# RENIN ANGIOTENSIN ALDOSTERONE SYSTEM INHIBITORS [ RAASi] - HYPERKALEMIA


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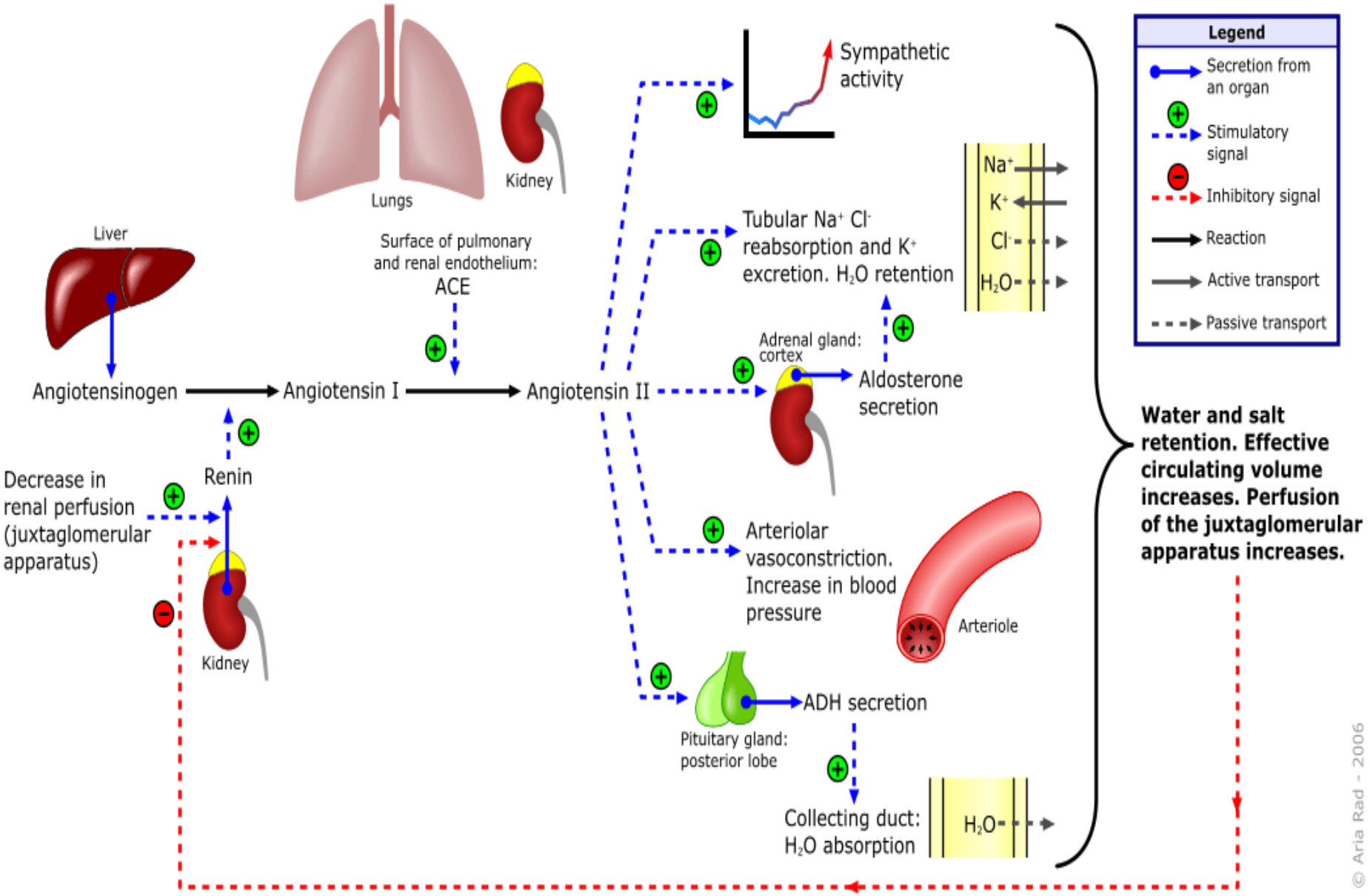
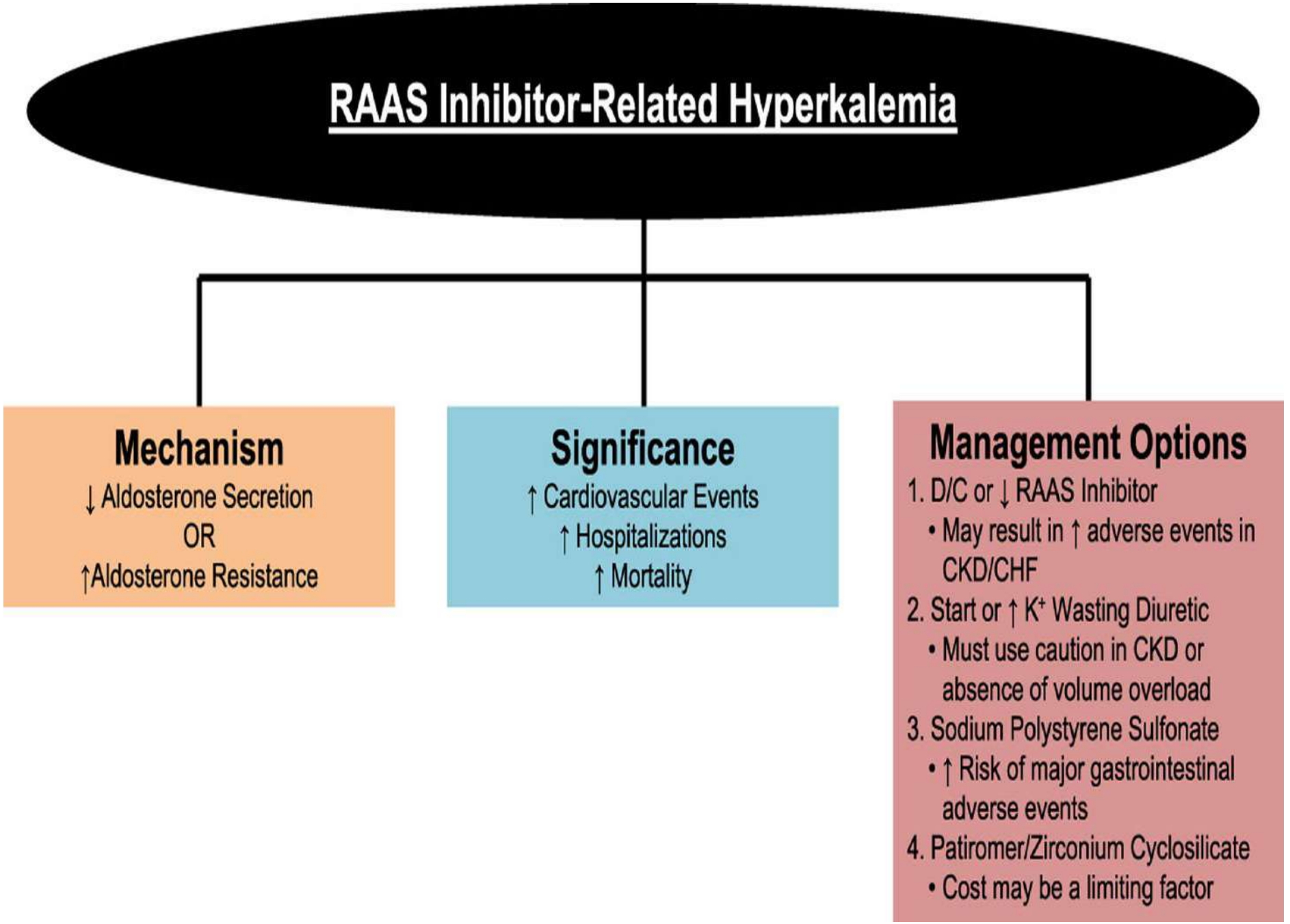
# Renin-angiotensin-aldosterone system



# RAAS inhibitors (RAASi) cause hyperkalemia

Two primary pathways:

- **Reduced Aldosterone Production:**
  - **ACE Inhibitors (e.g., Lisinopril):** Block the conversion of Angiotensin I to Angiotensin II , hence lower aldosterone levels.
  - **Angiotensin Receptor Blockers (ARBs, e.g., Losartan):** Blocks binding of angiotensin II to its receptors.
  - **Direct Renin Inhibitors (e.g., Aliskiren):** Block the system at its earliest stage → preventing the formation of Angiotensin I and II.
- **Aldosterone Resistance (Receptor Blockade):**
  - **Mineralocorticoid Receptor Antagonists (MRAs, e.g., Spironolactone, Eplerenone):** block aldosterone from binding to its receptors in the distal nephron preventing sodium reabsorption and potassium secretion.


RAAS Inhibitor-Related Hyperkalemia
Mechanism
↓ Aldosterone Secretion
OR
↑Aldosterone Resistance
Significance
↑ Cardiovascular Events
↑ Hospitalizations
↑ Mortality
Management Options
1. D/C or ↓ RAAS Inhibitor
• May result in ↑ adverse events in CKD/CHF
2. Start or ↑ K+ Wasting Diuretic
• Must use caution in CKD or absence of volume overload
3. Sodium Polystyrene Sulfonate
• ↑ Risk of major gastrointestinal adverse events
4. Patiromer/Zirconium Cyclosilicate
• Cost may be a limiting factor

# Hyperkalemia-Related Discontinuation of RAAS Inhibitors and Clinical Outcomes in CKD

## Population

Population-based cohort study

Adults with RAASi-related hyperkalemia and CKD ($K^+ \geq 5.5$ mmol/L)

N = 7,200 in Manitoba
N = 71,290 In Ontario

## Methods

RAASi continuers
vs
RAASi discontinuers

Intention-to-treat approach

**Sensitivity Analysis:**
Time-dependent analysis and 1:1 propensity match

## Results

**Reference: RAASi Continuation**

| | Mortality | CV Mortality | Fatal and Non-Fatal CV Events | Dialysis |
|---|---|---|---|---|
| | HR (95% CI) | | | |
| Manitoba | 1.32 (1.22-1.41) | 1.28 (1.13-1.44) | 1.17 (1.11-1.24) | 1.65 (1.41-1.85) |
| Ontario | 1.47 (1.41-1.52) | 1.32 (1.25-1.39) | 1.18 (1.15-1.22) | 1.11 (1.08-1.16) |

**Sensitivity Analysis:**

| Mortality | CV Mortality |
|---|---|
| 1.36 (1.22-1.52) | 1.35 (1.13-1.64) |

**CONCLUSION:** Hyperkalemia-related RAASi discontinuation is associated with higher mortality and cardiovascular events compared with continuation in patients with CKD.

*Silvia Juliana Leon, Reid Whitlock, Claudio Rigatto, et al*

@AJKDonline | DOI: 10.1053/j.ajkd.2022.01.002

AJKD

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

JASN
Journal of the American Society of Nephrology

## 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*

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

## 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) |

**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**

# STOP ACEi TRIAL

## Does the discontinuation of RAS inhibitors improve eGFR in patients with advanced CKD?

#NephJC

- Open-Label Randomized Control Trial
- 39 Centers United Kingdom
- 411 Adults Stage 4 or 5 CKD (eGFR < 30 mL/min/1.73m²)
- > 2 mL/min/1.73m² per year eGFR decline over 2 year
- RAS inhibitor > 6 months (ACEi or ARB)

| | 1° Outcome eGFR (by MDRD*) | 2° Outcome (ESKD or RRT) | MACE |
|---|---|---|---|
| ✓ Continue RAS inhibitor n=205 | 13.3±0.6 mL/min/1.73m² | 56% (115/205) | 43% (88/205) |
| 3 years | P = 0.42 (-2.5 to 1.0) | HR =1.28 (0.99 to 1.65) | Similar |
| ✗ Discontinue RAS inhibitor n=206 | 12.6±0.7 mL/min/1.73m² | 62% (128/206) | 52% (108/206) |

**Conclusion:** Among patients with advanced and progressive chronic kidney disease, the discontinuation of RAS inhibitors was not associated with a significant between-group difference in the long-term rate of eGFR decline.

*Modification of Diet in Renal Disease

**Reference:** STOP ACEi trial investigators, Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease.

Visual Abstract by: Dana Larsen, MD @dana_m_larsen