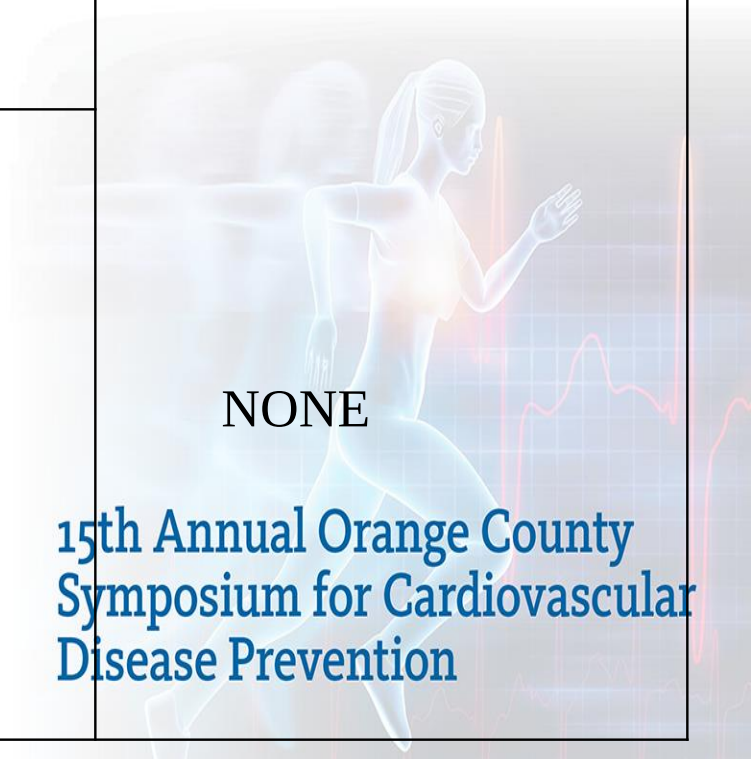
# Pillars of Therapy for Prevention of CVD in CKD Patients
# The Cardiorenal Syndrome

CHRISTIAN W. MENDE MD
FACP,FACN,FASN,FASH,FAHA
Clinical Professor of Medicine,
University of California, San Diego
La Jolla, Calif.

15th Annual Orange County Symposium for Cardiovascular Disease Prevention

# *FACULTY DISCLOSURE*

| Company | Nature of Affiliation | Unlabeled Product Usage |
|---|---|---|
| | | NONE |
| • Boehringer Ingelheim<br>• Lilly<br>• AstraZeneca<br>• Bayer<br>• Casana<br>• KBP<br>• Sc Pharma | Speakers Bureau and /or Advisory Boards | |



15th Annual Orange County Symposium for Cardiovascular Disease Prevention

# Cardiorenal Syndrome ( CRS )

Definition :

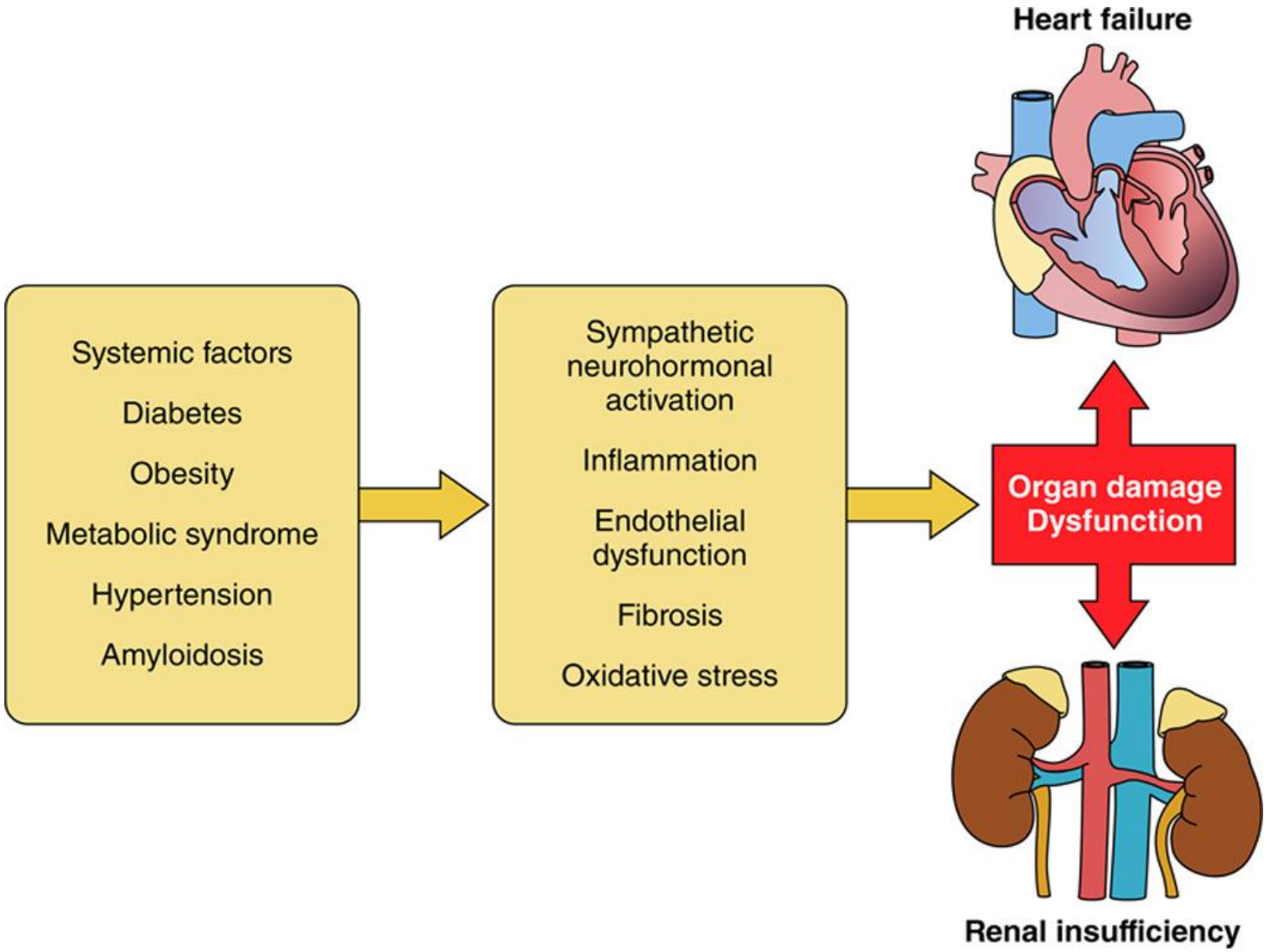
A syndrome encompassing a spectrum of disorders involving both the heart and kidneys in which acute or chronic dysfunction of one organ may induce acute or chronic dysfunction in the other organ .

This requires the presence of signs and symptoms of structural or functional cardiac and renal abnormalities .

Interactions between heart and kidney include :

- Hemodynamics
- CVD existing in both organs
- Neurohormonal activation ( RAAS , Aldosterone , SNS , Vasopressin )
- Cytokines ( IL6 , TGF beta, TNF alpha )
- CKD associated anemia , inflammation , metabolic acidosis and insulin resistance

AHA Scientific Statement , Circulation 2019 ; 139 : e 840




Faiez Zannad. Circulation. Cardiorenal Syndrome Revisited, Volume: 138, Issue: 9, Pages: 929-944, DOI: (10.1161/CIRCULATIONAHA.117.028814)

# Chronic Kidney Disease ( CKD)

Chronic Kidney disease is common

**14% US adults or 37 Million ( 1 in 7 )**

present in **42 % Diabetes / 25% Hypertension / 40% CVD / 18% Obesity**

2018 = 780,000 had ESKD and 181,000 started dialysis ( USRDS 2020 )

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

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

OR

2) Albuminuria $\geq 30$ mg /g creatinine ( UACR )

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

1) Cardiovascular Disease ( MI, CVA, HF, PAD , Afib . )
2) CKD Progression

KDIGO 2023

# eGFR and Urine Albumin-Creatinine Ratio (UACR mg/g)

**Normal loss of eGFR 0.7-1.0 ml / year** ( after age 40 )

Chronic kidney disease in Diabetes = 2 – 5 ml / year eGFR decline

a) **without albuminuria** eGFR loss may be < 2 ml /year

b) with UACR > 900 mg eGFR decline can be 4 – 6 ml /year
(CREDENCE / DAPA CKD / EMPA CKD )

Observe for rapidly progressive CKD ≥ 5 ml/year decline
Non-diabetic CKD causes to be excluded

UACR testing best early AM sample .

Falsely elevated:
- post strenuous exercise
- fever, infection
- UTI
- uncontrolled hypereglycemia
- menstrual period

# Albuminuria

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

Present in many Conditions :

Metabolic Syndrome , Prediabetes
Diabetes
Obesity
Renal Diseases ( Glomerulonephritis, Lupus, etc. )
Heart Failure
Hypertension

Significance

**Sign of endothelial Dysfunction** ( " renal hCRP " ) with Risk for
Cardiovascular disease, heart failure
Progression to higher albuminuria levels
CKD progression
**Criterium for CKD ( even with normal eGFR )**

# Albuminuria Testing (UACR )in US adults at risk for Chronic Kidney Disease ( CKD )

192,108 adults from **NHANES** data for 2007 -2018 and **Optum** health records with 97% hypertension or 26% diabetes , age ~60 , ~eGFR 84 ml/min

**17.5 % UACR done**

Estimated prevalence of UACR ~ 13.4 %

65 % ( 2/3) patients with UACR not done

Conclusion :

**CKD diagnosis missed in 21,231** ( 13.4% cohort = 1/7 )

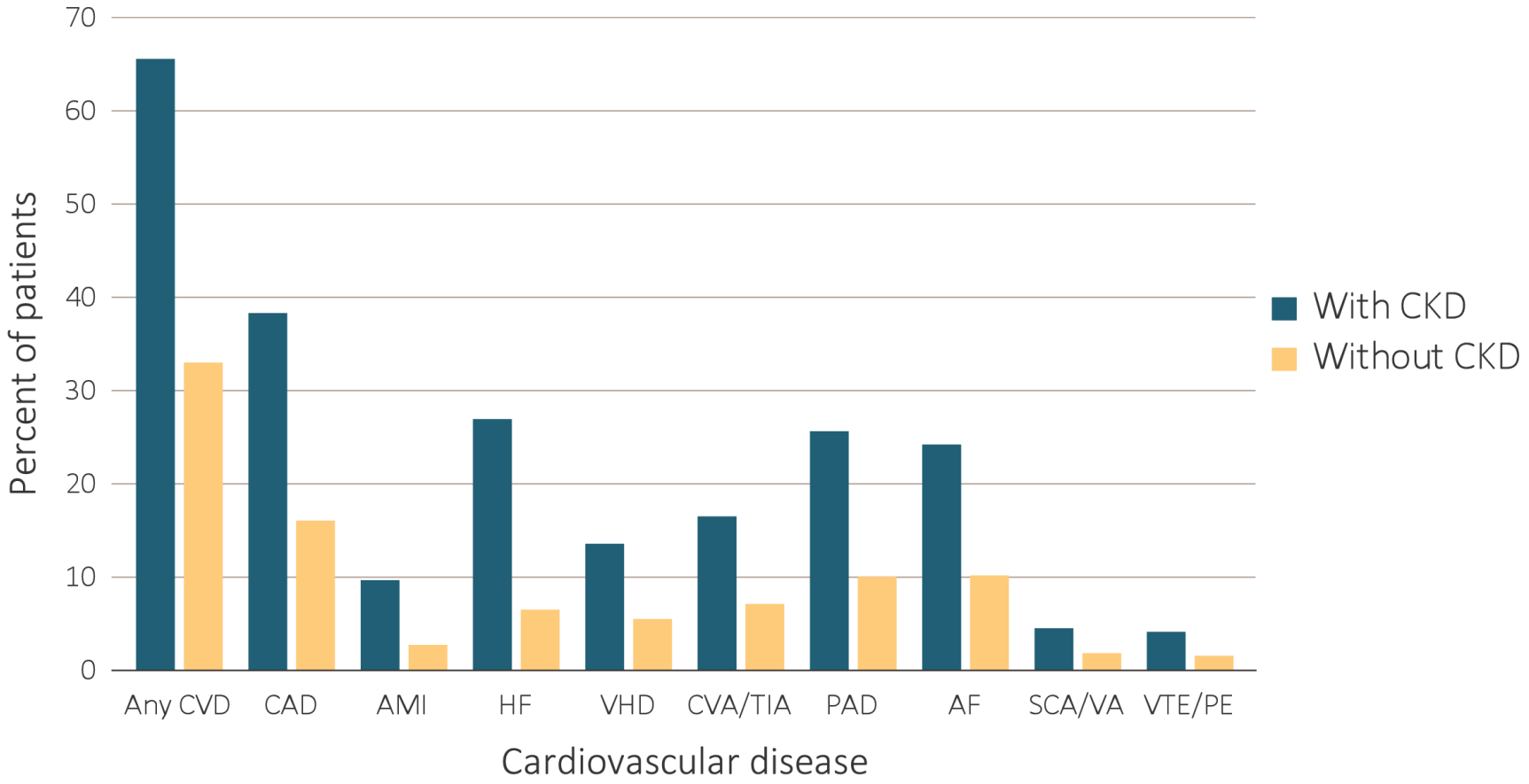
Consequences : **Reduced odds for receiving Therapy**

ACEinhib / ARB = 2.4 fold , SGLT2 inhib. = 8.2 fold,

BP control < 140/90mmHg = 1.2 fold

Chu D et.al. JAMA 2023 ; 6 (7) e 2325230

# Prevalence of cardiovascular Diseases with or without CKD, 2016

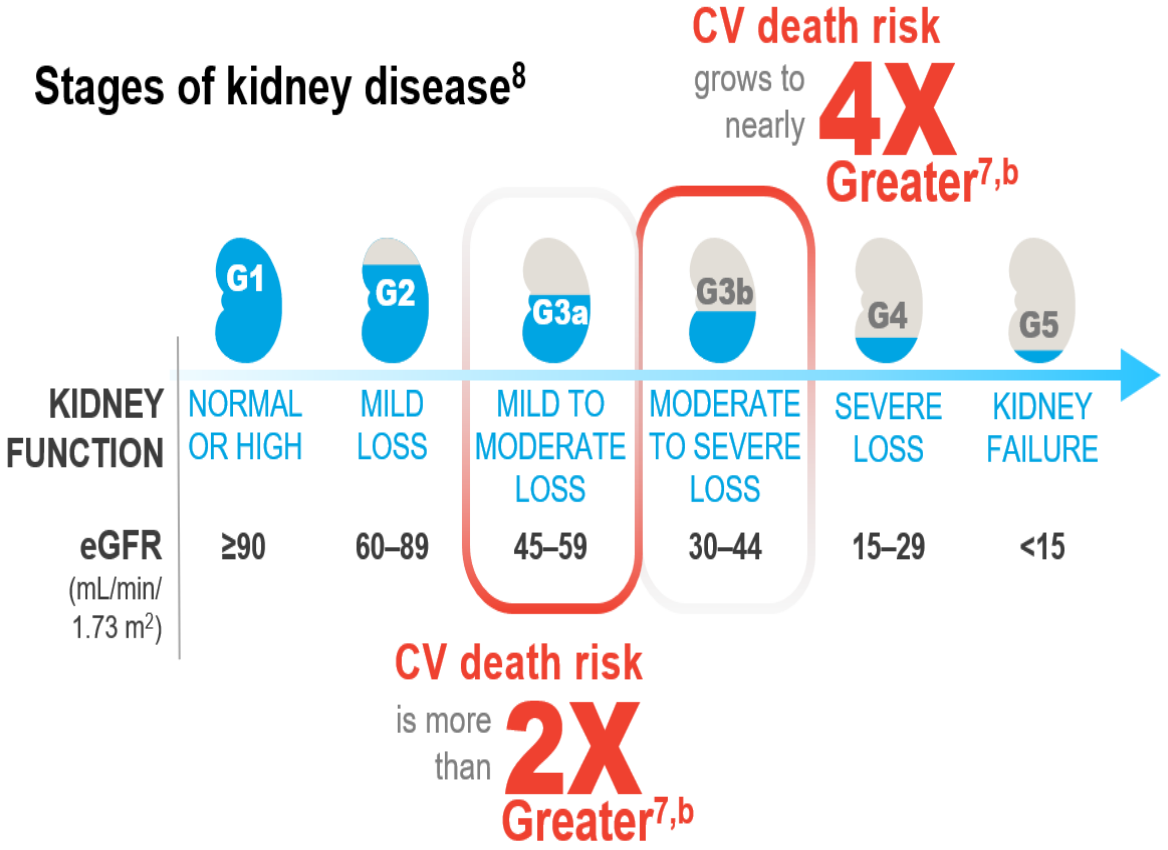



*Data Source:* ***Medicare 5% sample***.

*Abbreviations: AF, atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CKD, chronic kidney disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; CVD, cardiovascular disease; HF, heart failure; PAD, peripheral arterial disease; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; VHD, valvular heart disease; VTE/PE, venous thromboembolism and pulmonary embolism*

# When Left Undertreated, CKD Can Lead to CV Death[1-3]

- Despite managing risk factors and treatment with ACEi/ARB therapy, patients with CKD may still have a substantial risk of worsening kidney function[4-6,a]
- Declining eGFR is associated with an increasing risk of CV death[7,b]




[a]Studies included patients with diabetic kidney disease.[4-6]

[b]Meta-analysis of 1,024,977 participants. Comparisons are risk of CV death relative to reference patients with an eGFR 90–104 mL/min/1.73 $m^2$ and ACR <10 mg/g. Participants with an eGFR 45–59 mL/min/1.73 $m^2$ and ACR 30–299 mg/g had an adjusted HR of 2.27 in patients with diabetes and 2.57 in patients without diabetes. Those with an eGFR 30–44 mL/min/1.73 $m^2$ and ACR 30–299 mg/g had an adjusted HR of 3.62 in patients with diabetes and 3.52 in patients without diabetes.[7]

ACEi=angiotensin-converting enzyme inhibitor; ACR=albumin-to-creatinine ratio; ARB=angiotensin receptor blocker; CKD=chronic kidney disease; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HR=hazard ratio.

1. Wirtz HS, et al. *J Am Heart Assoc*. 2020;9(16):e015042; 2. Ronco C, et al. *J Am Coll Cardiol*. 2008;52(19):1527-1539; 3. Centers for Disease Control and Prevention. Reviewed January 2015. https://www.cdc.gov/diabetes/projects/pdfs/ckd_summary.pdf. Accessed December 14, 2022; 4. Brenner BM, et al. *N Engl J Med*. 2001;345(12):861-869; 5. Lewis EJ, et al. *N Engl J Med*. 2001;345(12):851-860; 6. Lewis EJ, et al. *N Engl J Med*. 1993;329(20):1456-1462; 7. Fox CS, et al. *Lancet*. 2012;380(9854):1662-1673; 8. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int*. 2013;3(suppl 1):1-150.

# Cardiovascular Risks in CKD
## Traditional and Non- traditional

**Cardiovascular Risk in CKD ( MI, CVA , HF ) greater than CKD Progression:**

**70 % CVD Mortality**
**4 % reach ESRD** ( Dialysis , Transplantation )

1) CKD patients with
eGFR 30 - 60 ml/min = **18** Million
e GRR < 30 ml/min = **1** Million

**17 Million died from CV Events**

2) **eGFR < 45 ml /min = MAJOR Risk Factor for CVD** ( +/- Diabetes )

**4 – fold greater Risk for Mortality and Heart Failure** than eGFR > 60

# Traditional CVD Risk Factors in CKD

Age
Male Gender
Hypertension
Hyperlipidemia
Diabetes ,
    a) Metabolic Syndrome ,
    b) Insulin Resistance ( by HOMA R )
Smoking
Obesity
Poor Diet
Physical Inactivity

# NON-traditional CVD Risk Factors in CKD

1) **Insulin Resistance**
2) **Oxidative stress / ROS** ( elevated Reactive Oxygen Species )
3) **Inflammation elevated hCRP,** IL6, TNF alpha , Fibrinogen
4) **Activation of RAAS and Sympathetic System ( elevated Aldosterone )**
5) **Endothelial Dysfunction : elevated ADMA with reduced NO Production**
6) **Vascular Calcifications ( Low Fetuin A )**

LDL oxidation : Hypertriglyceridemia , low HDL , elevated : Lpa , Homocystine , APO B
oxidized small dense LDL

Hyperuricemia

Hyperleptinemia

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

Abnormal Calcium / Phosphate Metabolism with elevated FGF 23 , PTH

AGE's ( Advanced Glycation Products in T2DM ) and AGE free adducts ( Hydroimidazolones )

Myocardial Fibrosis ( elevated Cystatin C inhibits Cathepsin )

LVH , Atrial Fibrillation

# CKD and Heart Failure

**Reduced eGFR ( < 60 ml/min) or albuminuria ( > 30m g/g)** (1)

**independently from each other increase HF Risk** :

**eGFR 45 -60 ml /min = x 2**
**30- 45 ml /min = x 4**

**Accord Study** (2)

1,573 T2D patients with rapid eGFR loss followed for 4 years

**Any eGFR loss of 5 ml /min associated with 3,2 x Risk of HF**

( irrespective of baseline eGFR )

**Cardiovascular Health Study** (3)

4,378 ( community based cohort) , age 72 , 7 year follow up,

**Any decline > 3ml /min = 1,4 x HF Risk**


1) Fox ,CS et.al Lancet 2021 ;380 : 1662
2) Junior CRB et. al. Cardiovascular Diabetology ( BMC) 2023 ;22: 131
3) Shlipak MG et.al J Am Soc. Nephrol. 2009 ; 20(12) : 2625

# 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

**KDIGO 2023 GOAL < 120 mmHg** ( if tolerated )

Control of SBP to < 130 mmHg has **NOT** been shown to

1) slow progression of established CKD
2) but reduces CV Events

( AASK , REIN-2 , SPRINT except MDRD ( UACR > 1000 mg/g )

# Hyperlipidemia in CKD

Mixed dyslipidemia : elevated Triglycerides and LDL , low HDL

**Lowering LDL :**

**NO slowing of CKD progression but reduced CVD Events**

KDIGO 2023

1) age **≥ 50** and **eGFR < 60** ml/ min = Statin or Stain / Ezetimibe
2) age **< 50** and **eGFR ≥ 60** ml/min = Statin
3) age 18- 49 and CKD = Statin only for
   CAD , Diabetes prior CVA ( ischemic)
   > 10 % estimated 10 risk for CAD death or MI

# Renal Risk of Visceral Obesity

## New Onset CKD

- **ARIC** : 10,096 participants without hypertension or T2D screened for new onset CKD .
  BMI < 26.2 vs. 30.4 = **CKD HR 1.24**

- **Physician Health Study** : 11,104 healthy males followed 14 years
  compared BMI < 22.6 vs. > 26.6 = **CKD = HR 1.45**

- **Kaiser Permanente Study** 177,670 patients, age ~ 45,
  without hypertension or CKD , 25 year follow .
  **CKD HR** **BMI < 25** compared vs.
  BMI 25 - 30 = **HR 1.65**
  BMI > 30 = **HR 3.1**
  BMI > 35 = **HR 4.39**

# Cardiorenal Benefits of Weight Loss Surgery

Retrospective Swedish study of 5,321 type 2 diabetes patient comparing gastric by pass surgery ( GBP )
vs. controls in a 4.5 year follow up .
Baseline data : age 18- 65 , BMI > 40, eGFR 100 ml/min

Results :

**Reduction of Events**

Cardiovascular 67 % HF
64 % CV death

Renal ( eGFR loss of 50 % )
41 % with eGFR > 60 ml/min
60 % with eGFR 30 - 45
45 % new onset UACR > 300 mg/g

Liakopoulos V et. al. Diabetes Care . 2020 ;43 : 1175

# What Drugs are available for the treatment of Cardiorenal Events ?

1) **Ace inhibitors or Angiotensin receptor blockers ( ARB's )** reduce

a) albuminuria 40-50 % b) progression of CKD 20 %

c) Hypertension d) HF

**Reduce eGFR slope by ~ 1 ml /year**

2) **Sodium glucose cotransport inhibitors** ( SGLT2 inhibitors) reduce

a) albuminuria 35- 45 %

b) CKD progression 35 - 45 % d) HF admissions and CV death by 23%

e) CV death by 14%

**Reduced eGFR slope by 1.4 – 1.9 ml/ year**

3) **Mineralocorticoid Antagonist** ( Finerenone)

a) albuminuria reduction 31% b) CKD progression 18%

c) HHF 22% d) myocardial infarction

**Reduce eGFR slope by 1.3 ml /year** ( on ACEI/ ARB )

4) **GLP 1 agonists**

a) NOT FDA approved for CKD ( FLOW study results 2024 )

b) reduce albuminuria 24 % ( Semaglutide )

c) reduce CV Events

**Reduce eGFR slope by 0.87 ml /year**

# Cardiorenal Benefits of SGLT2 inhibitors (Meta-analysis )

90,400 patients ( 13 trials) 15,400 w/o T2D , eGFR 37- 85 ml/min

**SGLT2 therapy** compared to " placebo " ( patients were on standard therapy : incl. ACE inhib. / ARB )

**Benefits**

Renal **37%** slower CKD progression ( ≥ 50% eGFR decline) +/- T2D

**23%** lower AKI incidence

Cardiovascular **23%** reduced CV death / admission for HF

**14 %** lower CV mortality

All cause mortality 31% lower ( only Dapagliflozin )

2) **Real World Data** : For every 1, 000 patients treated with a SGLT2 inhibitor for 1 year

**prevented** 11 eGFR progression of >50 ml/ min ( T2D) and **15** without T2D

4-5 AKI episodes

1) Cardio-renal Trialist consortium Lancet , Nov. 6/ 2022 ( online)

2) Brosius F Clin J Am Soc Nephrol 2023 , 1

# Cardiorenal Benefits of Mineralocorticoid Receptor Antagonists

## Cardiovascular

**Spironolactone** 30% reduced CV death or HFrEF progression ( RALES ) (1)

**Finerenone** 13% reduced CV death, nonfatal MI/ CVA or HHF ( DKD only) (2)

## Renal

**Spironolactone** ( limited to eGFR > 45 ml/ min, and K < 4.5 meq/L) , **3 fold risk of hyperkalemia**

reduced (2, 3, 4 )

34% ESKD incidence ( Taiwanese retrospective CKD study of 13 years , 3 fold hyperkalemia)

30 -50% Albuminuria

**Finerenone** reduced ( DKD only)

23% Renal composite ( 57% eGFR decline, ESKD, renal death)

31% Albuminuria


1) Pitt,B et.al. NEJM 1999;34:709
2) Agarwal R et. al. Europ Heart J 2022;43:474
3) Yang CT et.al. J of Clin Medicine 2018;7:459
4 )Bianchi S et. al. Kidney Int 2006;70 :2116

# Cardiorenal Benefits of GLP 1- RA ( DKD only)

## Cardiovascular

reduced ( Meta -analysis of 8 CVOT ) (1)

**14**% of 3- MACE ( non fatal MI/ CVA , CV death )
**13 %** CV death
**10 %** Myocardial infarction

## Renal

reduced (**no** completed designated renal outcome trial completed ) (1, 2, 3 )

**21 %** composite renal endpoint ( 50% eGFR decline, ESKD, renal death )
**24 %** albuminuria (4)
**13 %** new onset UACR > 300 mg /g


1) Marx N et. al. Circulation 2022;146 :1882
2) Granata A et. al. Clinical Kidney J. 2022 ;15: 1657
3) Schecter M et. al. Cardiovascular Diabetology 2023 ;22 : 126
4) Shaman AM et. al. Circulation 2021 :145 :575

# Reduction of Albuminuria leads to Renoprotection (Meta-analysis)

21 Trials and 78,342 Patients with Albuminuria

Age 12- 68, eGFR 19- 92 ml/ min, followed for 11- 56 months (1)

28 cohorts ; 693,816 patients ( 80% diabetes) > 18 years old ,

eGFR > 60 ml /min , UACR $\geq$ 30 mg/g followed up to 3 years (2)

**Conclusion :**

**30% Reduction of Albuminuria = 22% ESRD Risk Reduction**

( Findings are consistent regardless of Drug Class )

(1) REASSURE Consortium Heerspink, H. et. al. 2015 JASN 26 ; (8) : 2055

(2) Consortium Meta analysis Coresh J et. al. 2019 Lancet Diabetes Endocrinol. 7 (2) :115

# 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

# RAAS Blockade Discontinuation

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

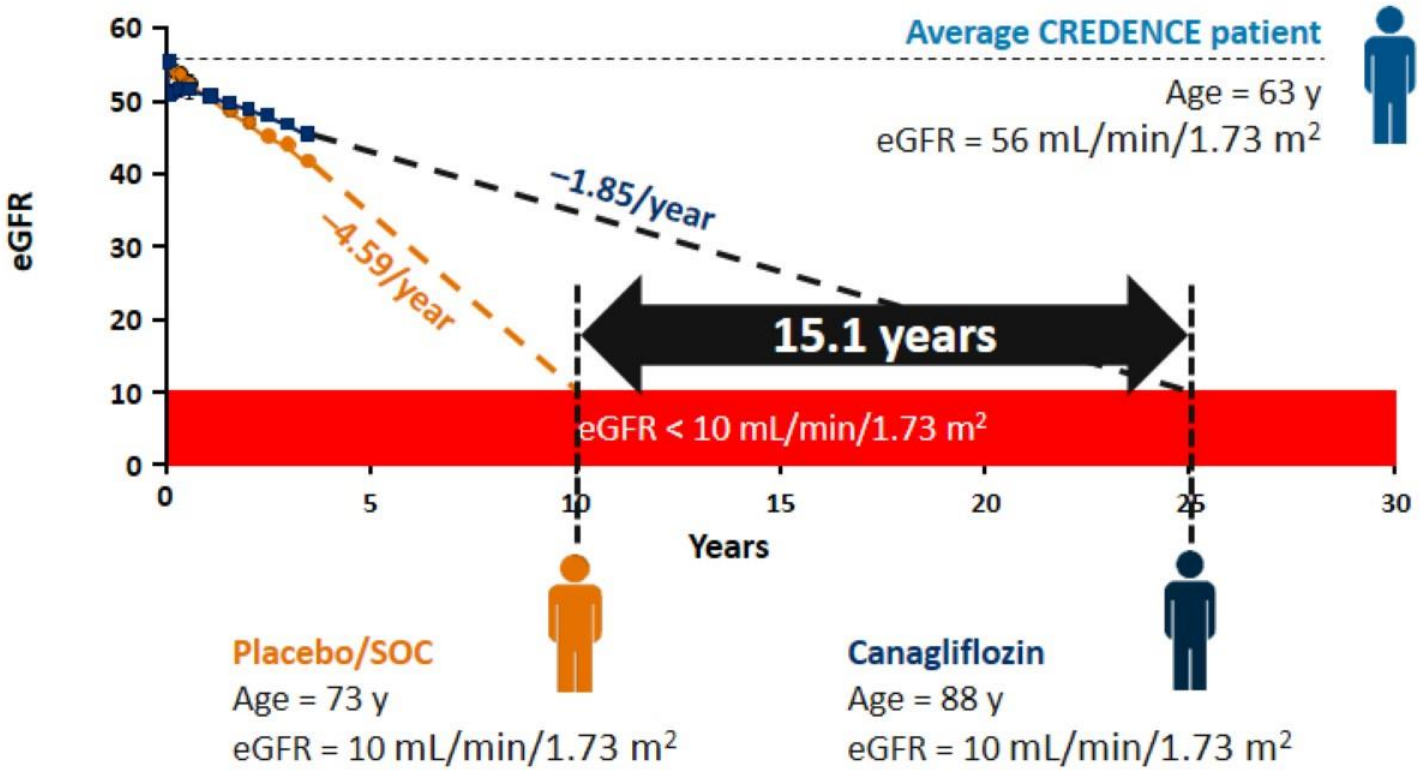
205,108 US patients , including > **20,000 with Heart Failure** stopped RAAS blockade

because of hyperkalemia :

**Mortality doubled** (compared to patients continued on maximum does )

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

# Projected Effects of Canagliflozin on eGFR




Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306.

# SGLT inhibitors Therapy in CKD

1) **Delay to Kidney Failure** ( eGFR 10 ml/min) (1)

| Baseline eGFR ml/ min = | Delay to Kidney Failure in years |
|---|---|
| 85 | 26.6 |
| **75** | **19.5** |
| 60 | 17.8 |
| **45** | **15.7** |
| 30 | 8.9 |
| **20** | **1.9** |

2) Estimation of **Event Reduction** per 1,000 patient/years

| | Diabetes | No Diabetes |
|---|---|---|
| **CKD progression** | **11** | **15** |
| **CV Events** | **11** | **2** |
| **AKI** | **4** | **5** |

**(1)** Fernandez-Fernadez B Sara,fides P et.al. EMPA-KIDNEY : Clin Kidney J 2023 ;16( :1183
(2) SMART C investigators Meta analysis, Lancet 2022 ; 400 :1788

# **Renal Effects of SGLT2 inhibitors** (2)

1) **Reduced reabsorption of Na and Glucose** lowers tubular oxygen and ATP requirement with **improved cortical hypoxia** ( Dekker CCJ 2020 Nephrol Transpl 35: i 3)

2) **Reduced intraglomerular pressure** ( 5-7 mmHg ) secondary to afferent vasoconstriction and efferent vasodilation **reduction of albuminuria ( ~ 35 % )**

3) **Reduced Angiotensinogen** production ( proximal tubule) ~ 60%

( Satou R 2019 Am J Physio Renal )

4) **Lower tubular injury markers KIM - 1** ( 22% ) **with lower AKI risk** ( ~ 25%)

( Dekkers CCL 2018 Diabet Obes Metab 20 ; 1988)

5) **NHE -3** ( Na/ H exchange isoform 3 ) **partially co - blocked** by SGLT2 inhibition with increased urinary Na excretion

(Pessoa TD 2014 JASN ;25 : 2028 )

6) **Podocyturia in DKD reduced** ( immunocytical staining of cell stroma)

( Durcan E 2022 , J of Diabetes 14 : 236 )

# Adverse Effects of SGLT2 inhibition

**Risks**

3,57 x Mycotic genital infections ( Diabetes only)

8% UTI increase ( more in female )

5% Amputations lower limbs 5 1000 patient / years vs. 4 in placebo group
HR 1.05 *

2 x DKA but only 0.3% of total
2 / 30,000 ( T2D ) vs 1/ 30,000 ( no T2D) *

SMART-C investigators Meta analysis Lancer 2022 ;400 : 1788

* PI = Jardiance ( incl. EMPA KIDNEY ) 9 / 2023

# When NOT to use a SGLT2 Inhibitor

1) Pregnancy and Lactation
2) Type I diabetes
3) Baseline eGFR < 20 ml/ min
   do not stop if during therapy if eGFR falls below 25 ml/min unless hemodialysis is initiated
4) Pediatric patients ( < 18 years old )
5) Polycystic kidney disease (PCK) , relative only
6) Patients on immunosuppressive therapy ( relative only )
   a ) Renal transplant patients
7) Severe allergic reaction ( anaphylaxis, angioneurotic edema )
8) Recurrent DKA ( no identifiable cause )
9) Chronic obstructive uropathy , suprapubic cystostomy , chronic UTI , indwelling catheter, neurogenic bladder = **all relative risk with no data .**

# Therapy of CKD ( KDIGO 2023 )

**Lifestyle**

Increased physical activity ( exercise > 150 min /week )

Stop smoking

Achieve a BMI close to 25 ( definitely < 30 )

Diet : eGFR < 60 ml /min reduce Protein intake to < 0.8 g / kg / day
( more plant based protein)

reduce Na ≤ 2 gm /day ( = salt ≤ 5 gm )

**RAAS Therapy**

CKD or Hypertension and
UACR > 30 mg/ g ( irrespective of etiology )

Heart Failure or Hypertension

**SGLT2 inhibitors**

CKD and Heart Failure

Diabetes and Heart Failure

eGFR ≥ 20 ml /min and UACR > 200 mg /g

eGFR ≥ 20 - ≤ 45 ml /min and UACR < 200 mg /g

**MRA**

Diabetes and eGFR ≥ 25 ml/ min , normal K and UACR > 30 mg /g
despite RAAS and SGLT2 inhibitor therapy

High risk of CKD progression or CV events with residual UACR > 30 mg /g

# Conclusions

1) **Albuminuria** ( UACR ≥ 30 ) **and / or eGFR < 60 ml/min**
predict CV Morbidity, Total Mortality and Renal Outcome

2) **eGFR < 60 ml/min is a CV Risk Factor** independent of
any other Co-morbidity or conventional Risk Factors

3) **Albuminuria with normal eGFR is a Risk Factor** for
a) renal Function Loss
b) CV Events and Heart Failure ( with or w/o Diabetes )

4) **Reduction of Albuminuria** irrespective of Drug used
a) **reduces renal Function Loss** ( almost % for % )
b) **reduces CV events , Heart Failure and Total Mortality**