Secondary hypertension

JASMINE TAN

21 OCTOBER 2020

GREENLANE MEDICAL SPECIALISTS

Objectives

Who should be screened ?

Recognition of resistant hypertension

Overview of common secondary causes of hypertension

- Obstructive sleep apnoea
- Renal parenchymal disease
- Renovascular causes
- Primary Aldosteronism

Case discussions

Secondary hypertension

Identified by a specific etiology

Often resistant to standard antihypertensive treatment

Remediable to specific therapeutic strategies

Who should be suspected?

Severe or resistant hypertension

Juvenile hypertension

Rapid onset of hypertension

Acute exacerbation of preexisting hypertension

Resistant hypertension

Variation in the prevalence of resistant hypertension due to different definitions

Prevalence rate 2-10% in primary care setting/ general population

- 40% in those with CKD

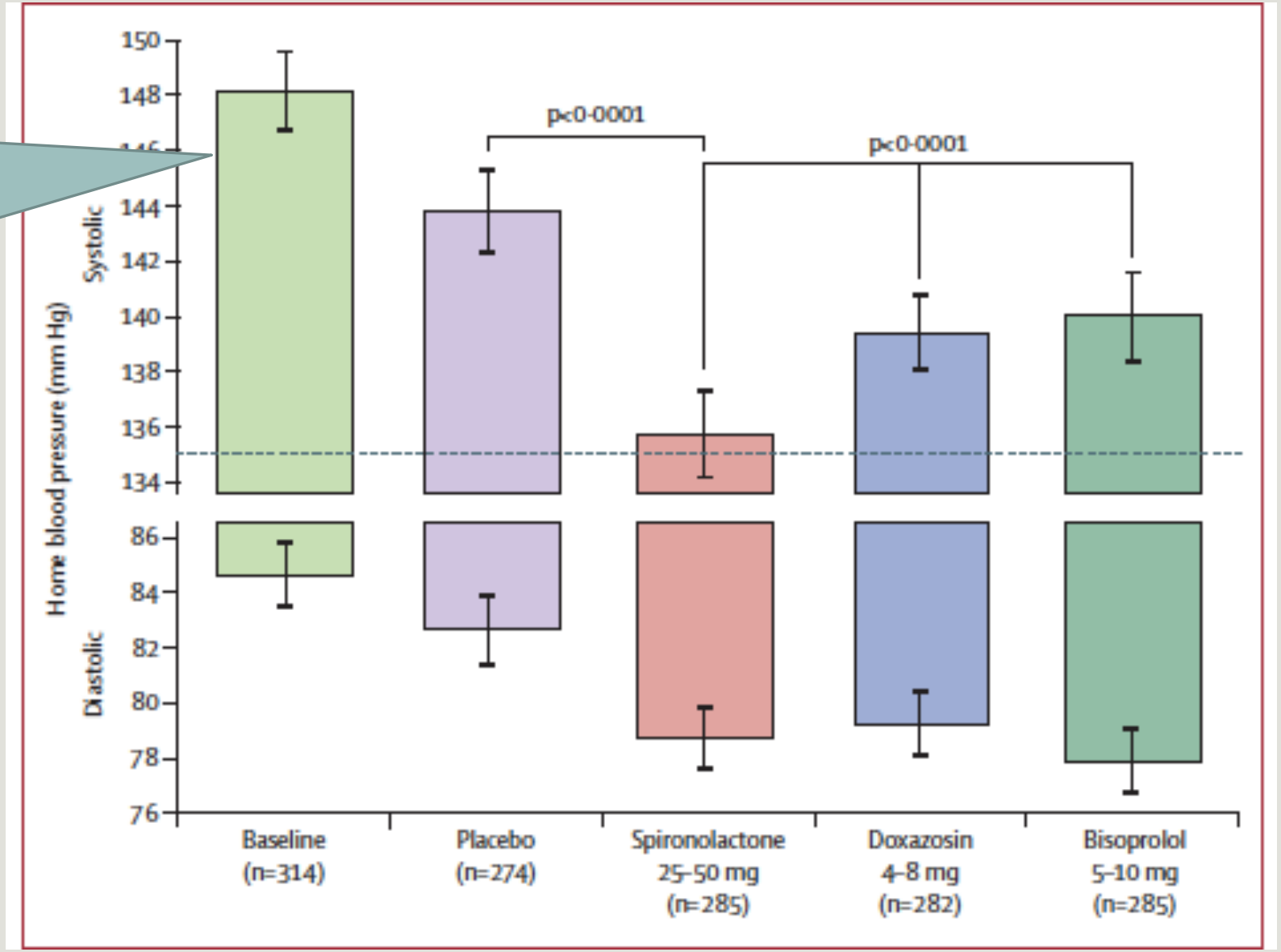
Resistant hypertension is a diagnosis of exclusion after ensuring medication compliance and excluding apparent resistant hypertension

Resistant hypertension

- Failure to achieve BP goal in spite of the use of ≥3 antihypertensive agents of different classes at maximally tolerated doses, including a diuretic.
- Includes patients with target BP on ≥4 antihypertensive agents
- Prevalence reported to be ~10 – 20 % of hypertensive patients with higher risk for cardiovascular events and CKD development
- Optimal treatment regimen is undefined. Pathway-2 trial showed benefit with the addition of Spironolactone, compared to other antihypertensive agents, added to standard regimen

Hypertension. 2018 November ; 72(5): e53–e90.

Baseline anti-HTN treatment included:
ACEi or ARB
CCB
Diuretic



Spironolactone controlled BP in almost 60% of patients and was well tolerated without excess AEs

Lancet 2015; 386: 2059-2068.

Obstructive sleep apnoea (OSA)

- Sleep disordered breathing characterized by episodes of complete or partial upper airway obstruction
  - Repetitive oxygen desaturation
  - Sleep fragmentation

- Snoring; ESS > 10 points suggest excessive daytime sleepiness; AHI ≥ 15 events per hour of sleep assessed on polysomnography

- OSA syndrome is associated with elevated frequency of CV events at night associated with midnight BP surge

Hypertens Res 2009; 32: 537 – 541.

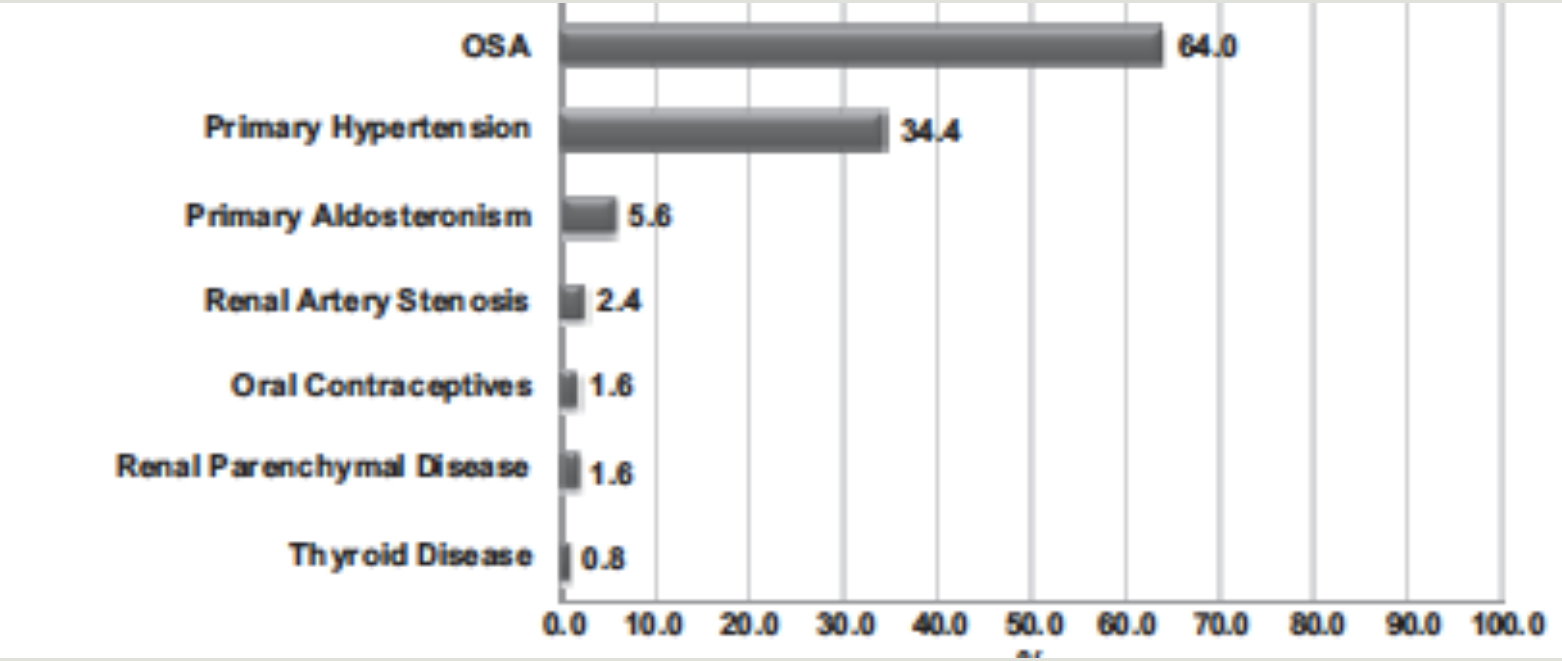
Diagnostic clues

Symptoms	Daytime sleepiness, reduced concentration, depression Headache/malaise at wakening or in the morning Marked snoring, frequent awakening during the night, nocturia, nocturnal dyspnea
Examination findings	Obesity Micrognathia
Investigation findings	Resistant morning hypertension including nocturnal hypertension (BP ≥ 120/70mmHg) Left ventricular hypertrophy Sleep-onset cardiovascular events (including arterial fibrillation and ventricular arrhythmia) Metabolic syndrome – diabetes, hypercholesterolemia, NAFLD

Obstructive sleep apnoea

Common in patients with hypertension (prevalence 37 – 56%).

Higher in resistant hypertension.



Age 52 ± 1 years

43% males

Systolic BP 176 ± 31 mmHg

Diastolic BP 107 ± 19 mm Hg

6.4% with concomitant other secondary causes

Hypertension. 2011;58:811-817.

Risk factors for OSA

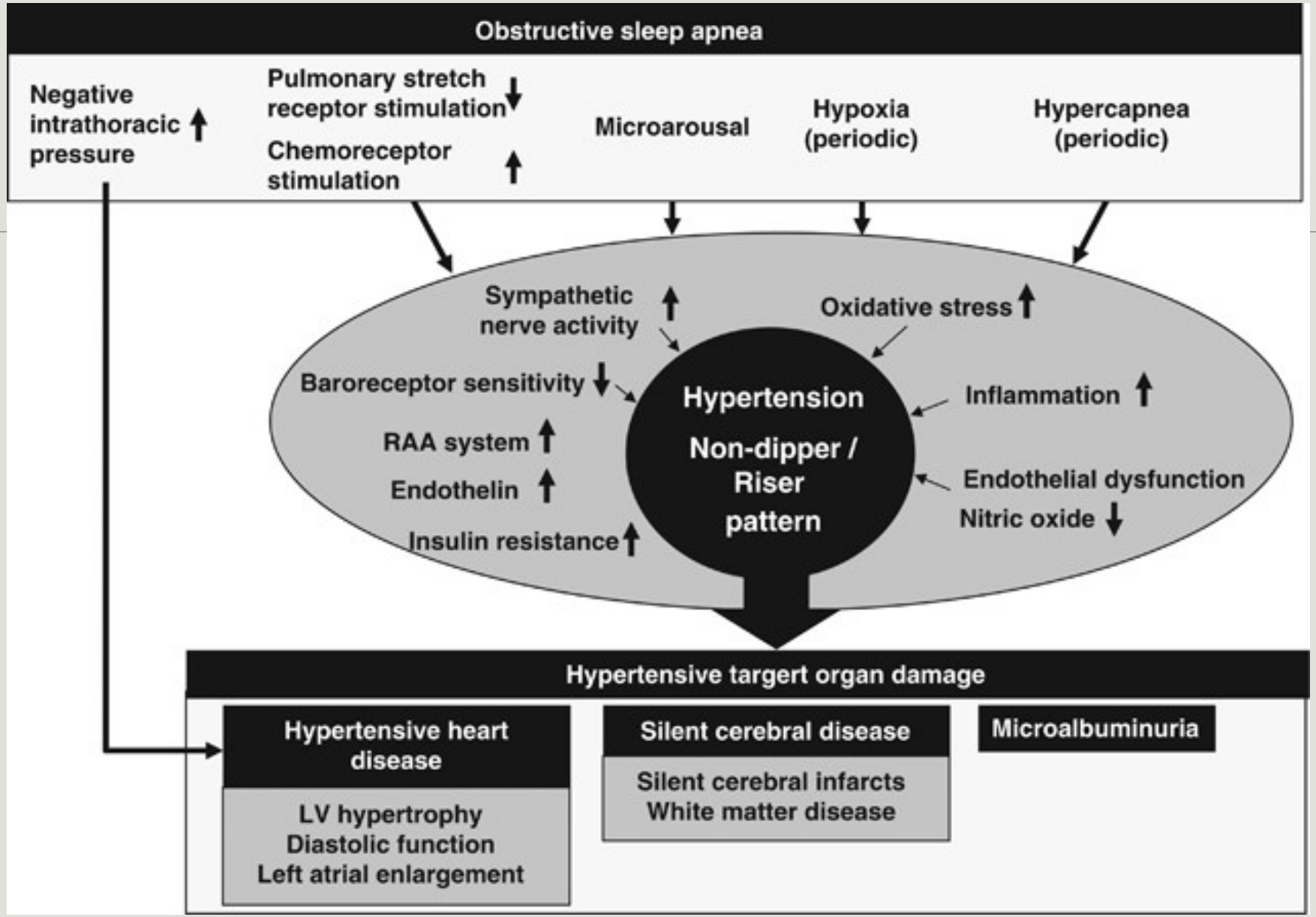
Table 4. Predictors of Obstructive Sleep Apnea Among Patients With Resistant Hypertension

	Univariate			Multivariate		
Variable	OR	*P*	β Coefficient	SE	OR (CI)	*P*
Male	3.00	0.006				
Large neck circumference	2.77	0.032	1.55	0.65	4.7 (1.3–16.9)	0.02
Waist circumference	1.40	0.42				
Snoring	5.43	0.001	1.31	0.55	3.7 (1.3–11.0)	0.02
Metabolic syndrome	2.63	0.015				
Age >50 y	4.97	<0.001	1.63	0.52	5.2 (1.9–14.2)	0.002
Systolic nondipping	0.60	0.20				
Diastolic nondipping	0.81	0.62				
Epworth Sleepiness Scale	1.24	0.61				
Obesity	2.20	0.038				
Constant	. . .	. . .	−3.36	0.97	0.035	0.001

Data are presented as odds ratios (95% CIs).

Neck circumference of 41 cm or 43 cm for women and men, respectively

Hypertension. 2011; 58:811-817.



Hypertens Res 2009; 32: 537 – 541.

Management

Highlights importance of 24 hour ABPM to identify non-dippers

OSA confirmation with polysomnography study

Weight loss, reduce alcohol drinking

CPAP therapy most beneficial in moderate to severe OSA syndrome (ie. AHI >20)

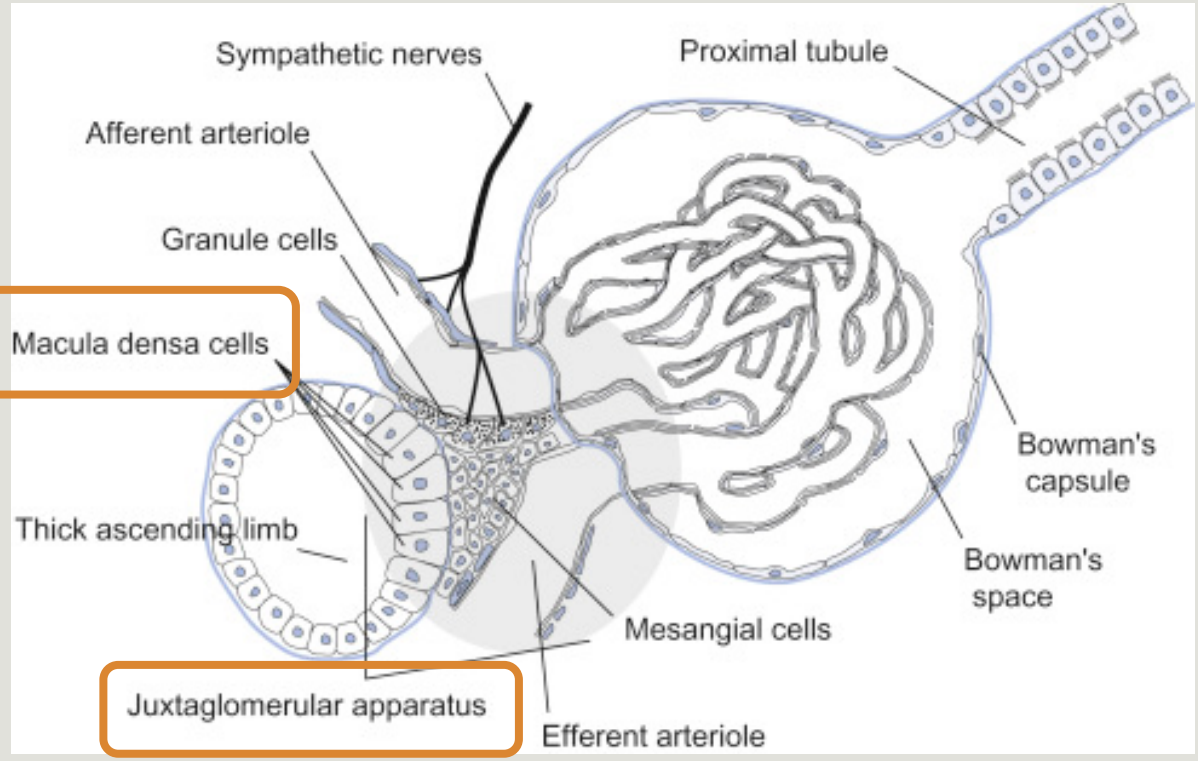
- Attenuates reduction of NO production and increased inflammation
- Decreases nocturnal BP surge and nocturnal hypertension; selectively reduces BP in non-dippers
- Modest BP reduction in milder forms
- CPAP therapy compliance key

No specific medical therapy or class of antihypertensive agents

Hypertens Res 2009; 32: 537 – 541.

Renal parenchymal hypertension

- Most common form of secondary hypertension
- Diabetic nephropathy, Chronic GN, nephrosclerosis, polycystic kidney disease (PKD)
- Bidirectional relationship between CKD and hypertension
- Renal ischaemia (macro- & micro-)
- Pathogenesis:
  - Sodium and fluid retention
  - Upregulation of RAS system



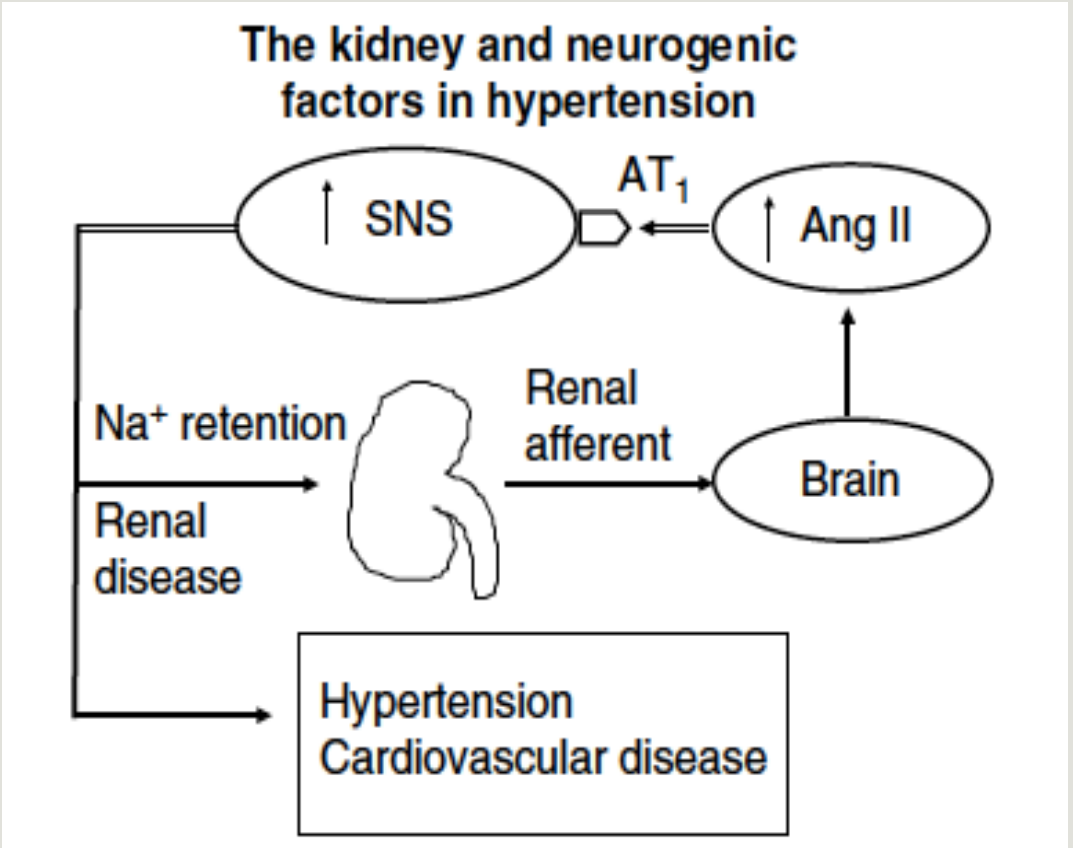
↑ renin

Kidney International 2006; 69, 967–973.

Renal parenchymal hypertension

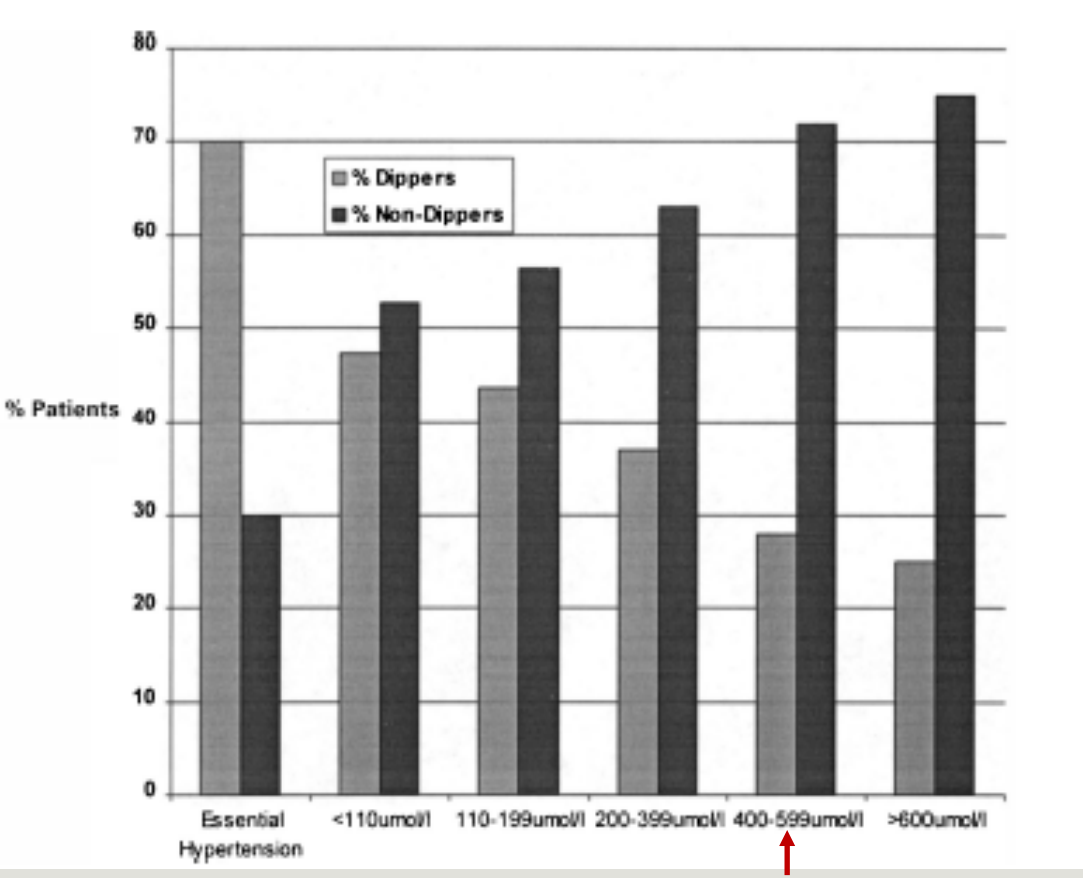
Mechanisms

- Increased sodium sensitivity and fluid retention
- Upregulation of RAS system; Ang II
- SNS over-activity via renal afferent nerve stimulation driven by renal ischemia
- Increased endothelin production; endothelial dysfunction
  - Higher levels of of ET-1 and ET 3 in patients with CKD and ESRD
- Inhibition of NO synthesis
- Iatrogenic: Cyclosporin, steroids, NSAIDs, EPO



Kidney International 2006; 69, 967–973.

Non-dippers & nocturnal hypertension



- 74 – 82% in patients with CKD and haemodialysis patients
- Correlates to degree of renal impairment
- Mechanisms
  - Obstructive sleep apnoea and oxygen desaturation
  - Excessive extracellular volume
  - Uremic neuropathy
  - Restless legs syndrome

2 – 2.5 times more anti-HTN agents in patients with Cr ≥ 400 umol/L

NDT 1997; 12: 2301 – 2307.

Management

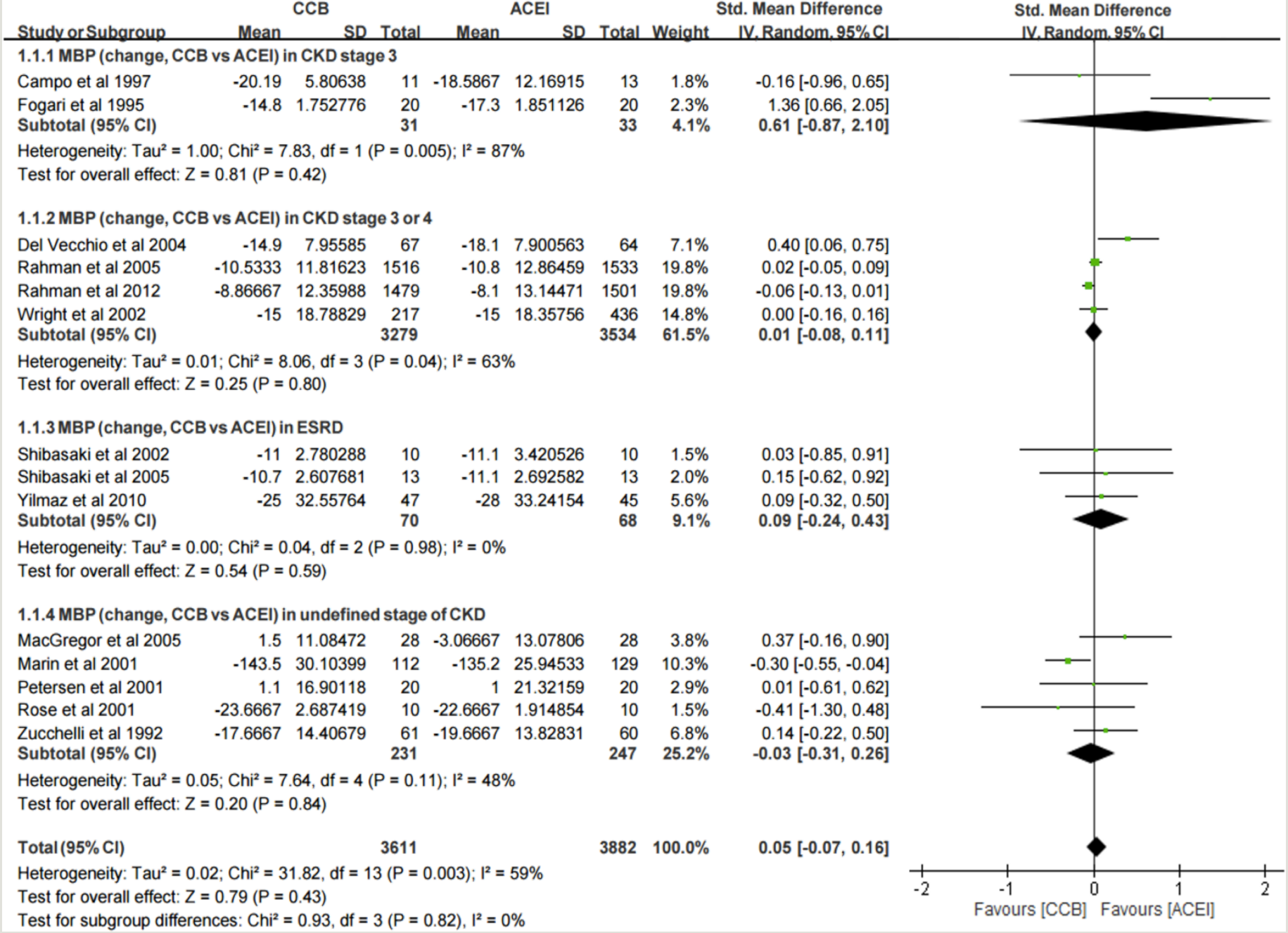
Dietary salt and fluid restriction

RAS inhibitors first line treatment

Adrenergic blockers

Calcium channel blockers non-inferior to ACEi and ARB in CKD 3 – 5 (meta-analysis of 21 RCTs)[1]

1. PLoS One 2017; 12(12): e0188975



Lower MBP observed in ACEI group compared with CCB group only in the 1st year of follow-up. No significant differences in long-term follow-up

No significant inter-group differences with stroke or CVA events, dialysis events, and proteinuria

Renovascular hypertension

Conditions resulting in reduced renal blood flow, contribute to renovascular hypertension via RAAS activation (intra-renal ischaemia)

<1% of patients with mild-moderate HTN

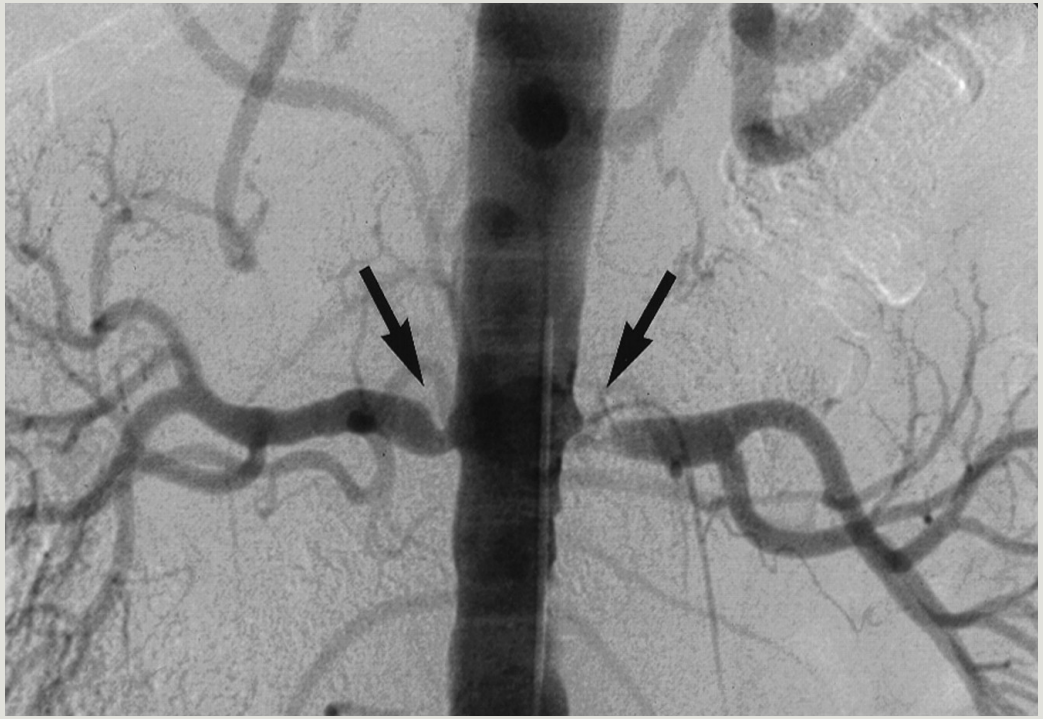
> 75 – 80% reduction in lumen diameter: hemodynamically significant

Disease	Incidence
Atherosclerosis	60 -80%
Fibrous dysplasia	20 – 40%
Arterial aneurysm	<5%
AV malformation	<1%

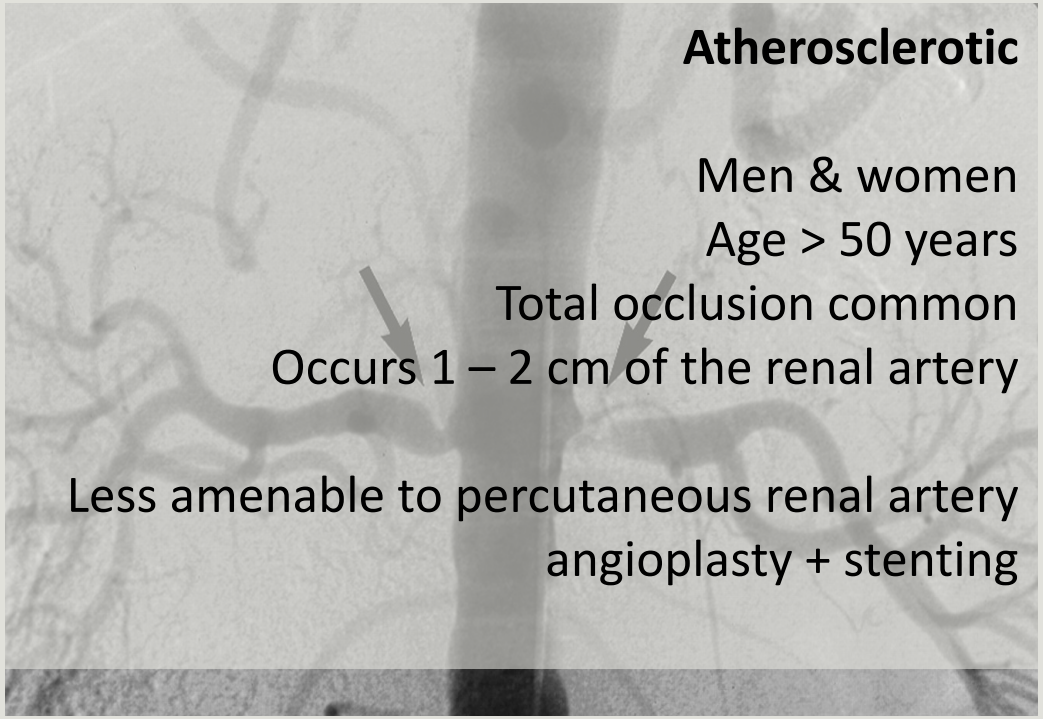
Diagnostic clues

- Onset of hypertension before the age of 30 years or severe hypertension after the age of 55
- Accelerated, resistant or malignant hypertension
- Development of new azotemia or worsening renal function after administration of an ACE inhibitor or ARB agent
- Unexplained atrophic kidney or size discrepancy between kidneys of > 1.5 cm
- Sudden, unexplained pulmonary edema
- Unexplained renal dysfunction, including individuals starting renal replacement therapy
- Abdominal bruit
- Other vascular diseases such as peripheral artery disease
- Hypokalemia

Types of renal artery disease



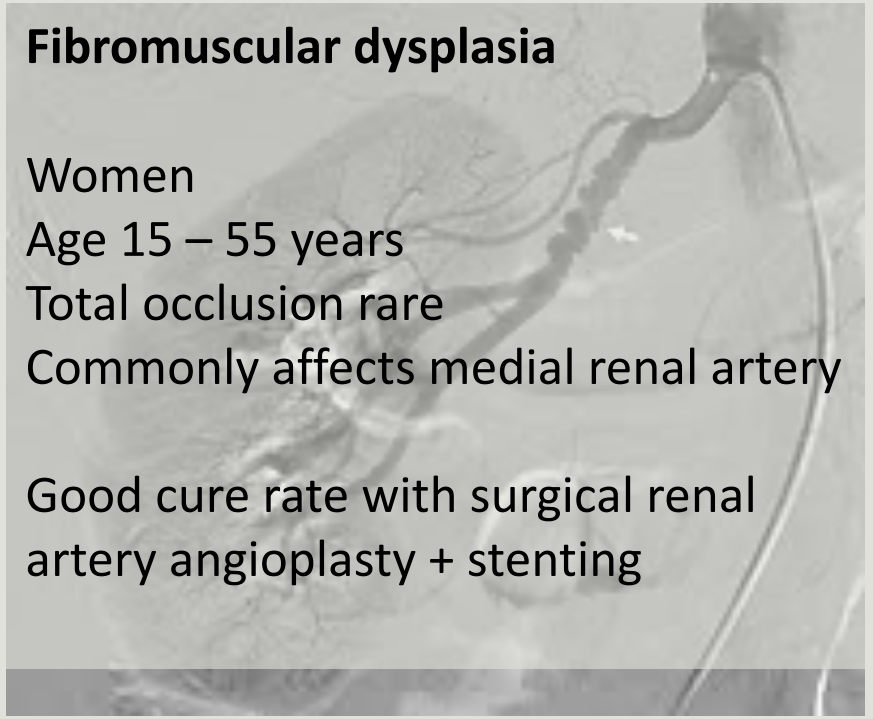
Renal artery disease



Atherosclerotic

Men & women
Age > 50 years
Total occlusion common
Occurs 1 – 2 cm of the renal artery

Less amenable to percutaneous renal artery angioplasty + stenting



Fibromuscular dysplasia

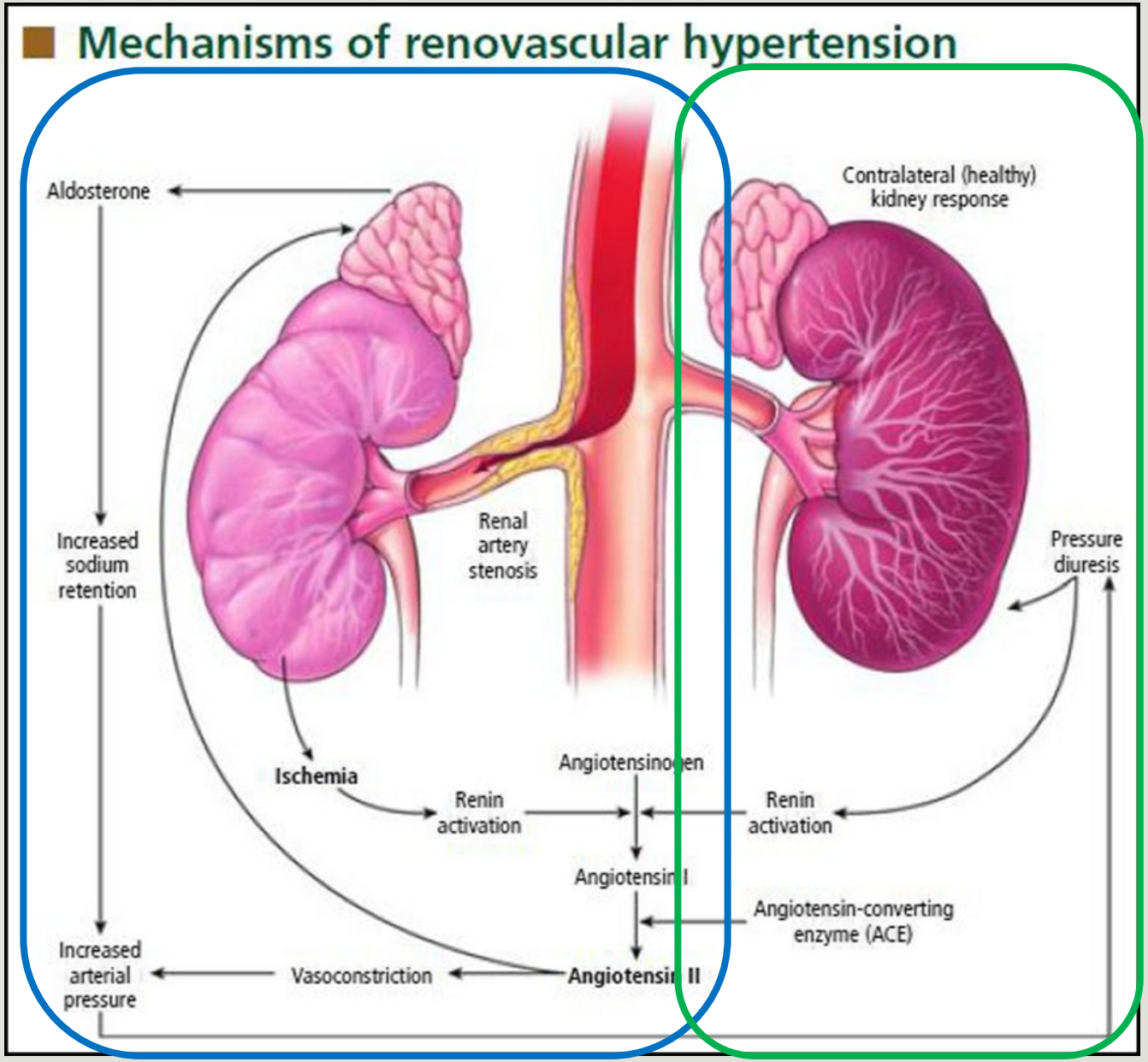
Women
Age 15 – 55 years
Total occlusion rare
Commonly affects medial renal artery

Good cure rate with surgical renal artery angioplasty + stenting

Imaging for renal artery disease

Imaging modalities	Pros	Cons
Angiography	Gold standard; provides direct vision to stenosis Diagnostic and therapeutic procedure	Invasive
Renal artery duplex ultrasound	High sensitivity and specificity Inexpensive Minimal risk to patient	Operator dependent Resource dependent
CT renal angiogram	High sensitivity and specificity	Additional radiation Contrast exposure Expensive
MRA	High sensitivity and specificity	May overestimate disease severity Expensive

Circulation 2006; 113:e463 – 54.



- Increased secretion of renin of the affected kidney
- RAAS upregulation and increased Ang II & aldosterone levels
- Increased BP resulting from Ang II effects, sodium and fluid reabsorption

- Pressure diuresis in contralateral kidney may result in plasma volume contraction
- Potentiate RAAS cascade

Journal Clin Hypertens 2013; 15(9): 694-698

Management

- Angioplasty in fibrous renal artery disease mainstay therapy
  - Contraindication of RAAS blockade in pregnancy
  - Favourable long term prognosis; 11 – 23% require repeat angioplasty in restenosis

Management

Atherosclerotic RAS

- Effective RAAS blockade is associated with lower CHF, renal and mortality events versus other antihypertensive agents
- Reduce progression of atherosclerotic RAS (statin, BP, smoking cessation)
- STAR, ASTRAL, CORAL studies: Revascularization in addition to optimal medical therapy did not confer renal or mortality benefit (excluded: high grade stenosis, RAS blockers not optimized in groups)
- Investigate for associated coronary, carotid and peripheral artery disease and abdominal aortic aneurysm

Ann Intern Med 2009; 150(12):840-848
NEJM 2009; 361:1953-62
Clin J Am Soc Nephrol 2016; 11: 1180-118

Who should be revascularized in atherosclerotic RAS?

Patients with haemodynamically significant (>70%) RAS and:

- Resistant hypertension on maximally tolerated antihypertensive agents
- Recurrent pulmonary oedema or unstable angina with Stage 2 hypertension
- eGFR <45ml/min/1.73m^2 with global renal ischaemia or progressive renal dysfunction in unilateral RAS with solitary kidney or bilateral RAS without any other renal pathology *

* Kidney length >7cm

Primary Aldosteronism (PA)

- PA accounts for 5 – 10% of patients with hypertension; 20 – 30 % of resistant hypertension

- Initial screening with elevated aldosterone: renin ratio (ARR) in the context of normal serum potassium; requires confirmatory testing
  - Suppression of renin secretion
  - Blunted renin response to normal physiological stimulants
  - Inappropriate and non-suppressible aldosterone production

J Clin Endo Metab. 2020; 105(12): 1–13.
Hypertension. 2018; 72(5): e53–e90.

Primary aldosteronism (PA)

- Spectrum of PA phenotypes (normotensive – subclinical or non-classical PA)
  - Normotensive participants with a suppressed renin had a 68% higher risk of incident hypertension in the next 5 years when compared to normotensive participants with a normal renin
- Associated with excess cardiovascular risk for the same degree of hypertension in those with essential hypertension
- Positive association between OSA severity and PA

J Clin Endo Metab. 2020; 105(12): 1–13.
Hypertension. 2018; 72(5): e53–e90.

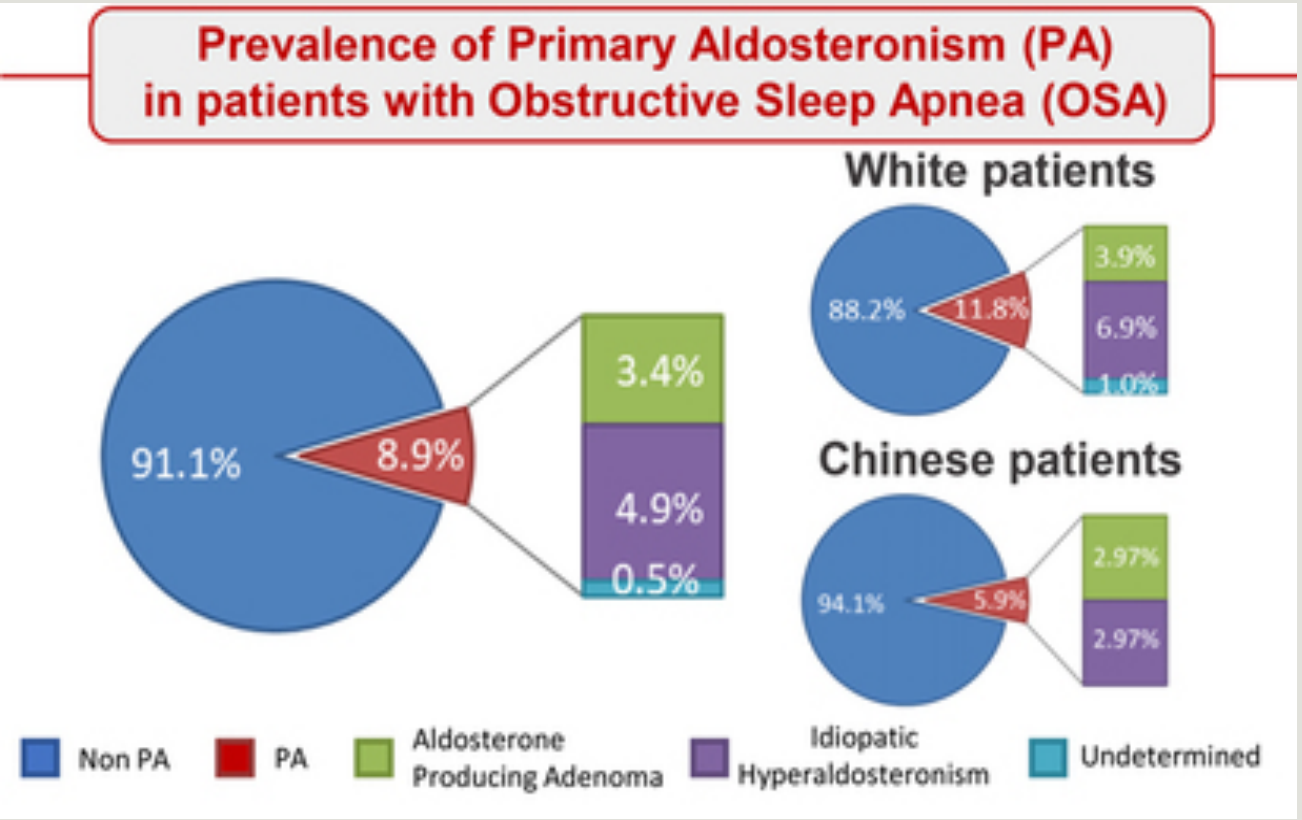
Excess cardiovascular damage in PA

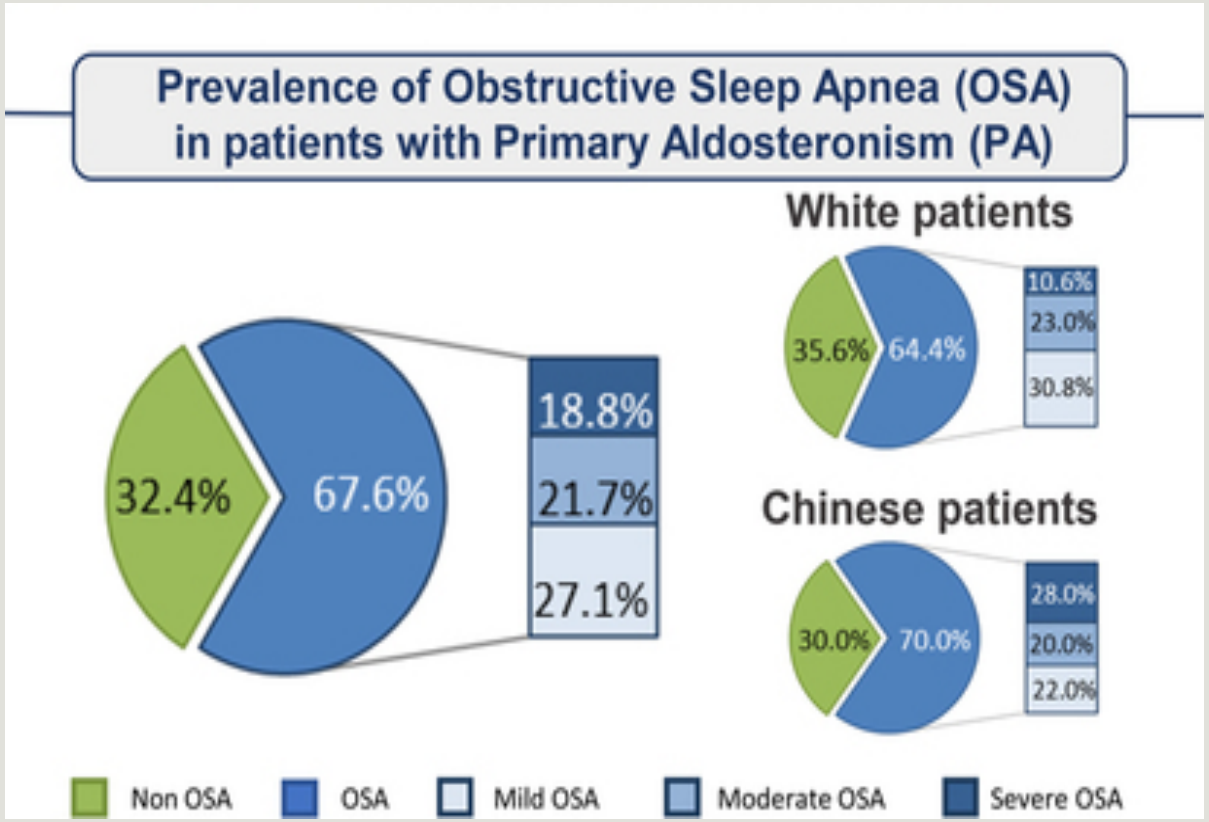
Table 3. Rate of Cardiovascular Events and Cardiac Structure in Primary Aldosteronism Patients and Controls

	Primary Aldosteronism (n = 124)	Essential Hypertension (n = 465)	Odds Ratio (95% CI)	p Value
Stroke (%)	12.9	3.4	4.2 (2.0–8.6)	<0.001
Myocardial infarction (%)	4.0	0.6	6.5 (1.5–27.4)	<0.005*
Atrial fibrillation (%)	7.3	0.6	12.1 (3.2–45.2)	<0.0001*
Echocardiographic LVH (%)	34	24	1.6 (1.1–2.5)	<0.01
Electrocardiographic LVH (%)	32	14	2.9 (1.8–4.6)	<0.001

*Fisher exact test.
CI = confidence interval; LVH = left ventricular hypertrophy.

J Am Coll Cardiol. 2005;45 (8):1243





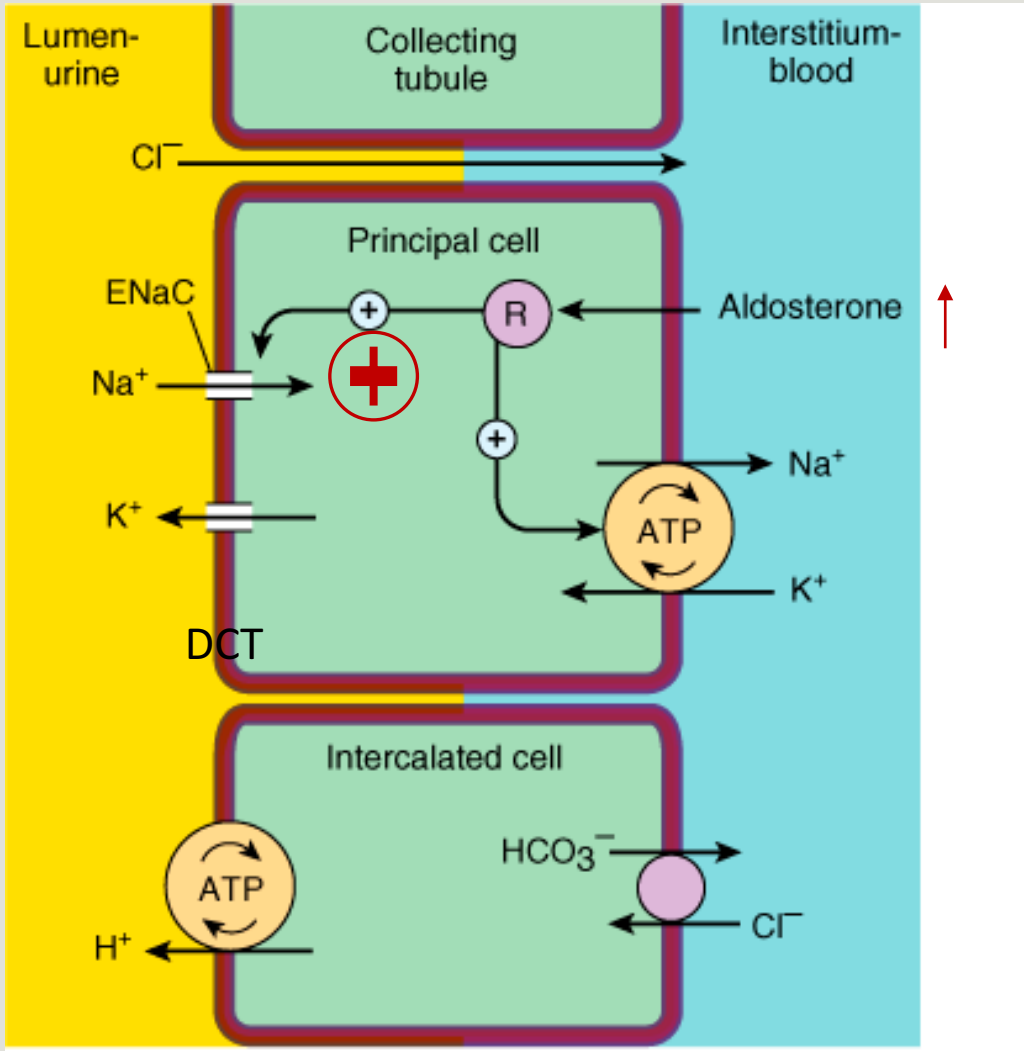
Prevalence of OSA in patients with PA is similar to that observed in the general hypertensive population

In white patients, aldosterone levels contribute to the severity of OSA

Hypertension. 2019; 74 (6) : 1532-1540

Clinical presentations

- Hypertension with spontaneous or provoked hypokalemia serum potassium <3.5 mmol/L (9 – 37%)
  - Volume expansion
  - SNS activation
  - Metabolic alkalosis
- Adrenal lesion & hypertension
- Onset of hypertension at young age (<30 yrs)
- Family history:
  - Early onset hypertension
  - CVAs at young age (<40 years)
  - First degree relatives with PA
- Resistant hypertension



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Influence of antihypertensive agents

	PAC	*PRA*	*ARR*
ACE inhibitors/ARBs	↓	↑↑	↓[a]
β-blockers	↓	↓↓	↑[b]
Renin inhibitor	↓	↓↓	↑[b]
Ca channel blockers	→~↓	↑	↓[a,c]
Aldosterone antagonists, Thiazide diuretics	↑	↑↑	↓[a]

Hypertension Res 2014; 37: 349–361

The Journal of Clinical Endocrinology & Metabolism, 2020, Vol. 105, No. 12, 1–13
doi:10.1210/clinem/dgaa606
Approach to the Patient

ENDOCRINE SOCIETY

Approach to the Patient

Evolution of the Primary Aldosteronism Syndrome: Updating the Approach

Anand Vaidya[1] and Robert M. Carey[2]

[1]Center for Adrenal Disorders, Division of Endocrinology, Diabetes, & Hypertension, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115; and [2]Division of Endocrinology and Metabolism, University of Virginia Health System, Charlottesville, Virginia 22903

ORCiD number: 0000-0002-0314-9252 (A. Vaidya).

Simplified diagnostic pathway

- Inclusion pathway in the setting of repeated tests showing:
  - Low plasma renin (< 5 – 8 mU/L) in the absence of beta-blocker use and/or
  - Aldosterone > 415 pmol/L especially in resistant hypertension +/- hypokalaemia

- Exclusion pathway:
  - Unsuppressed renin (> 8.5 mU/L)in the absence or after cessation of Spironolactone/ Amiloride/high dose diuretics, or
  - Aldosterone concentration < 140 pmol/L

J Clin Endo Metab. 2020; 105(12): 1–13.

PA subtypes

Subtypes	Frequency
Idiopathic hyperplasia, bilateral (IHA)	60 – 65%
Aldosterone-producing adenoma (APA)	30 – 35%
Primary adrenal hyperplasia, unilateral	2 – 3%
Glucocorticoid-remediable aldosteronism (GRA)/ familial hyperaldosteronism FH type 1	<1%
Familial hyperaldosteronism type 2	<1%
Familial hyperaldosteronism type 3	<1%
Aldosterone-producing adenoma or carcinoma or ectopic lesion	<1%

Ann Med 2013;45:375

Directed management of PA

Bilateral adrenal hyperplasia

Aldosterone-producing adenoma

Other antihypertensive agents:
Amiloride
ACEI
ARB
CCB

MR antagonist

Selective MRA
Eplerenone

Non-selective MRA
Spironolactone

Laparoscopic adrenalectomy
(30 – 60% cure of HTN)

Monitor renal function post op
- Reduced intra-glomerular pressure
- Fludrocortisone

Titrated till normalization of plasma renin concentration (8 – 10 mU/L)

Case discussions

Case 1

Which of the following statements is false:

A. Elimination of coffee consumption will have no significant effect on BP on frequent caffeine drinkers.

B. Alcohol intake is associated with hypertension

C. Dietary sodium to potassium ratio < 1.0 reduces blood pressure

D. Eliminating Cox-2 inhibitors will not lower BP.

Case 1

Which of the following statements is false:

A. Elimination of coffee consumption will have no significant effect on BP on frequent caffeine drinkers.

B. Alcohol intake is associated with hypertension

C. Dietary sodium to potassium ratio < 1.0 reduces blood pressure

D. Eliminating Cox-2 inhibitors will not lower BP.

NSAIDS and hypertension

Blocking Cox-1 and 2 isoenzymes, result in reduced prostaglandin formation and attenuates afferent vasodilation

Dose-related sodium and water retention

Cox-2 inhibitors vs placebo; RR 1.61 (95% CI 0.91 – 2.84)

Non-selective NSAIDs vs placebo; RR 2.5 (95% CI 1.0 – 2.26)

Arch Intern Med. 2005 Mar 14;165:490-6.

Table 2. Common prescription and nonprescription drugs that can raise BP

Prescription Drugs	Nonprescription Drugs
Anabolic steroids	Anabolic steroids
Antidepressants	Caffeine
Monoamine oxidase inhibitors	Cocaine
Selective serotonin reuptake inhibitor	Ethanol (in excess)
Selective norepinephrine uptake inhibitors	Glycyrrhizic acid (contained in some licorice, cough drops, and chewing tobacco)
Norepinephrine transporter inhibitors	NSAIDs
Calcineurin inhibitors	**Sympathomimetic and illicit drugs**
Cyclosporin	Amphetamines
Tacrolimus	Cocaine
Glucocorticoids	Sympathomimetic nonprescription medications (decongestants)
Erythropoietin	Nasal sprays
Contraceptives	**α-Adrenergic herbal supplements**
Estrogen containing	Ephedra (Ma-Huang)
Progesterone containing	Caulophyllum thalictroides (blue cohosh)
NSAIDs	Citrus aurantium
Sympathomimetics	Synephrine, *N*-methyltyramine (bitter orange)
VEGF inhibitors	1,3-Dimethylamylamine
Tyrosine kinase inhibitors	
Amphetamines (in context of ADHD)	

NSAID, non-steroidal anti-inflammatory drugs; VEGF, vascular endothelial growth factor; ADHD, attention-deficit hyperactivity disorder.

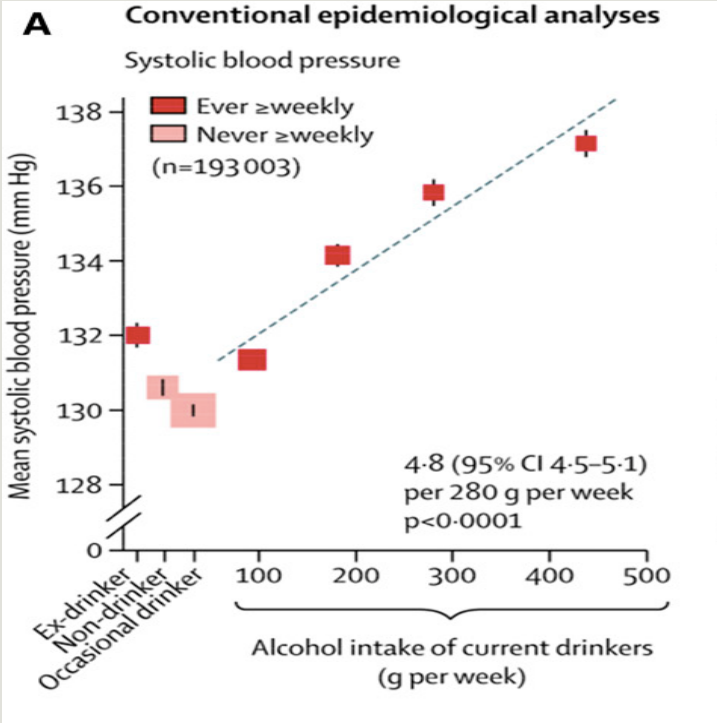
Caffeine and hypertension

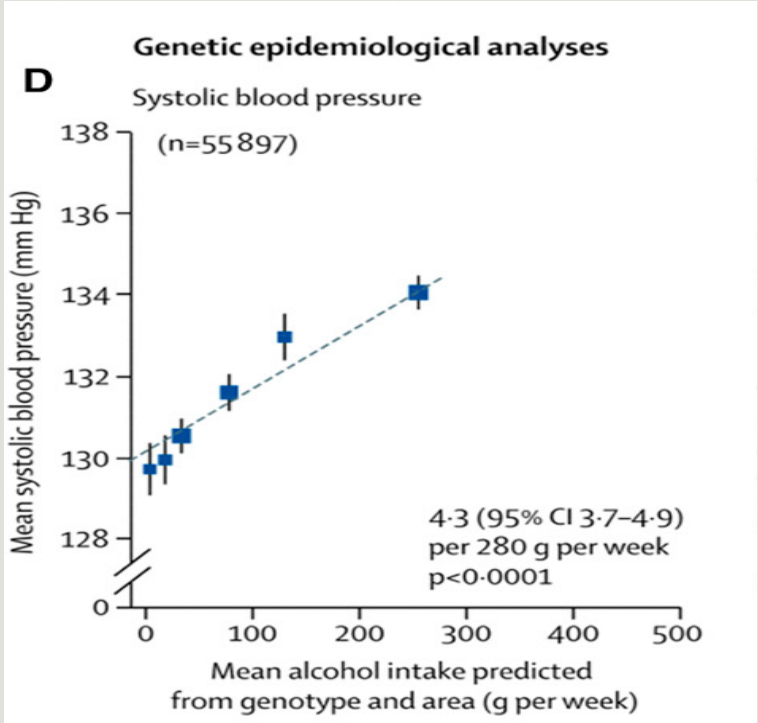
Acute rise of 10 mmHg in infrequent drinkers

Little or no effect in habitual coffee drinkers

Nurses' Health Study showed daily intake of up to 6 cups of coffee or black tea was not associated with an increase risk of hypertension

Alcohol and hypertension



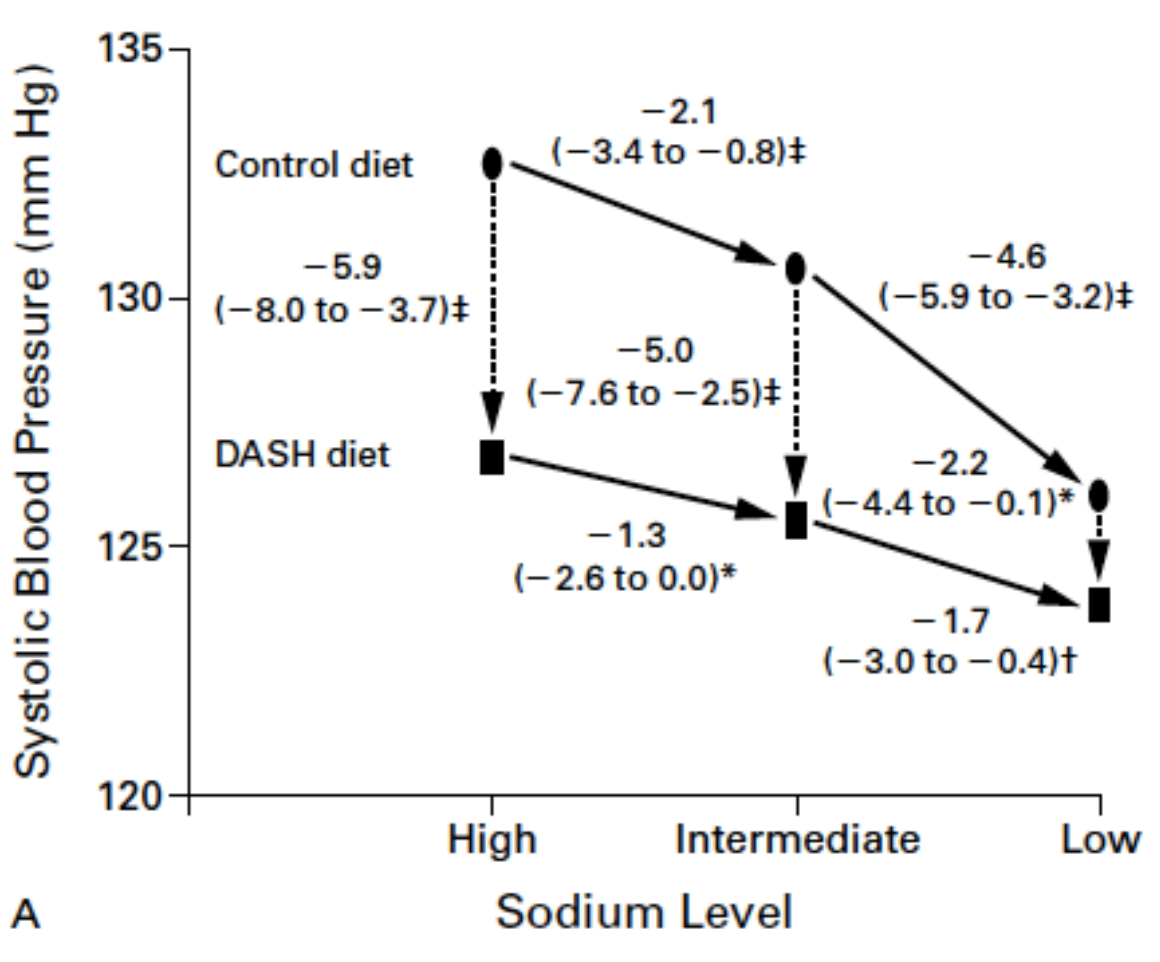


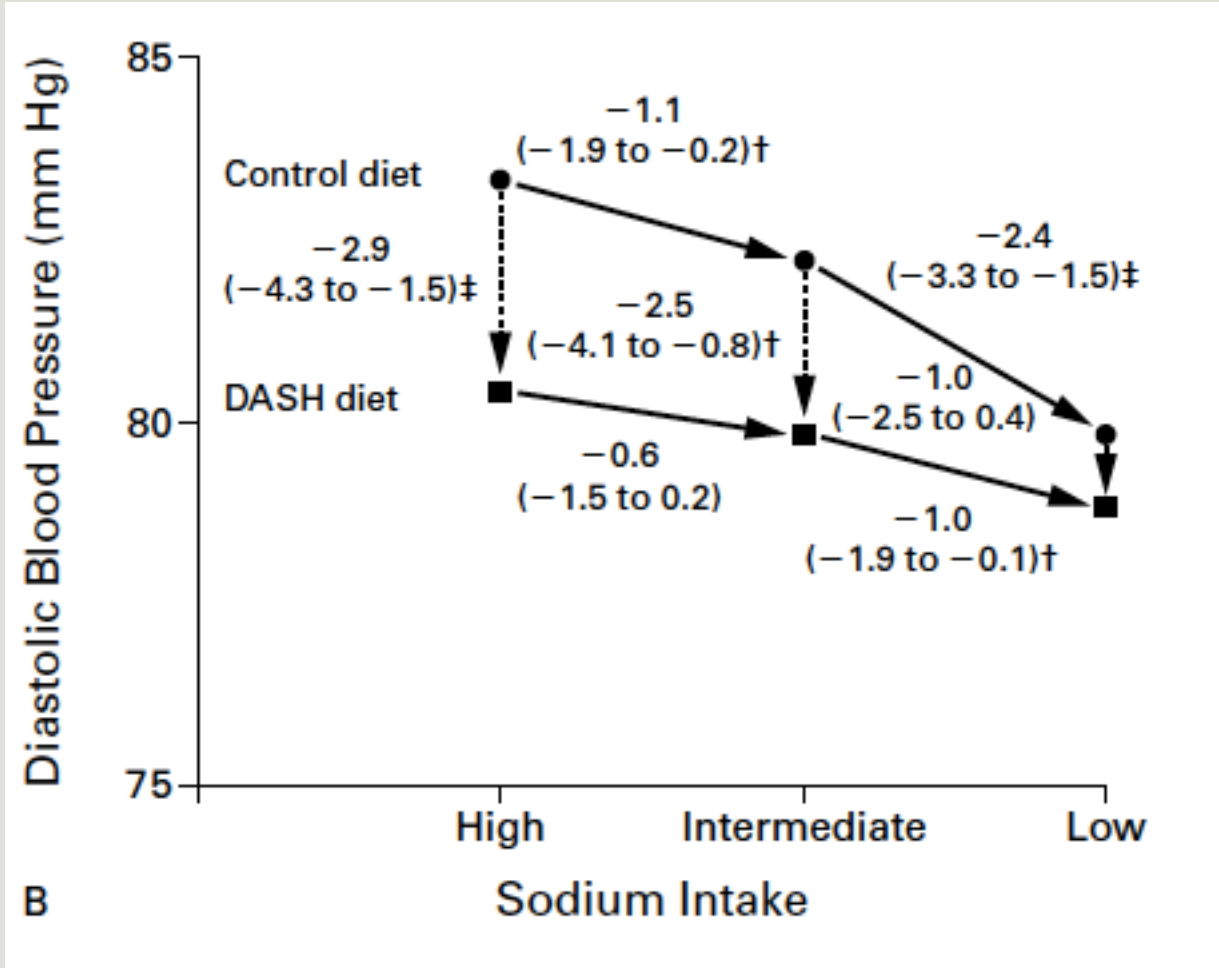
Positive association between alcohol intake and systolic BP

(adjusted for age, socioeconomic factors and smoking)

Aim for 2 or less standard drinks (20g pure alcohol)/day with avoidance of binge drinking

Lancet 2019; 393: 1831–1842.





- Salt reduction improved both SBP and DBP
- Na:K ratio <1 was associated with SBP and DBP beyond simply salt restriction within the low sodium phase in the DASH diet

Adv. Nutr. 2014; 5: 712–741
NEJM 2001; 344 (1): 3-10.

Case 2

62 year old woman with T2D for 12 years and hypertension for 10 years. She presents with a recent exacerbation of hypertension, with clinic BP 180/110 mmHg. Her examination was non-contributory.

Her medications include Valsartan, Frusemide, Verapamil, Vitamin E, and Vitamin C. She had recently started on a herbal tea to help with sleep.

Her laboratory findings today:

Na 144 mmol/L; K 2.6 mmol/L; Bicarb 35 mmol/L; Cl 95 mmol/L. Renin <2 mU/L; aldosterone <70 pmol/L

3 months ago: Na 138 mmol/L; K 4.5 mmol/L; Bicarb 26 mmol/L; Cl 101 mmol/L

What is her diagnosis?

A. Cushing's disease
B. Primary Aldosteronism
C. Apparent mineralocorticoid excess
D. Additional diuretic effect with herbal preparation

Case 2

62 year old woman with T2D for 12 years and hypertension for 10 years. She presents with a recent exacerbation of hypertension, with clinic BP 180/110 mmHg. Her examination was non-contributory.

Her medications include Valsartan, Frusemide, Verapamil, Vitamin E, and Vitamin C. She had recently started on a herbal tea to help with sleep.

Her laboratory findings today:

Na 144 mmol/L; K 2.6 mmol/L; Bicarb 35 mmol/L; Cl 95 mmol/L. Renin <2 mU/L; aldosterone <70 pmol/L

3 months ago: Na 138 mmol/L; K 4.5 mmol/L; Bicarb 26 mmol/L; Cl 101 mmol/L

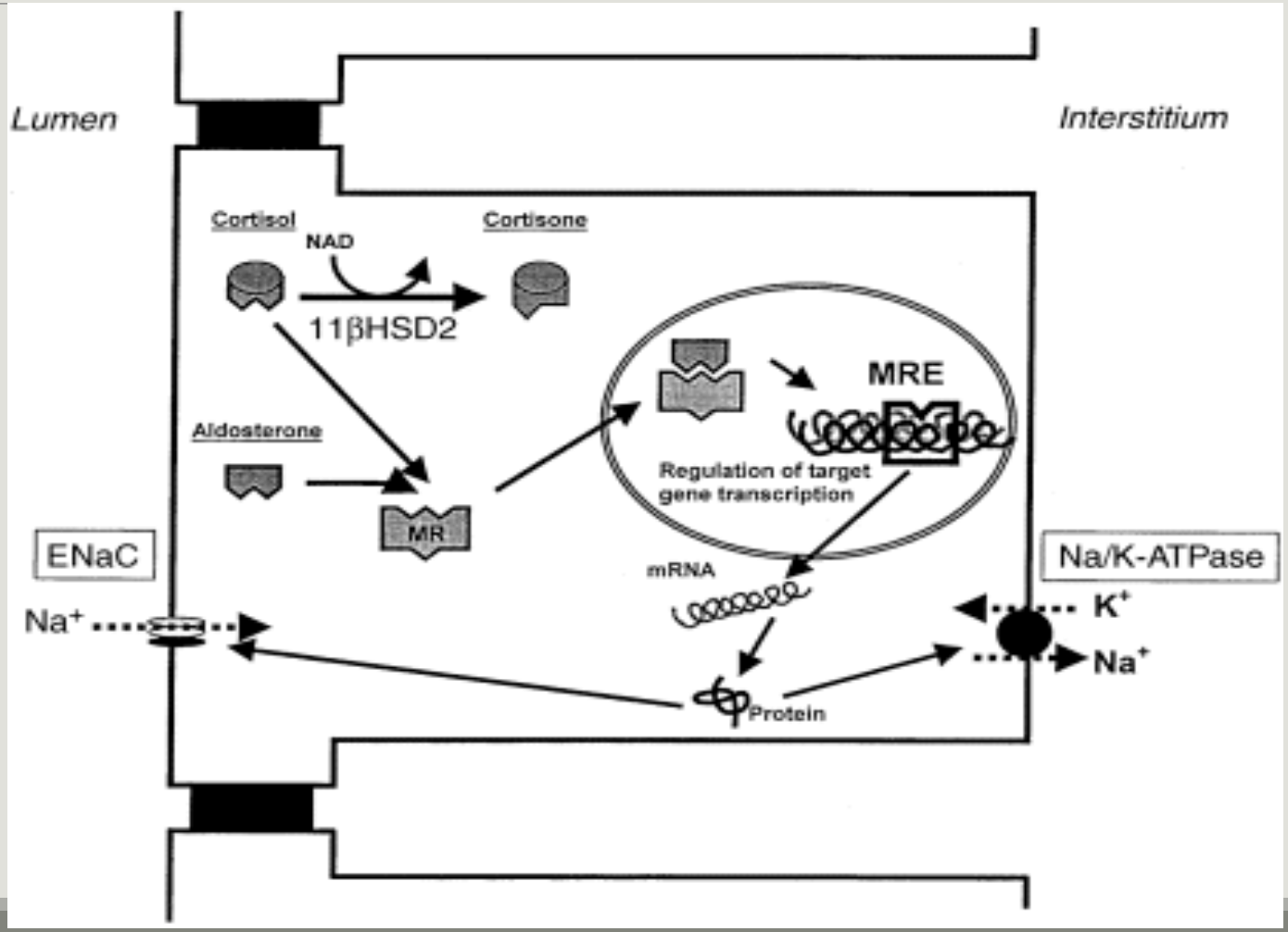
What is her diagnosis?

A. Cushing's disease
B. Primary Aldosteronism
C. **Apparent mineralocorticoid excess**
D. Additional diuretic effect with herbal preparation

Acquired apparent mineralocorticoid excess

Glycyrrhizic Acid (Licorice)

- Inactivates 11BHSD 2
- Increases cortisol binding to mineralocorticoid receptor causing sodium retention + potassium loss
- Low renin, low aldosterone, metabolic alkalosis



Case 3

A 48-year-old woman is referred for difficult-to-control hypertension. The following drugs have been tried and stopped because of side effects: Amlodipine (edema), Metoprolol (excessive fatigue), Chlorthalidone (severe hypokalemia).

Her BP is improved but still elevated at 152/96 mmHg on Losartan 100 mg. Her family history is notable for her father, who has severe hypertension, diabetes, and CKD; her mother is healthy and normotensive. She has no history of pulmonary edema, and the results of physical examination are unremarkable. She is afraid to try Spironolactone because she read about the risk of hyperkalemia.

What is the next best step?

A. Reassure her and start Spironolactone with careful monitoring of potassium
B. Start Clonidine or Hydralazine because she may tolerate them better
C. Retry a lower dose of Chlorthalidone and monitor the potassium
D. Evaluate her for Primary Aldosteronism

Case 3

A 48-year-old woman is referred for difficult-to-control hypertension. The following drugs have been tried and stopped because of side effects: Amlodipine (edema), Metoprolol (excessive fatigue), Chlorthalidone (severe hypokalemia).

Her BP is improved but still elevated at 152/96 mmHg on Losartan 100 mg. Her family history is notable for her father, who has severe hypertension, diabetes, and CKD; her mother is healthy and normotensive. She has no history of pulmonary edema, and the results of physical examination are unremarkable. She is afraid to try Spironolactone because she read about the risk of hyperkalemia.

What is the next best step?

A. Reassure her and start Spironolactone with careful monitoring of potassium
B. Start Clonidine or Hydralazine because she may tolerate them better
C. Retry a lower dose of Chlorthalidone and monitor the potassium
D. **Evaluate her for Primary Aldosteronism**

Thanks

Comments & questions

Causes of secondary hypertension

Table 13-1 Findings suggesting major types of secondary hypertension and examinations necessary for differential diagnosis

Underlying disease	*Suggestive findings*	*Examinations necessary for differential diagnosis*
Secondary hypertension in general	Severe hypertension, resistant hypertension, hypertensive crisis and juvenile hypertension	
Renovascular hypertension	Rapid deterioration of the renal function after the administration of RA system inhibitors, laterality in the kidney size, hypokalemia and abdominal vascular bruit	Renal artery ultrasonography, abdominal CTA, abdominal MRA, renoscintigraphy, PRA and PAC
Renal parenchymal hypertension	Increase in the serum Cr level, proteinuria, hematuria and a history of kidney disease	Seroimmunological test, abdominal CT, ultrasonography and kidney biopsy
Primary aldosteronism	Hypokalemia, adrenal incidentaloma	PRA, PAC, load test, adrenal CT and adrenal venous blood collection
Sleep apnea syndrome	Snoring, obesity, daytime sleepiness and morning/nighttime hypertension	Polysomnography
Pheochromocytoma	Paroxysmal/labile hypertension, palpitation, headache and sweating	Blood/urinary catecholamines and their metabolites, abdominal ultrasonography/CT and MIBG scintigraphy
Cushing's syndrome	Central obesity, moon face, striated skin and hyperglycemia	Cortisol, ACTH, abdominal CT, cephalic MRI and dexamethasone suppression test
Sub-clinical Cushing's syndrome	Adrenal incidentaloma	Cortisol, ACTH, abdominal CT and dexamethasone suppression test
Drug-induced hypertension	Previous drug administration, hypokalemia	Confirmation of previously administered drugs
Aortic coarctation	Differences in blood pressure between the upper and lower limbs, vascular murmurs	Thoracic/abdominal CT, MRI/MRA and angiography
Hypothyroidism	Bradycardia, edema, hypoactivity and increases in the levels of lipids, CPK and LDH	Thyroid hormone, TSH, autoantibody and thyroid ultrasonography
Hyperthyroidism	Tachycardia, sweating, weight loss and a decrease in the cholesterol level	Thyroid hormone, TSH, autoantibody and thyroid ultrasonography
Hyperparathyroidism	Hypercalcemia	Parathyroid hormone
Brainstem vascular compression	Facial spasm, trigeminal neuralgia	Brain MRI/MRA

Hypertension Research 2014; 37, 349–361