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Les HTA secondaires

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Pourquoi ce sujet ?

L'HTA secondaire, un mythe ?

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Hypertension

A Prospective Study of the Prevalence of Primary Aldosteronism in 1,125 Hypertensive Patients

Therefore, overall the prevalence of the disease was 11.2%, without gender differences (11.7% in men, 10.6%. in women).

Rossi et al, JACC, 2006

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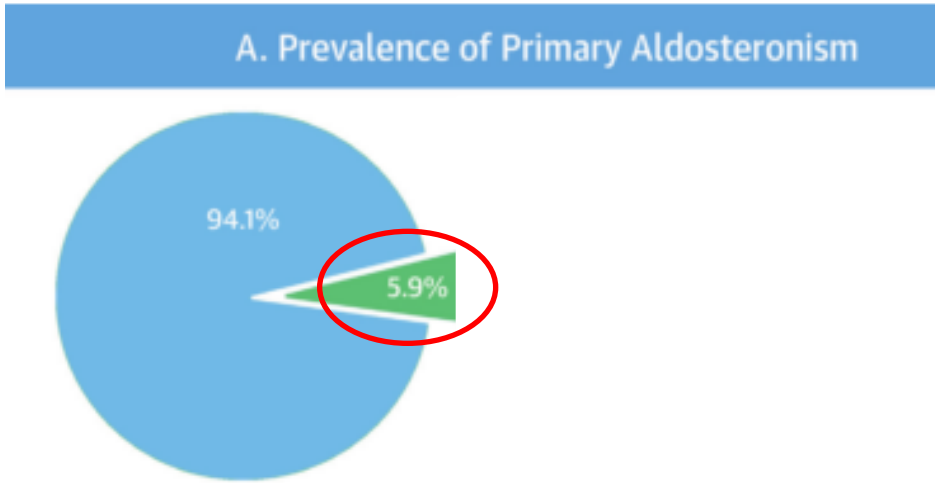
Prevalence and Clinical Manifestations of Primary Aldosteronism Encountered in Primary Care Practice

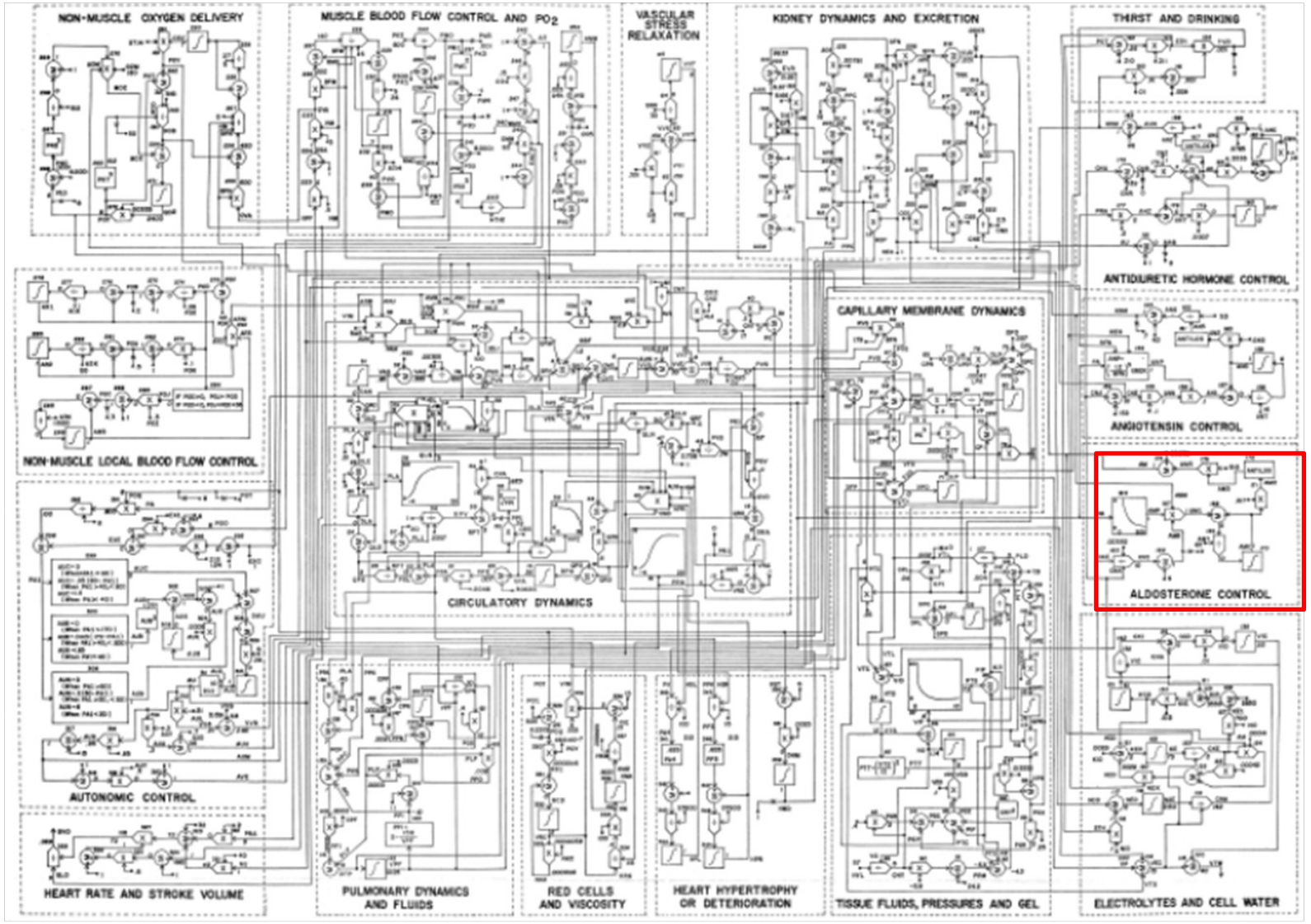


Monticone, S. et al. J Am Coll Cardiol. 2017;69(14):1811-20.

Les HTA secondaires, une **REALITE !!**

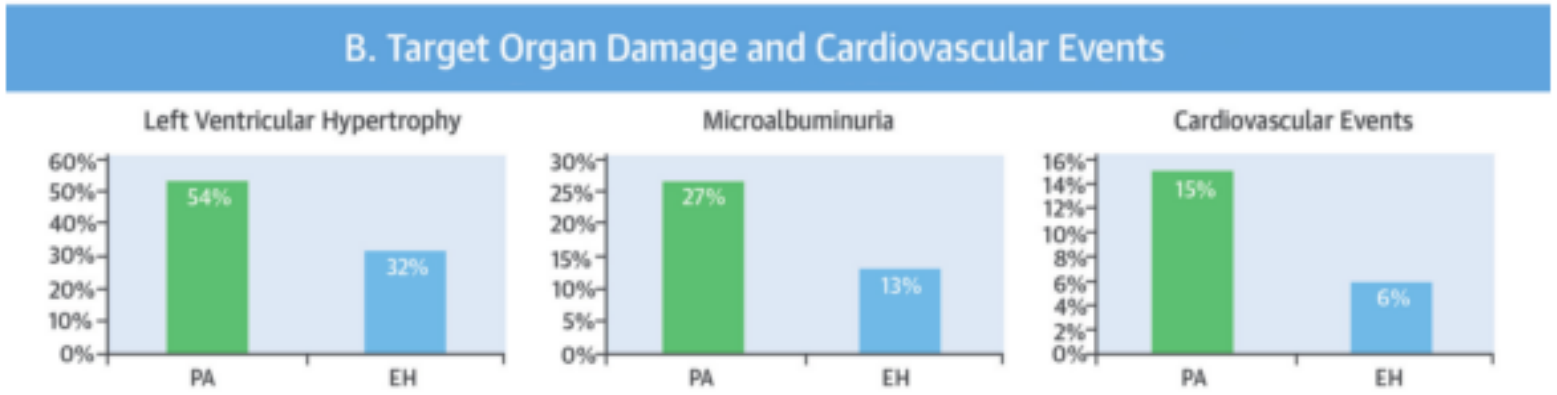
6 à 10 % de tous les patients hypertendus !

L'HTA secondaire, une **opportunité** !



Une physiopathologie simple ! *Modèle de Guyton, 1972*

L'HTA secondaire, une **opportunité** !

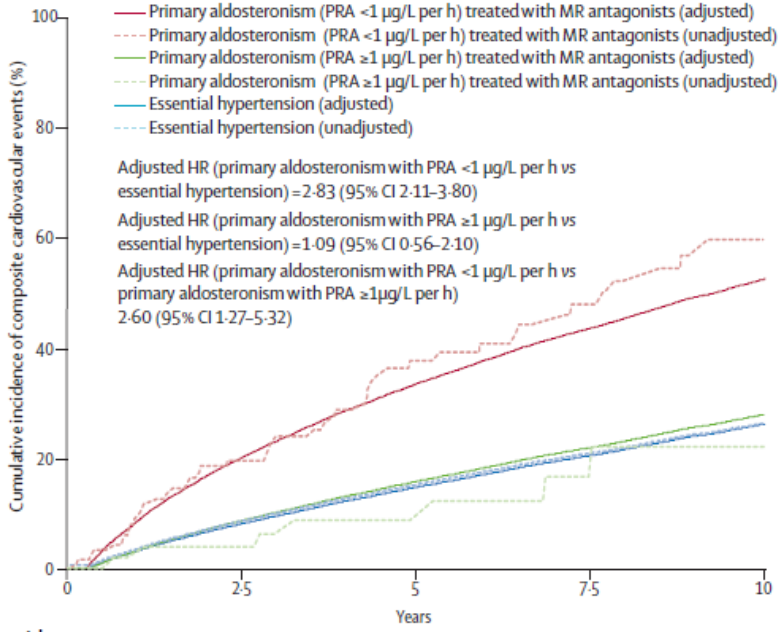


Monticone, S. et al. J Am Coll Cardiol. 2017;69(14):1811-20.

Cardiometabolic outcomes and mortality in medically treated primary aldosteronism: a retrospective cohort study

Gregory L Hundemer, Gary C Curhan, Nicholas Yozamp, Molin Wang, Anand Vaidya

Lancet Diabetes Endocrinol, 2018



De guérison ou

D'avoir un traitement spécifique !

Quand penser à une HTA secondaire ?

HTA résistante vraie

Conditions found to cause pseudo-resistance or resistance to blood pressure-lowering treatment

Causes of pseudo-resistant hypertension
Poor adherence to and persistence with treatment
White coat phenomenon
Poor BP measurement method
Marked brachial artery calcification (Osler phenomenon)
Clinician inertia (inadequate doses, inappropriate combinations of BP-lowering drugs)
Munchausen syndrome (rare)
Causes of resistant hypertension
Behavioural factors
Overweight/obesity
Physical inactivity
Excess daily dietary sodium
Excess habitual alcohol consumption
Use of drugs or substances that may increase BP
Undetected secondary hypertension

Quand penser à une HTA secondaire ?

HTA résistante vraie

HTA du sujet jeune

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

Routine test	Clinical utility
Fasting blood glucose (and HbA1c if fasting blood glucose is elevated)	Assessing CVD risk and comorbidities
Serum lipids: total cholesterol, LDL cholesterol, HDL and non-HDL cholesterol, triglycerides	Assessing CVD risk
Blood sodium and potassium, haemoglobin and/or haematocrit, calcium, and TSH	Screening secondary hypertension (primary aldosteronism, Cushing's disease, polycythaemia, hyperparathyroidism, and hyperthyroidism)
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)
12-lead ECG	Assessing HMOD (left atrial enlargement, left ventricular hypertrophy) Assessing irregular pulse and other comorbidities (atrial fibrillation, previous acute myocardial infarction)

Quand penser à une HTA secondaire ?

TABLE 13. Patient characteristics that should raise the suspicion of secondary hypertension

Younger patients (<40 years) with grade 2 or 3 hypertension or hypertension of any grade in childhood
Sudden onset of hypertension in individuals with previously documented normotension
Acute worsening of BP control in patients with previously well controlled by treatment
True resistant hypertension hypertension
Hypertensive emergency
Severe (grade 3) or malignant hypertension
Severe and/or extensive HMOD, particularly if disproportionate for the duration and severity of the BP elevation
Clinical or biochemical features suggestive of endocrine causes of hypertension
Clinical features suggestive of atherosclerotic renovascular disease or fibromuscular dysplasia
Clinical features suggestive of obstructive sleep apnea
Severe hypertension in pregnancy (>160/110 mmHg) or acute worsening of BP control in pregnant women with preexisting hypertension

"Diagnostic suspicion (Table 13) should prompt immediate referral to specialized hypertension centers where the appropriate diagnostic tests and subsequent treatments can be performed"

HTA secondaire : que disent les recommandations ?

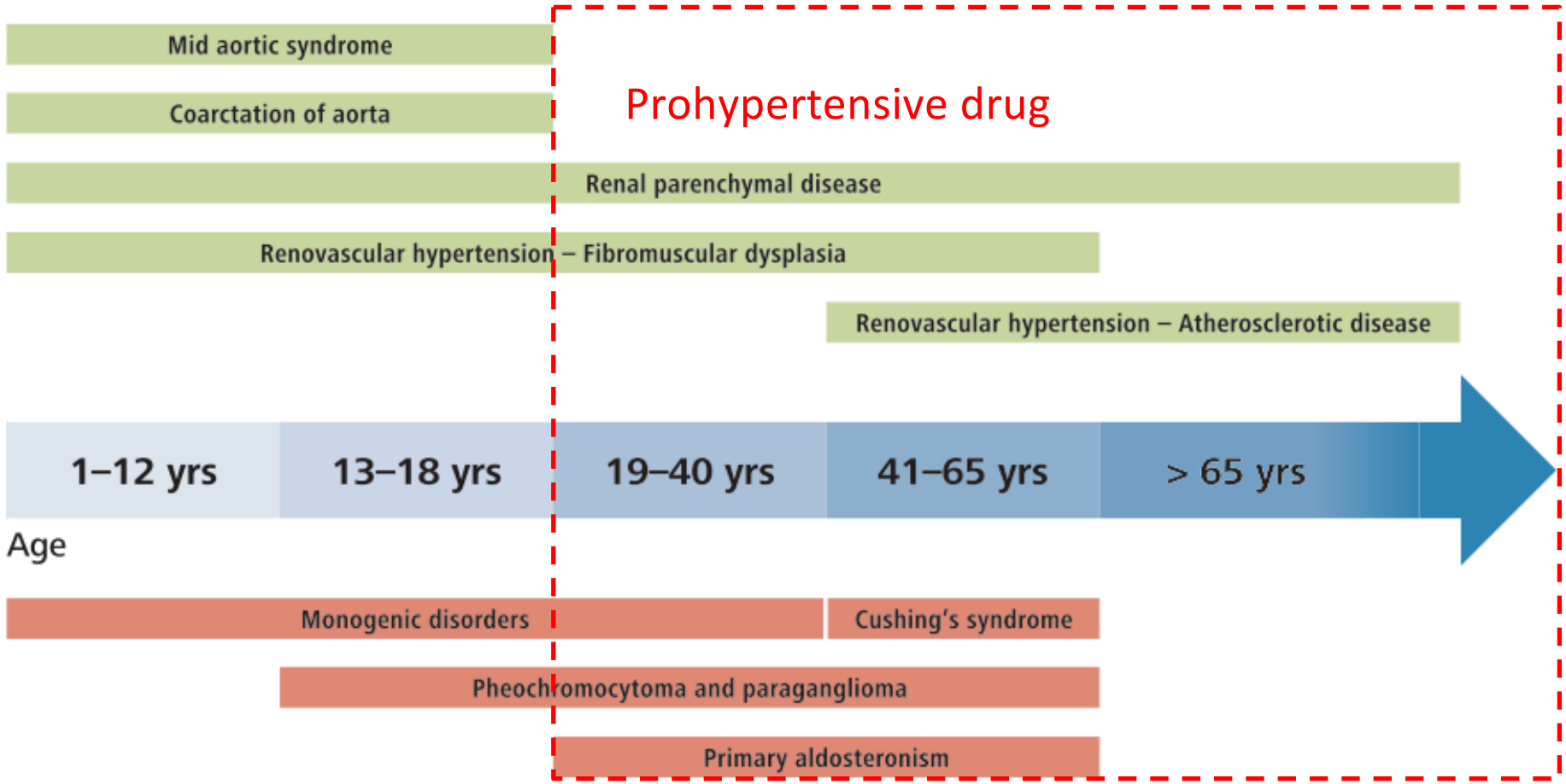
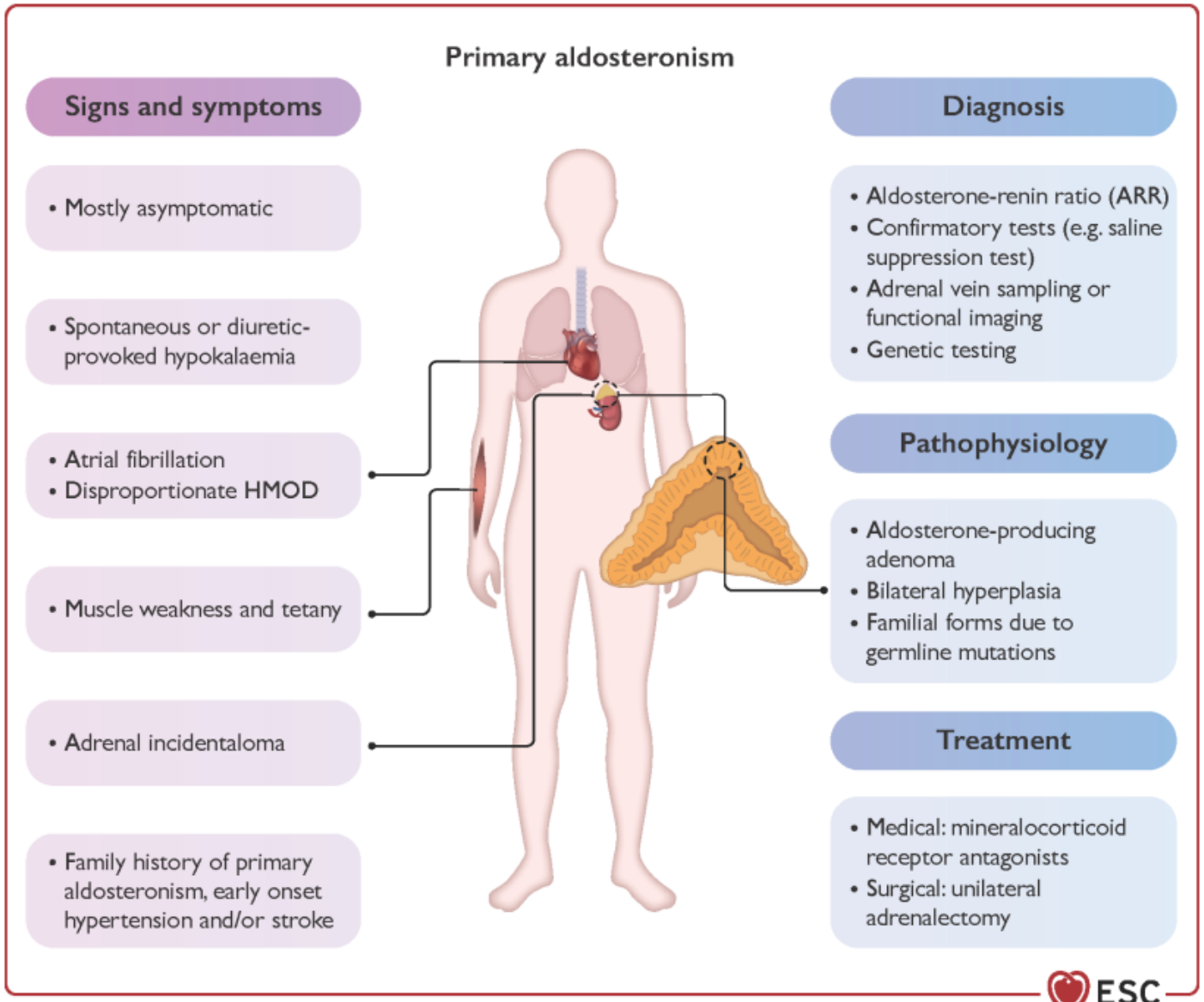


FIGURE 7 Incidence of selected forms of secondary hypertension according to age.

Figure 13

Summary of primary aldosteronism as a common form of secondary hypertension



2024 ESC Guidelines for the management of elevated blood pressure and hypertension
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae178)

HTA secondaire : que disent les recommandations ?

TABLE 14. Rare genetic causes of secondary hypertension [343]

Condition	Phenotype	Mechanism and Treatment
Liddle syndrome	Hypokalemia, metabolic alkalosis, low PRA or PRC, low PAC	Increased renal tubular ENaC activity; responds to treatment with amiloride
Apparent mineralocorticoid excess	Hypokalemia, metabolic alkalosis, low PRA or PRC, low PAC	Decreased 11β-hydroxysteroid dehydrogenase isoenzyme 2; responds to spironolactone
Gordon syndrome	Hyperkaliemia, metabolic acidosis, low PRA or PRC, low/normal PAC	Overactivity of the sodium-chloride cotransporter; responds to thiazides
Geller syndrome	Pregnancy-exacerbated hypertension, low PRA or PRC, low PAC	Agonist effect of progesterone on the mineralocorticoid receptor (which is constitutively active); responds to amiloride, spironolactone activates instead of blocking the receptor
Glucocorticoid-remediable aldosteronism (familial hyperaldosteronism type 1)	Hypokalemia, metabolic alkalosis, low PRA or PRC, increased PAC	Chimeric *CYP11B1/CYP11B2* gene; responds to glucocorticoids
Familial hyperaldosteronism type 2	Hypokalemia, metabolic alkalosis, low PRA or PRC, increased PAC	Increased activity of CLCN2 chloride channel; responds to steroidal MRA
Familial hyperaldosteronism type 3	Hypokalemia, metabolic alkalosis, low PRA or PRC, increased PAC	Loss of selectivity of KCNJ5 potassium channel; patients who do not respond to steroidal MRA require bilateral adrenalectomy
Familial hyperaldosteronism type 4	Hypokalemia, metabolic alkalosis, low PRA or PRC, increased PAC	Increased activity of CACNA1H calcium channel; responds to steroidal MRA
PASNA syndrome (primary aldosteronism, seizures and neurological abnormalities)	Hypokalemia, metabolic alkalosis, low PRA or PRC, increased PAC; neurological defects coexists	Increased activity of CACNA1D calcium channel; responds to steroidal MRA and CCB
11beta-hydroxylase deficiency	Hypokalemia, metabolic alkalosis, low PRA or PRC, low PAC, virilization of female individuals	Reduced activity of 11β-hydroxylase with increase of DOC and androgens; responds to glucocorticoids
17alpha-hydroxylase deficiency	Hypokalemia, metabolic alkalosis, low PRA or PRC, low PAC, pseudohermaphroditism in male individuals	Reduced activity of 17α-hydroxylase with increase of DOC and reduction of androgens; responds to glucocorticoids
Autosomal dominant hypertension with brachydactyly [342]	Brachydactyly type E (BDE), short stature, severe hypertension (salt-independent, age-dependent), high risk of death from stroke before age 50	PDE3A mutations upregulated the cAMP-hydrolytic activity that results in lower cAMP levels in vascular smooth muscle cells

New recommendations (5)

Recommendations	Class	Level
Diagnosing hypertension and investigating underlying causes cont.		
Objective evaluation of adherence (either directly observed treatment or detecting prescribed drugs in blood or urine samples) should be considered in the clinical work-up of patients with apparent resistant hypertension, if resources allow.	IIa	B
If moderate-to-severe CKD is diagnosed, it is recommended to repeat measurements of serum creatinine, eGFR, and urine ACR at least annually.	I	C
Coronary artery calcium scoring may be considered in patients with elevated BP or hypertension when it is likely to change patient management.	IIb	B
Patients with resistant hypertension should be considered for referral to clinical centres	IIa	B
It is recommended that patients with hypertension presenting with suggestive signs, symptoms, or medical history of secondary hypertension are appropriately screened for secondary hypertension.	I	B
Screening for primary aldosteronism by renin and aldosterone measurements should be considered in all adults with confirmed hypertension (BP ≥140/90 mmHg).	IIa	B

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Drugs and conditions that affect aldosterone, renin, and aldosterone-to-renin ratio (1)

Factor	Effect on plasma aldosterone levels	Effect on renin levels	Effect on ARR
Serum potassium status			
Hypokalaemia	↓	→↑	↓ (FN)
Potassium loading	↑	→↓	↑
Sodium restriction	↑	↑↑	↓ (FN)
Sodium loading	↓	↓↓	↑ (FP)

Drugs and conditions that affect aldosterone, renin, and aldosterone-to-renin ratio (2)

Factor	Effect on plasma aldosterone levels	Effect on renin levels	Effect on ARR
Drugs cont.			
Potassium-sparing diuretics	↑	↑↑	↓ (FN)
Potassium-wasting diuretics	→↑	↑↑	↓ (FN)
Alpha-2 agonists (clonidine, methyldopa)	↓	↓↓	↑ (FP)
NSAIDs	↓	↓↓	↑ (FP)
Steroids	↓	→↓	↑ (FP)
Contraceptive agents (drospirenone)	↑	↑	↑ (FP)

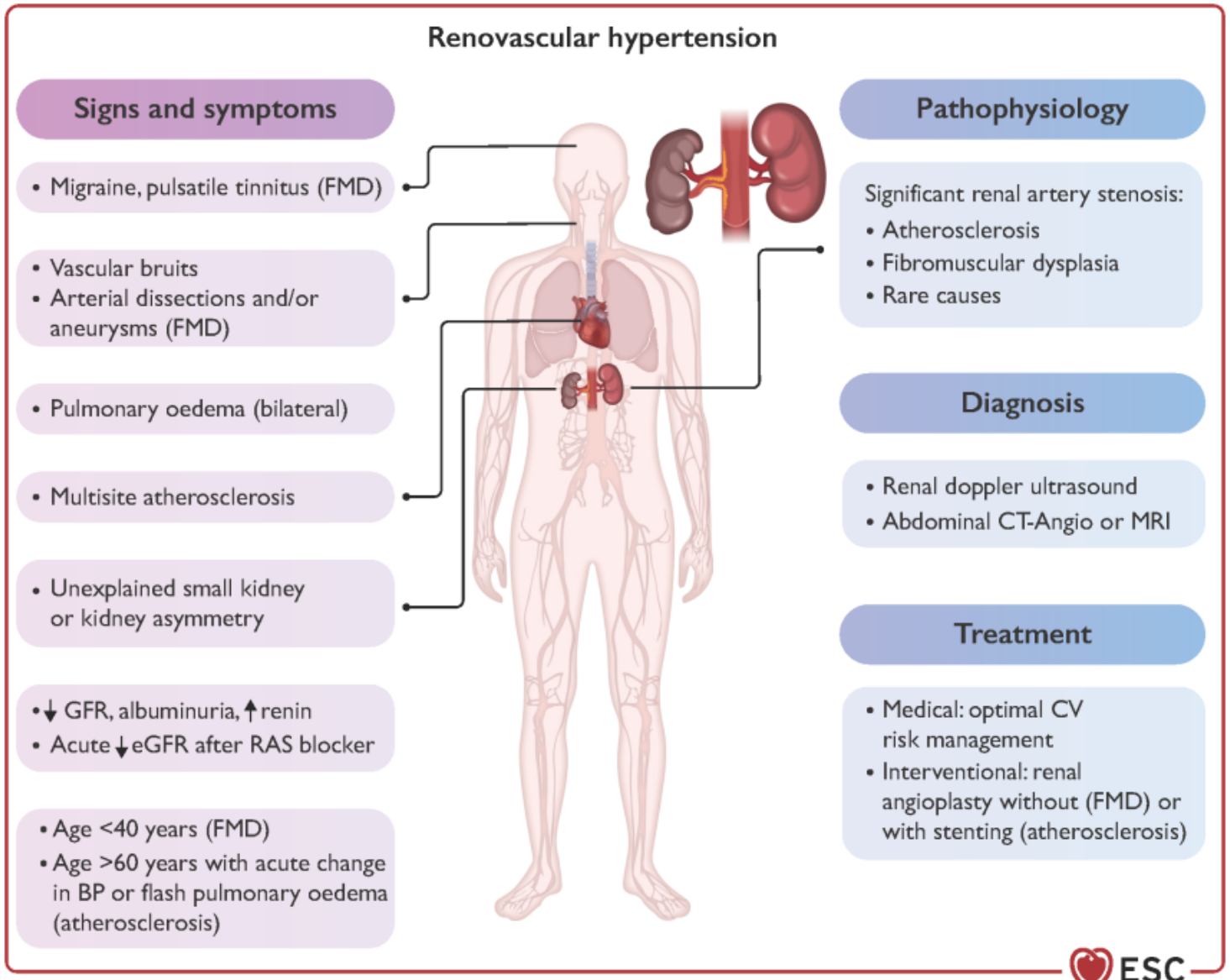
Drugs	Effect on aldosterone	Effect on renin	Effect on ARR	Interpretation when testing on drug
Beta-blockers	↓	↓↓	↑ (FP)	Increased ARR clinically not important (false-positive) if aldosterone low
Clonidine	↓	↓↓	↑ (FP)	Same as for beta-blockers
Methyldopa	↓	↓↓	↑ (FP)	Same as for beta-blockers
Calcium blockers (DHP)	↔↓	↔↑	↓ (FN)	Considered non-interfering in the 2020 Italian guidelines
Verapamil	↔	↔	↔	Considered non-interfering
ACEI	↓	↑↑	↓ (FN)	High renin does not exclude PA, testing must be repeated off-drug; low renin is strong predictor of PA
ARB	↓	↑↑	↓ (FN)	Same as for ACE inhibitors
Potassium-wasting diuretics	↔↑	↑↑	↓ (FN)	Considered prohibited during testing
MRA	↔/↑	↔/↑↑	↔/↓ (FN)	Previously considered prohibited during testing; based on the recent data may be continued (also during a confirmatory test and AVS), especially in patients with severe hypokalemia and/or poor BP control, and diagnosis of PA can be made in patients on MRA if aldosterone is high and renin low. However, if renin is not suppressed, then MRA should be discontinued for 4–6 weeks before retesting
Alpha-blockers	↔	↔	↔	Considered non-interfering
Moxonidine	↔	↔	↔	Single study in normotensives; considered non-interfering in the 2020 Italian guidelines
Hydralazine	↔	↔	↔	Rarely used nowadays; considered non-interfering

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARR, aldosterone-to-renin ratio; AVS, adrenal venous sampling; BP, blood pressure; DHP, dihydropyridines; FN, false negatives; FP, false positives; MRA, mineralocorticoid receptor antagonist; PA, primary aldosteronism.

Front. Pharmacol., 13 May 2021. Volume 12 - 2021 | https://doi.org/10.3389/fphar.2021.684111

Figure 14

Summary of renovascular disease as a common form of secondary hypertension



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HTA secondaire : que disent les recommandations ?

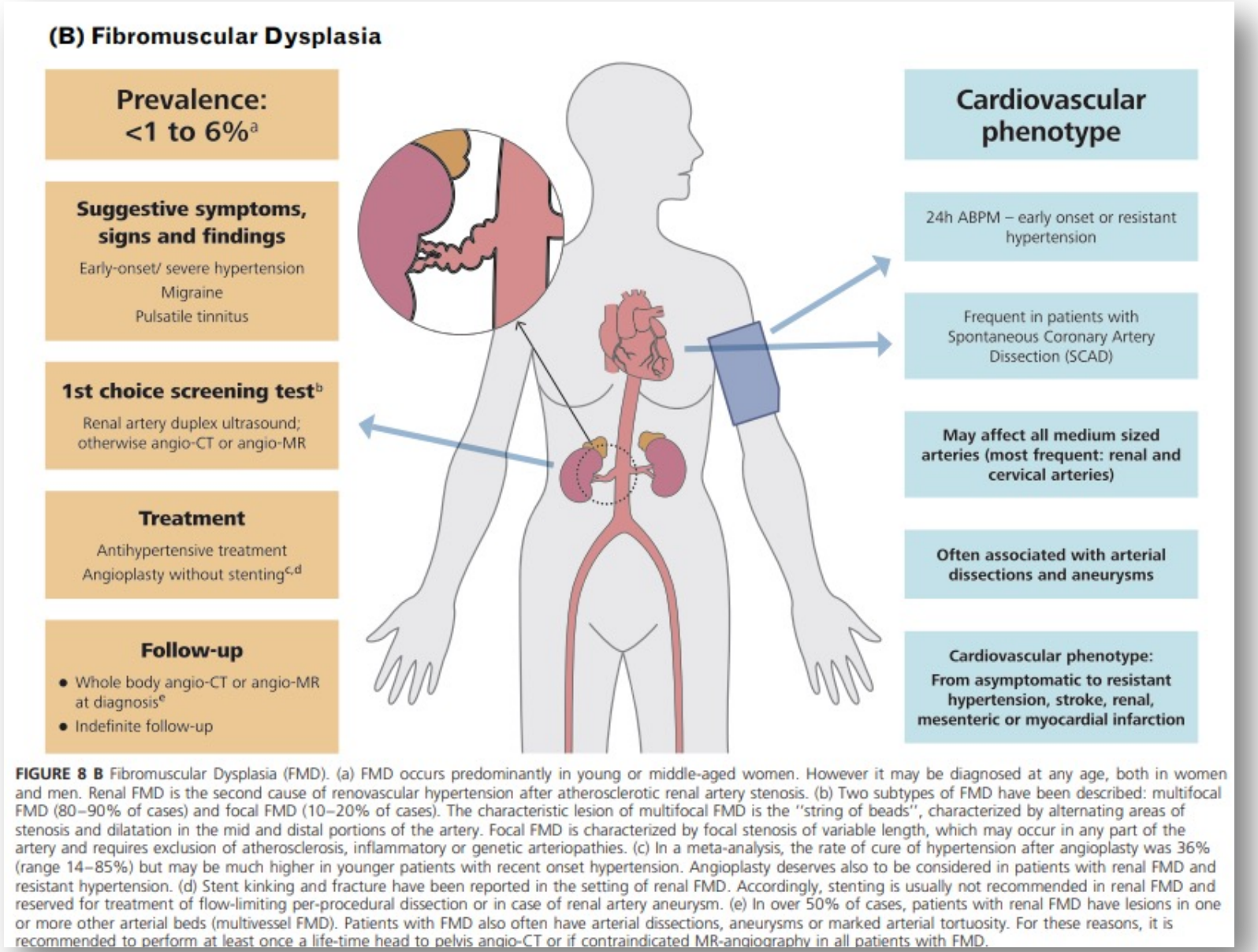
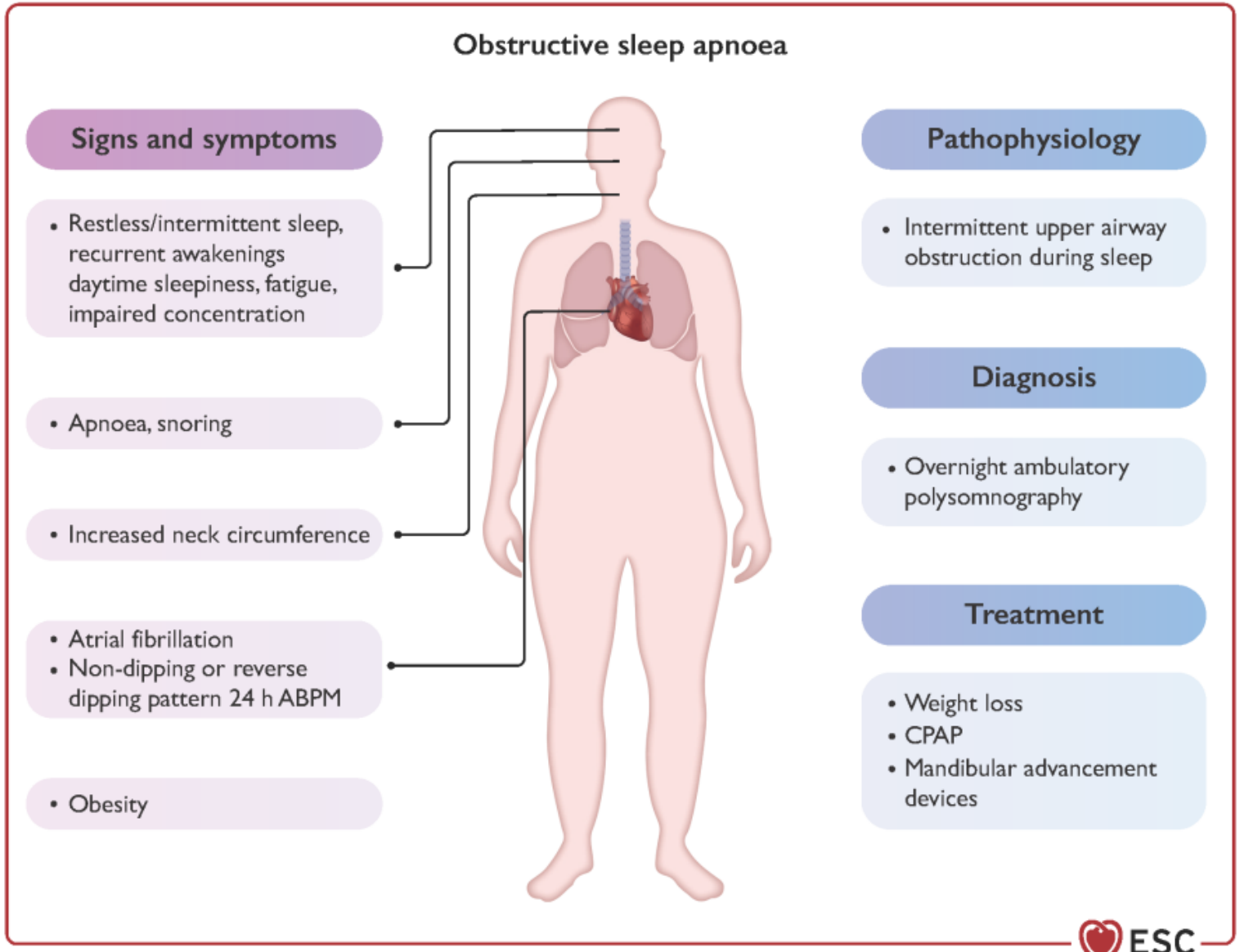


FIGURE 8 B Fibromuscular Dysplasia (FMD). (a) FMD occurs predominantly in young or middle-aged women. However it may be diagnosed at any age, both in women and men. Renal FMD is the second cause of renovascular hypertension after atherosclerotic renal artery stenosis. (b) Two subtypes of FMD have been described: multifocal FMD (80–90% of cases) and focal FMD (10–20% of cases). The characteristic lesion of multifocal FMD is the ''string of beads'', characterized by alternating areas of stenosis and dilatation in the mid and distal portions of the artery. Focal FMD is characterized by focal stenosis of variable length, which may occur in any part of the artery and requires exclusion of atherosclerosis, inflammatory or genetic arteriopathies. (c) In a meta-analysis, the rate of cure of hypertension after angioplasty was 36% (range 14–85%) but may be much higher in younger patients with recent onset hypertension. Angioplasty deserves also to be considered in patients with renal FMD and resistant hypertension. (d) Stent kinking and fracture have been reported in the setting of renal FMD. Accordingly, stenting is usually not recommended in renal FMD and reserved for treatment of flow-limiting per-procedural dissection or in case of renal artery aneurysm. (e) In over 50% of cases, patients with renal FMD have lesions in one or more other arterial beds (multivessel FMD). Patients with FMD also often have arterial dissections, aneurysms or marked arterial tortuosity. For these reasons, it is recommended to perform at least once a life-time head to pelvis angio-CT or if contraindicated MR-angiography in all patients with FMD.

Figure 15

Summary of obstructive sleep apnoea as a common form of secondary hypertension



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Optional tests that should be used to screen for secondary hypertension in the presence of suggestive signs, symptoms, or medical history

Cause of secondary hypertension	Screening test
Primary aldosteronism	Aldosterone-to-renin ratio Helpful information can also be provided by reviewing prior potassium levels (hypokalaemia increases the likelihood of coexistent primary hyperaldosteronism)
Renovascular hypertension	Renal doppler ultrasound Abdominal CT angiogram or MRI
Phaeochromocytoma/paraganglioma	24 h urinary and/or plasma metanephrine and normetanephrine
Obstructive sleep apnoea syndrome	Overnight ambulatory polysomnography
Renal parenchymal disease	Plasma creatinine, sodium, and potassium eGFR Urine dipstick for blood and protein Urinary albumin-to-creatinine ratio Renal ultrasound

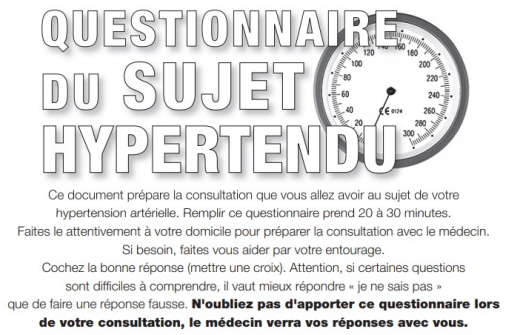
Optional tests that should be used to screen for secondary hypertension in the presence of suggestive signs, symptoms, or medical history

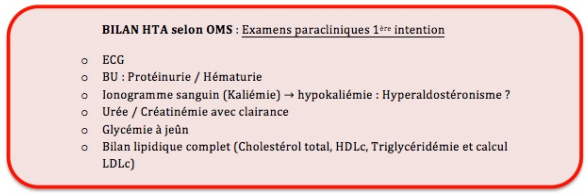
Cause of secondary hypertension	Screening test
Cushing's syndrome	24 h urinary free cortisol Low-dose dexamethasone suppression test
Thyroid disease (hyper- or hypothyroidism)	TSH
Hyperparathyroidism	Parathyroid hormone Calcium and phosphate
Coarctation of the aorta	Echocardiogram Aortic CT angiogram

Table 10. Causes of Secondary Hypertension With Indications for Additional Testing and Diagnostic Screening Tests (con't.)

Drug or alcohol induced[11]	2%–20%	Sodium-containing antacids; antidepressants; nicotine (smoking); alcohol; NSAIDs; oral contraceptives; cyclosporine or tacrolimus; sympathomimetics (decongestants, anorectics); cocaine, amphetamines and other illicit drugs; neuropsychiatric agents; erythropoiesis-stimulating agents; cancer treatment (VEGF inhibitors, Bruton tyrosine kinase inhibitors and others), clonidine withdrawal; herbal agents (Ma Huang, ephedra)	Fine tremor, tachycardia, sweating (cocaine, ephedrine, MAO inhibitors); acute abdominal pain (cocaine)	Urinary drug screen (illicit drugs)	Response to withdrawal of suspected agent

HTA secondaire : Quel bilan ?





- Bilan urinaire des 24h
  - Protéinurie, créatininurie
  - Natriurèse
  - Cortisol libre urinaire
  - Sédiment urinaire
  - ECBU
- Test de freinage minute

- **Bilan biologique**
  - Aldostérone, rénine en condition standardisée :
    - Stop traitement interférant 2 à 6 semaines avant
    - Normokaliémie, consommation normosodée
    - Allongée ou assis depuis au moins 30 minutes
  - Test dynamique (freination sodée)
  - PTH, TSH, métanéphrines plasmatique
- **Bilan morphologique**
  - Echodoppler des artères rénales
  - TDM des surrénales +/- angioscanner des artères rénales
- **(Polygraphie du sommeil)**

Conclusion

Les HTA secondaires, c'est

- **Fréquent**
  - 6-10% de tous les hypertendus au moins
- **Grave**
  - Sur-risque cardiovasculaire et de mortalité net
- **Curable ou accessible à un traitement spécifique**

Mais largement sous diagnostiquée !