Renal Pharmacology: RAAS Inhibitors and Renoprotective Therapy

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Renal Pharmacology: RAAS Inhibitors and Renoprotective Therapy

Level: PA/Medical Student **Duration:** 60–90 minutes **Version:** 2026-02-12

Learning Objectives

By the end of this module, students will be able to:

1. **Explain** the renin-angiotensin-aldosterone system (RAAS) anatomy and physiology
2. **Classify** RAAS inhibitors by mechanism (ACEi, ARB, DRI, ARNI, MRA)
3. **Compare** efficacy, side effects, and contraindications of RAAS inhibitors
4. **Apply** RAAS inhibitor therapy in proteinuric kidney disease, hypertension, and heart failure
5. **Monitor** renal function and electrolytes during RAAS inhibition
6. **Identify** why dual/triple RAAS blockade failed in clinical trials
7. **Integrate** newer agents (ARNI, finerenone) into modern renoprotective strategy

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RAAS Physiology Review

The Cascade

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Juxtaglomerular apparatus detects ↓ perfusion pressure / ↓ Na+ delivery
                          ↓
            Renin release from granular cells
                          ↓
        Angiotensinogen (hepatic) → Angiotensin I
                          ↓
    ACE (lung endothelium) → Angiotensin II
                          ↓
    AT1 receptor activation (kidney, vessels, heart)
                          ↓
    ↑ GFR (efferent vasoconstriction), ↑ Na+ reabsorption,
    ↑ sympathetic tone, ↑ aldosterone, ↑ vasopressin
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Physiologic Effects of Angiotensin II (AT1 Receptor)

Target	Effect	Relevance
Glomerulus	☐ Efferent vasoconstriction (>afferent)	☐ GFR, but reduces peritubular capillary hydrostatic pressure
Proximal tubule	☐ Na☐ reabsorption	Volume expansion
Collecting duct	☐ Aldosterone secretion	K☐ wasting, Na☐ retention
Sympathetic	☐ Norepinephrine	☐ HR, ☐ contractility, vasoconstriction
Adrenal	☐ Aldosterone synthesis	Hypokalemia risk
Heart	☐ Myocardial hypertrophy	LV remodeling in HF
Vessels	☐ Vasoconstriction, ☐ smooth muscle proliferation	Hypertension, arterial stiffness

Counter-Regulatory Mechanism: Bradykinin

- **ACE** (angiotensin-converting enzyme) is identical to **kininase II**
- Inhibiting ACE ☐ ☐ bradykinin accumulation
- **Bradykinin effects:** ☐ vasoconstriction, ☐ nitric oxide, ☐ prostaglandins
- **Clinical manifestation:** ACEi cough (15–20% incidence) due to pulmonary bradykinin accumulation

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ACE INHIBITORS (ACEi)

Mechanism of Action

ACE inhibitors competitively block **angiotensin-converting enzyme**, preventing conversion of angiotensin I ☐ angiotensin II. Result: ☐ Ang II-mediated efferent vasoconstriction, ☐ aldosterone, ☐ sympathetic tone.

Pharmacokinetics

Agent	Metabolism	Half-life	Dosing	Onset
Lisinopril	Renal (unchanged)	12–13 hrs	10–40 mg daily	2–4 hrs
Enalapril	Hepatic ☐ active metabolite enalaprilat	11 hrs	10–40 mg daily	1 hour
Ramipril	Hepatic ☐ ramiprilat	13–17 hrs	2.5–10 mg daily	1–2 hrs
Perindopril	Hepatic ☐ perindoprilat	3–10 hrs	4–8 mg daily	1–2 hrs
Captopril	Renal (40%), hepatic (60%)	2–3 hrs	25–150 mg BID-TID	15–30 min

Agent	Metabolism	Half-life	Dosing	Onset
Fosinopril	Hepatic + renal	12 hrs	10–40 mg daily	1 hour

Key Points: - Lipophilic agents (ramipril, perindopril) may have superior tissue penetration - Renal excretion (lisinopril) allows accumulation in renal insufficiency - Hepatic metabolism (enalapril, fosinopril) safer in ESRD

Renal Hemodynamic Effects

Acute Effects (hours–days): - ☐ Efferent arteriolar vasoconstriction ☐ ☐ intraglomerular pressure - ☐ GFR (expected, typically 10–30% drop) - ☐ Renal plasma flow (afferent remains relatively constant) - ☐ Glomerular hyperfiltration (beneficial in proteinuria)

Chronic Effects (weeks–months): - ☐ Glomerulosclerosis (reduced Ang II-mediated fibrosis) - ☐ Interstitial fibrosis - ☐ Proteinuria (via hemodynamic + tubular effects) - Slowing of GFR decline in CKD

Clinical Efficacy

Hypertension: - ☐ BP 8–15 mmHg systolic; effect modest, synergistic with other agents - Works best in renin-dependent hypertension (renovascular, RAS-activated states)

Proteinuric CKD: - ☐ **Proteinuria 30–50%** independent of blood pressure lowering - **KDIGO 2021:** ACEi/ARB recommended for CKD with albuminuria (regardless of hypertension status) - ☐ **ESRD progression:** Landmark trials (Collaborative Study Group trial 1993) show ACEi slows progression of diabetic nephropathy

Heart Failure: - ☐ **Mortality 16%** (SAVE trial, post-MI LV dysfunction) - ☐ HF hospitalizations - ☐ Ventricular remodeling

Post-MI: - ☐ Mortality, reinfarction, HF when started early

Adverse Effects

1. Hyperkalemia

- **Mechanism:** ☐ Aldosterone ☐ ☐ collecting duct Na☐-K☐ exchange
- **Risk factors:** CKD (especially eGFR <30), diabetes, NSAIDs, ACEi use
- **Clinical manifestation:** Asymptomatic hyperkalemia common; peaked T-waves, arrhythmias if severe
- **Management:** Monitor K☐ baseline, 1–2 weeks, then q3 months; restrict dietary K☐; consider potassium-binding agents (patiromer, sodium zirconium cyclosilicate); reduce dose or discontinue if K☐ >5.5 mmol/L with symptoms

2. Hypotension

- **Mechanism:** ☐ Ang II vasoconstriction
- **Risk:** Acute decompensation (sepsis, GI bleeding, diuretic excess)

- **Management:** Reduce dose; optimize intravascular volume; monitor BP at each visit

3. Acute Kidney Injury (AKI)

- **Mechanism:** ☐ Efferent vasoconstriction reduces intraglomerular pressure; risky in hypotension or volume depletion
- **Presentation:** Cr rise >30% within 1–4 weeks of initiation
- **Risk factors:** CKD (eGFR <45), bilateral RAS, single kidney with RAS, dehydration
- **Management:** Check Cr baseline, 1 week, 2 weeks, then q3 months; expect 10–30% rise; if >30%, review volume status, medications (NSAIDs, diuretics)

4. ACE Inhibitor Cough

- **Incidence:** 15–20% (more common in females, non-smokers)
- **Mechanism:** Bradykinin accumulation in lungs
- **Onset:** 1 day to weeks
- **Character:** Dry, persistent, worse supine or at night
- **Management:** Trial off agent; if suspect ACEi ☐ switch to ARB (no bradykinin accumulation; cough resolves in 50%–80%)
- **Note:** Cough NOT an adverse effect; does not indicate danger; discontinue if intolerable

5. Angioedema

- **Incidence:** 0.1–0.5% (higher in blacks)
- **Mechanism:** Bradykinin accumulation in subcutaneous tissues
- **Presentation:** Lip, tongue, face, airway swelling; can be life-threatening
- **Timing:** Can occur months–years after initiation
- **Management:** DISCONTINUE immediately; monitor airway; consider antihistamines, steroids if mild
- **Note:** Absolute contraindication to future ACEi; ARB typically safe but carries <10% cross-reactivity risk in angioedema

6. Pregnancy Concerns

- **Teratogenicity:** ACEi contraindicated in 2nd–3rd trimester (renal dysgenesis, oligohydramnios, neonatal AKI/death)
- **1st trimester:** Relative risk; emerging data suggest possible association with cardiac anomalies; cautious use only if no alternative
- **Lactation:** Minimal transfer to breast milk; generally safe

Contraindications and Cautions

Absolute Contraindication	Rationale
Bilateral renal artery stenosis (RAS)	ACEi-induced AKI from ☐ efferent vasoconstriction
Single kidney with RAS	Same mechanism
Pregnancy (2nd–3rd trimester)	Teratogenicity
Previous ACEi-related angioedema	Absolute contraindication

Absolute Contraindication	Rationale
Relative Caution	**Action**
eGFR <30	Monitor closely; hyperkalemia risk; reduce dose
K☐ >5.0 mmol/L	Avoid; causes further ☐ K☐
Acute decompensation/hypotension	Defer initiation; reduce dose if on agent
NSAIDs + ACEi (dual)	"Triple whammy" if diuretic added; AKI risk

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ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)

Mechanism of Action

ARBs are **selective antagonists of AT1 receptors**, blocking Ang II action without affecting bradykinin. Result: ☐ Ang II effects WITHOUT ☐ bradykinin (hence, no cough).

Note: AT2 receptors (minority) promote vasodilation, anti-fibrosis; ARBs block AT1, leaving AT2 unopposed—possible additional benefit.

Pharmacokinetics

Agent	Metabolism	Half-life	Dosing	Onset
Losartan	Hepatic ☐ active metabolite EXP3174	2–3 hrs	50–100 mg daily	1 hour
Valsartan	Minimal metabolism	6–7 hrs	80–320 mg daily	1–2 hrs
Irbesartan	Minimal metabolism; hepatic (80%)	11–15 hrs	150–300 mg daily	1–2 hrs
Olmesartan	Minimal metabolism	13 hrs	20–40 mg daily	1–2 hrs
Telmisartan	Minimal metabolism	24 hrs	40–80 mg daily (longest half-life)	1–2 hrs
Candesartan	Minimal metabolism	9 hrs	16–32 mg daily	1–2 hrs

Key Points: - All ARBs reach similar efficacy (no superiority demonstrated) - Telmisartan longest half-life; once-daily dosing convenient - Losartan undergoes hepatic activation to metabolite EXP3174 (more potent)

Renal and Cardiovascular Effects

Similarities to ACEi: - ☐ Efferent vasoconstriction ☐ ☐ intraglomerular pressure - ☐ Proteinuria (30–50% reduction) - ☐ GFR acutely (10–30% expected) - ☐ ESRD progression in proteinuric CKD - ☐ Mortality post-MI and in HF

Differences from ACEi: - NO cough (no bradykinin) - NO angioedema (rare; <0.1% vs. ACEi 0.5%) - Equipotent BP lowering - Equipotent renal protection

Clinical Efficacy

Hypertension: - ☐ BP 8–15 mmHg (similar to ACEi)

CKD with Proteinuria: - ☐ Proteinuria 30–50% - ☐ ESRD progression (IDNT, RENAAL trials vs. placebo in diabetic nephropathy)

Heart Failure: - ☐ Mortality, HF hospitalizations (CHARM, VALSARTAN trials)

Post-MI: - ☐ Mortality, reinfarction (similar to ACEi)

Adverse Effects

Hyperkalemia (same as ACEi) - ☐ Aldosterone ☐ ☐ K☐ excretion - Monitor K☐; caution with eGFR <30, NSAIDs, other RAAS inhibitors

Hypotension (same as ACEi) - ☐ Ang II vasoconstriction - Risk in volume depletion, acute illness

AKI/Creatinine Rise (same as ACEi) - ☐ Efferent vasoconstriction - Expected 10–30% rise; monitor for >30% rise - Caution in RAS, single kidney, dehydration

Angioedema (rare; <0.1%) - Much rarer than ACEi - Mechanism unclear (not bradykinin-related) - If angioedema occurs ☐ DO NOT switch to ACEi (cross-reactivity risk)

Cough: ABSENT (major advantage over ACEi)

Hyperuricemia: ARBs (particularly losartan) have mild uricosuric effect (losartan blocks urate reabsorption in proximal tubule)—slight ☐ in uric acid with losartan vs. other ARBs

Contraindications

- Bilateral RAS or single kidney with RAS (AKI risk)
- Pregnancy (teratogenicity, 2nd–3rd trimester)
- K☐ >5.0 mmol/L
- Acute decompensation/hypotension (caution)

DIRECT RENIN INHIBITORS (DRI)

Mechanism

Aliskiren directly binds the **active site of renin**, blocking the initial step of the RAAS cascade (renin release ☐ angiotensinogen cleavage).

Theoretical advantage: More “upstream” blockade than ACEi/ARB; prevents all Ang II production.

Pharmacokinetics

Property	Value
Dose	150–300 mg daily
Metabolism	Minimal (CYP3A4 substrate—drug interactions)
Half-life	24 hrs
Onset	2–4 weeks (slow; accumulation)
Bioavailability	2.5% (poor; enhanced by high-fat meal)

Clinical Efficacy

Limited evidence: - ☐ BP 8–10 mmHg (similar to ACEi/ARB) - ☐ Proteinuria (modest; less robust than ACEi/ARB) - **NO mortality benefit demonstrated** in CKD or HF (unlike ACEi/ARB)

ALICANTE trial (2013): Aliskiren added to losartan in CKD + hypertension ☐ no difference in renal outcomes vs. losartan alone; safety concerns (hyperkalemia, AKI)

Adverse Effects

- **Hyperkalemia:** ☐ risk when combined with ACEi/ARB (see dual RAAS blockade below)
- **AKI:** Similar to ACEi/ARB; caution in volume depletion
- **Diarrhea:** 2–3% (unique to aliskiren; often reversible)
- **Cough/Angioedema:** NOT increased (unlike ACEi)

Clinical Role

Limited; rarely used monotherapy due to: - Modest efficacy - No mortality benefit - Poor bioavailability - Drug interactions (CYP3A4) - Hyperkalemia risk when combined

Specific use: Occasionally added in resistant hypertension (as triple therapy), but ACEi/ARB preferred first-line.

ANGIOTENSIN II RECEPTOR-NEPRILYSIN INHIBITOR (ARNI)

Mechanism: Sacubitril/Valsartan (Entresto)

Dual mechanism: 1. **Valsartan** = ARB component (Ang II blockade) 2. **Sacubitril** = Neprilysin inhibitor (☐ natriuretic peptide degradation ☐)

Key biology: Neprilysin breaks down natriuretic peptides (ANP, BNP, C-type NP). Inhibiting neprilysin ☐ ☐ circulating NP levels ☐ enhanced natriuresis, vasodilation, anti-fibrosis.

Pharmacokinetics

Property	Value
Dosing	49/97 mg (sacubitril/valsartan) BID (target); some formulations once-daily
Metabolism	Hepatic metabolism of sacubitril ☐ LBQ657 (active)

Property	Value
Half-lives	Valsartan 9–11 hrs; sacubitril metabolites 10–11 hrs
Onset	2–4 weeks full effect

Clinical Efficacy: Heart Failure

PARADIGM-HF Trial (2014)—Landmark: - **Population:** ~8,400 patients with HFrEF (LVEF ≤35%) - **Primary endpoint:** CV death or HF hospitalization - **Result:** Sacubitril/valsartan ☐ primary endpoint **20% vs. enalapril** - **Mortality:** ☐ CV death 16%; ☐ all-cause death 16% - **Conclusion:** Superior to ACEi monotherapy in HFrEF

PROVE-HF Trial (2019): - ARNI ☐ natriuretic peptides more effectively than ACEi, suggesting superior neurohormonal modulation

Efficacy in CKD + Proteinuria

PIONEER Trial (2019): - **Population:** CKD Stage 3–4 + diabetes, proteinuria - **Design:** Sacubitril/valsartan vs. losartan - **Result:** ☐ Albuminuria 36% vs. 24% with losartan (modest additional benefit) - **Renal outcomes:** Similar to losartan - **Note:** ARNI not established as superior to ARB monotherapy for renal outcomes

Adverse Effects

Similar to ARB + neprilysin-specific:

Adverse Effect	Incidence/Note
Hyperkalemia	3–5% (PARADIGM-HF); risk with eGFR <60
Hypotension	7–9%; more than enalapril in some trials
AKI/Creatinine rise	Similar to ARB; monitor Cr baseline, 1–2 weeks
Cough	Absent (ARB component; no bradykinin)
Angioedema	Rare; avoid if history of ACEi angioedema
Neprilysin-specific:	
Amyloidosis risk (theoretical)	No clinical evidence in trials; neprilysin degrades amyloid-beta, but no ☐ amyloidosis observed

Drug Interactions

- **ACEi/ARB cannot be combined with ARNI** (dual Ang II blockade—hyperkalemia, AKI)
- **NSAIDs + ARNI:** Triple whammy if diuretic added
- **Lithium:** ☐ lithium levels (neprilysin inactivates lithium metabolism)

Contraindications

- Bilateral RAS or single kidney RAS
- K☐ >5.0 mmol/L

- eGFR <15 (caution; limited data)
- Pregnancy (2nd–3rd trimester; teratogenicity)
- History of ACEi/ARB angioedema (avoid ARNI as well)

NON-STEROIDAL ALDOSTERONE ANTAGONIST: FINERENONE

Mechanism

Finerenone is a **non-steroidal mineralocorticoid receptor (MR) antagonist**—selective MR antagonist with reduced androgen/progesterone receptor interactions vs. spironolactone.

Mechanism distinct from spironolactone: - Does NOT directly inhibit aldosterone synthesis - Binds MR with **subtype selectivity** (MR over AR, PR) - Transrepressive mechanism (blocks pro-inflammatory/pro-fibrotic genes) - Anti-inflammatory, anti-fibrotic independent of Na☐-K☐ exchange

Pharmacokinetics

Property	Value
Dosing	10 mg daily (initiate); 20 mg daily if tolerated
Metabolism	Hepatic (CYP3A4); minimal renal excretion
Half-life	4–6 hrs
Onset	2–4 weeks

Clinical Efficacy: Landmark Trials

FIDELIO-DKD Trial (2020)—Type 2 Diabetes + CKD

- **Population:** ~13,400 patients with T2DM, CKD Stage 3–4, albuminuria
- **Background therapy:** ACEi/ARB in 90%, including with spironolactone in 3%
- **Primary endpoint:** Composite of CV death, non-fatal MI, non-fatal stroke, HF hospitalization, or renal events (doubling Cr, ESRD, renal death)
- **Result:** Finerenone ☐ primary endpoint **18%** vs. placebo
- **Renal-specific outcomes:** ☐ ESRD progression 25%; ☐ progression to CKD Stage 4 26%
- **Key finding:** Benefit over and above ACEi/ARB—evidence of non-RAAS MR-mediated renal protection

FIGARO-DKD Trial (2021)—T2DM + CKD Stages 2–3

- **Population:** ~7,400 patients with earlier CKD (Stage 2–3) and albuminuria
- **Result:** Finerenone ☐ CV death, HF hospitalization, renal progression **18%**
- **Note:** Earlier CKD stage; still renoprotective

Proposed Renal Mechanisms Beyond Aldosterone

1. **Transrepression:** Blocks MR-mediated inflammation, reduces IL-6, TNF-α
2. **Anti-fibrotic:** ☐ TGF-β signaling, ☐ myofibroblast activation

3. **Endothelial:** ☐ nitric oxide, ☐ oxidative stress
4. **Podocyte:** ☐ proteinuria via reduced foot process effacement
5. **Glomerular:** ☐ SGLT1 expression (possible glucose-related protection)

Adverse Effects

Hyperkalemia (most clinically significant) - **Incidence:** 2–3% in FIDELIO (vs. 1% placebo) - **Risk factors:** eGFR <30, diabetes, concurrent ACEi/ARB, NSAIDs - **Management:** K☐ monitoring baseline, week 4, then every 3 months; consider potassium-lowering agent (sodium zirconium cyclosilicate, patiromer) if K☐ rises; dose reduction or discontinuation if K☐ >6.0 mmol/L

Hypotension - **Incidence:** 3–4% - **Mechanism:** ☐ Aldosterone ☐ Na☐ wasting - **Management:** Monitor BP; adjust diuretics/other agents if needed

Urinary Tract Infection (UTI) - **Incidence:** 4.5% (finerenone) vs. 3.6% (placebo) in FIDELIO - **Mechanism:** Unclear; possibly immune modulation - **Management:** Standard UTI management; not contraindication

Anemia (modest) - **Incidence:** 1–2% - **Mechanism:** Possible effect on erythropoiesis

Hypoglycemia (paradoxically) - **Incidence:** Slight ☐ with finerenone + SGLT2i in some analyses - **Mechanism:** Potential SGLT-related effect; unclear

Contraindications and Cautions

Contraindication	Rationale
K☐ >5.5 mmol/L at baseline	Hyperkalemia risk
eGFR <25 (CKD Stage 5)	Insufficient data; caution
Type 1 diabetes (off-label)	Limited evidence; primarily T2DM trials
Caution	
eGFR 25–30	Monitor K☐ closely; may need dose adjustment
ACEi/ARB + NSAIDs (triple)	Triple whammy—AKI, hyperkalemia risk
Spironolactone co-use	Additive K☐ rise; avoid dual MRA therapy

Clinical Role and Integration

KDIGO 2021 Update: - Finerenone recommended for CKD + diabetes + albuminuria, independent of RAAS inhibitor use - Position: Add to ACEi/ARB (not alternative)

Modern renoprotective regimen: 1. **SGLT2 inhibitor** (e.g., dapagliflozin, empagliflozin) — 39% ☐ ESRD progression 2. **ACEi or ARB** (not dual) — 30–50% ☐ proteinuria 3. **Finerenone** (if eGFR >25, K☐ <5.5) — additional 18–25% renal benefit 4. **GLP-1 agonist** (if T2DM + overweight) — weight loss, CV benefit

DUAL AND TRIPLE RAAS BLOCKADE: Why It Failed

Historical Context: Rationale for Dual Blockade

- **Concept:** Block RAAS at multiple points ☐ greater neurohormonal suppression ☐ better renal protection
- **Theoretical basis:** ACEi ☐ Ang II but ☐ renin (compensatory); ARB ☐ Ang II but ☐ renin; combination = maximal Ang II suppression
- **1990s–2000s enthusiasm:** Multiple small studies suggested dual blockade benefit

Major Clinical Trials: Null Results

VA NEPHRON-D Trial (2014)

- **Population:** ~1,448 veterans with CKD Stage 3–4 + hypertension
- **Intervention:** Losartan monotherapy vs. losartan + lisinopril
- **Results:**
  - NO difference in primary endpoint (GFR decline)
  - ☐ Hyperkalemia: 5.0% (dual) vs. 2.6% (mono)
  - ☐ AKI: 1.3% (dual) vs. 0.6% (mono)
- **Conclusion:** Dual RAAS blockade = hyperkalemia + AKI **without renal benefit**

ONTARGET Trial (2008)—Post-MI, High CV Risk

- **Population:** ~25,620 patients with prior MI, stroke, or high CV risk
- **Intervention:** Ramipril monotherapy vs. valsartan monotherapy vs. ramipril + valsartan
- **Results:**
  - **Dual therapy did NOT improve CV outcomes** vs. monotherapy
  - ☐ Renal dysfunction: 13.5% (dual) vs. 10.2–11.6% (mono)
  - ☐ Hyperkalemia: 4.2% (dual) vs. 1.7% (ramipril alone)
  - ☐ Syncope: 0.3% (dual) vs. 0.1% (mono)
- **Conclusion:** ACEi + ARB = harm (☐ AKI, hyperkalemia, syncope) without benefit

ACCOMPLISH Trial (2008)—Hypertension

- **Population:** ~11,506 with hypertension + high CV risk
- **Intervention:** Benazepril/amlodipine vs. benazepril/HCTZ
- **Note:** Not true dual RAAS blockade, but ACEi + diuretic vs. ACEi monotherapy
- **Result:** ACEi/amlodipine superior to ACEi/HCTZ (supporting RAAS-sparing diuretics)

Mechanisms of Dual RAAS Blockade Failure

1. **Hyperkalemia:** Sequential ☐ aldosterone ☐ severe K☐ retention
2. **AKI:** Efferent vasoconstriction from dual ☐ Ang II + volume depletion risk
3. **Counter-regulatory activation:** Renin ☐ dramatically with dual blockade (feedback loop); breakthrough Ang II production possible
4. **Glomerular hemodynamic collapse:** Too much efferent vasodilation ☐ loss of driving pressure for filtration
5. **Blunted efficacy:** Physiologic adaptation/escape (aldosterone escape phenomenon observed in some dual-therapy patients)

Current Consensus

Guidelines unanimously recommend: - **Monotherapy** with ACEi OR ARB (NOT both) - **Exception:** ARNI (sacubitril/valsartan) = ARB + neprilysin inhibitor (different mechanism—valsartan component within ARNI is permissible) - **Addition of finerenone:** OK with ACEi/ARB monotherapy (non-overlapping mechanism)

MONITORING AND MANAGEMENT DURING RAAS INHIBITION

Baseline Assessment (Pre-Initiation)

Parameter	Action
Renal function	Baseline eGFR, Cr
Potassium	Baseline K☐ (defer if K☐ >5.0)
Blood pressure	Baseline BP; assess volume status
Pregnancy status	Confirm not pregnant (2nd–3rd trimester risk)
Medications	Review NSAIDs, diuretics, other RAAS agents
History	Prior ACEi angioedema? RAS? Kidney disease?

Post-Initiation Monitoring

First 1–2 weeks: - **Cr + eGFR:** Check at 1 week; expect 10–30% rise - **K☐:** Check at 1 week; expect modest ☐ - **BP:** Monitor for hypotension - **Symptoms:** Dizziness, syncope, hyperkalemia signs (palpitations, weakness)

Weeks 2–8: - **Cr + eGFR:** Check again at 2 weeks if initial rise >30% - **K☐:** Check at 2 weeks if on diuretic or eGFR <45 - **BP:** Titrate dose to target

Months 2–3 onward: - **Cr, eGFR, K☐:** Every 3 months × 1 year, then annually if stable - **More frequent monitoring (monthly) if:** - eGFR <45 - K☐ at upper limit of normal - Recent dose escalation - Concurrent NSAIDs or diuretics

Interpretation of Creatinine Rise

Cr Rise	Timing	Interpretation	Action
10–30%	1–2 weeks	Expected; reflects ☐ intraglomerular pressure	Continue agent; recheck in 2 weeks
>30% (but <50%)	1–4 weeks	May be pre-renal or hemodynamic	Review volume status, BP, diuretics; recheck Cr; if stable, continue
>50% or progressive	Ongoing	Suggests pre-renal (volume depletion, hypotension) or AKI	STOP agent; evaluate for RAS, dehydration; recheck Cr in 1 week

When to Hold or Discontinue RAAS Inhibitors

Scenario	Action
K□ >6.0 mmol/L with symptoms	HOLD; treat hyperkalemia
Cr rise >50% from baseline	HOLD; investigate pre-renal causes
Symptomatic hypotension	HOLD; reassess intravascular volume
Angioedema (ACEi)	DISCONTINUE; NEVER restart; avoid ARB if ACEi angioedema
Persistent dry cough (ACEi)	DISCONTINUE; consider ARB if intolerable
Acute illness (sepsis, GI bleed)	Temporarily HOLD; restart when stable
Planned contrast study	HOLD day of procedure (especially if eGFR <45)
Pregnancy planned or confirmed	DISCONTINUE (1st trim caution; 2nd–3rd trim contraindicated)

Clinical Scenarios

Scenario 1: CKD Stage 3b + Type 2 Diabetes + Proteinuria

Clinical: 58-year-old male with T2DM, BP 145/92, eGFR 38, uACR 180 mg/g (overt albuminuria), on metformin monotherapy, no current antihypertensive.

Labs: - Cr 1.6 mg/dL - K□ 4.3 mmol/L - Urine dip: 2+ protein

Plan: 1. **Start ACEi (lisinopril 10 mg daily) or ARB (losartan 50 mg daily)** - Both equipotent for proteinuria reduction and renal protection - Lisinopril slightly cheaper; losartan if cough develops 2. **Check Cr + K□ at 1 week** - Expect Cr □ 10–30% (acceptable) - K□ should remain <5.0 3. **Goal BP:** <120 systolic (SPRINT-CKD suggests benefit of intensive control in CKD) 4. **Add SGLT2i (dapagliflozin 10 mg daily)** - □ ESRD progression, CV death - Continue metformin 5. **Lifestyle:** Sodium restriction <3 g/day, weight loss if overweight 6. **3-month reassess:** Recheck eGFR, K□, proteinuria; if stable and K□ <5.0, consider adding finerenone 10 mg daily 7. **Target:** CKD stabilization, □ proteinuria, BP control

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Scenario 2: Heart Failure with Reduced EF + Diabetes

Clinical: 62-year-old female with HFrEF (LVEF 28%), hypertension, T2DM, on carvedilol 25 mg BID.

Presentation: Dyspnea on exertion, 2+ lower extremity edema.

Labs: - Cr 1.3 mg/dL (eGFR 48) - K□ 4.5 mmol/L - BNP 650 pg/mL

Plan: 1. **Start ACEi (lisinopril 5 mg daily) or ARNI (sacubitril/valsartan 49/97 mg BID)** - ARNI preferred in HFrEF (PARADIGM-HF 20% mortality reduction) - If cost/access issue, ACEi acceptable - Do NOT start both ACEi and ARB (dual blockade) 2. **Verify not on NSAIDs or diuretics causing volume depletion** 3. **Check Cr + K□ at 1 week** - Expected Cr □ 10–30% - K□ should remain <5.5 4. **Titrate to target dose:** - ARNI: Escalate to 97/194 mg BID (if

tolerated) - Lisinopril: Target 10 mg daily 5. **Add beta-blocker** (carvedilol already on board) + **aldosterone antagonist** (spironolactone 25 mg daily or eplerenone 25 mg daily) - RALES trial: ☐ mortality 30% with spironolactone in HF - Monitor K☐ closely (goal K☐ 4.5–5.5) 6. **Diuretics:** If volume-overloaded, add furosemide (separate handout); do NOT defer diuretics to start RAAS inhibitors 7. **SGLT2i:** Add dapagliflozin 10 mg daily (☐ HF hospitalization) 8. **3-month reassess:** BNP, Cr, K☐, weight, EF (echo); adjust doses

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Scenario 3: Dual RAAS Blockade (Incorrect) to Monotherapy (Correct)

Clinical: 72-year-old male with CKD Stage 4 (eGFR 22) referred on losartan 100 mg daily + lisinopril 10 mg daily (prescribed by cardiologist post-MI).

Recent labs: - K☐ 5.7 mmol/L (elevated) - Cr 2.8 mg/dL (Cr baseline pre-MI was 2.0; rise ☐0.8 in 3 months) - BP 128/76 (well-controlled)

Recognize: Dual RAAS blockade causing hyperkalemia + AKI

Plan: 1. **STOP lisinopril immediately** - Continue losartan 100 mg daily as monotherapy - Avoid ACEi/ARB combination (VA NEPHRON-D data) 2. **Recheck K☐ in 1 week** - Expect modest ☐ in K☐ (off one RAAS blocker) - Goal K☐ <5.0 3. **Recheck Cr in 1–2 weeks** - Expect Cr to stabilize/improve (off dual blockade) 4. **If K☐ remains >5.5 or Cr continues rising:** - Reduce losartan to 50 mg daily - Recheck K☐, Cr 5. **Add orthogonal agent for post-MI benefit:** - If ACEi stopped due to K☐/AKI, consider ARB monotherapy (already on losartan) - Alternative: Beta-blocker optimization, ACE-free regimen with eplerenone (selective MRA) 6. **Dietary counseling:** K☐-restricted diet, fluid restriction if volume overloaded

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Practice Questions

Question 1

A 52-year-old woman with CKD Stage 3a (eGFR 56) and hypertension (BP 162/98) is started on lisinopril 10 mg daily. After 1 week, she develops a persistent dry cough and her serum creatinine has risen from 1.0 to 1.15 mg/dL. K☐ is 4.6 mmol/L.

Which of the following is the MOST appropriate next step?

A) Continue lisinopril; cough is expected and will resolve
B) Increase lisinopril to 20 mg daily to improve BP control
C) Switch to losartan 50 mg daily for ACEi cough
D) Discontinue lisinopril and start amlodipine 5 mg daily
E) Add spironolactone 25 mg daily for additional BP control

Answer: C (switch to ARB; cough resolves in 50–80%)

Rationale: - ACEi cough affects 15–20% of patients; related to bradykinin accumulation in lungs - Cough NOT dangerous but intolerable if persistent - ARB substitution resolves cough in majority (no bradykinin effect) - Cr rise 10–30% expected (acceptable); K☐ stable - Continue monitoring Cr; expect stabilization in 2–4 weeks - Amlodipine suitable alternative if ARB cough develops (rare)

Question 2

A 65-year-old male with LVEF 32%, CKD Stage 4 (eGFR 28), and hypertension is on lisinopril 10 mg daily and carvedilol 25 mg BID. He is referred for worsening dyspnea. Labs show K□ 5.8 mmol/L, Cr 1.9 mg/dL (baseline 1.7), BNP 750 pg/mL.

Which of the following represents the BEST next step in pharmacologic management?

A) Increase lisinopril to 20 mg daily for additional neurohormonal suppression
B) Add eplerenone 25 mg daily for aldosterone antagonism
C) Add spironolactone 25 mg daily and monitor K□ closely
D) Discontinue lisinopril; start sacubitril/valsartan 49/97 mg BID
E) Add furosemide 40 mg daily without changing RAAS inhibitors

Answer: D (ARNI superior in HFrEF; allows removal of one RAAS inhibitor to improve K□)

Rationale: - **Hyperkalemia (K□ 5.8) limits adding MRA** (spironolactone, eplerenone) - Increasing lisinopril worsens hyperkalemia - **ARNI (sacubitril/valsartan)** provides ARB component + neprilysin inhibition (superior to ACEi in HFrEF per PARADIGM-HF) - Switching from lisinopril to ARNI = removes one RAAS inhibitor, lowers K□ - Once K□ improves, can add aldosterone antagonist if needed - Diuretics (furosemide) necessary for volume management but don't address hyperkalemia

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Question 3

A 48-year-old male with Type 2 diabetes, hypertension, CKD Stage 3b (eGFR 42), and overt albuminuria (uACR 220 mg/g) is on metformin and lisinopril 20 mg daily. His BP is 138/86 and his recent K□ is 4.9 mmol/L. His cardiologist recommends adding losartan 50 mg daily for additional renal protection.

Which of the following is the MOST appropriate response?

A) Agree with cardiologist; dual RAAS blockade provides additional renal benefit
B) Agree, but reduce lisinopril to 10 mg daily and start losartan 50 mg daily
C) Disagree; instead, optimize lisinopril dose and add finerenone 10 mg daily
D) Disagree; instead, add SGLT2 inhibitor (dapagliflozin) and continue lisinopril
E) Both C and D are correct

Answer: E (monotherapy RAAS inhibitor + finerenone + SGLT2i optimal; avoid dual blockade)

Rationale: - **VA NEPHRON-D and ONTARGET trials:** Dual RAAS blockade (ACEi + ARB) = □ hyperkalemia, □ AKI, NO additional renal benefit - **KDIGO 2021:** Avoid dual RAAS blockade in CKD - **Optimal modern approach:** 1. **RAAS monotherapy:** Continue lisinopril (already optimized 20 mg) 2. **Finerenone:** Add for additional renal protection (18–25% □ ESRD progression; FIDELIO-DKD data; different mechanism from ACEi) 3. **SGLT2i:** Add dapagliflozin for 39% □ ESRD progression (independent of RAAS inhibitors) 4. **BP target:** <130/80 per KDIGO 5. **Monitor K□ monthly** initially (goal <5.5)

Clinical Pearl Summary

1. **RAAS physiology:** Ang II drives efferent vasoconstriction (☐ intraglomerular pressure) and aldosterone-mediated Na☐ retention; RAAS inhibitors relieve both.
2. **ACEi mechanism:** ☐ Ang II + ☐ bradykinin ☐ cough (15–20%), angioedema (0.5%), but excellent renoprotection and mortality benefit.
3. **ARB mechanism:** ☐ Ang II WITHOUT bradykinin ☐ no cough, rare angioedema, equipotent renoprotection vs. ACEi.
4. **Renal effects common to ACEi/ARB:** ☐ Efferent vasoconstriction ☐ ☐ intraglomerular pressure ☐ ☐ proteinuria 30–50% + ☐ ESRD progression.
5. **Expected Cr rise 10–30% after ACEi/ARB initiation** is acceptable; reflects hemodynamic adaptation, not nephrotoxicity.
6. **Hyperkalemia:** Most significant adverse effect; risk ☐ with eGFR <30, NSAIDs, concurrent K☐-sparing agents, diabetes.
7. **Dual RAAS blockade failed in major trials** (VA NEPHRON-D, ONTARGET)— hyperkalemia, AKI, NO benefit. Monotherapy only.
8. **ARNI (sacubitril/valsartan):** Superior to ACEi in HFrEF (PARADIGM-HF 20% mortality reduction); ☐ proteinuria in CKD but not established as superior to ARB monotherapy for renal outcomes.
9. **Finerenone (non-steroidal MRA):** Adds to ACEi/ARB monotherapy (18–25% additional ☐ ESRD progression); mechanism includes anti-inflammatory, anti-fibrotic; hyperkalemia risk still present.
10. **Modern renoprotective regimen:** ACEi OR ARB monotherapy + SGLT2i + finerenone (if eGFR >25, K☐ <5.5) + GLP-1 agonist (if T2DM + obesity).

References

1. **KDIGO 2021 Clinical Practice Guideline** — CKD: Evaluation and Management. *Kidney Int Suppl* 11:309–427. (RAAS inhibitor recommendations, monitoring)
2. **PARADIGM-HF Trial (2014)** — McMurray JJV, et al. Angiotensin-Neprilysin Inhibition vs. Enalapril in Heart Failure. *N Engl J Med* 371:993–1004. (ARNI superiority in HFrEF)
3. **VA NEPHRON-D Trial (2014)** — Fried LF, et al. Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy. *N Engl J Med* 369:1892–1903. (dual RAAS blockade failure)
4. **ONTARGET Trial (2008)** — The Telmisartan Randomized Assessment Global Endpoint Trial. *Lancet* 372:547–553. (dual RAAS blockade in post-MI patients)
5. **FIDELIO-DKD Trial (2020)** — Bakris GL, et al. Finerenone in Patients with Diabetic Kidney Disease. *N Engl J Med* 383:1888–1900. (finerenone efficacy + safety)
6. **FIGARO-DKD Trial (2021)** — Pitt B, et al. Cardiovascular and Renal Outcomes with Finerenone in CKD. *N Engl J Med* 385:2684–2695. (finerenone in earlier CKD)

7. **Collaborative Study Group Trial (1993)** — Lewis EJ, et al. The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy. *N Engl J Med* 329:1456–1462. (ACEi landmark in diabetic nephropathy)
8. **Brater DC (2006)** — Pharmacokinetics and Pharmacodynamics of Diuretics. *Clin Pharmacokinet* 45:857–870. (electrolyte management)
9. **Pfeffer MA, et al. (1992)** — SAVE Trial. Effect of Captopril on Mortality and Morbidity in Patients with Left Ventricular Dysfunction. *N Engl J Med* 327:669–677. (ACEi post-MI)
10. **Lexicomp, UpToDate, Micromedex** — Drug information, dosing, adverse effects, interactions (subscription-based resources).

See Also

Related Student Handouts

- Diuretics
- Immunosuppressive Therapy in Nephrology
- CKD Overview and Classification
- Diabetic Kidney Disease
- Hypertension Management
- GDMT: Four Pillars of Therapy
- SGLT2 Inhibitors in Kidney Disease

Clinical Content (01-Clinical-Medicine/Nephrology)

- Essential Renal Laboratory Tests
- Hypertension Management Hub
- CKD Hub - Full Clinical Reference
- Cardio-Renal Ecosystem Hub

Atomic Notes (ZK)

- RAAS System and Blood Pressure Regulation

Butler-COM Resources

- Butler COM - Nephrology Deep Dive
- Butler COM - Heart Failure GDMT Deep Dive

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Clinical Resources

- Clinical Review: Lab Perspective Ldh And Bicarb — Comprehensive clinical review with PubMed references

- Clinical Review: Clincial Perspective Bicarb And Ldh — Comprehensive clinical review with PubMed references
- Clinical Review: Raasi Summary — Comprehensive clinical review with PubMed references
- Clinical Review: Sodium Bicarbonate Document — Comprehensive clinical review with PubMed references