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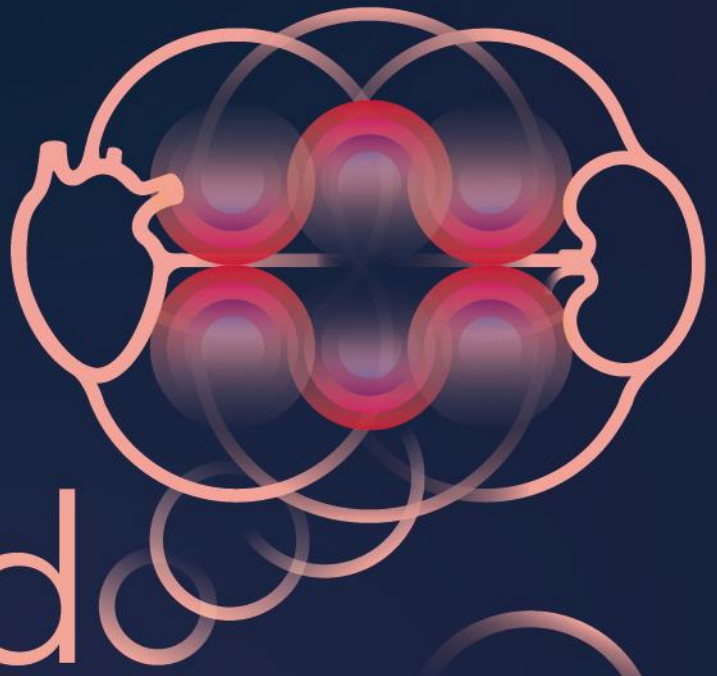

Module 1:
What is Driving Difficult-to-Control Hypertension?

This non-promotional educational slide deck has been developed and funded by AstraZeneca, in collaboration with *Think Aldo* Steering Committee members. Intended for healthcare professionals outside of the US only.

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Hypertension is a growing global health challenge

~1.4 billion of adults worldwide have hypertension (HTN), and this figure is growing[1,2]

Treated but uncontrolled hypertension (≥140/90 mmHg) is associated with increased risk of…

~1.6-fold
All-cause mortality

~3-fold
Cerebrovascular mortality

~2-fold
Cardiac mortality

~2-fold
CVD-specific mortality

…compared with normotension[3,a]

$3.7 trillion *global economic losses associated with CV diseases, including hypertension between 2011-2025, equating to around **2%** of GDP of low- and middle-income countries[2]*

[a]Prospective cohort study of US adults aged ≥18 years (N=13,947) enrolled in NHANES III (1988–1994; median follow-up 19.1 years). Mortality outcome events data presented as HR and 95% CI: all-cause (HR: 1.62; 95% CI: 1.35, 1.95), cerebrovascular disease–specific (HR: 3.01; 95% CI: 1.91, 4.73), heart disease–specific (HR: 2.19; 95% CI: 1.57, 3.05), and CVD-specific (HR: 2.23; 95% CI: 1.66, 2.99).

BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; ESC, European Society of Cardiology; ESH, EuropeanSociety of Hypertension; HR, hazard ratio; HTN, hypertension; NHANES III, Third National Health and Nutrition Examination Survey

1. NCD Risk Factor Collaboration (NCD-RisC). *Lancet* 2021;398:957–980; 2. WHO. Global report on hypertension 2025. Available at https://www.who.int/publications/b/81068 (Accessed April 2026); 3. Zhou D, et al. *Sci Rep* 2018;8:9418

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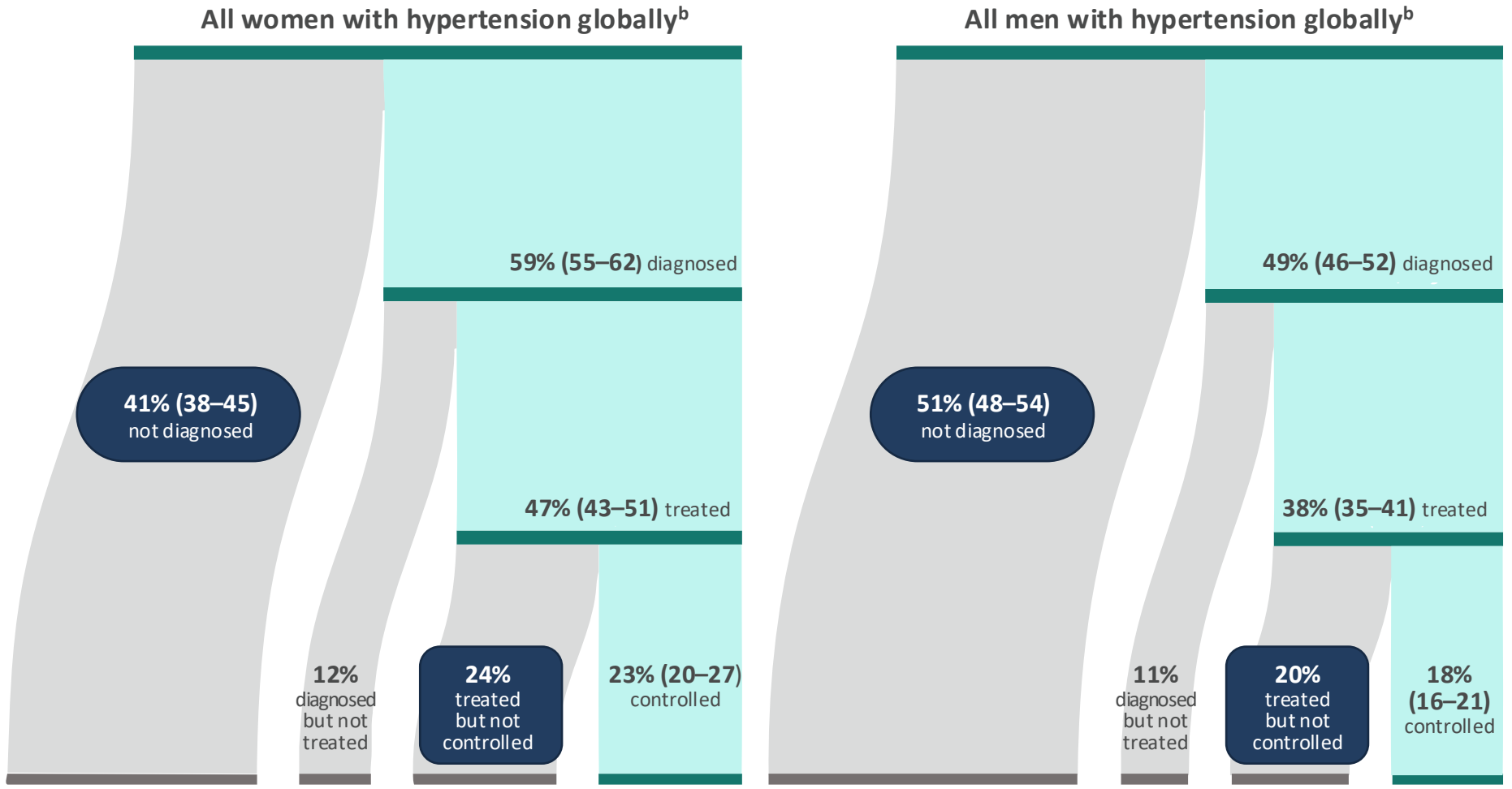
Most hypertension is not controlled

~80% of all hypertension cases globally are above target (BP ≥140/90 mmHg)[a]



Many patients with hypertension are **undiagnosed**

Less than half of patients with hypertension receive treatment

Of those treated, around half remain **uncontrolled** (BP ≥140/90 mmHg)

Refer to NCD Risk Factor Collaboration (NCD-RisC). *Lancet* 2021;398:957–980

[a]Control rates among treated patients with hypertension in 2019 were 23% (20–27) for women and 18% (16–21) for men; [b]Data are estimates (95% credible interval). Each stream shows the loss of people with hypertension throughout the treatment cascade and its associated percentage for women and men

BP, blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension

NCD Risk Factor Collaboration (NCD-RisC). *Lancet* 2021;398:957–980

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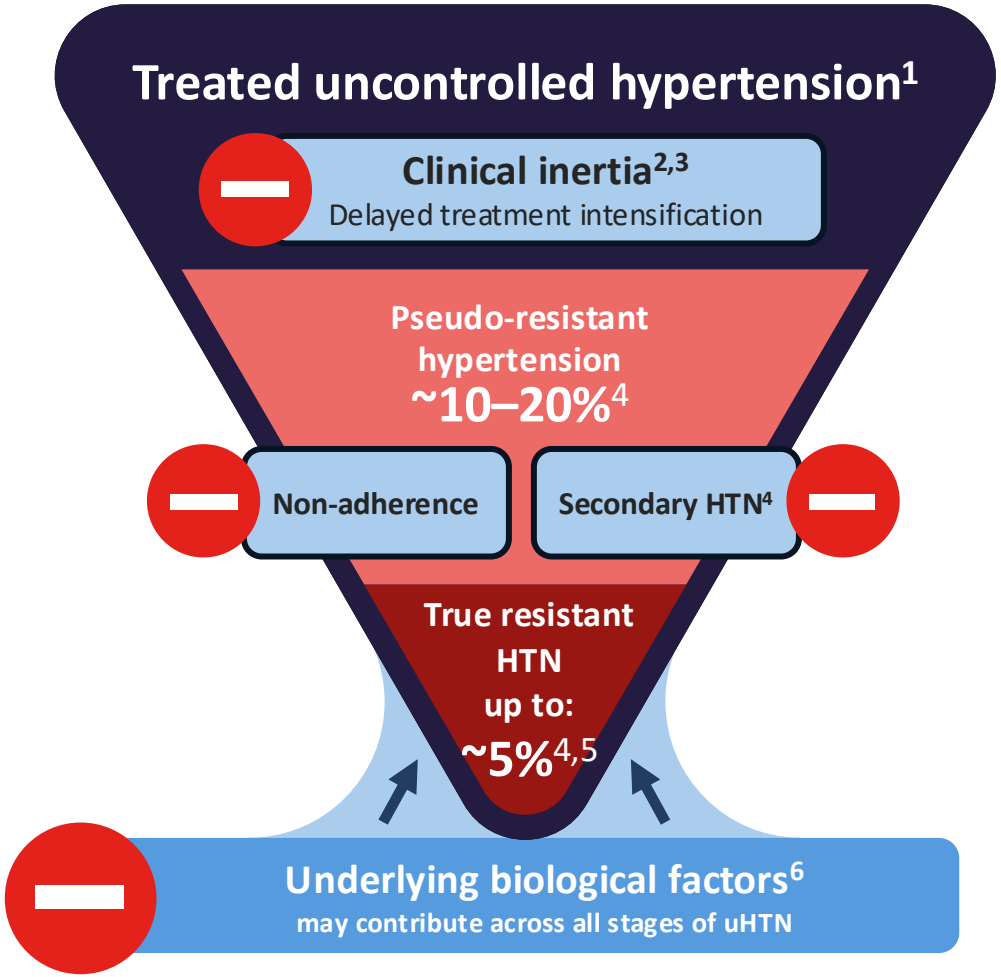
Why is hypertension difficult to control in some patients?



1. **Clinical inertia** may be due to a delay in treatment initiation, or adequate therapy intensification that contributes to high rates of treated, yet uncontrolled, hypertension[2,3]

2. **Pseudo-resistant hypertension** is uncontrolled BP that mimics resistant hypertension but results from **non-adherence** to therapy or the presence of **secondary causes**[4]

3. **Resistant hypertension** is when **BP remains** not at target despite lifestyle changes and treatment with maximally tolerated doses of a diuretic, a RAS blocker and a calcium channel blocker[7]

Refer to Alsharari R, et al. *J Hum Hypertens* 2022;36:337–340[1]

BP, blood pressure; HTN, hypertension; RAS, renin–angiotensin system; uHTN, uncontrolled hypertension

1. Alsharari R, et al. *J Hum Hypertens* 2022;36:337–340; 2. Viera AJ, et al. *Am Fam Physician* 2009;79:863–869; 3. WHO. Global report on hypertension 2025. Available at https://www.who.int/publications/b/81068 (Accessed April 2026); 4. Mancia G, et al. *J Hypertens* 2023;41:1874–2071; 5. Visco V, et al. *J Hum Hypertens* 2018;32:467–476 ; 6. Prejbisz A, et al. *Arterial Hypertens* 2024;28:91–146 ; 7.McEvoy JW, et al. *Eur Heart J* 2024;45:3912–4018

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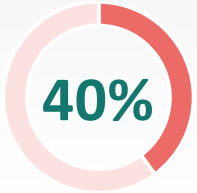
Clinical inertia contributes to high uncontrolled rates, but underlying physiological drivers are also likely to play an important role in difficult-to-control hypertension

~80% of patients with HTN have inadequately controlled HTN, **despite multiple antihypertensive treatment options**[1,2]

Clinical inertia

- **Delayed or absent treatment intensification** is common[3,a]

  Time to intensification:[2,a]



…of US adults with treated, uncontrolled BP were **on monotherapy**[4,b]

despite many patients with HTN requiring ≥2 anti-HTN medications to achieve BP control

→ Suboptimal treatment contributes to high rates of uncontrolled hypertension[2]

Beyond inertia[3,a]

- Inadequately controlled patients had **similar medication profiles** to controlled patients

→ Additional factors, including underlying biological drivers, may contribute to uncontrolled disease[5–7]

[a]Data from the EnligHTN study. EnligHTN analysis of 323,664 patients with HTN treated with ≥2 anti-HTN drugs (2018–2023) across Israel (Meuhedet), Spain (Telotròn), the US (IQVIA EMR + claims) and the UK (CPRD). Patients were classified as inadequately controlled or controlled based on first BP measurement at treatment index. Medication profiles characterised atindex and included the number, classes and duration of anti-HTN medications, as well as the time between prescription changes; [b]Data from the NHANES 2005-2016 study assessing 7,837 patients with complete BP data, self-reported HTN who were taking at least one class of antiHTN.

anti-HTN, antihypertensives; BP, blood pressure; CPRD, Clinical Practice Research Datalink; EMR, electronic medical record; HTN, hypertension

1. McCormack T, et al. Presented at ESC, August 28–31, 2025. Madrid, Spain; 2. NCD Risk Factor Collaboration (NCD-RisC). *Lancet* 2021;398:957–980; 3. McCormack T, et al. *J Hypertens* 2025;43(Suppl 1):58; 4. Derington CG, et al. *Hypertension* 2020;75:973–981; 5. Inoue K, et al. *Hypertension* 2020;76:113–120; 6. Brown JM, et al. *Ann Intern Med* 2020;173:10–20; 7. Townsend R, et al. *Am J Hypertens* 2026;39:161–170

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Hypertension that is difficult to control is associated with poor outcomes

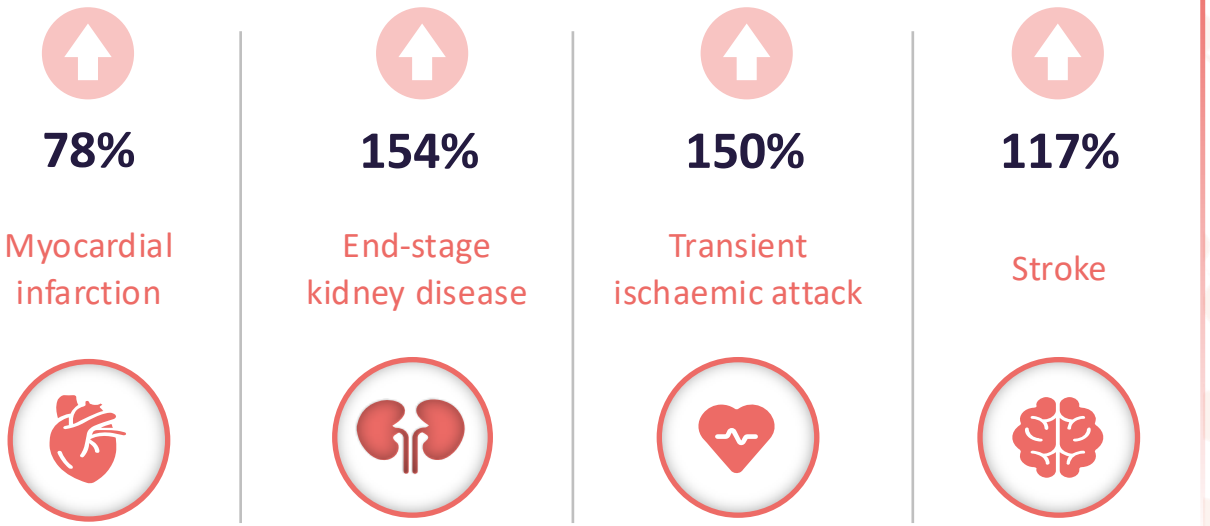
EnligHTN

A multinational, observational, longitudinal cohort study of >240,000 patients with HTN[a]

Patients were classified as inadequately controlled or controlled based on first BP measurement at treatment index

- **Controlled HTN:** first BP measurement at or below BP target[d] while concurrently treated **with ≥2 anti-HTN treatments** for ≥30 days (index date)
- **Inadequately controlled HTN:** first BP measurement above BP target[d] while concurrently treated with ≥2 anti-HTN treatments for ≥30 days (index date)

Patients with uHTN on ≥2 anti-HTN treatments had a higher risk of adverse outcomes compared with those with controlled HTN[a,b,c]



uHTN n=29,130 | **Controlled HTN** n=12,864 | **1–4 years** | **USA**

[a]EnligHTN study is an ongoing multinational, observational, longitudinal cohort study of patients with HTN. Data sources used secondary de-identified claims and EMR data of patients with HTN, Israel (Meuhedet), Spain (Telotròn), the US (IQVIA EMR + claims) and the UK (CPRD). Patient eligibility criteria: included patients aged ≥18 years with a reported diagnosis for HTN between 2018 and 2023 and treatment with ≥2 anti-HTNs. Patients with a record of a secondary cause of HTN were excluded
[b]data shown here from the US cohort of 41,994 patients with HTN. The entire study contained patients from the UK, Spain and Israel.
[c]Adjusted HR and 95% CI for these values: Myocardial infarction: 1.78 (1.48–2.12), End-stage kidney disease: 2.54 (1.79–3.59), Transient ischaemic attack: 2.50 (1.95–3.21), Stroke: 2.17 (1.79–2.64).
[d]BP targets defined as 130/80 mmHg (USA) and 140/90 mmHg (UK, Spain and Israel).
anti-HTN, antihypertensives; BP, blood pressure; CPRD, Clinical Practice Research Datalink; HTN, hypertension; uHTN, uncontrolled hypertension
McCormack T, et al. Presented at ESC, August 29–1 September 2025. Madrid, Spain

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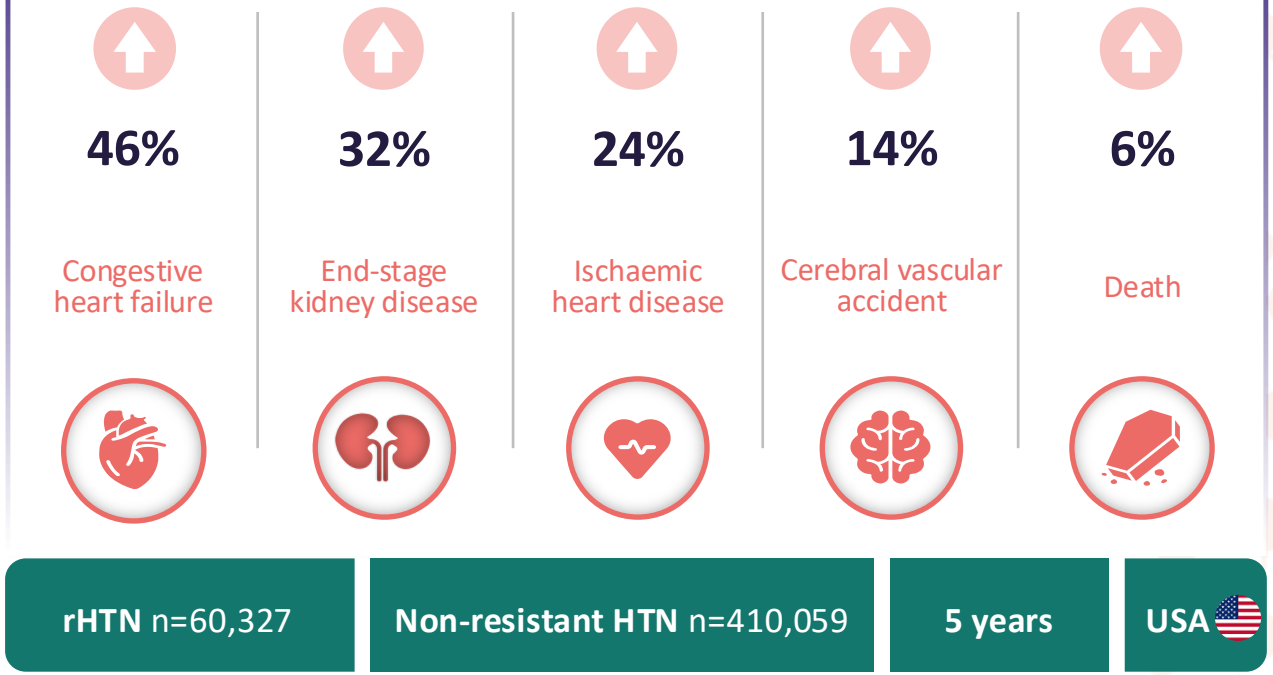
Hypertension that is difficult to control is associated with poor outcomes

A retrospective, longitudinal cohort study[1]

- **rHTN:** SBP ≥140 mmHg and/or DBP ≥90 mmHg while receiving ≥3 anti-HTN drugs, or if prescribed ≥4 anti-HTN drugs regardless of BP control
- All other patients with hypertension were categorised as having **non-resistant HTN**

Patients with rHTN have a **higher risk of poor outcomes** compared with those with non-resistant HTN[1,a]



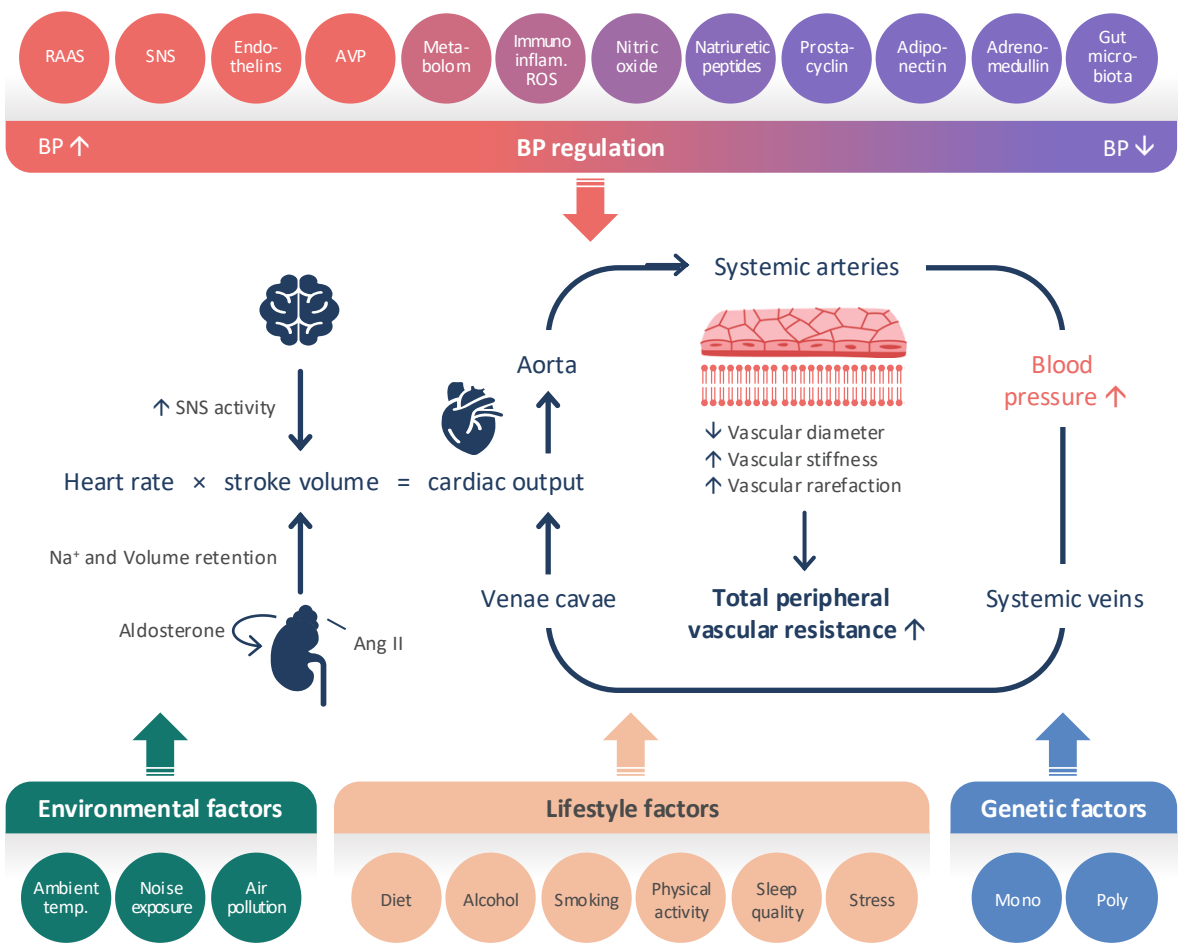
Uncontrolled and resistant hypertension carry a heavy mortality and morbidity burden, underscoring the need for improved management[1,2]

[a]Adjusted HR and 95% CI for these values: Congestive heart failure: 1.46 (1.40–1.52), End-stage kidney disease: 1.32 (1.27–1.37), Ischaemic heart disease: 1.24 (1.20–1.28), Cerebral vascular accident: 1.14 (1.10–1.19) and Death: 1.06 (1.03–1.08)
anti-HTN, antihypertensives; BP, blood pressure; DBP, diastolic blood pressure; HTN, hypertension; rHTN, resistant hypertension; SBP, systolic blood pressure

1. Sim JJ, et al. *Kidney Int* 2015;88:622–632; 2. McCormack T, et al. Presented at ESC, August 29–1 September 2025. Madrid, Spain

Think Aldo

The pathophysiology of hypertension involves many drivers and complex interactions, some of which are targeted by current treatment options



Targets of guideline-directed lifestyle interventions and medical therapy[1]

Physical activity changes[2]
- Increase daily physical activity
- Avoid sedentary lifestyle
- Isometric resistance exercise training

Lifestyle changes[2]
- Increase potassium intake
- Reduce salt intake
- Reduce alcohol intake
- No smoking

→ **Key drivers of hypertension[1]**
- Genetic factors
- Environmental factors
- Behavioural factors
- Socioeconomic and psychosocial factors

	→ **Key mechanisms of hypertension[3]**
Calcium channel blockers[3]	Vasoconstriction
Diuretics[3]	Sodium and fluid retention
Beta blockers[3]	SNS activation
ACEi or ARBs[3]	RAS pathway activation
MRAs[3]	Aldosterone action
Aldosterone production is not fully addressed at its source with current treatment options[1,4]	Circulating aldosterone

Refer to Mancia G, et al. *J Hypertens* 2023;41:1874–2071[1]

ACEi, angiotensin-converting enzyme inhibitor; Ang II, angiotensin II; ARB, angiotensin II receptor blocker; AVP, arginine vasopressin; BP, blood pressure; MRA, mineralocorticoid receptor antagonist; RAAS, renin–angiotensin–aldosterone system; RAS, renin–angiotensin system; ROS, reactive oxygen species; SNS, sympathetic nervous system

1. Mancia G, et al. *J Hypertens* 2023;41:1874–2071; 2. WHO. Global report on hypertension 2025. Available at https://www.who.int/publications/b/81068 (Accessed April 2026); 3. Ojha U, et al. *Am J Cardio Drugs* 2022;22:271–285; 4. McEvoy JW, et al. *Eur Heart J* 2024;45:3912–4018

Think Aldo

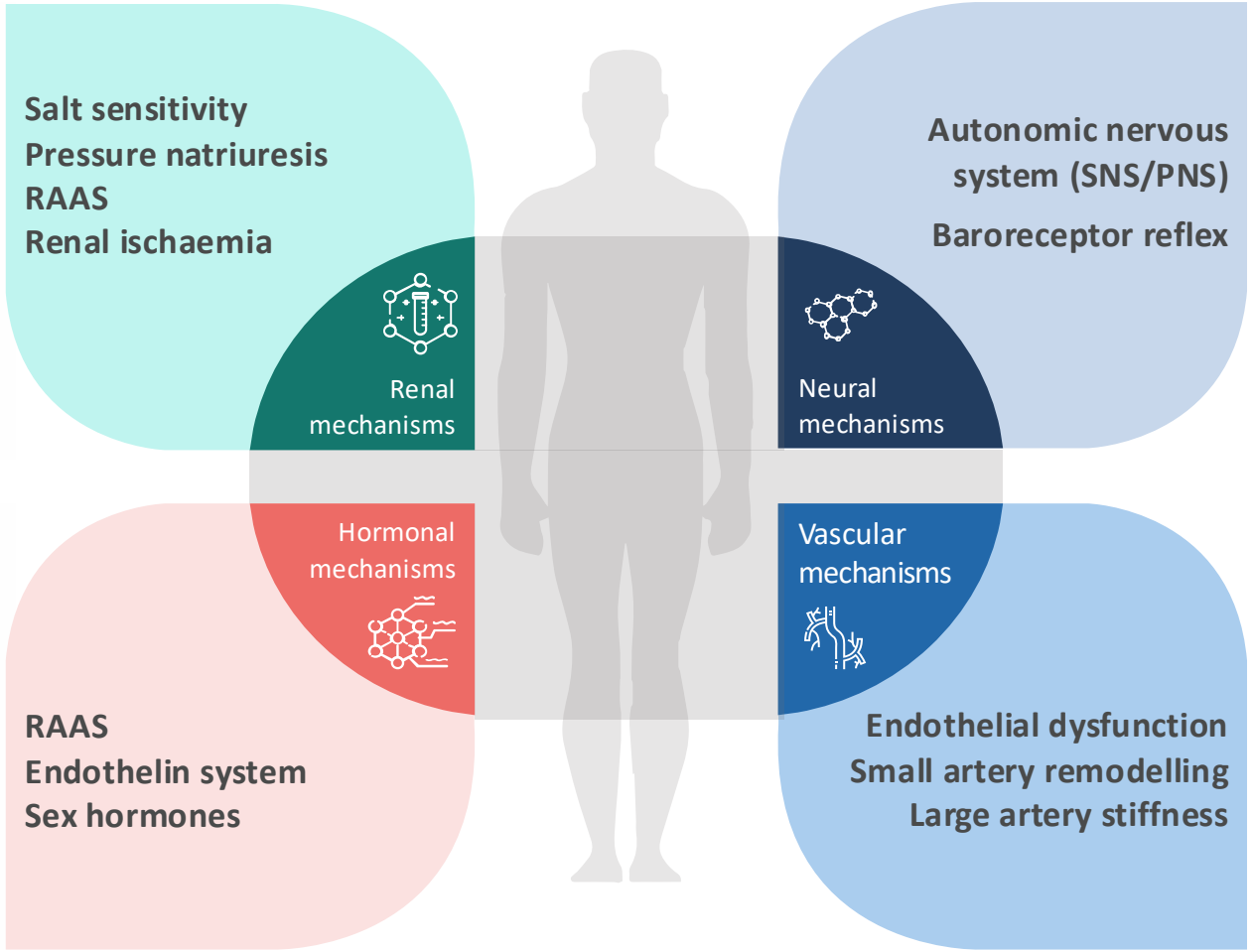
The pathophysiology of hypertension involves complex interactions

Genetic factors

- Biological sex
- BP-associated SNPs
- Monogenic forms of hypertension
- Epigenetic and foetal programming

Environmental factors

- Geopolitical status
- Noise pollution
- Air pollution
- Climate



Behavioural factors

- Physical activity
- Sedentary behaviour
- Sleep quality/quantity
- Dietary patterns
- Sodium and potassium intake
- Obesity
- Alcohol consumption
- Drugs or substances that increase BP

Socioeconomic and psychosocial factors

- Stress
- Low socioeconomic status
- Social deprivation
- Healthcare access
- Gender identity, roles and norms
- Gender-based violence
- Discrimination

Refer to McEvoy JW, et al. *Eur Heart J* 2024;45:3912–4018

Could underlying pathophysiological mechanisms contribute to hypertension that remains difficult to control in some patients?

BP, blood pressure; PNS, parasympathetic nervous system; RAAS, renin–angiotensin–aldosterone system; SNP, single nucleotide polymorphism; SNS, sympathetic nervous system

McEvoy JW, et al. *Eur Heart J* 2024;45:3912–4018

Aldosterone as a driver of hypertension

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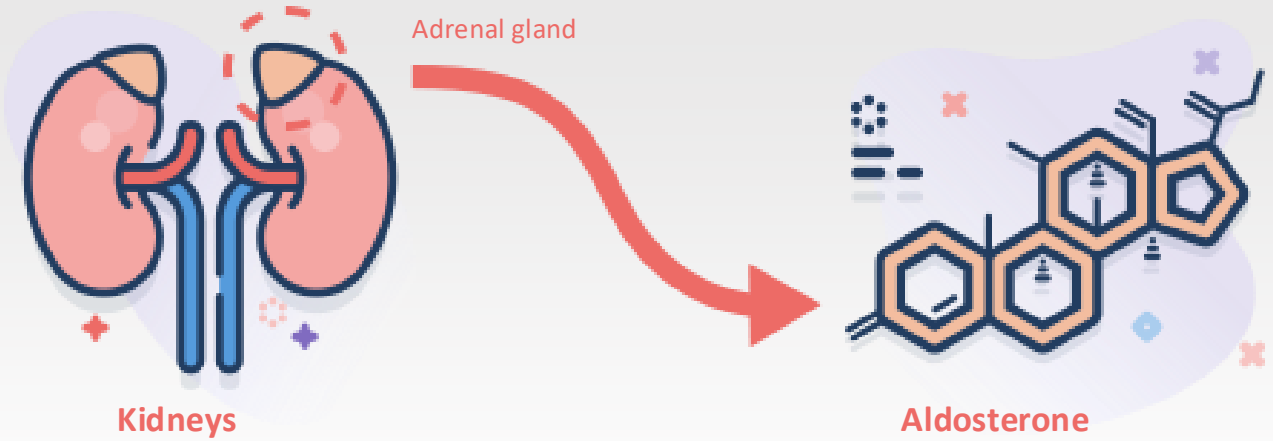
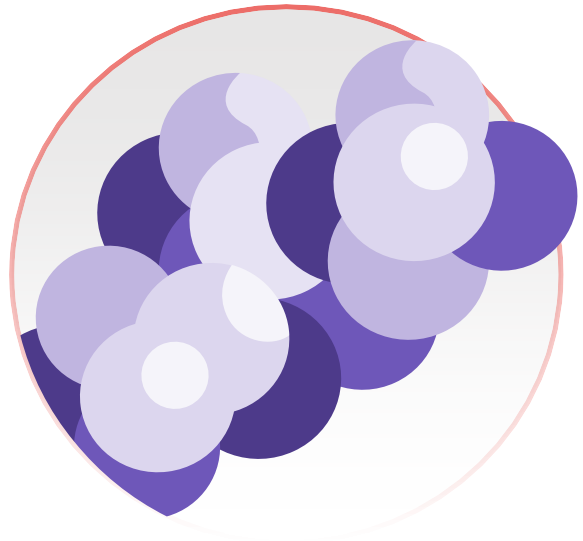
Aldosterone is a mineralocorticoid produced by the adrenal cortex





Aldosterone is a **mineralocorticoid** produced by **aldosterone synthase** (CYP11B2) in the **zona glomerulosa cells** in the **adrenal cortex**[1]

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

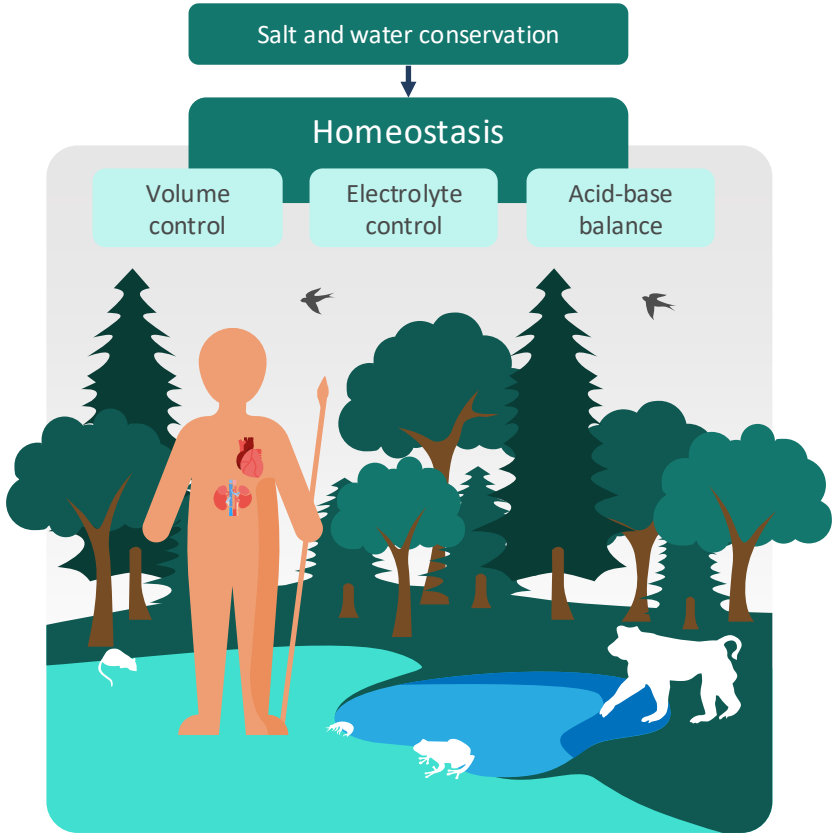
BP, blood pressure

1. Ekman N, et al. *Int J Mol Sci* 2025;26:540; 2. Brown JM, et al. *J Am Heart Assoc* 2024;13:e030142

Think Aldo

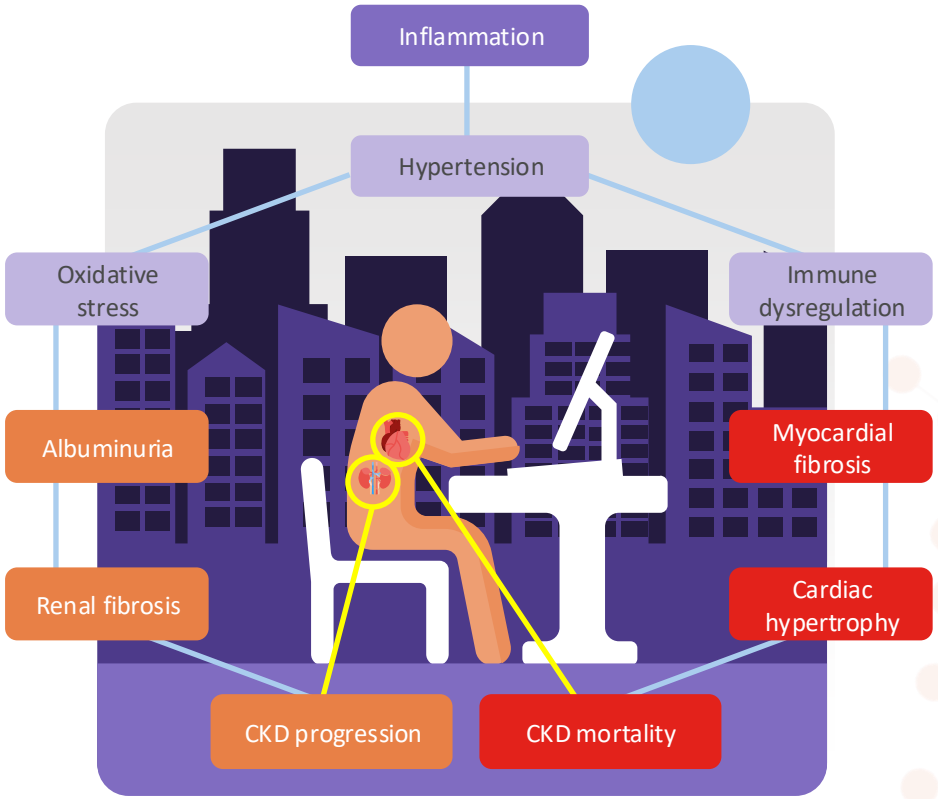
The role of aldosterone is defined by the environment

Low dietary sodium environment



In land vertebrates, the maintenance of fluid and electrolyte homeostasis is **fundamental for survival**[1,2]

High dietary sodium environment



However, in the context of modern sodium-rich diets, the role of aldosterone has become **maladaptive**[1,2]

Aldosterone

Refer to Strizzi CT, et al. *Int J Mol Sci* 2025;26:8829[1]

1. Strizzi CT, et al. *Int J Mol Sci* 2025;26:8829; 2. Vaidya A, et al. *Endocr Rev* 2018;39:1057–1088

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Inadequate aldosterone suppression in the context of high dietary sodium intake drives risk

In normal regulation:[1,2]

1. ↑ Dietary sodium intake
2. ↓ Renin activity
3. ↓ Aldosterone levels

In the context of the **modern high-sodium diet**, failure to appropriately downregulate aldosterone can synergistically contribute to hypertension and cardio-kidney disease[3–5]

The global mean salt intake of adults is **more than double** the WHO's **recommendation** for adults[3]

Together, high dietary sodium intake and inappropriate aldosterone production increase CV and kidney damage in the body[5]

CV, cardiovascular; WHO, World Health Organization

1. Scott JH, et al. Physiology, aldosterone. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2023; 2. Schweda F. *Pflugers Arch* 2015;467:565–576; 3. WHO. Sodium reduction. Available at: https://www.who.int/news-room/fact-sheets/detail/sodium-reduction (Accessed April 2026); 4. Acelajado MC, et al. *Hypertension* 2010;56:804–805; 5. Chen L, et al. *Horm Metab Res* 2024;56:99–106

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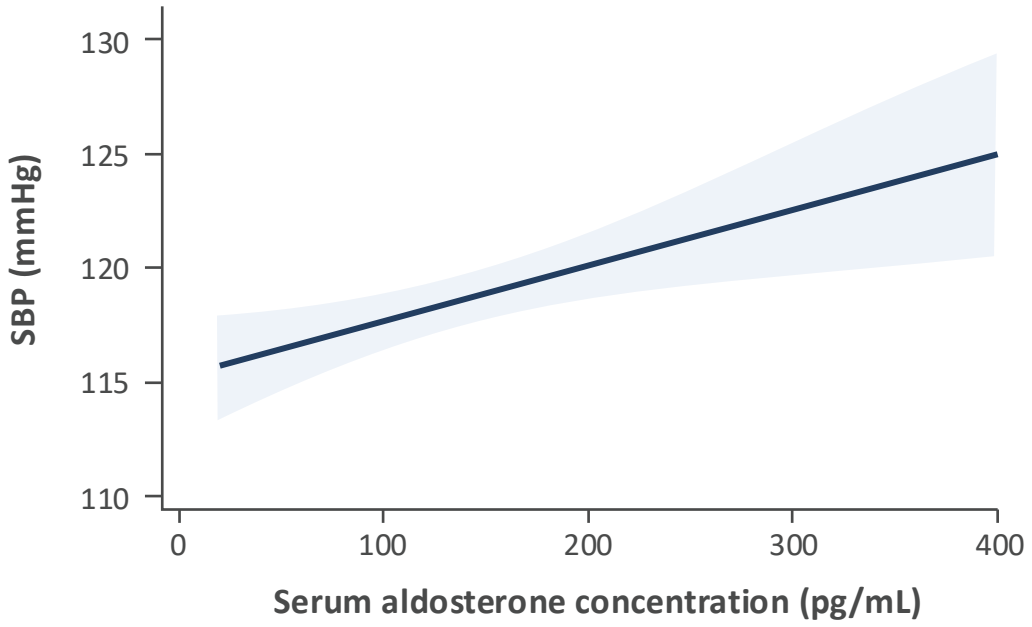
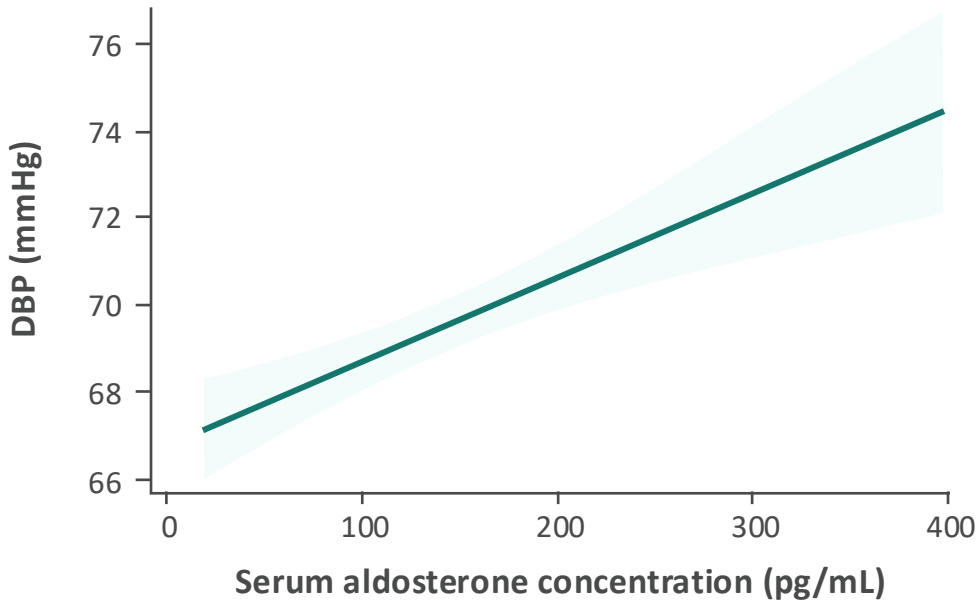
Higher levels of aldosterone drive increased blood pressure and hypertension risk

Association between serum aldosterone concentrations and BP at baseline[a,b]

Systolic[1]



Diastolic[1]



Refer to Inoue K, et al. *Hypertension* 2020;76:113–120:Online Supplement

Prospective, longitudinal cohort study of 948 adults (aged 46–88 years) from MESA[2]

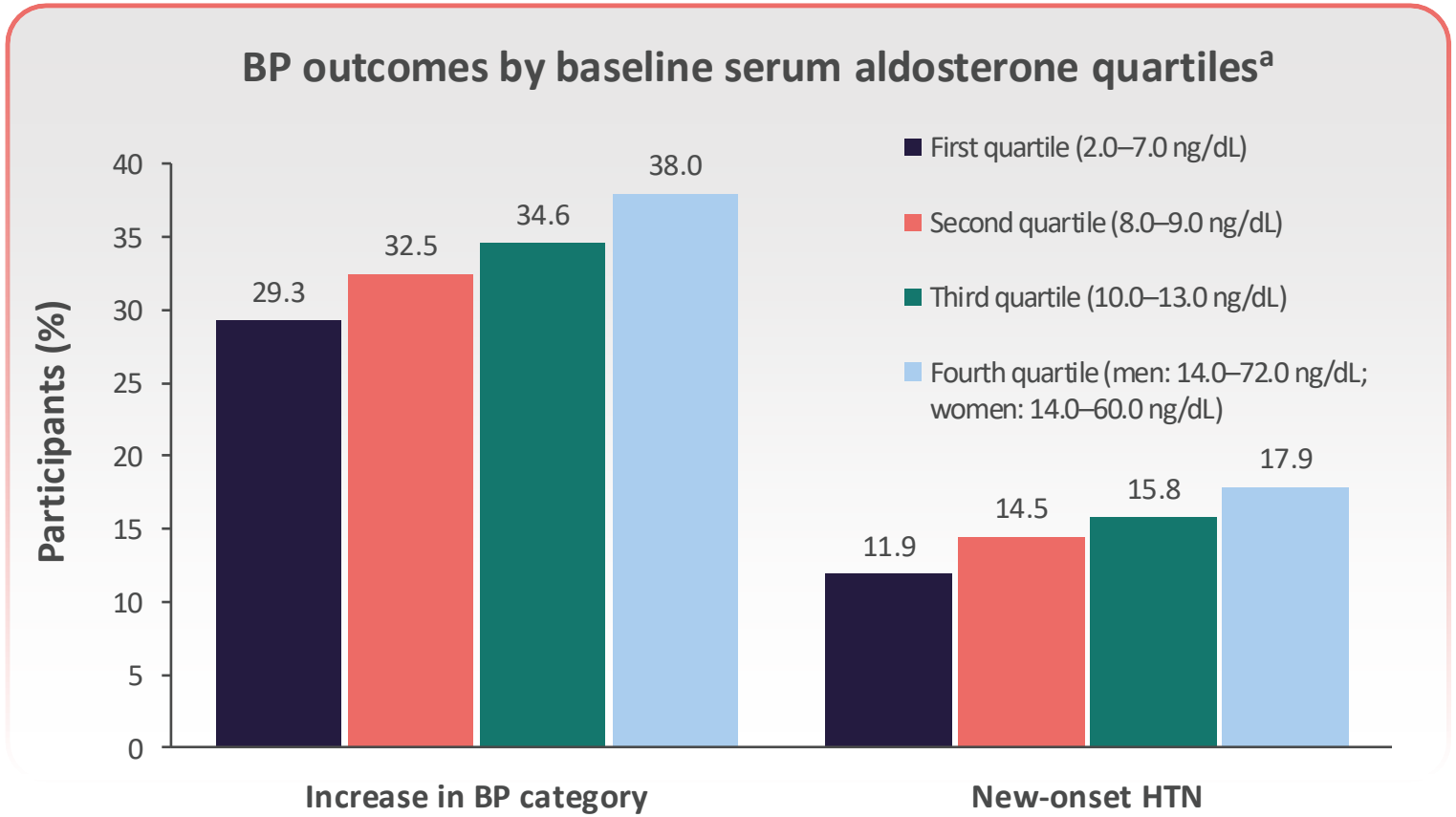
[a]Study included 948 US adults (46–88 years of age) from the multicentre longitudinal cohort MESA, recruited between July 2000 and August 2002, with follow-up through July 2015. Participants had measurements of serum aldosterone collected and had not taken anti-HTN medications. Results displayed represent the cohort of 700 participants who had follow-up coronary computed tomography scans[2]; [b]Adjusted for age, sex, CAC at exam 2 or 3, race, education, insurance status, income, smoking status, alcohol intake, physical activity, statin prescription, BMI, LDL, serum and urinary potassium, serum and urinary sodium, and plasma renin activity[1]

anti-HTN, antihypertensives; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcium; DBP, diastolic blood pressure; LDL, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; SBP, systolic blood pressure

1. Inoue K, et al. *Hypertension* 2020;76:113–120:Online Supplement 2. Inoue K, et al. *Hypertension* 2020;76:113–120

Think Aldo

Higher levels of aldosterone are positively correlated with increased BP and hypertension risk



Risk across quartiles[b]

- Increase in BP category:[c] ↑ **16%**
  Adjusted OR (95% CI): 1.16 (1.06, 1.27); P=0.002
- New-onset hypertension:[d] ↑ **17%**
  Adjusted OR (95% CI): 1.17 (1.02, 1.34); P=0.03

People with the **highest levels of aldosterone** were **more likely** to develop **high BP** or hypertension than those with the lowest levels

Refer to Vasan RS, et al. *N Engl J Med* 2004;351:33–41

[a]Patients with normal BP at baseline (N=1688) evaluated in the Framingham Offspring Study (1998–2001) to assess the age- and sex-adjusted incidence of increased BP and new-onset hypertension after approximately 4 years of follow-up. Mean aldosterone levels per quartile were evaluated for both men (n=717) and women (n=971). Mean aldosterone levels per quartile (ng/dL; men/women): quartile 1: 5.6/5.5, quartile 2: 8.5/8.5, quartile 3: 11.2/11.5, quartile 4: 19.1/18.9; [b]Risk adjusted for age, sex, baseline BP category, BP (systolic and diastolic), heart rate, BMI, percentage weight gain, diabetes and smoking status; [c]Defined as an increase of at least one BP category according to the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure;[d]Defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg or anti-HTN medication use
anti-HTN, antihypertensives; BMI, body mass index; BP, blood pressure; CI, confidence interval; HTN, hypertension; OR, odds ratio
Vasan RS, et al. *N Engl J Med* 2004;351:33–41

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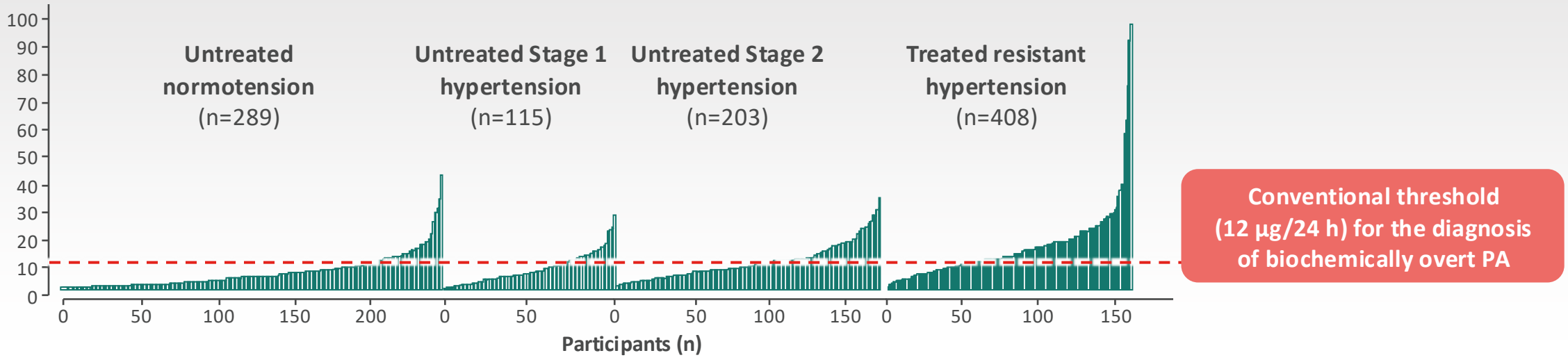
Inappropriate aldosterone production is an overlooked driver of uncontrolled hypertension

Every BP category had a **continuum of renin-independent aldosterone production**, where **greater severity** of production was associated with **higher BP**

US cross-sectional study:

Distribution of renin-independent aldosterone production by BP category[a,b]



Refer to Brown JM, et al. *Ann Intern Med* 2020;173:10–20

[a]The study pooled five study protocols from four distinct sites across the US (Birmingham, Alabama; Boston, Massachusetts; Charlottesville, Virginia; and Salt Lake City, Utah). Participants completed an oral sodium suppression test, regardless of aldosterone or renin levels, as a confirmatory diagnostic for PA and to quantify the magnitude of renin-independent aldosterone production. Urinary aldosterone was measured in participants in high sodium balance with suppressed renin activity. Biochemically overt PA was diagnosed when urinary aldosterone levels were higher than 12µg/24 h; [b]The unadjusted urinary aldosterone excretion rate in the context of high sodium balance and renin suppression. Vertical bars represent the unadjusted renin-independent aldosterone excretion rate (y-axis) for each individual participant, ordered from lowest to highest (x-axis)

BP, blood pressure; PA, primary aldosteronism

Brown JM, et al. *Ann Intern Med* 2020;173:10–20

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Aldosterone levels should be considered when hypertension is not responding well to current therapies

Considering the role that elevated levels of aldosterone plays in the underlying pathophysiology is important for the management of patients with hypertension who are reasonably adherent to therapy yet remain uncontrolled[1–3]

Guidelines acknowledge **elevated levels of aldosterone** as an **important contributor across wider hypertension**, not only in difficult-to-control cases[4–7]

Complications of aldosterone excess in HTN[8]

- Sodium reabsorption
- Impaired vasorelaxation
- Inflammation/fibrosis
- Vascular stiffness

BP-lowering effects of competitive aldosterone antagonist therapies

- Steroidal MRAs have been shown to have an effect in lowering BP in patients with hypertension[9]

Continue to Module 2 now!

BP, blood pressure, HTN, hypertension; MRA, mineralocorticoid receptor antagonist

1. Bakris G, et al. *J Clin Hypertens (Greenwich)* 2023;25:737–747; 2. Viera AJ, et al. *Am Fam Physician* 2009;79:863–869; 3. Stevens TM, et al. *Ann Hypertens* 2018;1:1005; 4. Adler GK, et al. *J Clin Endocrinol Metab* 2025;110:2453–2495; 5. Dogra P, et al. *Mayo Clin Proc* 2023;98:1207–1215; 6. Cohen JB, et al. *Ann Intern Med* 2020;174:289–297; 7. Liu Y, et al. *JAMA Surg* 2021;156:541–549; 8. Ananda R, et al. *Metabolites* 2025;15:553; 9. Kobayashi M, et al. *Eur Heart J* 2025;46:2618–2642

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