PROGRESSION OF KIDNEY DISEASE

Preventable or **inevitable?**

Goals of today's presentation

- Discuss the extent and ramifications of CKD and its progression
- Review the classes of CKD and the clinical importance of each
- Overview the mechanisms for CKD progression
- Identify the predictors for CKD progression
- Discuss the ways to slow CKD progression, both pharmacologic and nonpharmacologic interventions

The problem with CKD

CKD affects 37 million Americans, or 15% of the population.

9 out 10 people do not know they have CKD

Why CKD is important

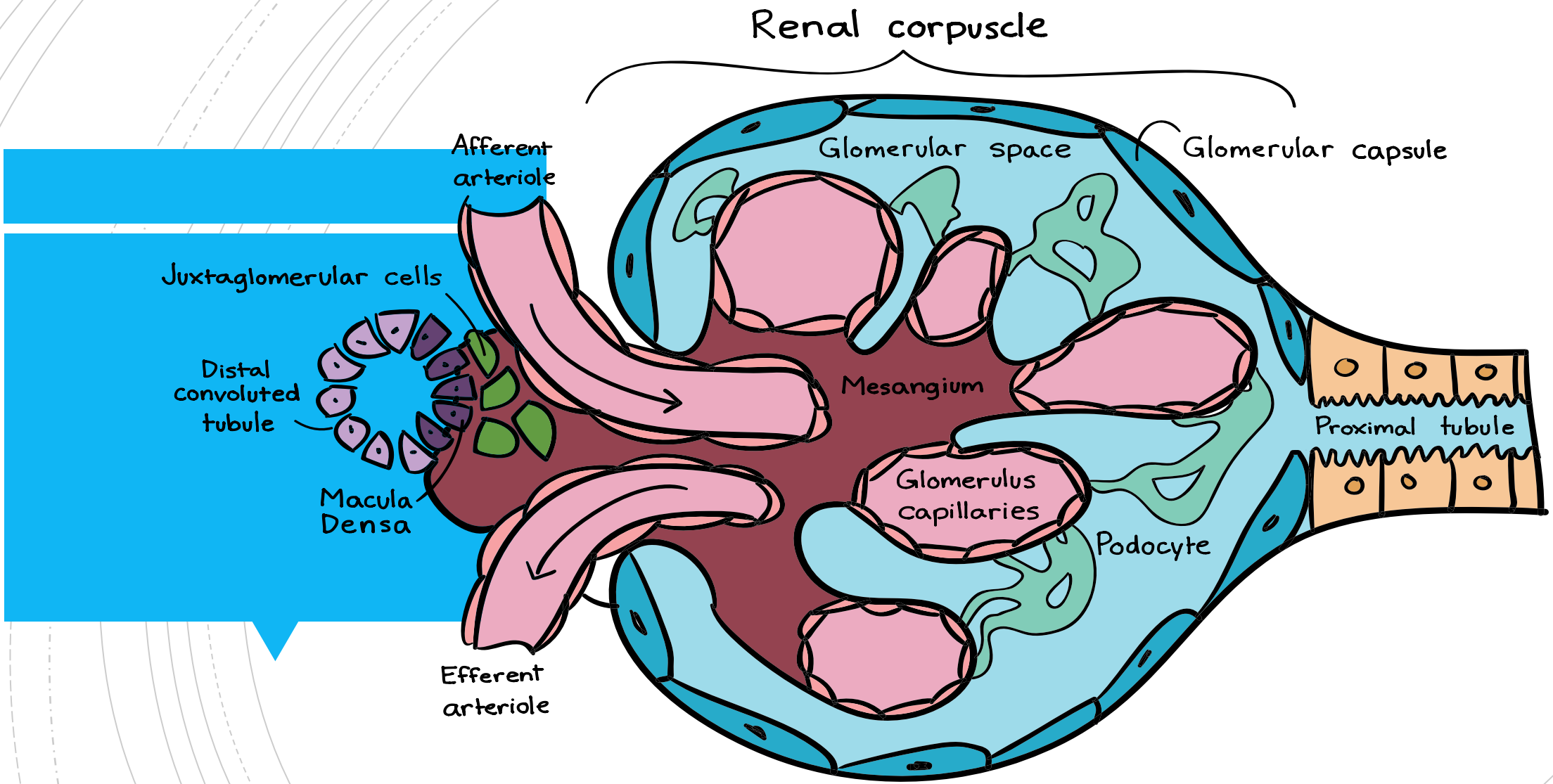
- It is a major risk factor for cardiovascular disease
- It is a cause of varying and progressive degrees of disability
- It carries a greater risk of ESKD

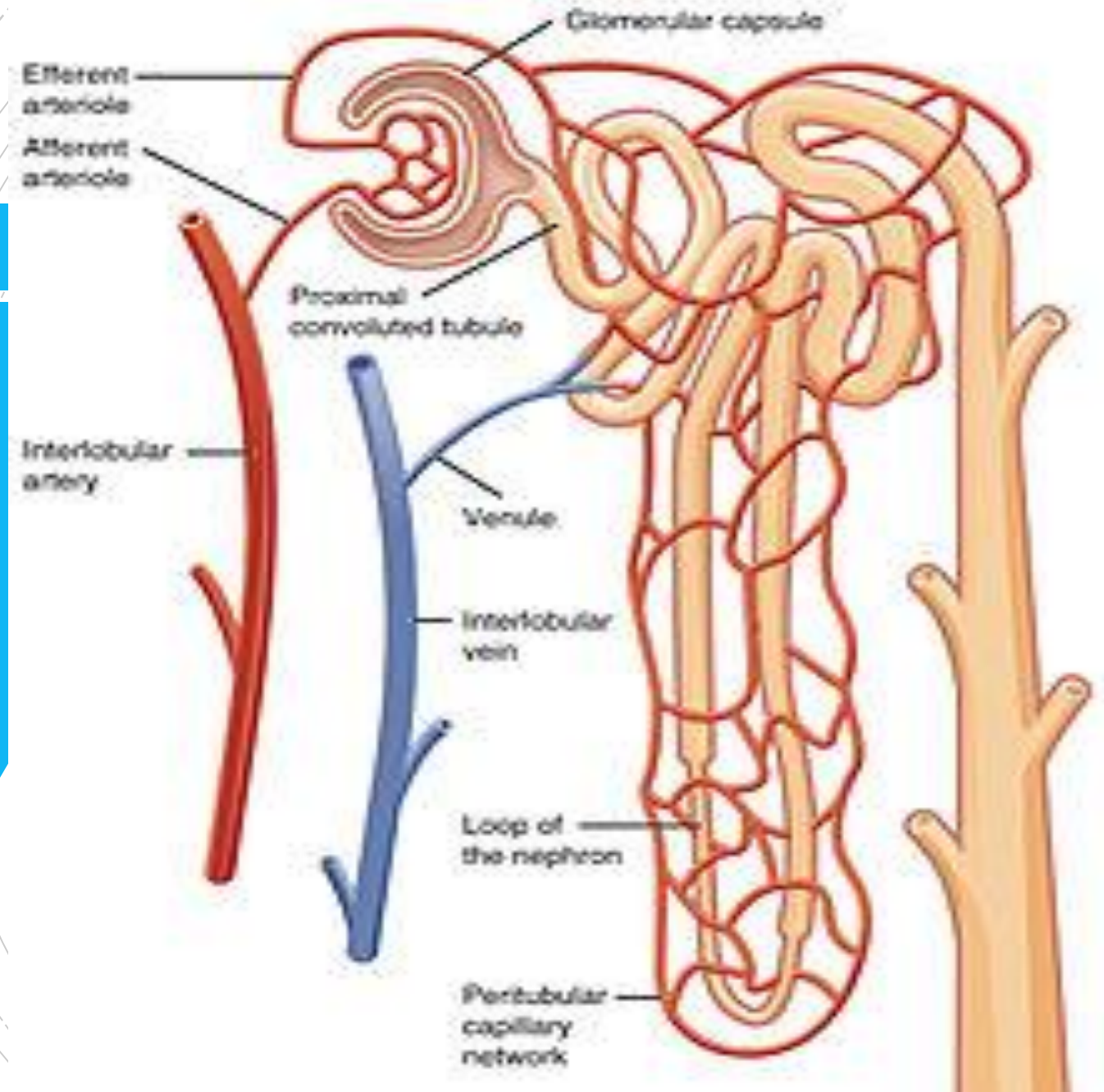
What causes CKD progression?

Hemodynamic factors- leading to tissue ischemia and downstream scarring

-Glomerular hypertension

-Intrarenal vascular hypertension

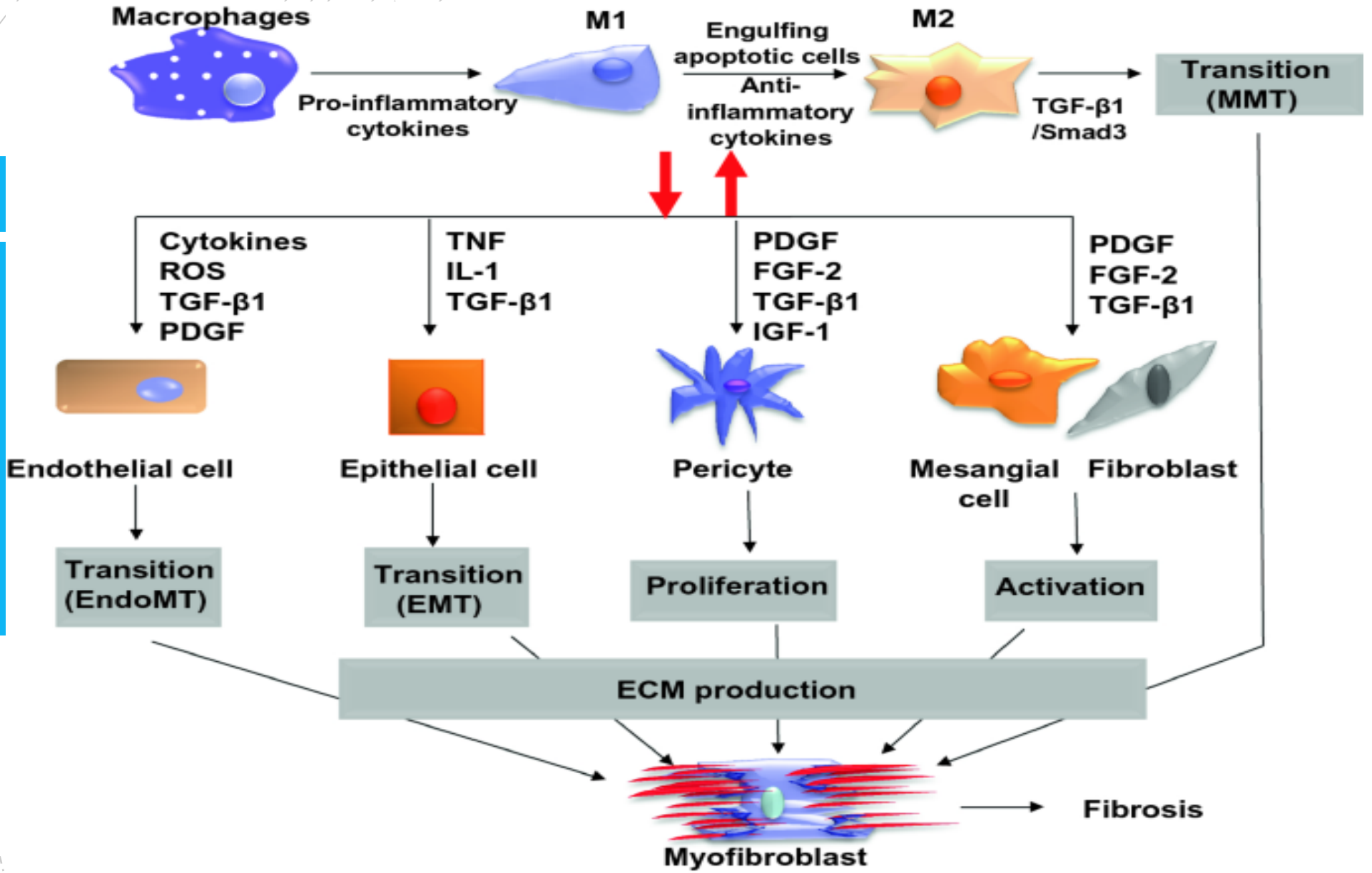

Renal corpuscle
Afferent arteriole
Glomerular space
Glomerular capsule
Juxtaglomerular cells
Distal convoluted tubule
Mesangium
Proximal tubule
Glomerulus capillaries
Macula Densa
Podocyte
Efferent arteriole


Glomerular capsule
Efferent arteriole
Afferent arteriole
Proximal convoluted tubule
Interlobular artery
Venule
Interlobular vein
Loop of the nephron
Peritubular capillary network

What causes CKD progression?

Inflammatory mediators and maladaptive mechanisms, leading to fibrosis :

- Prostaglandins
- Angiotensin and aldosterone
- Inflammatory molecules
  - (cytokines/chemokines)
- acidosis


Macrophages
M1
Pro-inflammatory cytokines
Engulfing apoptotic cells
Anti-inflammatory cytokines
M2
TGF-β1 /Smad3
Transition (MMT)
Cytokines ROS TGF-β1 PDGF
TNF IL-1 TGF-β1
PDGF FGF-2 TGF-β1 IGF-1
PDGF FGF-2 TGF-β1
Endothelial cell
Epithelial cell
Pericyte
Mesangial cell
Fibroblast
Transition (EndoMT)
Transition (EMT)
Proliferation
Activation
ECM production
Myofibroblast
Fibrosis

CKD staging

- CKD 1,2- eGFR > 60 (ml/min/1.73 m2)
- CKD 3a-eGFR 45-59
- CKD 3b-eGFR 30-44 Mild symptoms
- CKD 4- eGFR 15-29 Moderate symptoms
- CKD 5- eGFR <15 Severe symptoms
- CKD 5D- dialysis dependent (mild symptoms?)

Predicting when CKD might progress

- Advanced kidney disease
- Poorly controlled hypertension
- Heavy proteinuria
- Smokers
- Lack of control of underlying process causing kidney disease
- Progressive cardiopulmonary disease

Stopping progression of kidney disease- nonpharmacologic measures

- Smoking cessation
- Weight loss/exercise
- Dietary intervention
  - Sodium restriction
  - Modest protein restriction
  - Anti-inflammatory diet?
- Avoidance of kidney toxins

Stopping progression of kidney disease- pharmacologic measures

- Blood pressure control

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Blood pressure control in kidney disease

- Goal typically quite strict
- Should include inhibition of renin/angiotensin/aldosterone axis by ACE inhibitors, angiotensin blockers, then later aldosterone receptor blockers

Angiotensin effects:

efferent arteriole constriction

vasoconstriction

mesangial matrix

profibrotic mediator

Aldosterone effects:

Sodium and water resorption /retention

Raises blood pressure

Those with higher levels of aldosterone have greater progression of kidney disease

ACE inhibitors

Captopril

Enalopril (Vasotec)

Lisinopril (Prinivil,Zestril)

Ramipril

Benazepril (Lotensin)

Fosinopril

Quinapril (Accupril)

ARB agents

Azilsartan (Edarbi)

Candesartan (Atacand)

Eprosartan.

Irbesartan (Avapro)

Losartan (Cozaar)

Olmesartan (Benicar)

Telmisartan (Micardis)

Valsartan (Diovan)

Aldosterone receptor blockers

Spironolactone (Aldactone)

Eplerenone (Inspra)

Finerenone (Kerendia)

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- Diuretics another mainstay of therapy

Diuretics

Thiazide- like diuretics

- HCTZ
- Chlorthalidone
- Indapamide
- Metolazone (Zaroxolyn)

Loop diuretics

- Furosemide (Lasix)
- Torsemide (Demadex)
- Bumetanide (Bumex)

Blood pressure control in kidney disease

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- Diuretics another mainstay of therapy
- Will typically require multiple agents with dosing multiple times a day

Stopping progression of kidney disease- pharmacologic measures

- Blood pressure control
- SLGT2 inhibitors

SGLT2 inhibitors- awesome!

- Diabetic agents that work in the kidney tubule
- After glucose is filtered in the glomerulus, it is reabsorbed back into the blood circulation by the SGLT2 channel
- Sodium follows the glucose in the channel
- Inhibitors block BOTH glucose and sodium from moving back into the bloodstream, and it is then excreted in the urine
- The increase in sodium in the distal tubule feeds back to the afferent arteriole of the glomerulus causing it to dilate.

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SGLT2 inhibitors

Improved Glucose control

Improvement in Cardiovascular outcomes, especially in CHF

Improvement in Renal outcomes, including progression of kidney disease

Now indicated in heart failure and kidney disease, regardless of presence of diabetes

SGLT2

Canagliflozin (Invokana)

Dapagliflozin (Farxiga)

Empagliflozin (Jardiance)

Ertugliflozin (Steglatro)

Stopping progression of kidney disease- pharmacologic measures

- Blood pressure control
- SLGT2 inhibitors
- Alkali therapy
- Statin therapy
- Potassium control?
- Control of secondary hyperparathyroidism/ hyperphosphatemia?

Summary/take aways

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- Individuals are at varied risk for progression, and their course can be somewhat predicted
- Specific goals and drugs should be part of the care of the CKD patient
- Nephrology follow up should be in place by CKD 3B/4 for most patients
- Successful treatment requires patient AND nephrology effort and monitoring
- Stopping progression is the goal for every one involved with the care of the patient with CKD.

Questions?