Module 2:
Aldosterone Pathophysiology: Mechanisms and Clinical Consequences

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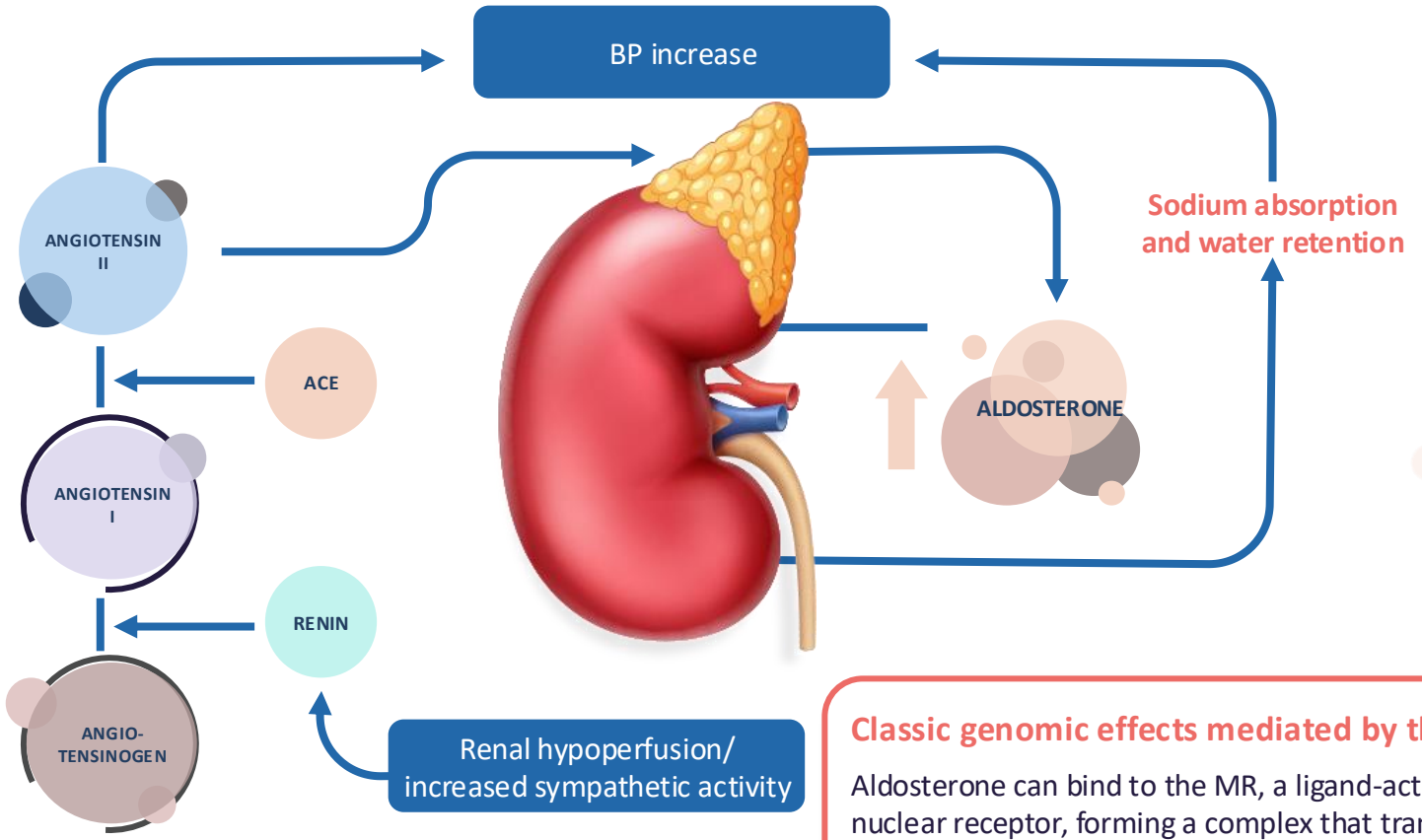
Aldosterone basics: Well established roles in fluid, electrolyte and BP regulation

1. Activation of RAAS in response to stimuli such as low BP or low serum sodium[1]

2. Increased aldosterone production causes water and sodium reabsorption, leading to plasma volume expansion and increased BP[1–3]

3. Elevations in BP and sodium lead to:[2]
   - Inhibition of renin release
   - Decreased RAAS activation
   - Reduced aldosterone production



Refer to Scott JH, et al. 2023[1], Papadopoulou-Marketou N, et al. 2000[2]; Triebel H, et al, 2024[3]; and Noh MR, et al. 2022[4]

Classic genomic effects mediated by the MR

Aldosterone can bind to the MR, a ligand-activated nuclear receptor, forming a complex that translocates to the nucleus to regulate gene transcription[5,6]

Aldosterone production increases when the RAAS is activated when the kidneys detect reduced sodium concentrations, low BP and low kidney perfusion[1]

ACE, angiotensin-converting enzyme; BP, blood pressure; RAAS, renin–angiotensin–aldosterone system; MR, mineralocorticoid receptor

1. Scott JH, et al. Physiology, aldosterone. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2023; 2. Papadopoulou-Marketou N, et al. Hyperaldosteronism. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc. 2000; 3. Triebel H, Castrop H. *Eur J Physiol* 2024;476:705–713; 4. Noh MR, et al. *Int J Mol Sci* 2020;21:1647; 5. Chai W, et al. *Br J Pharmacol* 2005;145:664–671; 6. Verhovez A, et al. *Curr Signal Transduc Ther* 2012;7:132–141

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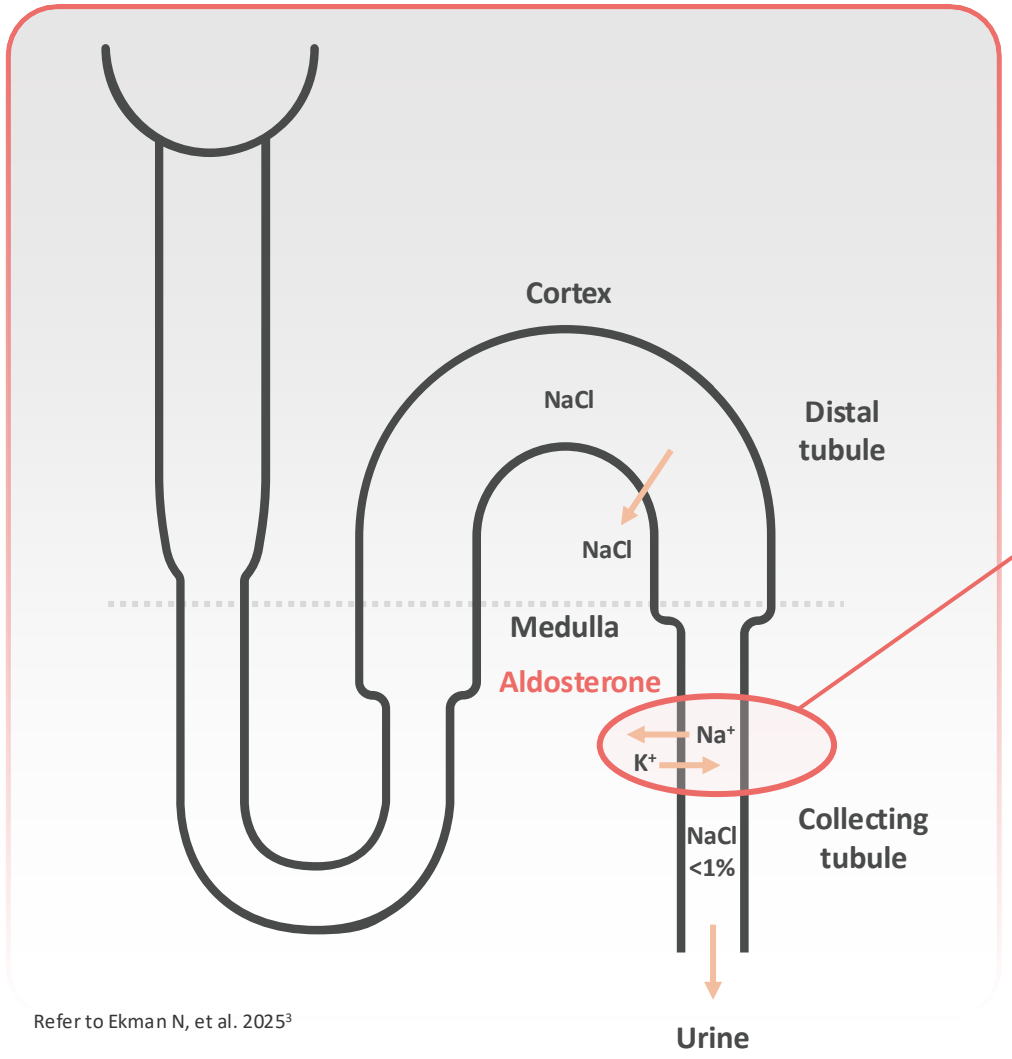
Aldosterone's primary target is the late distal tubule and collecting duct of nephrons in the kidney



Refer to Ekman N, et al. 2025[3]

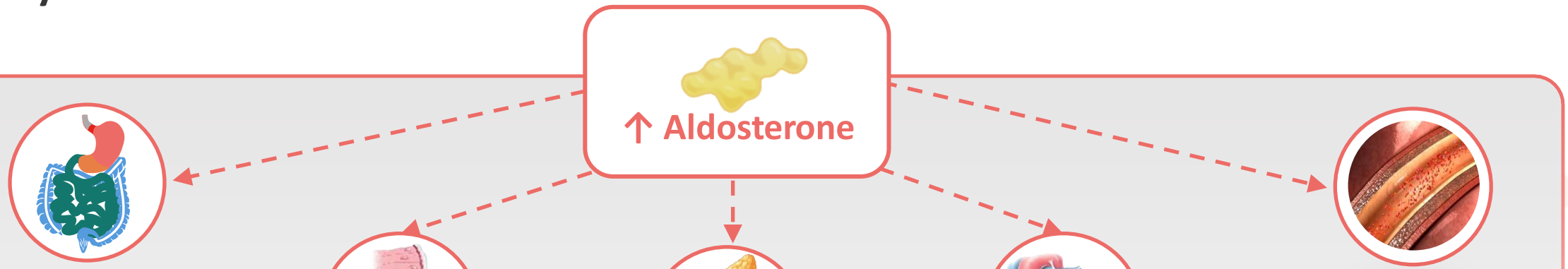
Depending on the specific physiologic parameters, aldosterone may:[1,2]

- Increase sodium reabsorption
- Increase water retention
- Increase potassium excretion
- Increase acid (H+) excretion
- Increase HCO_3^- excretion and chloride reabsorption

H^+, hydrogen ion; HCO_3^-, bicarbonate; Na^+, sodium ion; NaCl, sodium chloride; K^+, potassium ion

1. Vaidya A, et al. *Endocr Rev* 2018;39:1057–1088; 2. Scott JH, et al. Physiology, aldosterone. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2023; 3. Ekman N, et al. *Int J Mol Sci* 2025;26:540

Although predominantly known for its activity in the kidney, aldosterone also acts in many other tissues



Gastrointestinal tract

Hyperaldosteronism stimulates sodium absorption in the colon and the small intestine[1]

It also promotes H^+ excretion and K^+ secretion in the colon[1]

Respiratory system

Modulate ion transport, influencing the ENaC by activating or increasing its expression, which can affect lung fluid balance[2]

Kidney

Multiple pathways influenced by elevated levels of aldosterone result in interstitial fibrosis, decreased kidney blood flow and decreased eGFR, leading to kidney failure[3]

Heart

Increases calcium currents in cardiomyocytes contributing to hypertrophy when levels of aldosterone are elevated[4]

Vasculature

Increases intracellular calcium, modulates ion channels, enhances the vascular response and promotes vascular remodelling at physiological subnanomolar aldosterone concentrations[5]

This broad expression of MR beyond the kidney explains how aldosterone drives effects that extend further than haemodynamic changes

eGFR, estimated glomerular filtration rate; ENaC, epithelial sodium channel; H^+, hydrogen ion; K^+, potassium ion; MR, mineralocorticoid receptor

1. Rajendran VM, et al. *Compr Physiol* 2018;8:1513–1536; 2. Fei X, et al. *Mol Cell Probes* 2021;57:101709; 3. Ogata H, et al. *Hypertension* 2021;78:411–421; 4. He BJ, et al. *Trends Endocrinol Metab* 2013;24:21–30; 5. Wehling M, et al. *Circ Res* 1995;76:973–979

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Elevated levels of aldosterone can drive pathogenic effects both through elevations in BP and via direct, haemodynamically independent actions on target organs

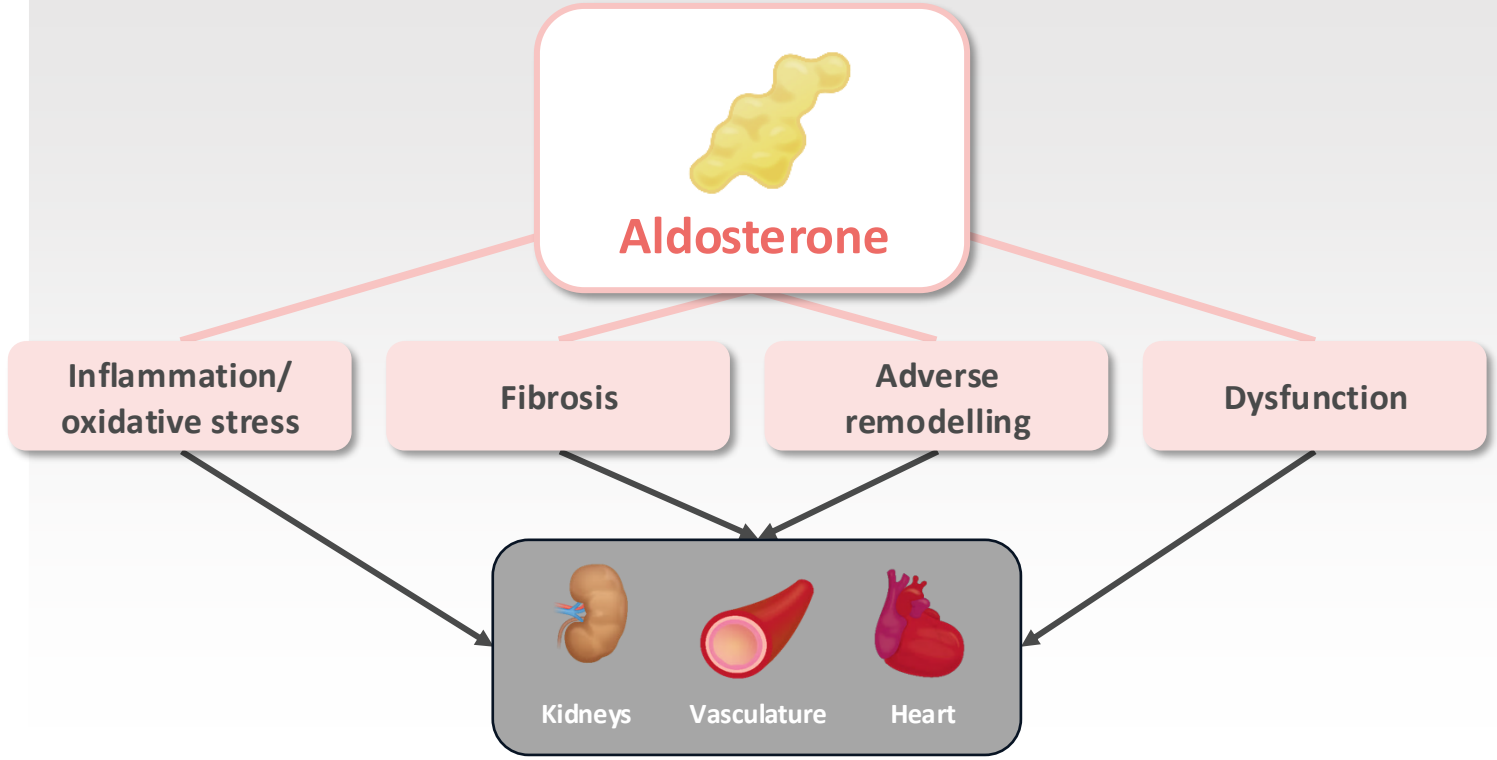
Aldosterone action drives higher BP[1]

- Aldosterone
- Na^+ reabsorption
- Plasma volume
- BP

In the context of **high dietary sodium intake**, aldosterone that is not appropriately suppressed can **contribute to hypertension and associated adverse outcomes**[2]

Aldosterone as a regulator of BP and driver of hypertension is covered in Module 1

Elevated levels of aldosterone can also induce direct organ damage, independent of BP[3,4]



Such effects occur via widely distributed MRs across key target organs, and through proposed MR-independent pathways[1,3]

BP, blood pressure; MR, mineralocorticoid receptor; Na^+, sodium ion

1. Ekman N, et al. *Int J Mol Sci* 2025;26:540; 2. Chen L, et al. *Horm Metab Res* 2024;56:99–106; 3. Verhovez A, et al. *Curr Signal Transduct Ther* 2012;7:132–141; 4. Inoue K, et al. *Hypertension* 2020;76:113–120

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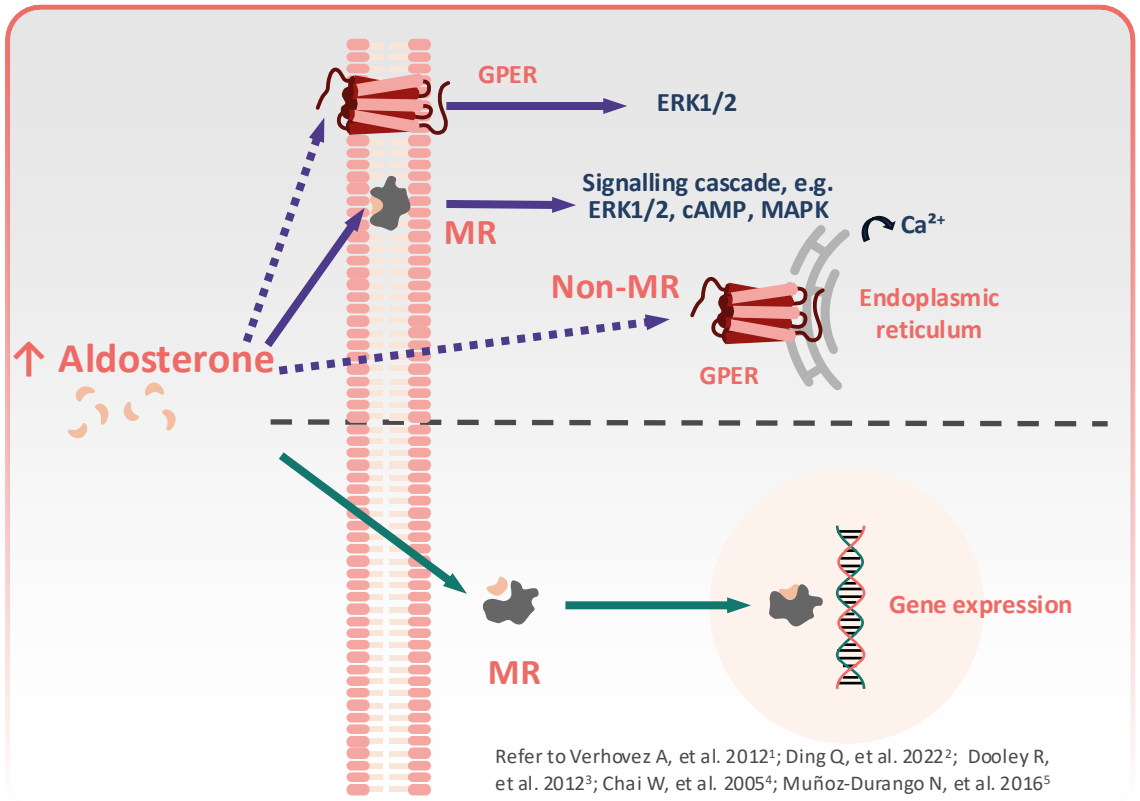
Beyond classic genomic effects, aldosterone triggers rapid non-genomic responses, which can be activated through both MR and non-MR pathways



Refer to Verhovez A, et al. 2012[1]; Ding Q, et al. 2022[2]; Dooley R, et al. 2012[3]; Chai W, et al. 2005[4]; Muñoz-Durango N, et al. 2016[5]

Rapid non-genomic effects[1–3]

- Act independently of gene transcription most notably on mononuclear leukocytes, endothelial cells, VSMCs and cardiomyocytes
- Involve membrane-bound MRs and other probable receptors (e.g. GPER)
- Signalling cascades include intracellular calcium fluxes and kinases such as MAPKs
- Regulate electrolyte channels (e.g. activation of the NHE)
- Trigger rapid cellular responses (seconds to minutes)

Classic genomic effects[1,3,4,5]

- Aldosterone binds to intracellular MRs
- The aldosterone–MR complex enters the nucleus to regulate gene transcription that control electrolyte and fluid balance, including those encoding ENaC and ROMK
- Lead to protein synthesis involved in electrolyte and fluid balance
- Delayed onset: effects occur after hours

The existence of **parallel MR-dependent and MR-independent pathways** positions elevated levels of aldosterone as a multifaceted effector of organ damage even when classical MR signalling is blocked and standard RAAS inhibition is in place[6–8]

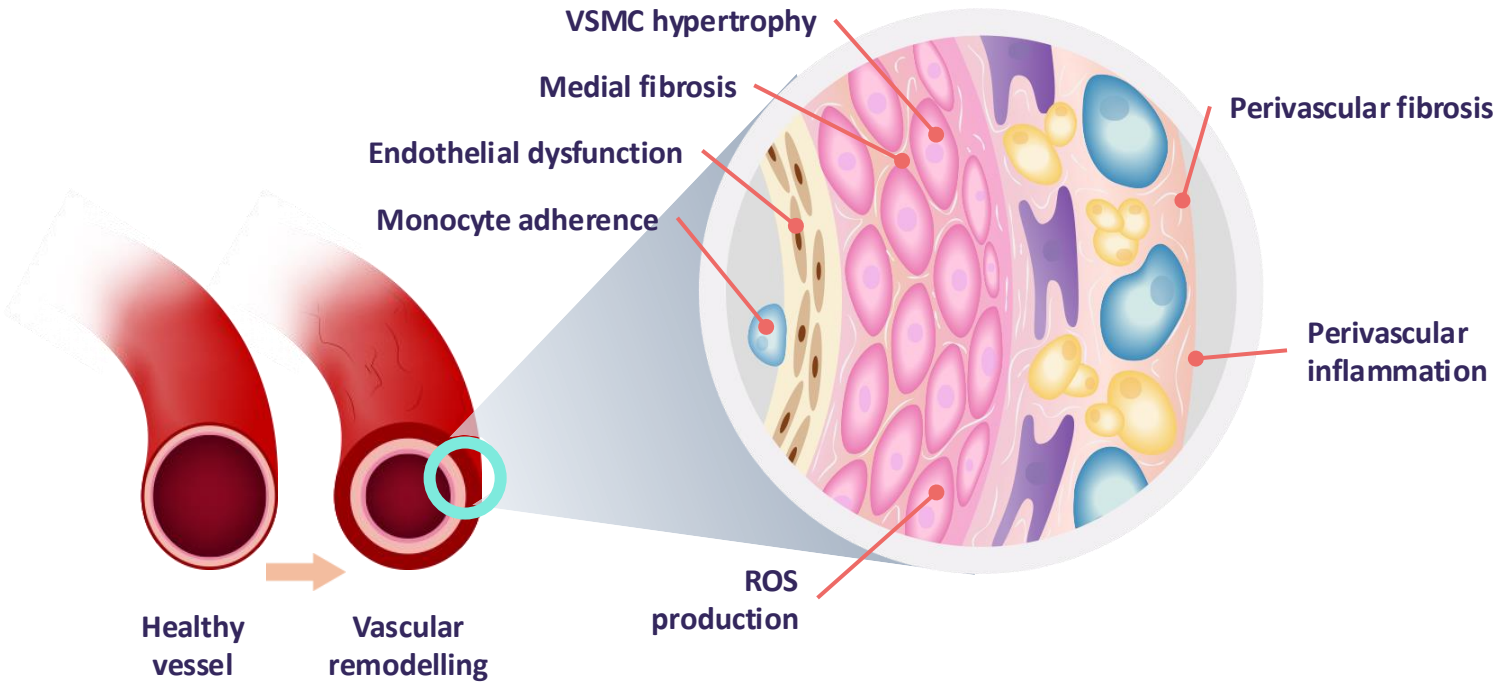
Ca^{2+}, calcium ions; cAMP, cyclic adenosine monophosphate; ENaC, extracellular calcium channel; ERK1/2, extracellular signal-regulated kinase 1/2; GPER, G protein-coupled oestrogen receptor; MAPK, mitogen-activated protein kinase; MR, mineralocorticoid receptor; NHE, NaH exchanger; RAAS, renin–angiotensin–aldosterone system; ROMK, renal outer potassium channel; VSMCs, vascular smooth muscle cells

1. Verhovez A, et al. *Curr Signal Transduc Ther* 2012;7:132–141; 2. Ding Q, et al. *Pharmacol Res Perspect* 2022;10:e00995; 3. Dooley R, et al. *Mol Cell Endocrinol* 2012;350:223–234; 4. Chai W, et al. *Br J Pharmacol* 2005;145:664–671; 5. Muñoz-Durango N, et al. *Int J Mol Sci* 2016;17:797; 6. Good DW. *Hypertension* 2007;49:728–739; 7. Brown JM. *J Am Heart Assoc* 2024;13:e030142; 8. Fioretti F, et al. *J Am Coll Cardiol* 2025; 86:354–373

Think Aldo

Elevated levels of aldosterone can drive vascular remodelling and lead to CV damage

Key effects of elevated levels of aldosterone on the blood vessels[1–7]



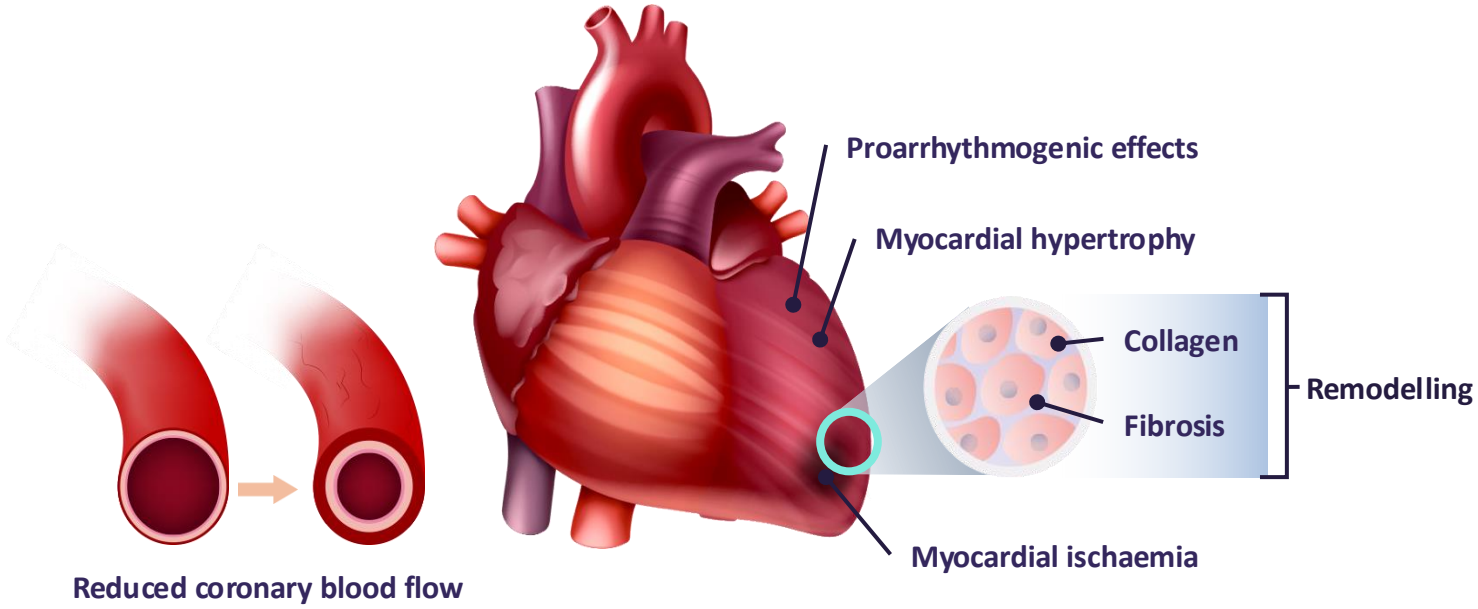
- Aldosterone acts directly on **endothelial** and **VSMCs** via MR, **independent of BP**[1,2]
- **In endothelial cells**, aldosterone–MR activation increases **oxidative stress**, **reduces nitric oxide bioavailability** and impairs endothelium-dependent **vasodilation**, driving **endothelial dysfunction**[1,2]
- **In VSMCs**, elevated aldosterone activates MR-dependent signalling, including **MAPK cascades**, increasing **pro-inflammatory** and **pro-fibrotic** mediators and extracellular matrix production; these changes drive **vascular remodelling**[1,2]
- These effects contribute to endothelial dysfunction and infiltration of inflammatory cells, enhancing the development of the atherosclerotic plaque, and favouring plaque instability, **arterial stiffness** and **calcification**, which may persist even when BP is controlled[1,3]

BP, blood pressure; CV, cardiovascular; MAPK, mitogen-activated protein kinase; MR, mineralocorticoid receptor; ROS, reactive oxygen species; VSMC, vascular smooth muscle cell

1. Verhovez A, et al. *Curr Signal Transduc Ther* 2012;7:132–141; 2. Muñoz-Durango N, et al. *Int J Mol Sci* 2016;17:797; 3. Buffolo F, et al. *Hypertension* 2022;79:1899–1911; 4. Briones AM, Touyz RM. Aldosterone/MR Signaling, Oxidative Stress, and Vascular Dysfunction. In: Harvey B, Jaisser F, eds. Aldosterone-Mineralocorticoid Receptor: Cell Biology to Translational Medicine. IntechOpen. 2019; 5. Pacurari M, et al. *Int J Inflam* 2014;2014:689360; 6. Rocha R, et al. *Am J Physiol Heart Circ Physiol* 2002;283:H1802–H1810; 7. Sherajee SJ, et al. *Arterioscler Thromb Vasc Biol* 2012;32:257–263

Elevated levels of aldosterone can impact LV cardiac remodelling and cardiac function, leading to CV morbidity

Key effects of elevated levels of aldosterone on the heart[1–5]



- **Direct cardiac injury:** Elevated levels of aldosterone promotes myocardial inflammation, fibrosis, hypertrophy and arrhythmogenic electrical changes, independent of BP[1]
- **Inflammation precedes fibrosis:** In a study with animal models, aldosterone in the presence of sodium triggered early microvascular and inflammatory injury that progressed to myocardial fibrosis[1]
- **Adverse remodelling and arrhythmias:** Elevated levels of aldosterone are also associated with left ventricular and atrial remodelling, collagen deposition and electrophysiological instability. In a study on rats where a myocardial infarction was experimentally determined by ligation of the left coronary artery, eplerenone administration reduced the collagen deposition and the cardiac remodelling of the viable myocardium without affecting infarct healing[1,4,5]

BP, blood pressure; CV, cardiovascular; LV, left ventricle; MR, mineralocorticoid receptor

1. Verhovez A, et al. *Curr Signal Transduc Ther* 2012;7:132–141; 2. Muñoz-Durango N, et al. *Int J Mol Sci* 2016;17:797; 3. Buffolo F, et al. *Hypertension* 2022;79:1899–1911; 4. Monzo L, et al. *Eur J Heart Fail* 2023;25:1742–1752; 5. Varadarajan V, et al. *Am J Hypertens* 2023;36:517–523

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Adverse CV outcomes driven by elevated levels of aldosterone can occur independently of BP

Elevated levels of aldosterone can drive adverse CV outcomes, independent of BP[1–4]

- High aldosterone levels can impact left **ventricular cardiac remodelling** and **function**, even when **BP is controlled**[1–3]
- Patients with PA treated with MRAs remain at higher risk of CV outcomes compared with patients with primary hypertension, **independent of BP control**[5,6]

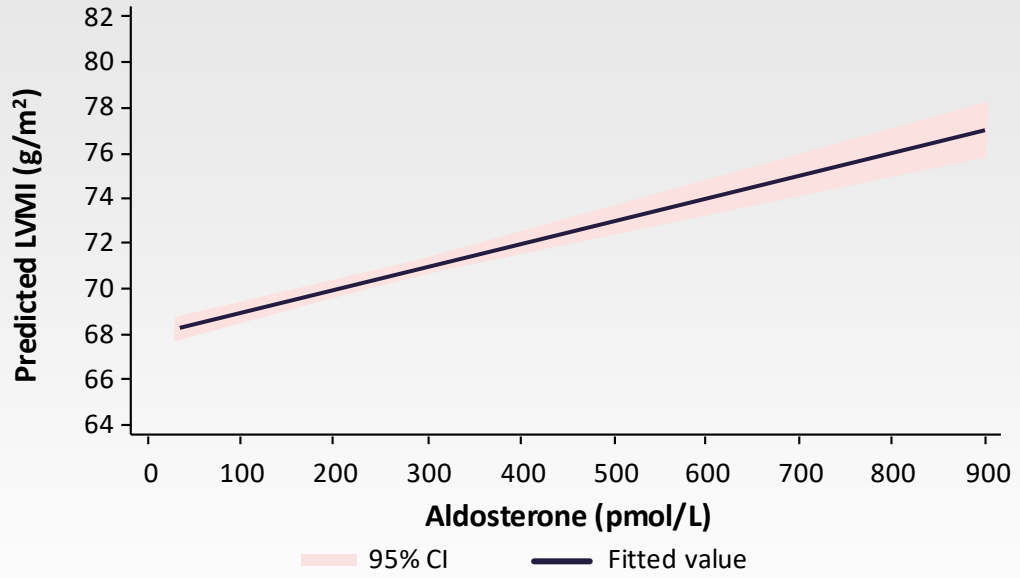
HR: 1.93
(95% CI: 1.54, 2.42)
Atrial fibrillation

HR: 1.91
(95% CI: 1.63, 2.25)
CV events

Adjusted HRs for patients with PA treated with MRAs versus hypertensive controls[6a]

This highlights a **pathogenic role of aldosterone that extends beyond its effects on BP**[6]

Association between excess aldosterone concentrations and LVMI among young males[4]



Aldosterone concentration was positively associated with LVMI in young males at 27 years of age,[b] **independent of systolic BP**, suggesting that aldosterone may contribute to **early cardiac remodelling** before the development of hypertension or arterial stiffness[4]

[a]Data based on a retrospective cohort study of patients with PA treated with MRAs (N=602), and age-matched patients with primary hypertension (N=41853) to determine risk for cardiac events; [b]In a longitudinal, population-based cohort study in young males at 27 years of age, β=0.009 (95% CI: 0.001, 0.017); *P*=0.027

BP, blood pressure; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; PA, primary aldosteronism

1. Monzo L, et al. *Eur J Heart Fail* 2023;25:1742–1752; 2. van Rooyen JM, et al. *Cardiovasc J Afr* 2020;31:130–135; 3. Varadarajan V, et al. *Am J Hypertens* 2023;36:517–523; 4. Ananda RA, et al. *Circulation* 2024;150:2019–2030; 5. Hundemer GL, et al. *Hypertension* 2018;72:658–666; 6. Hundemer GL, et al. *Lancet Diabetes Endocrinol* 2018;6:51–59

Think Aldo

PA is associated with a higher risk of CV events when compared with primary hypertension

Aldosterone can drive adverse CV outcomes, independent of BP[1]

Findings from 31 studies involving 3838 patients with PA and 9284 patients with primary hypertension showed that patients with PA had an enhanced CV risk after a median of 8.8 years from hypertension diagnosis, compared to patients with primary hypertension

Atrial fibrillation	Heart failure	LV hypertrophy	Coronary artery disease	Stroke
OR 2.05 (95% CI, 1.11–3.78)	OR 2.05 (95% CI, 1.11–3.78)	OR 2.29 (95% CI, 1.65–3.17)	OR 1.77 (95% CI, 1.10–2.83)	OR 2.58 (95% CI, 1.93–3.45)



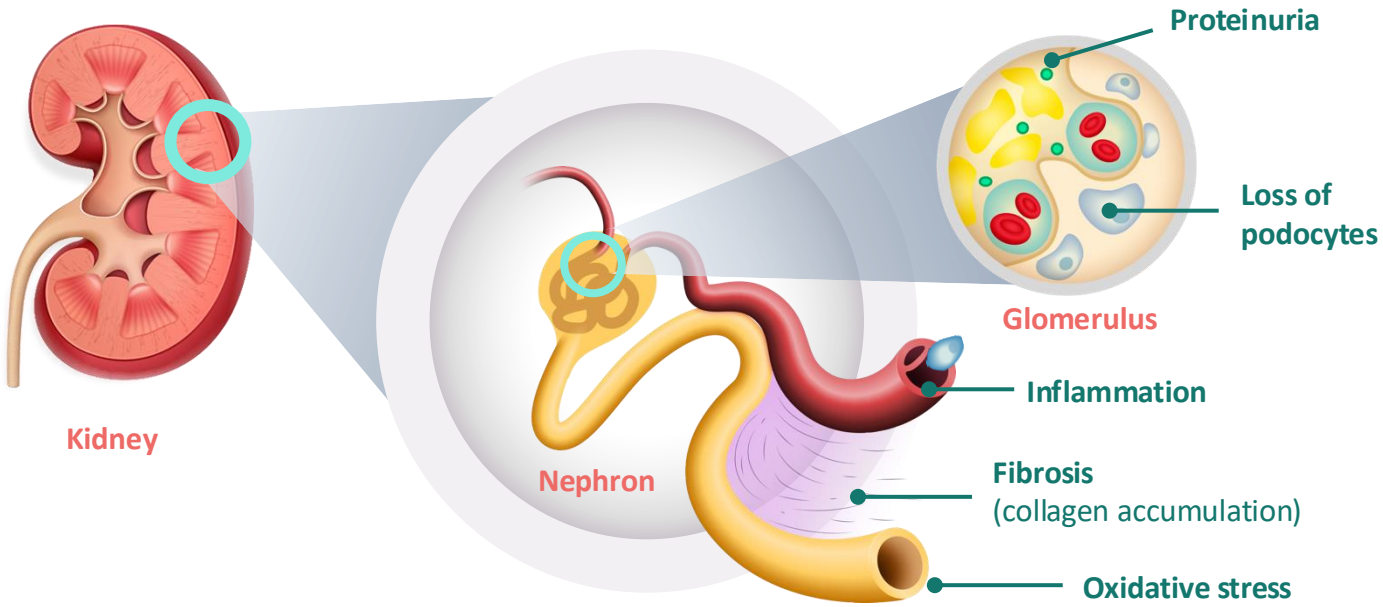


BP, blood pressure; CI, confidence interval; CV, cardiovascular; LV, left ventricle; OR, odds ratio; PA, primary aldosteronism

1. Monticone S, et al. *J Hypertens* 2018;36:e133

Elevated levels of aldosterone may induce fibrotic and inflammatory changes in the kidneys, leading to damage

Key effects of elevated levels of aldosterone on the kidneys[1–3]



- **Direct kidney injury:** Elevated levels of aldosterone are associated with proteinuria, podocyte loss, glomerular injury and nephrosclerosis independent of BP[1,2]
- **Mechanisms:** MR activation, oxidative stress and pro-inflammatory/fibrotic pathways (NF-κB, TGF-β and CTGF) promote podocyte damage, EMT and interstitial fibrosis[3]
- **Clinical impact and therapy:** Leads to nephron loss, CKD progression and CV and kidney syndrome; MR antagonists reduce proteinuria and kidney remodelling even without major BP lowering[1,2,4]

BP, blood pressure; CKD, chronic kidney disease; CTGF, connective tissue growth factor; CV, cardiovascular; EMT, epitheliałto-mesenchymal transition; MR, mineralocorticoid receptor; NF-κB, nuclear factor kappa B; TGF-β, transforming growth factor beta

1. Verhovez A, et al. *Curr Signal Transduc Ther* 2012;7:132–141; 2. Muñoz-Durango N, et al. *Int J Mol Sci* 2016;17:797; 3. Brem AS, et al. *Am J Kidney Dis* 2011;58:471–479; 4. Ogata H, et al. *Hypertension* 2021;78:411–421

Elevated levels of aldosterone can drive adverse kidney outcomes, some of which occur independently of BP

Patients with excess or dysregulated aldosterone are at an increased risk of **proteinuria, CKD progression and ESKD**[1,2]

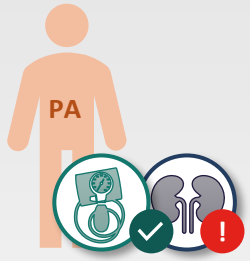
Patients with PA, compared with those with primary hypertension without PA, had an increased risk of:[1a]

- **Proteinuria** by **168%**

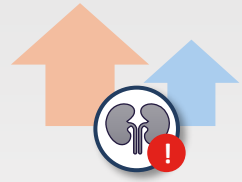
In patients with CKD, high serum aldosterone (highest versus lowest quartile) was **independently** associated with:[2b]

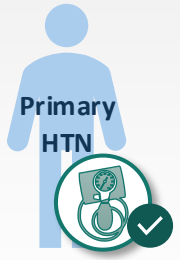
- **CKD progression** by **45%**
- **Developing ESKD** by **46%**

Such effects can occur independent of BP control[3]



Patients with PA had a **higher risk of developing CKD…**





…and a more **rapid decline in eGFR** compared with patients with primary hypertension…

…independent of BP control

This highlights aldosterone's direct pathogenic role in the kidney that **extends beyond its effects on BP**

[a]Data based on a quantitative review of 46 studies evaluating parameters of renal function in patients with PA (N=6056) compared with patients with hypertension without PA (N=9733) before and after treatment, followed for 8.5 years; [b]Data based on a multicentre, prospective, observational cohort study designed to investigate risk factors for death, cardiovascular disease and CKD progression in known patients with CKD (N=3939).
BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HTN, hypertension; PA, primary aldosteronism

1. Monticone S, et al. *J Hypertens* 2020;38:3–12; 2. Verma A, et al. *Eur Heart J* 2022;43:3781–3791; 3. Hundemer GL, et al. *Hypertension* 2018;72:658–666

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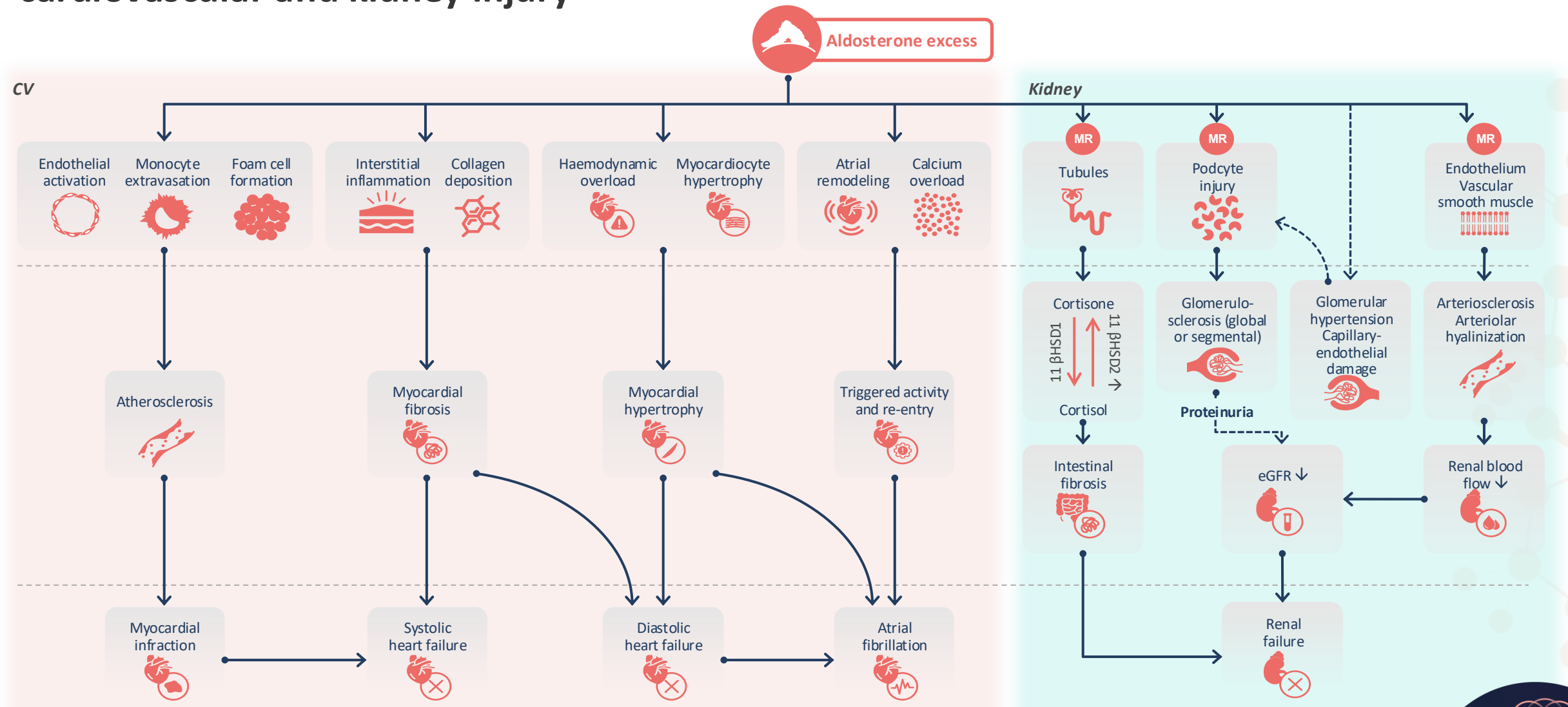
Elevated levels of aldosterone can act via multiple mechanistic pathways promoting cardiovascular and kidney injury



Refer to Buffolo F, et al. 2022[1] and Ogata H, et al. 2021[2]

CV, cardiovascular; eGFR, estimated glomerular filtration rate; MR, mineralocorticoid receptor

1. Buffolo F, et al. *Hypertension* 2022;79:1899–1911; 2. Ogata H, et al. *Hypertension* 2021;78:411–421.

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High aldosterone concentrations are associated with increased risk of mortality in patients with coronary artery disease or CKD

CV mortality in patients with coronary artery disease[1,a]

Aldosterone quartile[b]	CV mortality HR (95% CI)
1	Reference
2	1.63 (1.20, 2.20)
3	1.39 (1.01, 1.90)
4	1.58 (1.15, 2.16)

58% increased risk of **CV mortality** in those in the highest quartile of aldosterone compared with those in the lowest quartile[1]

All-cause mortality in patients with CKD[2,c]

Aldosterone quartile[d]	All-cause mortality HR (95% CI)
1	Reference
2	1.06 (0.89, 1.26)
3	1.13 (0.95, 1.34)
4	1.22 (1.02, 1.45)

22% higher risk for **all-cause mortality** in those in the highest quartile of serum aldosterone compared with those in the lowest quartile[2]

Via MR and non-MR pathways, elevated levels of aldosterone exerts BP-dependent and -independent effects that can lead to morbidity and can ultimately increase mortality risk in some patients[1–4]

[a]Results depicted are from a prospective cohort study of 3153 patients undergoing coronary angiography; [b]Q1: ≤48 pg/mL, Q2: 49–78 pg/mL, Q3: 79–123 pg/mL, Q4: ≥124 pg/mL; [c]Results depicted are from a multicentre, prospective, observation cohort study (CRIC) of 3680 patients with known CKD, defined as eGFR 20-70 mL/min/1.73 m^2; [d]Quartiles represented in IQR values; Q1: 5.6 ng/dL, Q2: 8.5 ng/dL, Q3: 11.0 ng/dL, Q4: 20.6 ng/dL
CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MR, mineralocorticoid receptor

1. Tomaschitz A, et al. *Eur Heart J* 2010;31:1237–1247; 2. Verma A, et al. *Eur Heart J* 2022;43:3781–3791; 3. Brown JM. *J Am Heart Assoc* 2024;13:e030142; 4. Good DW. *Hypertension* 2007;49:728–739

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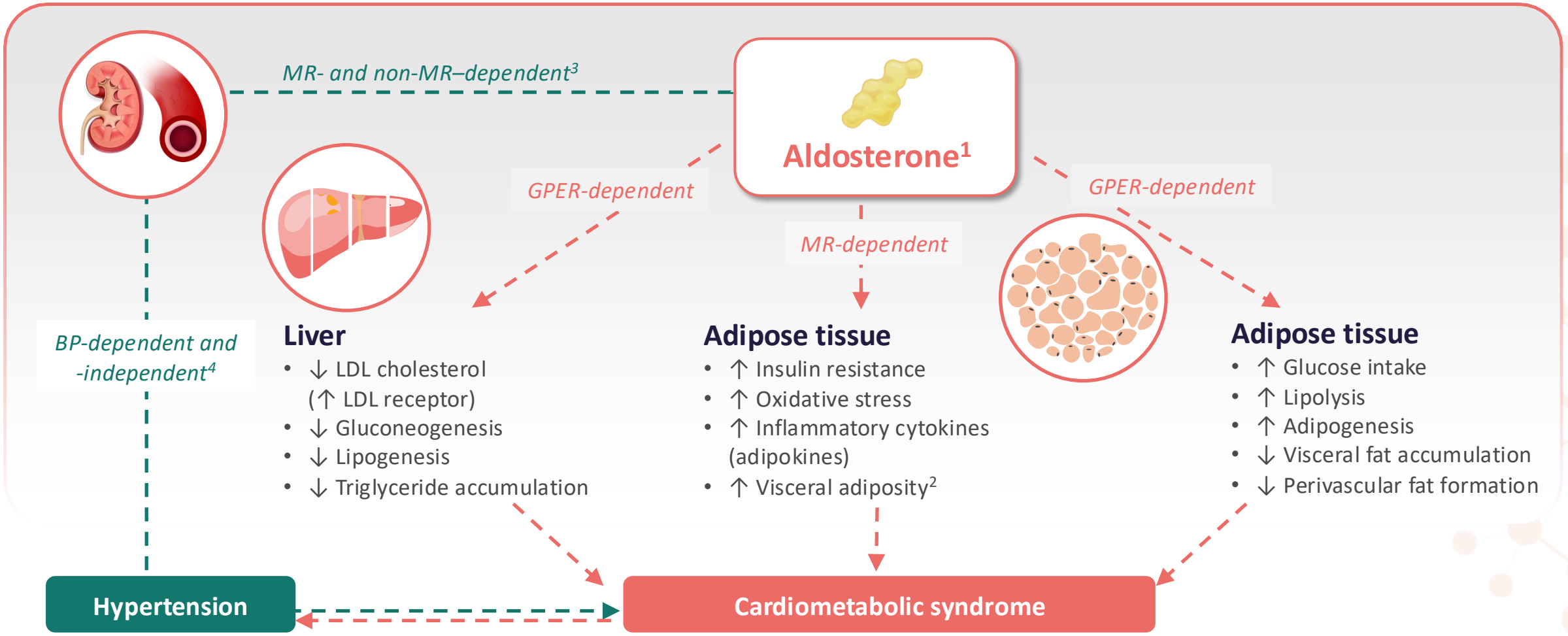
Excess aldosterone can also lead to cardiometabolic dysfunction through direct effects on adipose tissue and liver



Refer to Feldman RD, et al. 2023[1]; Rossi GP, et al. 2008[2]; Fioretti F, et al. 2025[3]; Brown JM. 2024[4]

BP, blood pressure; GPER, G protein-coupled oestrogen receptor; LDL, low-density lipoprotein; MR, mineralocorticoid receptor

1. Feldman RD, et al. *Can J Cardiol* 2023;39:1808–1815; 2. Rossi GP, et al. *J Clin Endocrinol Metab* 2008;93:2566–2571; 3. Fioretti F, et al. *J Am Coll Cardiol* 2025; 86:354–373; 4. Brown JM. *J Am Heart Assoc* 2024;13:e030142

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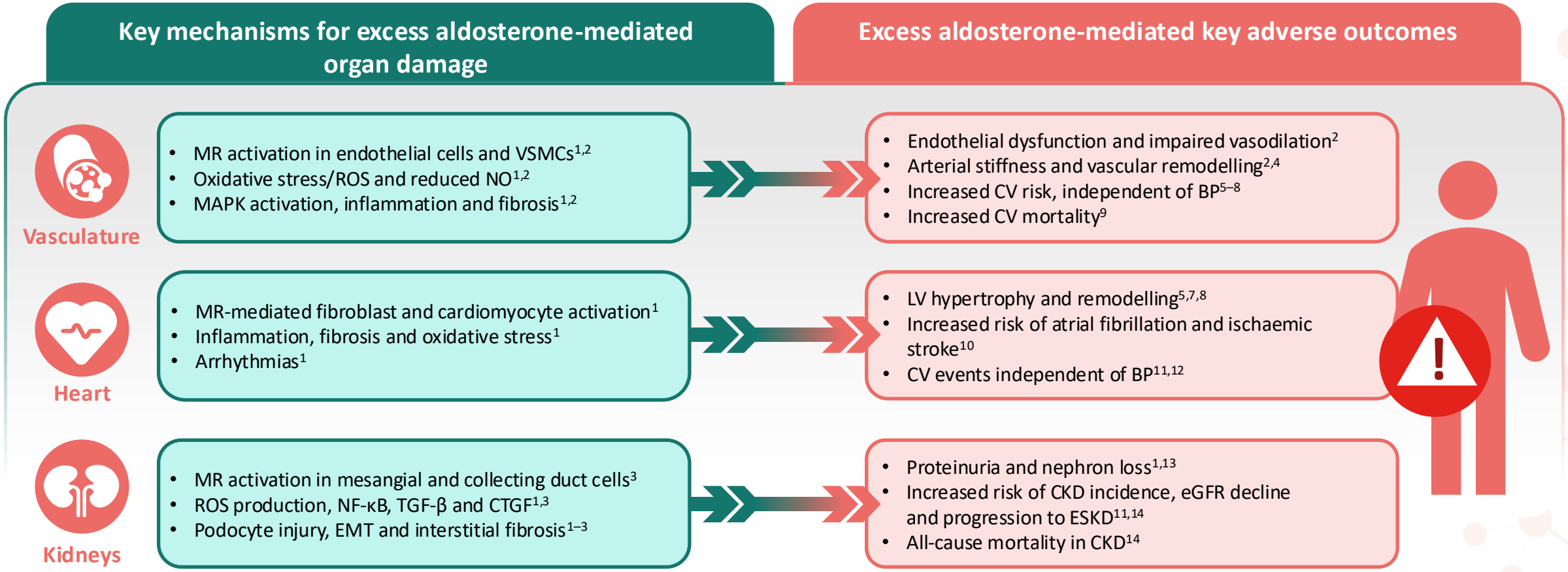
Summary: Excess or dysregulated aldosterone levels can induce direct organ damage and can lead to significant morbidity and mortality



BP, blood pressure; CKD, chronic kidney disease; CTGF, connective tissue growth factor; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EMT, epithelial-to-mesenchymal transition; ESKD, end-stage kidney disease; LV, left ventricle; MAPK, mitogen-activated protein kinase; MR, mineralocorticoid receptor; NF-κB, nuclear factor kappa B; NO, nitric oxide; ROS, reactive oxygen species; TGF-β, transforming growth factor beta; VSMC, vascular smooth muscle cell

1. Muñoz-Durango N, et al. *Int J Mol Sci* 2016;17:797; 2. Verhovez A, et al. *Curr Signal Transduc Ther* 2012;7:132–141; 3. Brem AS, et al. *Am J Kidney Dis* 2011;58:471–479; 4. Buffolo F, et al. *Hypertension* 2022;79:1899–1911; 5. Monzo L, et al. *Eur J Heart Fail* 2023;25:1742–1752; 6. van Rooyen JM, et al. *Cardiovasc J Afr* 2020;31:130–135; 7. Varadarajan V, et al. *Am J Hypertens* 2023;36:517–523; 8. Ananda RA, et al. *Circulation* 2024;150:2019–2030; 9. Tomaschitz A, et al. *Eur Heart J* 2010;31:1237–1247; 10. Lassen M, et al. Presented at ACC, March 29–31, 2025. Chicago, IL, USA. Poster; 11. Hundemer GL, et al. *Hypertension* 2018;72:658–666; 12; Hundemer GL, et al. *Lancet Diabetes Endocrinol* 2018;6:51–59; 13. Ogata H, et al. *Hypertension* 2021;78:411–421; 14. Verma A, et al. *Eur Heart J* 2022;43:3781–3791

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Take-home messages

The primary and evolutionary role of aldosterone is to facilitate **potassium excretion and sodium retention**, allowing for volume expansion and **maintenance of BP** in response to **hypoperfusion** or **volume depletion**[1,2]

Aldosterone acts through both the **MR and non-MR pathways**, with **widespread receptor expression** enabling **direct effects** across **multiple organ systems**[3–6]

In the context of **high dietary sodium intake**, aldosterone that is **not appropriately suppressed** can contribute to **hypertension** and **associated adverse outcomes**, via **BP-dependant mechanisms**[7,8]

Elevated levels of aldosterone can also drive **direct end-organ damage** through **BP-independent pathways**, contributing further to **CV** and **kidney disease**[4,5,9–13]

Understanding aldosterone pathophysiology may help improve CV and kidney outcomes

BP, blood pressure; CV, cardiovascular; MR, mineralocorticoid receptor

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