Secondary Forms of Hypertension: Diagnosis and Management

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Disclosures

- No conflicts of interest

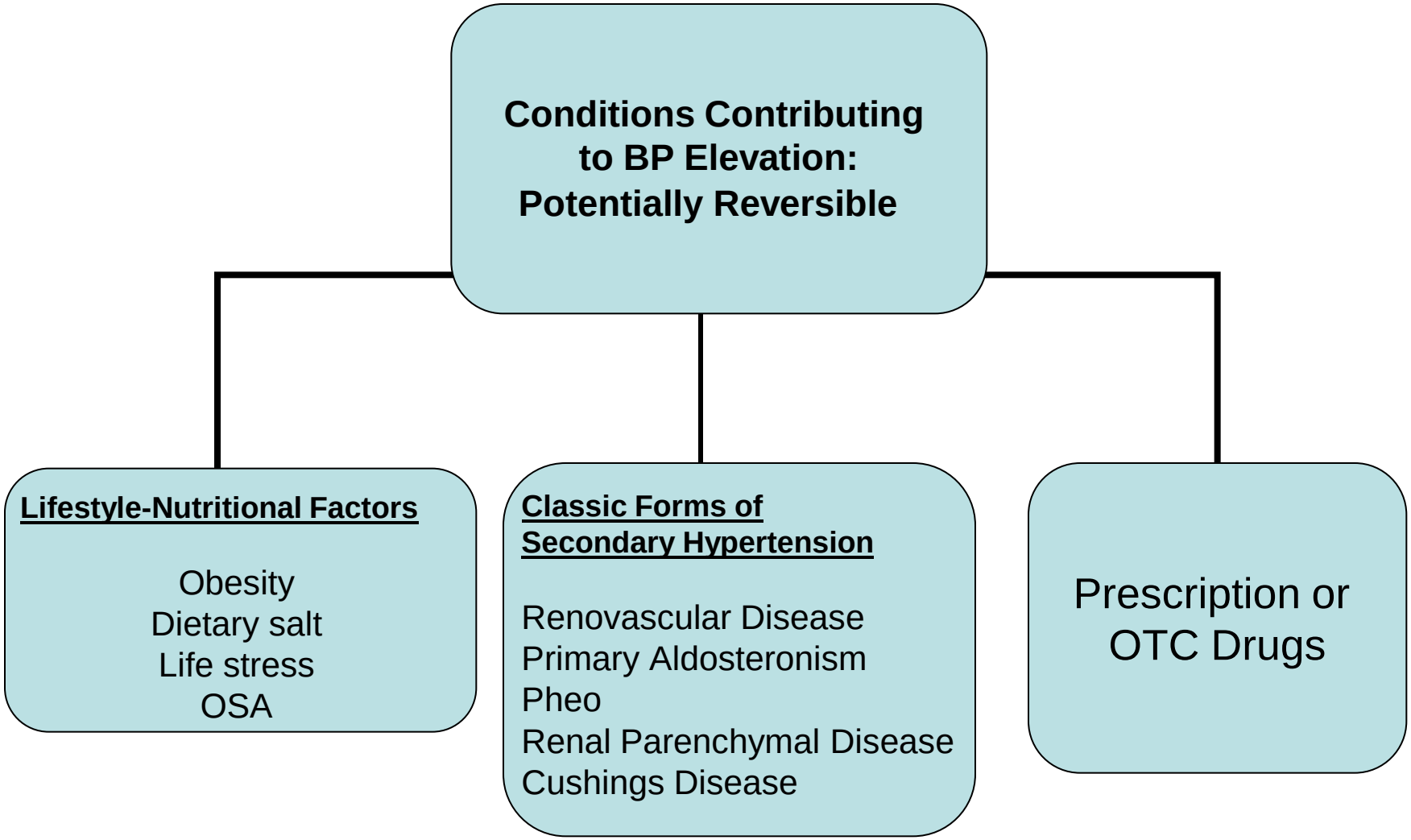
Types and Causes of Hypertension

Systolic and diastolic hypertension

- Primary, essential, or idiopathic
- Identifiable causes
  - Renal
    - Renal parenchymal disease
      - Acute glomerulonephritis
      - Chronic nephritis
      - Polycystic disease
      - Diabetic nephropathy
      - Hydronephrosis
    - Renovascular disease
      - Renal artery stenosis
      - Other causes of renal ischemia
    - Renin-producing tumors
    - Renoprival
    - Primary sodium retention: Liddle's syndrome, Gordon's syndrome
  - Endocrine
    - Acromegaly
    - Hypothyroidism
    - Hyperthyroidism
    - Hypercalcemia (hyperparathyroidism)
    - Adrenal disorders
      - Cortical disorders
        - Cushing's syndrome
        - Primary aldosteronism
        - Congenital adrenal hyperplasia
      - Medullary tumors: pheochromocytoma
    - Extra-adrenal chromaffin tumors
    - 11-β-hydroxysteroid dehydrogenase deficiency or inhibition (licorice)
    - Carcinoids
    - Exogenous hormones
      - Estrogen
      - Glucocorticoids
      - Mineralocorticoids
      - Sympathomimetics
      - Erythropoietin
    - Foods containing tyramine with monamine oxidase inhibitors
  - Coarctation of the aorta and aortitis
  - Pregnancy-induced
  - Neurological disorders
    - Increased intracranial pressure
    - Sleep apnea
    - Quadriplegia
    - Acute porphyria
    - Familial dysautonomia
    - Lead poisoning
    - Guillain-Barré syndrome
  - Acute stress
    - Psychogenic hyperventilation
    - Hypoglycemia
    - Burns
    - Alcohol withdrawal
    - Sickle cell crisis
    - After resuscitation
    - Perioperative
  - Increased intravascular volume (polycythemia)
  - Alcohol
  - Nicotine
  - Cyclosporine, tacrolimus
  - Other agents (see Table 15–5)

Systolic hypertension

- Increased cardiac output
  - Aortic valvular insufficiency
  - Arteriovenous fistula, patent ductus
  - Thyrotoxicosis
  - Paget's disease of bone
  - Beriberi
- Arterial rigidity


Conditions Contributing to BP Elevation: Potentially Reversible
Lifestyle-Nutritional Factors
Obesity
Dietary salt
Life stress
OSA
Classic Forms of Secondary Hypertension
Renovascular Disease
Primary Aldosteronism
Pheo
Renal Parenchymal Disease
Cushings Disease
Prescription or OTC Drugs

Agents that can interfere with blood pressure control

Non-narcotic analgesics (non-steroidal anti-inflammatory agents, selective COX-2 inhibitors, aspirin)
Sympathomimetic agents (decongestants, diet pills, cocaine)
Stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, methamphetamine)
Alcohol
Oral contraceptives
Cyclosporine
Erythropoietin
Natural licorice
Herbal compounds (ephedra or ma huang)

Clinical features of the different causes of secondary hypertension

Disorder	Suggestive clinical features
General	Severe or resistant hypertension
	An acute rise in blood pressure over a previously stable value
	Proven age of onset before puberty
	Age less than 30 years with no family history of hypertension and no obesity
Renovascular disease	An acute elevation in serum creatinine of at least 30 percent after administration of angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB)
	Moderate to severe hypertension in a patient with diffuse atherosclerosis, a unilateral small kidney, or asymmetry in renal size of more than 1.5 cm that cannot be explained by another reason
	Moderate to severe hypertension in patients with recurrent episodes of flash pulmonary edema
	Onset of stage II hypertension after age 55 years
	Systolic or diastolic abdominal bruit (not very sensitive)
Primary renal disease	Elevated serum creatinine concentration
	Abnormal urinalysis
Oral contraceptives	New elevation in blood pressure temporally related to use
Pheochromocytoma	Paroxysmal elevations in blood pressure
	Triad of headache (usually pounding), palpitations, and sweating
Primary aldosteronism	Unexplained hypokalemia with urinary potassium wasting; however, more than one-half of patients are normokalemic
Cushing's syndrome	Cushingoid facies, central obesity, proximal muscle weakness, and ecchymoses
	May have a history of glucocorticoid use
Sleep apnea syndrome	Primarily seen in obese men who snore loudly while asleep
	Daytime somnolence, fatigue, and morning confusion
Coarctation of the aorta	Hypertension in the arms with diminished or delayed femoral pulses and low or unobtainable blood pressures in the legs
	Left brachial pulse is diminished and equal to the femoral pulse if origin of the left subclavian artery is distal to the coarct
Hypothyroidism	Symptoms of hypothyroidism
	Elevated serum thyroid stimulating hormone
Primary hyperparathyroidism	Elevated serum calcium

PHEO: Symptoms

Cleveland Clinic
73/76 : 1 or more
55/76: at least 2

- **Headache**
- **Sweats**
- **Palpitation**

Pheo: Screening

- Spot urine:

  metanephrine/creatinine: mcg/mg = mg/24 hour

- Plasma Metanephrine

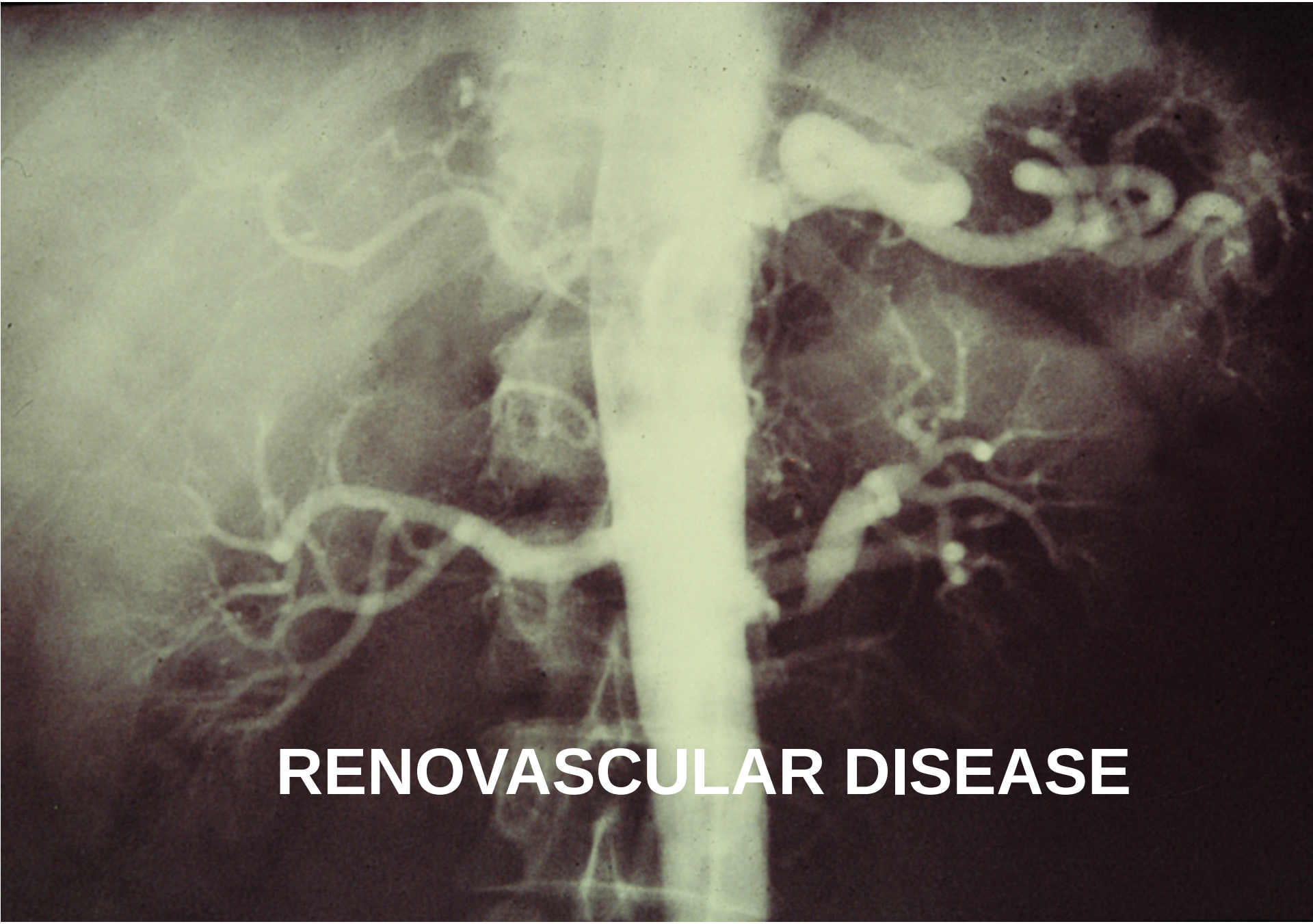
  100% sensitive (52/52)

  100% negative predictive value (162/162)

Cushing's Syndrome: Screening

Overnight Dexamethasone Suppression

- Dexamethasone 1 mg hs
- Plasma cortisol @ 8:00 AM
- Normal suppression: cortisol < 5 mcg/dl
- 10-20 % false positive



RENOVASCULAR DISEASE

RVH: Clinical Clues

- Severe HTN… > 180/120
- Unexplained loss of GFR with antihypertensive therapy, especially :
  - ↑ creat > 30-50% 1-4 weeks following ACE-I or ARB
- Severe HTN and
  - diffuse atherosclerosis + > 50 y/o
  - unexplained small kidney (<9cm) or asymmetry
  - Recurrent episodes (flash) pulmonary edema
- Systolic-Diastolic bruit

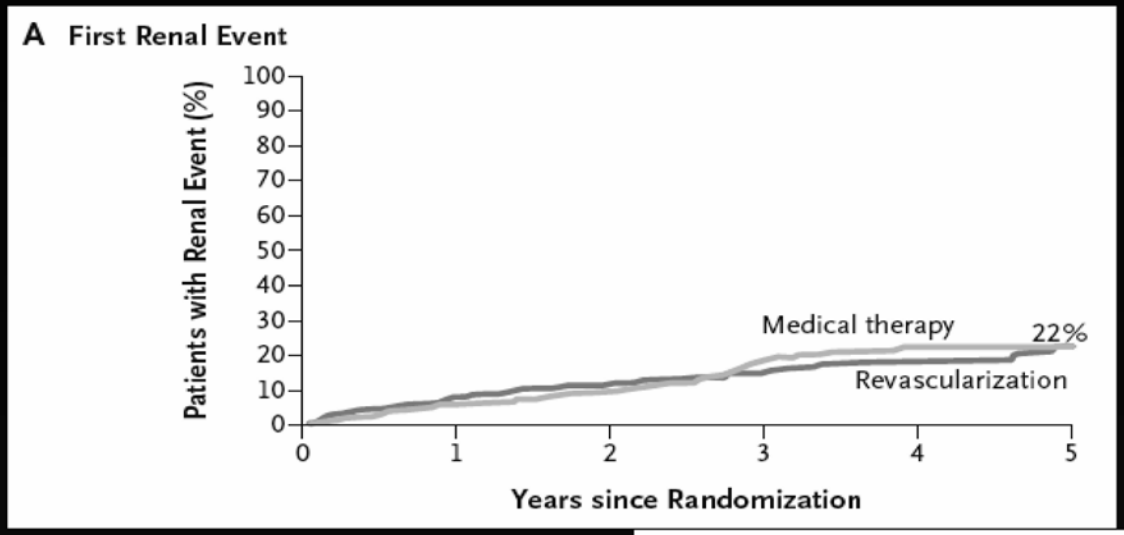
Atherosclerotic RAS: Prevalence of 50% or Greater Narrowing

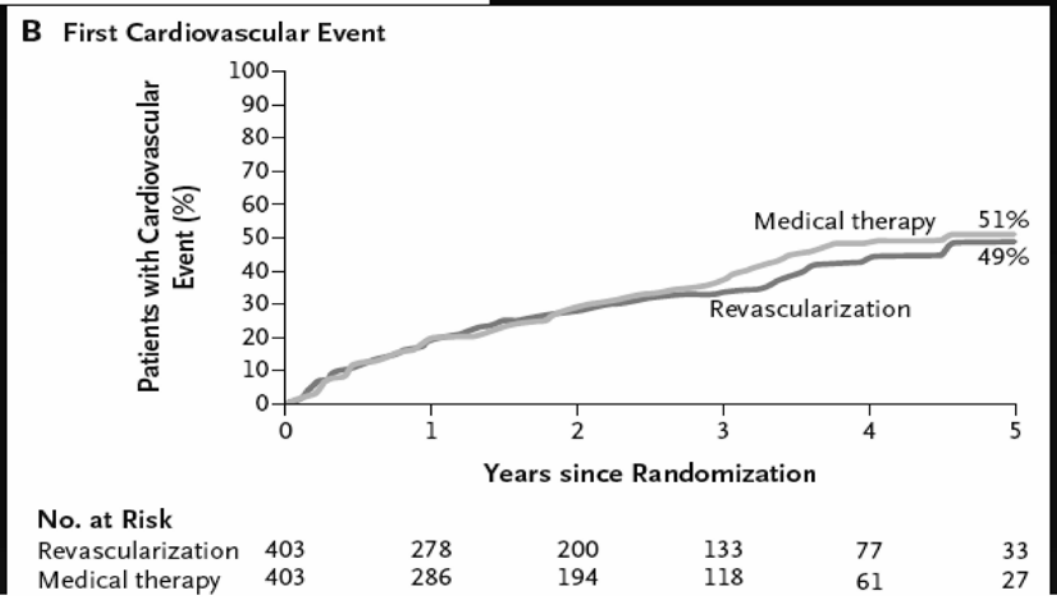
Overall:	11-42%
Autopsy:	4-50%
Under age 60:	5.5%
Over age 60:	16.4%
During cardiac cath:	
⊕ Coronary Stenosis	29%
θ Coronary Stenosis	10%
During aortic angiography:	
Aortic aneurysm	38%
Aortic occlusive disease	33%
Lower limb occlusive disease	39%

RAS + HTN ⟶ STENT ?

RAS + CKD ⟶ STENT ?

Renal and Cardiovascular Events in ASTRAL

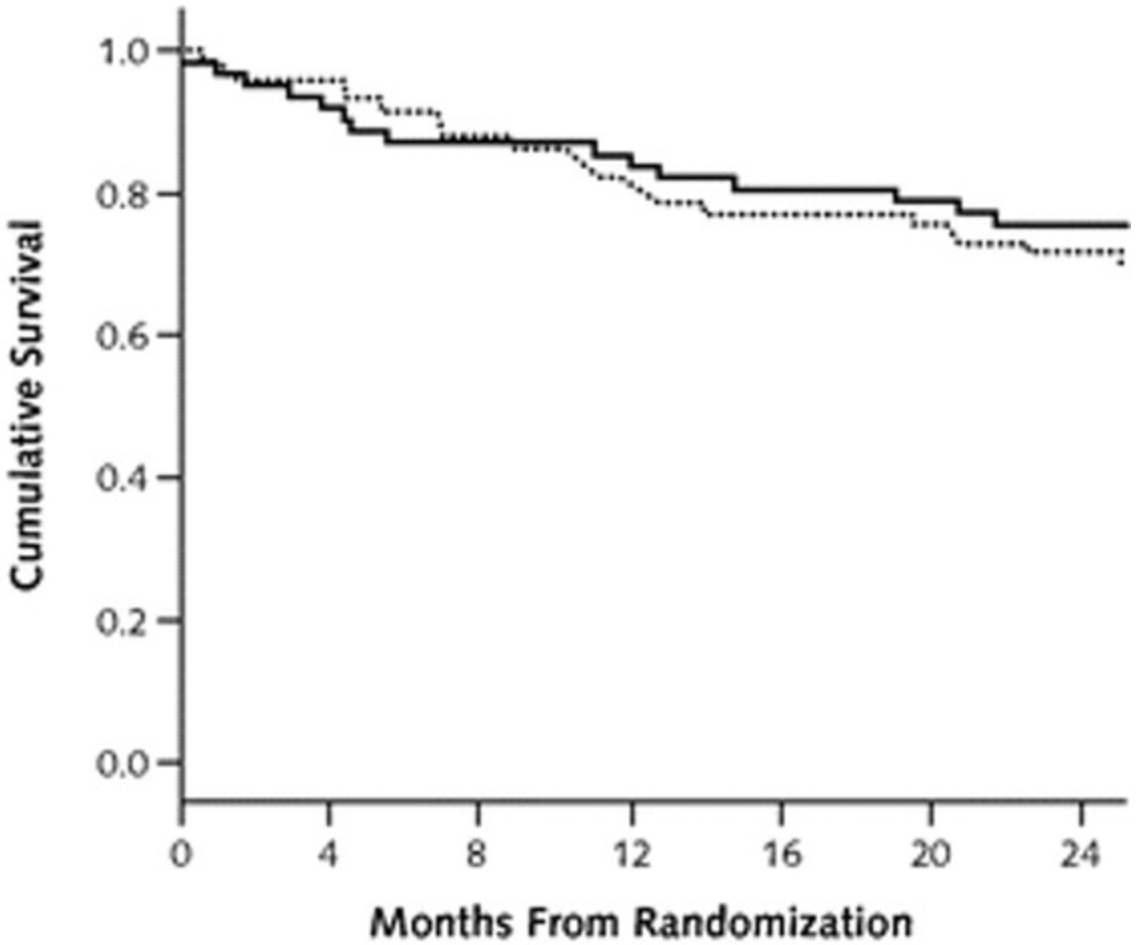




N. Engl.J.Med:
361: 1953-1962, 2009

mayo

STARS: Decline GFR or Death



Patients remaining, *n*					
Medication group	76	68	60	57	53
Stent group	64	54	52	50	46

RAS + HTN  STENT

RAS + CKD  STENT

Hypertensive patients with atherosclerotic renal artery disease, who have stable renal function and well managed blood pressure on medical therapy derive no proven benefit by revascularization

Criticism of ASTRAL Trial

Selection bias:

- Patients excluded if “definitely needed” revascularization

Many “stent” patients unlikely to benefit

- 17% never stented ….minimal RAS
- 39% showed only 50-70% stenosis

Cross over and **Intention to Treat Analysis**

- 6% of medical group crossed over for revascularization

STAR: Criticism

62% (40 of 64) randomized to stenting and analyzed (ITT) were unlikely to benefit:

- 12 < 50 % stenosis
- 22 50-70% stenosis
- 6 never stented

Bias in patient selection:

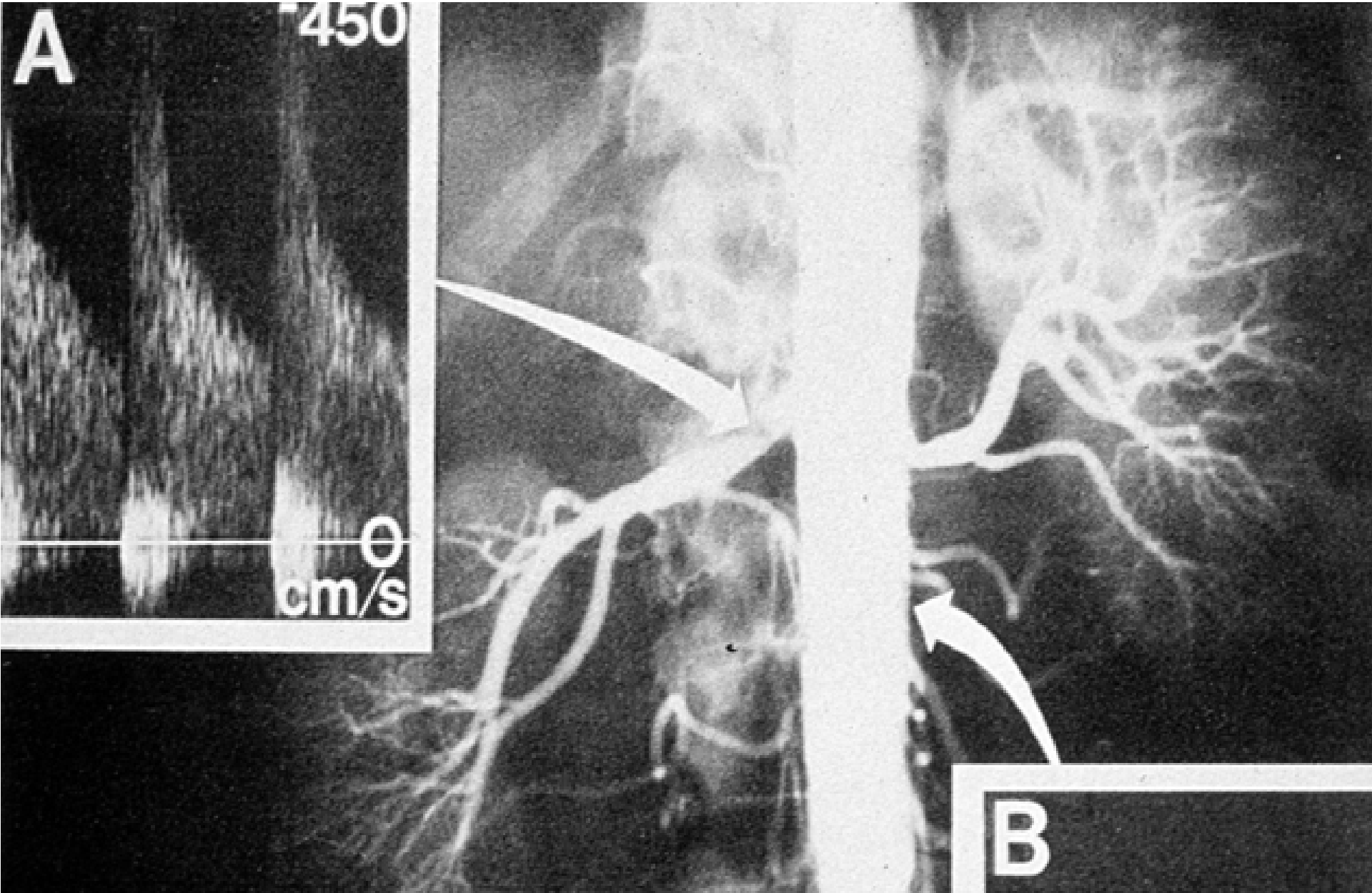
- Resistant hypertension (BP>140/90) excluded
- Flash pulmonary edema, rapid loss GFR excluded

Mann & Sos
J Clin Hyp 2010

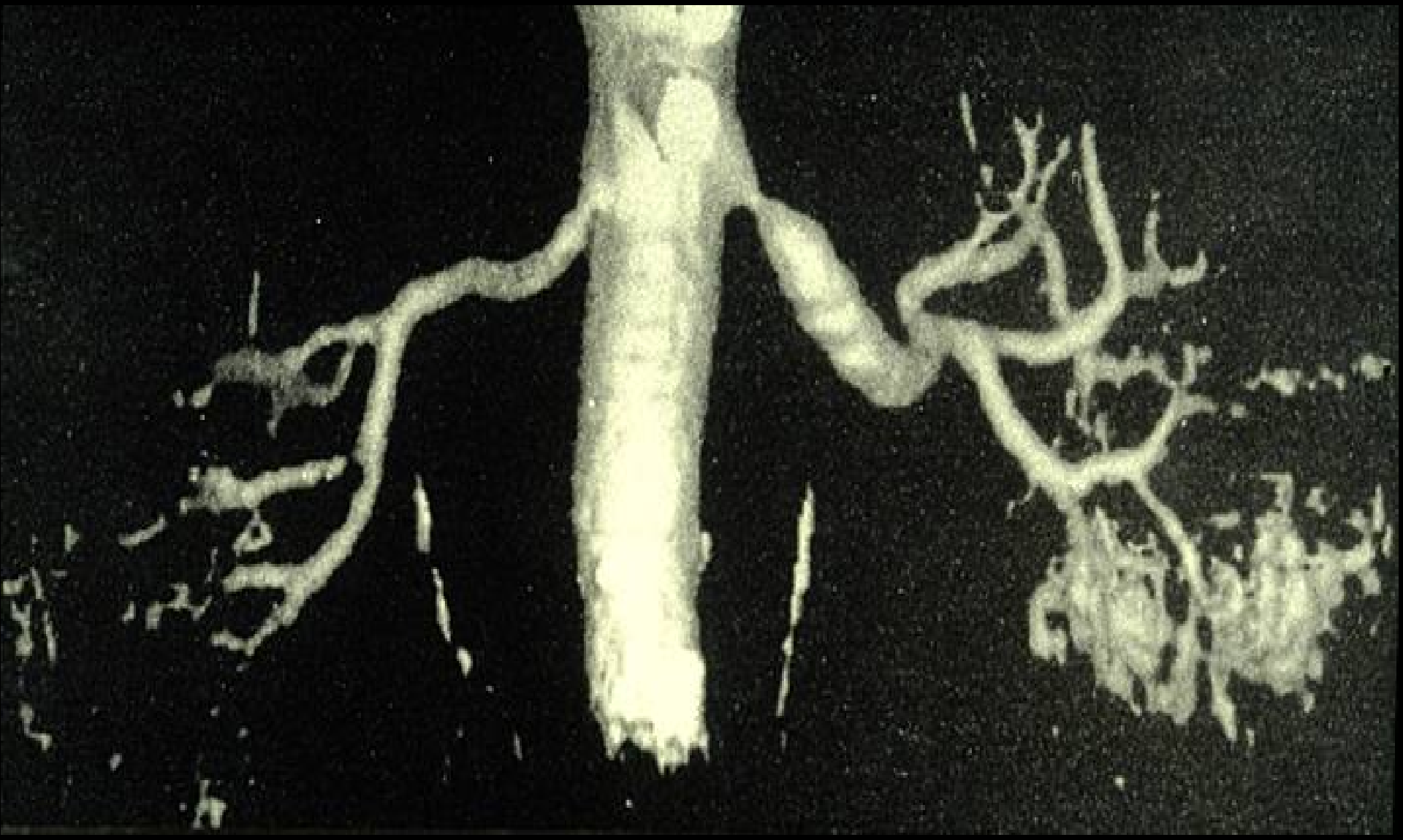
Considerations for RVH Screening

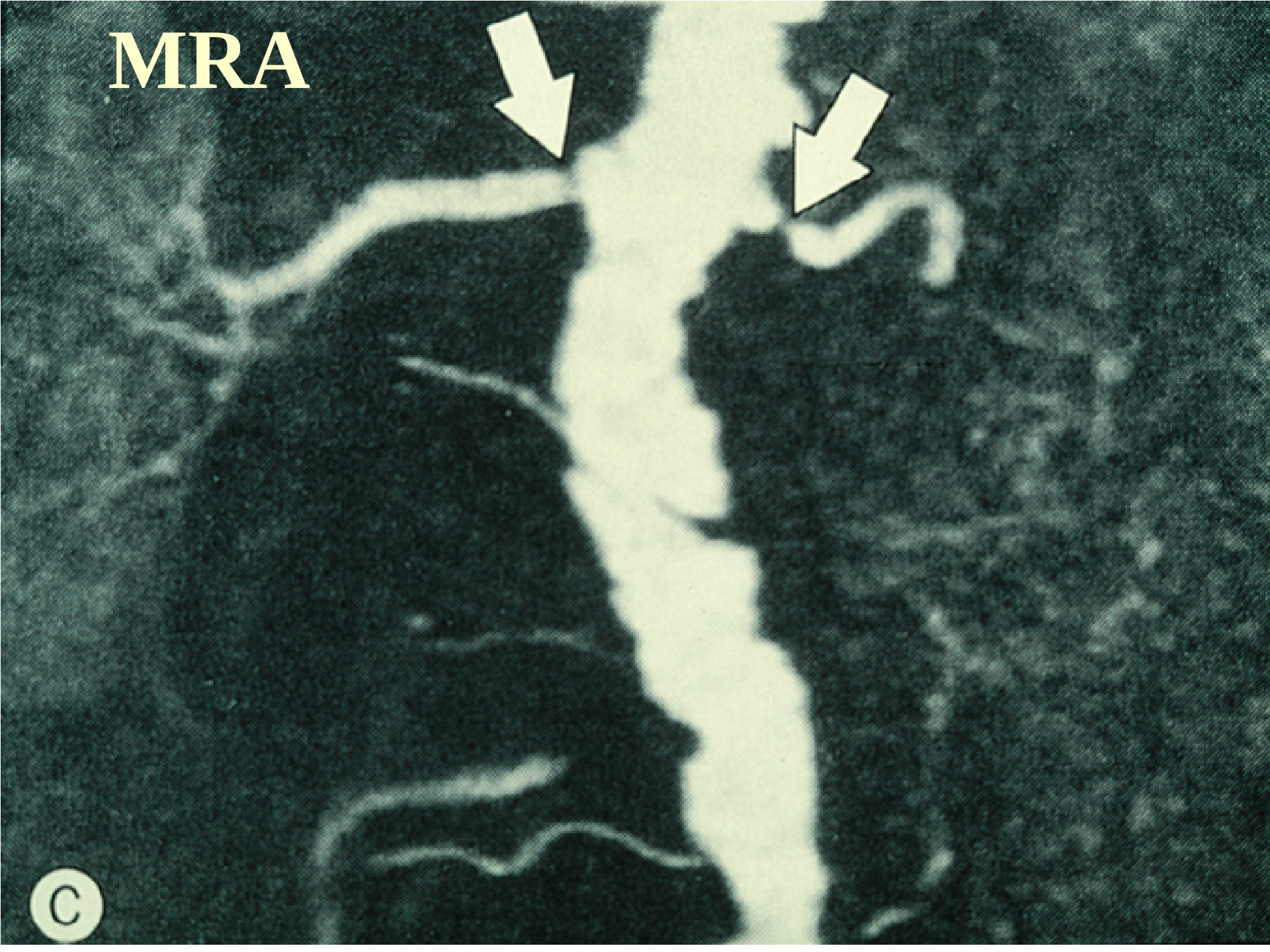
- What is probability of finding RAS?
- Will I intervene if RAS identified?
- Is BP controlled?...renal function stable? on medical therapy
- Will BP respond to intervention?
  - Short duration of ↑↑BP best predictor of BP response
  - No lab/radiology predictor of BP response
- What are risks of diagnostics?
- What are risks of intervention?

DUPLEX



CT Angiography



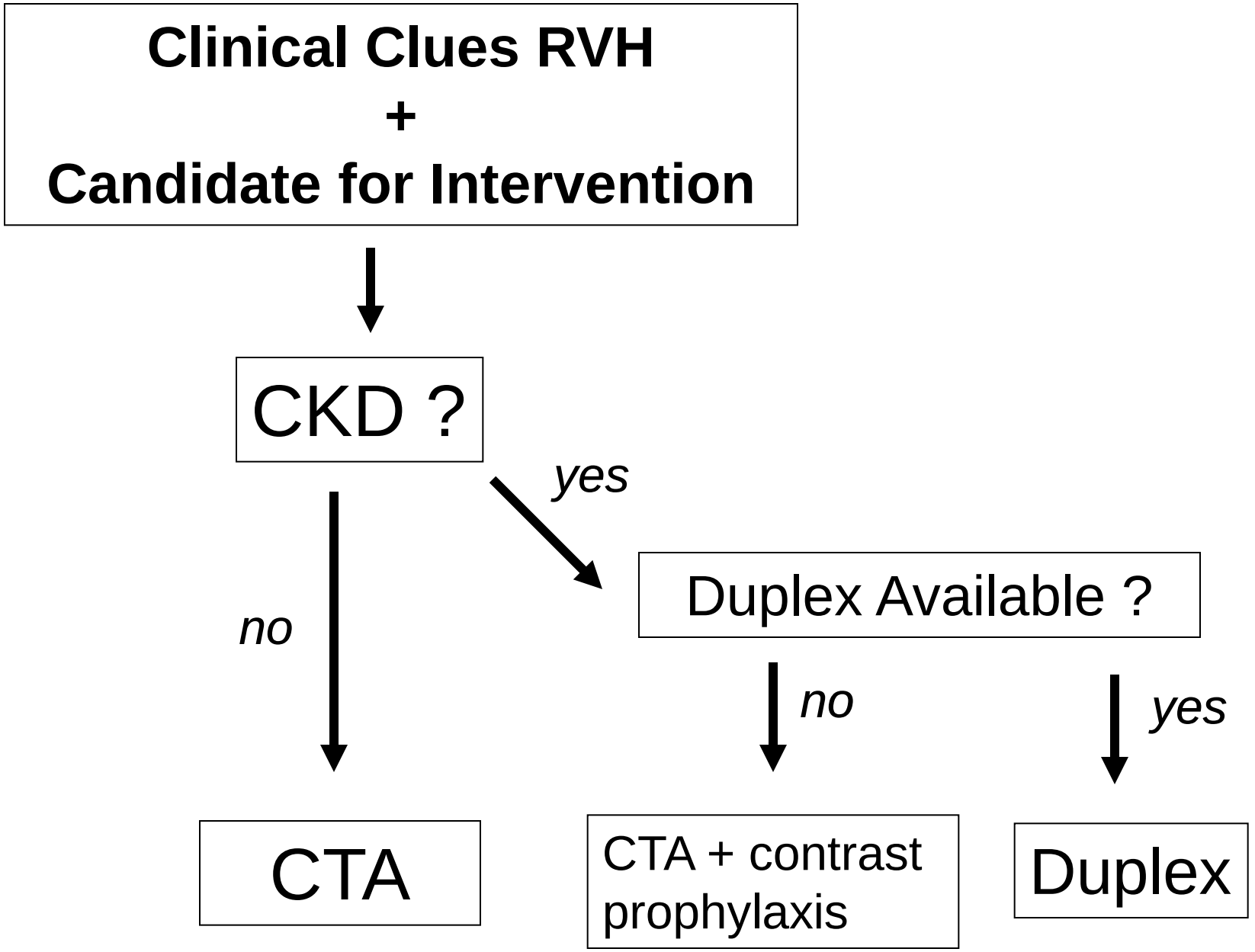

MRA
C

Diagnostic Tests for Renal Artery Stenosis

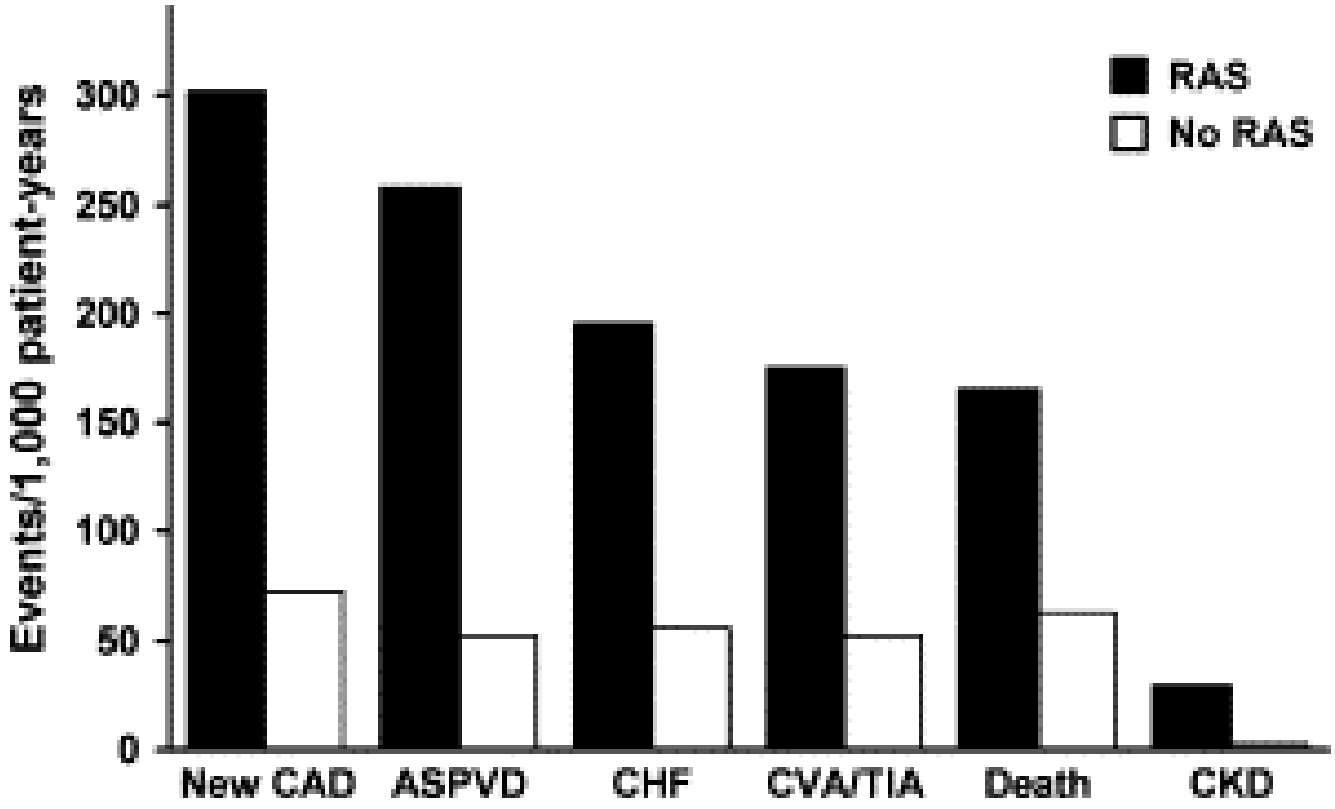
	duplex	**CTA**	**MRA**
principle	records velocity	Helical CT angiography	MR image
advantages	Noninvasive	Noninvasive High image quality	Noninvasive
limitations	•Time consuming •Technically difficult • not widely available	•IV contast •Poor imaging in FMD	•Gadolinium-NSF
positive test	•PSV >200cm/sec •RAR >3.5	Stenosis >75 % OR >50% + PSD	
Sensitivity / specificity	85% / 92%	96% / 97%	100% / 96%

Candidates for RAS Screening-Intervention

- Short duration of BP elevation
- Resistant HTN + clinical clues for RVH
- Intolerance to optimal medical therapy
- Progressive CKD + bilateral RAS or stenosis SFK
- Fibromuscular disease in young patient
- Recurrent flash pulmonary edema or refractory CHF

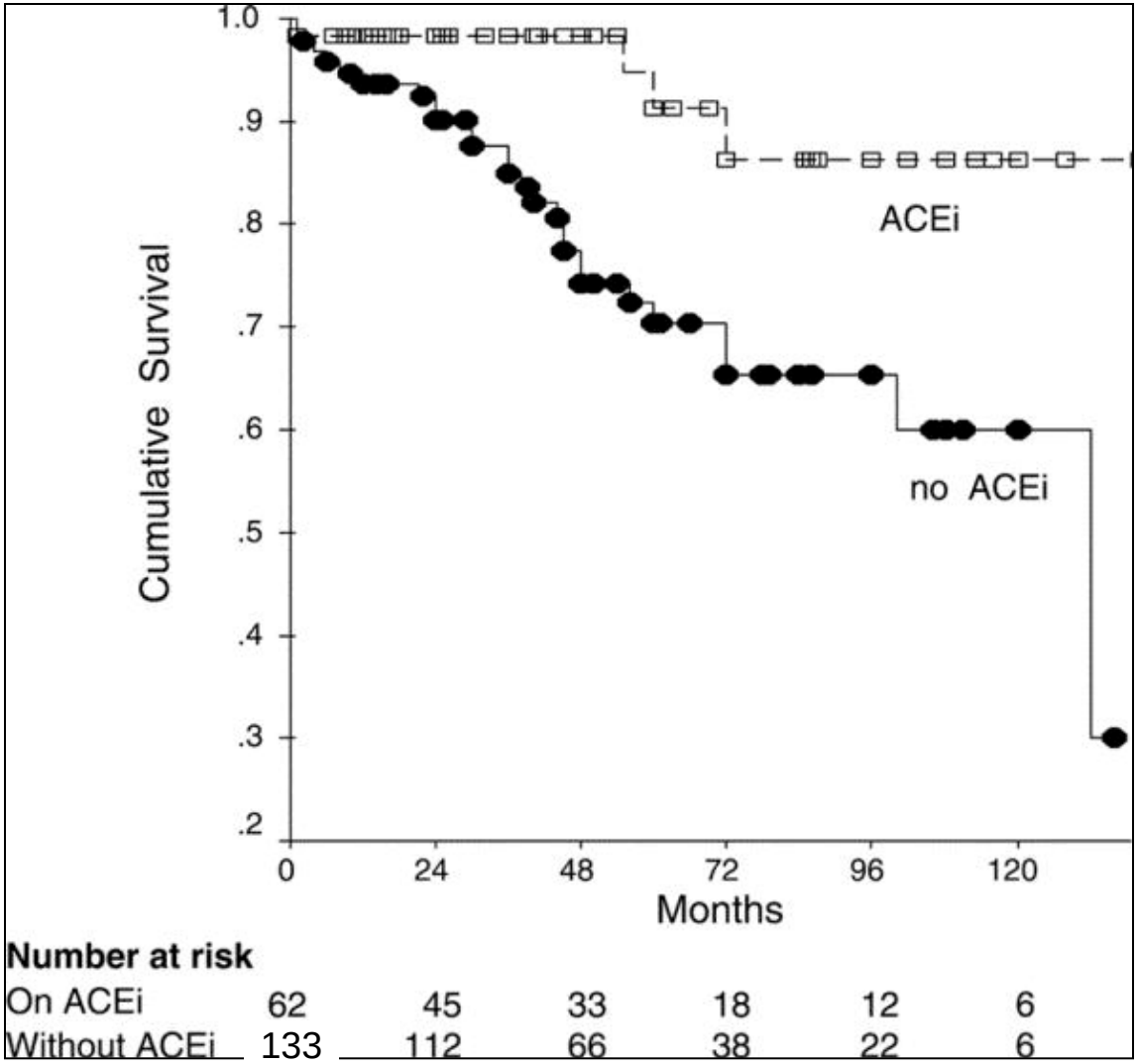

Clinical Clues RVH
+
Candidate for Intervention
CKD ?
yes
no
Duplex Available ?
no
yes
CTA
CTA + contrast prophylaxis
Duplex

New-Onset CV Event After Diagnosis of ARAS



Kalra
Kidney Int.
2005

ACE inhibitors Improve Survival in ARAS



Nephol Dial Transplant 2005

ACE Inhibitors Effectively Control Hypertension in ARAS

- Franklin (1986):Enalapril + HCTZ vs TT.. goal BP 96% v 82%
- In 4 other trials, 80-100% reach goal BP
- Discontinuation due to ↑ creat 0%- 3.5%

Textor
Role of Renin-Angiotensin System Blockade In Atherosclerotic Renal Artery Stenosis and Renovascular Hypertension
Hypertension, 2007

Medical Management of ARAS

Monitoring

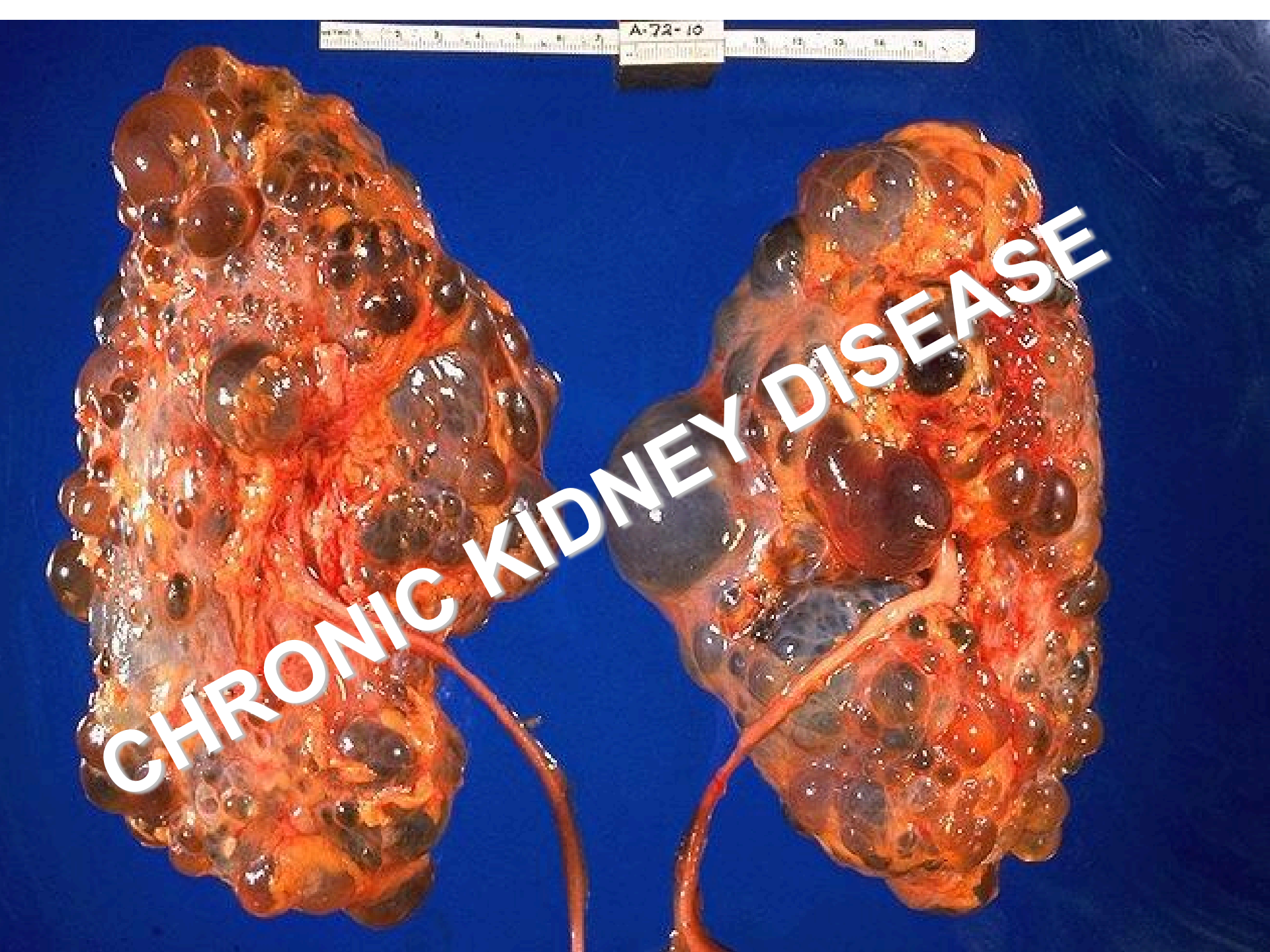
- GFR, proteinuria,lipids, glycemic control, K^+
- Duplex surveillance: Stenotic/Nonstenotic Kidney ?
  - Kidney size,
  - renal artery PSV (RAR)

Drug Therapy

- Treat BP to goal …<140/90 with ACE/ARB + add-on Rx
- Treat lipids to LDL < 80
- ASA/fish oil

Cardiovascular Lifestyle Modification

- Manage CV comorbidities
- Glycemic control
- Cessation of cigarette smoking is essential
  -


A-72-10
CHRONIC KIDNEY DISEASE

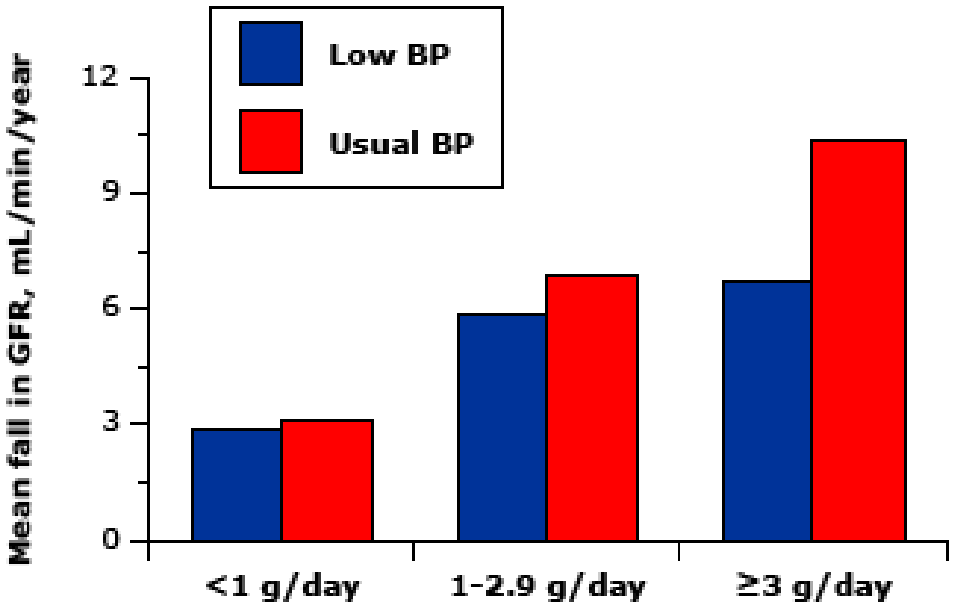
“Blood pressure should be reduced to levels less than 130/80 in patients with chronic kidney disease”
JNC 7, March 2003

- **Target BP in CKD is < 130/80**
  KDOQI 2004

Guidelines 2013 ?

The Importance of Proteinuria

Aggressive BP control preserves renal function in proteinuric patients



Low BP: MAP 92 =125/75
Usual BP:MAP 102 =140/90

NEJM 1994

Relative Risk of Major Complications of Chronic Kidney Disease

Cardiovascular mortality

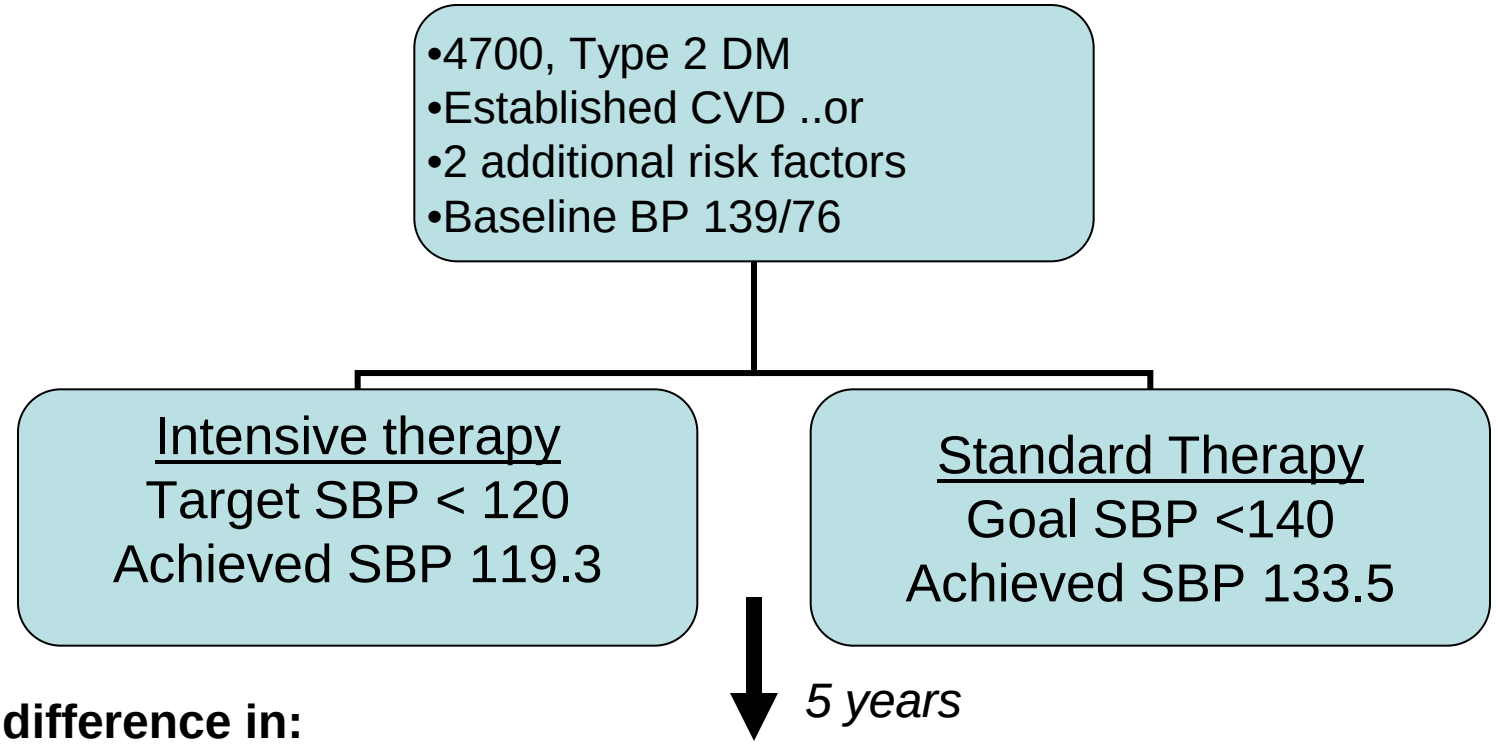
	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR >105	0.9	1.3	2.3	2.1
eGFR 90-105	Ref	1.5	1.7	3.7
eGFR 75-90	1.0	1.3	1.6	3.7
eGFR 60-75	1.1	1.4	2.0	4.1
eGFR 45-60	1.5	2.2	2.8	4.3
eGFR 30-45	2.2	2.7	3.4	5.2
eGFR 15-30	14	7.9	4.8	8.1

Kidney failure (ESRD)

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR >105	Ref	Ref	7.8	18
eGFR 90-105	Ref	Ref	11	20
eGFR 75-90	Ref	Ref	3.8	48
eGFR 60-75	Ref	Ref	7.4	67
eGFR 45-60	5.2	22	40	147
eGFR 30-45	56	74	294	763
eGFR 15-30	433	1044	1056	2286

KDIGO Report
Kidney Int. 2010

ACCORD BP Trial



No difference in:

- 1º composite outcome (nonfatal MI, nonfatal stroke, CV death)
- Annual all cause mortality

Differences:

- Fewer strokes in IT (0.32%) vs ST (0.53%), HR 0.63
  Absolute benefit 1 in 89
- More serious ADE in IT (3.3 vs 1.3 %)..syncope, renal failure , bradycardia, hyperkalemia

NEJM 2010

BP Targets in CKD: Importance of Proteinuria and Clinical Atherosclerosis

CKD	+	+	+	+	+	+
diabetes	-	+	+	-	-	-
proteinuria	-	-	+	+	-	-
atherosclerosis	-	-	-	-	+	-
Age >80	-	-	-	-	-	-
Target BP:	**140/90**	**140/90[1]**	**130/80**	**130/80**	**130-135[2]**	**150[2]**

[1] attempt SBP 130-135 if no side effects
[2] avoid DBP <60-65 in CAD

Drug Therapy in CKD

Goal BP depends on proteinuria

- > 500mg/day → 130/80
- < 500 mg/day → 140/90

Measure Home BP, ABP?

Sodium restriction

- 2gram Na+ = 5 gram salt ≈ 100 meq Na+

Diuretics

- GFR > 30 → thiazide …CTD > HCTZ
- GFR < 30 →
  - loop diuretics …furosemide bid, torsemide daily
  - High dose thiazides ? …CTD 50, HCTZ 50 bid

ACE or ARB in proteinuria, not both

Nocturnal administration of some agents

Sequence of Antihypertensive Therapy in CKD

	Proteinuria*		**No proteinuria**	
edema	Yes	No	Yes	No
1st drug	AI + D	AI	D	AI
2nd drug		nonDHP	DHP or AI	DHP
3rd drug	NonDHP	D	DHP or AI	D
4th drug	Spironolactone , loop + thiazide diuretic Labetalol , metoprolol**			

AI angiotensin inhibitor
D diuretic
NonDHP nondihydropyridine (diltiazam, verapamil)
DHP dihydropyridine (amlodipine, nifedipine)

* >500 mg protein per day
** compelling indication

Proteinuria Threshold for Intensive BP Control

KDIGO

- ACR < 30 mg/ g → < 140/90, no preferred agent
- ACR 30-300 mg/ g → <130/80, ACE-I or ARB

Up-to-Date (Bakris)

- PER < 500 mg/day → <140/90
- PER ≥ 500 mg/day → <130/80, ACE-I or ARB

Equivalents and Reconciliation of Guideline

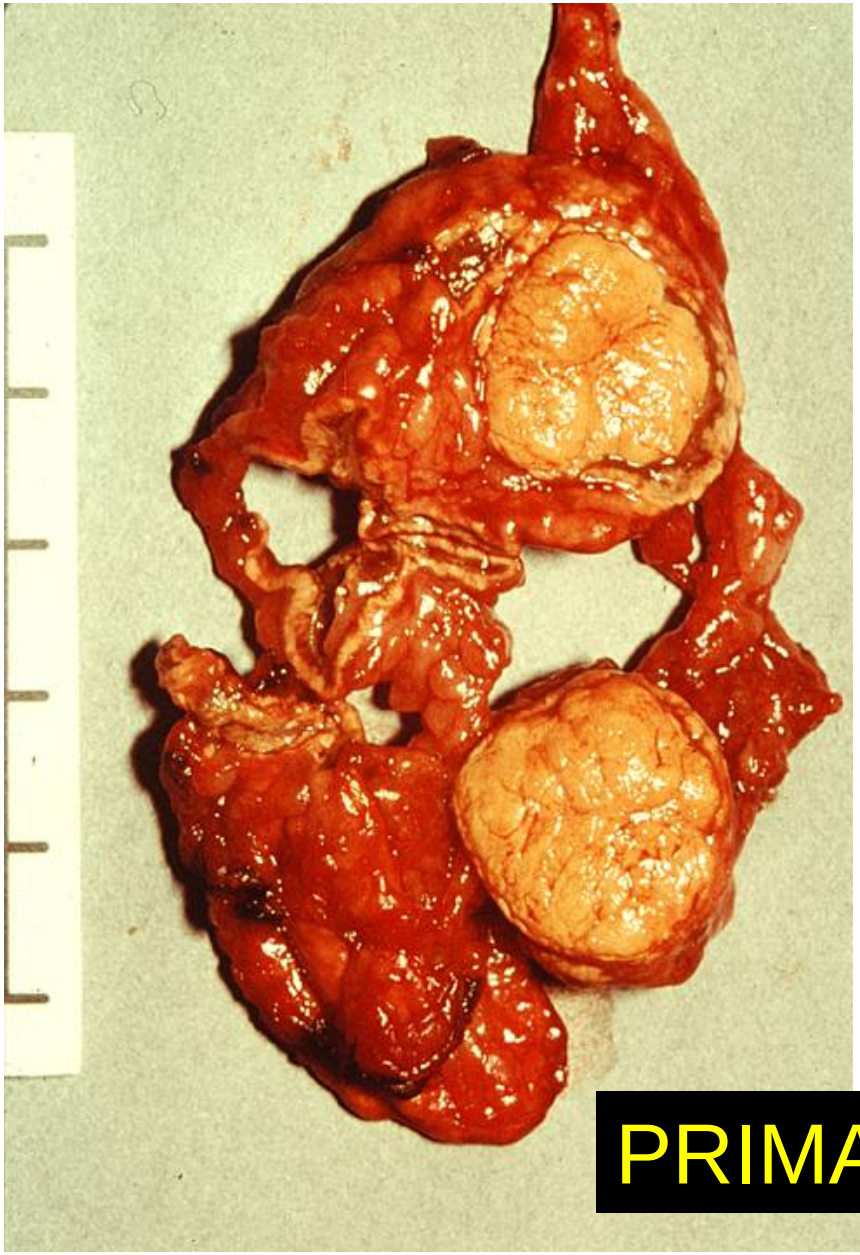
- ACR 30mg/g creat = PCR 150 mg/g creat
- 80 kg male x 25mg creat excretion per kg = 2g creat
- 150 mg protein/g creat x 2 g = 300 mg protein

Limitations of Using PCR Exclusively in CKD Management

Weight (kg)	100	67	67
gender	male	female	female
Creat excretion (mg/kg)	20-**25**	**15**-20	**15**-20
Projected creat excretion (mg)	2500	1000	1000
Projected creat excretion (G)	2.5	1.0	1.0
Protein excretion rate "*PER*" (mg)	1000	400	1000
protein-creat ratio "*PCR*" (mg/G)	400	400	1000

Management of Proteinuria

- ACE-I or ARB, no role for combination
- BP goal <130/80…. or lower
- Proteinuria goals
  - Nephrotic: < 3.5 Grams, ↓50% baseline,
  - Nonnephrotic < 1000 mg, ↓ 50% baseline
- Evaluation and monitoring
  - 24 hour urine for initial assessment
  - Calculate PCR off 24º urine
  - Monitor PCR and adjust therapy



PRIMARY ALDOSTERONISM

Primary Aldosteronism: Prevalence & Epidemiology

- 1955 - “20% → 10%” …Conn
- <3%

1980 PAC:PRA case-finding 1980

⬇

- Nonselect patients, 10%
- Resistant HTN 20%
- Prevalence ≈ severity HTN
  - Stage 1….2%
  - Stage 2….8%
  - Stage 3….13%
- No age, sex, racial differences

Primary Aldo: Clinical Features

- Hypertension:often severe, rarely malignant
- No Edema
- Hypokalemia is inconsistent
  - 50% APA
  - 17% IHA
  - normal K in most GRA
- Metabolic alkalosis
- Mild hypernatremia

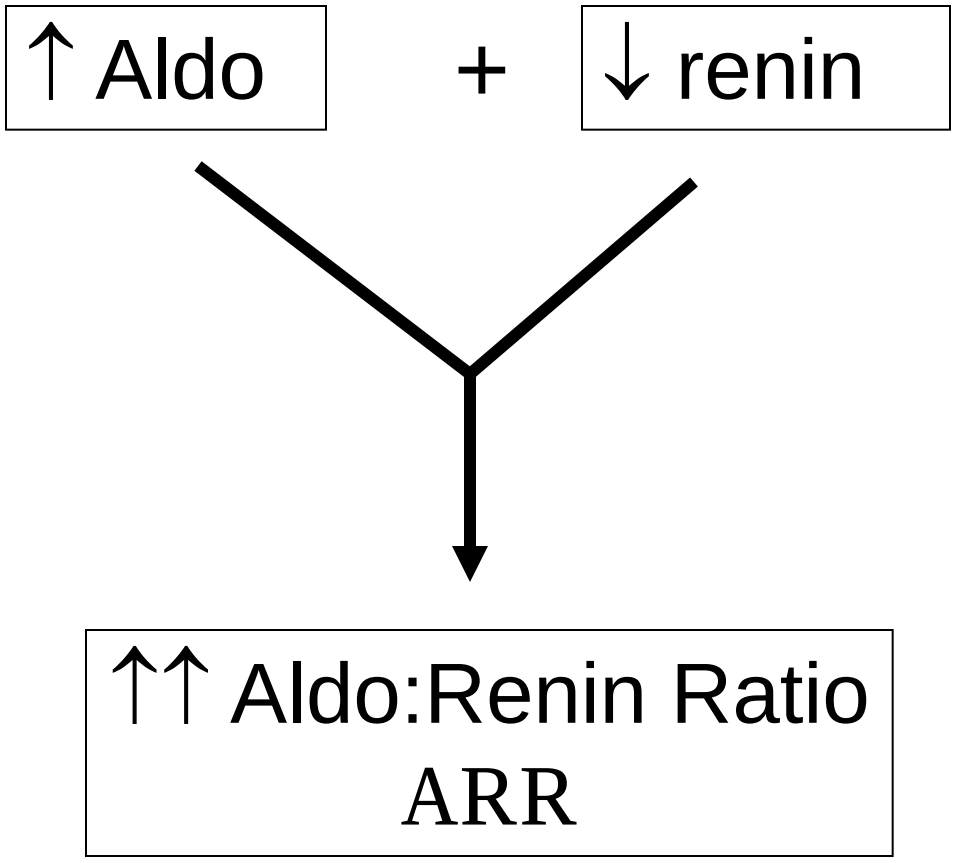
Subtypes of primary aldosteronism

Subtype	Relative Frequency (%)
Idiopathic Hyperaldosteronism	65
Aldosterone-producing adenoma	30
Unilateral adrenal hyperplasia	3
Aldo-producing adrenal carcinoma	1
Familial hyperaldosteronism	
Type I glucocorticoid-remediable aldosteronism	<1
Type II	<1
Ectopic Aldo-producing tumors	<1

Indications for Screening in Hypertensive Subjects

- Hypokalemia: spontaneous or induced by low dose diuretic
- Severe or resistant HTN
- adrenal incidentaloma
- FH early onset HTN or stroke (<40 y/o)
- 1st degree relatives with primary aldo

Hormonal Profile in Primary Aldosteronism



Screening: aldosterone to renin ratio

PAC / PRA

- Morning (?), ambulatory, paired PAC+PRA
- Most BP meds can be continued
  - Low PRA of 1º Aldo unresponsive to diuretics, ACE/ARB
  - High Aldo of 1º Aldo not suppressed by ACE/ARB
  - Captopril stimulation test in screening
  - Dihydropyridines have minimal effect
  - β blockers may ↓PRA but would not stimulate Aldo
- Avoid SPN, eplerenone 4-6 weeks… amiloride OK?
- Interpretation in context of medication
- PRC = PRA x 7

Primary Aldosteronism: Diagnosis

Plasma Aldosterone: Plasma Renin Activity

- **PA:PRA > 25**

and

- **Aldosterone >15 ng/dl**

Non suppression of Aldosterone with salt load

- IV: 2 liter NS/4 hour (serum Aldo > 10 ng/dl)
- Oral:1 tsp salt x 6 days (urine Aldo >14 mcg/24 hr)

Hypertension and Hypokalemia

↑ Aldo, ↓ PRA : Primary Aldo

↑Aldo, ↑ PRA : 2º HTN

- Renovascular disease
- Diuretic use
- Renin-secreting tumor, Malignant HTN, coarctation

↓↓ Aldo, ↓ PRA: other mineralocorticoid effect

- DOCA: tumors, CAH ↓17α OHase, ↓11β OHase
- Cushing's, Exogenous steroids
- Congenital hyperplasia
- Liddle's syndrome: gain-of-function mutation ENaC
- Apparent Mineralocorticoid Excess, licorice: ↓ 11β-HSD

Interpretation of Aldo-Renin Ratio

PAC, *ng/dL*	PRA, *ng/mL/h*	ARR	Interpretation
150	15	10	Secondary aldosteronism
15	3	5	Normal
6	< 0.6	10	Low-renin HTN, not PA
6	0.1	60	Low-renin HTN, not PA
			Misleading high ARR
15	1	15	Possible PA
15	< 0.6	25	Probable PA
27	< 0.6	45	Very likely PA

ARR—aldosterone–renin ratio; HTN—hypertension; PA—primary aldosteronism; PAC—plasma aldosterone concentration; PRA—plasma renin activity.

Primary Aldosteronism: Diagnosis

Plasma Aldosterone: Plasma Renin Activity

- PA:PRA > 25

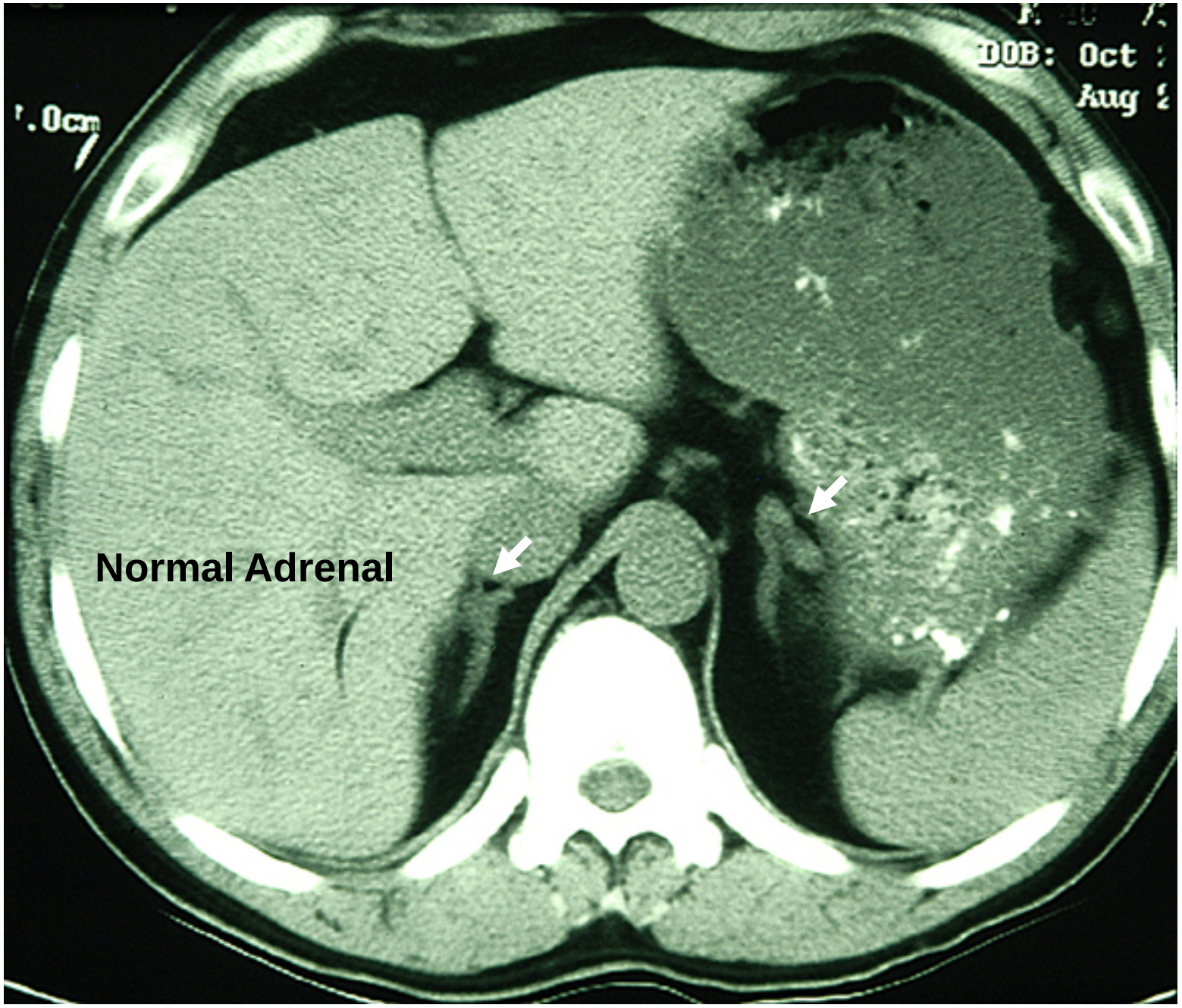
and

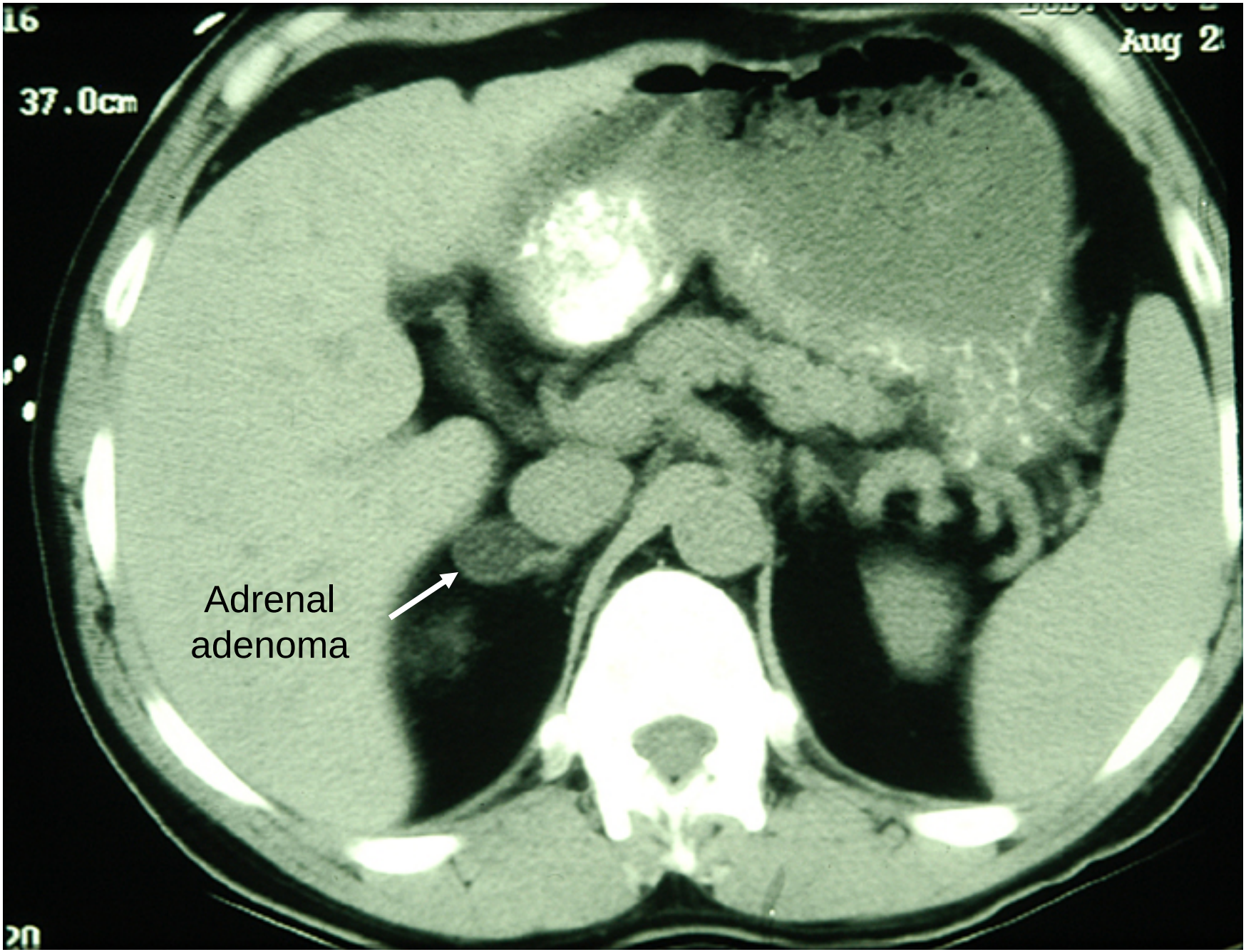
- Aldosterone >15 ng/dl

- **Non suppression of Aldosterone with salt load**
  - **IV: 2 liter NS/4 hour (serum Aldo > 10 ng/dl)**
  - **Oral:1 tsp salt x 6 days (urine Aldo >14 mcg/24 hr)**

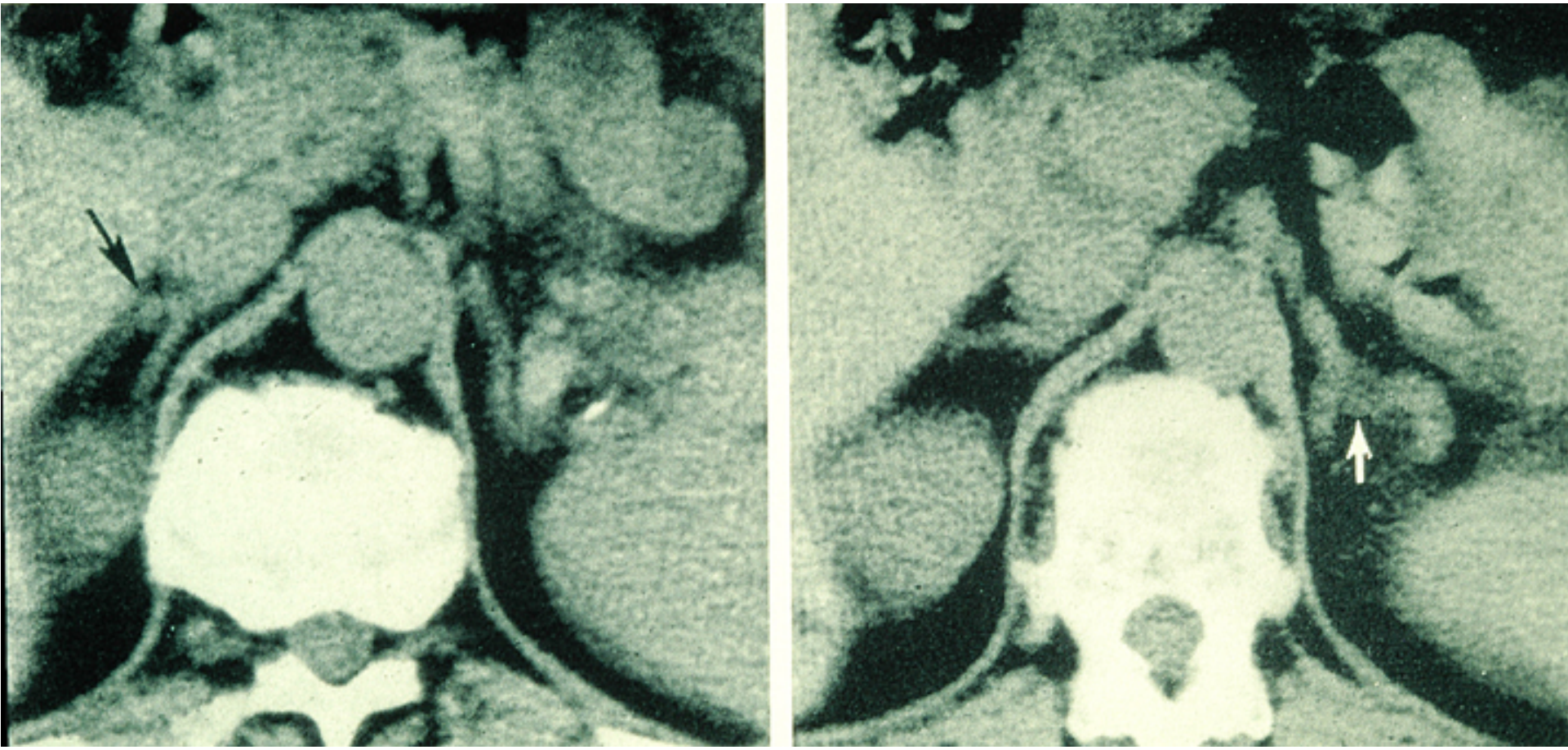
Oral salt load for 24 hour urine

- 1 teaspoon table salt daily…..OR
- Salt tablets:
  - 1gram NaCl, 2 tid = 6000mg NaCl = 100meq daily …OR
- High salt diet:
  - 5000mg Na =12g NaCl = >200 meq Na / day
- 3 days of salt loading $\rightarrow$ 24º urine on day 4
  - measure sodium, creatinine, aldosterone
- Explicit instructions on 24 Hr urine
- Goal: 24 hour urinary Na^+ > 200 meq/day
- Diagnosis: urinary aldosterone > 12 mcg/24 hours


Normal Adrenal


16
37.0cm
Aug 2
Adrenal
adenoma
20

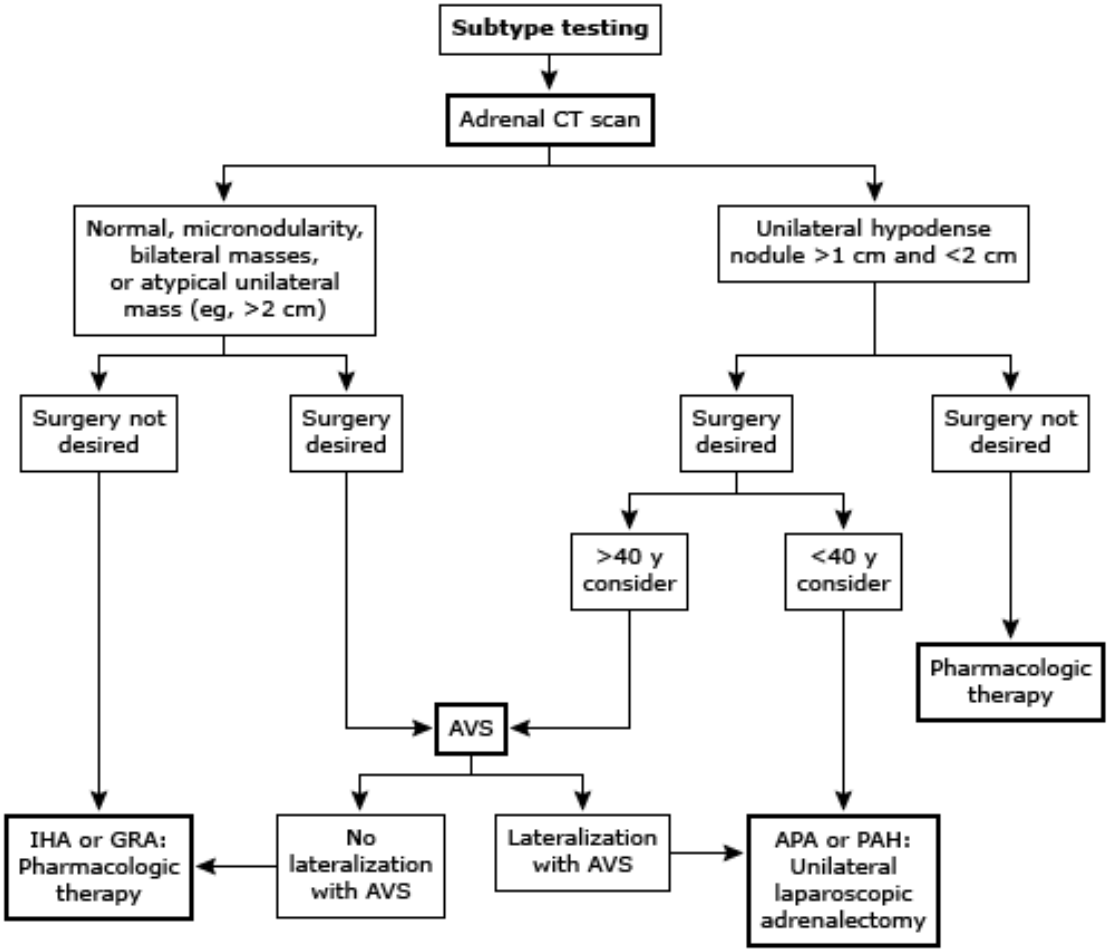
Bilateral Adrenal Hyperplasia



High Probability of APA

- High plasma aldosterone (>25 ng/dl)
- High urinary aldosterone (>30 mcg/24 hr)
- More severe hypertension
- More frequent hypokalemia
- Younger age (<50)

Subtype evaluation of primary aldosteronism



Medical Therapy: Mineralocorticoid Antagonists

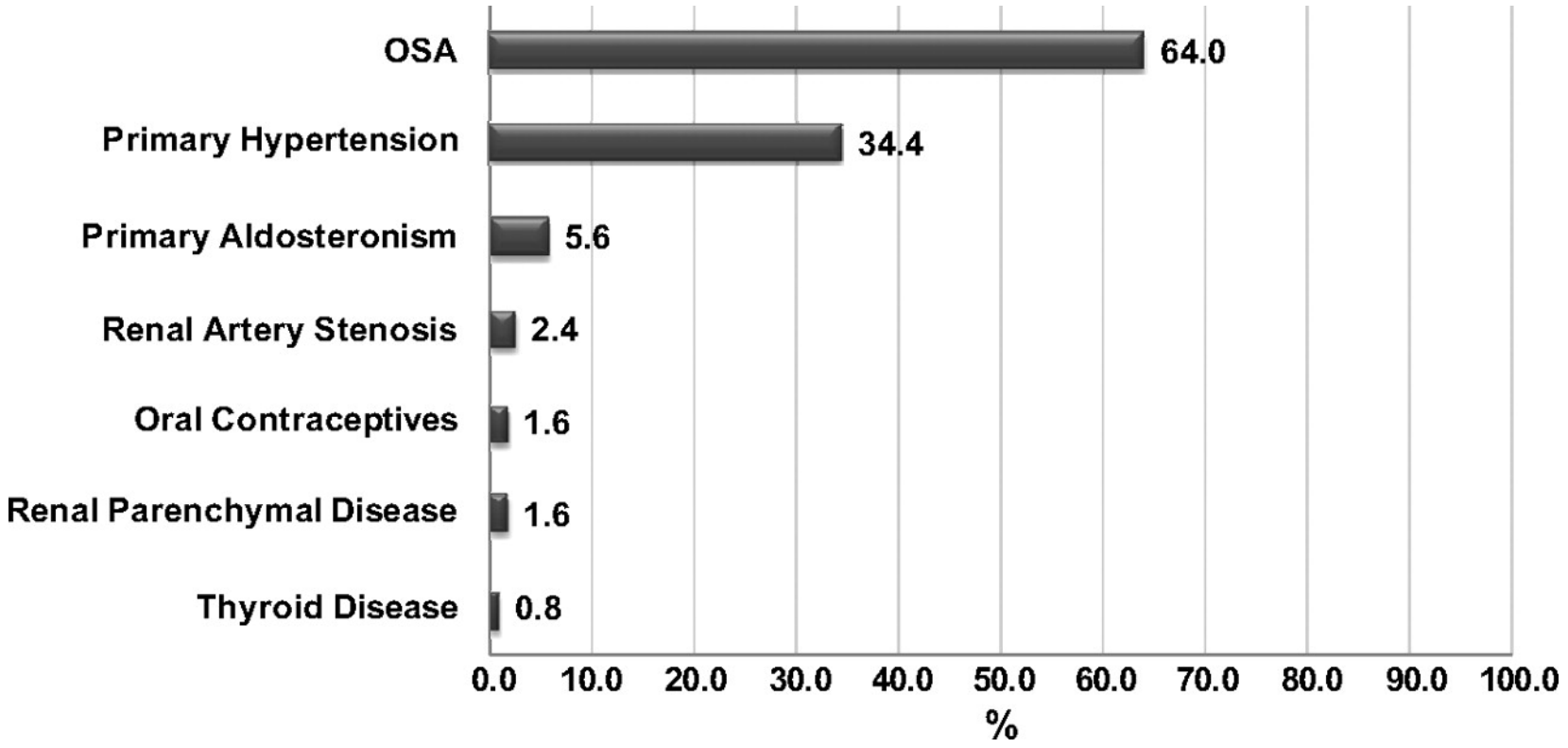
- IHA and nonsurgical APA patients
- Spironolactone: 1st line
  - 25-100 mg single daily dose
  - Androgen/progesterone receptor affinity→ gynecomastia, ED, menstrual irregularity
- Eplerenone: 2nd line
  - SPN derivative
  - Low progestin/androgen affinity → few side effects
  - Short duration, lower MR affinity→ bid, ½ potency SPN
  - $$$, 10x cost of SPN
- Amiloride: 3rd line
  - Blocks ENaC, not MR
  - 10-20 mg daily
- Adjunctive therapy
  - Thiazide
  - IHA → ACE-I, APA→ amlodipine

Obstructive Sleep Apnea

Obstructive Sleep Apnea

- OSA in RH: 71-85%
- Severity of apnea ≈ severity of hypertension
- Mechanism:
  - Hypoxia + ↑ R_{airway} → ↑ SNS outflow
- Screen: obesity, loud snoring, daytime sleepiness
- Response to CPAP variable
  - 5.5 hrs/night→↓ SBP_{amb}….. $14mm_{night}$ $9mm_{day}$

Prevalence of secondary causes of hypertension associated with resistant hypertension.



Pedrosa R P et al. Hypertension 2011;58:811-817

Effect of CPAP in Resistant HTN *

	CPAP (*n* = 29)		**Conventional Rx (n = 35)**	
	baseline	**Follow-up**	**baseline**	**Follow-up**
Day SBP	133.4	133	133	134
Day DBP	78.9	79	77.9	78.9
Night SBP	122.2	120.3	120.6	124.5
Night DBP	71.4	68.3	70.1	71.6

* All patients who completed follow-up

Lozano 2010
J Hypertension

Effect of CPAP in Resistant HTN **

	CPAP (*n* = 20)		Conventional Rx (n = 21)	
	baseline	**Follow-up**	**baseline**	**Follow-up**
Day SBP	140.7	134.4	140.6	140
Day DBP	82.4	78.8	82.1	82.4
Night SBP	128.2	122	129.6	129.1
Night DBP	74	68.5	75.5	74.8

** 24 hour BP < 125/80

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