Hypertension and Kidney

Christian W. Mende, MD

FACP,FACN,FASN,FAHA

Clinical Professor of Medicine,

University of California, San Diego

La Jolla, Calif.

FACULTY DISCLOSURE

Company	Nature of Affiliation	Unlabeled Product Usage
		NONE
• Boehringer Ingelheim • Lilly • AstraZeneca • Bayer	Speakers Bureau and Advisory Boards	

US HYPERTENSION (Adults)

Prevalence 45.6% (100.3 Mill.)

controlled 46.6%

Categories Normal BP < 120 / < 80 mmHg

Elevated BP 120 -129 / < 80 mmHg

Hypertension

Stage 1 BP 130 -139 / 80 - 89 mmHg

Stage 2 BP ≥ 140 / 90 mmHg

AHA / ACC 2017

Approach to Hypertension Therapy

Stage I BP 130 /80 to 139 /89 mmHg

1) evaluate underlying CVD Risk (ACC Calculator)

2) if **≤ 10% Risk = Non-pharmacological RX**
(2 /3 of Patients)

3) if **≥ 10% Risk = start Drug Therapy**
(1 /3 of Patients)

(BP of 130 /80 to 139 /89 mmHg will double Risk of Myocardial Infarction)

Hypertension in CKD

1) **Incidence up to 90 %**
2) associated with NON dipping (absent 10% nocturnal SBP decline)
3) 10 -30 % Masked hypertension (normal office , but elevated BP outside office)
4) 10- 20% White coat hypertension
5) **50% Refractory hypertension**

   def . : BP >130/ 80 mmHg despite full doses of 3 drugs including a diuretic

Control of SBP to < 130 mmHg has NOT been shown to slow progression of established CKD :

a) AASK , REIN-2 , SPRINT

b) exception : MDRD trial showed positive effect on eGFR progression (proteinuria of > 1000 mg)

Hypertension and CKD

1) **1/3** of Patients with Hypertension have **CKD** (2)

2) **60% need 3 or more drugs** f or BP control (3)

2) **Incidence of HF and Mortality in CKD (1)**

eGFR 45 – 60 ml/ min = x 2

30 – 44 ml/ min = X 4

(1) Fox CS et.al. 2012 Lancet ;38 :1662

(2) USRDS NIH 2020

3) Sinha AD. 2019 Clin J Am Soc. Nephrol 2019 ;14 :757

Chronic Kidney Disease (CKD)

Chronic Kidney disease is common

a) 15 % of adult USA population (= 37 Million , 1 out of 7)

b) **42 % of patients with type 2 diabetes**

CKD is diagnosed (when present for 3 months or longer) with :

1) Reduced kidney function (eGFR < 60 ml/ min)

OR

2) Albuminuria ≥ 30 mg /g creatinine (UACR)

BOTH are independent factors in establishing a diagnosis of CKD as well as assessing risk for

1) Cardiovascular Events
2) Heart Failure
2) CKD progression

Albuminuria

When to test for UACR (Urine/Albumin/Creatinine Ratio)

Present in many Conditions :

Metabolic Syndrome
Pre-diabetes
Diabetes
Obesity
Renal Diseases (Glomerulonephritis, Lupus, etc.)
Cardiovascular Disease (CAD, CVA , PVD)
Heart Failure
Hypertension (usually Stage II , uncontrolled SBP)

Significance

1) Sign of endothelial Dysfunction (" renal hCRP ")
2) Risk of Progression to higher albuminuria levels
3) Risk for CKD progression
4) Criterium for CKD , even with normal eGFR
5) Sustained > 30% Albuminuria Reduction = 24 % reduced ESKD Risk *

CURE – CKD Study

Cohort of > 2.6 Mill. adults and children from Provident Health Seattle and UCLA identified in 2006 - 2017 from electronic records at risk for CKD because of :

Prediabetes Diabetes Hypertension

606 00 adults with CKD noted (mean eGFR 53 ml/min)

only

8.7 % UACR tested

20.6 % with + UACR received ACE- inhibitors /ARB's

but

33% received potentially nephrotoxic drugs = NSAID/ PPI

Tuttle, KH et.al CKD-CURE Registry , JAMA 2020; 2(12): 1-14

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>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.

What is the Connection of Hypertension and Chronic Kidney Disease (CKD) ?

Role of Hypertension in causing CKD

a) primary etiology

b) major component of progression

Mechanism in Hypertension as a cause of CKD

1) **Glomerular hypertension** (normal ~ 50 -60 mmHg)

a) impaired autoregulation of glomerular pressure by hyalinosis (arteriolosclerosis) of afferent (preglomerular) = increased transmission of systemic BP

b) **endothelial dysfunction** , ROS with oxidative stress and reduced Nitric Oxide casing intrarenal vasoconstriction

2) **Activation** of

a) **RAAS** with elevated Angiotensin II and Aldosterone

b) **Sympathetic System** with renin release and vasoconstriction

3) **Upregulation of Mineralocorticoid receptor**

4) Salt sensitivity with volume expansion

End Result : Nephrosclerosis with ischemic glomeruli and CKD

Mechanism in the Development and Progression of CKD
(including CKD in Diabetes)

1) **Metabolic**

Hyperglycemia , Advanced Glycation Products (AGE's) , AGE adducts
Insulin Resistance
Obesity

2) **Hemodynamic**

Hyperfiltration, systemic and glomerular hypertension ,
Activation of RAAS (Angiotensin II , Aldosterone)
Sympathetic nervous system
Hypoxia (medulla , renal tubules)

3) **Inflammatory and Fibrotic Factors**

Cytokines : IL 6 , TGF beta , TNF alpha ,
Angiotensin II ,
Aldosterone , Mineralocorticoid receptor (MR) upregulation
Reactive Oxygen Species (ROS) , FGF 23 , PA-1 , Metalloproteinases

What Factors contribute to the Risk of DKD ?

Main Risk Factors of DKD :

1) **Hyperglycemia**

2) **Advanced glycation products (AGE's)** and metabolites (AGE free adducts)

3) **Hypertension** (BP > 130 / 80 mmHg)

4) **Obesity** (BMI ≥ 30)

Additional Risk Factors are :

Dyslipidemia (renal artery stenosis , arteriolar hyalinosis , nephrosclerosis)
Smoking (increases albuminuria and eGFR decline)
Age (eGFR loss of 0.7 ml/ year starting age 40)
Family history of CKD
Race (Afro- American , Hispanic , Pacific Islanders and American Indian)
High protein diet (above 1.2 gm of protein / kg weight per day)

How does Hyperglycemia affect the kidney ?

Hyperglycemia

causes increased **pre** glomerular vasodilation (TGF)

post glomerular vasoconstriction (RAAS)

both causing

a) hyperfiltration

b) glomerular hypertension

Consequences : damage to the filter (loss of podocytes , mesangial proliferation) with

a) loss of kidney function

b) albuminuria (subsequent interstitial fibrosis)

Indirect effects include renal injury secondary to :

Advanced glycation products (AGE's)

Renal insulin resistance

RAAS activation , MR upregulation

ROS and oxydative stress

Inflammation and Fibrosis

Mitochondrial dysfunction

Complications of CKD
(irrespective of etiology)

CKD is a major Non traditional risk factor for CV events :

Myocardial infraction

CVA

HF , atrial fibrillation

New onset Hypertension or Progression of Hypertension

Albuminuria per se with normal eGFR is an additional risk factor

a) endothelial dysfunction (renal hCRP)

b) progression of albuminuria and worsening underlying CKD

Combination of Diabetes and CKD = 4 fold increased Risk for CV Events and CV Mortality

CKD = 70% CV Mortality and only 4% reach ESKD

NON-traditional CVD Risk Factors in CKD

Oxidative stress / ROS

a) low SOD and Glutathione Peroxidase b) elevated Reactive Oxygen Species

Inflammation (elevated = hCRP, IL6, TNF alpha , Fibrinogen)

LDL oxidation , Hypertriglyceridemia , low HDL

a) elevated Lp a , Homocystine , APO B

Hyperuricemia

Hyperleptinemia

Anemia

a) Iron deficiency increases FGF 23 with increased risk of Heart Failure / mortality

Abnormal Calcium / Phosphate Metabolism with elevated

a) FGF 23 b) PTH

Endothelial Dysfunction

a) elevated ADMA with reduced NO Production

AGE's (Advanced Glycation Products in T2DM) and AGE free adducts (Hydro-imidazolones)

Activation of RAAS and Sympathetic System

Myocardial Fibrosis (elevated Cystatin C inhibits Cathepsin)

LVH , Atrial Fibrillation

DKD Progression and Cardiovascular Risk

30,222 type 2 diabetes , with newly diagnosed DKD
age 64 , eGFR 52 / ml/min, without HF, MI or CVA followed for 2 years :

DKD compared to T2D without CKD :

eGFR loss of 3.0 ml /min in 2 years **(1.5 ml /year)** increased cardiovascular risks by :

HF	50%
MI	39%
MACE	45%

Conclusion :

CKD strong independent risk factor for CVD

Cabrera, CS (AstraZenica + University Gothenburg) KI Reports 2020; 5 : 1651

CKD Blood Pressure Guidelines

(2017 AHA / ACC Guidelines)

BP < 130 / 80 mmHg

Use ACEI or ARB'S if > 30 mg /d Albuminuria

Lifestyle :

BMI > 20 – 25 ,
Salt < 5 gm (2000 mg Na)
Exercise 30 min 5 X / week

Hypertension Guidelines in CKD
(KDIGO 2021)

Blood Pressure Goal

SBP < 120 mmHg (if tolerated)

No DBP goal

Choice of Medications

1) RAAS Blockade if HTN + UACR > 30 mg/g
2) Thiazide diuretic
    a) Chlorthalidone , effective with **eGFR > 20** ml/ min
3) CCB

How to reduce the Risk of DKD with Diabetes

Control of all additional Risk Factors :

1) **Hyperglycemia**

control of A1C to below 7% , if tolerated without hypoglycemia

2) **Hypertension**

BP goals < 130/80 mmHg

(< 120/80 mmHg for urine albumin above 300 mg/g if tolerated)

3) Attain a weight as close as possible to " normal ", especially in **obesity**

4) Dyslipidemia

LDL levels < 100 mg% and < 55 mg /dl with established cardiovascular disease

5) **Discontinue smoking**

6) Avoiding exposure to toxic drugs

a) daily us of NSAID's , PPI

NON- Pharmacological Therapy in Hypertension

1) **Weight Loss** for overweight / obese Patients
(10 kg = 10 mmHg SBP reduction)
2) Healthy Diet = **DASH Diet**

3) **Sodium Restriction to < 3.7gm Salt** (1500 mg Na)*
= lower SBP by 4.4 mmHg
a) NHANES 2014 = 2.5 x greater (3750 mg Na)

4) **Increase Potassium** > 3,500mg (~ 45 meq) *
= SBP lower by 3.4 mmHg
best with Diet (Fruits) unless contra- indicated in CKD

5) Increased **physical Activity**
6) **Reduced Alcohol** Intake men 2 and women 1 Drink / Day

Whelton PK Circulation 2018 ; 137 : 247

WHO 2013 and AHA / ACC 2017

Choice of Medication with Comorbidities

(AHA / ACC 2017)

Diabetes or CKD

Start Drug Therapy at 130 /80 mmHg with

Goal : < 130 /80 mmHg

First Line: **HCTZ**

CCB

ACEI or ARB

UACR ≥ 30 mg/g = use ACEI or ARB (max. tolerated dose !)

Note : **Beta –Blockers = NOT first Line, unless HF or IHD**

NO Atenolol ! (inferior to other BB's)

How effective are antihypertensive Drugs ?

Systolic BP Reduction of 6 major Drug Classes

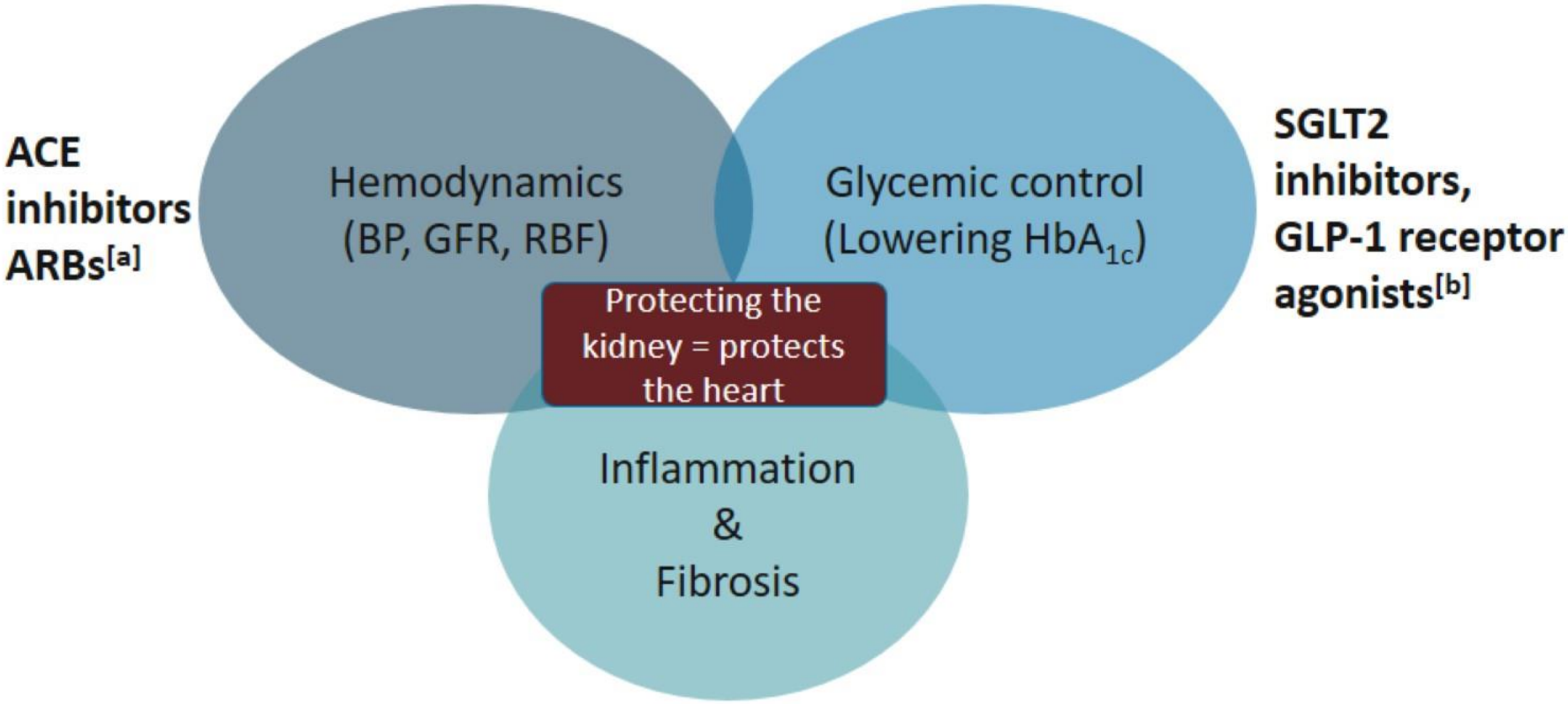
Mono therapy	**~ 10 -12 mmHg**
Adding second Drug	~ 5 mmHg
Adding third Drug	~ 5 mmHg

Adding MRA (Aldactone , Eplenerone) ~ 10 - 20 mmHg

Renal Denervation ~ 10 - 11 mmHg

Townsend R Kidney 360.asnjournals Jan. 2, 2020 (ahead of print)

Efficacious Treatments Are Available for DKD



Steroidal MRA: spironolactone, epleronone[c]
Nonsteroidal MRA: finerenone,* esaxerenone*[c]

*This agent has not yet been approved by the US FDA.

a. Zou H, et al. *Cardiovasc Diabetol*. 2017;16:1-11; b. Garcia-Carro C, et al. *J Clin Med*. 2019;8:1-16; c. Kolkhof P, et al. *J Endocrinol*. 2017;234:T125-T140.

What Drugs are available for the treatment of DKD ?

The following drugs are approved by the FDA and have shown to slow progression of DKD :

1) **Ace inhibitors or Angiotensin receptor blockers (ARB's**) reduce
   a) albuminuria by 40- 45 %
   b) progression of CKD by maximum of 20 %
   c) Hypertension control

2) **Sodium glucose cotransport inhibitors** (SGLT2 inhibitors) reduce
   a) albuminuria by 35- 45 %
   b) DKD progression by 35 - 45 % (**eGFR slope by 2- 3 ml/ year**)

3) **Mineralocorticoid Antagonist** (Finerenone)
   a) albuminuria reduction 31%
   b) CKD progression by 18% (**eGFR slope 1.3 ml/year**)

4) GLP 1 agonists are NOT FDA approved , but reduce albuminuria (~ 30 %) and may have kidney protective properties in DKD

Guidelines (KDIGO 2020) recommend starting doses in DKD :

Metformin (eGFR $\geq$ 30) and SGLT 2 inhibitor (eGFR $\geq$ 20 ml /min)

Drug-induced Reduction of Albuminuria and subsequent Renoprotection (Meta-analysis)

21 Trials and 78,342 Patients with Albuminuria, Age 12- 68, eGFR 19- 92 ml /min, followed for 11- 56 months .

Results (average for all trials)

Albuminuria Reduction = 19%

ESRD Risk Reduction = 17%

Conclusion :

30% Reduction of Albuminuria = 24% ESRD Risk Reduction

(Findings are consistent regardless of Drug Class)

REASSURE Consortium , Heerspink, H. etal. 2015 JASN ;26 (8) : 2055

Rational for RAAS Therapy in CKD

ACE-inhibitors or ARB's are 1st choice :

1) Lower Aldosterone levels
2) Reduce Angiotensin II with lower efferent tone
   = lower glomerular pressure
3) Reduce albuminuria
4) Benefit HF (if associated)
5) Benefits are uncertain for non - albuminuric CKD

Typical drug sequence in treatment of hypertension in CKD

RAAS + CCB = Chlorthalidone (Torsemide if eGFR < 20) + MRA

Sinha, AD and Agarwal, R Clin J Am Soc Nephrol. 2019 ; 14 : 757

Comparing First line Monotherapy
ACE inhibitors vs. ARB's

2,3 million hypertensives started on monotherapy of ACE inhibitor vs ARB evaluated between 1996 to 2018

(ALLHAT, HOPE , electronic health records)

Efficacy **No difference in Cardiovascular Outcome**

acute MI , CVA, Heart Failure

Safety ACE inhibitors exhibited increased Risk of

32% cough

3.3 fold angioneurotic edema

32% pancreatitis

GI bleeding

Chen RJ Hypertension 2021 ;78 :591

ACE inhibitors or ARB's are mainstay of drug therapy in CKD with reduction of

1) Aldosterone lowering peripheral vasoconstriction and systemic BP
2) Angiotensin II with efferent glomerular vasodilation lowering glomerular pressure

Sinha AD and Agarwal R Hypertension 2019 ; 49 :757

Association of Acute Plasma Creatinine Increase after RAAS Blockade

In a retrospective Study in Stockholm of 31,951 hypertensives followed for 3.5 years with

acute creatinine increase > 10% in first 2 months = associated with

1) **increased Mortality secondary to cardiovascular Events**

2) **ESRD** (excluded was an eGFR < 30 ml/ min).

Mortality increased by

15 % = Creatinine rise of 10 – 19 %

22 % = Creatinine rise of 20 – 30 %

55 % = Creatinine rise > 30 %

The Rise in Creatinine is presumed to be a " Biomarker "

and not an adverse outcome secondary to RAAS Blockade

Fu, EL. et. al. Clin J Am Soc Nephrol 2019 ; 14 : 1336

RAAS Blockade Discontinuation

1) 141,252 Veterans with CKD and Albuminuria whose RAAS blockade (ACEI or ARB) was discontinued for > 6months and followed for 4,9 years

Discontinuation of RAAS Blockade caused adverse Outcomes with increased Risk :

1) **74% Mortality**
2) **59 % ESKD**

Walther CP et.al. Nephrol Dial Transplant 2021; 36 (10) : 1893

2) 205,108 US patients , including > **20,000 with Heart Failure** stopped RAAS blockade because of hyperkalemia :

Mortality doubled

(compared to patients continued on maximum does)

Epstein M et.al Am J Manag Care 2015 ; 21 : s212

NSAID use in Hypertension and CKD

1) **Lower efficacy of ALL antihypertensive drugs , incl. Diuretics by 10 -15 % (except CCB's)**

2) Cause Salt Sensitivity (> 3-4 days of use)

3) In CKD stage 3 (< 60 ml GFR) and lower

a) Reduce GFR by 10-15 % (during therapy)
b) Risk of
   - Hyperkalemia
   - AKI
   - Heart Failure

Resistant Hypertension (RHT)

Definition:

NOT at BP Goal : 130 / 80 mmHg

despite 3 different antihypertensive Drug Classes in moderate to full Doses , including a Diuretic

Incidence:

2 -12 % of all hypertensive Patients

Kaiser PermanenteStudy Daughertey SL. et.al. 2012; 125 (3) :1635

NHANES Study Egan, BM et.al 2011 ; 124 (9) : 1046

Issues in Resistant Hypertension

1) **1/3 controlled by ABPM and therefore NOT " Resistant "**

2) **Adherence** German study using urine and blood drug analysis had only **53% compliance** (#)

3) Identify contributing Factors
Obesity , **excessive ETOH, high Salt Intake**

4) Stop interfering Substances
NSAID , Stimulants (Sympathomimetics, Ephedra)
Oral Contraceptives , Licorice

5) ***Low Use Mineralocorticoid Antagonists*** *:*
Aldactone (Eplenrenone) used in NHANES 3%
REGARDS 18 %

6) Identify secondary Causes

Jung O et.al. J.Hypertens 2013 ;31: 766-774
REGARDS Study :Calhoun DA. et.al Hypertension 2014 : 63 :451
AHA / ACC 2017

Chlorthalidone in Hypertension and CKD 4
(eGFR < 30ml/ min)

160 poorly **controlled hypertensive patients** , 76% with diabetes , on 3.4 BP meds

including ACEI , ARB, BB, CCB , 6**0 % on Loop diuretics**

Baseline data : BP 141/ 69 mmHg, **eGFR 23 ml/min** , UACR > 300 (69%) , NT-pro BNP ~ 545

81 placed on Chlorthalidone ~ 25 mg vs . continued BP meds in control group

followed for 12 weeks with 24 hr AMBP recordings

Results :

Chlorthalidone lowered

1) **BP 10.3 / 3.9 mmHg**
2) **UACR ~ 50% %**
3) NT- pro BNP ~ 11%

Conclusion :

Chlothalidone in CKD (stage 4) lowers BP effectively

Adverse Events :

Hypokalemia (10 vs 0) Hyperglycemia (18 vs 5), AKI (41 vs.12 = pre renal) , Hyperuricemia (20 vs 9)

Agarwal R et.al. NEJM 2021 ;385 : 2507

Therapy of Resitant Hypertension

Reduce Salt intake (measure urine spot Na)

Increased K intake by ~ 50 mEq / day

(SBP lowered BP 6.8 / 4.6 * in non-CKD hypertension)

Chlorthalidone 12.5 to 25 mg (instead of HCTZ)

ACE inhibitors or ARB's and CCB in full Doses

Aldactone (Eplenrenone , Amiloride)

If resting Pulse above 80/min add

Vasodilating Beta –Blocke (Nebivolol , Carvediolol)

Consider renal denervation (~ 10 mmHg SBP reduction)

Townsend RR. et.al. Hypertension , 2016; 68 :1073

* Binia ,A. et. al. J.Hypertension, 2015; 33:1509

CKD Diagnosis and Treatment

Screening and Diagnosis

Assess

- UACR
  – and –
- eGFR

Diagnose CKD if:

- Persistent UACR ≥30 mg/g
  – and/or –
- Persistent eGFR <60 mL/min/1.73 m^2

Risk Assessment

CKD associated with:

- ↑ ASCVD (increased risk if UACR ≥30 mg/g)
- ↑ HF
- ↑ ESKD
- ↑ Hypertension
- ↑ Arrhythmia
- ↑ Hypoglycemia

Prevention and Treatment

Goal-directed therapy

- BP control
- Glucose control
- Lipid control

Lifestyle

- Exercise (150 min/week)
- Nutrition (individualized, no dietary protein restriction)
- Weight loss (if obesity)
- No smoking

Medications

- Max-tolerated RASi if hypertension + albuminuria
- SGLT2i if eGFR ≥20 mL/min/1.73 m^2
- Nonsteroidal MRA (finerenone) if T2D + albuminuria[a]
- Consider GLP1-RA if T2D

[a] Outcomes evidence only available for finerenone. Albuminuria = UACR ≥30 mg/g.

ASCVD = atherosclerotic cardiovascular disease; BP= blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GLP1-RA = glucagon like peptide 1 receptor agonist; HF = heart failure; MRA = mineralcorticoid receptor agonist; RASi = renin angiotensin system inhibitor; SGLT2i = sodium glucose cotransporter 2 inhibitor; T2D = type 2 diabetes; UACR = urine albumin-creatinine ratio.