

Cardiorenal Syndrome and CKMS: Beyond Diuretics

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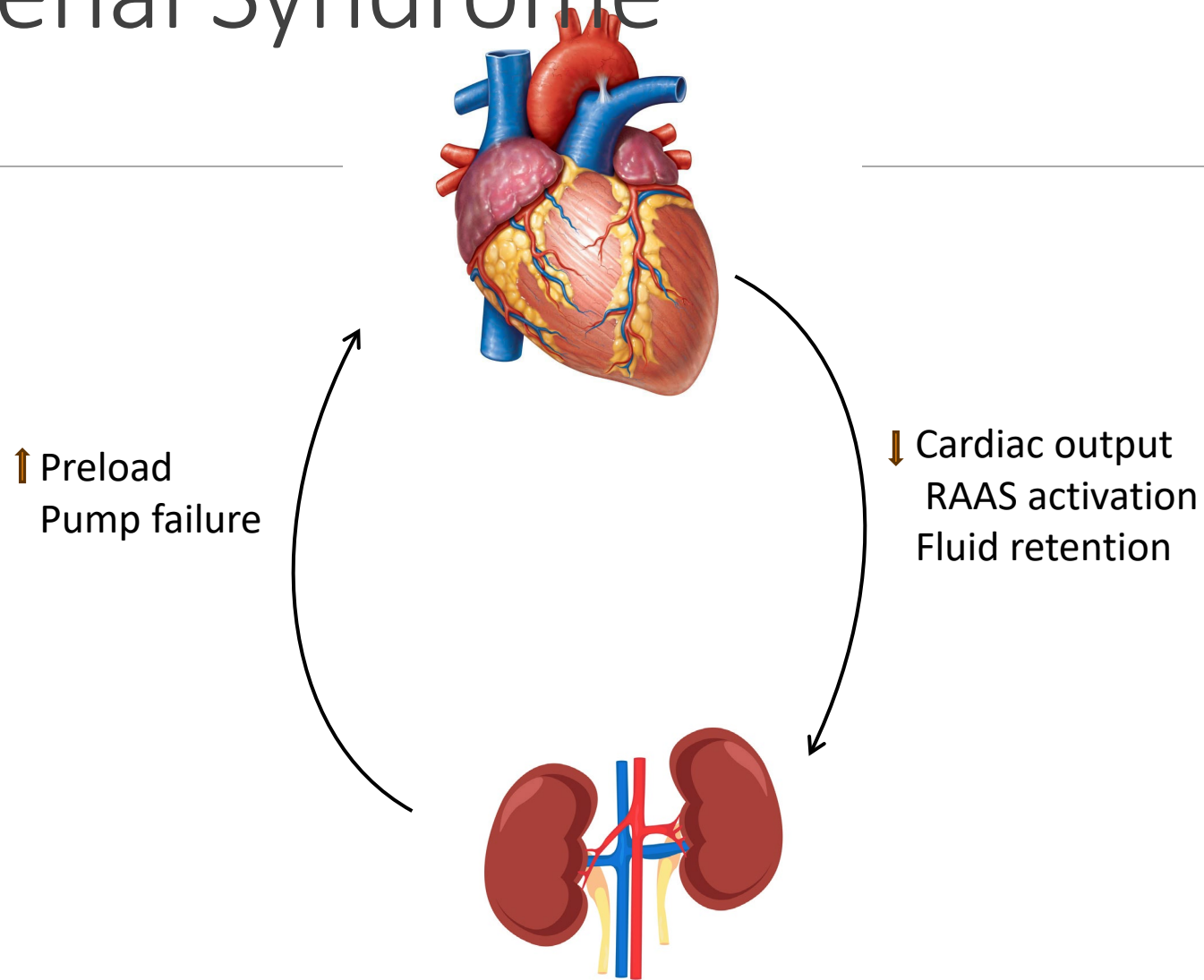
Financial Disclosures

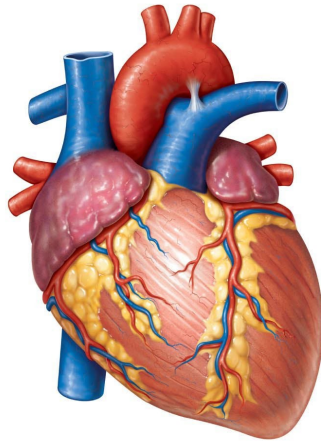
None

Learning Objectives

- Describe the spectrum of cardiovascular and renal disease overlap
- Review the optimal management of CKMS disease
- Explore considerations relevant to inpatient medicine

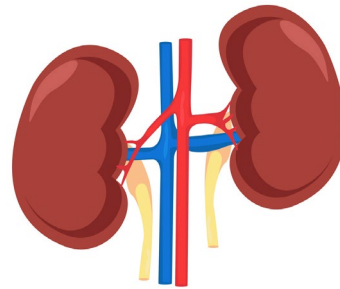
Cardiorenal Syndrome





↑ RA pressure
↑ Venous congestion

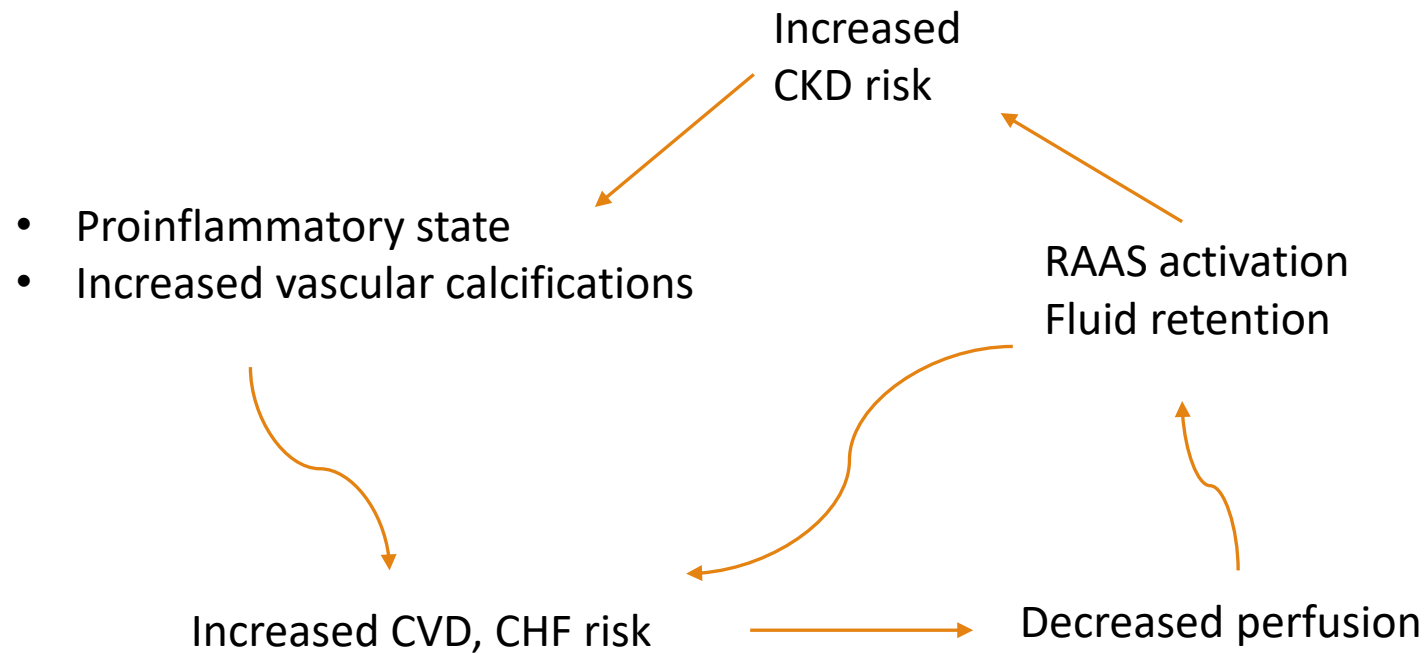
↑ Fluid retention
Oliguria
↑ Congestion



CKD and Cardiovascular Health

Major amplifier of cardiovascular risk

and vice versa



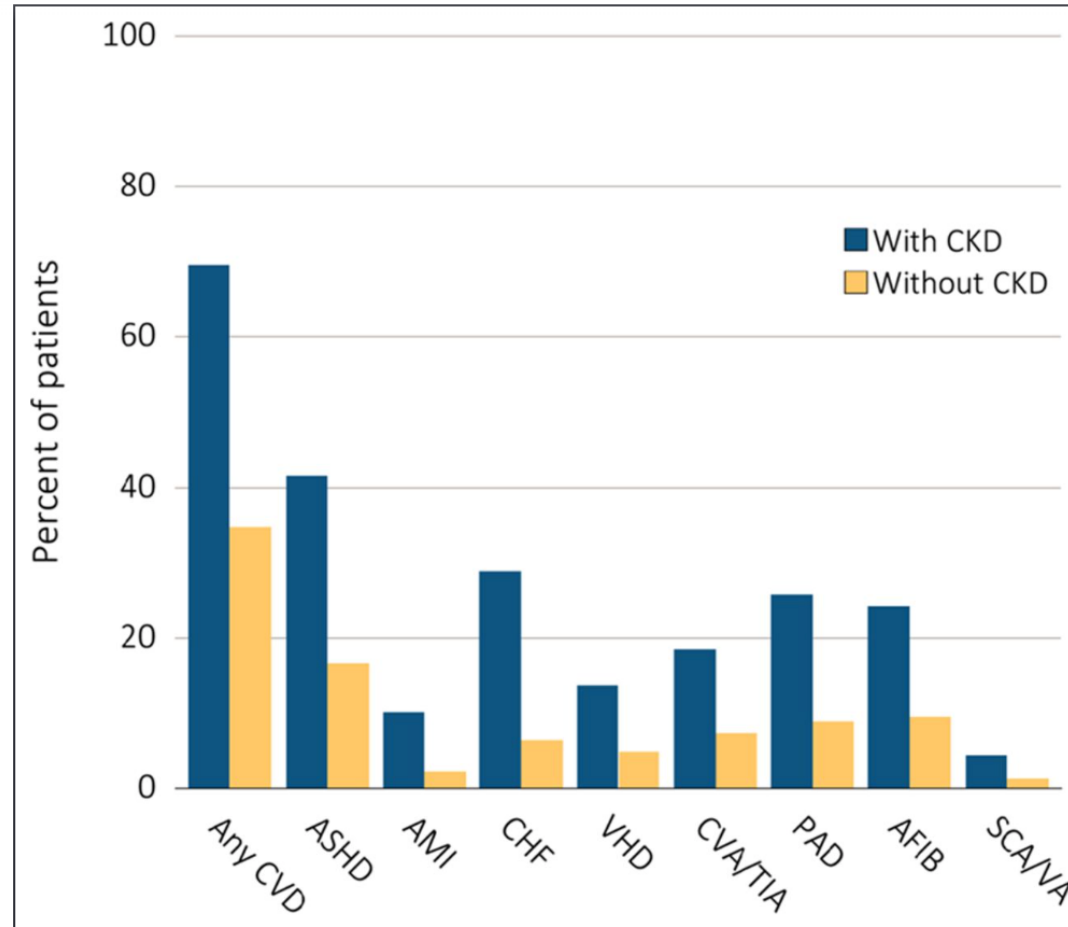
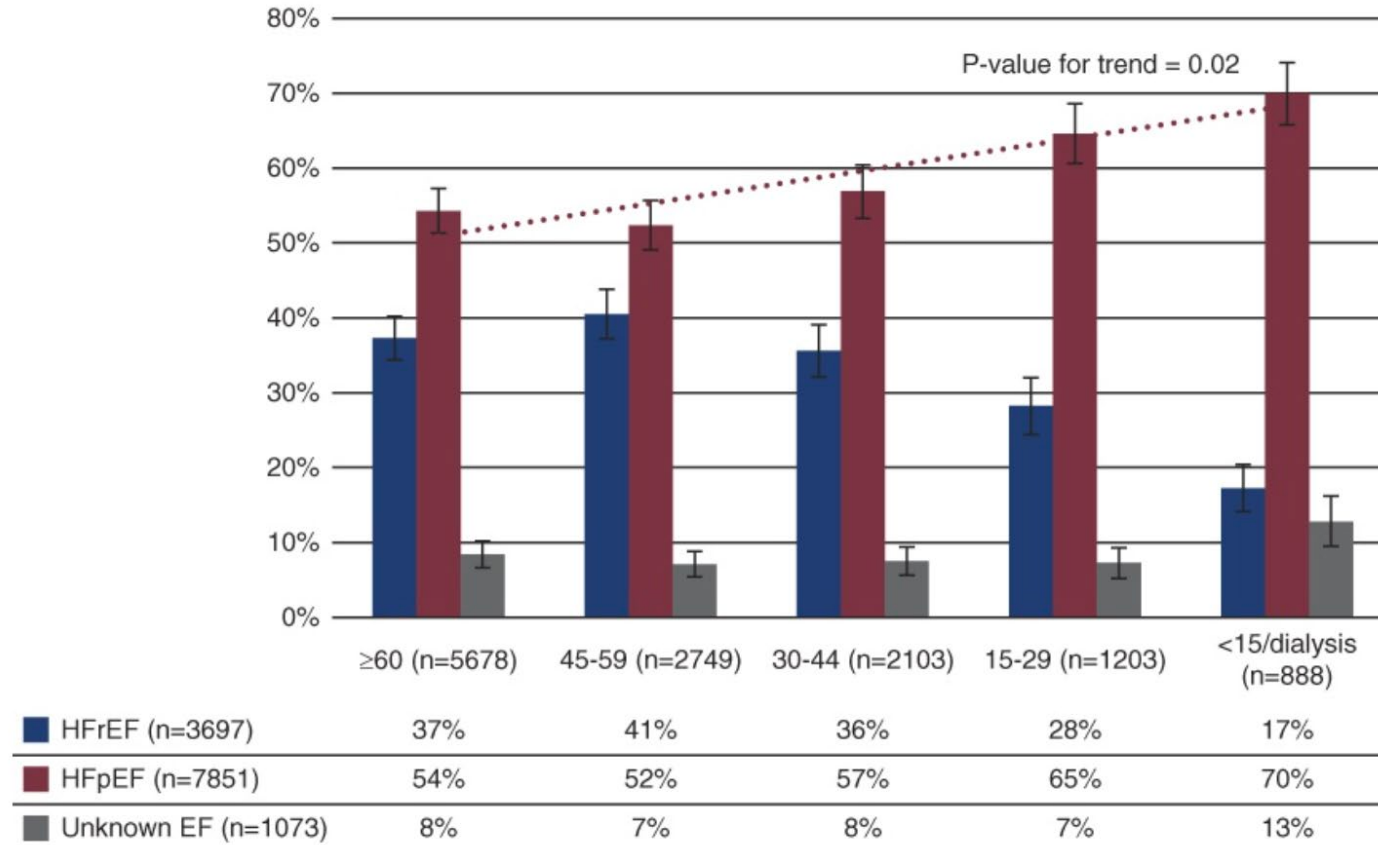


Chart 12-7. CVD in patients with or without CKD, 2013 (2015 USRDS Annual Data Report, volume 1, Figure 4.1).

Patients aged ≥ 66 , alive, without end-stage renal disease, and residing in the United States on December 31, 2013 with fee-for-service coverage for the entire calendar year. Totals of patients for the study cohort: N=1 238 888; with CKD=132 840; without CKD=1 106 048.

B

A					B				
	ACR <10	ACR 10-29	ACR 30-299	ACR >300		ACR <10	ACR 10-29	ACR 30-299	ACR >300
eGFR >105	1.1	1.5	2.2	5.0	eGFR >105	0.9	1.3	2.3	2.1
eGFR 90-105	Ref	1.4	1.5	3.1	eGFR 90-105	Ref	1.5	1.7	3.7
eGFR 75-90	1.0	1.3	1.7	2.3	eGFR 75-90	1.0	1.3	1.6	3.7
eGFR 60-75	1.0	1.4	1.8	2.7	eGFR 60-75	1.1	1.4	2.0	4.1
eGFR 45-60	1.3	1.7	2.2	3.6	eGFR 45-60	1.5	2.2	2.8	4.3
eGFR 30-45	1.9	2.3	3.3	4.9	eGFR 30-45	2.2	2.7	3.4	5.2
eGFR 15-30	5.3	3.6	4.7	6.6	eGFR 15-30	14	7.9	4.8	8.1

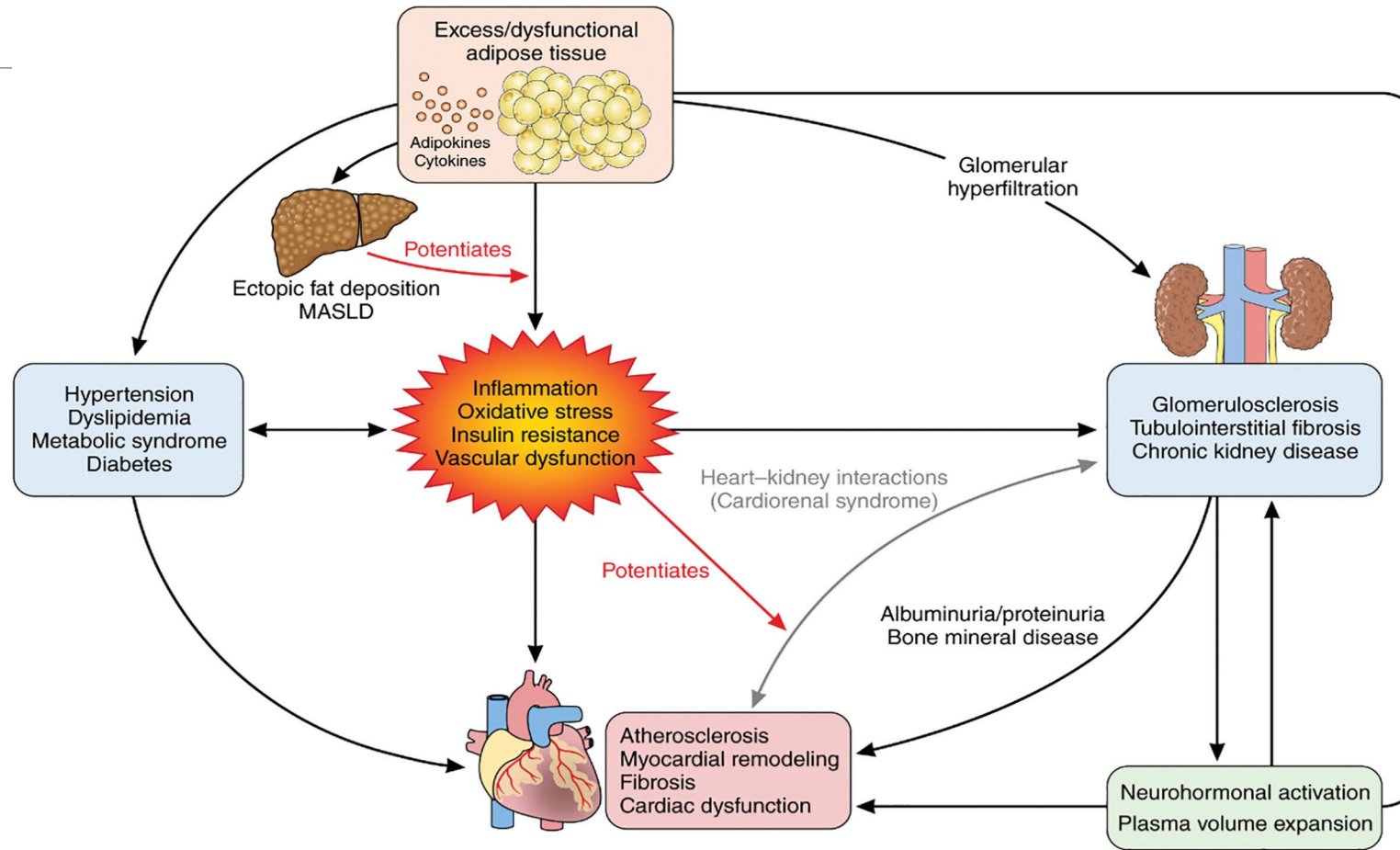
Chart 12-6. Adjusted relative risk of (A) all-cause mortality and (B) cardiovascular mortality in the general population categorized by KDIGO 2012 categories of chronic kidney disease.

Data are derived from categorical meta-analysis of population cohorts. Pooled relative risks are expressed relative to the reference (Ref) cell. Colors represent the ranking of the adjusted relative risks (green=low risk; yellow=moderate risk; orange=high risk; red=very high risk).

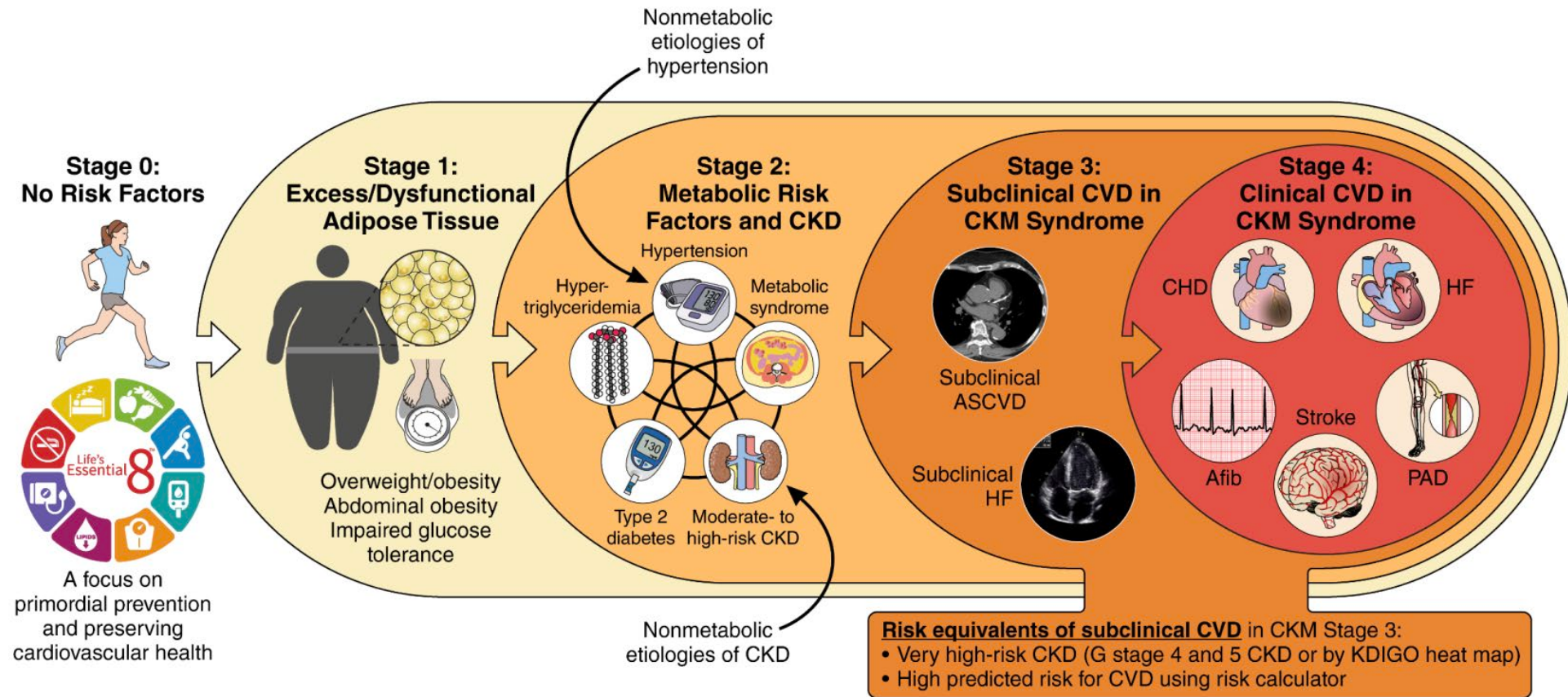
ACR indicates urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; and KDIGO, Kidney Disease: Improving Global Outcomes.

Modified from Levey et al⁸⁰ with permission from International Society of Nephrology. Copyright © 2011, International Society of Nephrology.

"Non-Hemodynamic Pathways"



What is CKMS?



What is CKMS?

“CKM syndrome includes both individuals at risk for CVD due to the presence of metabolic risk factors, CKD, or both and individuals with existing CVD that is potentially related to or complicates metabolic risk factors or CKD.”

What do we do with these ideas?

Table 2. Major Guidelines and Scientific Statements Used in the CKM Health Crosswalk

Prevention and Management of ASCVD
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease ⁶²
2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice ⁶³
2023 Standards of Medical Care in Diabetes ⁶⁴
2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults ⁶⁵
2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol ⁶⁶
2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults ⁶⁷
2022 AHA Scientific Statement: Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes ⁶¹
2021 AHA Scientific Statement on Weight-Loss Strategies for Prevention and Treatment of Hypertension ⁶⁸
2022 KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease ⁶⁹
2013 KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease ⁷⁰
Prevention and Management of HF

Prevention and Management of HF
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure ⁷¹
2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure ⁷²
2023 Standards of Medical Care in Diabetes ⁶⁴
2022 AHA Scientific Statement: Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes ⁶¹
2022 KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease ⁶⁹
Prevention and Management of AFib
2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation Developed in Collaboration With the EACTS ⁷³
2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation ⁷⁴
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure ⁷¹
2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure ⁷²
Management of CKM Health in CKD
2022 KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease ⁶⁹
2023 Standards of Medical Care in Diabetes ⁶⁴
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure ⁷¹
2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure ⁷²

CKMS Treatment

- Lifestyle modification
- 4 Pillars of Pharmacotherapy
 - RAAS Inhibition
 - SGLT-2 inhibitors
 - Nonsteroidal MRAs
 - GLP-1 agonists
- Addressing Comorbidities

Pharmacotherapy

RAAS blockade

SGLT-2 inhibitors

Pillar 1

Recommendation 3.6.1: We recommend starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with CKD and severely increased albuminuria (G1–G4, A3) without diabetes (1B).

Recommendation 3.6.3: We recommend starting RASi (ACEi or ARB) for people with CKD and moderately-to-severely increased albuminuria (G1–G4, A2 and A3) with diabetes (1B).

Practice Point 3.6.6: Consider starting people with CKD with normal to mildly increased albuminuria (A1) on RASi (ACEi or ARB) for specific indications (e.g., to treat hypertension or heart failure with low ejection fraction).

Pillar 2

Recommendation 3.7.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥ 20 ml/min per 1.73 m² with an SGLT2i (1A).

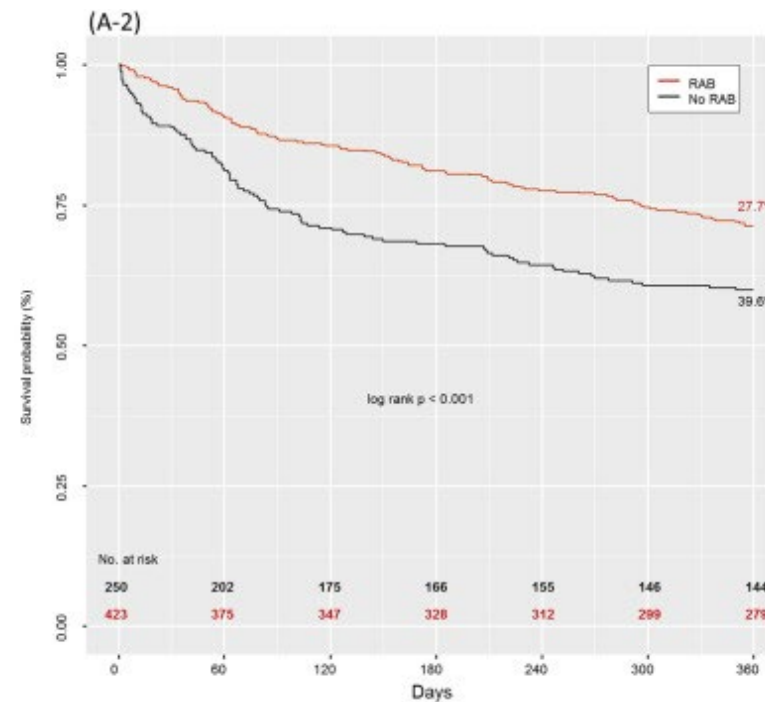
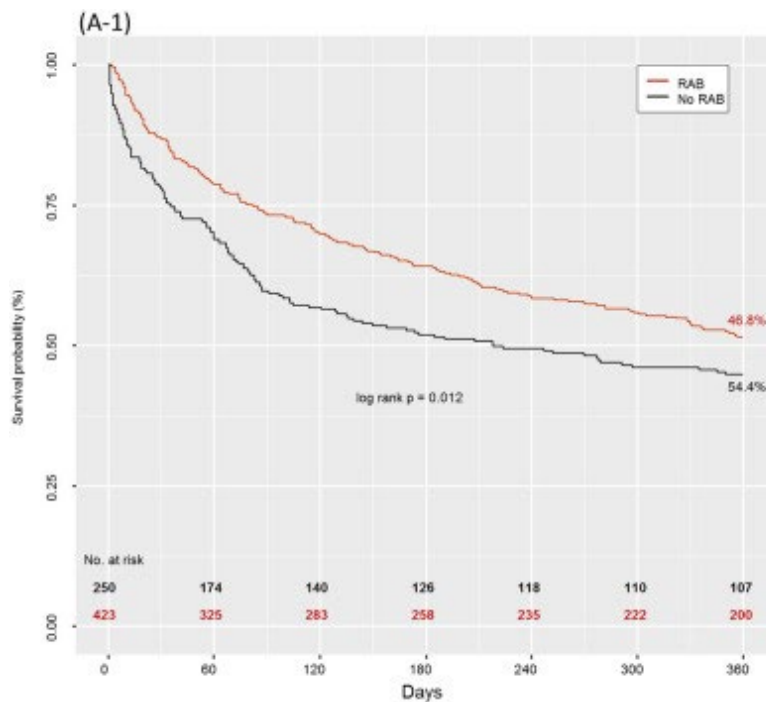
Recommendation 3.7.2: We recommend treating adults with CKD with an SGLT2i for the following (1A):

- eGFR ≥ 20 ml/min per 1.73 m² with urine ACR ≥ 200 mg/g (≥ 20 mg/mmol), or
- heart failure, irrespective of level of albuminuria.

Who should be on SGLT2i	
RECOMMENDATIONS	 Type 2 diabetes with CKD (eGFR ≥ 20 ml/min/1.73m ² (1A)
	 CKD (eGFR ≥ 20 ml/min/1.73 m ²) with Urine ACR ≥ 200 mg/g OR  Heart failure, irrespective of level of albuminuria (1A)
	 eGFR 20 to 45 ml/min per 1.73 m ² with Urine ACR < 200 mg/g (2B)

Initiation

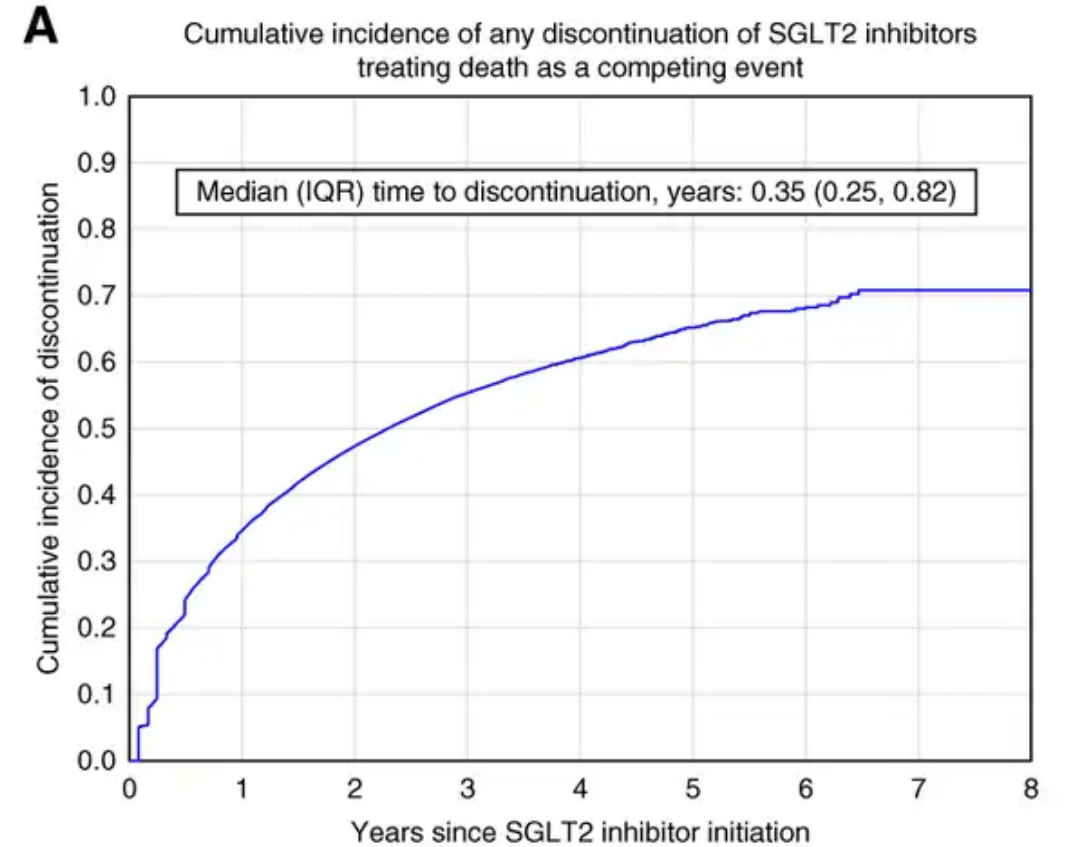
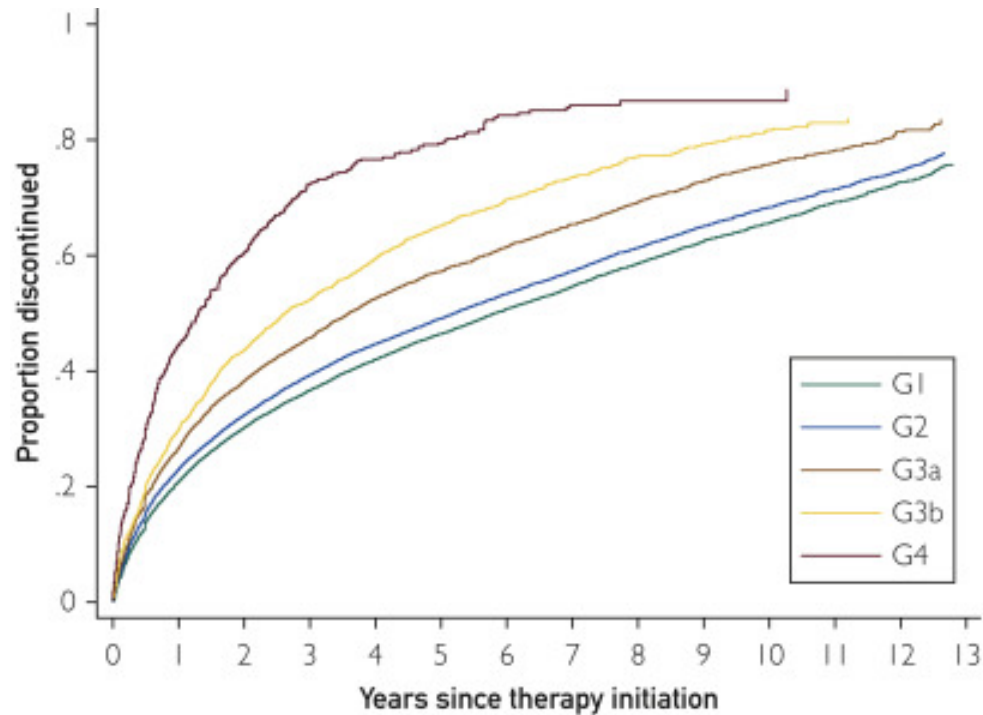
Earlier is better



Challenges

- Hyperkalemia
- AKI
- GFR decline
- Infection
- Hospitalization/Illness
- Surgery
- Contrast
- Cost

Discontinuation



Does restarting renin-angiotensin inhibitors improve clinical outcomes in those who have previously discontinued it ?

Target Trial Emulation Study



Osaka Consortium
for Kidney Disease
Research (OCKR)



eGFR 10-60
mL/min/1.73 m²



2005-2021



Discontinued
Renin-Angiotensin
System inhibitors
(RASi)



n=6065



66 years
Mean



62% Male



eGFR 40
mL/min/1.73 m²



37%
Restarted
RASi within
1 year

Patients were followed up
for a maximum of 5 years
after RASi discontinuation

Restarting RASi within a year after Discontinuation (versus not restarting RASi)



PRIMARY
OUTCOME

Composite outcome
(initiation of KRT,
≥50% decline in eGFR,
or kidney failure)

0.85

(95% CI 0.78-0.93)



SECONDARY
OUTCOME

All-cause death

0.70

(95% CI 0.61-0.80)



Incidence of
hyperkalemia
(between the
2 strategies)

HR 1.11

(95% CI 0.96-1.27)

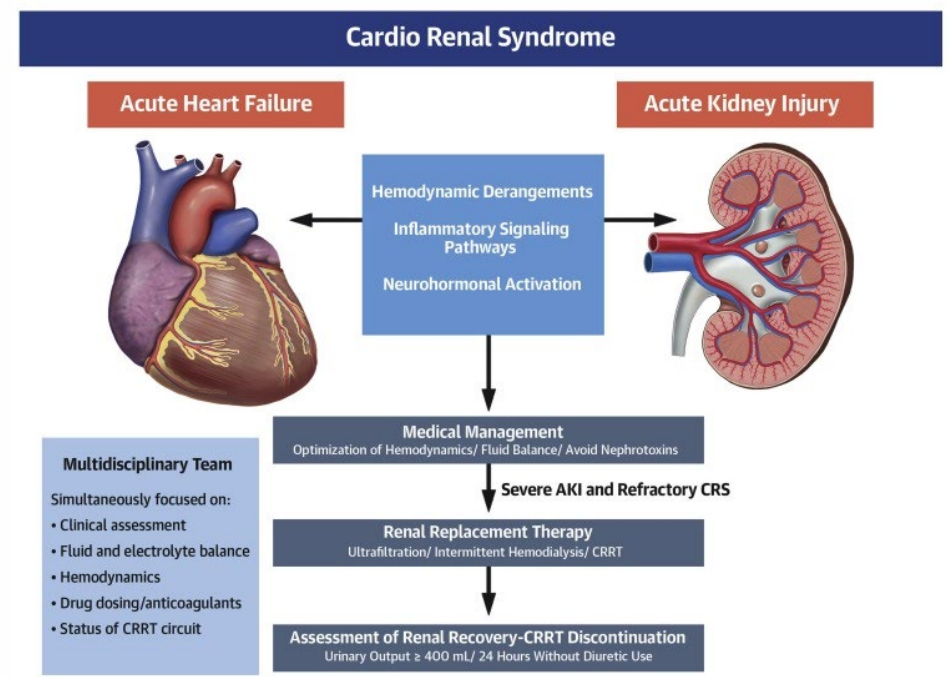
* KRT, Kidney Replacement Therapy; Kidney Failure, eGFR <5 mL/min/1.73 m²

Conclusions: Restarting RASi after discontinuation was associated with a lower risk of adverse kidney outcomes and mortality but not related to the incidence of hyperkalemia.

Koki Hattori, Yusuke Sakaguchi, Tatsufumi Oka, et al. *Estimated Effect of Restarting Renin-Angiotensin System Inhibitors after Discontinuation on Kidney Outcomes and Mortality*. JASN doi:10.1681/ASN.0000000000000425. Visual Abstract by Edgar Lerma, MD, FASN

AKI Management

CENTRAL ILLUSTRATION: Pathophysiology, Medical Management, and Use of Renal Replacement Therapy in Severe Acute Kidney Injury and Refractory Cardiorenal Syndrome



Jentzer, J.C. et al. J Am Coll Cardiol. 2020;76(9):1084-101.

RAAS blockade

Discontinue for:

- “Severe AKI”
- Hemodynamic instability
- Hypovolemia

Consider continuing:

- “Mild AKI”
- Cardiorenal picture, HFrEF indication

SGLT-2 inhibitors

Discontinue for:

- “Severe illness”
- Fasting, etc.

Consider continuing:

- HFrEF indication

Acute Kidney Injury

When to resume?

“As soon as such episodes have resolved”

Acute Kidney Injury

When to resume?

- Prior to discharge
- When follow-up, monitoring is feasible
- When strongly indicated

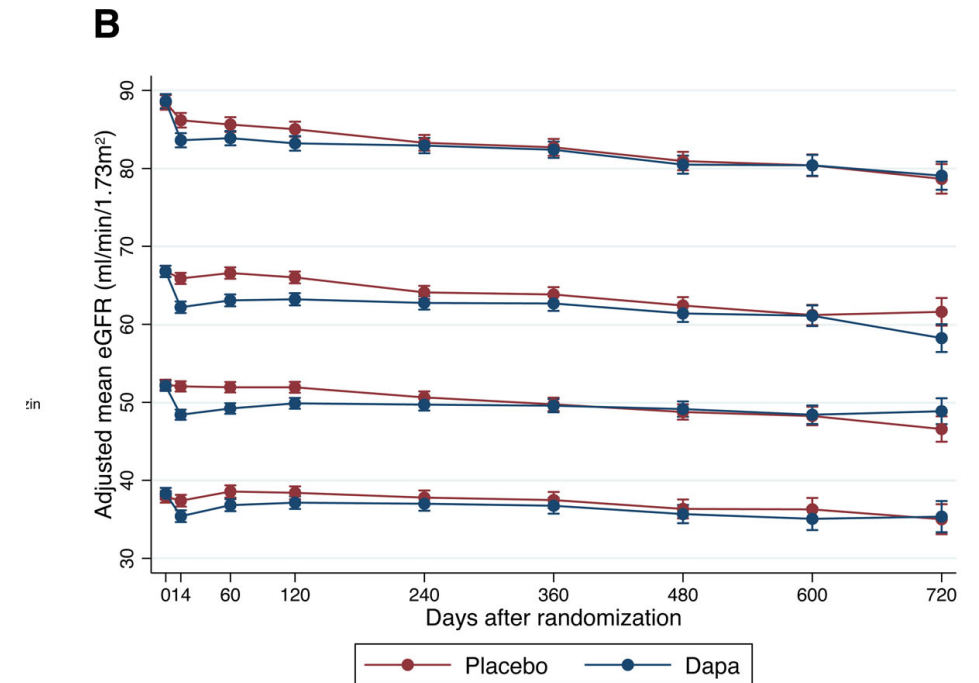
eGFR Decline vs AKI?

eGFR Decline?

Table 6. Serum Creatinine Level at Base Line and at Six-Week Follow-up (or at Last Follow-up If the Patient Was Not Alive at Week 6).*

BASE-LINE LEVEL ($\mu\text{mol/liter}$)	FOLLOW-UP LEVEL ($\mu\text{mol/liter}$)					
	PLACEBO GROUP (N = 118)			ENALAPRIL GROUP (N = 120)		
	≤ 120	121–150	>150	≤ 120	121–150	>150
≤ 120	50	8	1	38	5	9
121–150	12	18	12	13	14	12
151–300	0	4	13	0	10	19

* $P > 0.25$ for the difference between groups.



Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS).

Initial decline (dip) in estimated glomerular filtration rate after initiation of dapagliflozin in patients with heart failure and reduced ejection fraction: insights from DAPA-HF

eGFR Decline

Practice Point 2.1.4: Among people with CKD who initiate hemodynamically active therapies, GFR reductions of >30% on subsequent testing exceed the expected variability and warrant evaluation.

GFR Considerations

- SGLT-2i initiation?

- RAAS blockade?

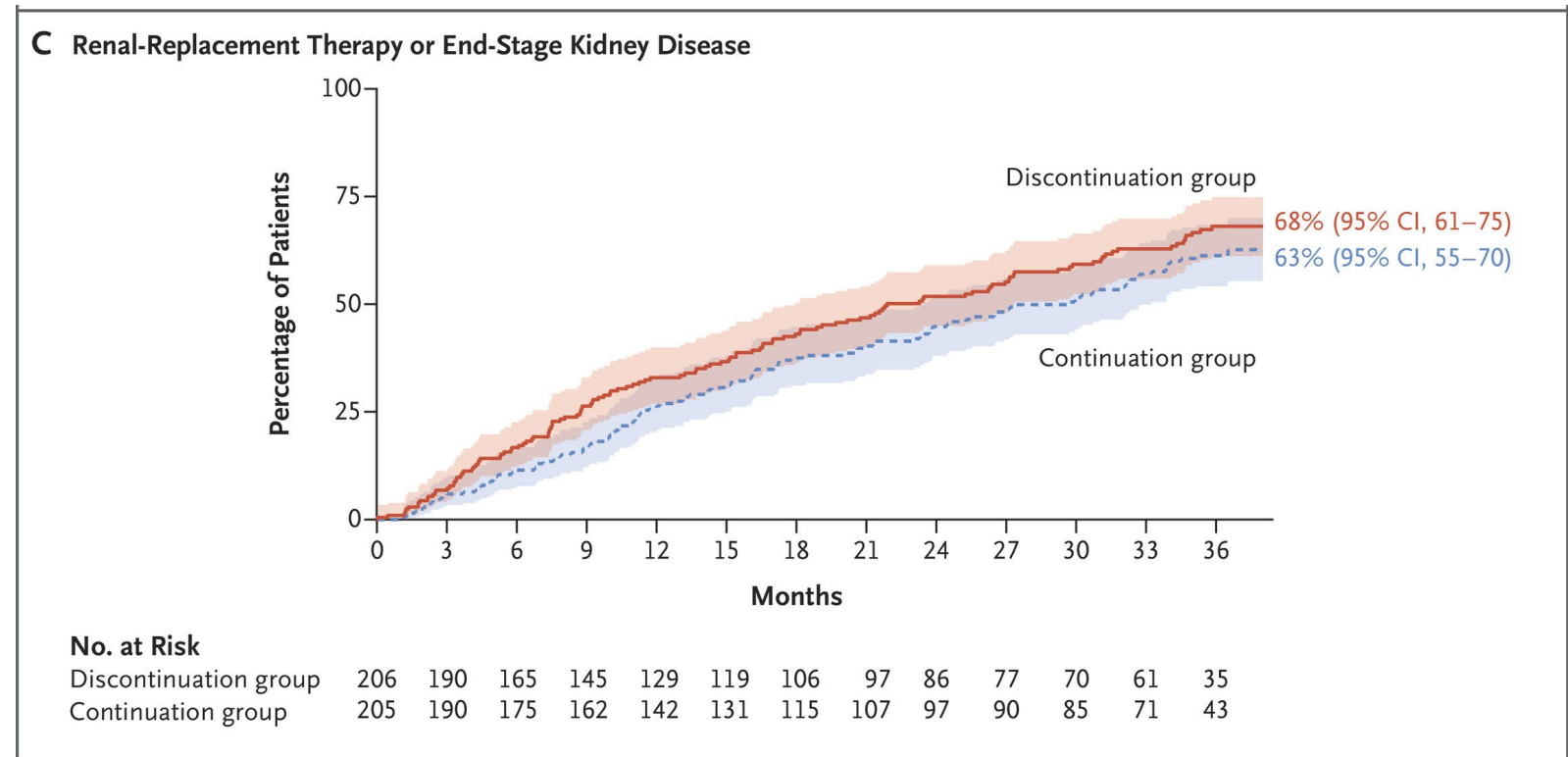
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Recommendation 3.6.3: We recommend starting RASi (ACEi or ARB) for people with CKD and moderately-to-severely increased albuminuria (G1–G4, A2 and A3) with diabetes (1B).

GFR Considerations

- SGLT-2i continuation?

- RAAS blockade?



Hyperkalemia

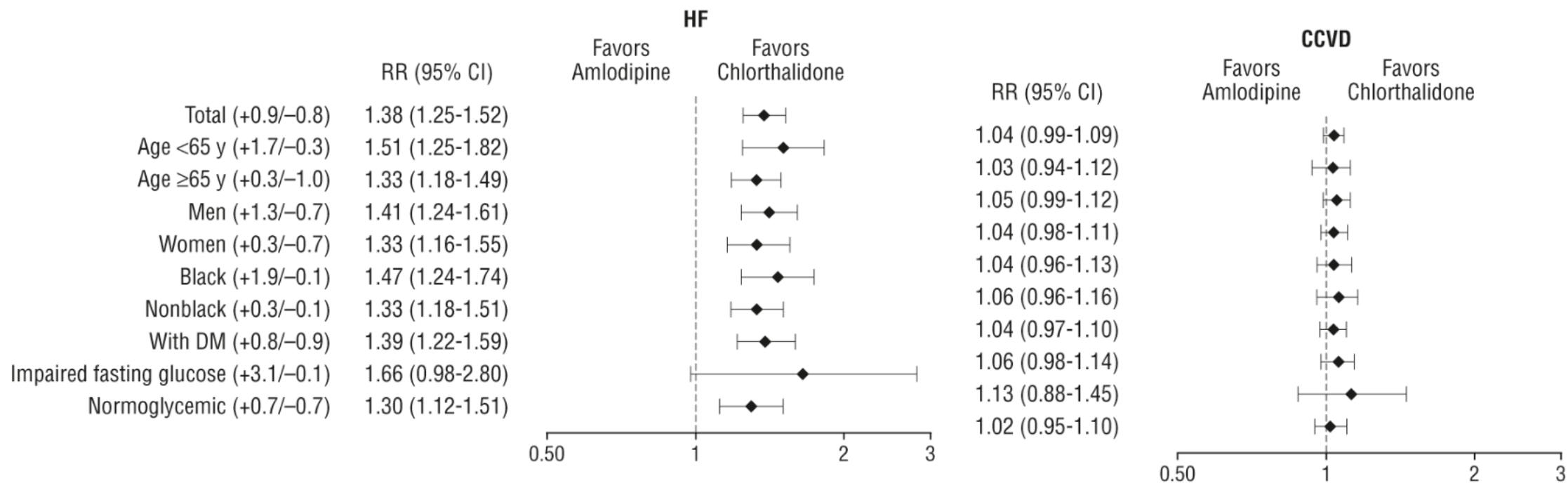
- Definitions:

- >5.0?
- >5.5?
- >6.0?
- >6.5?

ECG changes	+	Moderate	Severe	Severe
	-	Mild	Moderate	Severe
		5.0*–5.9	6.0–6.4	≥6.5
Potassium concentration (mmol/l)				

Step-wise management

1. Avoid concurrent K⁺ raising drugs
2. Dietary counseling
3. Optimize acidosis
4. Optimize medication regimen
5. Consider K binders
6. Discontinue RAAS blockade



Step-wise management

1. Avoid concurrent K⁺ raising drugs
2. Dietary counseling
3. Optimize acidosis
4. **Optimize medication regimen**
5. Consider K binders
6. Discontinue RAAS blockade

Diet

**kidney**
Nutrition Institute

HIGH POTASSIUM FOODS

The servings of fruits and vegetables are ½ cup fresh, ½ cup canned, ½ cup cooked, ¼ cup dried, and ½ cup juice.

Fruits

									
Apricot	Avocado	Banana	Cantalope	Coconut	Dry Fruits	Fresh Peaches	Honeydew	Jackfruit	
									
Kiwi	Mango	Nectarines	Oranges	Papaya	Plantain	Pomegranate	Prunes	Prune Juice	Raisins

Vegetables

									
Acorn Squash	Artichokes	Avocados	Beets	Beet Greens	Bok Choy	Brussel Sprouts	Butternut Squash	French Fries	Lima Beans
									
Mushrooms (cooked)	Okra	Parsnips	Potatoes	Pumpkin	Spinach (cooked)	Sweet Potatoes	Swiss Chard	Tomatoes	Rutabaga

Kidney Nutrition Institute

Potassium Binders



Withholding

- Pre-operative?
- RAAS blockade: *It depends*
- SGLT-2 inhibitors: 3-4 days
- Pre-contrast?
- Probably not

Take Home Points

- Remember the spectrum of metabolic illness and CKMS
- Long-term benefits of proven therapies for renal and CV outcomes
- Hospitalization represents a key opportunity to optimize medical regimen

Questions, Comments?

Key References

- *Drug stewardship for RAS inhibitors and SGLT2 inhibitors in chronic kidney disease: stay on, restart. Nephrol Dial Transplant, 2026, Vol. 41, No. 7*
- *Contemporary Management of Severe Acute Kidney Injury and Refractory Cardiorenal Syndrome: JACC Council Perspectives. JACC 76 (9): 1084-1101, September 2020*
- *Sodium-Glucose Cotransporter-2 Inhibitor and Glucagon-Like Peptide-1 Receptor Agonist Discontinuation in Patients with CKD. JASN 36(1) 87-98, January 2025*
- *Discontinuation of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Chronic Kidney Disease. Mayo Clin Proc 2019; 94 :2220–9*
- *Renin–Angiotensin System Inhibition in Advanced Chronic Kidney Disease. NEJM 387: 2021-2023, 2022.*
- *Estimated Effect of Restarting Renin-Angiotensin System Inhibitors after Discontinuation on Kidney Outcomes and Mortality. JASN 35 (10): 1391-1401, October 2024*