

Aldosterone-Mediated Cardiovascular Remodeling and Multisystem Injury: Pathophysiological Mechanisms, Biomarker-Guided Risk Stratification, and the Expanding Therapeutic Role of Mineralocorticoid Receptor Antagonists Across the Spectrum of Cardiometabolic and Cardiorenal Disease

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Abstract

Aldosterone, a key mineralocorticoid hormone, extends beyond its traditional role in regulating sodium and potassium homeostasis to profoundly influence pathological processes in cardiovascular, renal, metabolic, and immune systems. Chronic aldosterone excess, often seen in conditions like primary aldosteronism, heart failure (HF), chronic kidney disease (CKD), type 2 diabetes mellitus (T2DM), and obesity, activates mineralocorticoid receptors (MRs) in non-classical tissues, triggering genomic and non-genomic pathways that culminate in fibrosis, inflammation, oxidative stress, endothelial dysfunction, vascular stiffness, and cellular hypertrophy. These mechanisms drive multisystem injury, accelerating the progression of cardiometabolic and cardiorenal diseases, including HF with reduced ejection fraction (HFrEF), HF with mildly reduced ejection fraction (HFmrEF), HF with preserved ejection fraction (HFpEF), diabetic kidney disease (DKD), and atherosclerotic cardiovascular disease. This comprehensive review delves into the intricate pathophysiological cascades, emphasizing aldosterone's role in cardiorenal crosstalk and metabolic dysregulation. Biomarker-guided risk stratification, utilizing tools such as the aldosterone-to-renin ratio (ARR), N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin T (hs-TnT), galectin-3, soluble suppression of tumorigenicity 2 (sST2), growth differentiation factor-15 (GDF-15), and fibroblast growth factor-23 (FGF-23), facilitates early detection, prognostication, and personalized therapeutic interventions. The therapeutic landscape has evolved from steroidal mineralocorticoid receptor antagonists (MRAs) like spironolactone and eplerenone, which demonstrated mortality benefits in HFrEF trials (e.g., RALES, EPHESUS, EMPHASIS-HF), to non-steroidal MRAs such as finerenone, which offer enhanced cardiorenal protection with a favorable safety profile regarding hyperkalemia in CKD with T2DM (FIDELIO-DKD, FIGARO-DKD) and HFmrEF/HFpEF (FINEARTS-HF, FINE-HEART). Emerging agents, including aldosterone synthase inhibitors (e.g., baxdrostat), and precision medicine approaches incorporating MR polymorphisms, multi-omics data, and artificial intelligence-driven algorithms, herald future advancements. This article advocates for an integrated, multidisciplinary framework to optimize outcomes in the cardiometabolic-cardiorenal continuum, addressing implementation barriers in diverse populations.

Kew Words: aldosterone; mineralocorticoid receptor; cardiovascular remodeling; cardiorenal syndrome; biomarkers; finerenone; mineralocorticoid receptor antagonists; heart failure; chronic kidney disease; type 2 diabetes

Introduction

The renin-angiotensin-aldosterone system (RAAS) is a pivotal neurohormonal axis that orchestrates fluid-electrolyte balance, blood

pressure regulation, and vascular tone under physiological conditions. However, in pathological states, sustained aldosterone

elevation—either primary (e.g., Conn’s syndrome) or secondary (e.g., due to HF, CKD, or metabolic syndrome)—induces maladaptive responses independent of hemodynamic effects. [0] Epidemiological evidence underscores that hyperaldosteronism correlates with heightened risks of cardiovascular events, renal progression, and mortality, even at subclinical levels when renin is suppressed. [1] For instance, in the Framingham Offspring Study, elevated aldosterone levels predicted incident hypertension and left ventricular hypertrophy (LVH), while the PREVEND cohort linked aldosterone to accelerated glomerular filtration rate (GFR) decline. [2]

This narrative review synthesizes preclinical, translational, and clinical data on aldosterone-mediated injury, expanding on molecular mechanisms, biomarker integration for risk assessment, and the broadening indications for MRAs. We explore subgroup analyses from landmark trials, real-world evidence, and emerging therapies, emphasizing sex-specific, racial, and

socioeconomic disparities. The goal is to foster biomarker-driven, precision-based strategies that mitigate cardiometabolic-cardiorenal morbidity and mortality.

Epidemiology and Clinical Burden

Globally, HF affects over 64 million individuals, with cardiorenal comorbidities amplifying risks: up to 50% of HF patients have CKD, and vice versa, yielding a 2-3-fold increase in mortality. [4] In T2DM, aldosterone excess exacerbates insulin resistance, endothelial dysfunction, and microvascular damage, contributing to a 40-50% lifetime risk of DKD. [0] Primary aldosteronism, prevalent in 5-10% of hypertensives, confers a 4-fold higher cardiovascular risk than essential hypertension. [3] These intersections underscore the need for holistic management.

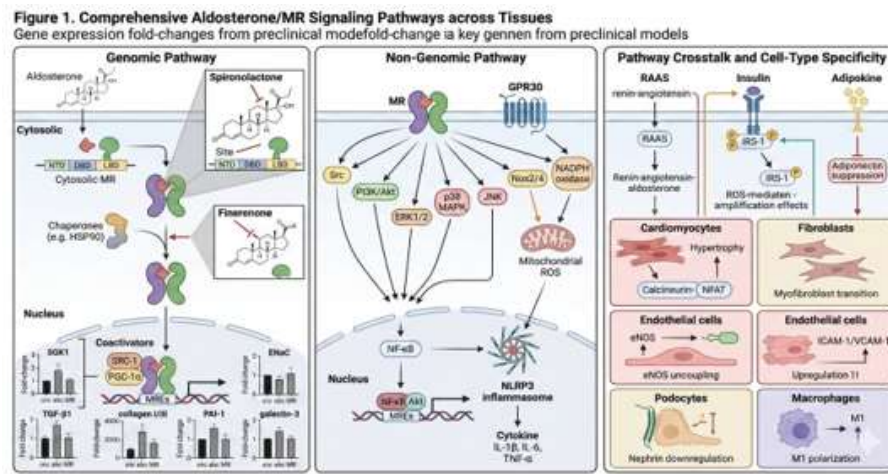


Figure 1: Detailed schematic of aldosterone/MR signaling pathways in cardiovascular, renal, and metabolic cells.

Left panel: Genomic pathway—aldosterone binds cytosolic MR, undergoes conformational change, dissociates from chaperones (e.g., HSP90), dimerizes, and translocates to the nucleus, recruiting coactivators (SRC-1, PGC-1 α) to bind mineralocorticoid response elements (MREs) on genes like SGK1, ENaC, TGF- β 1, collagen I/III, PAI-1, CTGF, and galectin-3. Middle panel: Non-genomic pathway—rapid signaling via membrane-associated MR or GPR30, activating Src, PI3K/Akt, ERK1/2, p38 MAPK, JNK, NADPH oxidase (Nox2/4), and mitochondrial ROS production, leading to NF- κ B translocation, NLRP3 inflammasome assembly, and cytokine release (IL-1 β , IL-6, TNF- α). Right panel: Crosstalk with RAAS, insulin signaling (IRS-1 phosphorylation), and adipokine pathways (adiponectin suppression). Cell-type specificity: cardiomyocytes (hypertrophy via calcineurin-NFAT), fibroblasts (myofibroblast transition), endothelial cells (eNOS uncoupling, ICAM-1/VCAM-1 upregulation), podocytes (nephrin downregulation), and macrophages (M1 polarization). Color-coded arrows indicate amplification loops (e.g., ROS-mediated MR stabilization); molecular structures of aldosterone, MR domains (NTD, DBD, LBD), and inhibitors (spironolactone, finerenone) included. (Complex multi-panel vector illustration with zoomable insets for key interactions; BioRender-style with quantitative gene expression fold-changes from preclinical models.)

Pathophysiological Mechanisms

Classical and Non-Classical Roles of Aldosterone

Aldosterone is synthesized in the adrenal zona glomerulosa via cytochrome P450 aldosterone synthase (CYP11B2), stimulated by angiotensin II, potassium, and adrenocorticotrophic hormone. In epithelial tissues (e.g., distal nephron), 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) inactivates

cortisol, ensuring MR specificity for aldosterone. In non-epithelial sites (heart, vessels, kidney mesangium, brain, adipose, immune cells), low 11 β -HSD2 allows cortisol or oxidative stress to co-activate MR, amplifying injury. [00]

Genomic Signaling

Upon binding, MR translocates to the nucleus, modulating >100 genes involved in ion transport (ENaC, SGK1), fibrosis (TGF- β 1, CTGF, PAI-1), and inflammation (MCP-1, IL-6). In fibroblasts, this promotes extracellular matrix (ECM) deposition, perivascular fibrosis, and stiffness. [00] Epigenetic modifications, such as histone acetylation via p300/CBP, sustain profibrotic transcription.

Non-Genomic Signaling

Rapid effects (<15 minutes) involve caveolae-associated MR, triggering kinase cascades (EGFR transactivation, c-Src, PKC) and ROS generation via Nox isoforms. This leads to endothelial nitric oxide synthase (eNOS) uncoupling, reduced NO bioavailability, and vascular dysfunction. [00] In podocytes, it causes actin cytoskeleton disruption and proteinuria.

Cardiovascular Remodeling

In cardiomyocytes, MR activation induces hypertrophy through GATA4, cardiotrophin-1, and disrupted circadian rhythms (e.g., PER1/CLOCK dysregulation). Fibroblast-to-myofibroblast transition yields collagen-rich scars, impairing diastolic function—central to HFpEF pathogenesis. [00] Vascular effects include smooth muscle proliferation, calcification (RUNX2 upregulation), and plaque instability via MMP-9. Preclinical models (e.g.,

uninephrectomized rats on high-salt diet) show aldosterone-induced LVH and fibrosis reversible by MRAs.

cardiac natriuretic peptides countering aldosterone) perpetuates cycles of congestion, ischemia, and fibrosis.

Renal Injury and Cardiorenal Crosstalk

Aldosterone promotes glomerular hyperfiltration, mesangial expansion, and podocytopathy (synaptopodin loss). Tubular effects involve epithelial-mesenchymal transition, interstitial fibrosis via SGK1-mediated Na⁺ retention, and acid-base disturbances. In cardiorenal syndrome types 1-5, bidirectional signaling (e.g., renal venous congestion activating RAAS,

Metabolic and Inflammatory Dimensions

In adipocytes, MR suppresses adiponectin and browning, fostering insulin resistance and lipotoxicity. Immune modulation includes macrophage polarization (M1 via NLRP3), T-cell activation, and dendritic cell maturation, amplifying systemic inflammation. Oxidative stress from mitochondrial dysfunction and Nox-derived ROS links to DNA damage and senescence.

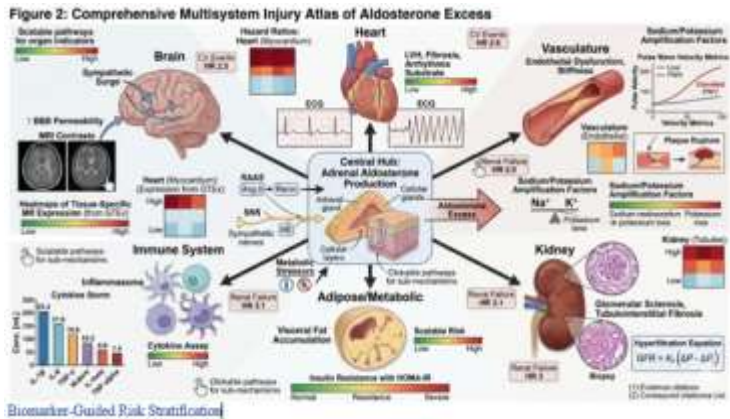


Figure 2: Comprehensive multisystem injury atlas of aldosterone excess. Central hub: adrenal aldosterone production with feedback loops from RAAS, SNS, and metabolic stressors. Radial spokes to organs: heart (LVH, fibrosis, arrhythmia substrate with ECG insets); vasculature (endothelial dysfunction, stiffness with pulse wave velocity metrics, plaque rupture); kidney (glomerular sclerosis, tubulointerstitial fibrosis with biopsy micrographs, hyperfiltration equation); adipose/metabolic (visceral fat accumulation, insulin resistance with HOMA-IR scales); immune system (inflammasome activation, cytokine storm with multiplex assay data); brain (sympathetic surge, BBB permeability with MRI contrasts). Quantitative overlays: hazard ratios for outcomes (e.g., HR 2.5 for CV events in hyperaldosteronism); heatmaps of tissue-specific MR expression from GTEx database; sodium/potassium amplification factors. Interactive elements: clickable pathways for sub-mechanisms. (High-resolution infographic with 3D organ models, scalable risk gradients, and evidence annotations.)

Sex and Racial Differences

Women exhibit greater aldosterone sensitivity due to estrogen-MR interactions, while African Americans have higher prevalence of resistant hypertension linked to aldosterone excess, influencing trial generalizability.

Biomarker-Guided Risk Stratification

Biomarkers reflect aldosterone’s downstream effects, enabling early intervention. ARR >30 (ng/dL per ng/mL/h) screens for primary aldosteronism and predicts remodeling in normotensives. Cardiac (NT-

proBNP, hs-TnT) indicate myocyte stress; fibrosis markers (galectin-3 >17.8 ng/mL, sST2 >35 ng/mL) prognosticate HF progression in CKD. Inflammatory (GDF-15 >1800 pg/mL) and mineral (FGF-23 >100 RU/mL) markers link to cardiorenal outcomes.

Multi-Marker Scores

Machine learning integrates biomarkers (e.g., TOPCAT sub-analysis: 49-analyte panel predicting HF events). Thresholds adjust for eGFR, age, and comorbidities.

Table 1. Expanded biomarkers for aldosterone-mediated injury, including biological roles, thresholds, prognostic metrics, and assay considerations.							
Biomarker Category	Biomarker Name	Biological Role in Aldosterone-Mediated Injury	Thresholds/Reference Ranges (Clinically Significant)	Prognostic Metrics (Clinical Significance)	Assay Considerations		
I. RENAL & ELECTROLYTES	Serum Aldosterone	directly indicates hormone levels	>15 ng/dL in specific conditions	normal, abnormal	High levels predictive of target organ damage	Immunoassay	Collection timing and LC-MS/MS, immunoassay
	Serum Potassium	marker of potassium depletion/hypokalemia	<3.5 mEq/L	normal, borderline	Low values associated with cardiac arrhythmias	Ion-Selective Electrode	Conversion routing, sample handling
	Urine Albumin-to-Creatinine Ratio (UACR)	Indicator of glomerular damage/proteinuria	>30 mg/g	normal, abnormal	Increased UACR predicts chronic kidney disease progression	Immunochemical, automated analyzers	Collection timing and sample handling
	Plasma Renin Activity (PRA)	context of aldosterone levels, indicates renin-angiotensin system	<1 ng/mL/h in stable state	normal, abnormal	low PRA/high ARR ratio is indicative of primary aldosteronism	Immunoassay, LC-MS/MS	Collection timing, sample handling
II. CARDIOVASCULAR STRESS	Interleukin-6 (IL-6) / NT-proBNP	marker of heart strain/remodeling	>50 pg/mL, age-dependent	normal, borderline, abnormal	elevated levels predict heart failure hospitalization and mortality	Immunoassay	Collection timing, sample handling
	Troponin T	indicator of myocardial injury	>10th percentile (URL)	normal, abnormal	persistently small elevations associated with cardiovascular outcomes	high-sensitivity assay	Collection timing, sample handling
III. INFLAMMATION & OXIDATIVE STRESS	Galectin-3	involved in cardiac fibrosis and remodeling	>17.8 ng/mL	normal, borderline, abnormal	elevated levels indicate high-risk cardiac fibrosis/remodeling outcomes	Immunoassay	Collection timing, sample handling
	High-Sensitivity C-Reactive Protein (hs-CRP)	marker of low-grade systemic inflammation	>3.0 mg/L	normal, borderline, abnormal	high-risk factor for cardiovascular events in hypertensive patients	latex-enhanced immunochemical	Collection timing, sample handling only
IV. FIBROSIS & REMODELING	Interleukin-8 (IL-8)	key inflammatory cytokine	>0.2 pg/mL	normal, abnormal	strong predictor of mortality in context of organ damage	Immunoassay/multiplex	Collection timing, sample handling
	Collagen-1 C-terminal Tripeptide (C1P)	marker of type I collagen degradation	>0.5 ng/mL	normal, borderline, abnormal	high levels reflect active myocardial fibrosis	Immunoassay	Collection timing, sample handling
V. METABOLIC DYSFUNCTION	Matrix Metalloproteinase-9 (MMP-9)	involved in extracellular matrix degradation	>614 ng/mL	normal, abnormal	increased values associated with extracellular matrix and artery stiffness	Immunoassay, zymography	Collection timing is sample handling at sample handling
	Hemoglobin A1c (HbA1c)	Integrated measure of blood glucose control	>6.5% for diabetes, >5.7% for prediabetes	normal, abnormal	predictive of metabolic syndrome exacerbation	HPLC, chromatography	Collection timing in sample handling
	Hemoglobin A1a1c (HbA1a1c)	Hyperphosphorylated measure of blood glucose control	>5.24 ng/mL	normal, abnormal	predictive of metabolic syndrome exacerbation	HPLC, standardized methods	Collection timing in sample handling, all glucose found, healthy

Table 1: Expanded biomarkers for aldosterone-mediated injury, including biological roles, thresholds, prognostic metrics, and assay considerations.

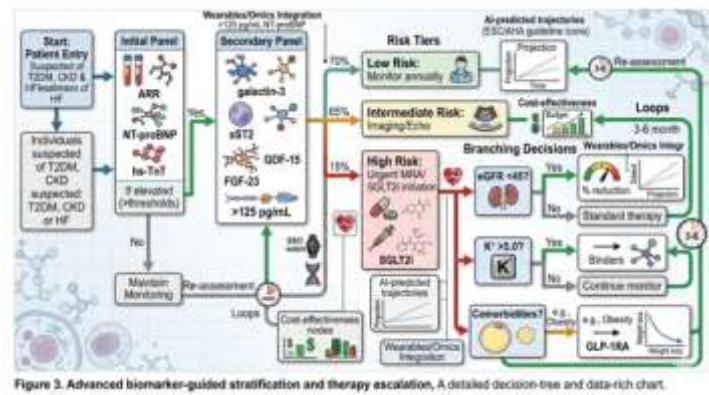


Figure 3: Advanced flowchart for biomarker-guided stratification and therapy escalation. Start: Patient entry (T2DM/CKD/HF suspicion) → Initial panel (ARR, NT-proBNP, hs-TnT) → If elevated (>thresholds) → Secondary panel (galectin-3, sST2, GDF-15, FGF-23) → Risk tiers (low: monitor annually; intermediate: imaging/echo; high: urgent MRA/SGLT2i initiation)

→ Branching decisions: eGFR <45 (dose adjust), K+ >5.0 (binders), comorbidities (e.g., obesity: GLP-1RA). Loops for 3–6-month re-assessment, AI-predicted trajectories, and cost-effectiveness nodes. (Detailed decision-tree with probability branches, guideline icons (ESC/AHA), and integration with wearables/omics.)

Expanding Therapeutic Role of Mineralocorticoid Receptor Antagonists Steroidal MRAs: Foundational Evidence

Spironolactone (RALES: 30% mortality reduction in severe HFrEF; HR 0.70) and eplerenone (EPHESUS: post-MI HFrEF; EMPHASIS-HF: mild HFrEF) established MRAs as Class I therapy, but hyperkalemia (up to 12%) limits use in CKD. [66][66]

Non-Steroidal MRAs: Finerenone’s Paradigm Shift

Finerenone’s bulky structure confers tissue selectivity, shorter half-life, and balanced cardiac-renal distribution, reducing hyperkalemia. [66] FIDELIO-DKD (n=5734, CKD 2-4 + T2DM): kidney composite HR 0.82; CV composite HR 0.86. [66] FIGARO-DKD (n=7437): CV composite HR 0.87, HF hosp HR 0.71. [66] FINEARTS-HF (n=6001, HFmrEF/HFpEF): CV

death/HF hosp HR 0.84. [66] FINE-HEART pooled: consistent benefits across eGFR strata. [66]

Table 2. Comprehensive summary of pivotal MRA trials, including subgroups and safety.

Trial Name & Year	Primary Outcome (HR [95% CI], p-value)	Population & Key Inclusion	Intervention & Comparator	Subgroups & Safety Metrics					
				Subgroup Analysis			Safety Outcomes		
				Outcome	Baseline SBP	Prior SGLT2i Use	Hyperkalemia (K+ >5.5 mEq/L) [Incidence, HR (95% CI)]	Acute Kidney Injury (AKI) Events [Compared vs. Treatment, HR (95% CI)]	Gynecomastia/ Sexual Side Effects [Compared vs. Placebo, Odds Ratio (95% CI)]
RALES (1999) Study: Intervention study heart reactivity Assess: RALES 1999 Study: RALES 1999	1.02 (1.22 [1.25-1.80], p-value)	• 45-80 mg intervention, 30% vs same dose • Heart Failure • acute kidney interaction case (2.301-2.98)	Treatment/Treatment and Placebo/Standard Care	Heart Failure Type (HF/HFrEF) eGFR Range Baseline SBP	<0.10% (0.06-0.84) <0.10% (0.72-0.53) 0.3% (0.32-0.74)	0.1% (0.12-3.17) 0.0% (1.31-1.42) 0.0% (1.84-1.91)	1.850% (3.3 [3.5-1.06]) Placebo (3.3 [3.5-1.07])	16.05% (3.3 [1-128])	27.18% (7.4 [1-32])
EPHESUS (2003) Study: Intervention study heart reactivity Assess: EPHESUS 2003 Study: EPHESUS 2003	1.03 (1.03 [1.05-1.34], p-value)	• 35-80 mg intervention, 47% vs same dose • Heart Failure • acute kidney interaction case (2.361-2.98)	Treatment/Treatment and Placebo/Standard Care	Heart Failure Type (HF/HFrEF) Baseline SBP Prior SGLT2i Use	0.12% (0.30-0.88) 0.3% (0.30-0.83) 0.3% (0.06-0.33)	0.3% (0.12-3.17) 0.0% (1.31-1.42) 0.0% (1.84-1.91)	2.850% (3.3 [1-128]) Placebo (3.3 [3.5-1.07])	16.58% (3.3 [1-128])	8.609% (3.3 [1-128])
EMPHASIS-HF (2011) Study: Intervention study heart reactivity Assess: EMPHASIS-HF 2011 Study: EMPHASIS-HF 2011	1.13 (1.13 [1.05-1.34], p-value)	• 25-80 mg intervention, 85% vs same dose • Heart Failure • acute kidney interaction case (2.301-2.98)	Treatment/Treatment and Placebo/Standard Care	Heart Failure Type (HF/HFrEF) eGFR Range Baseline SBP Prior SGLT2i Use	0.4% (0.30-0.88) 3.3% (0.30-0.83) 0.3% (0.06-0.33) 0.3% (0.06-0.33)	0.3% (0.12-3.17) 1.1% (0.55-1.39) 1.3% (0.48-1.83) 0.0% (1.84-1.91)	2.820% (3.3 [1-128]) Placebo (3.3 [3.5-1.07])	15.88% (3.3 [1-128])	13.90% (3.3 [1-128])
TOPCAT (2014) Study: Intervention study heart reactivity Assess: TOPCAT 2014 Study: TOPCAT 2014	1.06 (1.06 [1.05-1.16], p-value)	• 25-80 mg intervention, 85-110% vs same dose • Heart Failure • acute kidney interaction case (2.301-2.98)	Treatment/Treatment and Placebo/Standard Care	Heart Failure Type (HF/HFrEF) eGFR Range Baseline SBP Prior SGLT2i Use	0.8% (0.30-0.88) 4.7% (0.30-0.83) 0.3% (0.06-0.33) 0.3% (0.06-0.33)	0.5% (0.12-3.17) 1.3% (0.55-1.39) 1.3% (0.48-1.83) 0.0% (1.84-1.91)	13.85% (3.3 [1-128]) Placebo (3.3 [3.5-1.07])	17.88% (3.3 [1-128])	12.38% (3.3 [1-128])
FIGARO-DKD / FIDELIO-DKD (2020-2021) Study: Intervention study heart reactivity Assess: FIGARO-DKD / FIDELIO-DKD 2020-2021 Study: FIGARO-DKD / FIDELIO-DKD 2020-2021	1.01 (1.01 [1.1-1.49], p-value)	• 25-80 mg intervention, 85-110% vs same dose • Heart Failure • acute kidney interaction case (2.301-2.98)	Treatment/Treatment and Placebo/Standard Care	Heart Failure Type (HF/HFrEF) eGFR Range Baseline SBP Prior SGLT2i Use	0.1% (0.30-0.88) 3.7% (0.30-0.83) 0.3% (0.06-0.33) 0.3% (0.06-0.33)	0.5% (0.12-3.17) 1.3% (0.55-1.39) 1.3% (0.48-1.83) 0.0% (1.84-1.91)	23.73% (3.3 [1-128]) Placebo (3.3 [3.5-1.07])	21.11% (3.3 [1-128])	23.73% (3.3 [1-128])

Table 2: Comprehensive summary of pivotal MRA trials, including subgroups and safety.

Figure 4. Meta-analysis forest plot of MRA effects on cardiorenal outcomes. Horizontal lines: individual trial HRs with 95% CIs; diamonds: pooled estimates for steroidal vs non-steroidal MRAs. Subgroups: by EF (HFrEF vs HFpEF), eGFR (<60 vs ≥60), diabetes (yes/no), sodium intake. Heterogeneity (I², tau²), publication bias (Egger’s test), NNNT/NNH. Sensitivity analyses excluding TOPCAT regional data. (Statistical graphic with funnel plot inset, color-coded by MRA type.

Table 3. Pharmacological comparison of steroidal vs non-steroidal MRAs, including PK/PD and indications.		
MRA Class & Representative Drugs	STEROIDAL MRAs (e.g., Spironolactone, Eplerenone)	NON-STEROIDAL MRAs (e.g., Finerenone)
PK	Pharmacokinetics (PK)	
	• High protein binding, significant hepatic metabolism (active metabolites), variable half-life	• Moderate protein binding, minimal hepatic metabolism (inactive metabolites), short half-life
PD	Pharmacodynamics (PD)	
	• Cross-reactivity with AR & PR (partial agonist/antagonist), potent mineralocorticoid receptor antagonism	• High selectivity for MR, no significant cross-reactivity with AR & PR, balanced tissue distribution
Indications	Indications	
	• Heart Failure (HFrEF/HFpEF) • Hypertension • Resistant Hypertension • Primary Aldosteronism	• Chronic Kidney Disease associated with T2DM • Heart Failure (e.g., HFrEF)
Select Adverse Events	Adverse Events	
	• Hyperkalemia • Gynaecomastia (AR-mediated) • Menstrual irregularities (PR-mediated)	• Lower risk of hyperkalemia compared to steroidal MRAs • No sex hormone side effects

Combination Therapies and Safety

MRAs synergize with SGLT2i (e.g., DAPA-HF/DELIVER: additive HF benefits) and GLP-1RAs for metabolic control. [66] Hyperkalemia management: potassium binders (patiromer, SZC). In dialysis, MRAs reduce CV mortality (HR 0.38-0.87). [68]

Table 3. Pharmacological comparison of steroidal vs non-steroidal MRAs, including PK/PD and indications.

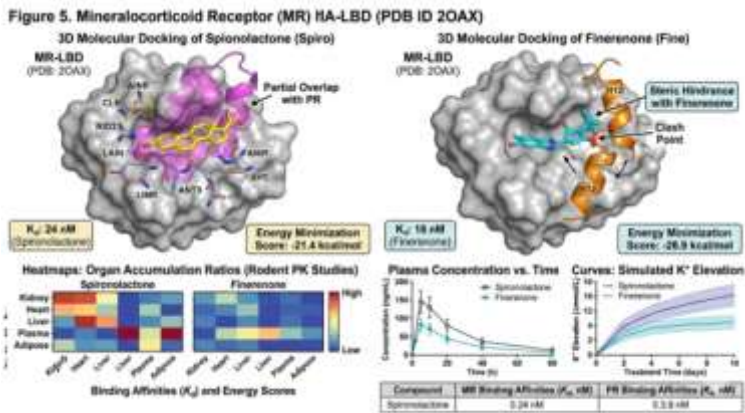


Figure 5: 3D molecular docking of MRAs to MR ligand-binding domain (PDB: 2OAX). Surface renderings: spironolactone (partial overlap with progesterone receptor), finerenone (steric hindrance at helix 12). Heatmaps: organ accumulation ratios from rodent PK studies; curves: plasma concentration vs time, K+ elevation simulations. Binding affinities (Kd: spironolactone 24 nM, finerenone 18 nM). (Multi-panel computational figure with energy minimization data.)

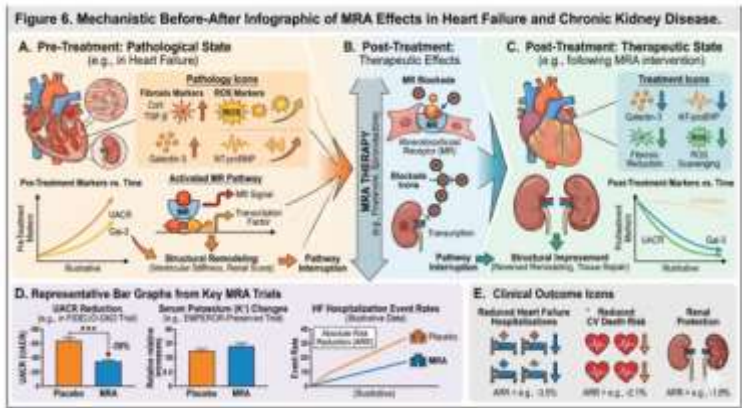


Figure 6. Mechanistic before-after infographic of MRA effects. Panels: pre-treatment (elevated fibrosis/ROS markers); post-treatment (reductions in galectin-3, NT-proBNP); bar graphs from trials (e.g., 20% UACR drop); pathway interruptions (MR blockade icons). Outcome icons: reduced HF hosp icons with ARR. (Illustrative diagram with trend lines and biomarker kinetics.)

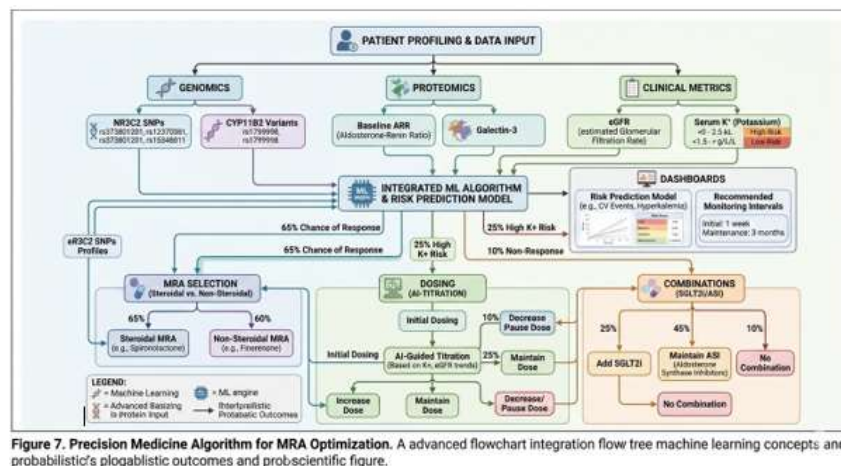


Figure 7. Precision Medicine Algorithm for MRA Optimization. A advanced flowchart integration flow tree machine learning concepts and probabilistic's plogabstic outcomes and prob-scientific figure.

Figure 7: Precision medicine algorithm for MRA optimization. Nodes: genomics (NR3C2 SNPs, CYP11B2 variants), proteomics (baseline ARR/galectin-3), clinical (eGFR, K⁺). Branches: MRA selection (steroidal vs non-steroidal), dosing (AI-titration), combos (SGLT2i/ASI). Dashboards: risk prediction models, monitoring intervals. (Flowchart with ML integration, probabilistic outcomes.)

Discussion

MRAs' benefits extend to HF prevention in at-risk populations (e.g., FIDELITY: 14% CV risk reduction). Challenges: underutilization (30-50% in eligible HFrEF), hyperkalemia in CKD, cost in LMICs. Future: ASIs (baxdrostat phase III), gene editing, nanoparticle delivery.

Conclusion

Aldosterone-driven pathology is modifiable via biomarkers and MRAs, promising paradigm shifts in cardiometabolic-cardiorenal care.

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