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Medical Urology: Hypertension, Fluids and Electrolytes, Nephrology

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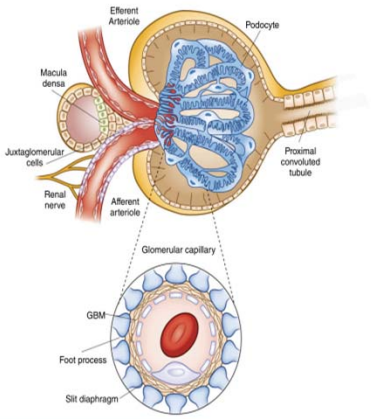
University of Minnesota

Outline

- GFR
- Solute transport and tubule function
- Disorders of water balance
- Acid base review
- Hypertension

Glomerular Structure

- Filter = glomerulus
- Endothelial cells
- Basement membrane
- Visceral epithelial cells
  = podocyte



Glomerular disease

Hematuria

Proteinuria

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Clin J Am Soc Nephrol 9: 1461–1469, 2014

Determinates of GFR

- Blood flow in the glomerulus
  – determined by afferent and efferent artery resistances
- Net ultrafiltration pressure across the glomerular capillary
  – Related to hydraulic and oncotic pressure

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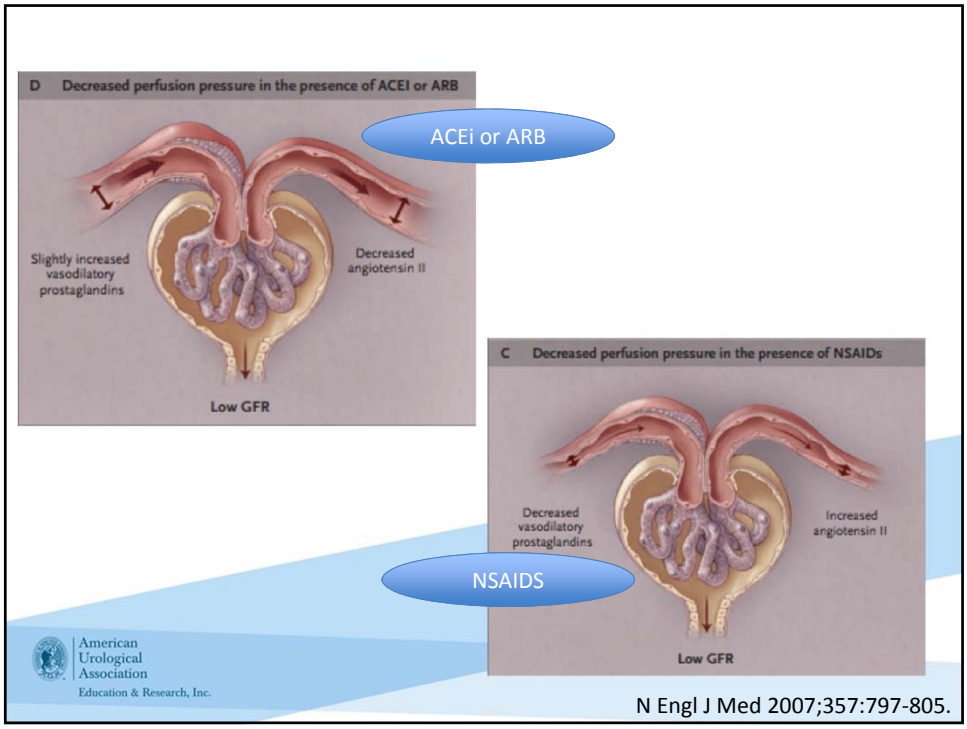

N Engl J Med 2007;357:797-805.

Estimate of GFR (eGFR)

- MDRD is the most common equation to estimate GFR
- Developed in patients with stable kidney disease
- Does not perform well in patients with normal renal function
  - Will under-estimate GFR
- Cannot use when creatinine is rising
  - i.e. in AKI with rising creatinine, eGFR is unreliable

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Case Examples

- 30 yo man, competitive body builder with large muscle mass
  - Creatinine is 2 mg/dL with eGFR 48 ml/min
  - What is GFR?
    - Iohexol based GFR >90 ml/min
- 70 yo man in ICU with septic shock. Creatinine went from 1 to 2 mg/dL in 24 hours. Urine output is 25 ml/24 hours
  - eGFR reported as 33
  - What is true GFR?
    - zero

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Diseases of the Glomerulus

Nephritic

- Hematuria
  - Red blood cell casts
  - Dysmorphic red blood cells
- Proteinuria
  - Usually 1-3 grams/24 hours
- Hypertension

Nephrotic

- Heavy proteinuria
  - >3.5 grams/24 hours
- Edema
- hypoalbuminemia

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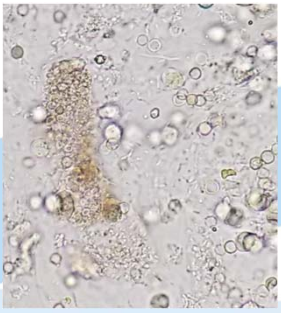
ARS Q1:

A 45 year old man with history of hepatitis C and tobacco use has microscopic hematuria. His creatinine is 1.3 mg/dL and urine protein is 1.5 gram in 24 hours. Which test is likely to aid in diagnosis?

a) Cystoscopy
b) Non-contrast CT scan
c) Kidney biopsy
d) Urine culture



RBC cast

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Answer: C

C. Kidney biopsy

- Nephritic and may have cryoglobulinemic MPGN related to hepatitis C
- Proteinuria is clue that this is glomerular process rather than lower urinary tract
- Non-contrast CT could assess for kidney stones but they are unlikely to cause proteinuria
- Unlikely UTI with this degree of proteinuria

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Key Points

- Altering renal hemodynamics impacts GFR
- Creatinine based estimated GFR formulas cannot be used if creatinine is not stable
- Hematuria + proteinuria suggests glomerular disease

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Solute and Water Transport

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Sodium

- 65% reabsorbed in proximal tubule
- 25% reabsorbed Ascending Limb of Henle
- Remainder reabsorbed in Distal Convoluted Tubule and Collecting Duct

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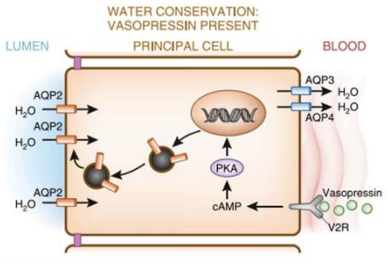
Water

- 65% reabsorbed in proximal tubule
- Fine tuning of hydration occurs in collecting duct
  - if water loading - 5% reabsorbed
  - if dehydrated - >24% reabsorbed

Desmopressin increases water reabsorption



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Clin J Am Soc Nephrol 10: 852–862, 2015

Tubular Transport of Substances Related to Kidney Stones

- Calcium
  - Majority is reabsorbed in proximal tubule
  - Reabsorbed via solute drag

Low salt diet → more sodium reabsorption → calcium is dragged from urinary space to blood

- Distal calcium channels regulated by PTH
  - High PTH and vitamin D – higher calcium reabsorption

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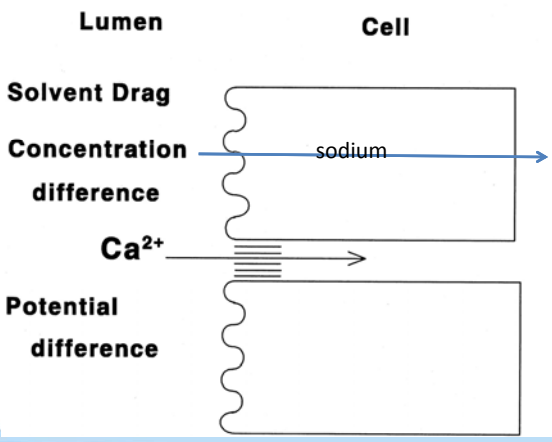
Calcium Reabsorption- Proximal Tubule



Low salt diet
higher calcium reabsorption

High salt diet
calcium remains in the urine

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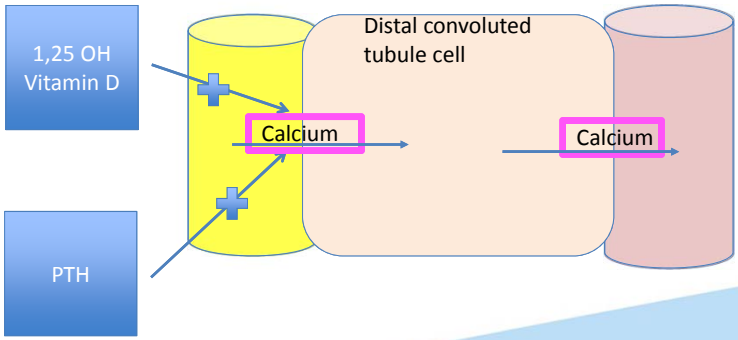
Frick K K , and Bushinsky D A JASN 2003;14:1082-1095

Calcium Reabsorption – Distal Convoluted Tubule



7-10% calcium reabsorbed in DCT

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Clin J Am Soc Nephrol 9: 2147–2163, 2014

ARS Q2:

A 48 year old obese man has recurrent kidney stones. 24 hour urine chemistry shows hypercalciuria and high urine sodium. In addition to recommending drinking 100 ounces fluid per day, what else will you advise?

a) Low calcium diet
b) Low salt diet
c) Hydrochlorothiazide
d) Furosemide

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Answer: B

B. Low salt diet

- High urinary sodium causes high urinary calcium
  - Calcium reabsorbed in proximal tubule via solute drag, it follows sodium reabsorption
- Low calcium diet is associated with increased risk for stone recurrence and does not lower urinary calcium
- Loop diuretics increase urine calcium
- Thiazide may reduce urine calcium but is not indicated if urine calcium can be reduced with low salt diet

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Tubular Transport of Substances Related to Kidney Stones

- Citrate
  - Reabsorbed in proximal tubule
  - Hypokalemia increases citrate reabsorption
  - ** thiazide diuretics cause hypokalemia which can result in low urinary citrate

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Hyponatremia

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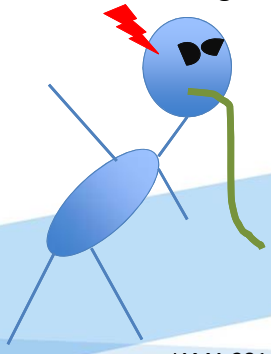
Hyponatremia=Water intoxication

Signs and Symptoms

- Mild decrease in serum sodium
  - neurologic symptoms, including gait instability, memory impairment, and cognitive decline
- sodium <125 meq/L
  - Headache, nausea, vomiting, seizures



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JAMA 281: 2299–2304, 1999

Clin J Am Soc Nephrol 10: 852–862, 2015

Age and Sex Associated with Different Sensitivities

- Children at higher risk for hypo-osmolar encephalopathy
- Majority of postoperative hyponatremia with fatal outcomes reported in women
  - especially postmenopausal women

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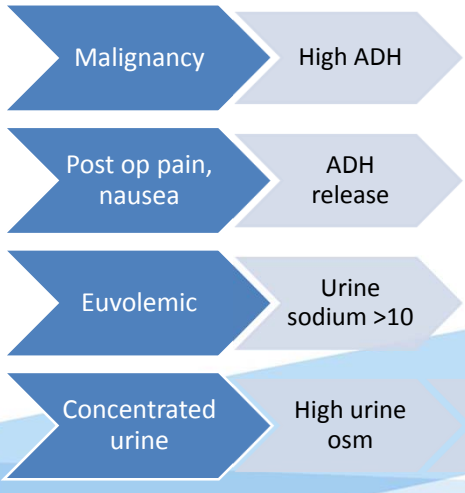
JAMA 281: 2299–2304, 1999

Clin J Am Soc Nephrol 10: 852–862, 2015

SIADH



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ARS Q3:

75 yo man with metastatic prostate cancer incidentally found to have sodium 125 on routine labs. He is admitted to hospital and noted to have fatigue but no other symptoms. Blood pressure is 120/70 without orthostasis. Urine osmolality is 550 mOsm/L, urine sodium is 40 meq/L. What is the treatment?

a) IV 3% saline
b) Fluid restriction
c) IV normal saline
d) Furosemide

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Answer: B

B. Fluid restriction

- He is not volume depleted, NS worsens hyponatremia in SIADH
- SIADH without symptoms
- Hypertonic saline not indicated
- Furosemide may be considered if cannot control hyponatremia with fluid restriction

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Obstructive Uropathy

Stage of obstruction	Afferent arteriole resistance	Glomerular capillary hydraulic pressure
1-2 hour unilateral	⇓	⇑
24 hour	⇑	⇓
After release	⇑	⇓

- Despite lack of direct glomerular damage, obstruction results in decrease in GFR
  - Due to increase pressure in tubules
  - alterations in renal hemodynamics

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Relief of Acute Obstruction

- Renal blood flow increases
  - Systemic natriuretic influences
    - Volume accumulation and natriuretic hormones
- Salt and water excretion 5-9 times normal after relief of obstruction
  - Natriuretic substances
  - Tubular cell injury
- Cannot concentrate nor dilute urine
- GFR remains low

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Post-Obstructive Diuresis Treatment

- Excessive volume replacement prolongs diuresis
- Volume or water replacement appropriate only when there is hypovolemia or hypernatremia
- Urine is isosthenuric
  - Replacement fluid: 0.45% saline at a rate less than urine output

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Metabolic Alkalosis

- Hypovolemic
  - Low urine chloride
  - Hypovolemic signals increase in aldosterone resulting in hydrogen secretion
  - Improves with volume expansion and potassium
- Hypervolemic
  - Glucocorticoid excess
  - Mineralocorticoid excess

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Type 1 RTA

- Most significant RTA to urologists
- Failure to excrete protons
- Non gap acidosis with hypokalemia
- High urine pH - hypocitraturia
- Calcium phosphate stones and nephrocalcinosis
- Tx potassium citrate

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Type 2 RTA

- Proximal tubule
- No hypocitraturia
- Unlikely to develop kidney stones

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Type 4 RTA

- More significant to internists
- Develops in setting of diabetes
- Hyporeninemic, hypoaldosterone
- Acidic urine with hyperkalemia and metabolic acidosis

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ARS Q4:

81 yo man post op day #1 after transurethral resection of bladder tumor has abdominal pain and the following labs:

- Sodium 129, Potassium 6, Bicarb 26, BUN 39, Creatinine 3.1 mg/dL (baseline 1), normal calcium and phosphorus

What is the cause of lab abnormalities?

a) Rhabdomyolysis
b) Acute tubular necrosis
c) Reabsorption of urine in peritoneal cavity
d) Low GFR

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Answer: C

C. Reabsorption of urine in peritoneal cavity

- Rhabdo unlikely in this short operation (more likely in longer operation and in obese patient)
- ATN or low GFR would not cause acute hyperkalemia in the absence of large potassium load

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Key Points

- Fine tuning of water balance occurs in collecting duct
  - Mediated by anti-diuretic hormone
    - Desmopressin
- Type 1 /distal RTA associated with calcium phosphate kidney stones
- Management of post obstructive diuresis includes hypotonic fluids at rate lower than urine output

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Hypertension - Definition

- Normal – BP < 120/80
- Pre-hypertension BP 120-139/80-89
- Hypertension BP >140/90
- Resistant hypertension
  - SBP >140 despite 3 medications, including a diuretic, at max dose

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Hypertension

- IDEALLY - Office BP should be measured according to American Heart Association guidelines
  - 3 blood pressures, 2 minutes apart with patient sitting quietly
  - This is used in hypertension trials
- This rarely occurs in typical clinic settings

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Blood Pressure Targets

- Generally target BP <140/90
  - In adults less than 60, initiate therapy for BP >140/90
- If no stroke or diabetes
- +/-chronic kidney disease
- Target <120 systolic (SPRINT trial)

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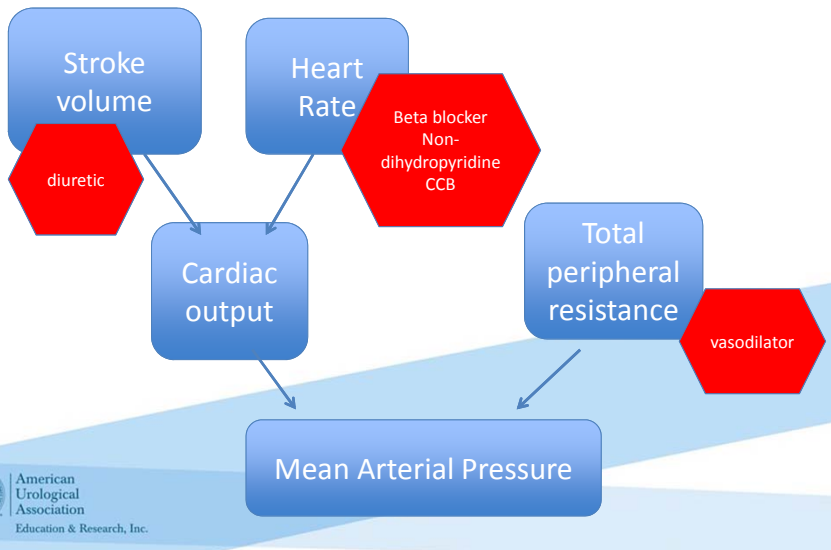
JAMA. 2014;311(5):507-520
NEJM 2015; 373 (22):

HTN



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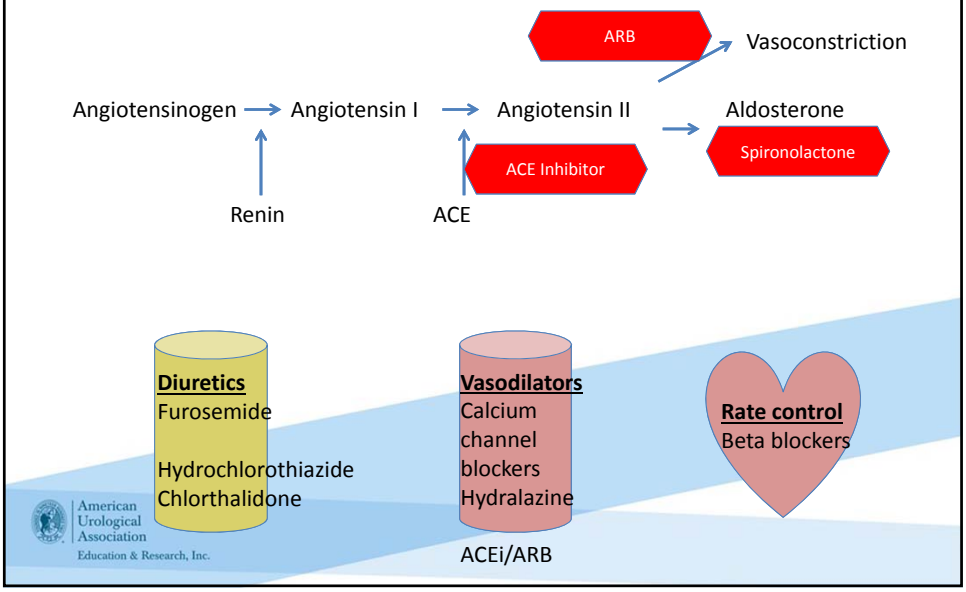
antiHTN Medication Review



BP Medications

- Thiazide (chlorthalidone, hydrochlorothiazide)
  - Hypokalemia, hyperglycemia, hypercalcemia, hypertriglyceridemia
- ACE inhibitor (lisinopril, enalapril, captopril)
  - Hemodynamic rise in creatinine, hyperkalemia
- Angiotensin receptor blocker (losartan, candesartan)
- Calcium channel blocker (amlodipine, diltiazem)
- Loop diuretic (furosemide)
- Beta blocker (metoprolol)
  - No benefit in absence of coronary artery disease

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Renal Artery Stenosis

- In unilateral renal artery stenosis
  - Renin is released
  - -> angiotensin II and aldosterone
  - -> contralateral kidney has natriuresis and maintains euvolemia
- In renal artery stenosis with solitary kidney
  - Renin is released
  - -> angiotensin II and aldosterone act to expand volume
  - -> no contralateral kidney to for natriuresis

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Atherosclerotic Renal Artery Stenosis

- Present 1-5% of people with hypertension
- Often in combination with coronary artery disease of peripheral artery disease
- Changes in renal blood flow seen with >70% renal artery lumen obstruction
- 10-20 mmHg pressure difference in aorta to post-stenotic renal artery results in increased renin

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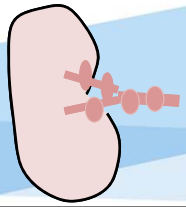
Derkx FH, Schalekamp MA. Renal artery stenosis and hypertension. Lancet 1994;344:237-9

Fibromuscular Dysplasia

- Medial fibroplasia – most common subtype
- Renal arteries in ~70% cases
- Cerebral arteries in ~25% cases
- Tends to affect women
- "beads on a string"
  - Serial intravascular webs with aneurysm in between



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Management – Renal Artery Stenosis

- Fibromuscular dysplasia (FMD)
  - General consensus is manage with angioplasty
    - Better control of BP
    - Avoid long term consequences of activated renin angiotensin aldosterone system
- Atherosclerotic renal artery stenosis (ARAS)
  - Manage medically
    - BP control with ACE/ARB and diuretic
    - Cholesterol control with statin

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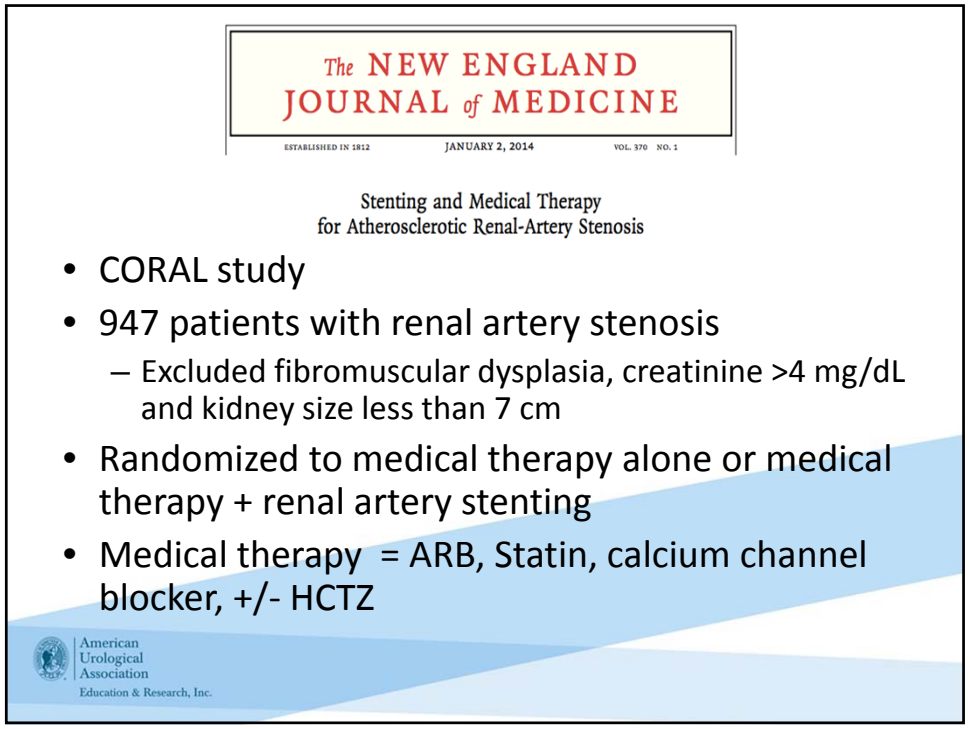

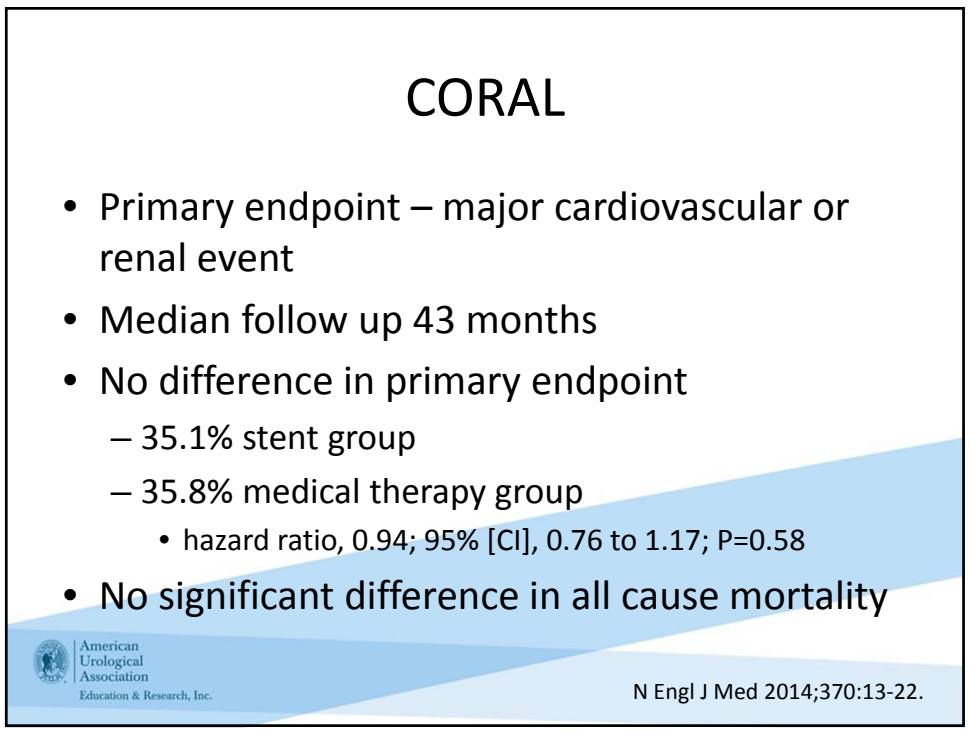

ARS Q5:

In a patient with 2 kidneys, unilateral renal artery stenosis, which medication should be added for renal protection and to get at the driving mechanism for HTN?

a) Lisinopril
b) Hydralazine
c) Metoprolol
d) Amlodipine

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Answer: A

A. Lisinopril

- High angiotensin II levels have negative impact on cardiovascular and renovascular systems
- OK if creatinine goes up by 30% (i.e. 1.3 to 1.7)
- Beta blockers cause fatigue and do not offer benefit
- Amlodipine and hydralazine are not renoprotective

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Bilateral Renal Artery Stenosis

- Management is expert opinion
- If no flash pulmonary edema, most would still use lisinopril
- Can expect and can permit hemodynamic rise in creatinine
  - Monitor closely

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Key Points

- Atherosclerotic renovascular disease is prevalent in patients with HTN and CKD
- CTA & MRA can aid in diagnosis
  - Risk of AKI with iodinated contrast and gadolinium associated with nephrogenic systemic fibrosis
- Duplex US is highly operator dependent
- Pursuing diagnosis may not be necessary as medical management is preferred over intervention

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Renal Denervation

- Physiologic basis:
  - Afferent artery has greatest innervation
  - Renal tubules and juxtaglomerular apparatus also innervated
- Procedure:
  - catheter-based radiofrequency denervation of the renal arteries
  - Less invasive compared to surgical denervation or nephrectomy

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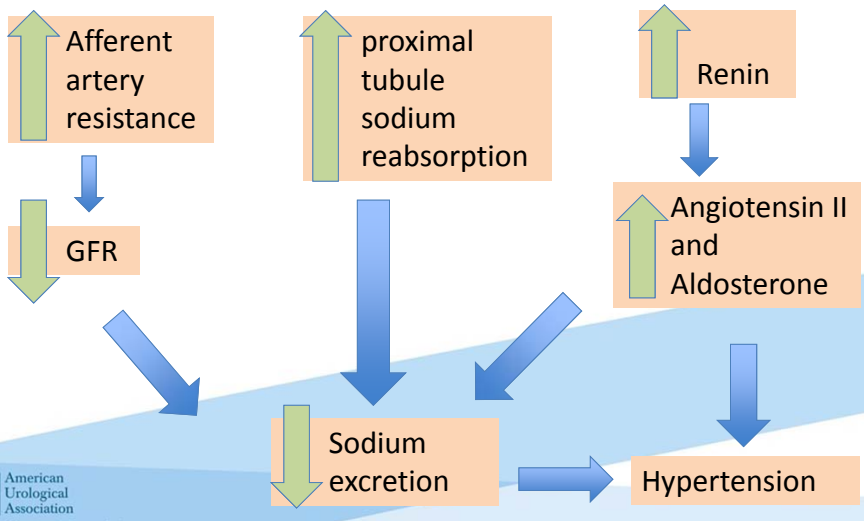
Am J Physiol Renal Physiol 309: F583–F594, 2015

Increased Renal Nerve Sympathetic Activity



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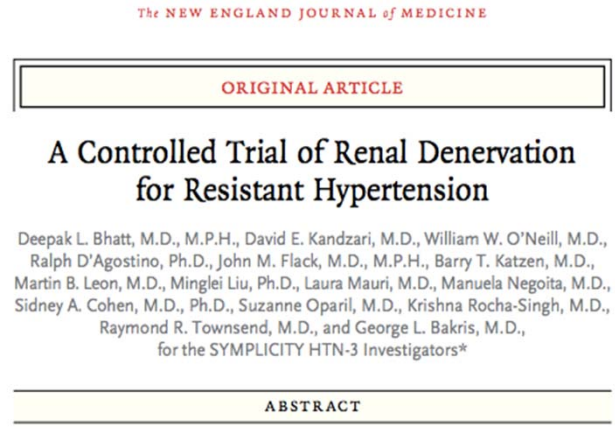
SYMPLICITY 3



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O'Neill, M.D., Ralph D'Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D., Martin B. Leon, M.D., Minglei Liu, Ph.D., Laura Mauri, M.D., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., and George L. Bakris, M.D., for the SYMPLICITY HTN-3 Investigators*

ABSTRACT

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N Engl J Med 2014;370:1393-401.

SYMPLICITY 3

- Randomized 2:1 to renal denervation vs sham procedure (renal angiography alone)
- Both groups had a decrease in both office blood pressure and 24 hour ambulatory blood pressure
- No benefit to renal denervation based on SYMPLICITY 3 results

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N Engl J Med 2014;370:1393-401.

Key Points

- BP goal 140/90 in patients with diabetes +/- CKD and age <60
- BP goal 120/80 consider in absence of diabetes or stroke history
- No benefit to stenting in renal artery stenosis (unless flash pulmonary edema)
- Not enough evidence to support FDA approval of system for renal denervation

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