

Michael Press, DO

- **Nephrologists** in Lawrenceville, GA
- Practicing for the last 12 years

- **Board Certified** in
- Internal Medicine
- Nephrology- Subspecialty

Medical School
Nova Southeastern

- **Hosp Affiliations**

- Eastside Medical
- Gwinnett Medical
- Emory John's Creek

Residency/Fellowship
Philadelphia, PA



Heart and Kidneys: A Love/Hate Relationship

Michael Press, D.O.

Georgia Nephrology

June 30, 2018

No Financial Relationships to disclose

Kidneys and Heart: A Love/Hate Relationship

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Heart and Kidneys: A Love Story

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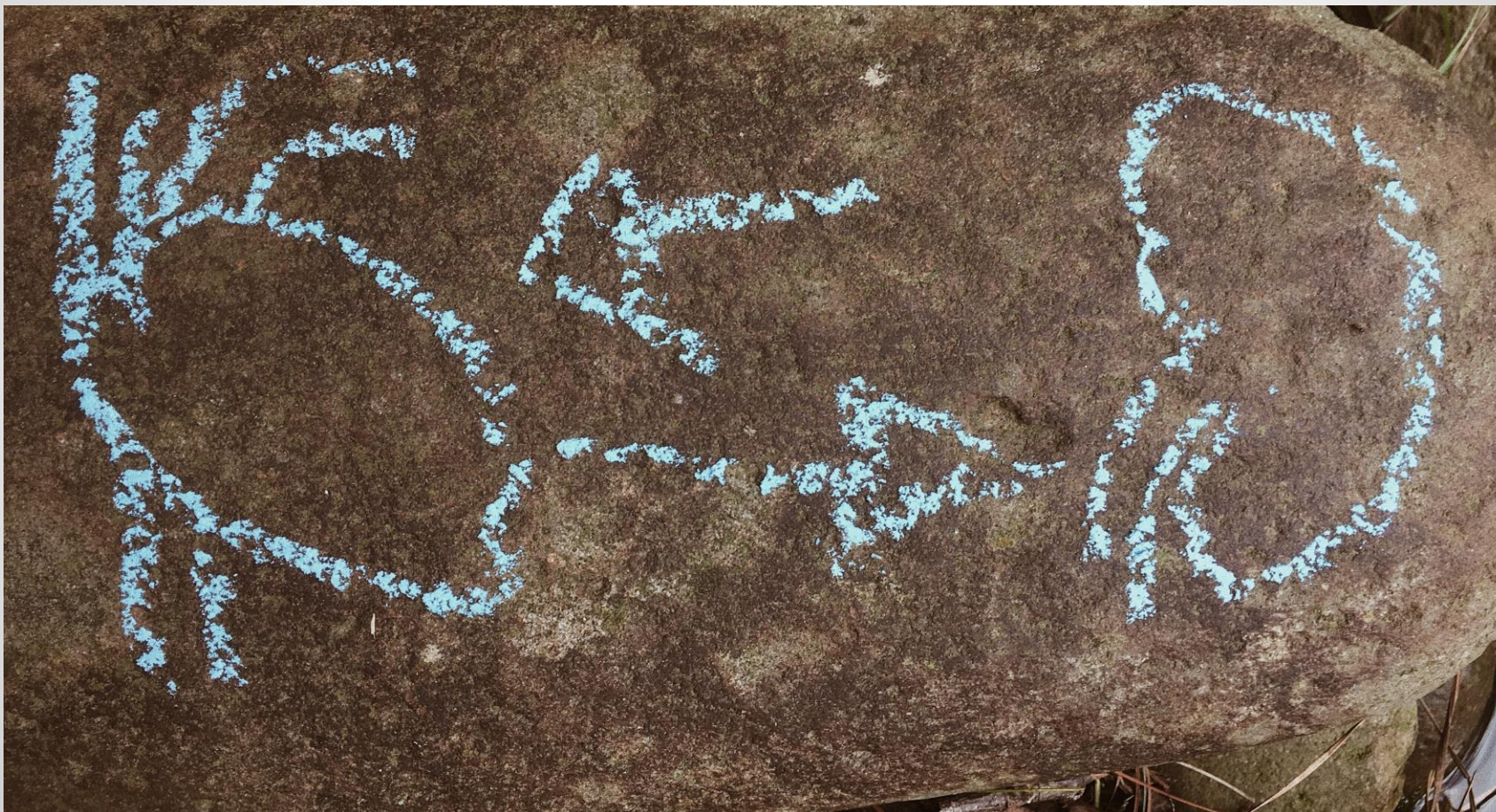
No Financial Relationships to disclose

Outline

- Cardiorenal Syndrome Basics
- Diuretic Classes and Mechanisms of Diuretic Resistance
- Renin Angiotensin System and more prominent side effects of agents
- Contrast Nephropathy
- Atheroembolic Renal Disease
- Indications for Dialysis in Hospitalized Patients

Seminal Moments in Cardiorenal Syndrome History

310 B.C.



2003



2006



☆ **Laurence Lesser**

From: mitchell

To: p...@aol.com

After u reduced his lasix he went into chf. Fyi but i am not keeping score. Lanny

Sent from my iPhone

2018





Cardiorenal Syndrome

- Definition
- Types
- Clinical Implications
- Mechanisms

Cardiorenal Syndrome (CRS) General Definition:

A pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ

CRS Type I (Acute Cardiorenal Syndrome)

Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury

CRS Type II (Chronic Cardiorenal Syndrome)

Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease

CRS Type III (Acute Renocardiac Syndrome)

Abrupt worsening of renal function (e.g. acute kidney ischaemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)

CRS Type IV (Chronic Renocardiac Syndrome)

Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events

CRS Type V (Secondary Cardiorenal Syndrome)

Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

[Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. J Am Coll Cardiol 2008; 52:1527.](#)

Cardiorenal: Clinical Implications

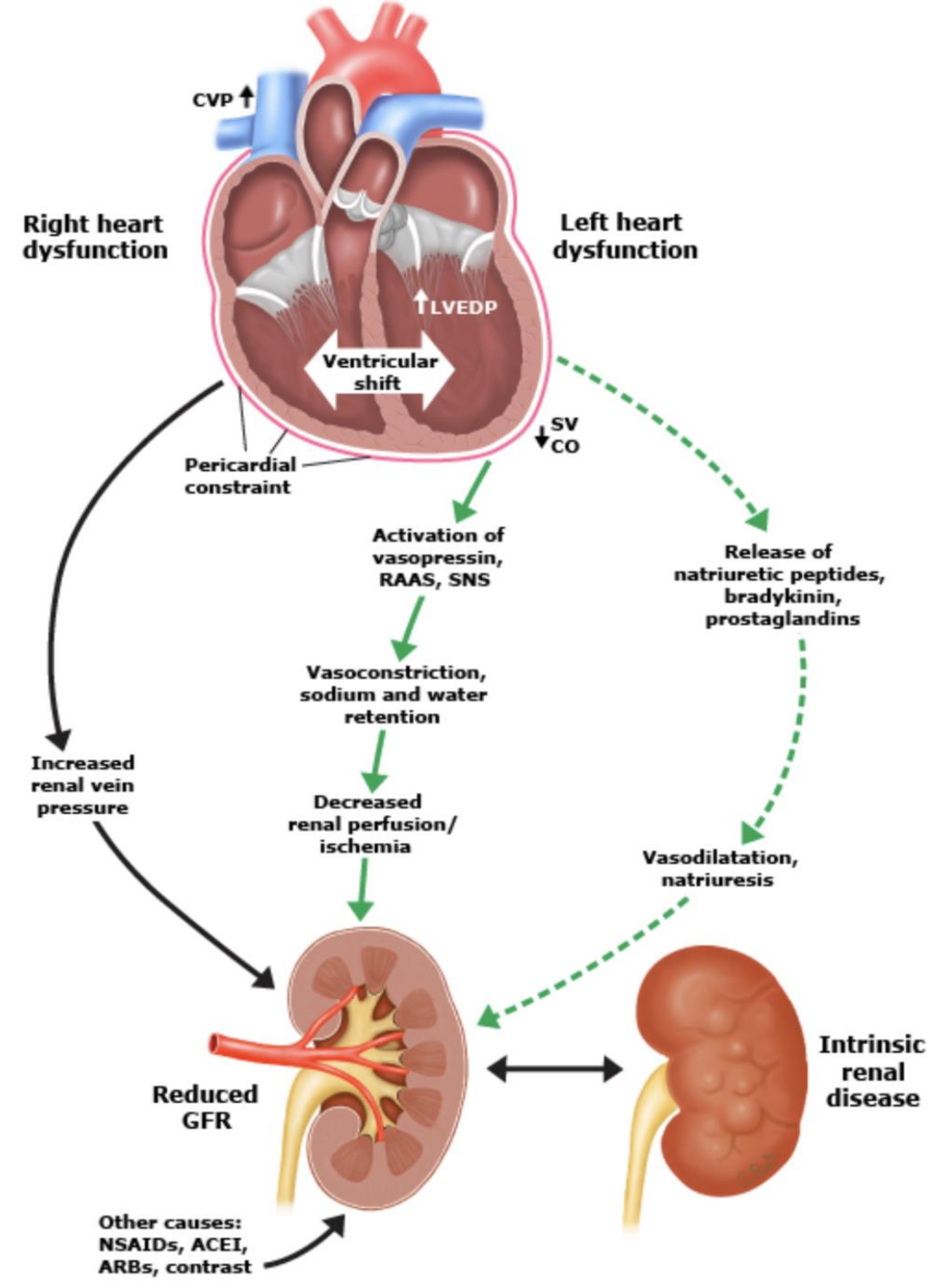
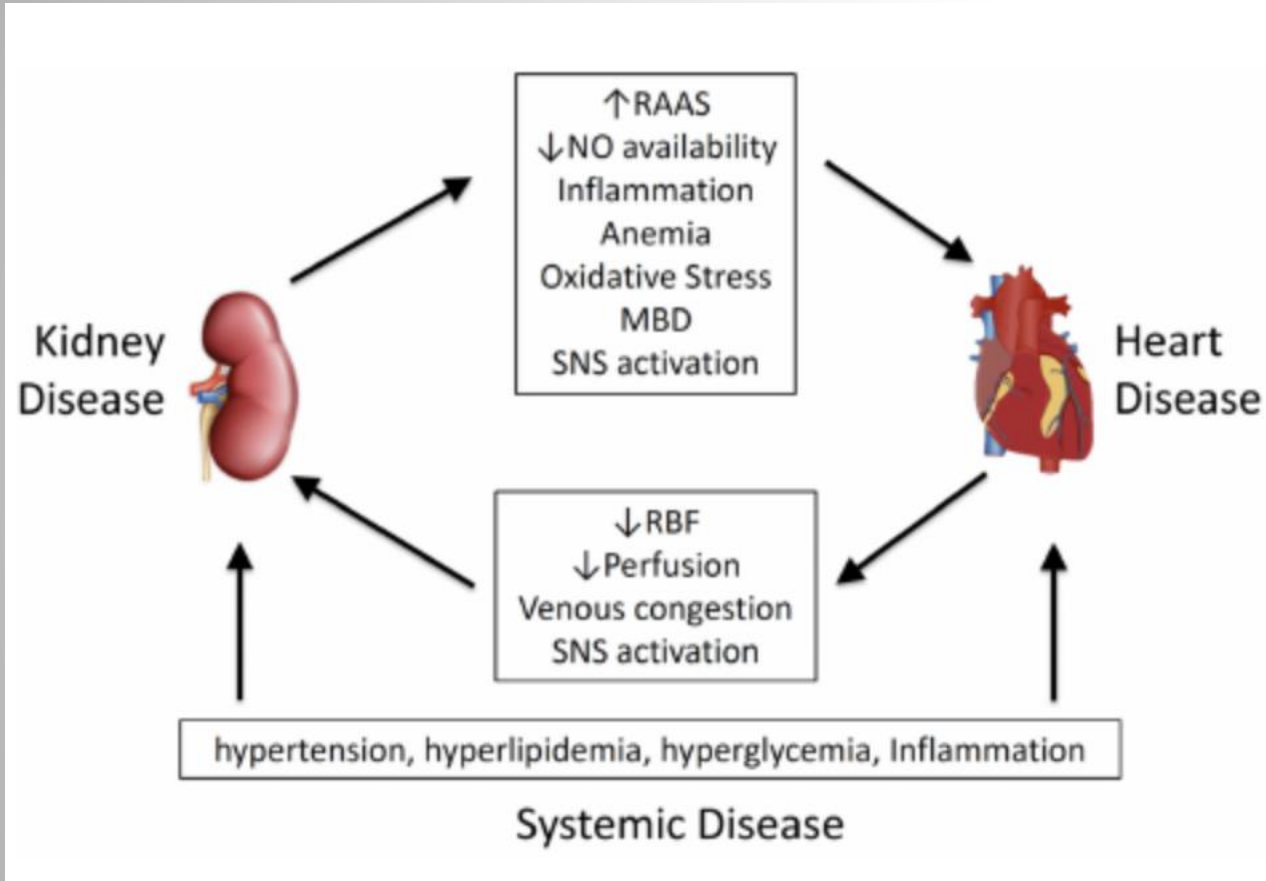
- Mortality is increased in patients with heart failure who have a reduced GFR ¹
- CKD patients are at increased risk of both ASCVD and CHF. ^{2 3}
- 30-60% of patients with CHF have CKD 3/4. ⁴
- CV disease is responsible for up to 50% of deaths in CKD stage 5. ^{2 3}

• ¹Smith GL, Lichtman JH, Bracken MB, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am. Coll Cardiol 2006; 47:1987.

• ²United States Renal Data System: Excerpts from the USRDS 2007 annual data report: atlas of end-stage renal disease in the United States. Minneapolis, MN 2007.

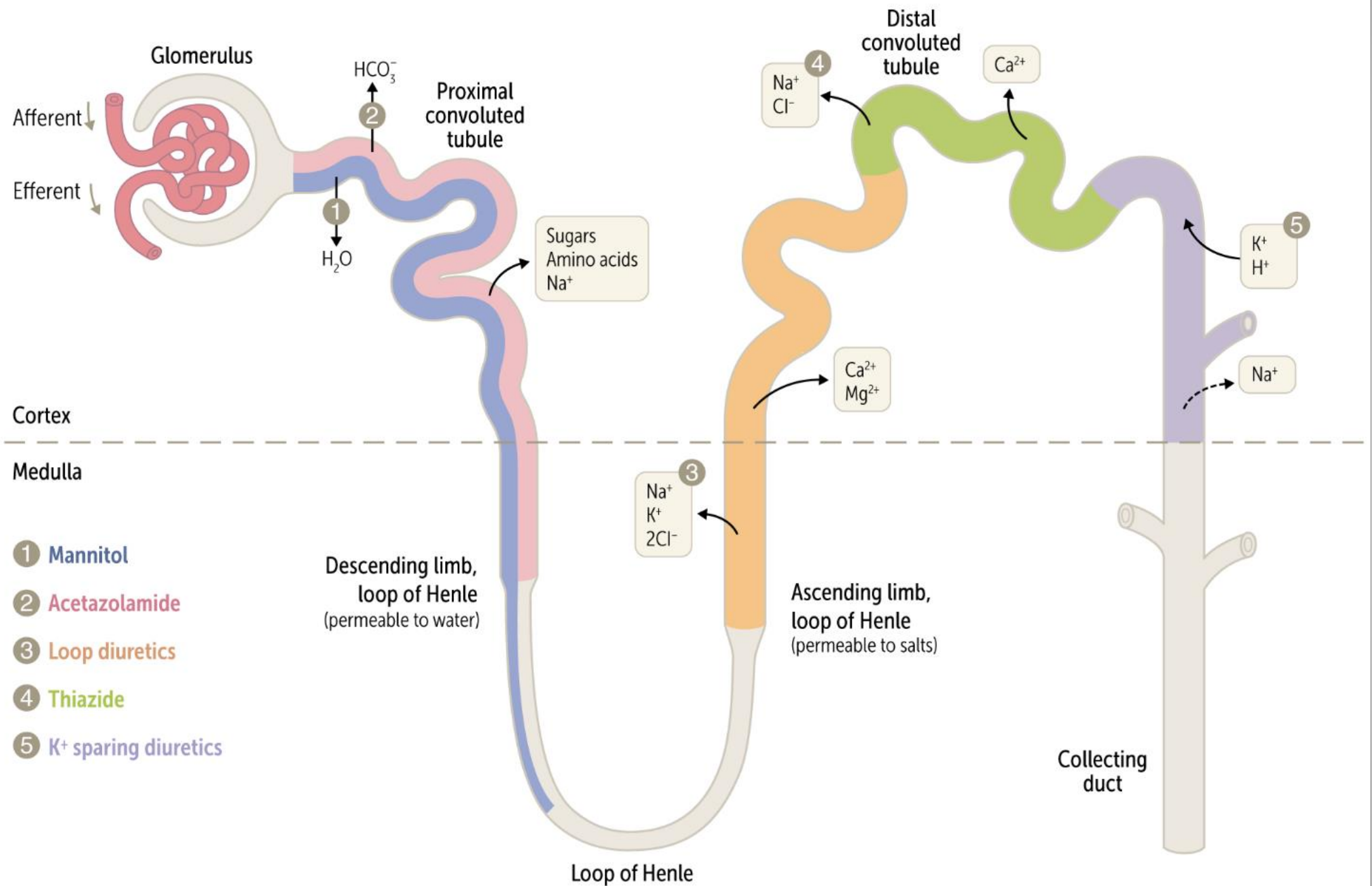
• ³Coresh J, Astor BC, Greene T, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003; 41:1.

• ⁴Ezekowitz J, McAlister FA, Humphries KH, et al. The association among renal insufficiency, pharmacotherapy, and outcomes in 6,427 patients with heart failure and coronary artery disease. J Am Coll Cardiol 2004; 44:1587.



Diuretic Classes

- Acetazolamide and Mannitol
- Loop Diuretics
- Thiazide or Thiazide-Like Diuretics
- Potassium-Sparing Diuretics
- Vasopressin antagonists?

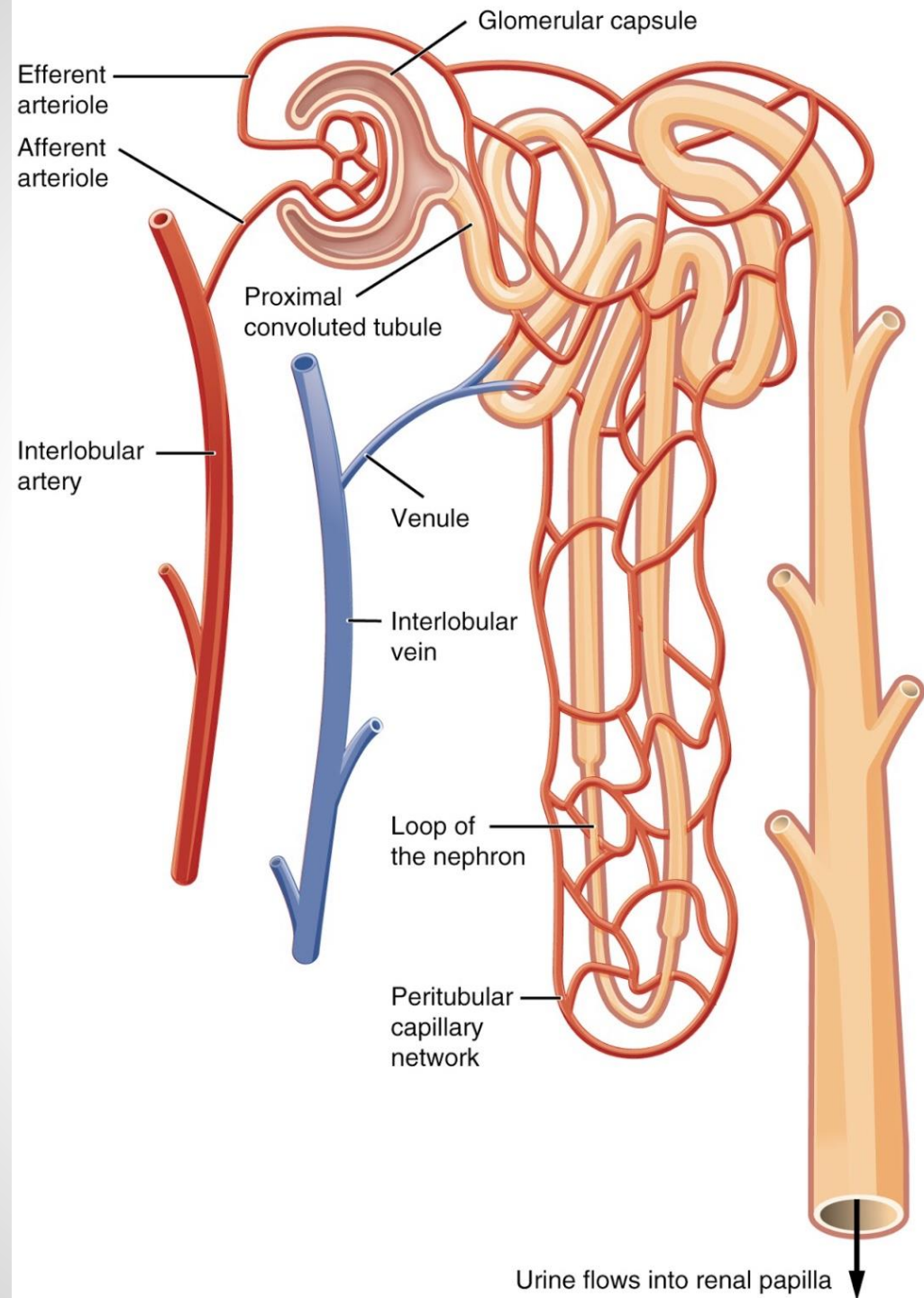


Acetazolamide and Mannitol

- Acetazolamide (Diamox)
 - Site of action: Proximal Tubule.
 - Proximal Tubule handles 60-65% of filtered sodium load but diuresis not as profound because water is reabsorbed along other points in the nephron.
 - Mechanism of action: Inhibits Carbonic Anhydrase.
 - Results in bicarbonate wasting.
 - Useful in patients who are prone to metabolic alkalosis from volume contraction (patients on multiple diuretics or patients with COPD).
 - Typical dose is 250 or 500 mg IV or PO. Can give Q12 but consider limiting doses so patients don't end up acidotic.
- Mannitol
 - Site of action: Proximal Tubule and Loop.
 - Mechanism of action: Non-reabsorbable sugar alcohol that causes sodium and water diuresis.
 - Generally not practical for treatment of edematous states because the osmotic load initially can result in fluid retention and worsening pulmonary congestion.

Loop Diuretics

- Sulfonamide Loops
 - Furosemide (Lasix)
 - Bumetanide (Bumex)
 - Torsemide (Demadex)
- Non-Sulfonamide Loops
 - Ethacrynic Acid (Edecrin)
 - More ototoxic than the others, limits use.
 - Relatively insoluble and difficult to give IV.
- Minimal evidence to suggest that patients who have allergies to sulfa antibiotics will be allergic to other sulfa drugs, therefore, it is expected that patients with sulfa antibiotic allergies will be able to tolerate sulfa-based diuretics.
- Site of action: Thick Ascending Limb of Loop of Henle
- Mechanism of action: Inhibition of the Na-K-2 Cl co-transporter.
- Highly protein-bound (enter the urinary space by tubular secretion in the proximal tubule, not glomerular filtration)
- Higher doses needed with worsening renal function
- Dose response phenomenon
 - Little dose-no effect
 - Higher dose-progressive diuresis
 - Maximum effective dose-no further dose increase will enhance diuresis



Relative Potency of Loops

- All loops will produce same diuretic effect at equipotent doses
- PO: Bumex 1 mg=Demadex 20 mg=Lasix 40
- Greater bioavailability and absorption with Bumex and Torsemide such that IV:PO is 1:1
- Bioavailability of PO only 50% therefore Lasix IV:PO is 1:2
- Demadex:Lasix 1:2, however, in later CKD stages it is more 1:1.
- Demadex has a longer half-life than Bumex or Lasix.
- Rationale for using IV over PO in heart failure patients
 - Decreased intestinal perfusion and/or mucosal edema slow drug delivery to the kidney
- When dosing loops in a patient with normal GFR, greater doses are often needed for CHF or nephrotic syndrome compared to cirrhosis.
 - Variety of reasons
 - Reduced renal perfusion
 - Diminished proximal secretion due to variety of reasons
 - Enhanced activity of sodium-retaining forces.
 - Binding of diuretic in urinary space by protein and hypoalbuminemia in nephrotic syndrome and competing anions in renal failure
 - Reduced cardiac output (CHF)
 - Renal Vasoconstriction (cirrhosis)

IV Loop Treatment in Heart Failure-Maximal Effective Doses ^{1 2}

- Normal GFR
 - Bumex 1 mg, Demadex 20 mg or Lasix 40 mg
- Moderate CKD (GFR 30-59)
 - Bumex 2-3 mg, Demadex 20-50 mg or Lasix 80 mg
- Severe CKD (GFR 15-29)
 - Bumex 8-10 mg, Demadex 50-100 mg or Lasix 200 mg

- 1Brater DC. Diuretic therapy. N. Engl J Med 1998; 339:387.
- 2Brater DC, Voelker JR. Use of diuretics in patients with renal disease. In: Pharmacotherapy of Renal Disease and Hypertension (Contemporary Issues in Nephrology), Bennett WM, McCarron DA (Eds), Churchill Livingstone, New York 1987. Vol 17.

Thiazide-Like or Thiazide-Type

- Site of action: Distal Convoluted Tubule
- Mechanism of action: Inhibition of the Na-Cl co—transporter
- Examples: Metolazone, Chlorthalidone and HCTZ
- Beneficial in the treatment of hypertension.
- Diuretic effect less profound compared to loops (only result in loss of 3-5% of filtered sodium).
 - A good adjunct to a patients being managed on a loop.

Potassium-Sparing Diuretics

- Site of action: Principal Cells of Cortical Collecting Duct
- Mechanism of action: Inhibition of the Epithelial Sodium Channel (Amiloride, Triamterene) or the mineralocorticoid receptor (Spironolactone, Eplerenone).
- Weak Diuretic Effect (responsible for excretion of 1-2% of filtered sodium load).
 - Good adjunct for patients already on a loop or thiazide diuretic
- Spironolactone
 - Less expensive, more side effects (gynecomastia, abnormal menses, ED, decreased libido)
- Eplerenone
 - More expensive but less side effects as it has greater specificity for the mineralocorticoid receptor.

Vasopressin Antagonists

- Examples:
 - Tolvaptan (Samsca)
 - Conivaptan (Vaprisol)
- Mechanism of action: Inhibition of aquaporins (V2 ADH receptors)
- Inhibit water reabsorption resulting in water diuresis.
- Should only really be used in overloaded patients who are hyponatremic.

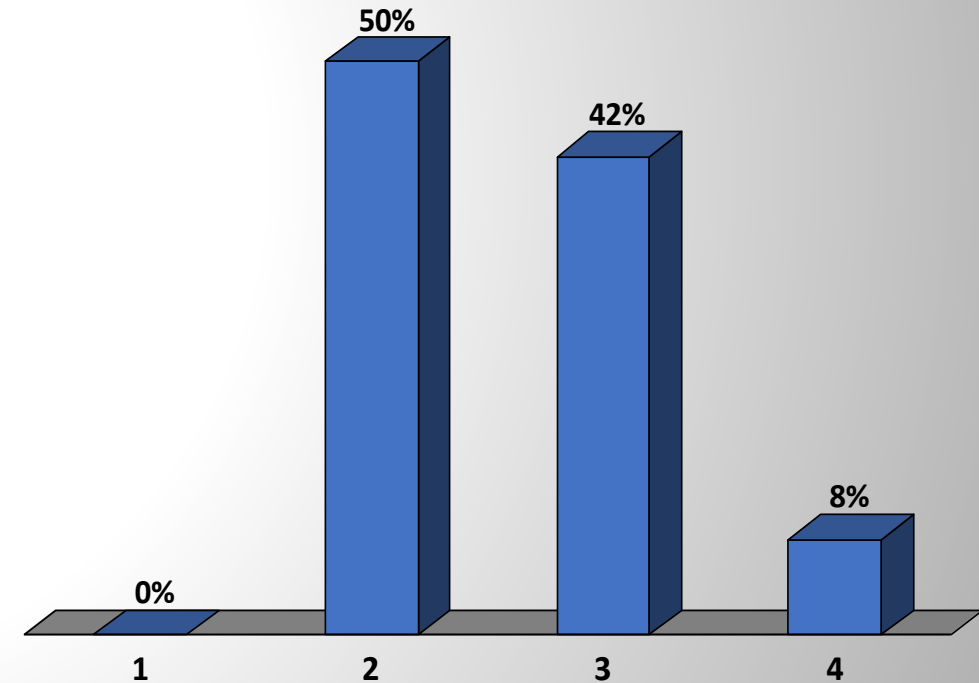
Notable Side Effects of Diuretics

- Volume Depletion
- Electrolyte Derangement
- Alkalosis
- Ototoxicity with loop diuretics
 - Deafness may be permanent but primarily occurs with high-dose IV therapy (Lasix doses above 240 mg/hr) or lower doses in patients on Aminoglycosides.
- Hypersensitivity (discussed in loop section)

The pattern of injury most commonly seen in cardiorenal syndrome is characterized by:

1. An abnormal renal ultrasound
2. Active urine sediment with numerous granular casts and, often, proteinuria.
3. Bland urine sediment, low urine sodium and high urine osmolality.
4. Active urine sediment showing WBC casts.

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 - c) Bland urine sediment, low urine sodium and high urine osmolality.
 - d) Active urine sediment showing WBC casts.

Evaluating Renal Function in the Cardiorenal Patient

- Acute Kidney Injury (AKI) associated with cardiorenal syndrome typically shows a hemodynamic pattern of injury compatible with pre-renal azotemia (decreased blood flow to the kidney, not a problem with the kidney itself).
- Tools to differentiate between pre-renal azotemia and intrinsic kidney disease include a UA, BMP, urine lytes, osmolality and creatinine.
- Pre-renal azotemia usually noted by a BUN:Cr ratio that is above 20:1.
- Urine is often bland (negative dipstick and no cellular elements aside from a few hyaline casts) and often concentrated (elevated urine specific gravity, urine osmolality, urine creatinine).

Evaluating Renal Function in the Cardiorenal Patient

- Measurement of the urine sodium concentration or calculation of FeNa
- Fractional Excretion of Sodium (FENa)

$$\text{FENa} = \frac{\text{Urine [Na]}}{\text{Plasma [Na]}} \times \frac{\text{Plasma [Cr]}}{\text{Urine [Cr]}} \times 100$$

<1% suggests Pre-renal

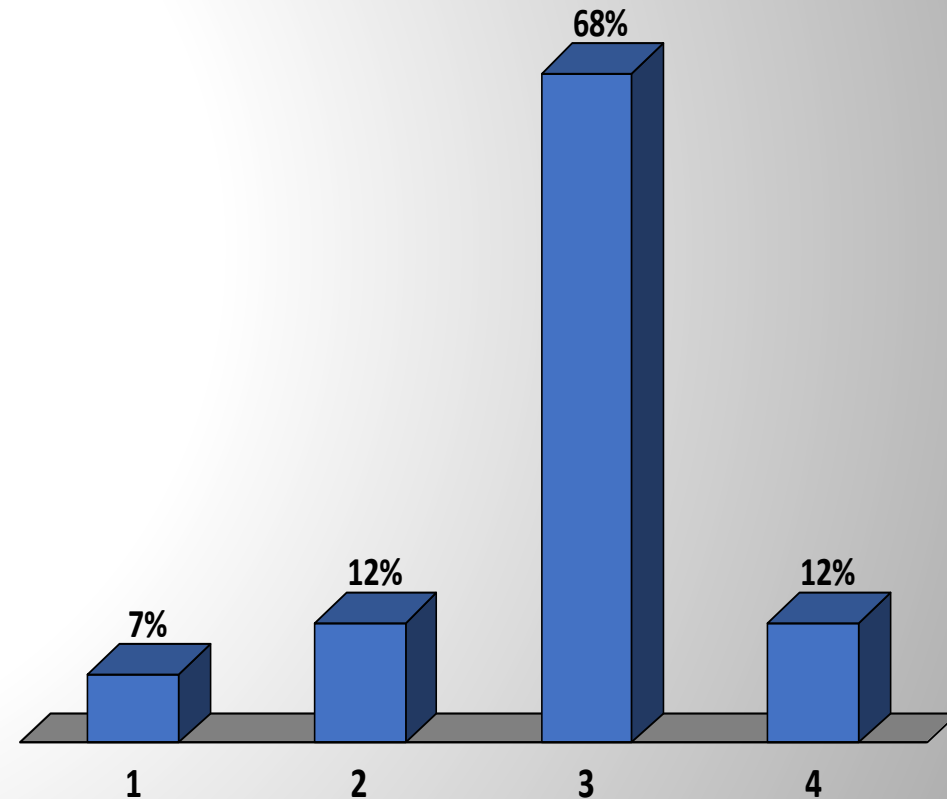
- Pre-renal azotemia can be dry (dehydration, diuretics) or wet (CHF), so clinical history and physical exam are important.
 - BUN/Cr ratio should not deter decongestive or diuretic therapies if evidence of clinical congestion is present.

Clinical and Laboratory Variables in the Differential Diagnosis Between Prerenal and Renal AKI

	Prerenal	Renal
History	GI, urinary, skin volume loss, blood loss or third spacing	Drugs or toxin exposure, hemodynamic change
Clinical presentation	Hypotension or volume depletion	No specific symptoms or signs
Laboratory studies		
BUN/S _{Cr}	>20	<20
Sediment	Normal to few casts	"Muddy brown" casts
U _{osm} (mmol/kg)	>500	<350
Proteinuria	None to trace	Mild to moderate
U _{Na} (mmol/l)	<20	>40
FE _{Na} (%)	<1	>1
FE _{Urea} (%)	<35	>35
U _{Cr} /S _{Cr}	<20	>40
Novel biomarkers	None	KIM-1, cystatin C, NGAL, CYR61, others

Which of the following is true regarding pre-renal azotemia?

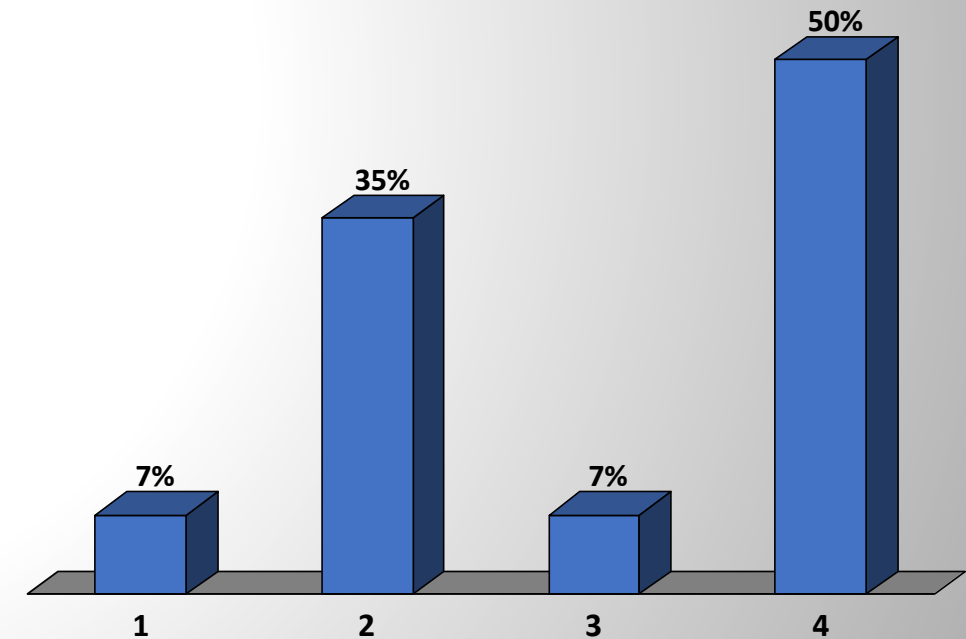
1. BUN to creatinine ratio is typically 10-15:1.
2. Characterized by a high urine sodium, low urine osmolality and numerous granular casts.
3. Can be seen in both volume-depleted and volume-overloaded patients.
4. It is the form of acute kidney injury least likely to be associated with the cardiorenal syndrome.



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All of the following are mechanisms which are helpful in overcoming diuretic resistance except

1. Dietary limitation of sodium
2. Changing posture to a supine position
3. Using more than one class of diuretic to enhance response
4. Using lower dose, but greater frequency, in a patient with CHF, cirrhosis or nephrotic syndrome



- All of the following are mechanisms which are helpful in overcoming diuretic resistance except
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Mechanisms of Diuretic Resistance

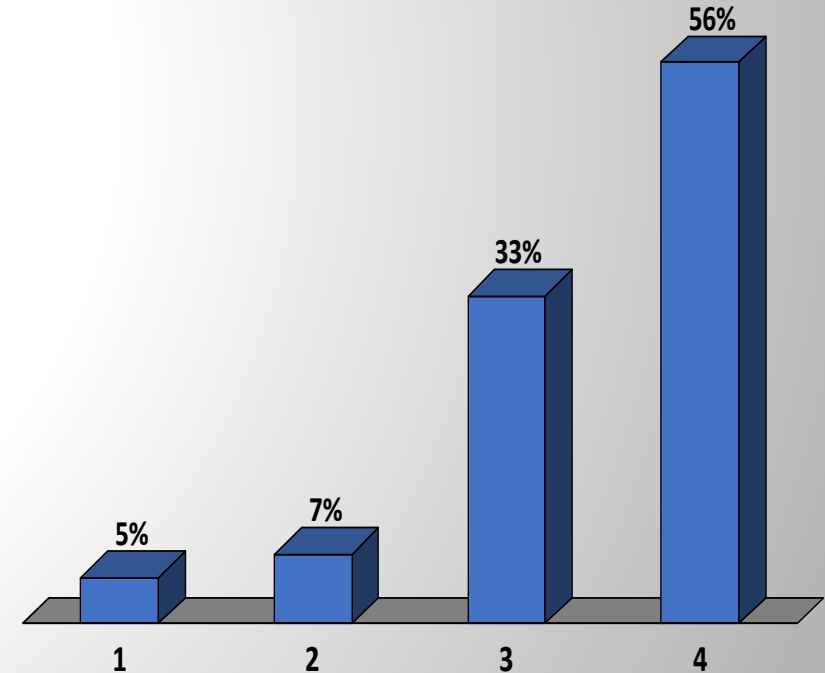
- Salt intake too high
 - High salt intake increases post-diuretic sodium absorption.
- Maximum effective dose not reached
- Compensatory reabsorption of sodium at other points in the nephron or at other points in a 24 hour period.
- Bioavailability not being considered
- Posture ¹
- No response to oral formulation
- No response to IV bolus therapy
- No response to infusion
- Hypoalbuminemia?

• ¹Ring-Larsen H, Henriksen JH, Wilken C, et al. Diuretic treatment in decompensated cirrhosis and congestive heart failure; effect of posture. Br Med J (Clin Res Ed) 1986; 292:1351.

Which of the following is true regarding intravenous diuretic therapy?

1. Bolus dosing associated with lower risk of ototoxicity
2. Infusion associated with lower risk of hypokalema
3. Efficacy of infusion similar to that of bolus in terms of diuretic response
4. Provides a similar diuretic response to ultrafiltration, however, ultrafiltration associated with better preservation of renal function at 96 hours and a lower risk of adverse events.

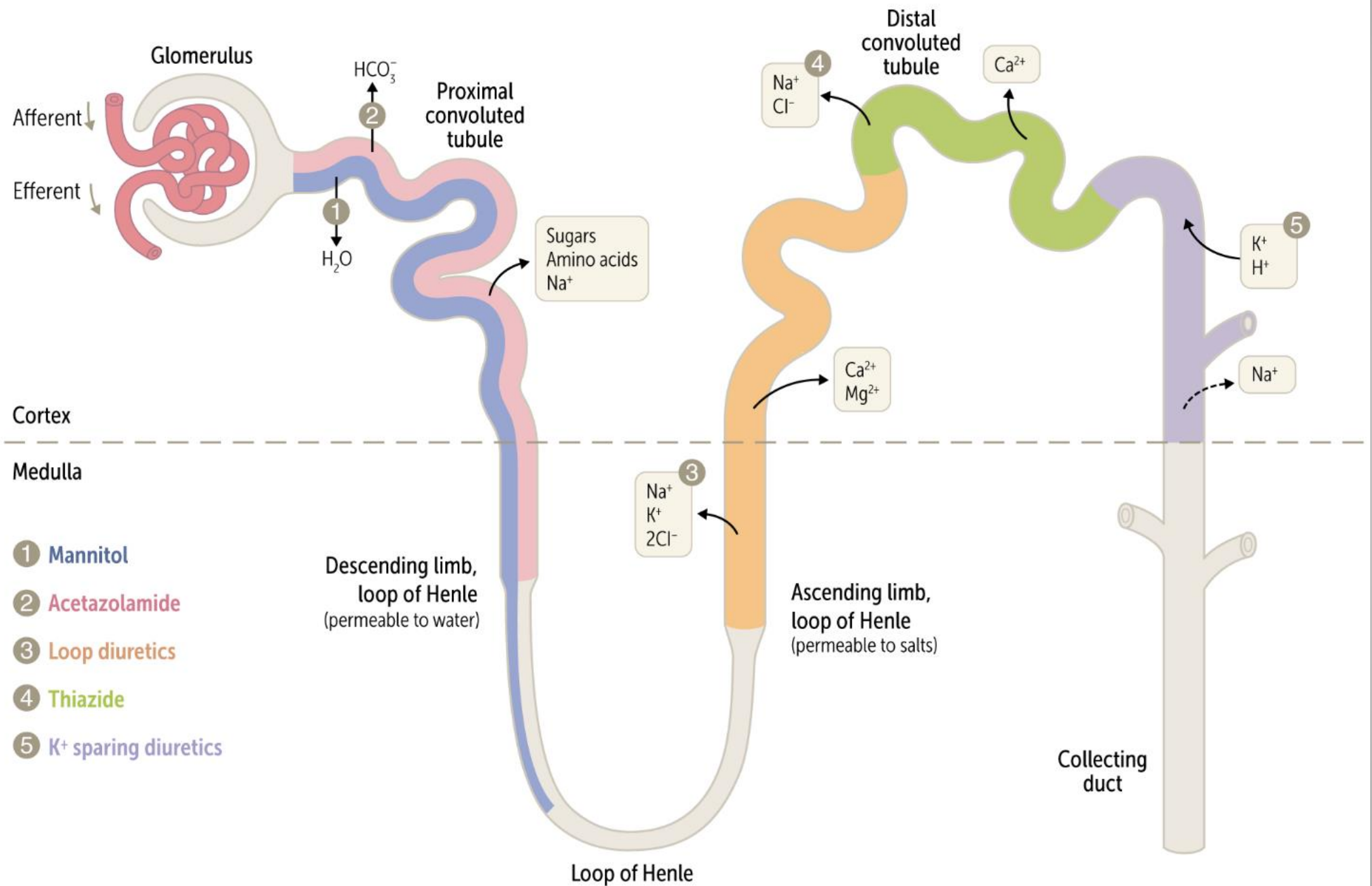
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- Which of the following is true intravenous diuretic therapy?
 - a) Bolus dosing associated with lower risk of ototoxicity
 - b) Infusion associated with lower risk of hypokalema
 - c) Efficacy of infusion similar to that of bolus in terms of diuretic response
 - d) Provides a similar diuretic response to ultrafiltration, however, ultrafiltration associated with better preservation of renal function at 96 hours and a lower risk of adverse events.

Overcoming Diuretic Resistance

- Encourage limitation of dietary sodium
 - Check 24 hour urine to exclude non-compliance with dietary sodium
 - Greater than 100 meq/d (>2.3 grams) indicates non-compliance.
- Titrate to achieve maximum effective dose
 - Find the dose-response threshold by increasing the diuretic dose, not the frequency.
 - If a patient does not respond to a particular dose, repeating that same dose will not help (same for IV diuresis).
- Compensatory reabsorption of sodium at other points in the nephron or at other points in a 24 hour period.
 - If response partial but inadequate, increase frequency of dosing.
 - Block nephron in multiple sites or consider increased dose frequency
 - The distal tubule reabsorbs 75-80% of the sodium delivered out of the loop of Henle, therefore, consider adding a thiazide
 - K-sparing is more helpful in curtailing potassium losses than it is in inducing an effective diuresis.
 - Stagger diuretic doses only if giving one PO and the other IV (give PO thiazides 2-5 hours prior as peak activity is 4-6 hours post-ingestion).



Overcoming Diuretic Resistance

- Bioavailability not being considered
 - If not responsive to maximally effective oral furosemide dose, try torsemide.
- Consider effect of posture on diuretic response
 - Supine position in hospitalized patients may enhance diuretic response.
- Consider IV if significant edema/CHF present and not responding to PO formulation
 - Change back to PO is reversible once cardiac function improves, intestinal edema decreases
- Consider infusion if not responding to IV boluses
- If no response to infusion, consider ultrafiltration.

Overcoming Diuretic Resistance

- Bolus Dosing versus Continuous Infusion¹
 - Bolus associated with greater likelihood of developing ototoxicity
 - Efficacy similar between the two
 - Before starting an infusion, give a test bolus dose to ensure the patient will respond
 - Bolus therapy results in a higher initial serum concentration and a higher initial rate of urinary diuretic excretion.
 - If renal function normal/near normal, and respond to a bolus
 - Start Lasix 5, if no response go to 10.
 - If severe kidney impairment (GFR below 30)
 - Start Lasix 20, if no response go to 40.

• ¹Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011; 364:797.

Overcoming Diuretic Resistance

- Slow continuous ultrafiltration (SCUF) — SCUF is used to treat isolated fluid overload
 - SCUF can safely remove up to 8 L of fluid per day. Neither replacement fluid nor dialysate fluid is used.
 - Convective solute loss is limited since the ultrafiltration rate is low compared with CVVH. There is no diffusive solute loss since dialysate fluid is not used.
 - The blood flow is generally 100 to 200 mL/min and the ultrafiltration rate 2 to 8 mL/min.
- Diuretics versus Ultrafiltration¹
 - CARRESS-HF, 188 patients with ADHF, worsened renal function (defined as an increase in the serum creatinine level of at least 0.3 mg/dL), and persistent congestion were randomly assigned to either stepped pharmacology therapy or ultrafiltration. The stepped pharmacologic care algorithm included bolus plus high doses of continuous infusion loop diuretic, the addition of metolazone, and selective use of inotrope or vasodilator therapy. The primary end point was the bivariate change in the serum creatinine level and body weight from baseline to 96 hours after enrollment.
 - Ultrafiltration was inferior to pharmacologic therapy with respect to the primary end point due to increase in serum creatinine in the ultrafiltration group in contrast to a fall in mean serum creatinine in the pharmacologic therapy group ($+0.23 \pm 0.70$ mg/dL versus -0.04 ± 0.53 mg/dL). There was no significant difference in weight loss at 96 hours between the ultrafiltration and pharmacologic therapy groups (5.7 ± 3.9 kg and 5.5 ± 5.1 kg).
 - A higher percentage of patients in the ultrafiltration group had serious adverse events (eg, HF, renal failure, anemia or thrombocytopenia, electrolyte disorder, hemorrhage, pneumonia, sepsis; 72 versus 57 percent).
 - *Thus, while ultrafiltration was an effective method for fluid volume removal, providing similar amounts of weight loss to stepped pharmacologic therapy, it was inferior to stepped pharmacologic therapy for preservation of renal function at 96 hours and was associated with a higher rate of adverse events.*

• ¹Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012; 367:2296.

Overcoming Diuretic Resistance

- Use of Albumin
 - Benefit not proven
 - One study showed a modest increase in sodium excretion but it was equivalent to the amount of sodium contained in the albumin solution.
 - Severe hypoalbuminemia (<2.0 g/dl) may have a role but not well studied.^{1 2}
- Dopamine
 - No benefit

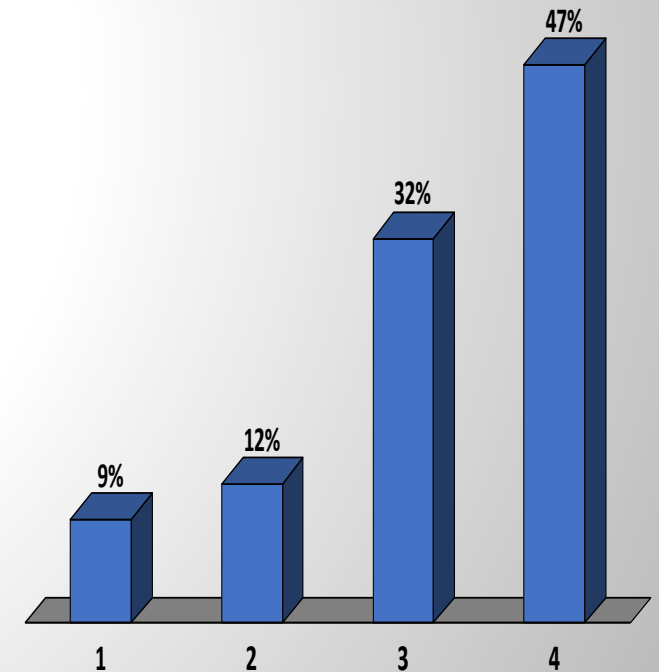
• ¹Filser D, Zurbruggen I, Mutschler E, et al. Co-administration of albumin and furosemide in patients with the nephrotic syndrome. *Kidney Int* 1999, 55:629.

• ²Chalasani N, Corski JC, Horlander JC Sr, et al. Effects of the albumin/furosemide mixtures on responses to furosemide in hypoalbuminemic patients. *J Am Soc Nephrol* 2001; 12:1010.

Which of the following is incorrect regarding RAAS blockers:

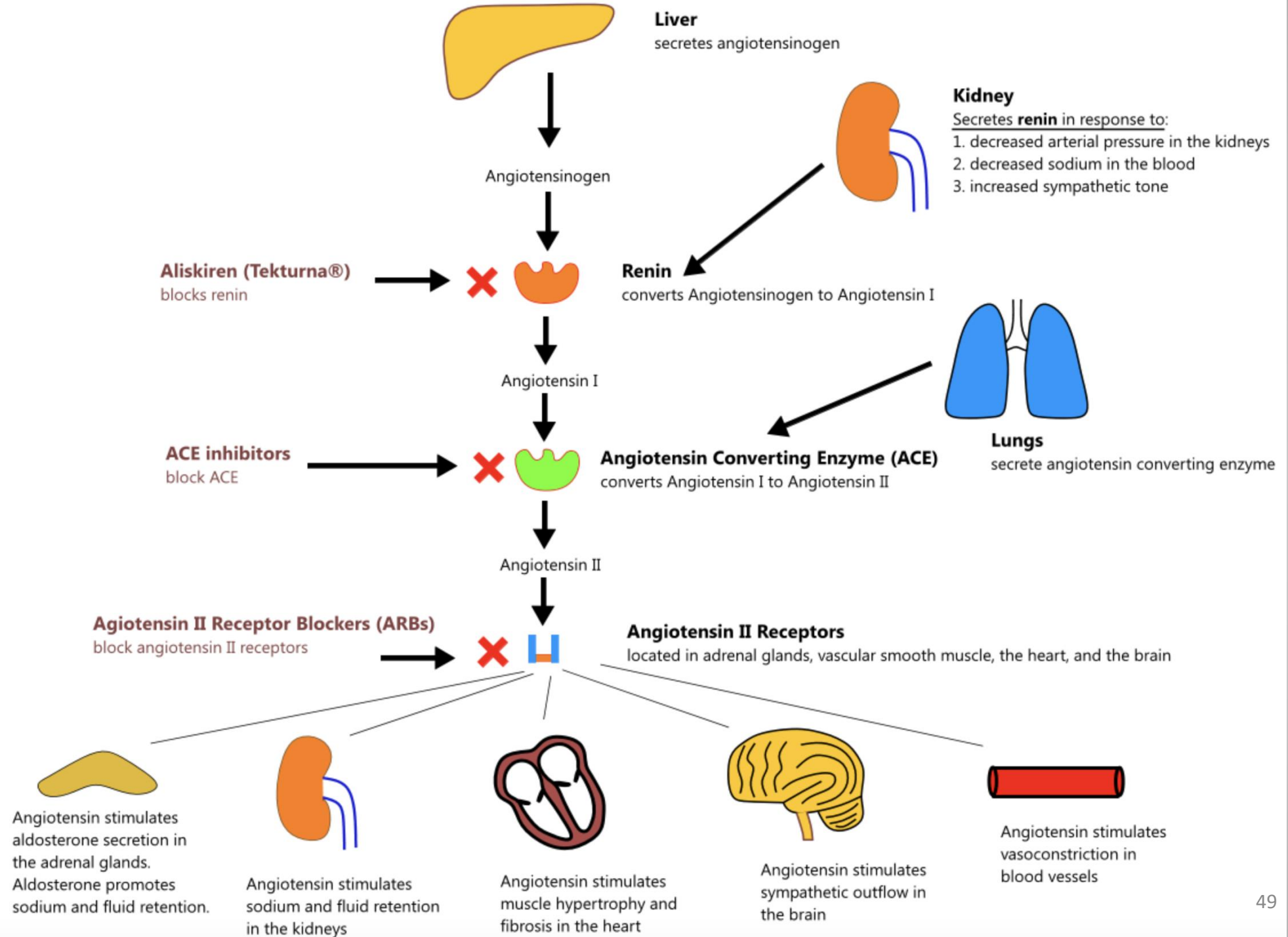
1. Side effects include cough, angioedema, teratogenicity and hyperkalemia
2. Discontinuation should be considered if creatinine increases by more than 30%
3. Combination therapy generally not recommended for treatment of hypertension
4. Patients with unilateral renal artery stenosis are more likely to experience an increase in creatinine

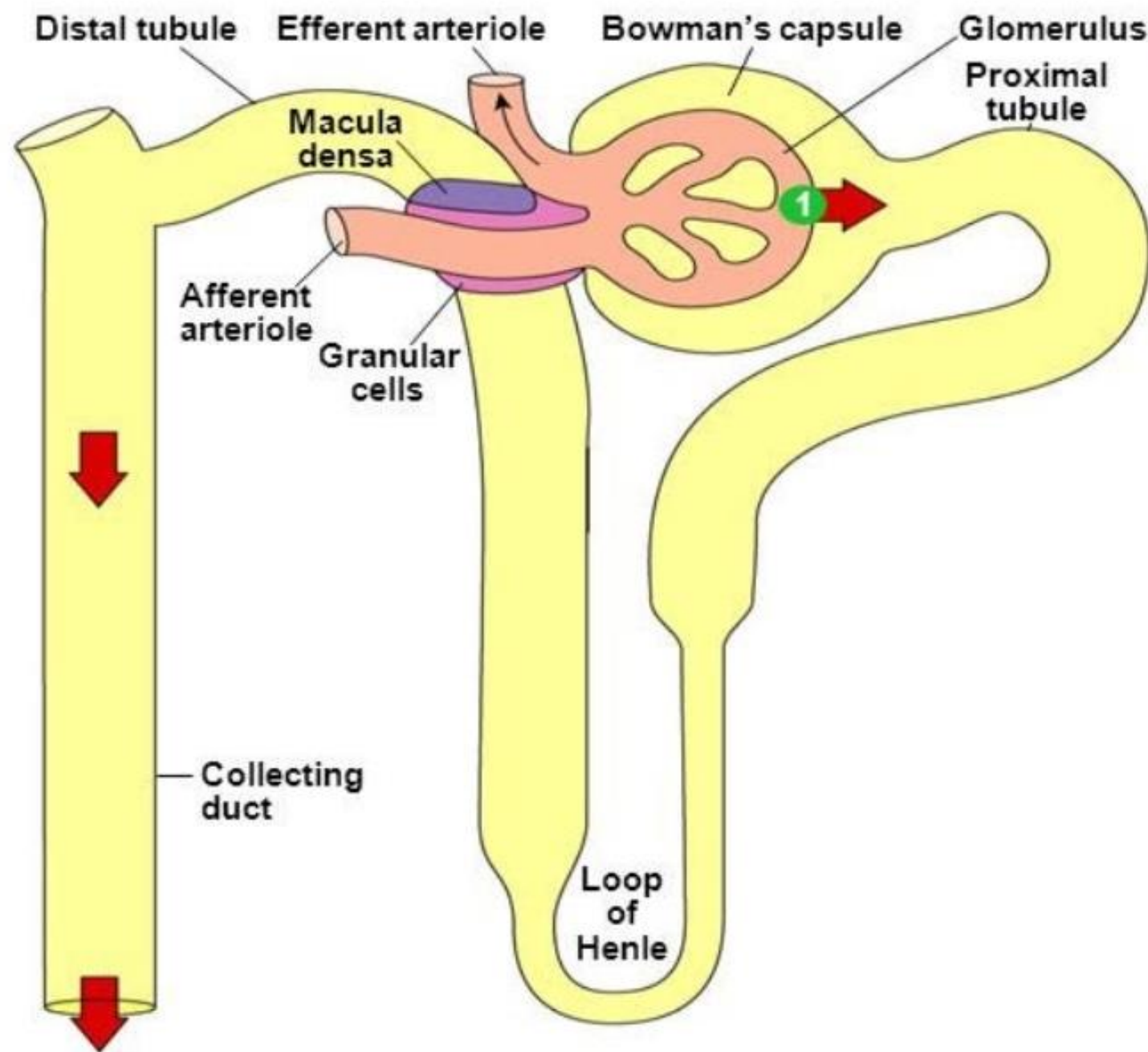
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Renin Angiotensin Aldosterone System





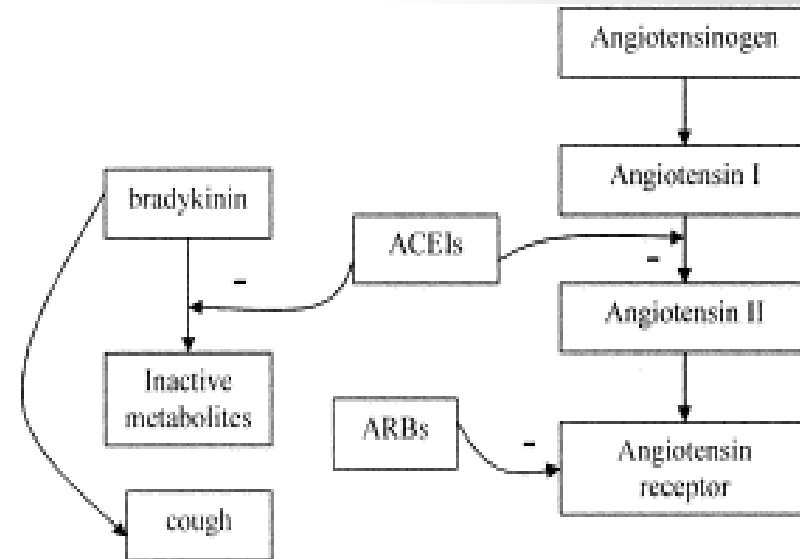
1 GFR increases.

ACEi indications

- Heart failure with reduced ejection fraction (HFrEF)
- Proteinuric chronic kidney disease, both diabetic and nondiabetic
- After a myocardial infarction in most patients, particularly those with heart failure or reduced systolic function.

Physiology of side-effects of RAAS inhibitors

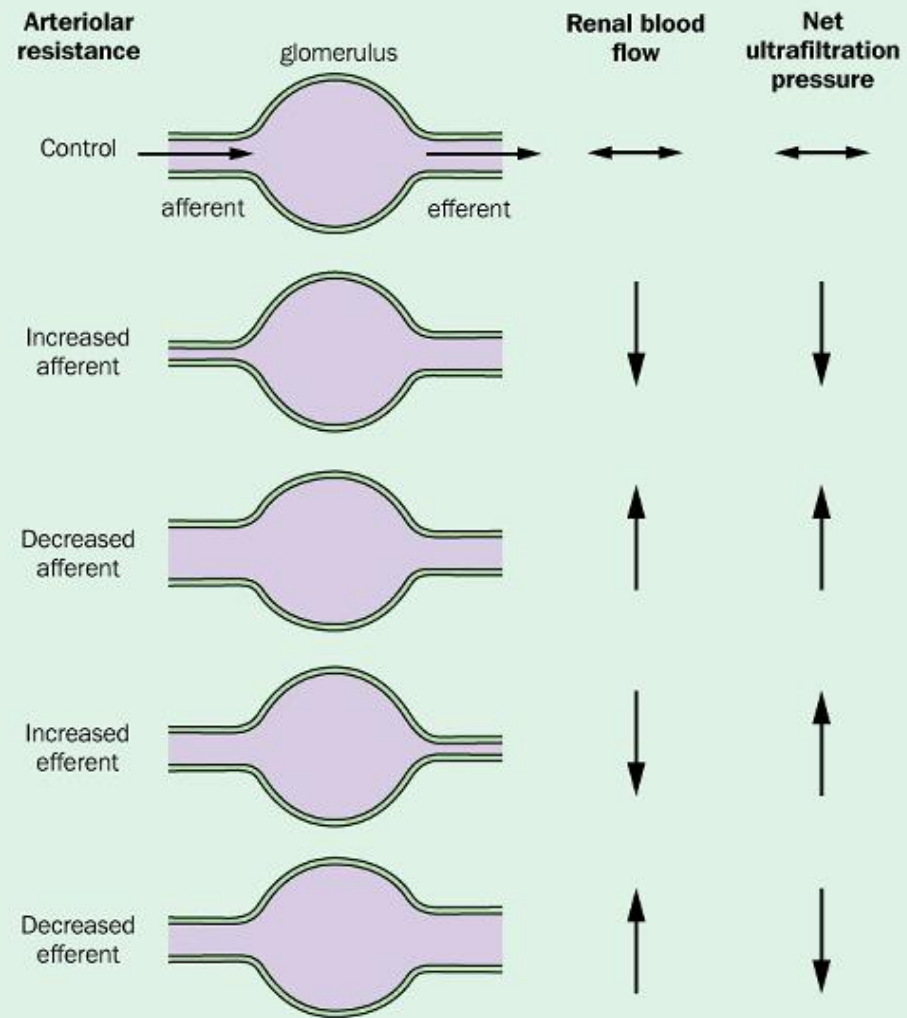
- Interferes with the activity of the renin-angiotensin-aldosterone system
 - Decreases systemic BP, intraglomerular pressure, reduces proteinuria and may antagonize the profibrotic effects of angiotensin II
 - Hyperkalemia
 - Hypotension
 - Early decrease in GFR
 - A 30% increase in serum creatinine is acceptable
- Interferes with the activity of other enzymes and receptors
 - Cough
 - Angioneurotic edema
 - (<1%) African-Americans > Caucasians
- Effects on the fetus
 - Absolutely contraindicated in pregnancy in the 2nd & 3rd trimesters



Reduction in GFR

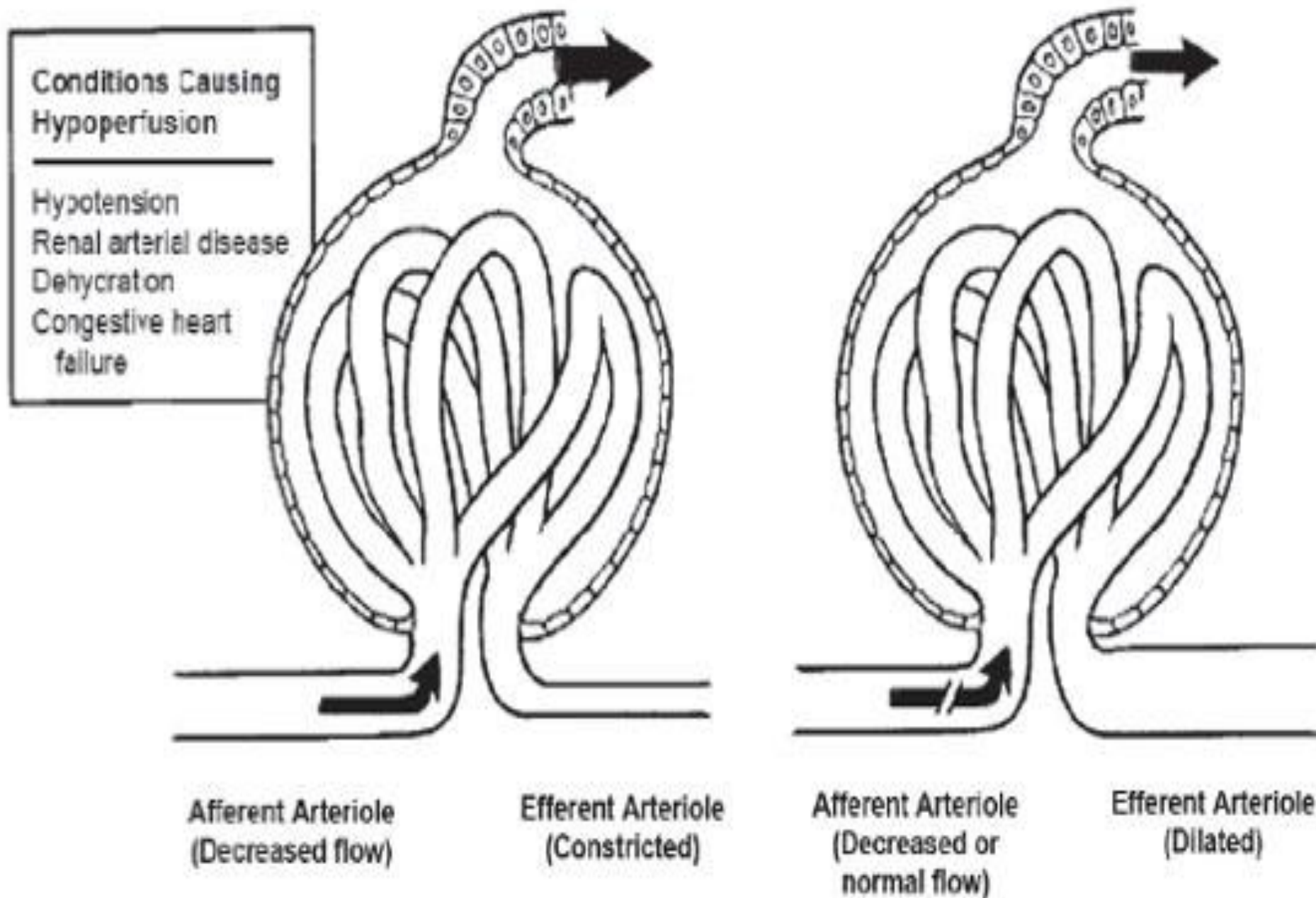
- Usually modest but may be severe.
- NO GFR CUTOFF WHEN CONSIDERING DISCONTINUATION OF A RAAS BLOCKER
- Fairly uncommon and less likely to occur if volume depletion avoided, no history of bilateral renovascular disease and diuretics are transiently held during the initiation period.
- Susceptible populations:
 - Bilateral renal artery stenosis, hypertensive nephrosclerosis, heart failure, polycystic kidney disease, or chronic kidney disease, acute volume loss.
 - Pathophysiology linked to reduced intrarenal perfusion.
- Generally begins a few days after the institution of therapy since angiotensin II levels are rapidly reduced.
 - Can repeat labs three to five days after ACE inhibitor is introduced in such high-risk patients.
- Consider holding a RAAS blocker if:
 - Hyperkalemia cannot be controlled with dietary restriction and medical therapy.
 - Serum creatinine concentration increases more than 30 percent above the baseline value within the first six to eight weeks.

Glomerular hemodynamics



HYPOPERFUSION

ACE INHIBITOR TREATED



Combination ACEi/ARB Therapy

- Multiple studies have demonstrated a higher risk for adverse effects.
- Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) ¹
 - Evaluated ramipril, telmisartan, and combination therapy in over 25,000 patients at high risk for cardiovascular events (diabetes or vascular disease).
 - Combined therapy compared to ramipril alone was associated with significant increases in the following adverse effects that were severe enough to require drug discontinuation: hypotensive symptoms (4.8 versus 1.7 percent), syncope (0.3 versus 0.2 percent), and renal dysfunction (1.1 versus 0.7 percent)
 - There was also a significant increase in hyperkalemia, defined as a serum potassium above 5.5 mEq/L (5.7 versus 3.3 percent), and an almost significant increase in overall mortality (12.5 versus 11.8 percent with ramipril alone, risk ratio 1.07, 95% CI 0.98-1.16).

• ¹ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril or both in patients at high risk for vascular events. N. Engl J Med 2008; 358:1547.

Combination ACEi/ARB Therapy

- An increased incidence of adverse events with combination therapy was also demonstrated in a meta-analysis of four randomized trials that compared 17,337 patients with chronic heart failure who received either an ACE inhibitor alone or the combination of an ACE inhibitor and an ARB¹.
 - Compared with patients who received an ACE inhibitor alone, those treated with both agents had significantly higher rates of the following complications: increased medication discontinuation due to adverse effects (15 versus 11 percent); worsening renal function, defined as an increase in creatinine of 0.5 mg/dL (44.2 micromol/L) or more over baseline (3.3 versus 1.5 percent); hyperkalemia (3.5 versus 0.7 percent); and symptomatic hypotension (2.4 versus 1.5 percent).
- Possible increased risk of cancer
 - Meta-analysis of trials of antihypertensive drugs, combination therapy with ARBs and ACE inhibitors compared with ACE inhibitors alone was associated with a significant increase in cancer incidence among 28,168 patients from two trials (2.3 versus 2.0 percent; risk ratio 1.14, 95% CI 1.02-1.28)²
- Combined therapy with both an ACE inhibitor and ARB is **not** recommended for the treatment of hypertension.

• ¹Phillips CO, Kashani A, Ko DK et al. Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction: A quantitative review of data from randomized clinical trials. Arch Intern Med 2007; 167:1930.

• ²Bangalore S, Kumar S, Kjeldsen SE, et al. Antihypertensive drugs and risk of cancer: network of meta-analyses and trial of sequential analyses of 324,168 participants from randomised trials. Lancet Oncol 2011; 12:65.

Thanks!!

Contrast Nephropathy

- Incidence
- Risk Factors
- Prophylaxis
- Treatment

Contrast Nephropathy

- Radiocontrast is nephrotoxic
 - Ionic > non-ionic
 - Hyperosmolar (1400-1800 mosm/kg) > hyposmolar (500-850 mosm/kg) > iso-osmolar (290 mosm/kg)
 - Most Hyperosmolar are ionic, most iso and hypo are non-ionic. There is a statistically significant benefit of iso over hypo but no difference in risk for RRT, CV outcomes or death.
- Pattern of injury is ATN
 - Contrast induces renal vasoconstriction resulting in medullary hypoxemia (FeNa < 1 initially).
 - Contrast is directly toxic to renal tubules.
 - May be due to functional changes in tubular epithelial cells (redistribution of membrane transport proteins as opposed to necrosis).
- Time Course
 - Creatinine increases within 24-48 hours following exposure.
 - Creatinine begins to plateau between 3-5 days, followed by recovery.
- Incidence
 - If no risk factors, particularly CKD, risk is \leq to 1%.
 - 9 to 38 percent with mild to moderate renal insufficiency and diabetes mellitus
 - 50 percent or more if the baseline plasma creatinine is greater than 4 to 5 mg/dL particularly in patients with diabetic nephropathy .

Contrast Nephropathy Risk Factors

- CKD (GFR below 60 ml/min, particularly those patients with DM).
- Diabetes
- Hypoperfusion from heart failure
- Volume Depletion
- Multiple Myeloma
- Older Age
- Type of Contrast used

Pre-Procedure Prophylaxis

- If possible, avoid contrast.
- If not possible, use lower doses of contrast (<125 ml), and hypo-osmolal or iso-osmolal nonionic contrast, and avoid repetitive, closely spaced studies (within 48-72 hours).
- Avoid volume depletion and non-steroidal antiinflammatory drugs (for 24-48 hours prior to procedure).
- If there are no contraindications to volume expansion, use isotonic intravenous fluids.
- Benefit of holding RAAS blockers is less clear (insufficient data, risk of HTN).

Pre-Procedure Prophylaxis

- IVF (0.9NS)
 - 1 ml/kg/hour x 6-12 hours prior to procedure, intraprocedure and 6-12 hours after
- Mucomyst (N-acetylcysteine)-No significant benefit ¹
 - Free radical scavenger; prevents oxidative tissue damage
 - 600mg po BID x 4 doses (2 before procedure, 2 after)
 - The largest randomized trial did not find improved outcomes with oral acetylcysteine in 4993 high-risk patients undergoing scheduled angiography
- Bicarbonate (JAMA 2004)
 - Alkalinizing urine should reduce renal medullary damage
 - D5W with 3 amps HCO₃; bolus 3 mL/kg 1 hour preprocedure, then 1mL/kg/hour for 4-6 hours starting at time of procedure.
 - Can use this regimen with or without NSS if performing outpatient cath.
 - Use if your patients are acidotic or on low end of normal.
- Saline vs. Bicarbonate-No proven benefit with Bicarbonate¹
 - The most definitive data are from a subsequently published randomized trial that included 4993 high-risk patients undergoing scheduled angiography that found that both treatments were associated with similar outcomes. ¹
 - ¹Weisbord SD, Gallagher M, Jneid H, et al. Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine. N Engl J Med 2018; 378:603.

Pre-Procedure Prophylaxis

- Oral salt loading
 - Benefit not clear. Two small trials have suggested that oral salt may be comparable with intravenous fluids.
- Oral sodium citrate
 - One randomized trial has demonstrated a benefit of oral sodium citrate (5 g in 200 mL water) one hour before and four hours after angiography. The risk of contrast nephropathy was lower among patients who received oral citrate compared with placebo.
- Atrial natriuretic peptide (anaritide)
 - Benefit seen in animal models, not in humans.
- Ascorbic Acid
 - Data are insufficient to support use.
- Trimetazidine
 - A cellular anti-ischemic agent, provided added protection to isotonic saline from contrast-mediated nephropathy in an initial, small, randomized, prospective study but a larger one may be helpful in better evaluating its' role.
- Inhibitors of vasoconstriction (Theophylline, aminophylline, nifedipine and captopril, prostaglandin E, fenoldopam, low-dose dopamine)
 - May be some benefit but data conflicting and additional studies are required.

Post-Procedure

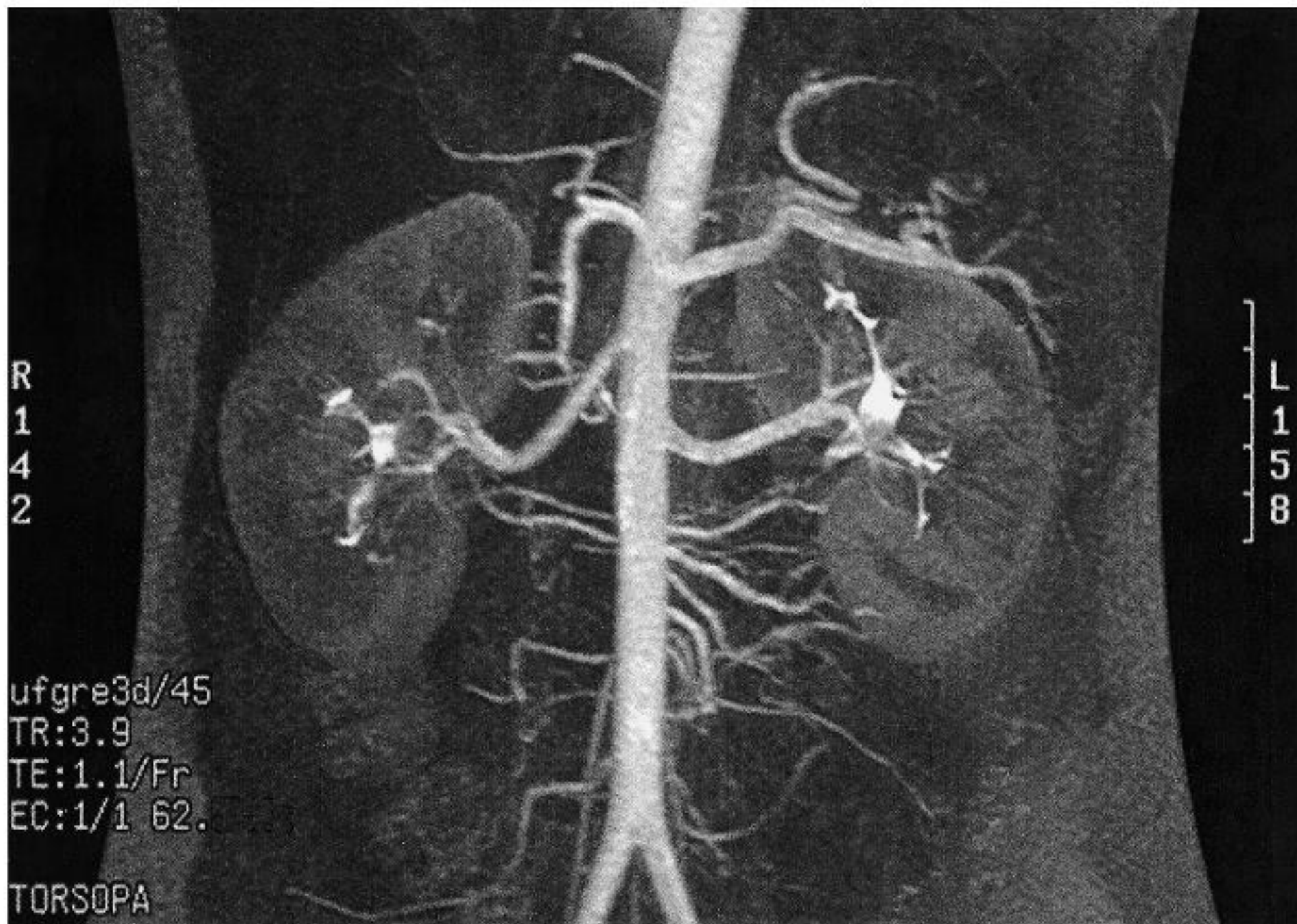
- Dialysis is of no proven benefit.

Atheroembolic Renal Disease



Atheroembolic disease

- Partial or total occlusion of multiple small arteries (or glomerular arterioles), leading to tissue or organ ischemia.
 - Can also affect large arteries during arteriography, angioplasty, or surgery but many cases are spontaneous.
- The incidence of atheroembolism after diagnostic cardiac catheterization
 - Clinical atheroembolism (cutaneous or renal) 1.4%
 - Acute renal failure 0.9%
- Most commonly presents subacutely
 - Progressive renal dysfunction occurs in staggered steps separated by periods of stable kidney function. In this setting, renal impairment is usually observed weeks rather than days after a possible insult
 - This form is most probably due to some combination of recurrent embolization and foreign-body reaction.

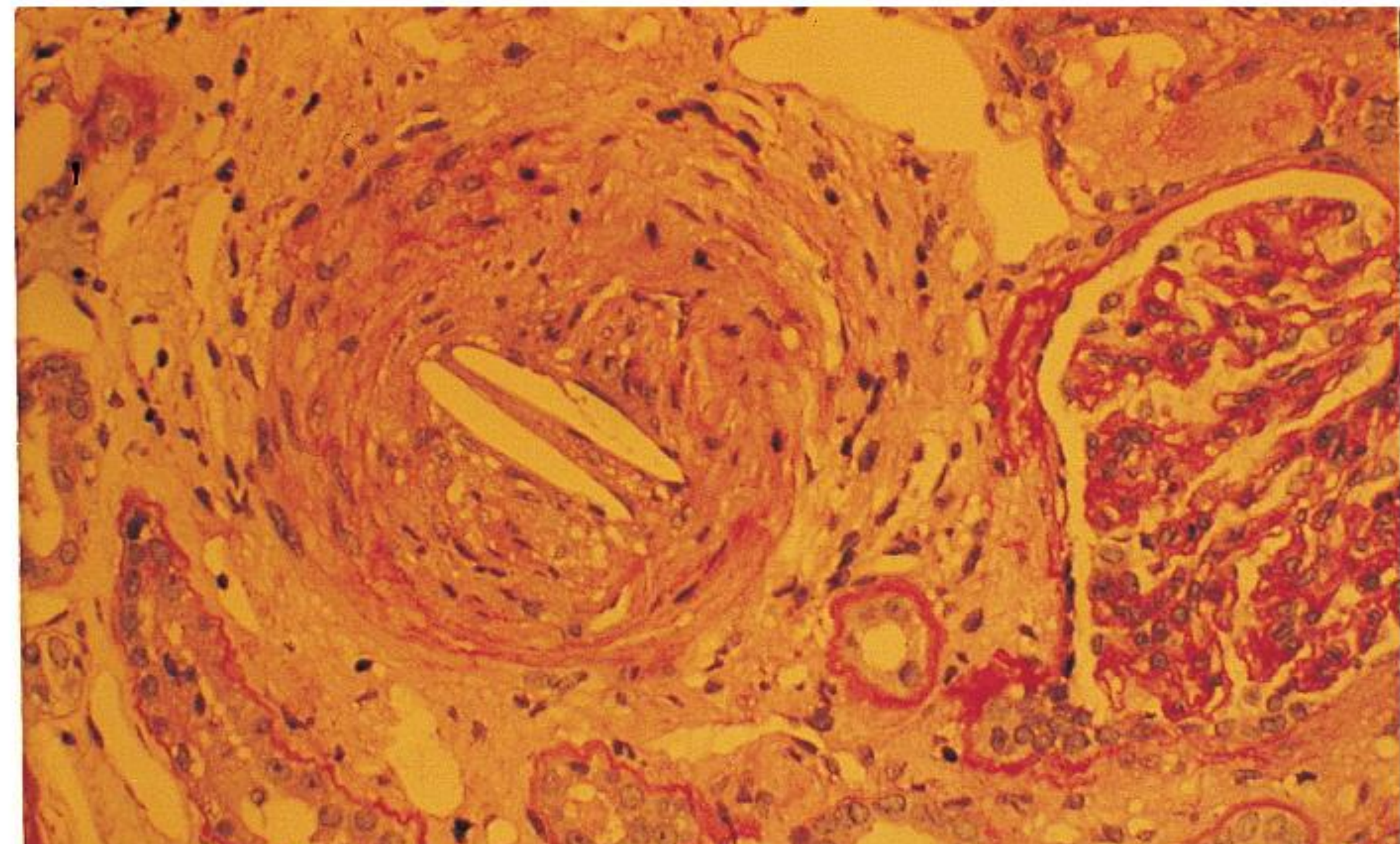




Livedo Reticularis







Diagnosis and Treatment

- Eosinophilia, eosinophiluria and hypocomplementemia
 - may reflect immunologic activation at the surface of the exposed atheroemboli
 - These findings generally resolve within one week
- There is no specific therapy for renal atheroembolic disease.
- Aspirin, statins, blood pressure control, cessation of smoking, glycemic control (if diabetic).
- Anticoagulation may interfere with the healing of ulcerated atheromatous plaques and may be harmful.
- In a study of 354 patients, 33 percent of patients developed end-stage renal disease, and 28 percent of patients died after a mean follow-up of two years.¹

• ¹ Scolari F, Ravani P, Gaggi R, et al. The challenge of diagnosing atheroembolic renal disease: clinical features and prognostic factors. Circulation 2007; 116:298.

Dialysis in the setting of AKI

- A
- E
- I
- O
- U

Dialysis in the setting of AKI

- Acidosis
- Electrolyte disorders (hyperkalemia)
- Intoxication
- Overload
- Uremia
 - GFR below 15 ml/min consistent with renal failure

Miscellaneous

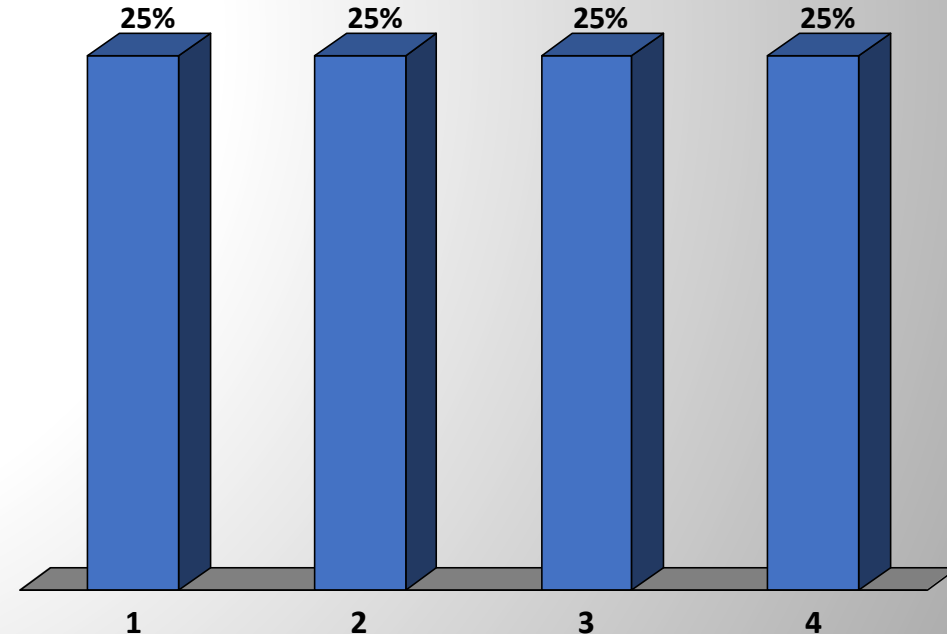
- Digoxin has a very large volume of distribution and is not amenable to HD
- Fenofibrate increases creatinine production (mechanism unknown) but does not affect GFR.
 - AKI can be seen in patients with advanced CKD (from rhabdo).
- Dronedarone impairs tubular secretion of creatinine.
 - AKI can be seen in patients that are hypovolemic or are in decompensated heart failure.

Questions

All of the following are true of atheroembolic renal disease EXCEPT:

1. Typically occurs after aortic manipulation but can also occur spontaneously.
2. Characterized by a protracted, sub-acute course with a low-likelihood of recovery.
3. Treatment involves use of anticoagulation.
4. Laboratory analysis may reveal depressed C3 and C4 as well as presence of urine eosinophils.

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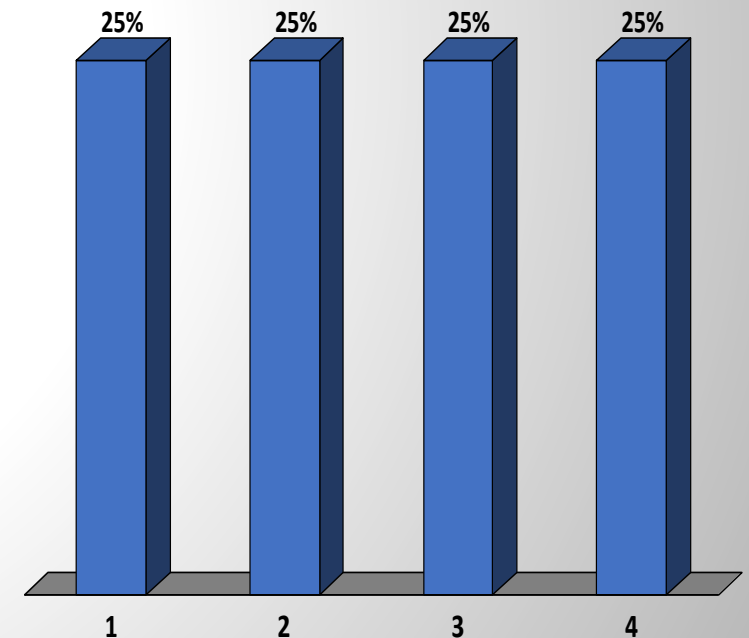


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Which of the following is false regarding contrast-induced nephropathy?

1. Risk factors include DM, pre-existing CKD and volume depletion.
2. Typically recovers within 5-7 days.
3. Pre-procedure prophylaxis should include hypotonic saline if no contraindication to volume expansion.
4. Non-ionic, iso-osmolal agents are safer than ionic, hyperosmolal agents.

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