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

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15th Annual Orange County Symposium for Cardiovascular Disease Prevention
# FACULTY DISCLOSURE

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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: e840
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) Albuminuric ≥ 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 hyperglycemia
- 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 < 140/90 mmHg = 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\(^7, b\).

**Stages of kidney disease\(^8\)**

<table>
<thead>
<tr>
<th>KIDNEY FUNCTION</th>
<th>G1</th>
<th>G2</th>
<th>G3a</th>
<th>G3b</th>
<th>G4</th>
<th>G5</th>
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<tr>
<td>eGFR (mL/min/1.73 m(^2))</td>
<td>≥90</td>
<td>60–89</td>
<td>45–59</td>
<td>30–44</td>
<td>15–29</td>
<td>&lt;15</td>
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**CV death risk**

- Risk grows to nearly 4X Greater\(^7, b\).
- Risk is more than 2X Greater\(^7, b\).

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\(^a\)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.

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 ( > 30mg/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
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 $\geq 50$ and eGFR < 60 ml/min = Statin or Stain / Ezetimibe
2) age < 50 and eGFR $\geq 60$ 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
3) Schecter M et. al. Cardiovascular Diabetology 2023;22:126
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 > 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
141,252 Veterans with CKD and Albuminuria whose RAAS blockade (ACEI or ARB) was discontinued for > 6 months 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 dose)

Projected Effects of Canagliflozin on eGFR

Average CREDENCE patient
Age = 63 y
eGFR = 56 mL/min/1.73 m²

Placebo/SOC
Age = 73 y
eGFR = 10 mL/min/1.73 m²

Canagliflozin
Age = 88 y
eGFR = 10 mL/min/1.73 m²

15.1 years

eGFR < 10 mL/min/1.73 m²

SGLT inhibitors Therapy in CKD

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

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<tr>
<th>Baseline eGFR ml/min</th>
<th>Delay to Kidney Failure in years</th>
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<td>85</td>
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<td>75</td>
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<td>30</td>
<td>8.9</td>
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2) Estimation of **Event Reduction** per 1,000 patient/years

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<td>CKD progression</td>
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<td>15</td>
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<tr>
<td>CV Events</td>
<td>11</td>
<td>2</td>
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<tr>
<td>AKI</td>
<td>4</td>
<td>5</td>
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(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**