Hypertension and Renal Disease: Pathophysiology, Progression, and Clinical Considerations

Kumari Usha MD
Nephrology
Banner Specialty Clinic

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Objectives

- Upon completion of this educational activity, the participant should be able to:
  - Understand Pathophysiology of Hypertension in Renal disease
  - Understand Resistant Hypertension and Refractory Hypertension
  - Understanding use of newer therapies for treatment of hypertension
  - Personalized treatment strategies – Pharmacologic and Nonpharmacologic treatment approach

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Hypertension and Renal Disease: Pathophysiology, Progression, and Clinical Considerations

- Hypertension and Renal disease are closely interlinked
- Independent Risk factor for progression of CKD

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Pathophysiology of Hypertension in Renal Disease

- Acute Glomerular Disease
  - Sodium retention and volume expansion evidenced by suppression of RAAS and increased ANP
  - Increased Na,K ATPase activity in CCT
- Acute Vascular Disease
  - Increased activity of RAAS

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CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health and CKD is classified based on cause, GFR category, and albuminuria category (CGA).

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range			Description and range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30-300 mg/g 3-30 mg/mmol	A3 Severely increased >300 mg/g >30 mg/mmol
G1	Normal or high	>90			
G2	Mildly decreased	60-89			
G3a	Mildly to moderately decreased	45-59			
G3b	Moderately to severely decreased	30-44			
G4	Severely decreased	15-29			
G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

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Pathophysiology of Hypertension in Renal Disease

- Chronic Kidney Disease
  - Prevalence of Hypertension in CKD is 80-85%
    - 65% in CKD stage 2 to 95% in stage 4-5
  - Hypertension and CKD mutually supportive for pathophysiology of renal and CV damage

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Pathophysiology of Hypertension in Renal Disease

- Renin Angiotension Aldosterone System
  - Angiotensin 1 undergoes multiple cleavage pathway leading to 6 hormones target 6 receptors
    - AngII, Ang1-9, Ang1-7, AngIII, AngA, Alamandine
    - PRR, AT1R, AT2R, AT4R, MASR, MRGDR
  - AT1R stimulation –
    - Vasoconstriction, Sodium reabsorption, Aldosterone secretion, Inflammation , Fibrosis
  - AT2R, AT4R, MASR,MRGDR stimulation-
    - Vasodilation, Natriuresis, Inhibits inflammation and fibrosis

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Pathophysiology of Hypertension in Renal Disease

- Brown et al in 2020-
  - Incomplete suppression of Aldosterone that worsen severity of Hypertension but only few patients had increased Aldosterone for diagnosis of Primary Hyperaldosteronism
- AngII activates Aldosterone synthesis and RAC1 activation
- RAC1 stimulates MR receptors in absence of Aldosterone
- RAC1 stimulation-
  - Podocyte foot process effacement, slit diaphragm remodeling, development of proteinuria and myocardial hypertrophy
- Hypertension leads to glomerular endothelial damage leading to sclerosis due to overproduction of Ang II

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Pathophysiology of Hypertension in Renal Disease

- NO and GMP signaling
  - NO – vasodilator- counteracts effects of vasoconstrictive mediators- ET1
  - NO stimulates cGMP pathway
    - Inhibition of renin secretion, modulation of the expression of NHE3, NKCC, ENaC and Na/K-ATPase at basolateral membrane
  - Dysregulation of NO-cGMP pathway plays an important role in genesis of maintaining of arterial hypertension causing renal and CV damage.

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Pathophysiology of Hypertension in Renal Disease

- Endothelins
  - ET-1, ET-2, ET-3- act on ETAR and ETBR
  - ETAR activation causes
    - Contraction of VSMC, mesangial cells,
    - Effacement in podocytes,
    - Proliferation and migration of immune cells
    - Stimulation of AngII
    - Stimulates extracellular matrix production and tissue fibrosis
  - ETBR counter regulates ETAR
  - Expression ratio ETAR:ETBR in Renal artery is ~ 90:10, Renal vein ~98:2

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Pathophysiology of Hypertension in Renal Disease

- Increased Sympathetic activity
  - Stimulation of Cardiac , vascular receptors and renal factors
  - Increased renin
  - Increased sodium absorption
  - Increased CO
  - Increased vascular resistance

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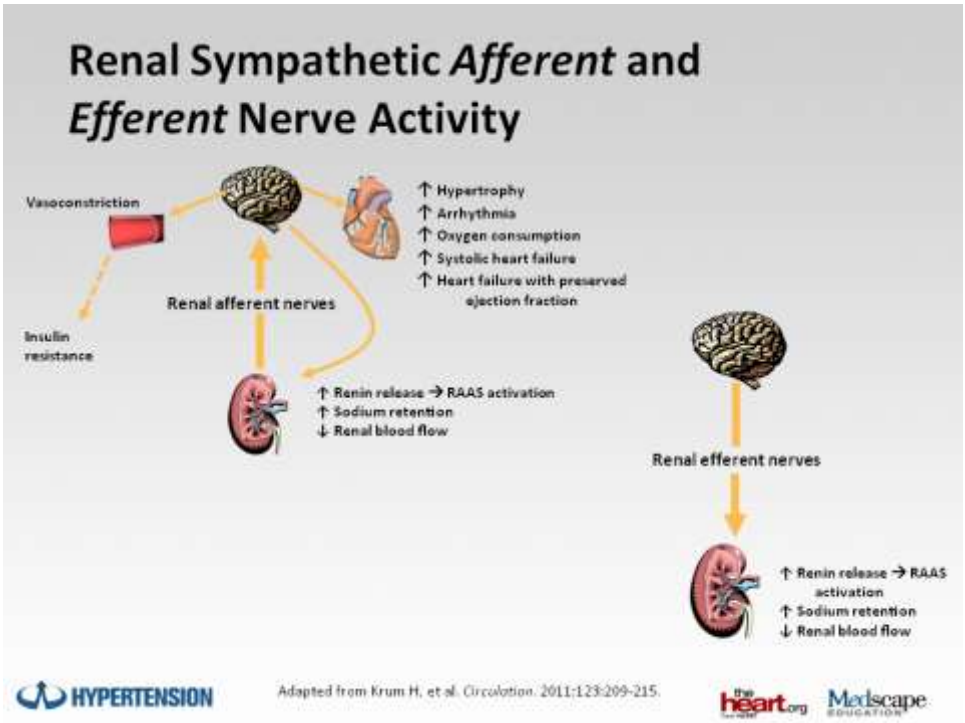

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Pathophysiology of Hypertension in Renal Disease

- Secondary Hyperparathyroidism
  - PTH increases intracellular calcium concenteration in VSMC – vasoconstriction
- Erythropietin
  - Hypertension related to degree in rise of HCT

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Pathophysiology of Hypertension in Renal Disease

- Immune System
  - Hypertensive millieu activates immune system – perpetuates and exacerbates hypertension in vicious cycle.
  - Angiotensin receptors expressed on monocytes, macrophages, granulocytes, B and T lymphocytes
  - T cell can synthesize autocrine hormones – RAAS – enhance expressions of TNF and IL-17
  - Macrophages and Dendritic cells have MR receptors- stimulation
    - Secretion of proinflammatory cytokines and differentiation into M1 macrophage

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Pathophysiology of Hypertension in Renal Disease

- FGF 23
  - FGF23 increases Aldosterone secretion directly and through RAAS,
  - Aldosterone stimulates bone secretion of FGF23 –MR present in bone
  - FGF 23 promotes expression of NCC n the distal tubule thus increasing Sodium absorption
  - FGF 23
    - Myocardial hypertrophy, ventricular dysfunction, cardiac fibrosis

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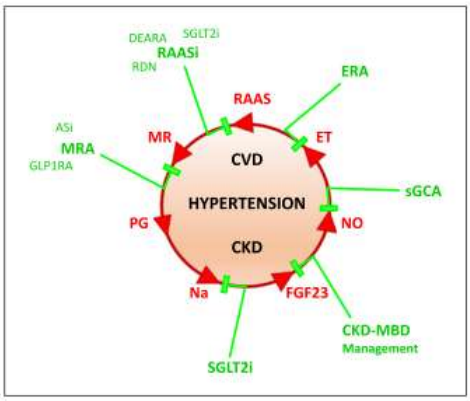

Fig. 1. Hypertension, CVD, and CKD merge in a self-perpetuating cycle sustained by physiological and biological alterations. New drugs lower BP by targeting altered mechanism, breaking the vicious cycle. ASi, aldosterone synthase inhibitors; CKD-MBD, chronic kidney disease-mineral bone disease; DEARA, dual endothelin angiotensin receptor antagonists; ERA, endothelin receptor antagonists; ET, endothelin; FGF23, Fibroblasts Growth Factor 23; GLP1RA, GLP1 receptor agonists; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonists; Na, sodium; NO, nitric oxide; PG, prostaglandins; RAAS, renin-angiotensin-aldosterone system; RAASi, RAAS inhibitors; RDN, renal denervation; sGCA, soluble guanylate-cyclase activators SGLT2i, sodium-glucose cotransporter 2 inhibitors.

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Hypertension and Renal Disease: Clinical Considerations

	Appropriate BP measurement methods for management of hypertension include: self-measured BP,* daytime ABPM, and high-quality office BP (AOBP or office BP using standard procedure[5])
Higher-risk population[6]	
• Known ASCVD* • Heart failure • Diabetes mellitus • Chronic kidney disease (including a history of kidney transplant) • Age ≥65 years[6] • Calculated 10-year risk of ASCVD event ≥7.5%[6]	<130/80 mmHg, with a secondary recommendation to achieve a BP <120/80 mmHg
Lower-risk	
• None of the above risk factors	<130/80 mmHg

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Hypertension and Renal Disease: Clinical Considerations

Checklist for accurate measurement of blood pressure

Key steps for proper BP measurements	Specific instructions
Step 1: Properly prepare the patient	1. The patient should avoid caffeine, exercise, and smoking for at least 30 minutes before measurement. 2. Ensure the patient has emptied their bladder. 3. Have the patient relax, sitting in a chair (feet on floor, back supported) for ~5 minutes. 4. Remove all clothing covering the location of cuff placement. 5. Neither the patient nor the observer should talk during the rest period or during the measurement. The patient should refrain from using electronic devices (eg, phone, tablet, computer) during the measurement. 6. Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria.
Step 2: Use proper technique for BP measurements	1. Use a BP measurement device that has been validated, and ensure that the device is calibrated periodically.* 2. Support the patient's arm (eg, resting on a desk). 3. Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum). 4. Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used. 5. Use an oscillometric device, if available. If taking auscultatory readings, either the stethoscope diaphragm or bell may be used.
Step 3: Take the proper measurements needed for diagnosis and treatment of elevated BP/hypertension	1. At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings. 2. Separate repeated measurements by 1 to 2 minutes. 3. For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff 20 to 30 mmHg above this level for an auscultatory determination of the BP level. 4. For auscultatory readings, deflate the cuff pressure 2 mmHg per second, and listen for Korotkoff sounds.
Step 4: Properly document accurate BP readings	1. Record SBP and DBP. If using the auscultatory technique, record SBP and DBP as onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even numbers. 2. Note the time of most recent BP medication taken before measurements.
Step 5: Average the readings	1. Use an average of ≥2 readings obtained on ≥2 occasions to estimate the individual's level of BP.
Step 6: Provide BP readings to patient	1. Provide patients the SBP/DBP readings both verbally and in writing.

BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure.

* Devices should be checked at least twice yearly against a mercury sphygmomanometer for accuracy.

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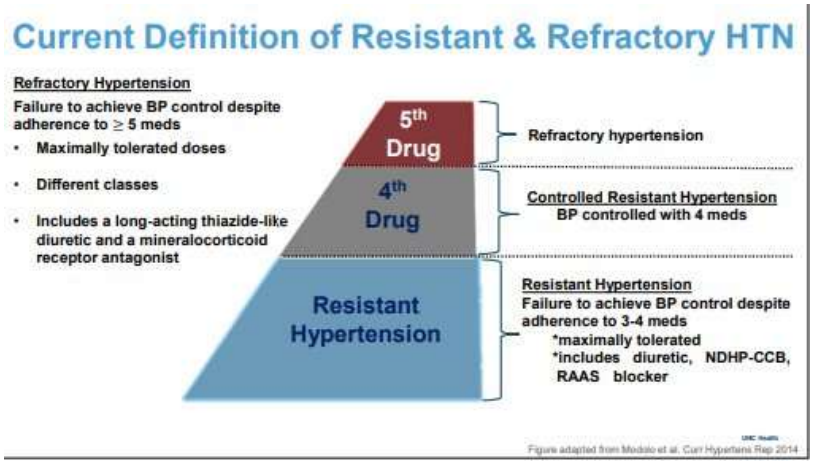
Resistant vs Refractory Hypertension



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Resistant vs Refractory Hypertension

- Definitions of resistant hypertension and refractory hypertension are different
- Refractory hypertension = uncontrolled BP despite treatment with 5 medications
  - Maximally tolerated doses
  - Different classes
  - Includes a long-acting thiazide like diuretic and a mineralocorticoid receptor antagonist
- Refractory hypertension is not common

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Resistant vs. refractory hypertension

- Resistant hypertension is characterized by persistent fluid retention that is multifactorial in etiology (CKD, hyperaldosteronism, obesity, sodium intake)
- Hypothesis is that refractory hypertension is characterized by increased sympathetic output

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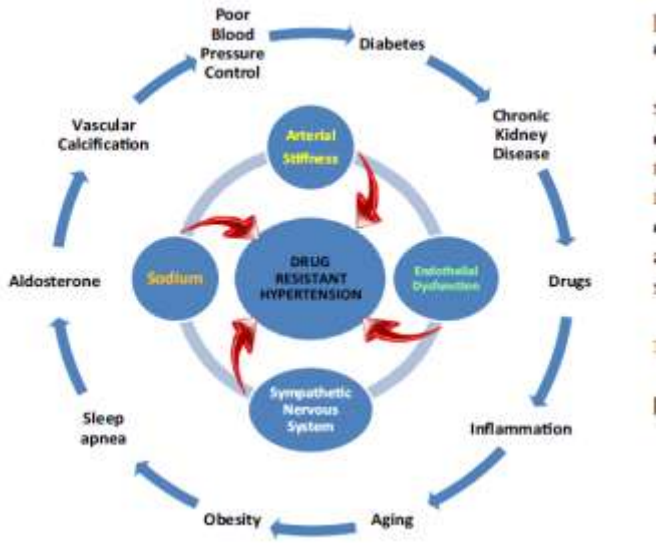
Resistant Hypertension



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Hypertension and Renal Disease: Clinical Considerations

Table 2. Comorbidities and Drugs Interfering With Blood Pressure Control

Comorbidities	Interfering Drugs
Smoking	NSAIDs
Smokeless tobacco	Sympathomimetics
Obesity/insulin resistance	Nasal decongestants
Obstructive sleep apnea	Appetite suppressants
Excess alcohol intake	Cocaine
Anxiety	Stimulants
Hyperventilation	Methylphenidate
Panic attacks	Amphetamine
Chronic pain syndromes	Caffeine
	Oral contraceptives (estrogen)
	Adrenal steroids
	Natural licorice
	Tacrolimus, cyclosporine
	Erythropoietin
	Herbals (ephedra, ma huang)

NSAIDs, nonsteroidal anti-inflammatory drugs.

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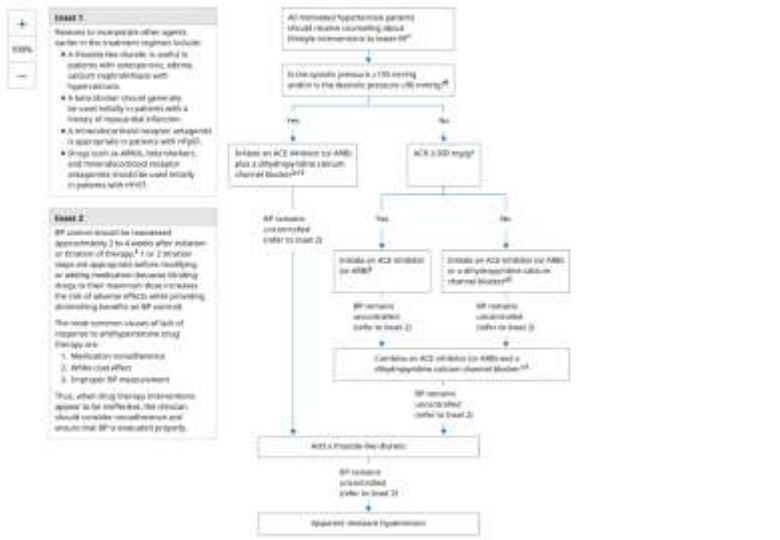
Approach to antihypertensive drug therapy: Patients without indications for a specific drug (Inset 1)



ACE: angiotensin-converting enzyme; ACR: albumin-to-creatinine ratio; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; BP: blood pressure; CKD: chronic kidney disease; ESKD: end-stage kidney disease; HFpEF: heart failure with preserved ejection fraction; HFrEF:

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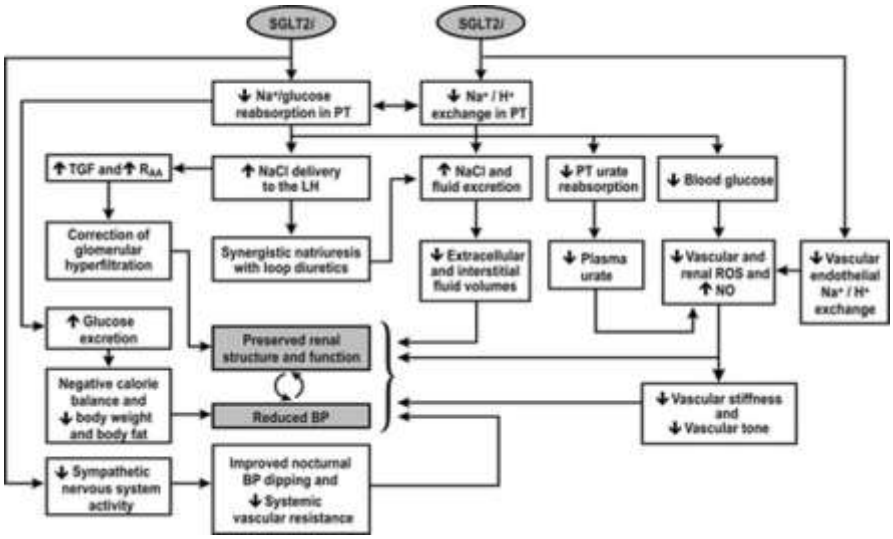

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Hypertension and Renal Disease: Clinical Considerations

- Mineralocorticoid receptor antagonists
  - RAS blockade – Aldosterone escape phenomenon
  - MRAs – lower residual albuminuria and ameliorate kidney fibrosis
  - Steroidal MRAs- Spironolactone, eplerenone
    - Gynecomastia, higher incidence of Hyperkalemia, worsening renal function-AKI
  - Nonsteroidal MRAs- Finerenone and esaxerenone
    - Similar reductions in proteinuria with lower risk of hyperkalemia

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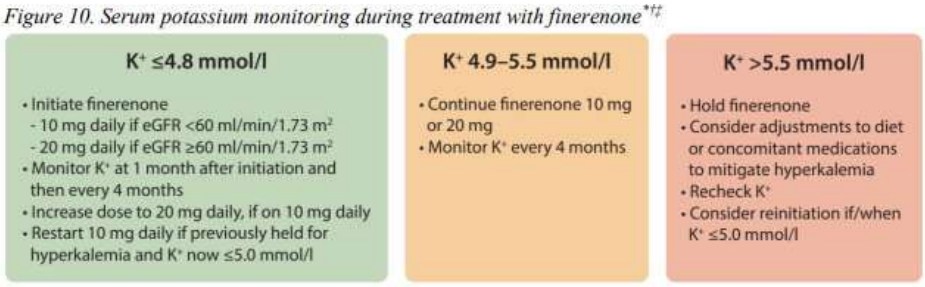
Hypertension and Renal Disease: Clinical Considerations



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Hypertension and Renal Disease: Clinical Considerations

- GLP1RA
  - Reduces SNS activity
    - through the antagonism of GLP1R in the brain and the carotid body
    - decreases vascular smooth cells tone
  - Enhances natriuresis by inhibiting the sodium-hydrogen antiporter 3 (NHE3)

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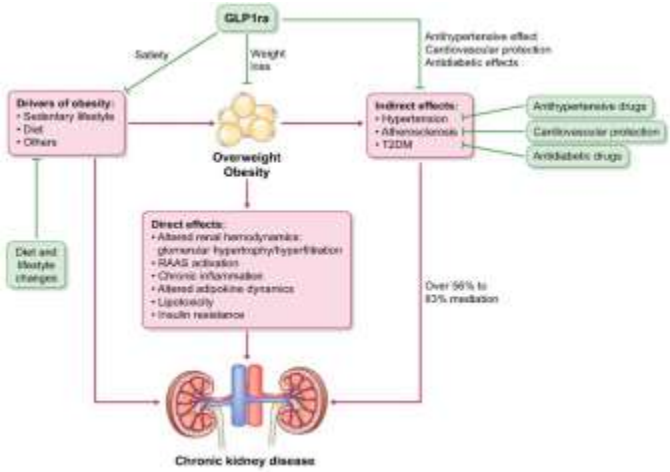
Hypertension and Renal Disease: Clinical Considerations



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Hypertension and Renal Disease: Clinical Considerations

- Aldosterone Synthase inhibitors
  - Baxdrostat,
    - 800 patients with uncontrolled hypertension (73 percent had resistant hypertension)
    - At 12 weeks, baxdrostat (at 1 to 2 mg once daily) reduced seated systolic pressure by 8.7 to 9.8 mmHg relative to placebo; severe hyperkalemia developed in 2.3 and 3.0 percent of patients treated with 1 and 2 mg of baxdrostat, respectively.
  - Baxdrostat may be used as alternatives in patients who have side effects to mineralocorticoid receptor antagonists.
    - https://www.uptodate.com/contents/whats-new-in-nephrology-and-hypertension/abstract/19

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Hypertension and Renal Disease: Clinical Considerations

- Endothelin antagonists
  - Aprocitentan approved for treating Hypertension
    - Non-selective ET-1 antagonist
    - Used in combination with other antihypertensives
    - Causes headache, flushing, peripheral edema, hepatotoxicity
  - Sparsentan(ARB +ET-1 antagonist) approved for use in IgA nephropathy

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Hypertension and Renal Disease: Clinical Considerations

- Renal denervation
  - RADIANCE Clinical Trial Program (US ablation) and the SPYRAL HTN (RF ablation) Clinical Trials demonstrated renal denervation efficacy in reducing BP at 6 months against sham controls in both home and office measurements and a costeffectiveness analysis concluded that RDN performed with catheter-based radiofrequency can be a cost-effective strategy for uncontrolled hypertension. However, in the cited trials eGFR <45 ml/min/1.73m2

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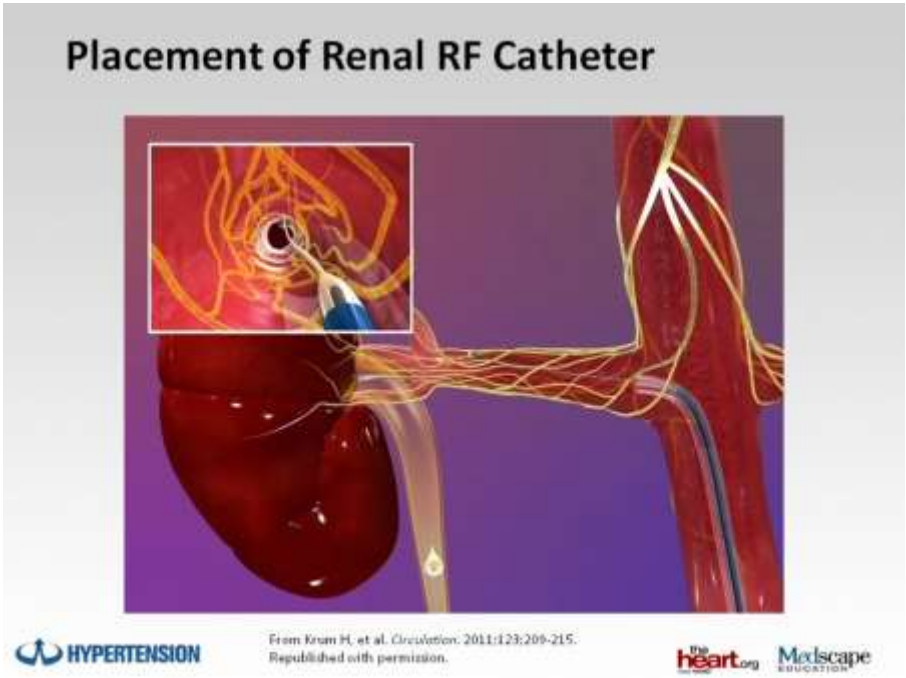

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Conclusion

- Hypertension is an independent risk factor for CKD and uncontrolled hypertension causes increased CV morbidity in CKD patients
- Understanding pathophysiology of hypertension in renal disease helps in choosing appropriate antihypertensive medication , adding another BP medication for good control of BP
- There is difference in Resistant Hypertension and Refractory Hypertension
- Individualized treatment of hypertension- Non pharmacologic and pharmacologic treatment.

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