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How do I investigate suspected secondary hypertension?

Marie Freel

British Pharamcological Society Hypertension Training Day

15th March 2017

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Secondary hypertension

- 5-10% of ‘essential’ hypertension cases
- Clinical ‘clues’ important
- Age based approach essential

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Secondary hypertension according to age

Age group	% with underlying cause	Most common cause
Children (<12 years)	70-85%	Renal parenchymal disease Coarctation of aorta
Adolescents (12-18 years)	10-15%	Renal parenchymal disease Coarctation of aorta
Young adults (19-39 years)	5%	Fibromuscular dysplasia Renal parenchymal disease
Middle aged adults (40-65 years)	8-12%	Primary Aldosteronism Obstructive Sleep Apnoea Cushing's syndrome Phaeochromocytoma
Older adults	17%	Atherosclerotic renovascular disease Renal failure hypothyroidism

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Secondary hypertension

- 5-10% of ‘essential’ hypertension cases
- Clinical ‘clues’ important
- Age based approach essential
- Consider if:
  - Severe or resistant hypertension
  - Child/adolescent
  - Worsening of previously stable hypertension
  - Malignant hypertension
  - No other risk factors identified and age <30

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Case 1: Just another case of hypertension…….?

- 32 y female
- 3 years of hypertension, well controlled on ramipril
- But now BP difficult to control (162/95 mm/Hg) despite addition of amlodipine
- UE: Na 136, K 4.1 Cl 95 Ur 4.2 Cr 68
- Plasma aldosterone (supine) 420 pmol/L (100-400), plasma renin activity (PRC) 1.2 µIU/ml (5-44.9)
  - Aldosterone to renin ratio (ARR) **350**

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The myths of Primary Aldosteronism (PA)?

- PA is a rare cause of hypertension
- Serum potassium must be normal
- All the drugs must be stopped!
- Making the diagnosis doesn't matter- just lower the blood pressure!

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Hypertension

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

Gian Paolo Rossi, MD, FACC, FAHA, Giampaolo Bernini, MD, Chiara Caliumi, MD, Giovambattista Desideri, MD, Bruno Fabris, MD, Claudio Ferri, MD, Chiara Ganzaroli, MD, Gilberta Giacchetti, MD, Claudio Letizia, MD, Mauro Maccario, MD, Francesca Mallamaci, MD, Massimo Mannelli, MD, Mee-Jung Mattarello, MD, Angelica Moretti, MD, Gaetana Palumbo, MD, Gabriele Parenti, MD, Enzo Porteri, MD, Andrea Semplicini, MD, FAHA, Damiano Rizzoni, MD, Ermanno Rossi, MD, Marco Boscaro, MD, Achille Cesare Pessina, MD, PHD, Franco Mantero, MD, for the PAPY Study Investigators

Padova, Ancona, Reggio Emilia, Pisa, L'Aquila, Palermo, Legnano, Roma, Firenze, Torino, and Reggio Calabria, Italy

Frequency of aldosteronism in hypertension:

4.8% Aldosterone Producing Adenoma
6.4% Idiopathic Hyperaldosteronism

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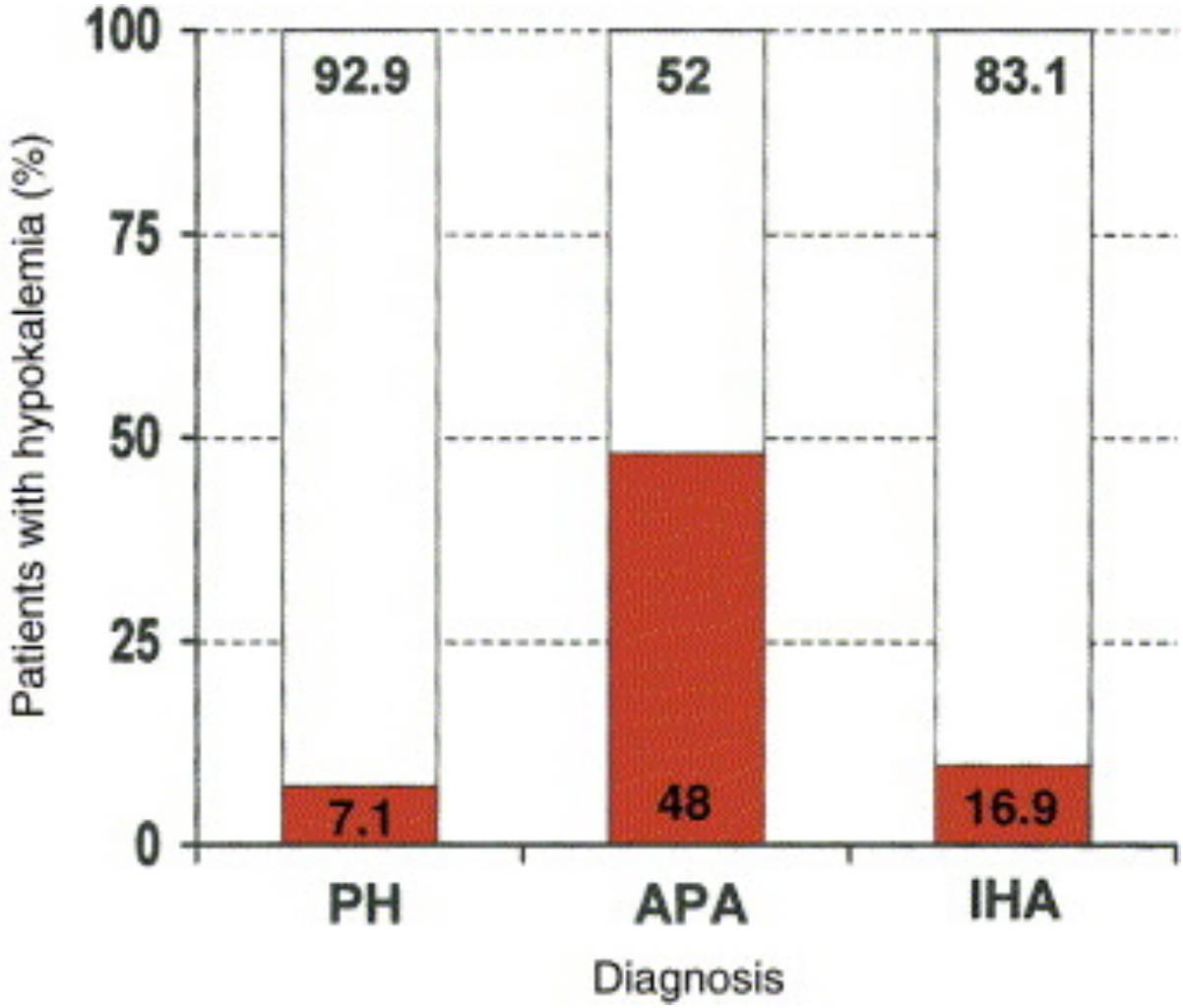
Hypokalaemia and Primary Aldosteronism



Rossi et al. J Am Coll Cardiol 2006

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The myths of Primary Aldosteronism (PA)?

- PA is a rare cause of hypertension
- Serum potassium must be normal
- All the drugs must be stopped
- Making the diagnosis doesn't matter- just lower the blood pressure!

Drug	Effect on aldosterone	Effect on renin	Effect on ARR
B-blocker	↓	↓↓	↑
Centrally acting	↓	↓↓	↑
NSAIDs	↓	↓↓	↑
K-wasting diuretics	↔↑	↑↑	↓
K-sparing diuretics	↑	↑↑	↓
ACEi/ARB	↓	↑↑	↓
Ca channel blockers (DHP)	↔↓	↑	↓

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The myths of Primary Aldosteronism (PA)?

- PA is a rare cause of hypertension
- Serum potassium must be normal
- All drugs must be stopped
- Making the diagnosis doesn't matter- just lower the blood pressure!

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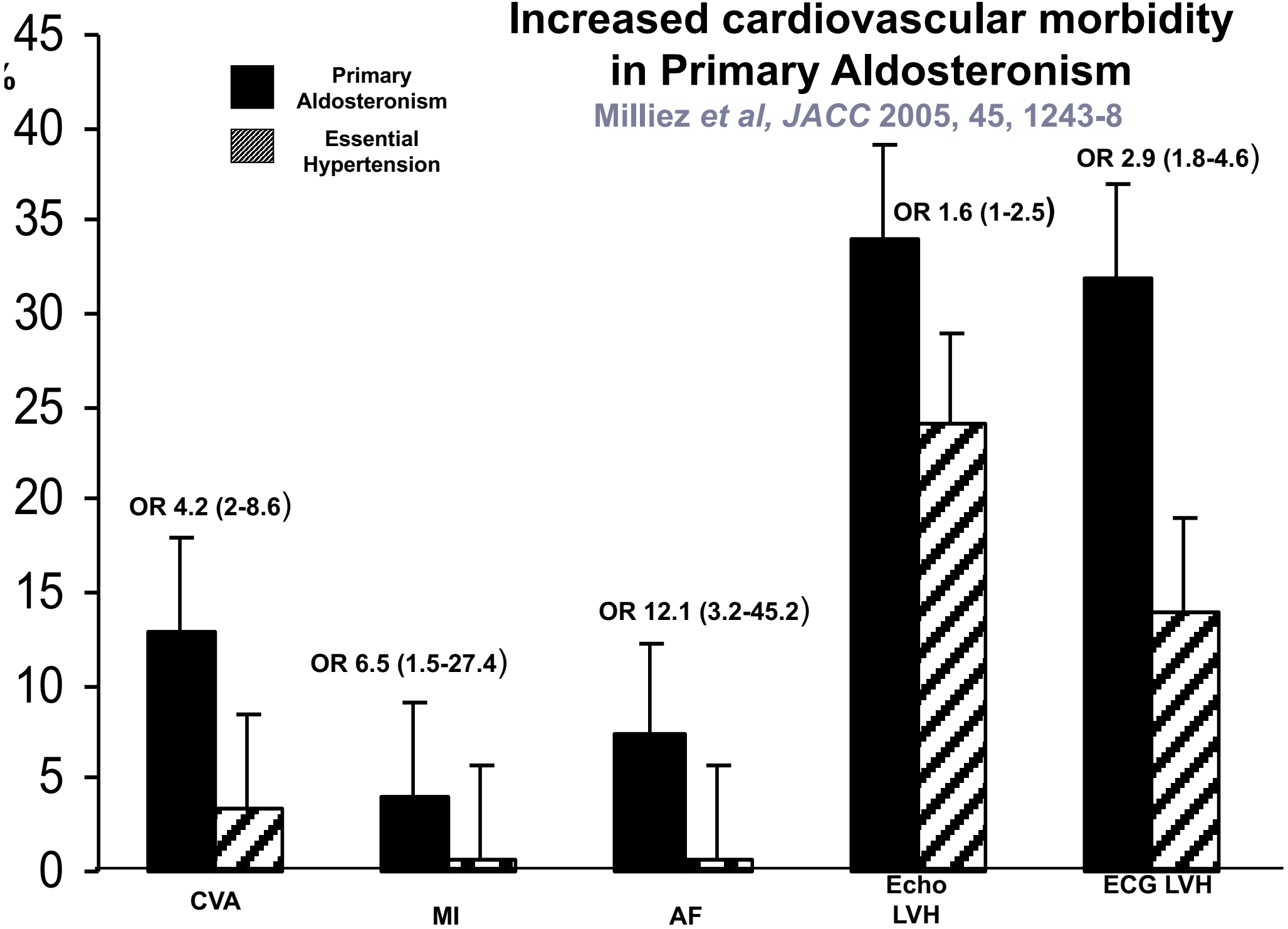
Lower the blood pressure stupid.

(Gordon McInnes)

izquotes.com

Increased cardiovascular morbidity in Primary Aldosteronism

Milliez *et al, JACC* 2005, 45, 1243-8



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Aldosterone and cardiovascular complications

Table 3. Published Series on Primary Aldosteronism and Cardiovascular Complications

	Number of patients		Blood Pressure		
Published Series	Cases	Controls	Cases	Controls	Conclusions
Takeda et al[25]	224 patients with surgically proven APA	224 sex- and age-matched patients with EH	170±26/94±15	179±25/106±17	Myocardial infarction (1.8% vs 4.0%) Heart failure (3.6% vs 4.0%)
Milliez et al[4]	124 patients with PA	465 patients with EH of similar age, sex, and BP	176±23/107±14	174±20/106±14	Myocardial infarction (4.0% vs 0.6%; OR, 6.5) Atrial fibrillation (7.3% vs 0.6%; OR, 12.1)
Catena et al[27]	54 patients with PA	323 patients with EH of similar age, sex, BMI, severity, and duration of HTN	167±16/103±9	166±18/103±8	Cardiovascular events more frequent in PA patients (35% vs 11%; OR, 4.61; $P<0.001$) Sustained arrhythmia (15% vs 3%; OR, 4.93) Cerebrovascular events (11% vs 3%; OR, 4.36) Coronary heart disease (20% vs 8%; OR, 2.80)
Current study	459 patients with PA	1290 patients with EH matched for age, sex, and BP	151±24/88±13	150±22/87±13	Myocardial infarction (4.4% vs 1.7%; OR, 2.8) Atrial fibrillation (3.9% vs 1.1%; OR, 4.3) Coronary artery disease (5.7% vs 2.8%; OR, 2.2) Heart failure (4.1% vs 1.2%; OR, 3.5)

Savard et al Hypertension 2013

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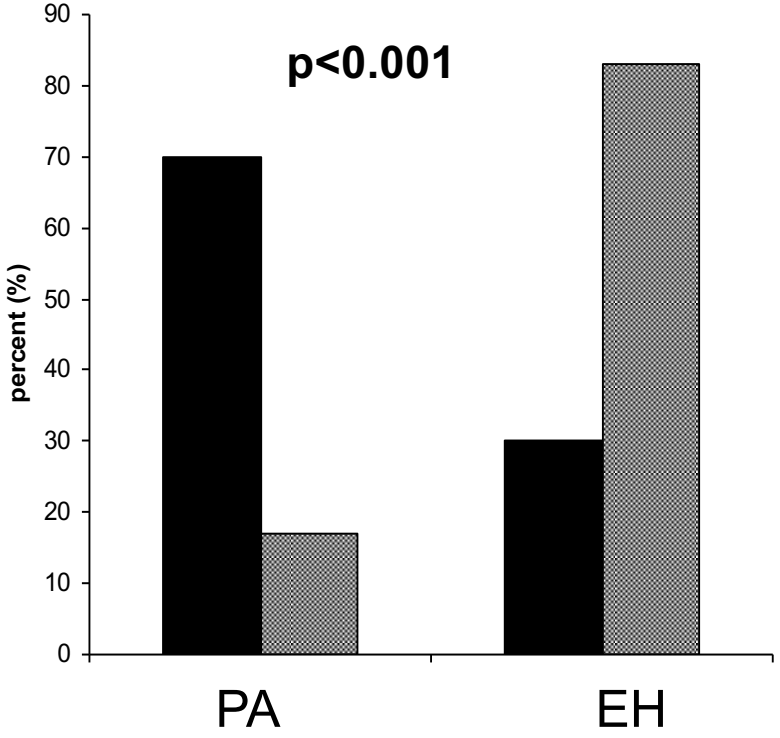
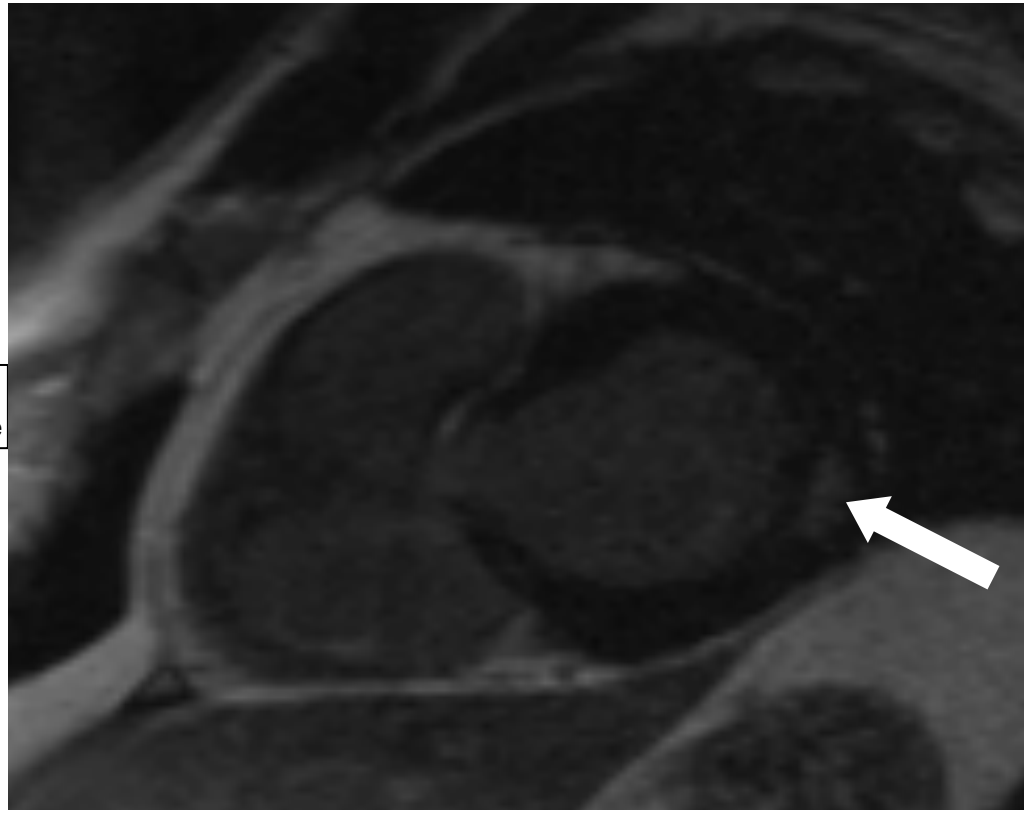
Myocardial fibrosis more common in PA versus EH patients





Freel et al. Circ CV Imaging 2013

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Diagnosis of PA

SPECIAL FEATURE

Clinical Practice Guideline

The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline

John W. Funder, Robert M. Carey, Franco Mantero, M. Hassan Murad, Martin Reincke, Hirotaka Shibata, Michael Stowasser, and William F. Young, Jr

Hudson Institute of Medical Research (J.W.F.), Clayton, VIC 3168, Australia; University of Virginia Health System (R.M.C.), Charlottesville, Virginia 22908; University of Padova (F.M.), 35122 Padua, Italy; Mayo Clinic, Evidence-based Practice Center (M.H.M.), Rochester, Minnesota 55905; Klinikum of the Ludwig-Maximilians-University of Munich (M.R.), 80366 München, Bavaria, Germany; Oita University (H.S.), Oita 870-1124, Japan; University of Queensland (M.S.), Brisbane, Australia; and Mayo Clinic (W.F.Y.), Rochester, Minnesota 55905

J Clin Endocrinol Metab 2016

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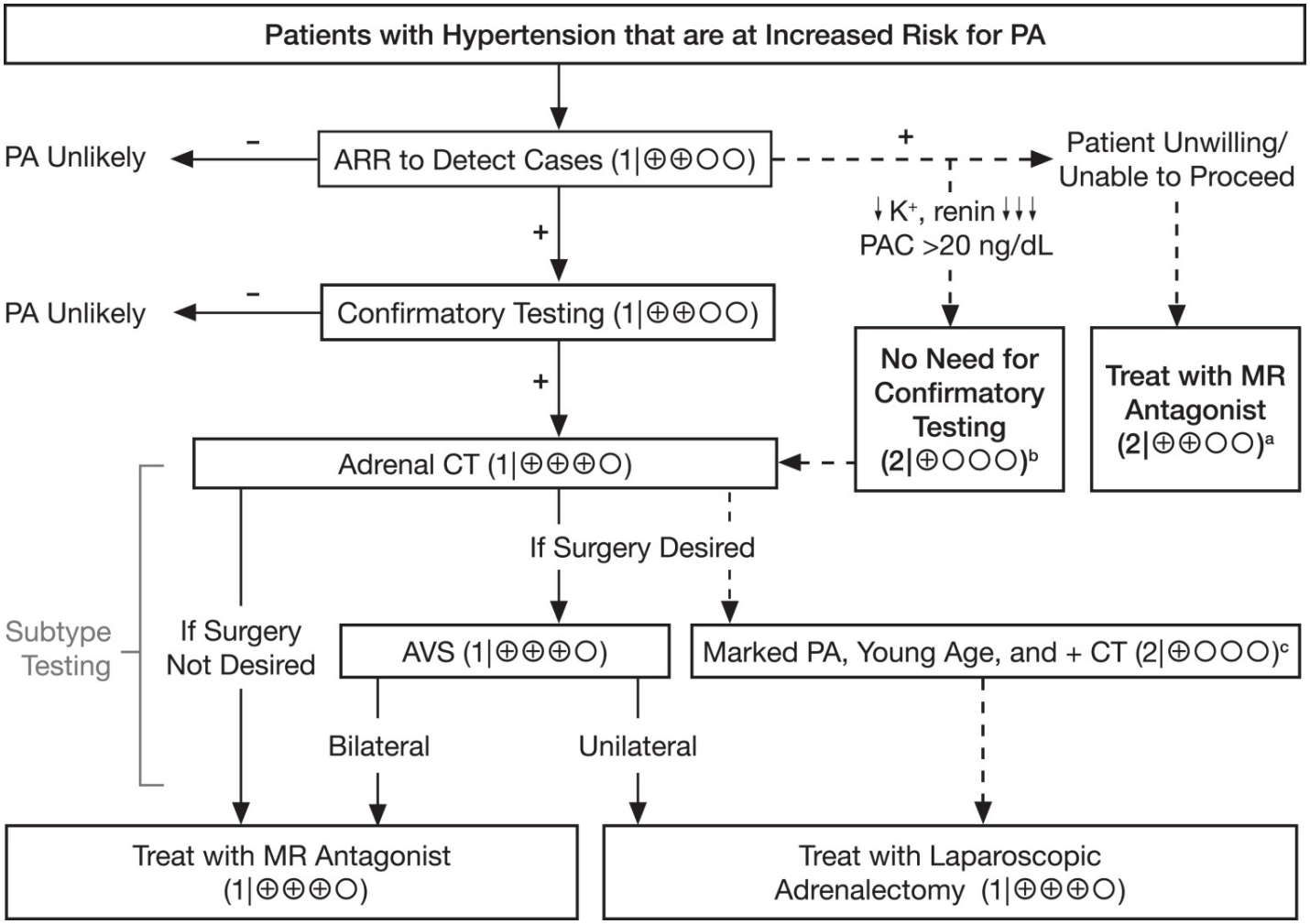
Diagnosis of PA: a guideline based approach



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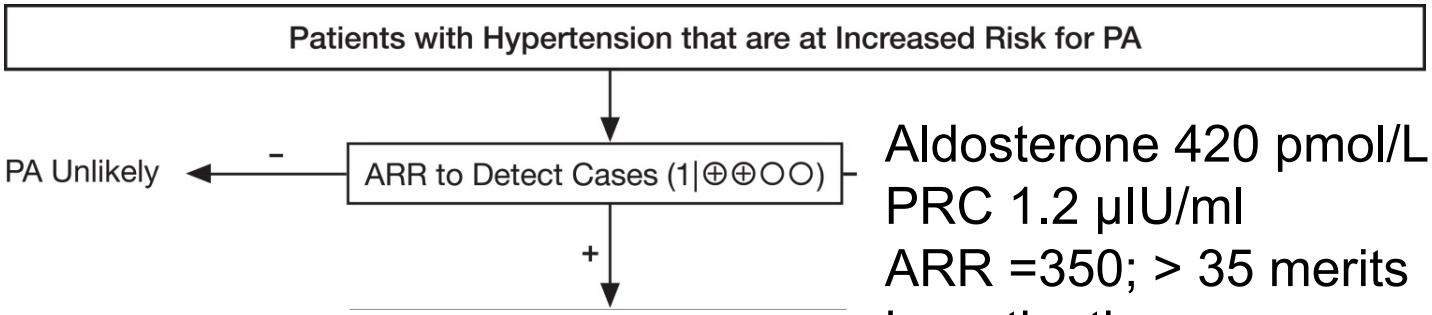
Diagnosis of PA: a guideline based approach



Aldosterone 420 pmol/L
PRC 1.2 µIU/ml
ARR =350; > 35 merits investigation

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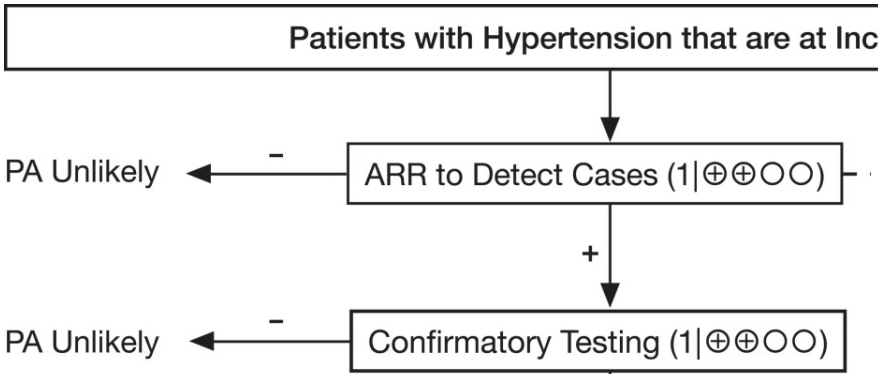
Diagnosis of PA: a guideline based approach



Aldosterone 420 pmol/L
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Saline suppression test
2 litres saline/4 hours:
Baseline: PRC 1.1/aldo 410
4 hours: PRC<0.5/aldo 305

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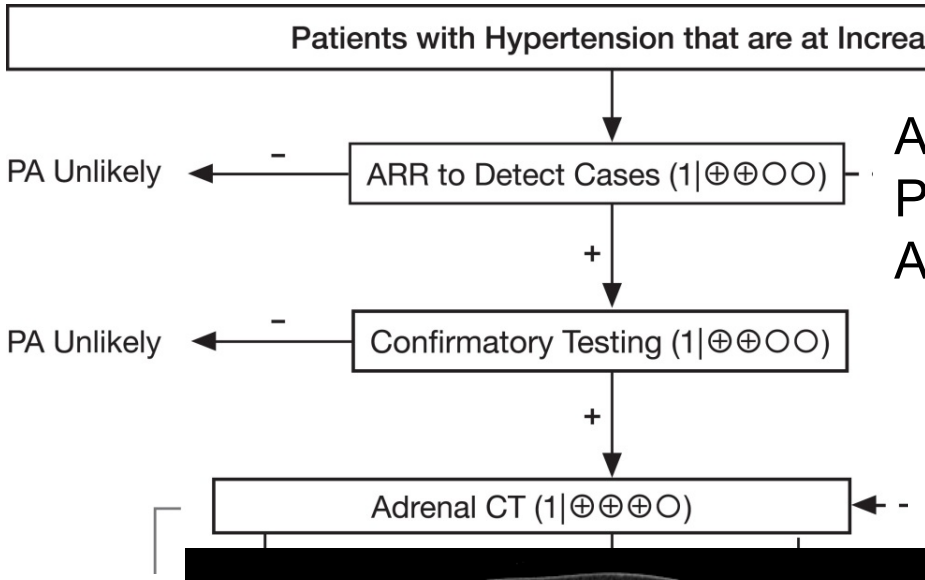
Diagnosis of PA: a guideline based approach



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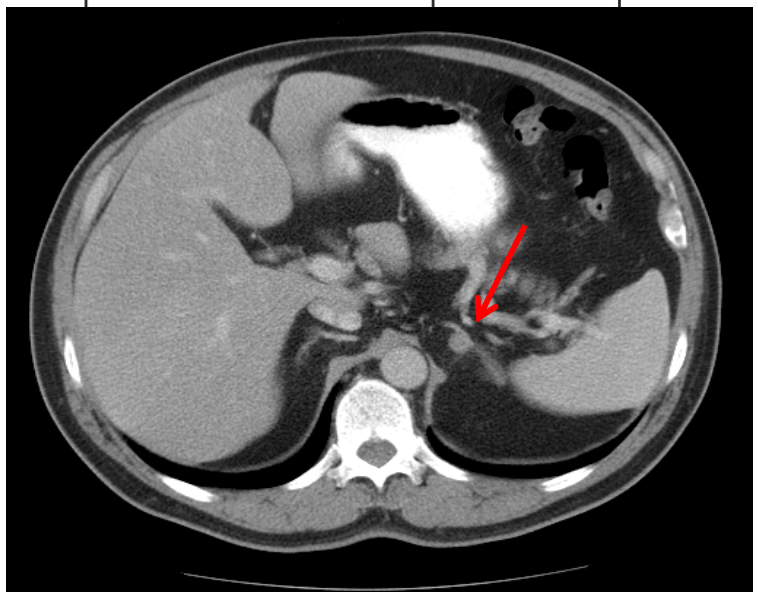

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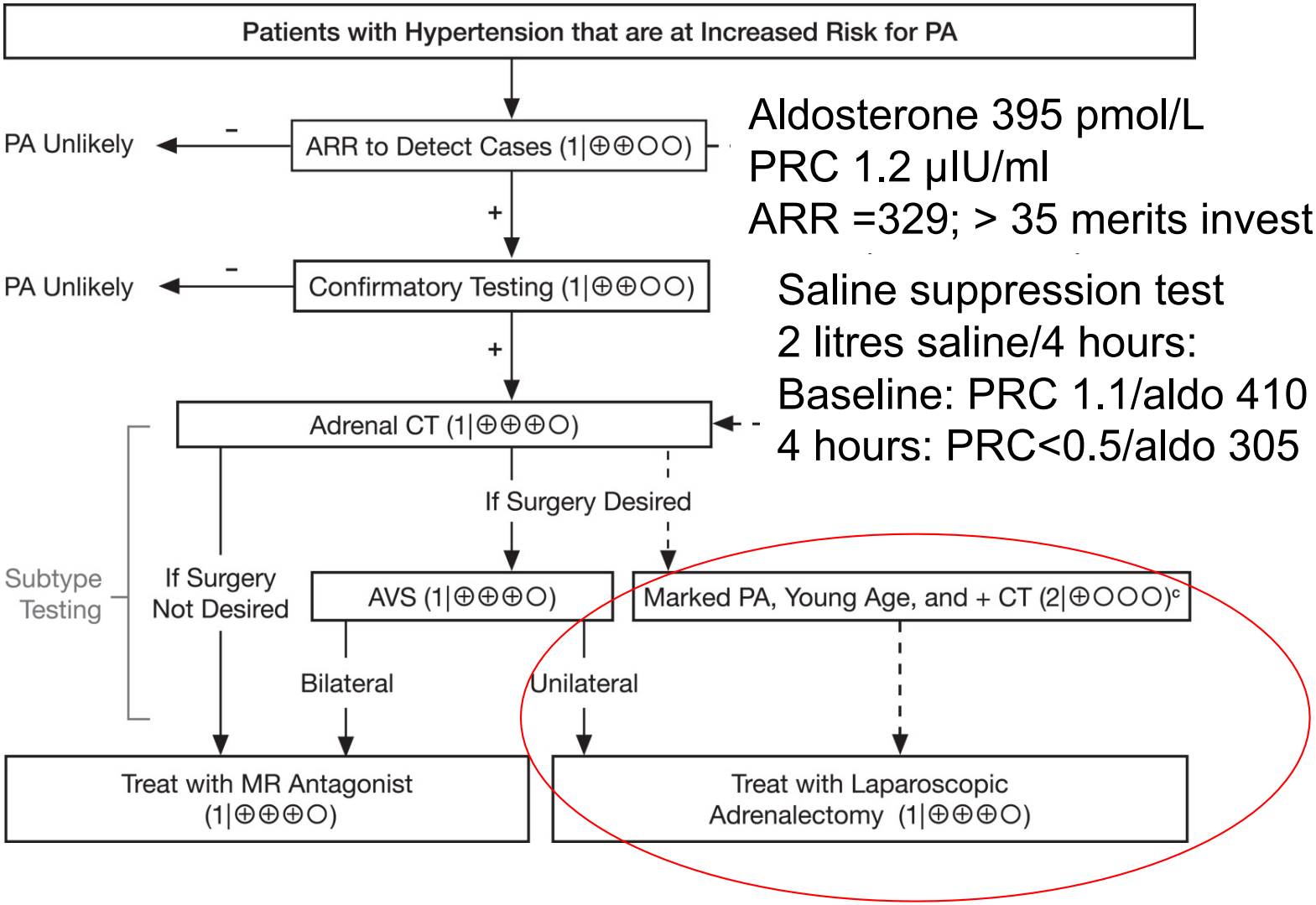
Diagnosis of PA: a guideline based approach



Aldosterone 395 pmol/L
PRC 1.2 µIU/ml
ARR =329; > 35 merits investigation

Saline suppression test
2 litres saline/4 hours:
Baseline: PRC 1.1/aldo 410
4 hours: PRC<0.5/aldo 305

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PA subtype classification- adenoma v hyperplasia

- CT has insufficient sensitivity and specificity
- Adrenal vein sampling (AVS)
- To confirm unilateral aldosterone excess
- Recommended in all patients > ~~40~~ 35 years or in young patients with no visible adenoma on CT
- **Only performed if surgery indicated**

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Adrenal Vein Sampling (AVS)

- Technical issues: right adrenal problematic
  - 74% success for right adrenal (384 patients)
  - 97% success rate in Mayo clinic

  (Rossi JCEM 2001)

- Lack of consensus on technique or interpretation

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Alternatives to AVS

- Clinical prediction of aldosterone producing adrenal adenoma:
  - Size ~ 1cm
  - K < 3.5 mmol/l
  - eGFR> 100

  100% specificity

  (Kupers et al, JCEM 2012)

- ^{11}C-Metomidate PET CT

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PA: outcome after surgery

- BP improves in almost all, serum [K] normalises in 100%
- Long-term cure rates of hypertension 30-60%
- Persistent hypertension more likely if:
  - 2 or more anti-hypertensive agents
  - Older age
  - ↑ serum creatinine
  - Longer duration of hypertension

  } Coexisting primary hypertension

- So, need to manage expectations

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Case 1 outcome:

- Left adrenalectomy
- 3 months later:
  - BP 128/82 mm/Hg on amlodipine only
  - PRC now 14 μIU/ml
  - Plasma aldosterone: 285 pmol/L

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Case 2: to stent or not to stent

- 24 year old female, referred to MAU with ‘hypertension’ and ‘headache’
- Recently stopped OCP due to blood pressure
- PMH: ‘pyelonephritis’
- No FH
- O/E:
  - Lean. BP 195/130 mm/Hg, pulse 92.
  - CV exam normal, femoral pulses palpable
  - Fundoscopy: bilateral flame haemorrhages, no papilloedema
  - Urinalysis: +++ protein; UE: eGFR normal, [K] 3.2

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Malignant (accelerated) hypertension

- Severe hypertension with **bilateral retinal haemorrhages and exudates** +/- papilloedema
- No absolute blood pressure level (usually > 180/120 mm/Hg) to confirm or exclude diagnosis
- Always merits investigation for secondary cause
  - Renal artery stenosis cause of up to 45% cases of malignant hypertension

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Target organ damage in accelerated hypertension

- Brain
  - Risk of intracerebral haemorrhage
  - Hypertensive encephalopathy
  - Can be a consequence of head trauma
- Heart
  - Can result in LVSD
  - Loop diuretic remains treatment of choice
- Vessels
  - Acute aortic dissection
  - Rapid lowering of BP needed
- Kidneys
  - ‘chicken and egg’
  - Haematuria and elevated creatinine characteristic of ‘malignant’ nephrosclerosis

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Basic investigations

- ECG
- Urinalysis and formal ACR
- Echo
- CT brain
- Consider:
  - CT chest if dissection suspected
  - Urgent renal imaging

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Management of accelerated hypertension

- If no evidence of target organ damage present, then slow reduction with oral drugs preferred
  - Calcium channel blocker
  - Beta blocker
  - ACE inhibitor often ok
- Parenteral drugs can lower more quickly and be rapidly reversed
  - GTN/labetolol most commonly
- Targets
  - Aim to reduce MAP 10-20% in first hour, 5-15% over next 24h
  - Exceptions are aortic dissection and ICH

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Case 2: investigations

- Plasma renin concentration: 211 µIU/ml (5-44.9)
- Plasma aldosterone: 507 pmol/L (100-400)
- US renal tract:
  - The right kidney measures 9.6 cm and the left kidney 10.7 cm in length. Both kidneys appear normal with no focal abnormality or hydronephrosis visualised.
- Next investigation??

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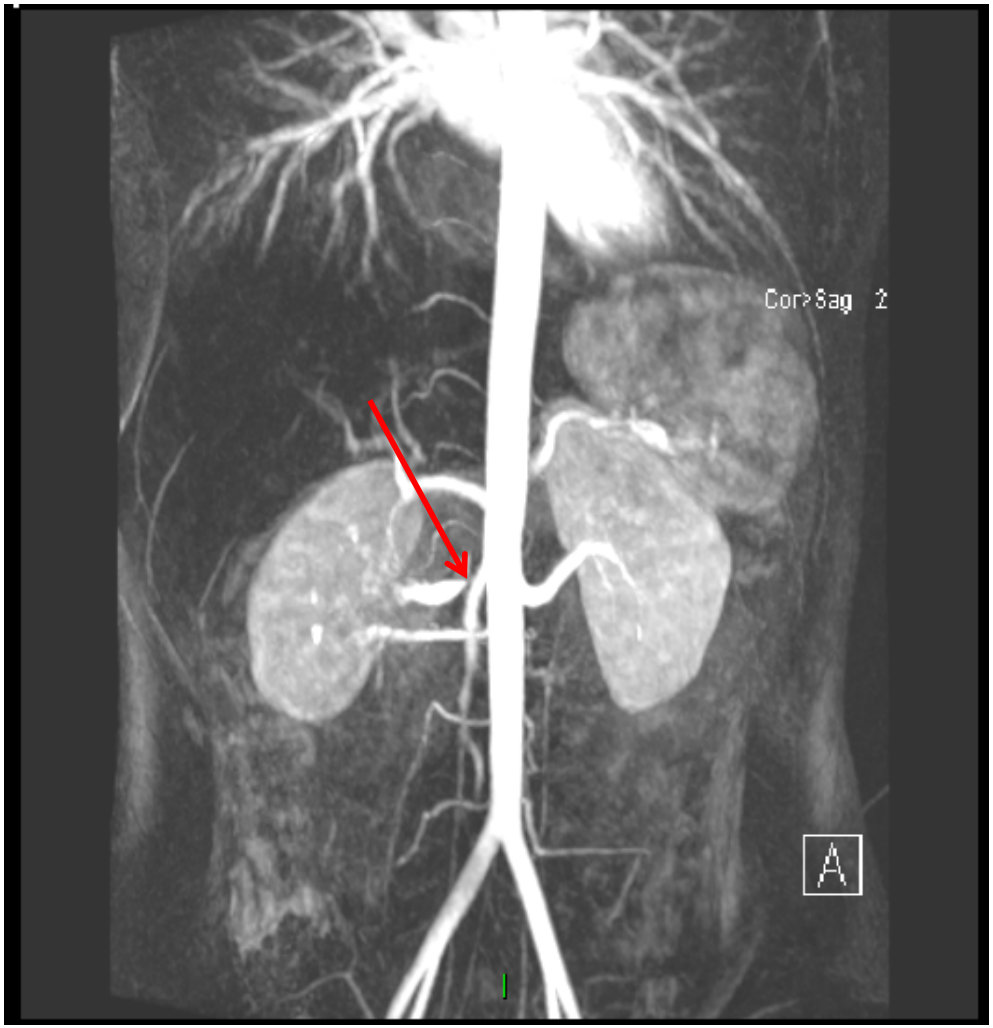
Renal MR angiogram



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Renal fibromuscular dysplasia (FMD)

- Non-inflammatory non-atherosclerotic disorder causing renal artery stenosis
- Unusual, <1% of cases of hypertension
- Can involve other arteries
- Bilateral in 35-50%

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Clinical features

- Hypertension
- Activation of RAAS
- Symptoms of extra-renal FMD
  - Mesenteric ischaemia most common
- Clinical suspicion:
  - Severe/resistant hypertension
  - Hypertension <35y
  - Sudden rise in BP
  - Significant increase in creatinine after ACEi/ARB without drop in BP

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Management of FMD

- Control blood pressure:
  - ACEi usually ok (watch Cr); only contraindicated in severe bilateral disease
  - But young woman of child-bearing age……
- Stenting of renal artery
  - Usually percutaneous
  - Hypertension cure rates 20-80%
  - Stabilises renal function

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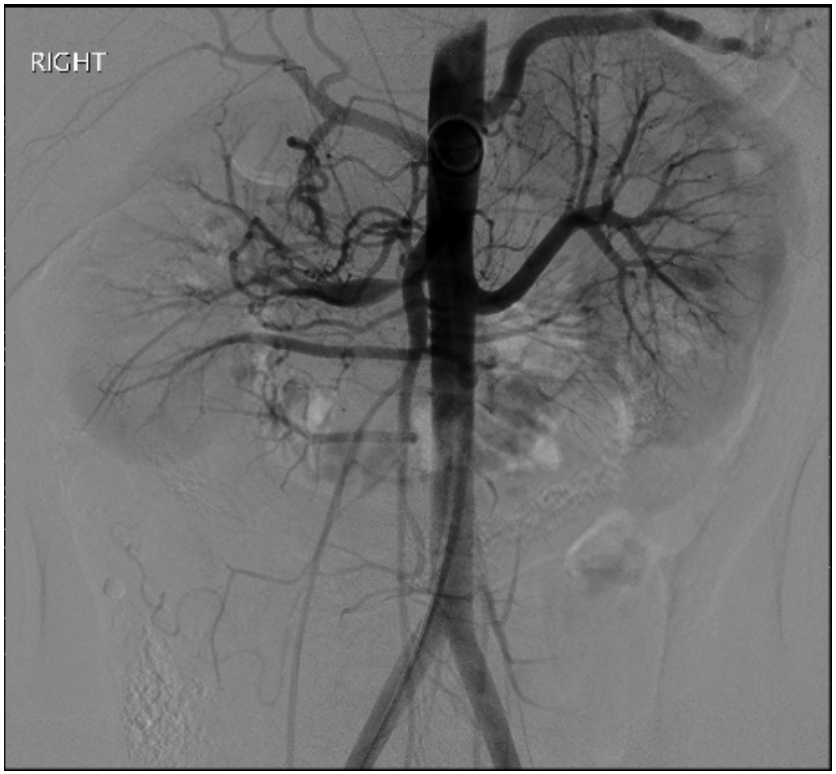
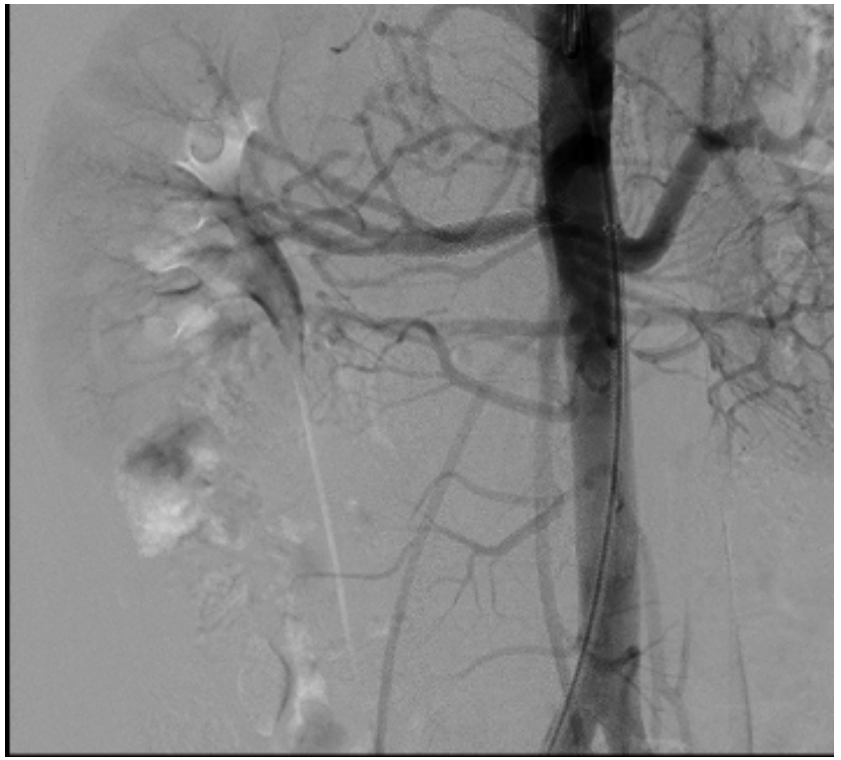
MR angiogram of case 2





- Left renal artery stenosis confirmed
- BP improved with ACEi and thiazide diuretic
- Underwent PTA of renal artery May 2016
- BP now 125/69 on no treatment

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Renal artery stenting in atherosclerotic renovascular disease

- 3 large, randomised clinical trials since 2009
  - ASTRAL n=806; > 40% stenosis
    - (NEJM 2009 361:1953-1962)
  - STAR n=140; >40% stenosis
    - (Ann Int Med 2009 150:840-848)
  - CORAL n=947; >60% stenosis
    - (NEJM 370:13-22)
- All show NO BENEFIT in renal artery stenting compared to medical therapy in atheromatous reno-vascular disease

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Hypertension and hypokalaemia

Disorder	Plasma renin	Plasma aldosterone
Primary Aldosteronism	↓	↑
Renovascular disease	↑	↑
Renin producing tumours	↑	↑
Liddle's syndrome	↓	↓
Cushing's syndrome	↓	↓
11β-hydroxylase deficiency	↓	↓
17α-hydroxylase deficiency	↓	↓
Syndrome of apparent mineralocorticoid excess	↓	↓

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Case 3: spells, sweating and flushing

- 39 year old man, ex-professional rugby player
- Presented with chest pain and hypertension
- Previous ‘episodes’
  - During exercise: ‘grey’ ‘sweaty and clammy’, headache, vomiting
- On arrival:
  - BP 190/110, ST elevation, positive troponin, pulmonary oedema
- Treatment:
  - IV metoprolol: BP rose to 230/150

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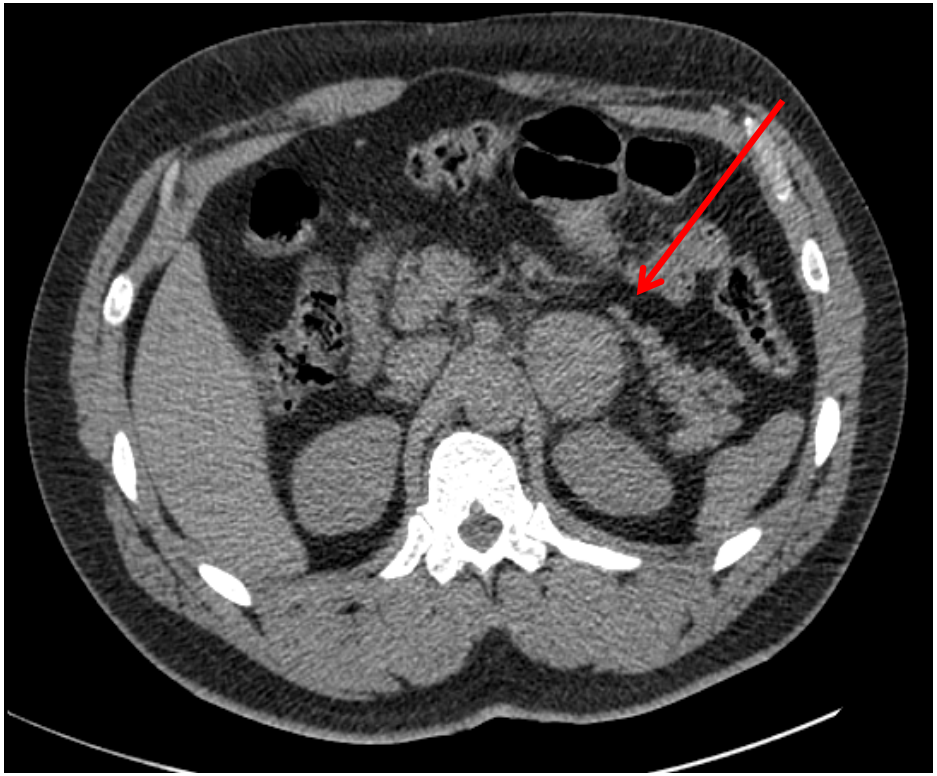
Case 3:

- Coronary angiogram: normal coronary arteries
- CT abdomen:



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Case 3:

U Catecholamine Mets View Cumulative Results

Time Collected	10-Jan-2014 08:00	Time Received	13-Jan-2014 16:03
Time Reported	13-Feb-2014 11:23	Order Number	N,14.8007656.F
Status	Final	Source System	Telepath
Comments	Analysis performed at Biochemistry Dept, Crosshouse Hospital Results phoned to M Freel. bb262767y		

Test	Result	Ref. Range (Units)	Abnormality
24h U Van'lic Acid.	* **665**	<35 umol/24h (umol/24h)	+
24h U 5HIAA	39	<50 umol/24h (umol/24h)	
24h U H'vanillic Ac	* **42**	<40 umol/24h (umol/24h)	+
24h U Noradrenaline	* **43094**	<900 nmol/24h (nmol/24h)	+
24h U Adrenaline	* **42822**	<230 nmol/24h (nmol/24h)	+
24h U Dopamine	* **4229**	<3300 nmol/24h (nmol/24h)	+
24h U Fr Normet'ine	* **8584**	<650 nmol/24h (nmol/24h)	+
24h U Fr Metad'line	* **12368**	<350 nmol/24h (nmol/24h)	+

* Abnormal ** Not in use

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Phaeochromocytoma

- Accounts for <0.2% of patients with hypertension
- Indications for screening:
  - Headache, sweating and tachycardia
  - ‘spells’ with palpitations, headache, pallor
  - Genetic predisposition
  - Adrenal adenoma

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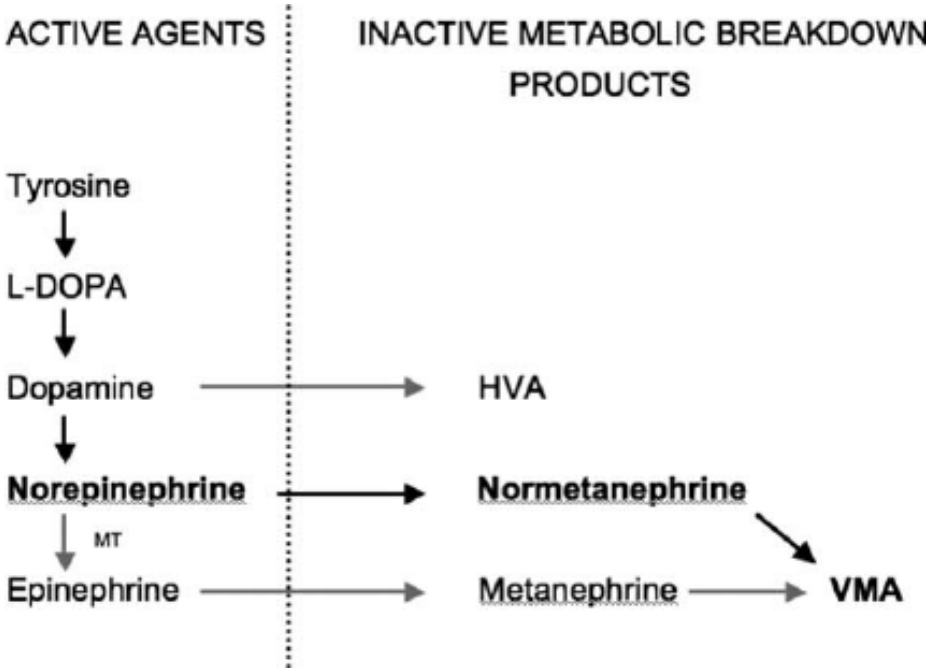
Phaeochromocytoma-screening



- 24h urine fractionated metanephrines
  - 98% sensitivity/specificity
- Plasma metanephrines
  - From cannula, supine, fasting
  - Very sensitive, less specific (77-85%)
  - Reserve for cases with high clinical suspicion

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Phaeochromocytoma: false positive results

- Any acute illness, esp CV/MI/CCF/OSA
- **Tricyclic anti-depressants**
- Decongestant cold remedies
- Amphetamines/cocaine
- Buspirone and most psychoactive agents
- Prochlorperazine
- Ethanol

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Imaging in phaeochromocytoma

- CT or MRI both very sensitive but 70% specificity due to ‘incidentalomas’
  - Heterogeneous, vascular, cystic, dense adrenal lesions
- No concern about use of IV contrast if not alpha-blocked
- Diagnostic ^{123}I-MIBG if:
  - Large phaeo (>10 cm)
  - Paraganglioma

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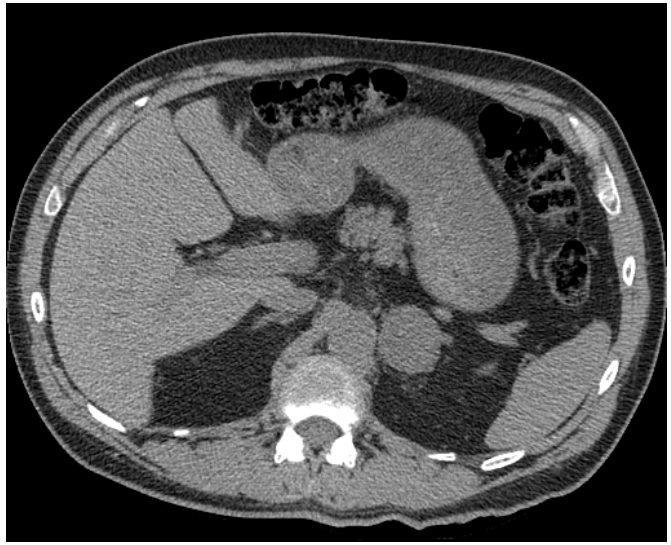
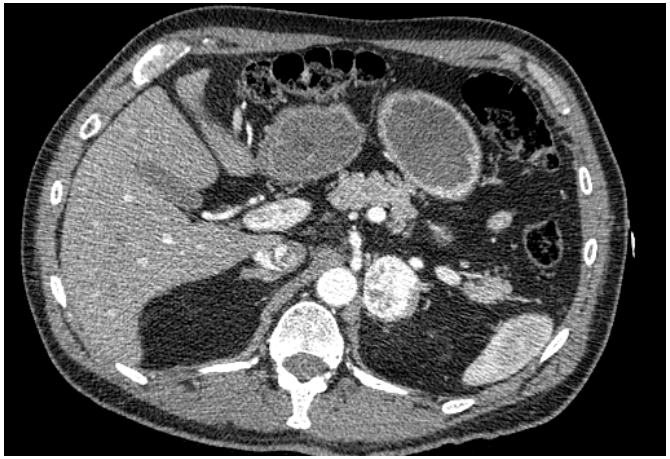
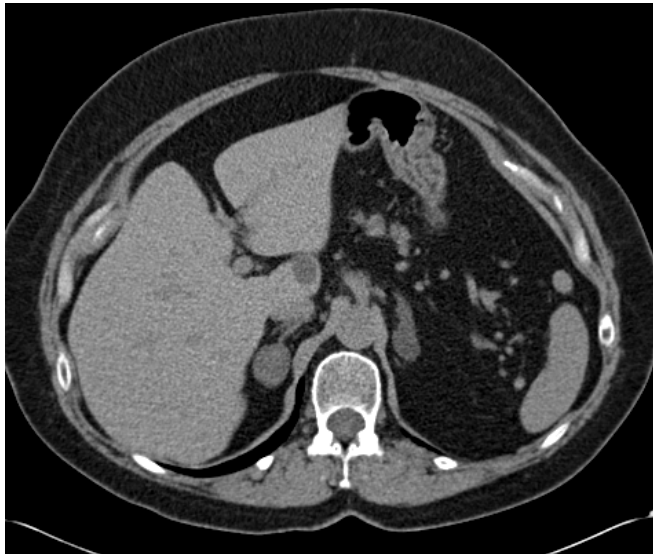
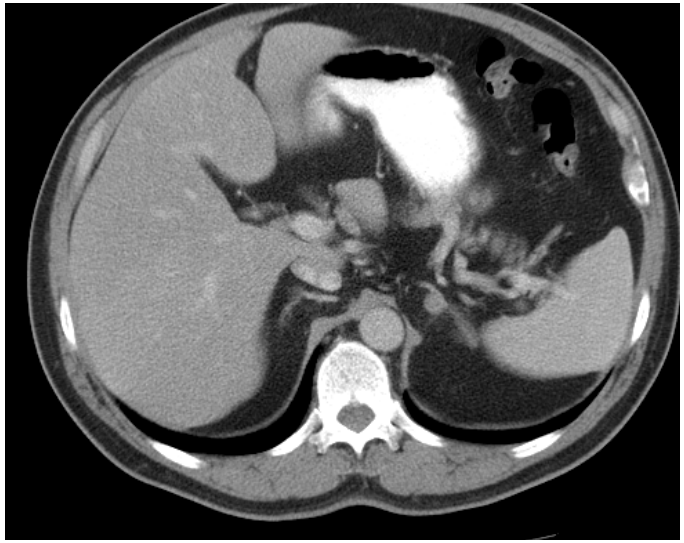
Phaeochromocytoma: imaging characteristics









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Phaeochromocytoma-key points

- It is not common
- Beware of interfering medications
- Pallor and headache are good discriminating symptoms
- If symptoms present, diagnosis should be straightforward

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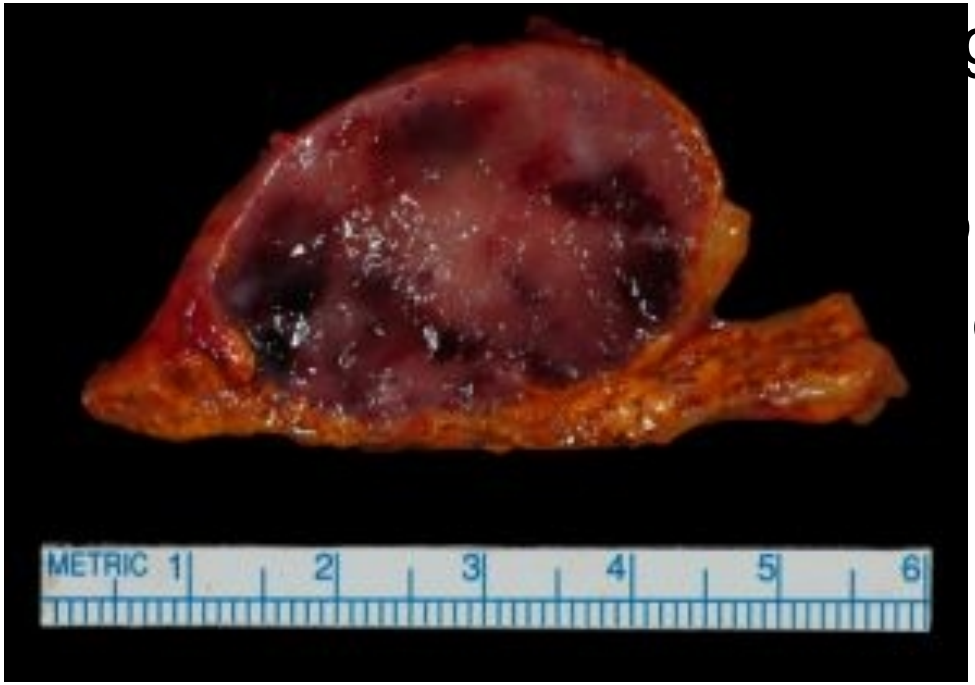
Case 3 outcome



g bd, labetolol 200

my

ormal LV systolic

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Case 4:

- 53 year old woman
- Referred to MAU
  - Abdominal distension and leg ‘oedema’
- No significant past medical history
  - Keen cyclist
  - Unable to cycle for several weeks; ‘muscle fatigue’
- On examination
  - BP190/105, blood glucose 12.4 mmol/L
  - ‘Obese abdomen’ ‘non pitting leg oedema’
  - CONSTIPATION

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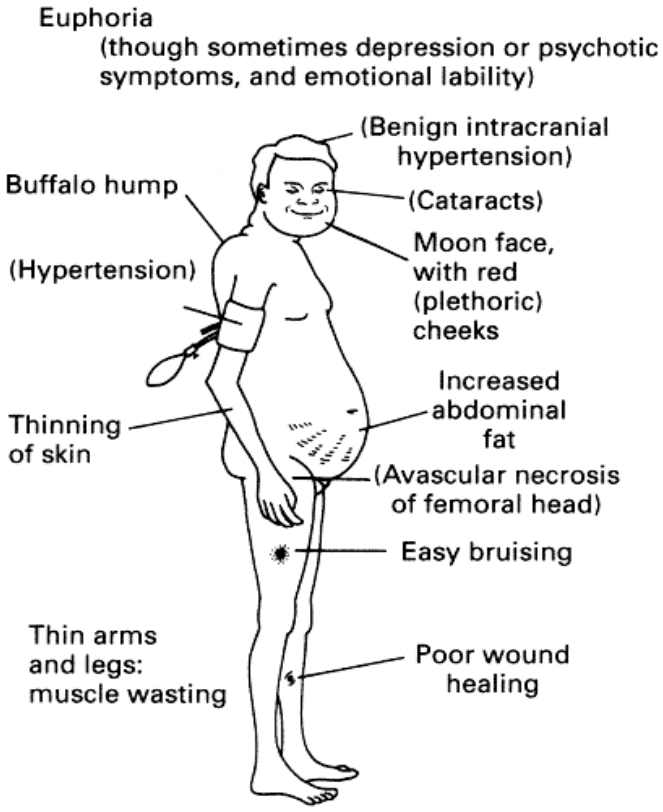
Clinical suspicion is key in Cushing's



Also:

Osteoporosis
Tendency to hyperglycaemia
Negative nitrogen balance
Increased appetite
Increased susceptibility to infection
Obesity

- Easy bruising
- Facial plethora
- Striae
- Proximal myopathy

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Case 4

- More detailed history
  - 2 years of weight gain
  - Significant muscle weakness
  - Thinning of skin and bruising
- More detailed examination
  - Facial plethora
  - Proximal myopathy
- Screening tests
  - 24h urine free cortisol 410 (<250 nmol/24h)
  - Plasma cortisol after 1 mg overnight dex suppression test: 589 nmol/L
  - Plasma cortisol after low dose DST: 375 nmol/L
  - Early morning plasma ACTH 1 mu/l

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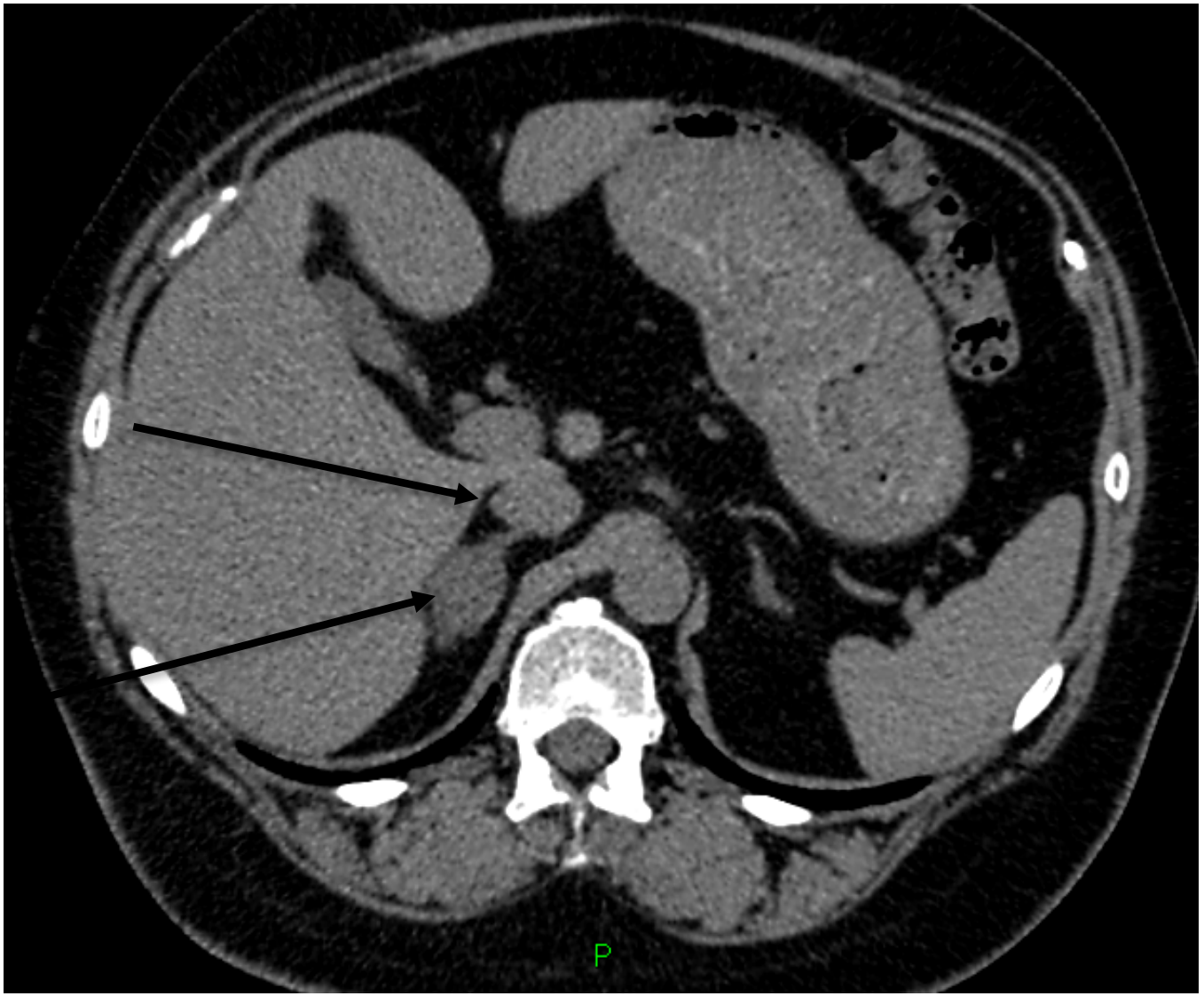
EM- adrenal CT scan



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Case 4: outcome

- Adrenalectomy December 2016
  - Benign cortical adenoma confirmed on histology
- Currently:
  - Lost 8 kg
  - BP 109/61 mm/Hg (reduced from 4 to 2 agents)
  - Starting to exercise again

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Summary

- Majority of hypertension is ‘primary’
- Consider screening if:
  - Young
  - Malignant hypertension
  - Resistant hypertension
  - Newly uncontrolled hypertension
- Main screening tests:
  - ARR (beware but don’t be put off by drugs)
  - 24h urinary metanephrines
  - Renal ultrasound
  - Renal doppler or MRA renal arteries
  - Screen for cortisol excess if high clinical suspicion