with aquaresis and abnormal liver function tests and higher discontinuation rate (23% vs. 14% in the placebo group).

REPRISE	CKD G3–G4

Study population
n=1390
18–55 years old + (eGFR 25–65 ml/min per 1.73 m^2)
56–65 years old + (eGFR 25–44 ml/min per 1.73 m^2)

Ability to tolerate tolvaptan after an 8-week run-in

Dose of tolvaptan
120 mg/d (61%), 90 mg/d (30%), 60 mg/d (10%)

Main results
- Primary endpoint: Reduced rate of decline in eGFR by –2.34 ml/min per 1.73 m^2 in the tolvaptan vs. –3.61 ml/min per 1.73 m^2 in the placebo; P <0.001).

Adverse effects
Reversible increases in the ALT (to >3 times normal range)
5.6% in tolvaptan group vs. 1.2% in the placebo group

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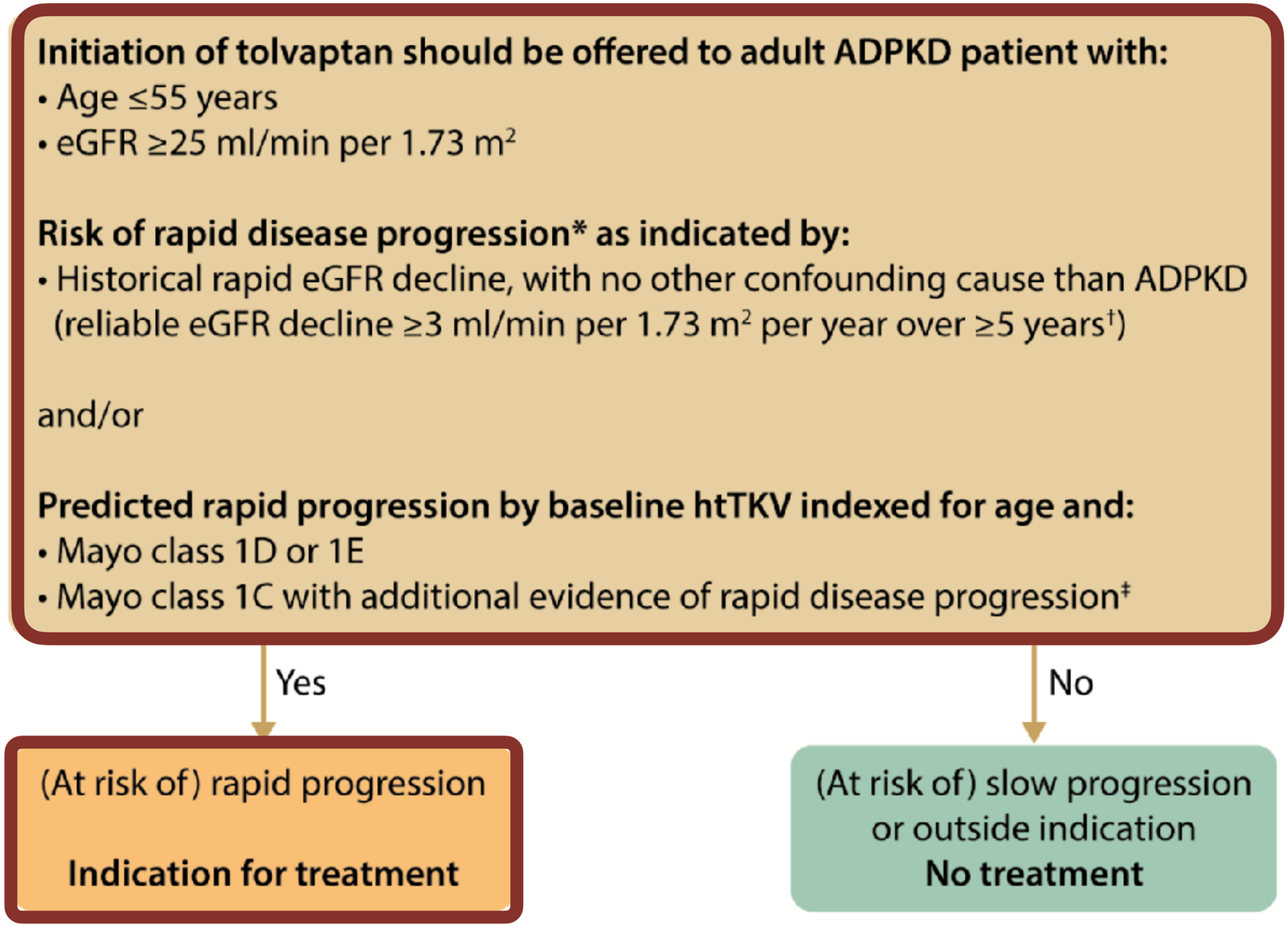
KDIGO algorithm to decide to whom to prescribe tolvaptan



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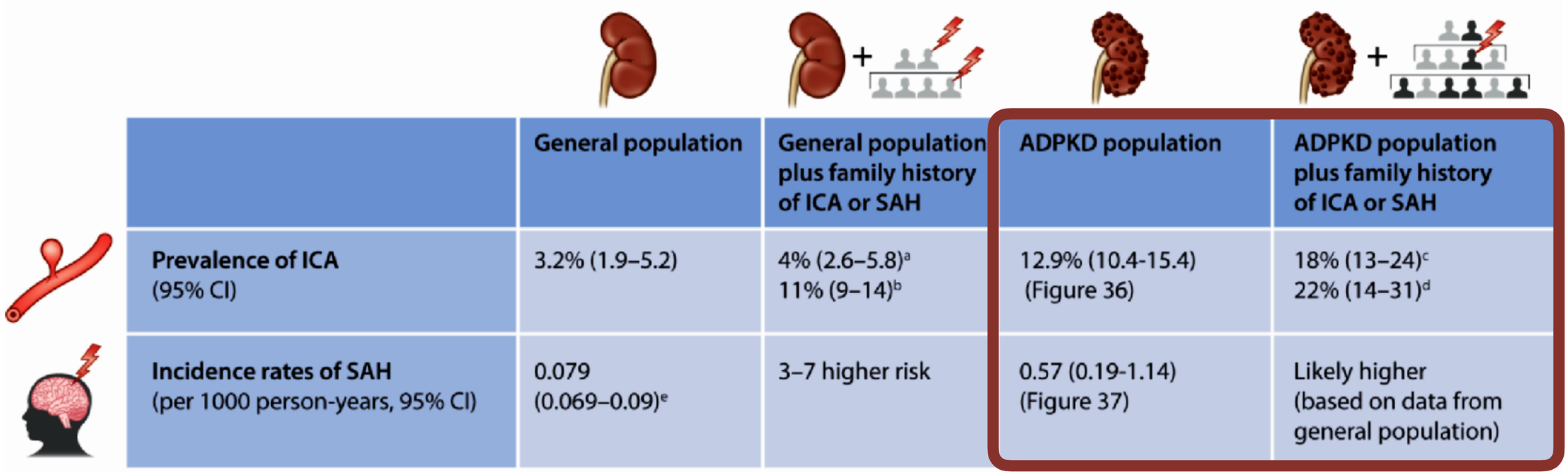
Intracranial aneurysms (ICA)

- **Recommendation: We recommend informing adults with ADPKD about increased risk for intracranial aneurysms (ICA) and subarachnoid hemorrhage (SAH; Figure 35) (1C).**



	General population	General population plus family history of ICA or SAH	ADPKD population	ADPKD population plus family history of ICA or SAH
Prevalence of ICA (95% CI)	3.2% (1.9–5.2)	4% (2.6–5.8)[a] 11% (9–14)[b]	12.9% (10.4-15.4) (Figure 36)	18% (13–24)[c] 22% (14–31)[d]
Incidence rates of SAH (per 1000 person-years, 95% CI)	0.079 (0.069–0.09)[e]	3–7 higher risk	0.57 (0.19-1.14) (Figure 37)	Likely higher (based on data from general population)

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Risk factors of intracranial aneurysms (ICA) or subarachnoid hemorrhage (SAH)

	Predictors for prevalent ICA or rupture of ICA and strength of the association
Evidence for association with ICA/SAH in ADPKD population	1 Family history of SAH or ICA (stronger association when first-degree relative) – *Strong* 2 Personal history of SAH or ICA – *Strong* 3 Female sex – *Moderate* 4 *PKD1* genotype - *Moderate* 5 Tobacco smoking (especially >20 pack-years) - *Strong* 6 Uncontrolled hypertension - *Moderate* 7 Early onset hypertension (<35y) - *Moderate* 8 Severity of ADPKD – *Weak*
Evidence in non-ADPKD population	• Japanese or Finnish ancestry • Alcohol in large quantity (risk factor for ICA rupture)

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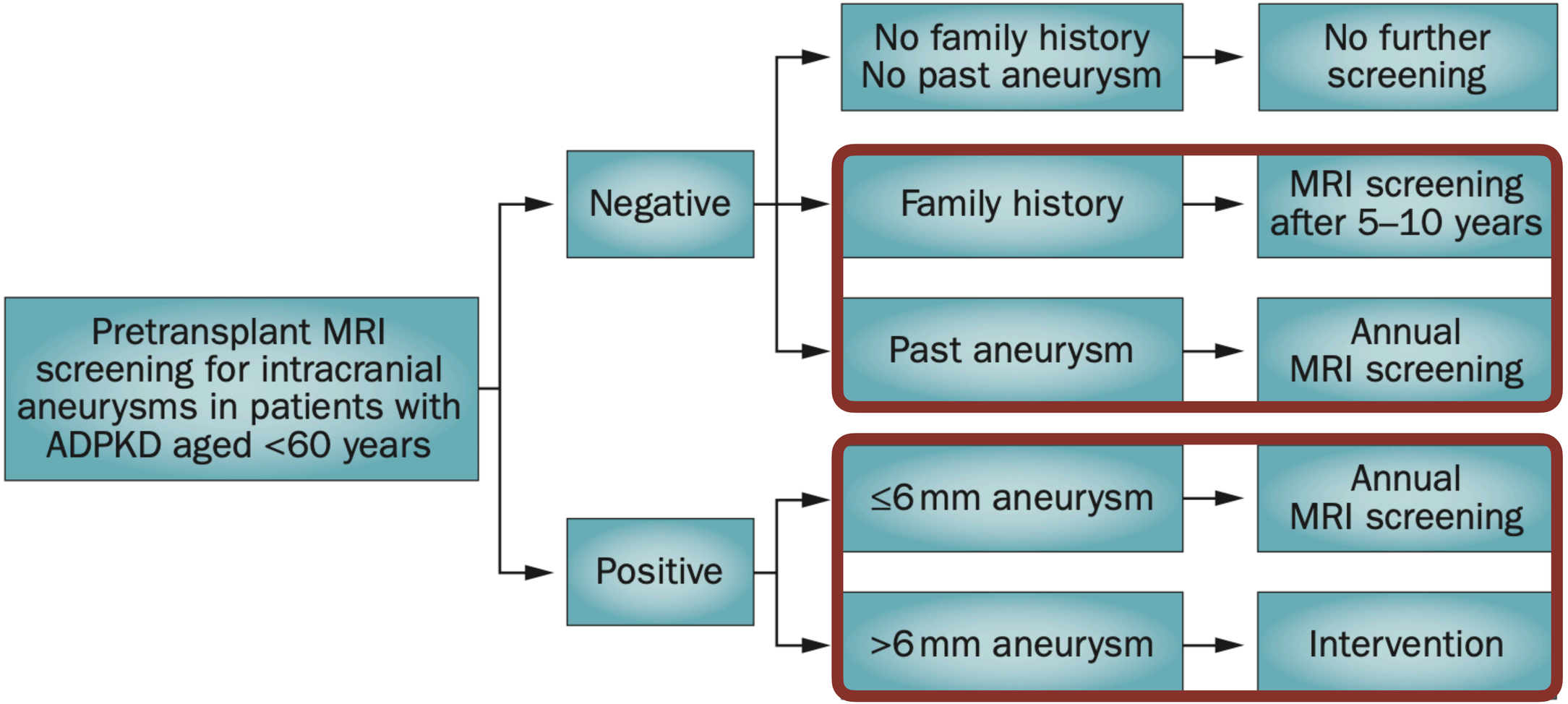
Pretransplant screening and follow-up monitoring for intracranial aneurysms in patients with ADPKD aged <60 years.



Kanaan N, et al. Nat Rev Nephrol. 2014; 10(8):455-65.

Intracranial aneurysms (ICA)

Recommendation	Evidence
We recommend screening for ICA in people with a personal history of SAH or a positive family history of ICA, SAH, or unexplained sudden death if the person will be eligible for treatment and has reasonable life expectancy.	**1D**
When one or several ICAs are identified, treatment options, such as conservative management and microvascular or endovascular repair, should be assessed within a multidisciplinary setting at centers of expertise with high ICA case volumes.	

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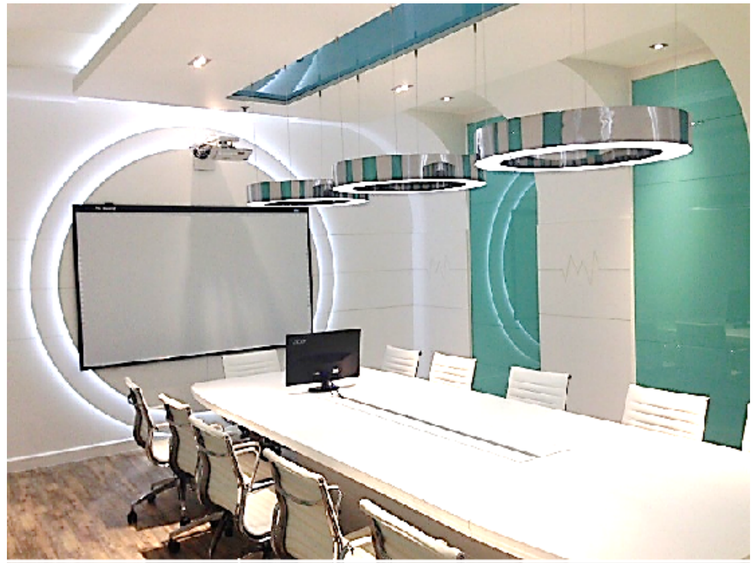
DEPARTMENT OF MEDICINE
PHRAMONGKUTKLAO HOSPITAL

NEPHROLOGY
PHRAMONGKUTKLAO HOSPITAL



Intelligence Dialysis Center
Nephrology Unit
Phramongkutklao Hospital and College of Medicine