

Mineralocorticoid receptor antagonists

Aldosterone antagonists at the mineralocorticoid receptor, used for their survival benefit in heart failure and their effect in resistant hypertension, and limited above all by hyperkalaemia.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/mineralocorticoid-receptor-antagonists>

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Quick revision

One Liner: MRAs competitively block aldosterone at the mineralocorticoid receptor, so sodium and water are not retained and potassium is - which is simultaneously the reason they improve survival in heart failure and the reason hyperkalaemia dominates their monitoring.

1. Mechanism: competitive blockade of aldosterone at the mineralocorticoid receptor in the distal tubule and collecting duct. [2]
2. The result is that sodium reabsorption with water retention does not occur, while potassium is retained instead of being secreted. [2]
3. Aldosterone also acts on non-epithelial tissue, so blocking it reduces vascular stiffness and cardiac fibrosis as well as fluid. [2]
4. Hyperkalaemia is the defining hazard of the class and the reason renal function and potassium must be followed. [2]
5. Spironolactone is non-selective and also binds androgen and progesterone receptors, which is where gynaecomastia comes from. [2]
6. Eplerenone keeps the steroid scaffold but binds its receptor selectively, which is what spares most of the anti-androgen effects. [4]
7. Finerenone is non-steroidal and selective, with no relevant affinity for androgen, progesterone, oestrogen or glucocorticoid receptors. [5]
8. RALES established the survival benefit of spironolactone in severe heart failure with reduced ejection fraction. [2]
9. Eplerenone and finerenone are both CYP3A substrates, so strong CYP3A inhibitors are contraindicated with them. [4][5]

Overview

1. Mineralocorticoid receptor antagonists sit at the far end of the renin-angiotensin-aldosterone system. Aldosterone is synthesised in the zona glomerulosa of the adrenal cortex, and its release is driven principally by angiotensin II, adrenocorticotrophic hormone and extracellular potassium. It acts on mineralocorticoid receptors on principal cells of the renal cortical collecting duct, increasing the abundance of epithelial sodium channels at the apical membrane and activating the basolateral sodium-potassium ATPase. [3]
2. Blocking that receptor is therefore a diuretic action with an unusual electrolyte signature: sodium and water are not retained, and potassium is. That single fact explains both halves of the class - its usefulness in fluid overload and resistant hypertension, and the hyperkalaemia that governs who can be given it. [2]
3. What lifted these drugs above the other potassium-sparing diuretics is what aldosterone does outside the nephron. It increases vascular stiffness and remodelling and increases cardiac inflammation, fibrosis and remodelling, and mineralocorticoid receptors are present in non-epithelial tissue including heart and blood vessels. Blocking them is why the class carries a prognostic benefit in heart failure rather than a symptomatic one. [2][5]
4. Three agents now define the group. Spironolactone is the original, non-selective and cheap, with the widest set of indications and the endocrine side effects that follow from its receptor promiscuity. Eplerenone is steroidal but selective, approved after myocardial infarction and for hypertension. Finerenone is non-steroidal, selective, and approved for a different problem entirely - chronic kidney disease associated with type 2 diabetes. [2][4][5]

Classification and drug examples

Intro: The clinically useful split is chemical - steroidal versus non-steroidal - because it predicts receptor selectivity, and receptor selectivity predicts the endocrine adverse effects that make patients stop taking these drugs.

1. Name: Steroidal, non-selective

1. Note: A steroid backbone that resembles aldosterone closely enough to bind other steroid receptors as well as the mineralocorticoid receptor.

Name: Spironolactone

Route: Oral

Note: A non-selective antagonist that can also bind androgen and progesterone receptors, giving it both its dermatological off-label uses and its endocrine adverse effects. [2] [2]

2. Name: Steroidal, selective

2. Note: Retains the steroid scaffold but binds the mineralocorticoid receptor preferentially, which markedly reduces the anti-androgen effects without removing them.

Name: Eplerenone

Route: Oral

Note: Binds human mineralocorticoid receptors selectively relative to recombinant human glucocorticoid, progesterone and androgen receptors. Indicated after myocardial infarction with reduced ejection fraction, and for hypertension. [4] [4]

3. Name: Non-steroidal, selective

3. Note: A different chemical class altogether, developed to separate mineralocorticoid receptor blockade from every other steroid receptor.

Name: Finerenone

Kerendia

Route: Oral

Note: A non-steroidal, selective antagonist with high potency for the mineralocorticoid receptor and no relevant affinity for androgen, progesterone, oestrogen or glucocorticoid receptors. [5] [5]

Mechanism of action

Summary: These drugs competitively block aldosterone at the mineralocorticoid receptor. In the nephron that stops sodium reabsorption and water retention and preserves potassium; in heart and vessels it blocks the receptor overactivation that contributes to fibrosis and inflammation.

Target: The mineralocorticoid receptor, in renal collecting duct principal cells and in non-epithelial tissue including heart and blood vessels

1. Step: 1

1. Title: Aldosterone is released and acts on a nuclear receptor

1. Detail: Synthesis in the zona glomerulosa is regulated by angiotensin II, adrenocorticotrophic hormone and extracellular potassium. Circulating aldosterone has a plasma half-life of under 20 minutes and acts through nuclear cytosolic receptors that regulate gene transcription. [3][5]

2. Step: 2

2. Title: The receptor drives sodium in and potassium out

2. Detail: Aldosterone increases the abundance of epithelial sodium channels at the apical membrane of collecting duct principal cells and activates the sodium-potassium ATPase at the basolateral membrane, so sodium moves into the extracellular space while potassium is taken up and secreted into the urine. [3]

3. Step: 3

3. Title: The drug occupies the receptor competitively

3. Detail: A mineralocorticoid receptor antagonist competitively blocks aldosterone receptor-mediated action, so

sodium reabsorption with water retention does not occur and potassium is retained rather than lost. [2]

4. Step: 4

4. Title: Non-epithelial blockade limits remodelling

4. Detail: Mineralocorticoid receptors are present in non-epithelial tissue such as heart and blood vessels, and receptor overactivation is thought to contribute to fibrosis and inflammation. Blocking it reduces vascular stiffness and remodelling and reduces cardiac inflammation, fibrosis and remodelling. [2][5]

5. Step: 5

5. Title: Selectivity decides the side effect profile

5. Detail: Spironolactone also binds androgen and progesterone receptors, which produces the breast and menstrual effects and also its off-label dermatological action through blockade of dihydrotestosterone at androgen receptors. Eplerenone and finerenone are selective, and finerenone has no relevant affinity for androgen, progesterone, oestrogen or glucocorticoid receptors. [2][4][5]

Major clinical uses

1. Drug: Spironolactone

1. Indication: Heart failure with reduced ejection fraction

1. Line: guideline-directed

1. Note: Guideline criteria describe NYHA class II to IV with creatinine clearance above 30 mL/min and serum potassium below 5 mEq/L; RALES showed a 30% relative risk reduction in all-cause mortality in class III to IV disease with an ejection fraction below 35%. [2]

2. Drug: Spironolactone

2. Indication: Resistant hypertension

2. Line: add-on

2. Note: Defined as blood pressure above goal despite optimal doses of three agents including a diuretic; spironolactone outperformed bisoprolol and doxazosin as the added fourth drug. [2]

3. Drug: Spironolactone

3. Indication: Primary hyperaldosteronism

3. Line: first-line

3. Note: A directly mechanistic indication: the drug blocks the receptor the excess hormone is acting on. [2]

4. Drug: Spironolactone

4. Indication: Oedema secondary to cirrhosis, and oedema of nephrotic syndrome not controlled by alternatives

4. Line: first-line

4. Note: Described as the main option for ascites in cirrhosis once dietary salt restriction is insufficient. [2]

5. Drug: Spironolactone

5. Indication: Acne vulgaris in adult women, and hirsutism

5. Line: alternative

5. Note: Off-label and not FDA approved. High-level evidence is specifically described as lacking for the acne indication, so use follows careful selection after primary therapy. [2]

6. Drug: Eplerenone

6. Indication: Improving survival in stable adults with symptomatic heart failure and reduced ejection fraction of 40% or less after an acute myocardial infarction

6. Line: guideline-directed

6. Note: Studied in EPHEUS in patients clinically stable 3 to 14 days after infarction with left ventricular dysfunction and either diabetes or clinical heart failure. [4]

7. Drug: Eplerenone

7. Indication: Hypertension in adults, alone or with other antihypertensives

7. Line: add-on

7. Note: An approved indication in its own right, not only an alternative to spironolactone. [4]
8. Drug: Finerenone
8. Indication: Chronic kidney disease associated with type 2 diabetes, to reduce sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction and heart failure hospitalisation
8. Line: guideline-directed
8. Note: Studied in FIDELIO-DKD and FIGARO-DKD, where the placebo-corrected relative reduction in urinary albumin-to-creatinine ratio was 31% and 32% respectively at month 4. [5]

Pharmacokinetics

1. Drug: Spironolactone
1. Route: Oral
1. Absorption: Available as tablets and as an oral suspension
1. Metabolism: See prescribing reference
1. Elimination: See prescribing reference
1. Half Life: See prescribing reference
1. Dose Adjust: Frequency and dose adjustment depend on the clinical indication and the presence of renal impairment [2]
2. Drug: Eplerenone
2. Route: Oral
2. Absorption: Film-coated tablets
2. Metabolism: CYP3A substrate
2. Elimination: See prescribing reference
2. Half Life: Full antihypertensive effect is apparent within about four weeks
2. Dose Adjust: Capped in the presence of a moderate CYP3A inhibitor; contraindicated with strong CYP3A inhibitors and at a creatinine clearance of 30 mL/min or less [4]
3. Drug: Finerenone
3. Route: Oral
3. Absorption: Film-coated tablets
3. Metabolism: CYP3A4 substrate
3. Elimination: See prescribing reference
3. Half Life: See prescribing reference
3. Dose Adjust: Dosed according to serum potassium and eGFR measured before initiation and periodically during treatment [5]
1. Potassium and renal function are not incidental monitoring for this class; they are the parameters that decide whether a dose is given at all. Eplerenone labelling sets measurements before starting, within the first week and one month after starting or after any dose adjustment, then periodically. [4]
2. Serum potassium and eGFR are measured in every patient before finerenone is started, and the drug is not initiated where serum potassium is above 5.0 mEq/L. More frequent checks apply to anyone taking a drug that impairs potassium excretion. [5]
3. Because two members are CYP3A substrates, an interaction check is part of starting them. A new moderate CYP3A inhibitor, an ACE inhibitor, an angiotensin receptor blocker or a non-steroidal anti-inflammatory drug is a trigger for rechecking potassium and creatinine within days. [4]
4. This page gives no dose regimens by design. Doses depend on indication, renal function, serum potassium and interacting drugs, and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Hyperkalaemia

1. Detail: The most common electrolyte adverse effect of the class. With finerenone it was the most frequently reported adverse reaction at 14.0% versus 6.9% on placebo across the two pivotal studies. [2][5]
2. Effect: Breast and reproductive effects
2. Detail: The most common non-electrolyte adverse effect of spironolactone. Men may experience gynaecomastia, loss of libido and general feminisation; women may experience menstrual irregularities. [2]
3. Effect: Hypotension and hyponatraemia
3. Detail: Reported in at least 1% of patients on finerenone and more frequently than on placebo, alongside hyperkalaemia. Dehydration and hyponatraemia are also described with spironolactone. [5][2]
4. Effect: Gastrointestinal and neurological effects
4. Detail: Nausea, vomiting, diarrhoea or anorexia, and headache, drowsiness, asterixis, confusion or coma, are described with spironolactone in decreasing order of frequency, along with skin rashes. [2]
1. Effect: Severe hyperkalaemia
1. Detail: Hospitalisation attributable to hyperkalaemia occurred in 0.9% of patients on finerenone versus 0.2% on placebo, and hyperkalaemia led to permanent discontinuation in 1.7% versus 0.6%. Risk rises as kidney function falls and with higher baseline potassium.
1. Action: Serum potassium is measured before initiation and periodically thereafter, and the dose adjusted or the drug withheld accordingly. [5]
2. Effect: Hyperkalaemia in higher-risk subgroups on eplerenone
2. Detail: In EPHESUS, rates of hyperkalaemia on eplerenone versus placebo were increased in patients with proteinuria (16% versus 11%), diabetes (18% versus 13%) or both (26% versus 16%).
2. Action: Baseline renal function and proteinuria status inform whether the drug is appropriate before it is started. [4]
3. Effect: Hepatotoxicity
3. Detail: Rare reports of spironolactone causing liver toxicity manifesting as elevations in serum aminotransferases and alkaline phosphatase in a hepatocellular mixed pattern after nearly one month of treatment.
3. Action: The reported cases resolved over time after discontinuation of the drug. [2]
4. Effect: Overdose
4. Detail: For finerenone the most likely manifestation of overdose is hyperkalaemia.
4. Action: Treatment is interrupted immediately and standard management of hyperkalaemia initiated. [5]
1. Drug: Spironolactone
1. Effect: Feminisation of male fetuses was seen in animal studies, and the drug carries the corresponding pregnancy caution. [2]
2. Drug: Eplerenone
2. Effect: Gynaecomastia and abnormal vaginal bleeding were reported with eplerenone but not with placebo in EPHESUS, and the rates increased with increasing duration of therapy - so selectivity reduces rather than removes these effects. [4]
3. Drug: Finerenone
3. Effect: Adverse reactions occurring in at least 1% of patients and more frequently than placebo are hyperkalaemia, hypotension and hyponatraemia. [5]

Contraindications, precautions and interactions

1. Spironolactone is contraindicated in hyperkalaemia, in Addison's disease, and with concomitant eplerenone. Renal impairment is not itself a labelled contraindication: renal function and volume status are monitored during therapy and worsening renal function is a recognised risk, with the thresholds recorded under cautions below. [2][1]
2. Eplerenone is contraindicated at a serum potassium above 5.5 mEq/L at initiation, at a creatinine clearance of 30 mL/min or less, and with concomitant strong CYP3A inhibitors. [4]
3. Finerenone is contraindicated in hypersensitivity to any component, with concomitant strong CYP3A4 inhibitors, and in adrenal insufficiency. [5]

1. Heart failure guideline thresholds exclude spironolactone where serum creatinine exceeds 2.5 mg/dL in men or 2.0 mg/dL in women, estimated glomerular filtration rate is below 30 mL/min, or serum potassium exceeds 5.0 mEq/L. [2]

2. Finerenone is not initiated where serum potassium is above 5.0 mEq/L, and more frequent monitoring applies to anyone with additional hyperkalaemia risk factors. [5]

3. Advanced age, high dose, decreased renal function and type 2 diabetes each raise the likelihood of spironolactone-related hyperkalaemia and should shape the decision to start. [2]

4. End-stage renal disease, whether or not the patient is on dialysis, is not a setting in which spironolactone is generally recommended. [2]

1. With: Beta blockers, ACE inhibitors and angiotensin receptor blockers

1. Effect: Co-administration with spironolactone has been identified in cohort studies as a risk for severe hyperkalaemia, which is the everyday version of this interaction because these drugs are so often prescribed together. [2]

2. With: Strong CYP3A inhibitors - for example ketoconazole, itraconazole, nefazodone, clarithromycin, ritonavir and nelfinavir

2. Effect: Contraindicated with eplerenone, and strong CYP3A4 inhibitors are likewise contraindicated with finerenone because exposure rises. [4][5]

3. With: Moderate CYP3A inhibitors - for example erythromycin, saquinavir, verapamil and fluconazole

3. Effect: The eplerenone dose is capped, and potassium and creatinine are rechecked within 3 to 7 days of the interacting drug being started. [4]

4. With: Grapefruit and grapefruit juice

4. Effect: Concomitant intake is avoided with finerenone, for the same CYP3A4 reason. [5]

5. With: Non-steroidal anti-inflammatory drugs and potassium supplements

5. Effect: Any agent that impairs potassium excretion or raises serum potassium compounds the principal hazard of the class and prompts more frequent monitoring. [5]

Comparison tables

Title: Spironolactone, eplerenone and finerenone side by side

Caption: One receptor, three molecules, three different reasons to choose them. Therapy is governed by a prescribing reference and the treating clinician.

1. Key: feature

1. Label: Feature

1. Is Row Header: true

2. Key: spiro

2. Label: Spironolactone

3. Key: eple

3. Label: Eplerenone

4. Key: fine

4. Label: Finerenone

1. Feature: Chemistry

1. Spiro: Steroidal

1. Eple: Steroidal

1. Fine: Non-steroidal [2][4][5]

2. Feature: Receptor selectivity

2. Spiro: Non-selective - also binds androgen and progesterone receptors

2. Eple: Selective for the mineralocorticoid receptor relative to glucocorticoid, progesterone and androgen receptors

2. Fine: Selective, with no relevant affinity for androgen, progesterone, oestrogen or glucocorticoid receptors [2][4][5]

3. Feature: Headline indication

- 3. Spiro: Heart failure with reduced ejection fraction, resistant hypertension, hyperaldosteronism, cirrhotic oedema
- 3. Eple: Post-myocardial-infarction heart failure with reduced ejection fraction; hypertension
- 3. Fine: Chronic kidney disease associated with type 2 diabetes [2][4][5]
- 4. Feature: Endocrine adverse effects
- 4. Spiro: Gynaecomastia, loss of libido, feminisation, menstrual irregularity
- 4. Eple: Gynaecomastia and abnormal vaginal bleeding reported, increasing with duration
- 4. Fine: Not a described feature of the drug [2][4][5]
- 5. Feature: CYP3A interaction
- 5. Spiro: Not the defining interaction for this agent
- 5. Eple: Strong CYP3A inhibitors contraindicated; moderate inhibitors cap the dose
- 5. Fine: Strong CYP3A4 inhibitors contraindicated; grapefruit avoided [4][5]
- 6. Feature: Potassium threshold before starting
- 6. Spiro: Guidelines describe serum potassium below 5 mEq/L for the heart failure indication
- 6. Eple: Contraindicated above 5.5 mEq/L at initiation
- 6. Fine: Not initiated above 5.0 mEq/L [2][4][5]

High-yield exam pearls

- 1. Pearl: The whole class trades sodium for potassium.
- 1. Why: Aldosterone normally drives sodium reabsorption through epithelial sodium channels while potassium is secreted. Blocking the receptor stops the sodium and water retention and stops the potassium loss, which is exactly why hyperkalaemia is the price of the diuresis. [2][3]
- 2. Pearl: Gynaecomastia is a selectivity problem, not a class effect.
- 2. Why: Spironolactone is a non-selective antagonist that also binds androgen and progesterone receptors. Eplerenone binds the mineralocorticoid receptor selectively, and finerenone has no relevant affinity for androgen, progesterone, oestrogen or glucocorticoid receptors. [2][4][5]
- 3. Pearl: Selective does not mean endocrine-free.
- 3. Why: Gynaecomastia and abnormal vaginal bleeding were reported with eplerenone but not with placebo in EPHEUS, and the rates increased with increasing duration of therapy. The difference from spironolactone is one of degree. [4]
- 4. Pearl: Finerenone is the kidney drug of the group.
- 4. Why: It is indicated to reduce sustained estimated glomerular filtration rate decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction and heart failure hospitalisation in adults with chronic kidney disease associated with type 2 diabetes - a different indication from the other two. [5]
- 5. Pearl: Spironolactone is the fourth drug in resistant hypertension.
- 5. Why: Tested against bisoprolol and doxazosin as the added fourth agent, spironolactone was superior to both in reducing systolic home blood pressure, and against clonidine it was non-inferior on the primary endpoint and preferable on secondary ambulatory measures. [2]
- 6. Pearl: Two of the three are CYP3A substrates with hard interaction limits.
- 6. Why: Strong CYP3A inhibitors are contraindicated with eplerenone and with finerenone, and grapefruit is specifically avoided with finerenone. Spironolactone does not carry that particular restriction. [4][5]
- 7. Pearl: Potassium and renal thresholds gate initiation, not just monitoring.
- 7. Why: Eplerenone is contraindicated at a serum potassium above 5.5 mEq/L at initiation or a creatinine clearance of 30 mL/min or less, and finerenone is not initiated if serum potassium is above 5.0 mEq/L. These are entry criteria, checked before the first dose. [4][5]

Common exam traps

- 1. Trap: "MRAs are just potassium-sparing diuretics."

1. Correction: The diuresis is only part of it. Aldosterone binds mineralocorticoid receptors in non-epithelial tissue too, and drives increased vascular stiffness and remodelling and increased cardiac inflammation, fibrosis and remodelling. Blocking those effects is what underlies the survival benefit. [2]
2. Trap: "Switching from spironolactone to eplerenone removes the hyperkalaemia risk."
2. Correction: It removes much of the anti-androgen effect, not the potassium effect. Eplerenone is contraindicated at a serum potassium above 5.5 mEq/L at initiation, and in EPHESUS hyperkalaemia rates were higher in patients with proteinuria, diabetes, or both. [4]
3. Trap: "Hyperkalaemia on an MRA is usually the drug acting alone."
3. Correction: It is frequently synergistic. Cohort studies identified co-prescription of a beta blocker, an ACE inhibitor or an angiotensin receptor blocker as a risk for severe hyperkalaemia on spironolactone, alongside advanced age, higher dose, reduced renal function and type 2 diabetes. [2]
4. Trap: "Spironolactone can be used in any patient with heart failure."
4. Correction: Guideline criteria are explicit: it is indicated in NYHA class II to IV heart failure with reduced ejection fraction where creatinine clearance is above 30 mL/min and serum potassium is below 5 mEq/L, and it is contraindicated in hyperkalaemia and renal impairment. [2]
5. Trap: "Finerenone and spironolactone are interchangeable."
5. Correction: They are not. Finerenone is a non-steroidal agent approved for chronic kidney disease associated with type 2 diabetes, is a CYP3A4 substrate with strong inhibitors contraindicated, and is additionally contraindicated in adrenal insufficiency. [5]
6. Trap: "Spironolactone's dermatological use is a well-evidenced indication."
6. Correction: Acne vulgaris and hirsutism are off-label, non-FDA-approved uses, and the evidence for the acne indication is specifically described as lacking high-level support, so patient selection is meant to follow a failed trial of primary therapy. [2]

Self-test questions

1. Question: What is the immediate renal consequence of blocking the mineralocorticoid receptor?
 1. Sodium reabsorption with water retention does not occur, and potassium is retained
 2. Sodium is retained while potassium is lost in the urine
 3. Both sodium and potassium are retained
 4. Water is retained without any change in sodium handling
1. Explanation: Aldosterone binds its receptors at the distal tubules and collecting duct and causes sodium reabsorption with potassium secretion. Competitively blocking that receptor means the sodium reabsorption and water retention do not happen, and potassium is retained instead - the mechanism behind both the diuresis and the hyperkalaemia. [2]
2. Question: Why does spironolactone cause gynaecomastia when eplerenone largely does not?
 1. Spironolactone is given at much higher doses in every indication
 2. Spironolactone is a non-selective antagonist that also binds androgen and progesterone receptors
 3. Eplerenone is not absorbed well enough to reach endocrine tissue
 4. Spironolactone directly stimulates oestrogen synthesis in the testis
2. Explanation: Spironolactone is a non-selective mineralocorticoid receptor antagonist that can also bind androgen and progesterone receptors, which is why men may experience gynaecomastia, loss of libido and general feminisation and women may experience menstrual irregularities. Eplerenone binds the mineralocorticoid receptor selectively relative to glucocorticoid, progesterone and androgen receptors. [2][4]
3. Question: Which trial established the mortality benefit of spironolactone in severe heart failure?
 1. EPHESUS
 2. PATHWAY-2
 3. RALES

4. FIDELIO-DKD

3. Explanation: The Randomized Aldactone Evaluation Study used spironolactone in NYHA class III to IV heart failure with an ejection fraction below 35%, and was stopped early on positive findings including a 30% relative risk reduction in all-cause mortality. EPHESUS studied eplerenone after myocardial infarction, PATHWAY-2 studied resistant hypertension, and FIDELIO-DKD studied finerenone in diabetic kidney disease. [2]

4. Question: For which population is finerenone indicated?

1. Adults with resistant hypertension who have failed three agents
2. Adults with chronic kidney disease associated with type 2 diabetes
3. Patients with ascites secondary to cirrhosis
4. Adults with primary hyperaldosteronism

4. Explanation: Finerenone is a non-steroidal mineralocorticoid receptor antagonist indicated to reduce the risk of sustained estimated glomerular filtration rate decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction and hospitalisation for heart failure in adult patients with chronic kidney disease associated with type 2 diabetes. [5]

5. Question: A patient is due to start eplerenone. Which finding is a contraindication at initiation?

1. Serum potassium of 4.2 mEq/L
2. Creatinine clearance of 55 mL/min
3. Serum potassium above 5.5 mEq/L
4. A history of gynaecomastia on spironolactone

5. Explanation: Eplerenone is contraindicated in all patients with a serum potassium above 5.5 mEq/L at initiation, a creatinine clearance of 30 mL/min or less, or concomitant administration of strong CYP3A inhibitors. Previous gynaecomastia on spironolactone is in fact one of the reasons a clinician might choose eplerenone instead. [4][2]

6. Question: Why are strong CYP3A4 inhibitors contraindicated with finerenone?

1. They block the drug's absorption, making it ineffective
2. Finerenone is a CYP3A4 substrate, so exposure rises and the risk of adverse reactions increases
3. They induce metabolism of finerenone to a toxic metabolite
4. They antagonise the drug at the mineralocorticoid receptor

6. Explanation: Finerenone is a CYP3A4 substrate. Concomitant use with a strong CYP3A4 inhibitor increases finerenone exposure, which may increase the risk of adverse reactions, so the combination is contraindicated and grapefruit intake is avoided. [5]

7. Question: Which co-prescriptions most commonly compound the hyperkalaemia risk of spironolactone?

1. Statins and proton pump inhibitors
2. Beta blockers, ACE inhibitors and angiotensin II receptor blockers
3. Thiazide diuretics and loop diuretics
4. Inhaled corticosteroids and long-acting beta agonists

7. Explanation: Cohort studies identified beta blockers, ACE inhibitors and angiotensin receptor blockers co-administered with spironolactone as risks for the development of severe hyperkalaemia. Advanced age, high-dose spironolactone, decreased renal function and type 2 diabetes add to that risk. [2]

Frequently asked questions

1. Question: Why do these drugs raise potassium?

1. Answer: Aldosterone normally makes the collecting duct reabsorb sodium and secrete potassium. Blocking its receptor removes the signal for that potassium secretion, so potassium is retained. The effect is inseparable from the therapeutic one, which is why serum potassium is measured before starting and repeatedly afterwards. [2][3]

2. Question: Why does spironolactone cause breast symptoms in men?

2. Answer: Because it is not a clean drug at the receptor level. As well as the mineralocorticoid receptor it binds androgen and progesterone receptors, so gynaecomastia, loss of libido and feminisation can follow. That same

anti-androgen activity is what underlies its off-label use in acne and hirsutism. [2]

3. Question: Is eplerenone free of those endocrine effects?

3. Answer: Not entirely. It is selective for the mineralocorticoid receptor, and that is the reason a clinician might switch to it - but gynaecomastia and abnormal vaginal bleeding were still reported with eplerenone and not with placebo in EPHESUS, with rates rising the longer treatment continued. [4]

4. Question: What makes finerenone different from the other two?

4. Answer: It is non-steroidal, it has no relevant affinity for the other steroid receptors, and its approved indication is chronic kidney disease associated with type 2 diabetes rather than heart failure or hypertension. It is also contraindicated in adrenal insufficiency and with strong CYP3A4 inhibitors. [5]

5. Question: Why is an MRA added to heart failure treatment that already includes an ACE inhibitor and a beta blocker?

5. Answer: Because aldosterone does more than move salt. It increases vascular stiffness and remodelling and increases cardiac inflammation, fibrosis and remodelling, and blocking that adds prognostic benefit beyond what upstream blockade achieves. The cost is that the same three-drug combination is the classic setting for severe hyperkalaemia. [2]

6. Question: Where does spironolactone fit in resistant hypertension?

6. Answer: As the added fourth agent when blood pressure remains above goal on optimal doses of three drugs including a diuretic. Compared head to head, it reduced systolic home blood pressure more than bisoprolol or doxazosin, and against clonidine it was non-inferior on the primary endpoint and better on ambulatory secondary measures. [2]

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