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Session Title

The Spectrum of Primary Aldosteronism: Challenges in the Diagnosis and Management

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Speaker's affiliation: King Chulalongkorn Memorial Hospital, Thai Red Cross Society, and Faculty of Medicine, Chulalongkorn University

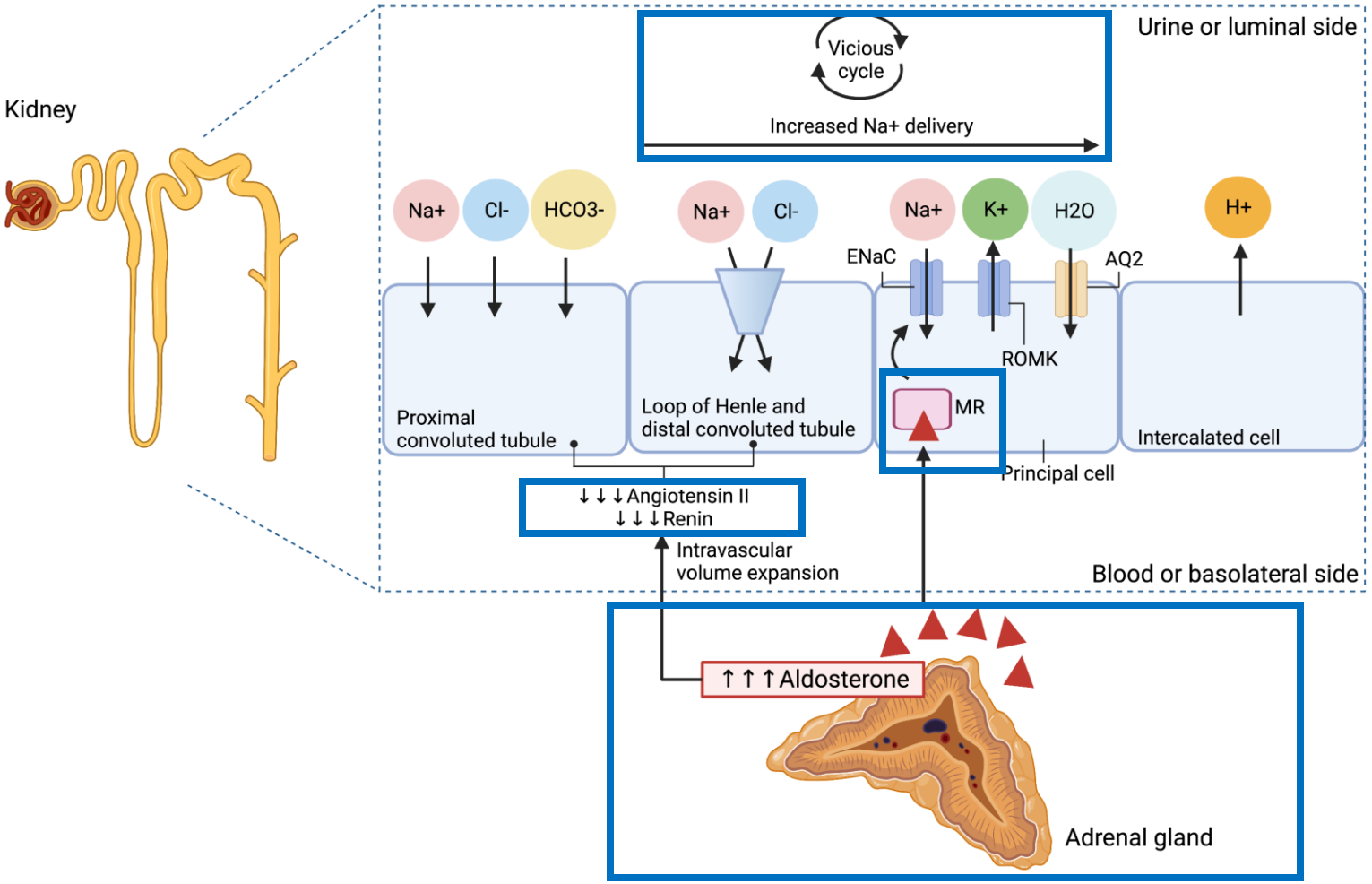
Outline

Part I: Clinical Presentations & Case Detection

Part II: The Continuum of Renin-Independent Aldosteronism and Clinical Relevance

Part I: Clinical Presentations & Case Detection

Pathophysiologic Renin-Independent Aldosteronism



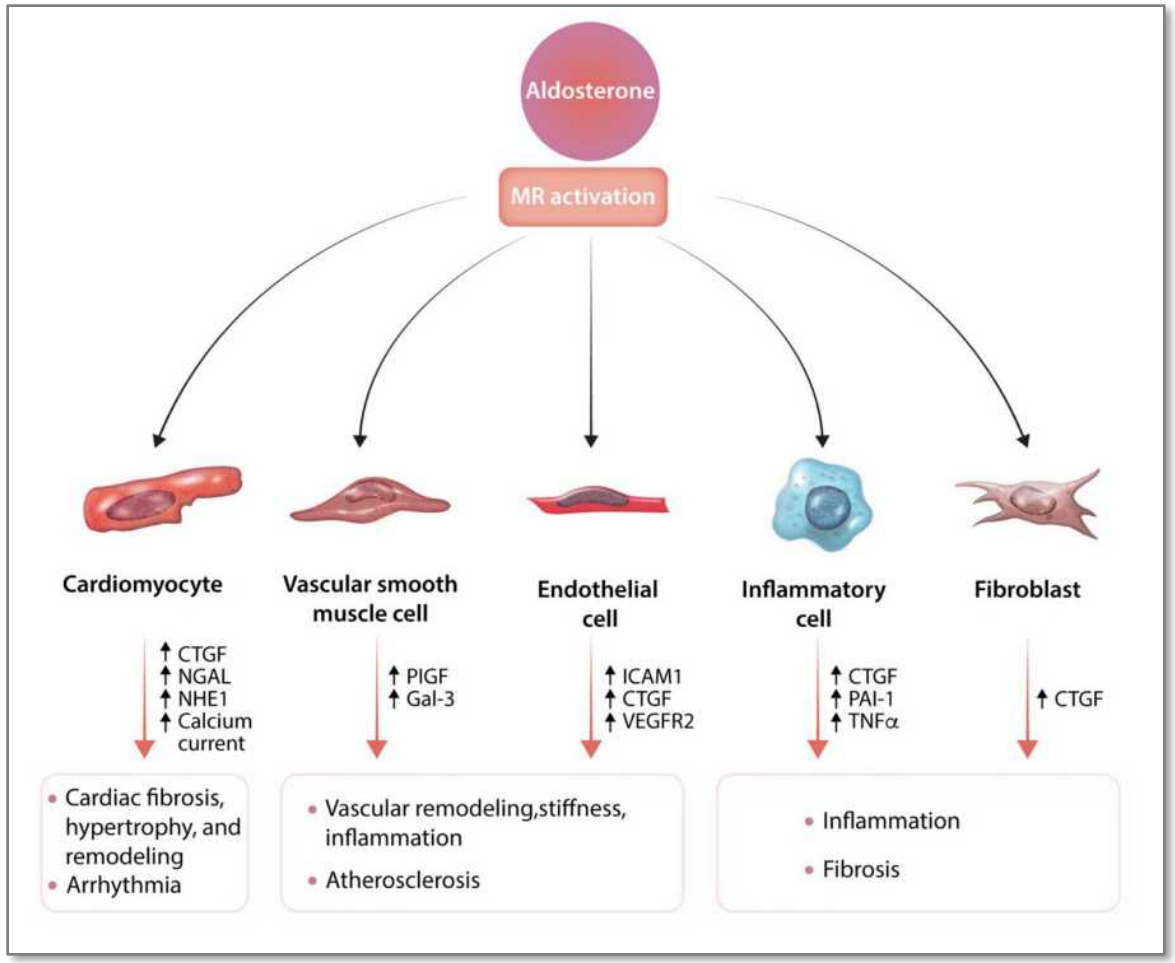
MR, mineralocorticoid receptor; ROMK, renal outer medullary potassium channel

Adapted from Turcu AF et al. Nat Rev Endocrinol 2022. PMID: 36045149.

Hallmark Biochemical Diagnosis

- **Renin suppression AND**
- **Inappropriate/dysregulated/non-suppressible aldosterone production**

Excess aldosterone/mineralocorticoid receptor activation causes deleterious effects on the CV/renal system



Direct effect

↑ Blood pressure/ Hypertension

↑ Cardiovascular events & mortalities/end-stage kidney disease

Image from Parksook WW, Williams GH. Cardiovasc Res 2022. PMID: 35388416; Brown JM. J Am Heart Assoc 2024. PMID: 38497438.

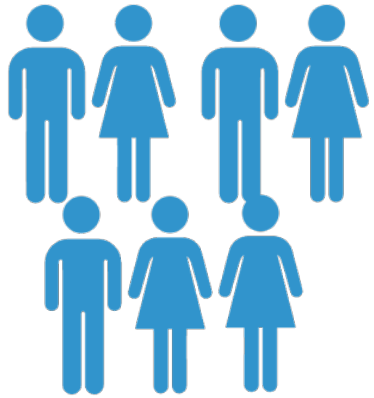
Primary aldosteronism patients had increased CV events and target organ damage than essential hypertension

31 studies
Median time = 8.8 years

Primary Aldosteronism

n= 3838

Essential Hypertension



n= 9284

⇧ Stroke, CAD, AF, HF, risk of diabetes, metabolic syndrome, LVH

CAD, coronary artery disease; AF, atrial fibrillation; HF, heart failure; LVH, left ventricular hypertrophy

Monticone S et al. Lancet Diabetes Endocrinol 2018. PMID: 29129575.

Multiple large observational studies have shown that **PA-specific treatment mitigated CV outcomes**.

Hundemer GL et al. JAMA Cardiol 2018. PMID: 30027227; Hundemer GL et al. Lancet Diabetes Endocrinol 2018. PMID: 29129576; Rossi GP et al. Hypertension 2013. PMID:23648698; Wu VC et al. Eur J Endocrinol 2021. PMID: 34851859; Hundemer GL et al. Hypertension 2018. PMID: 29987110.

In patients WITHOUT overt PA, treatment with MR blockade has shown benefits for CV/kidney outcomes in large clinical trials

RALES, 1999

THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

BERTRAM PITT, M.D., FAIEZ ZANNAD, M.D., WILLEM J. REMME, M.D., ROBERT CODY, M.D., ALAIN CASTAIGNE, M.D., ALFONSO PEREZ, M.D., JOLIE PALENSKY, M.S., AND JANET WITTES, PH.D., FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS*

EPHESUS, 2003

Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction

Bertram Pitt, M.D., Willem Remme, M.D., Faiez Zannad, M.D., James Neaton, Ph.D., Felipe Martinez, M.D., Barbara Roniker, M.D., Richard Bittman, Ph.D., Steve Hurley, B.S., Jay Kleiman, M.D., and Marjorie Gatlin, M.D., for the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators*

EMPHASIS HF, 2011

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D., and Bertram Pitt, M.D., for the EMPHASIS-HF Study Group*

REMINDER, 2014

Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: The Randomized Double-Blind Reminder Study

FIDELIO, 2020

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*

FIGARO, 2021

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

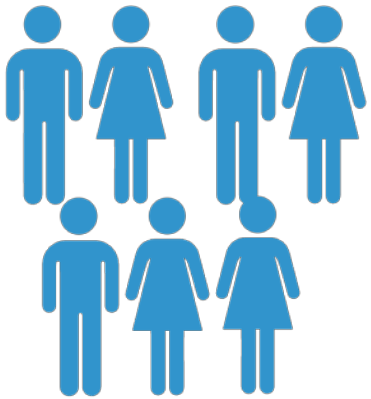
B. Pitt, G. Filippatos, R. Agarwal, S.D. Anker, G.L. Bakris, P. Rossing, A. Joseph, P. Kolkhof, C. Nowack, P. Schloemer, and L.M. Ruilope, for the FIGARO-DKD Investigators*

PA, primary aldosteronism; MR, mineralocorticoid receptor

Diagnosing Primary Aldosteronism

"**Categorical construct**" – binary disease (PA & no PA)

Population



Screening Test

Plasma/Urine aldosterone
Renin
ARR

Aldosterone Suppression Test

e.g., oral sodium loading,
Saline suppression test

DIAGNOSTIC THRESHOLDS

Overt PA

No PA

ARR, aldosterone-to-renin ratio; PA, primary aldosteronism

Estimating the Prevalence of Primary Aldosteronism

“Categorical construct”

Less stringent cutoffs

e.g., PAC ≥10 ng/dL

More stringent cutoffs

e.g., PAC ≥20 ng/dL

PAC, plasma aldosterone concentration

Primary Aldosteronism as a Binary Disease

Pros: Pragmatic

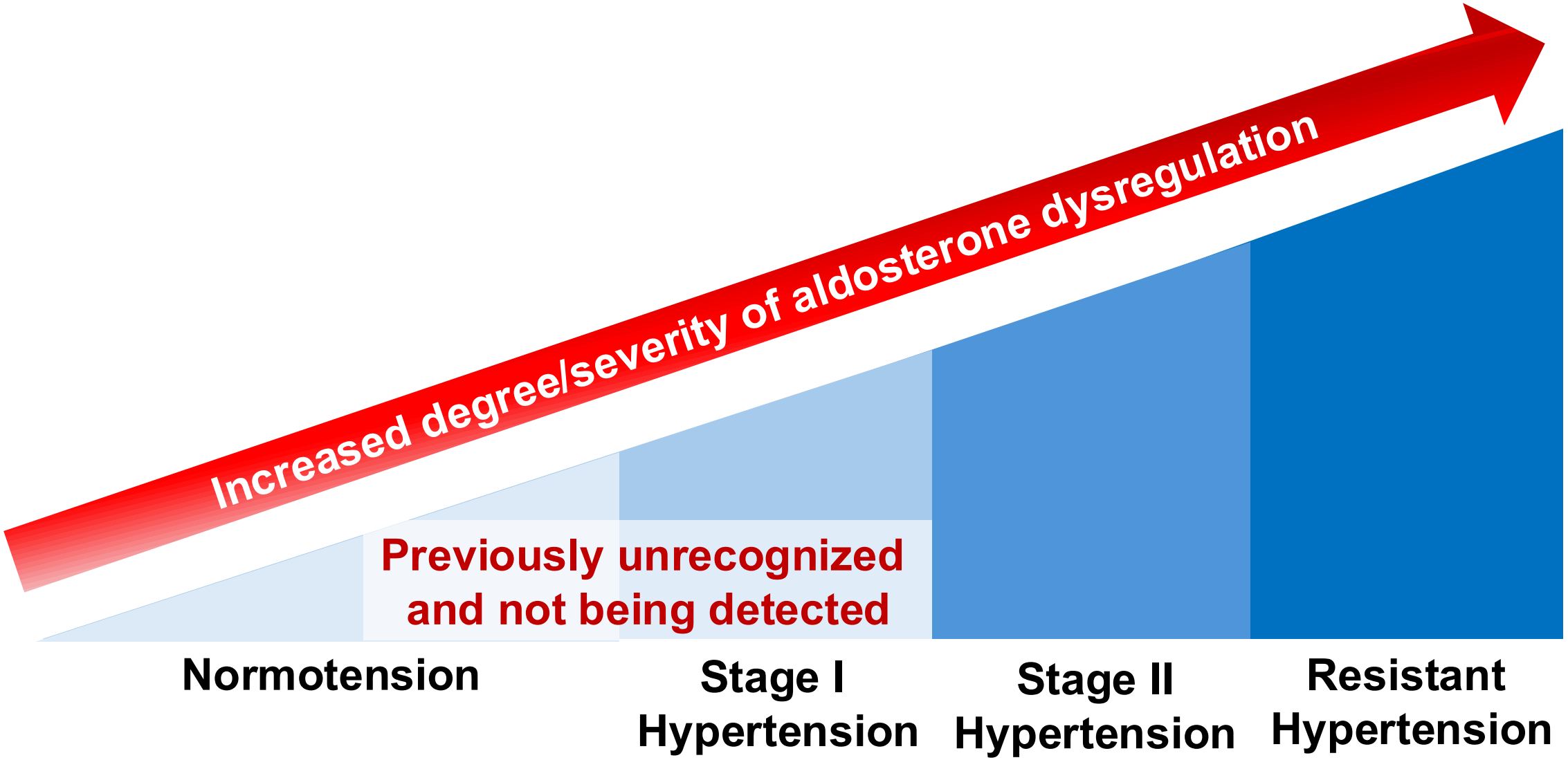
Cons: Arbitrary cutoffs and may not capture patients with milder disease

ARR, aldosterone-to-renin ratio; PAC, plasma aldosterone concentration

Naruse M et al. Eur J Endocrinol 2023. PMID: 36726325.

Primary Aldosteronism as a Continuum?

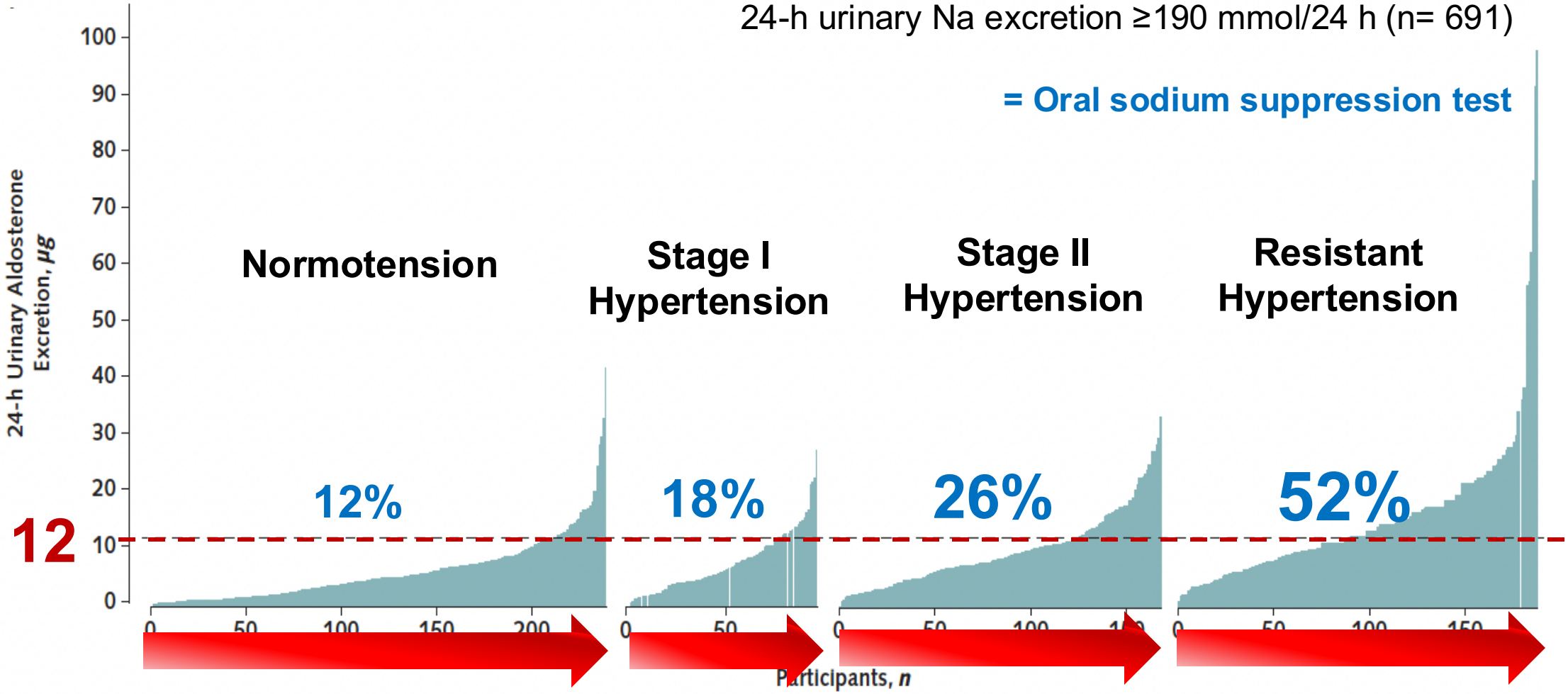
Continuum of Renin-Independent Aldosteronism



Primary aldosteronism exists across a broad continuum

All participants had suppressed renin &
24-h urinary Na excretion ≥190 mmol/24 h (n= 691)

= Oral sodium suppression test



Brown JM et al. Ann Intern Med 2020. PMID: 32449886.

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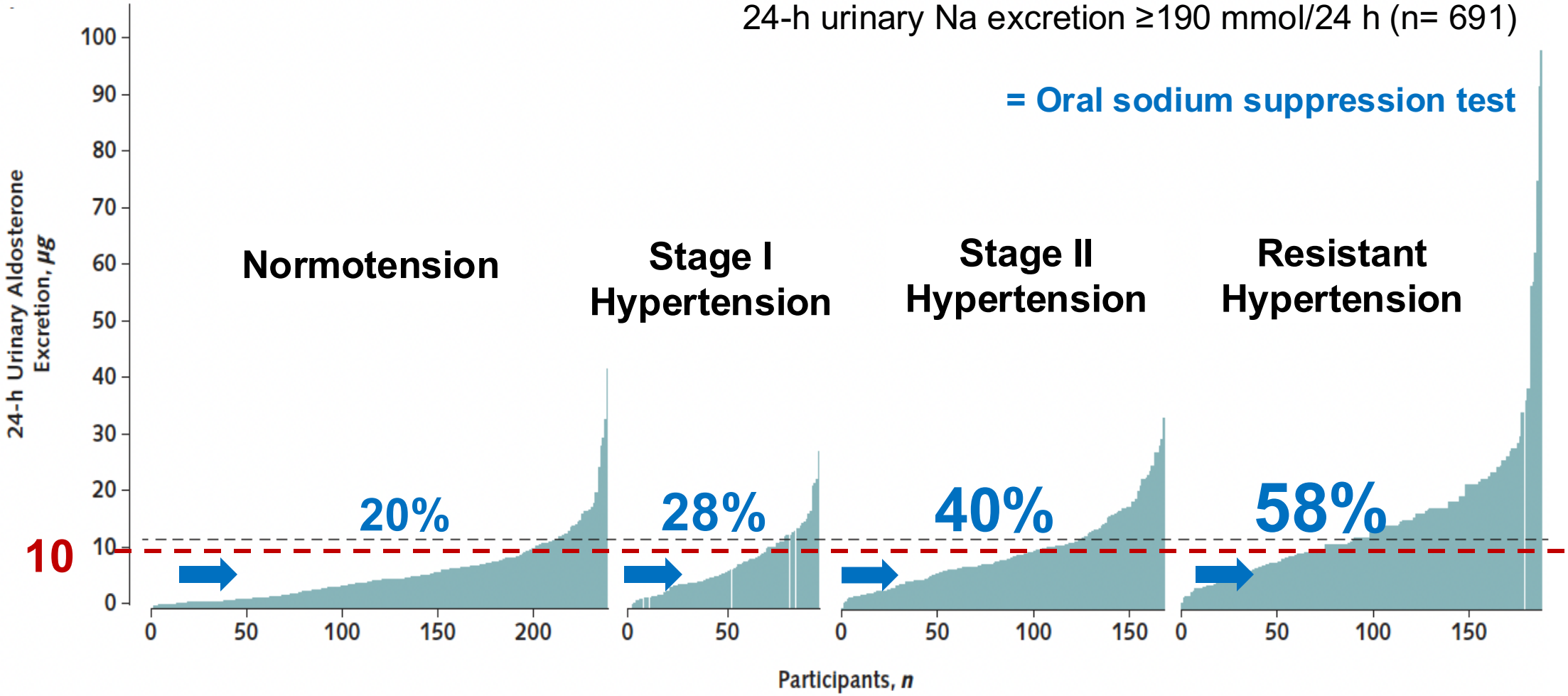
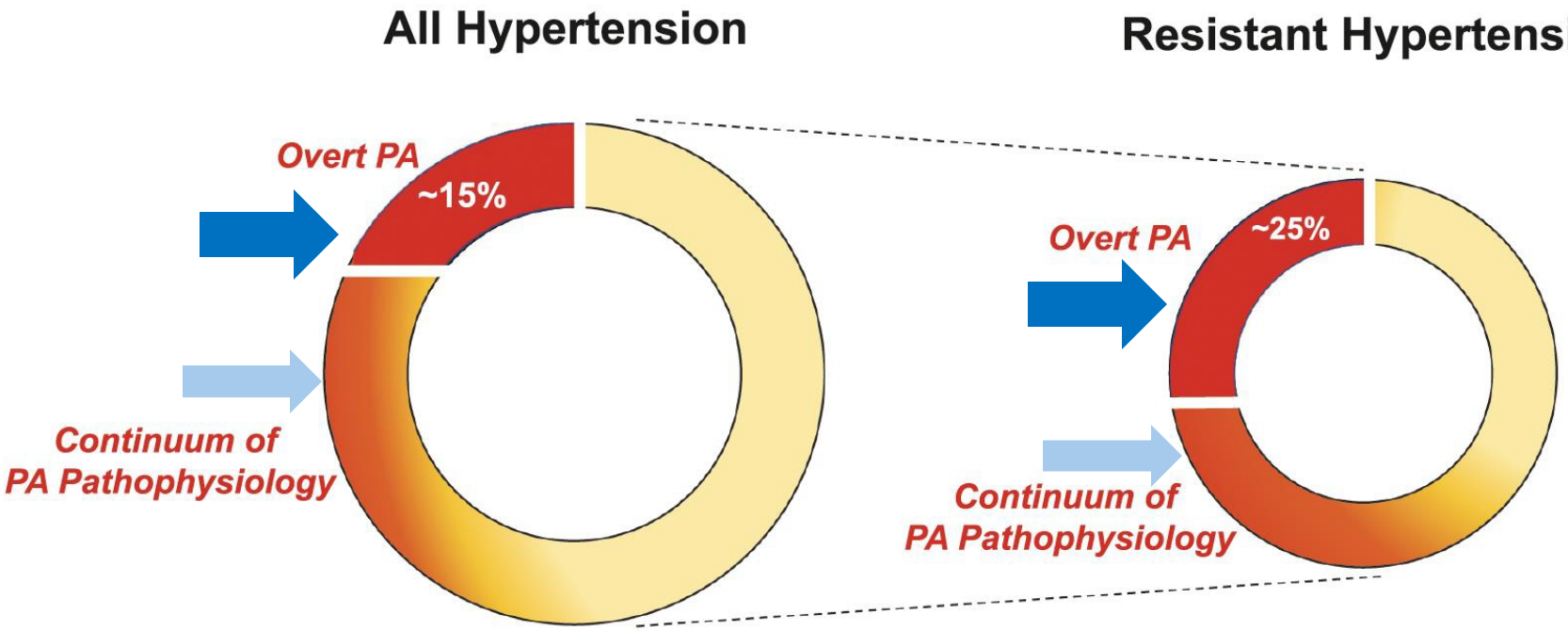


Brown JM et al. Ann Intern Med 2020. PMID: 32449886.

Prevalence of Primary Aldosteronism



Other groups with high prevalence, e.g.,

- Hypertension with hypoK
- Hypertension with AF
- Young adults (<40 YO)
- BP ≥160/100 mmHg (≥ Grade 2 hypertension)

Image from Vaidya A et al. Am J Hypertens 2022. 1. Brown JM. Ann Intern Med 2020; 2. Sinclair AM et al. Arch Intern Med 1987; 3. Vasan RS et al. N Engl J Med 2004; 4. Markou A et al. J Clin Endocrinol Metab 2013; 4. Baudrand R et al. Hypertension 2017; 5. Inoue K et al. Hypertension 2020; 6. Monticone S et al. J Am Coll Cardiol 2017; 7. Baudrand R et al. J Clin Endocrinol Metab 2016.

Recent guidelines broaden screening indications from high-risk groups to all hypertensives.

Hypertension Guidelines: ESC 2024, AHA ACC 2025

★ Recommend screening in all hypertensives.

Recent Hypertension Guidelines

Recommendations for Primary Aldosteronism		
COR	**LOE**	**Recommendations**
1	**C-EO**	1. In adults with hypertension, screening for primary aldosteronism is recommended in the presence of any of the following conditions to increase rates of detection, diagnosis, and specific targeted therapy: resistant hypertension (regardless of whether hypokalemia is present), hypokalemia (spontaneous or diuretic induced), OSA, incidentally discovered adrenal mass, family history of early-onset hypertension, or stroke at a young age (<40 years).
2b	**C-EO**	2. In adults with stage 2 hypertension, screening for primary aldosteronism may be considered to increase rates of detection, diagnosis, and specific targeted therapy.

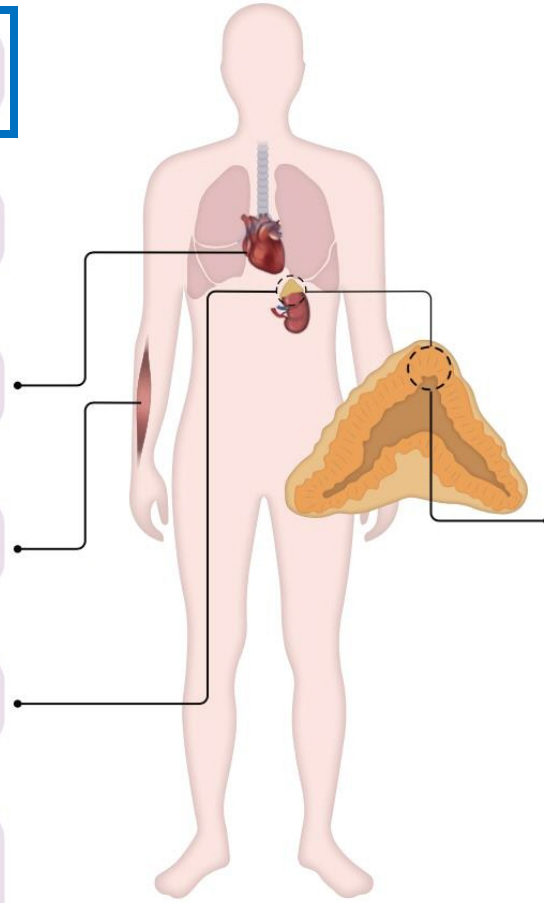
Growing evidence supports that primary aldosteronism occurs across the full breadth of hypertension severity, with higher prevalence of primary aldosteronism as the severity of hypertension increases.[3,10] The prevalence of primary aldosteronism is approximately 5% to 10% among individuals with stage 1 hypertension and 11% to 22% among individuals with stage 2 hypertension, which varies depending on the modality of testing and testing thresholds used to diagnose primary aldosteronism.[3,10] The prevalence of primary aldosteronism may be similar among individuals with stage 2 hypertension and those with resistant hypertension.[3] Studies from Australia and Japan

Jones DW et al. AHA ACC Guideline. Hypertension 2025. PMID: 40811516.

Recent Hypertension Guidelines

Signs and symptoms

- Mostly asymptomatic
- Spontaneous or diuretic-provoked hypokalaemia
- AF
- Disproportionate HMOD
- Muscle weakness and tetany
- Adrenal incidentaloma
- Family history of primary aldosteronism, early onset hypertension and/or stroke



Does the patient have any of the following conditions associated with secondary HTN?

- Drug-resistant/induced HTN
- Abrupt onset of HTN
- Onset of HTN at <30 y
- Exacerbation of previously controlled HTN
- Disproportionate TOD for degree of HTN
- Accelerated/malignant HTN
- Onset of diastolic HTN in older adults (age ≥65 y)
- Unprovoked or excessive hypokalemia
- Insomnia or daytime sleepiness
- Concomitant adrenal nodule
- History of early-onset stroke
- Family history of primary aldosteronism

YES

Screen for primary aldosteronism and other secondary forms of HTN [1]

Image adapted from 1. McEvoy JW et al. Eur Heart J 2024. PMID: 39210715; 2. Jones DW et al. AHA ACC Guideline. Hypertension 2025. PMID: 40811516.

Wrap Up #1

- PA occurs across diverse clinical presentations.
- Prevalence increases with BP severity.
- Patients with mild clinical symptoms
  - e.g., mild hypertensives without hypokalemia, were previously undetected and unrecognized, thus missing the chance to receive appropriate/curative treatment.

Part II: The Continuum of Renin-Independent Aldosteronism and Clinical Relevance

Continuum of Renin-Independent Aldosteronism

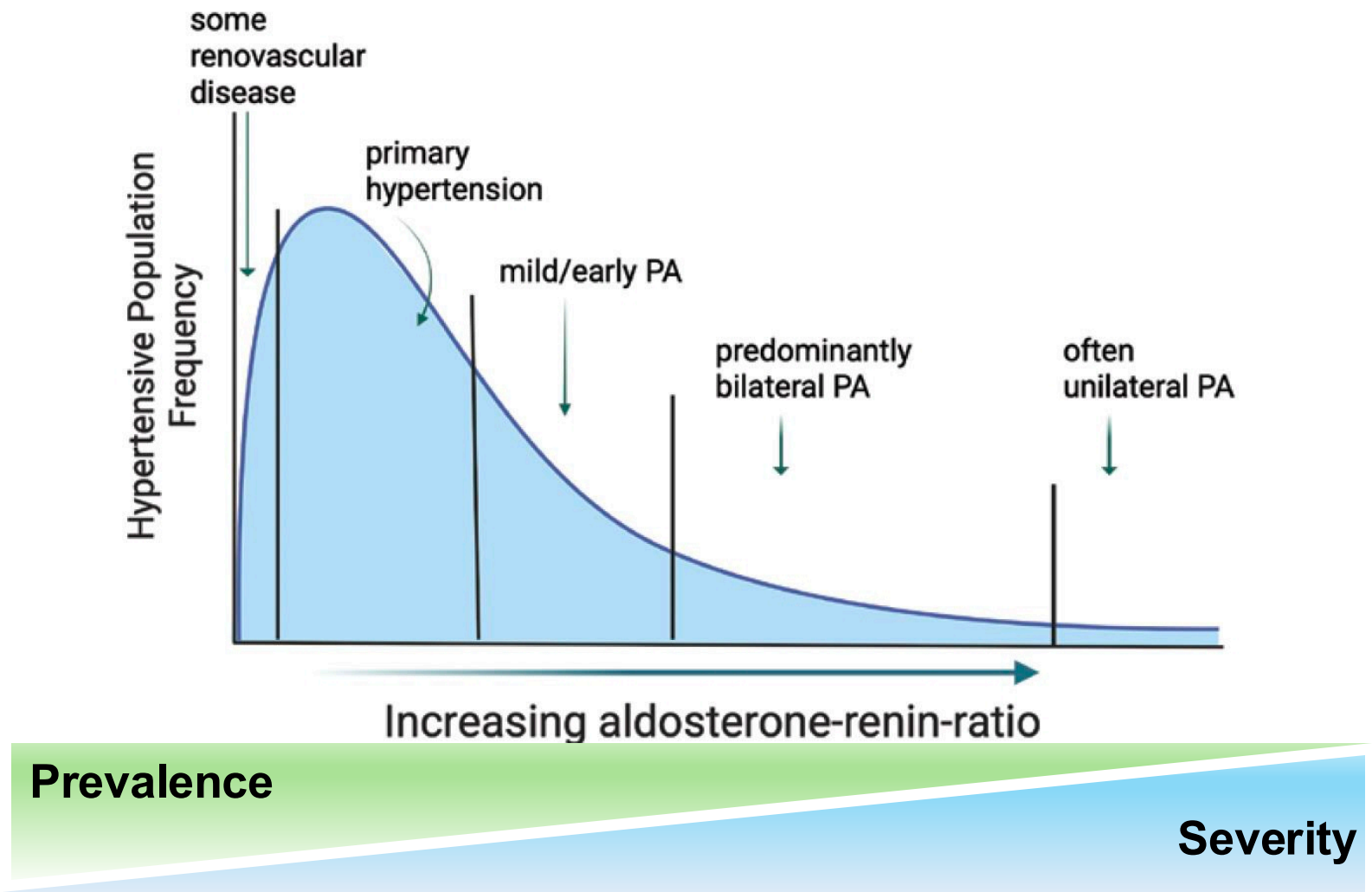


Image from Kline GA et al. Am J Hypertens 2025. PMID: 40887827.

Although there is no standard definition of severity, the proportion of patients with lateralizing PA increased with the severity of clinical presentation.

Key parameters for classification

- Serum potassium (K)
- Blood pressure (BP)
- Basal plasma aldosterone concentration (PAC)

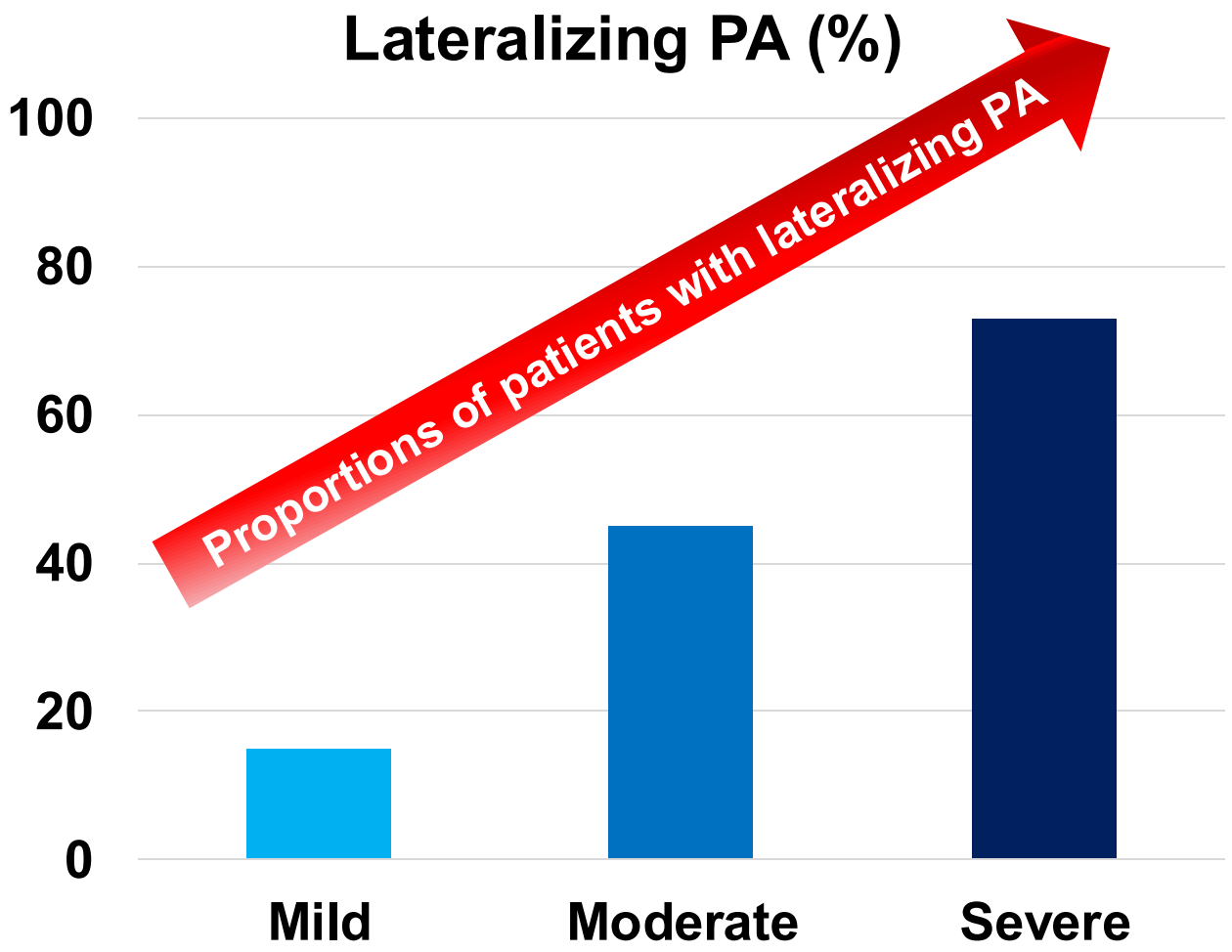
Grading Criteria

- Mild (3–4 points)
- Moderate (5–7 points)
- Severe (8–9 points)

Validation

Retrospective analysis

N = 2,593 PA patients across 26 centers (2004–2024)

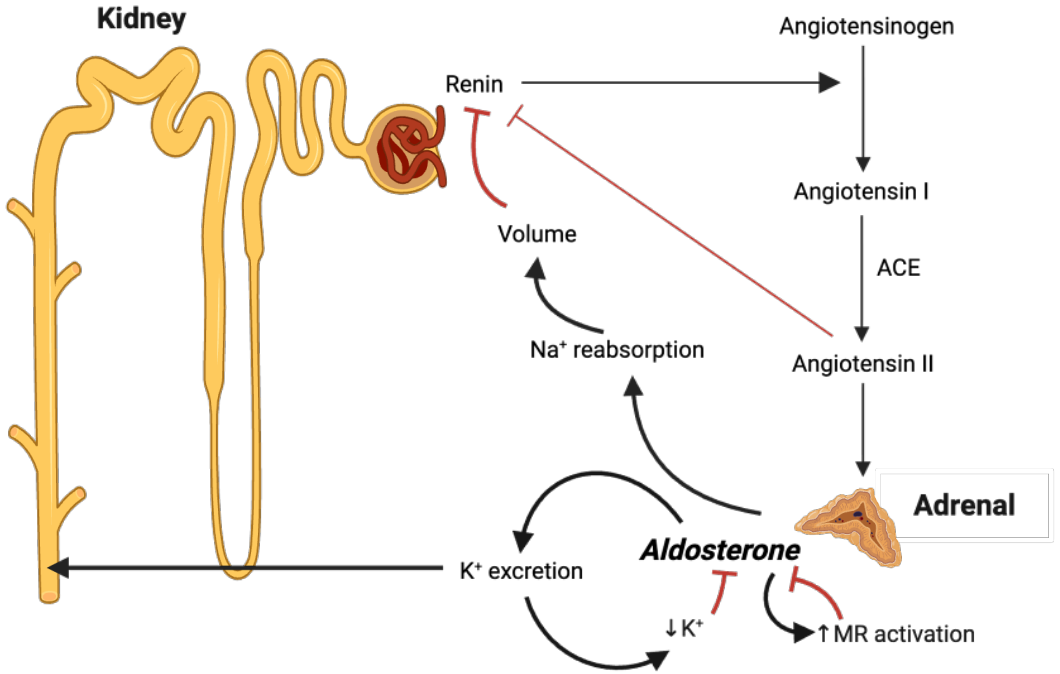


Murakami M et al. Eur J Endocrinol 2025. PMID: 40485198.

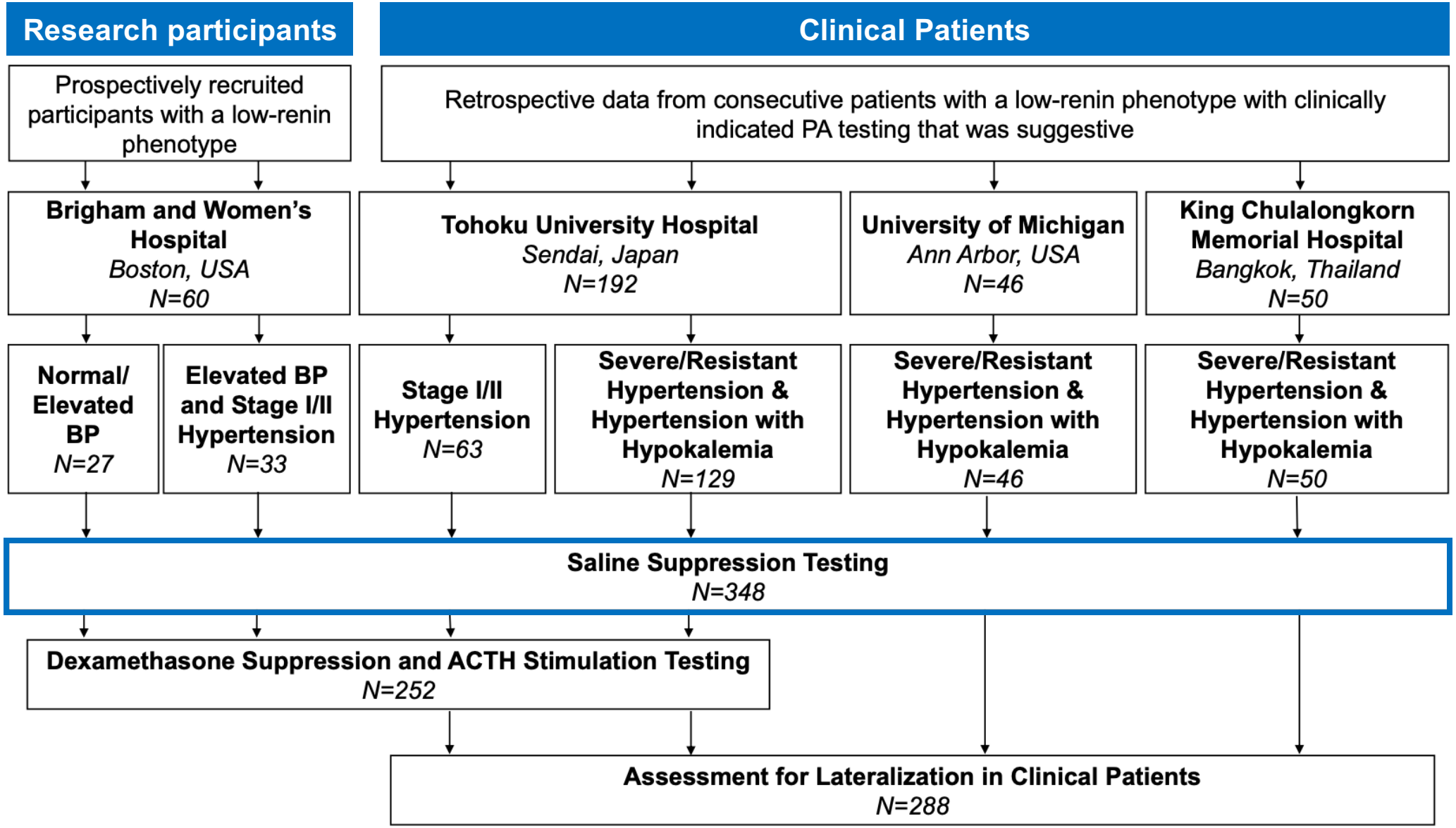
Aldosterone Suppression Testing

- Previously known as “confirmatory testing”

- Widely used tests assess Angiotensin II-independent aldosterone production, e.g.,
  - Oral sodium loading test
  - Saline suppression test

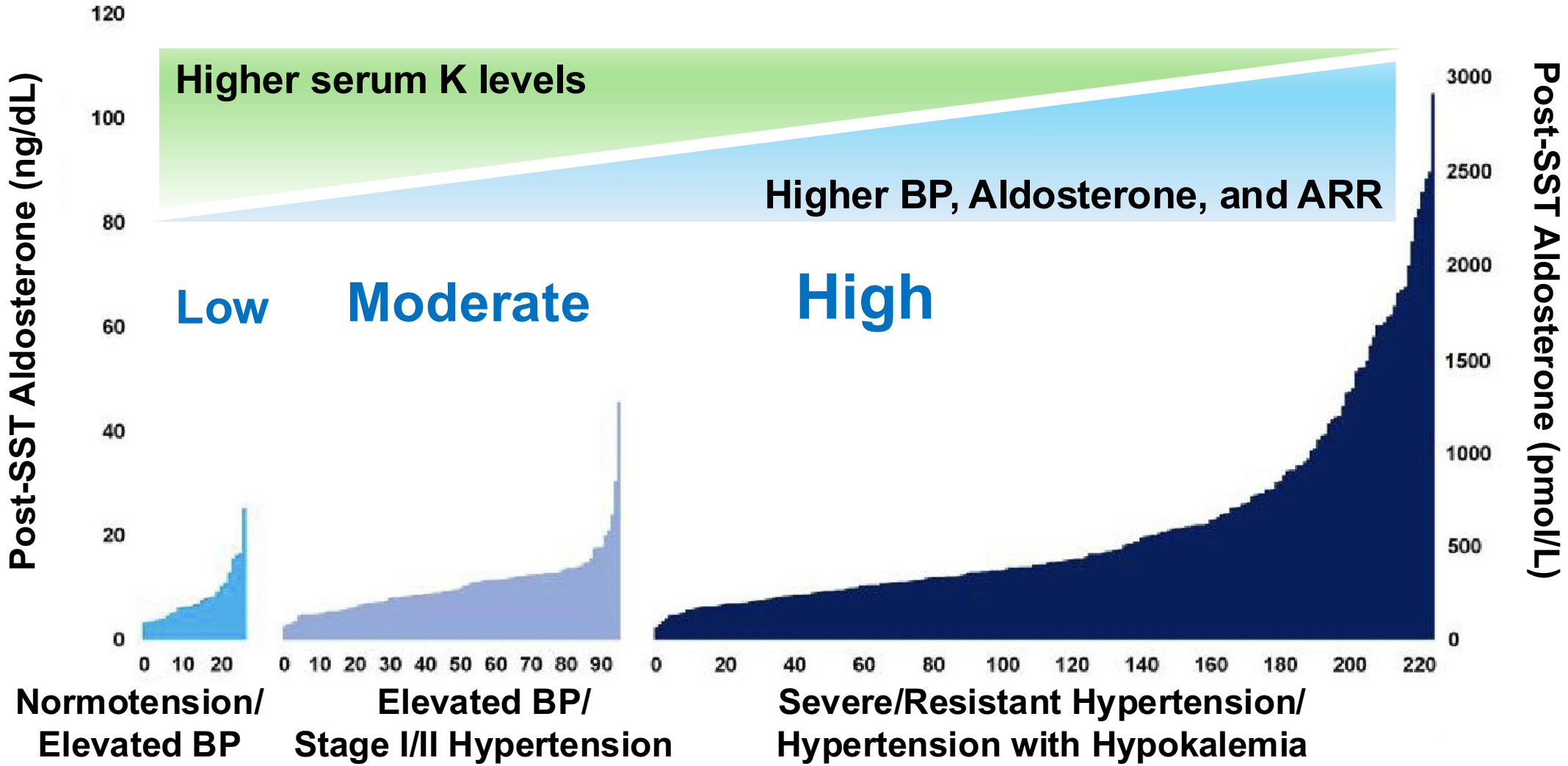


Created with Biorender



Parksook WW et al. J Clin Endocrinol Metab 2024. PMID: 38450549.

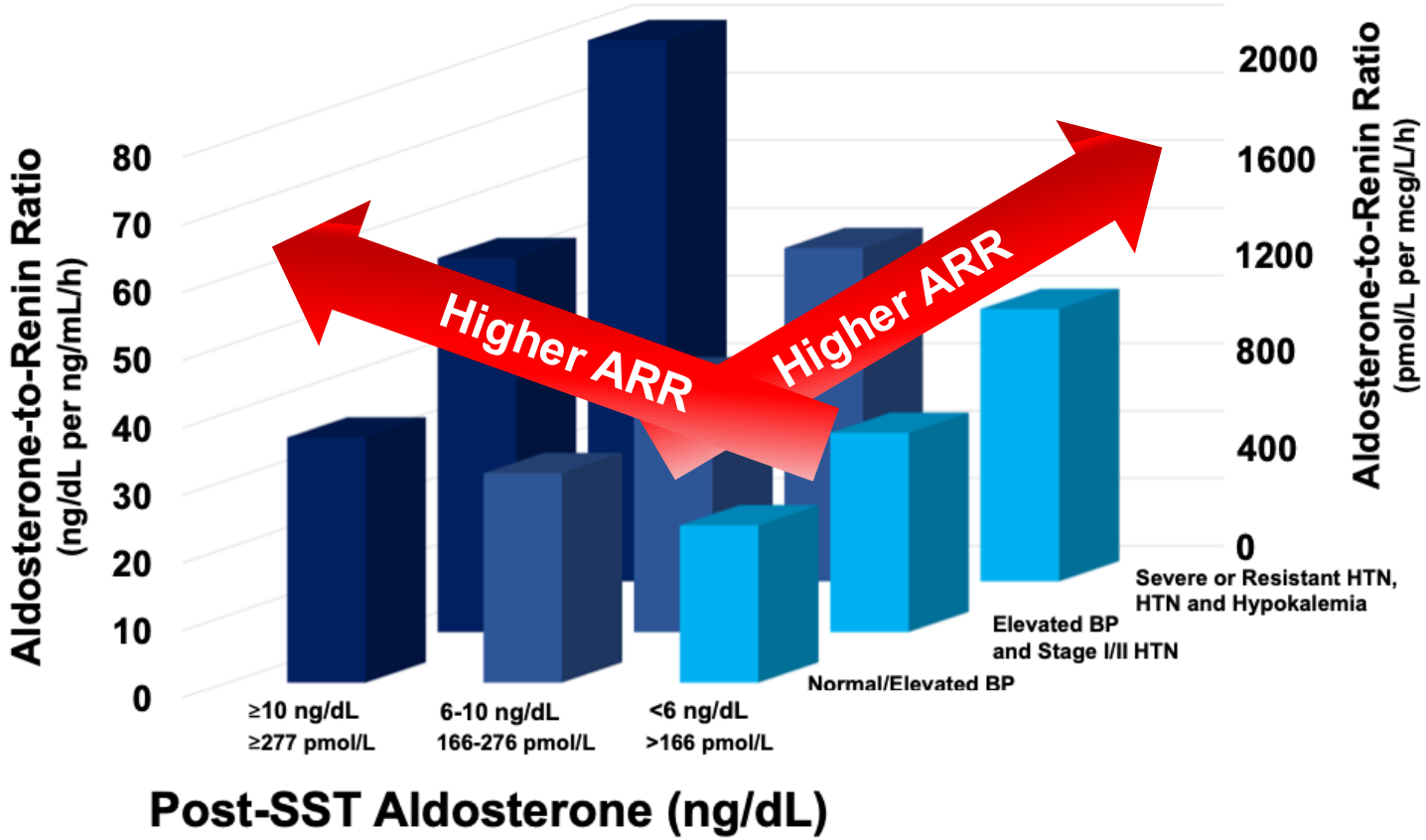
A Spectrum of Renin-Independent Aldosteronism



SST, saline suppression test

Parksook WW et al. J Clin Endocrinol Metab 2024. PMID: 38450549.

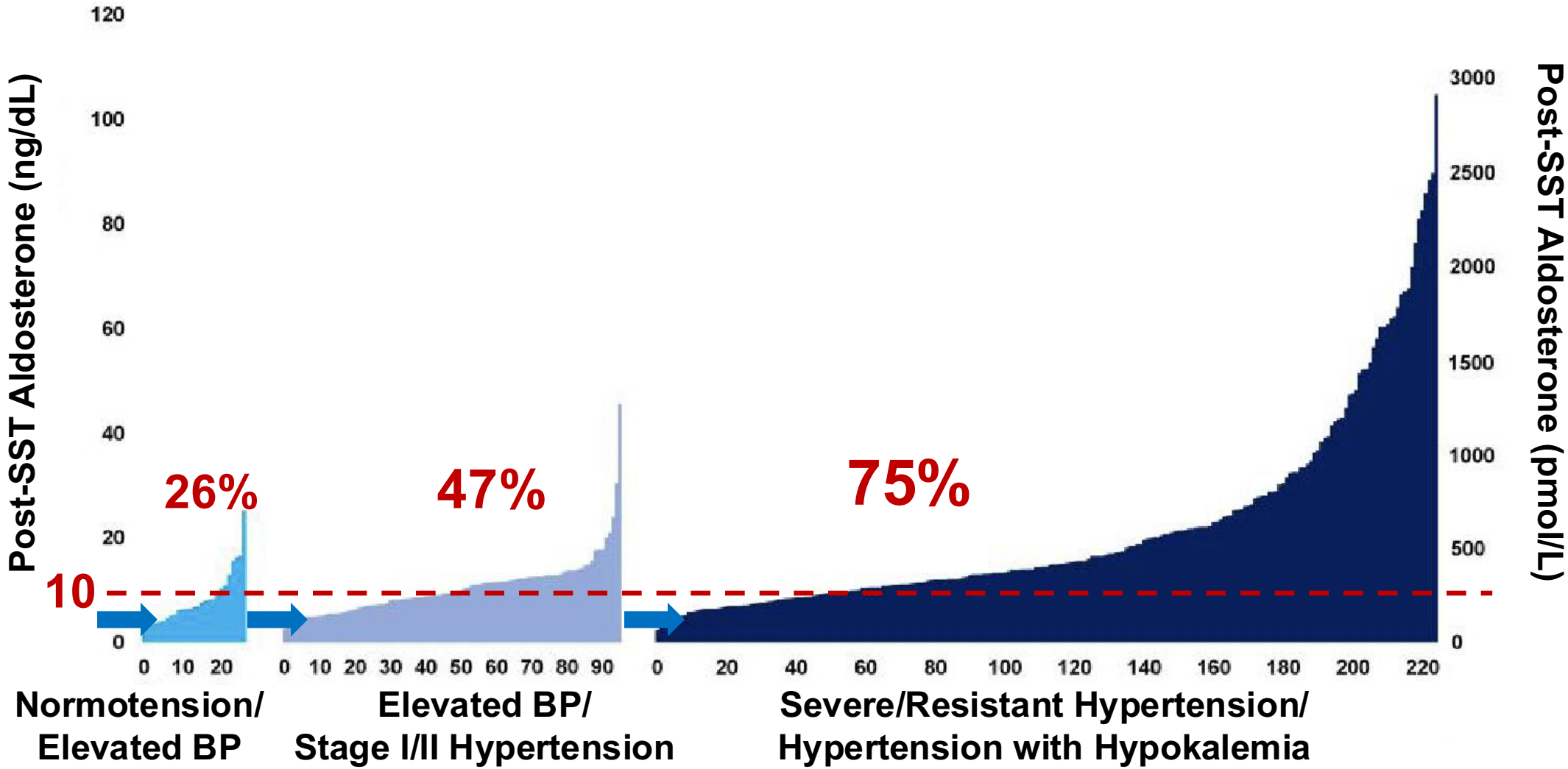
Higher ARR with increased Hypertension Severity and Post-SST Aldosterone Levels



SST, saline suppression test; ARR, aldosterone-to-renin ratio

Parksook WW et al. J Clin Endocrinol Metab 2024. PMID: 38450549.

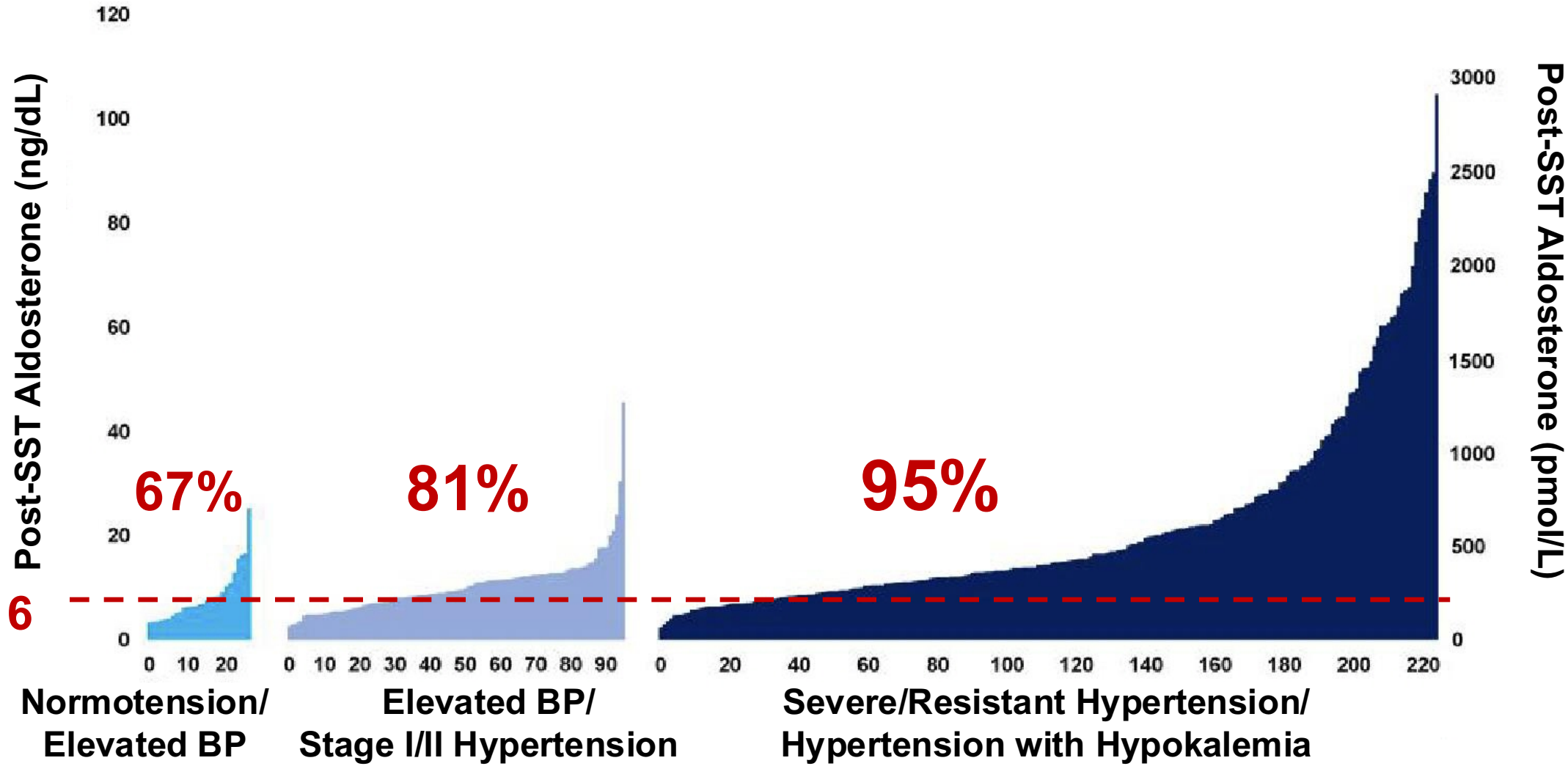
A Spectrum of Renin-Independent Aldosteronism



SST, saline suppression test

Parksook WW et al. J Clin Endocrinol Metab 2024. PMID: 38450549.

A Spectrum of Renin-Independent Aldosteronism



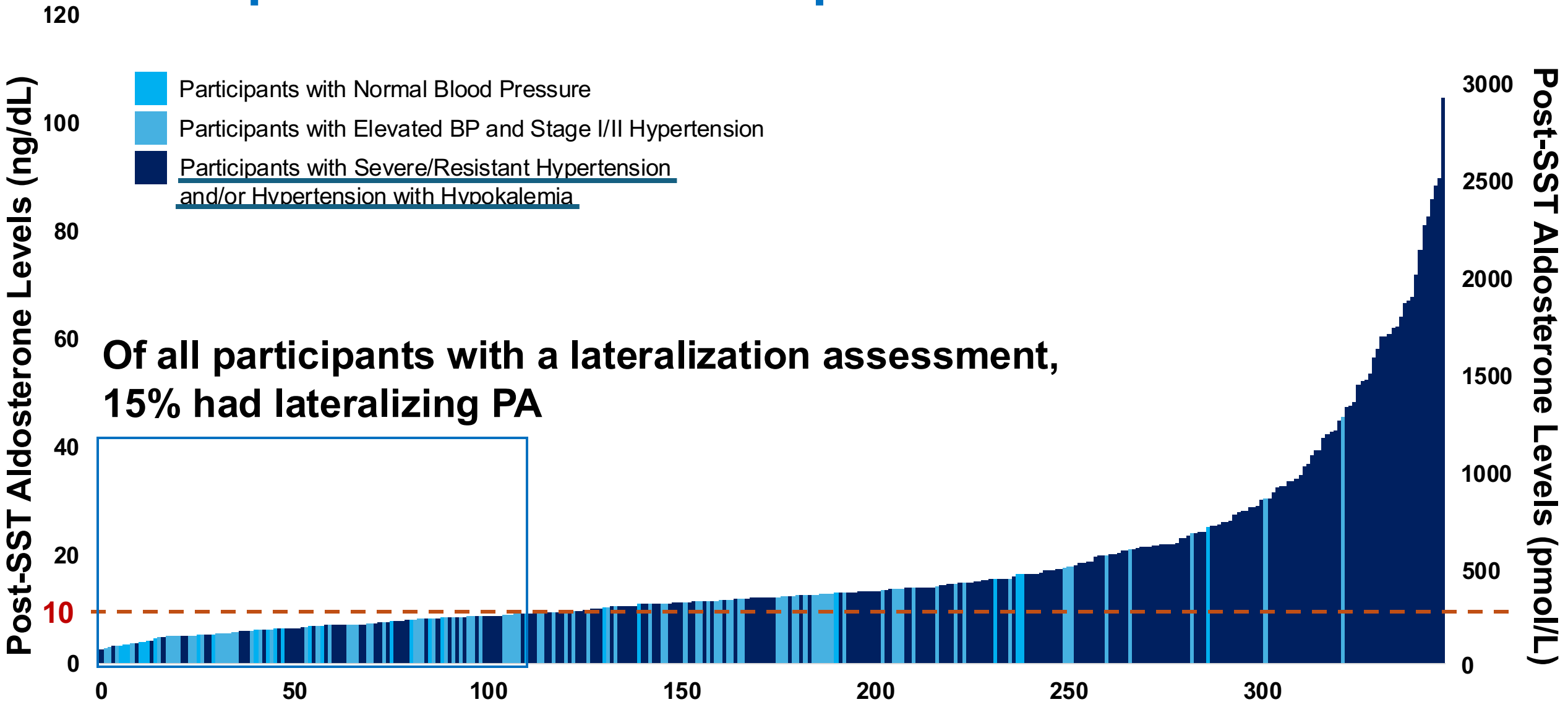
SST, saline suppression test

Parksook WW et al. J Clin Endocrinol Metab 2024. PMID: 38450549.

In the context of **low-renin**, there is a **continuum of non-suppressible and renin-independent aldosterone production**.

Those with **more severe hypertension** tend to have a **higher ARR, post-SST aldosterone**, and **proportion of post-SST aldosterone over conventional thresholds**.

A Spectrum of Renin-Independent Aldosteronism

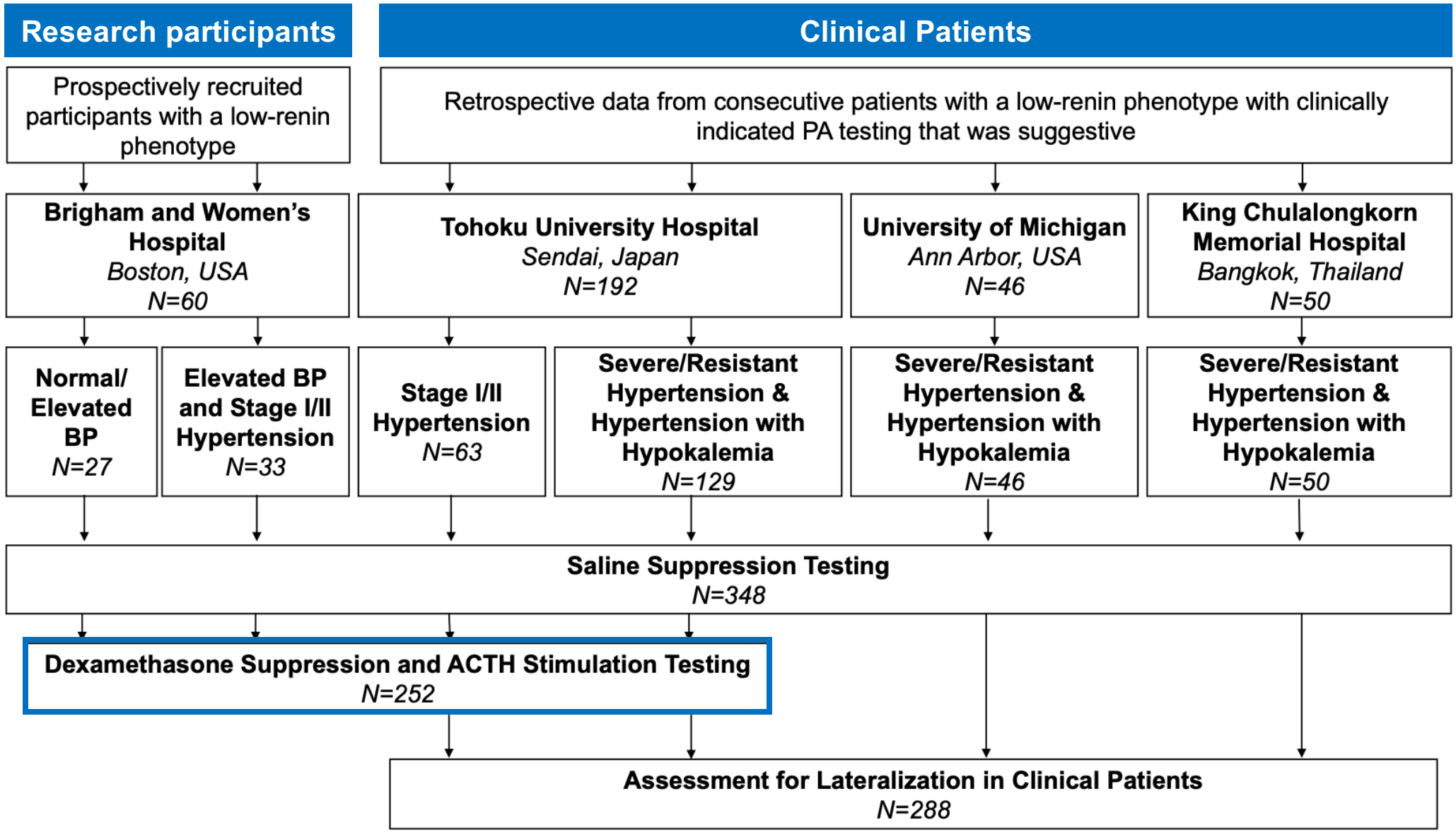


SST, saline suppression test

Parksook WW et al. J Clin Endocrinol Metab 2024. PMID: 38450549.

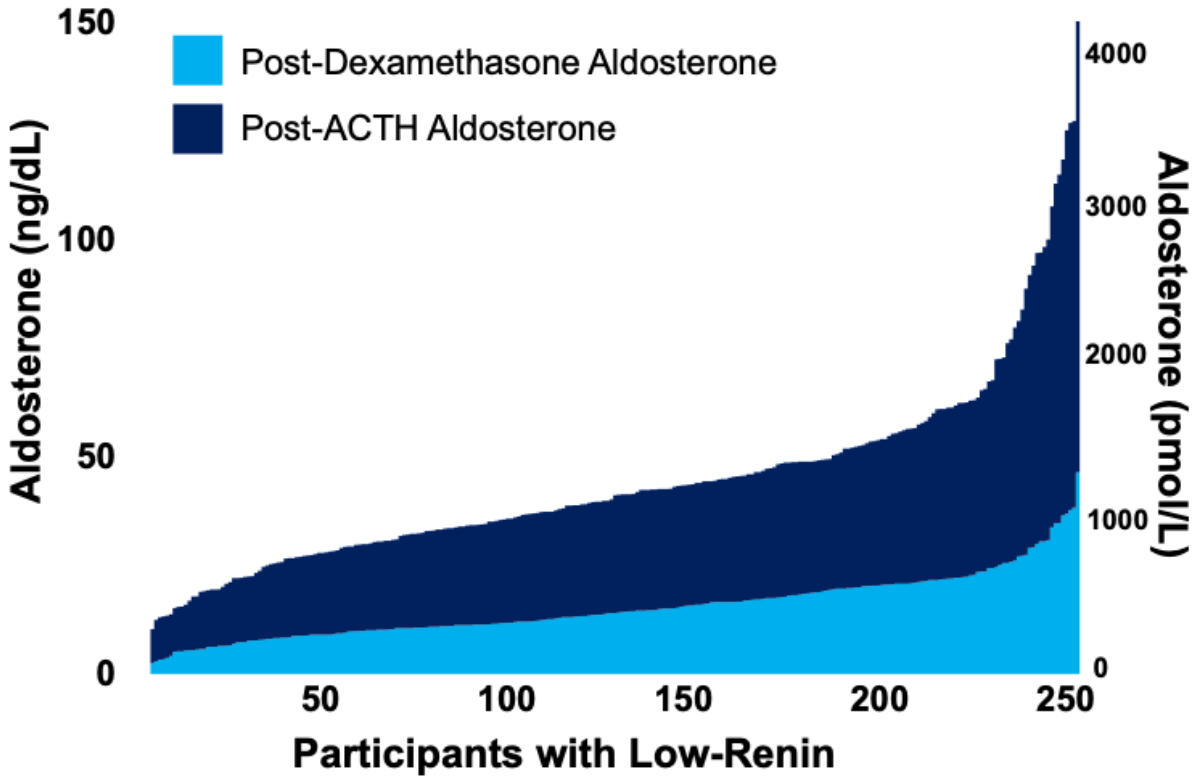
The **continuum** of non-suppressible and dysregulated aldosterone production **transcends conventional diagnostic criteria** that had been recommended to confirm and exclude PA.

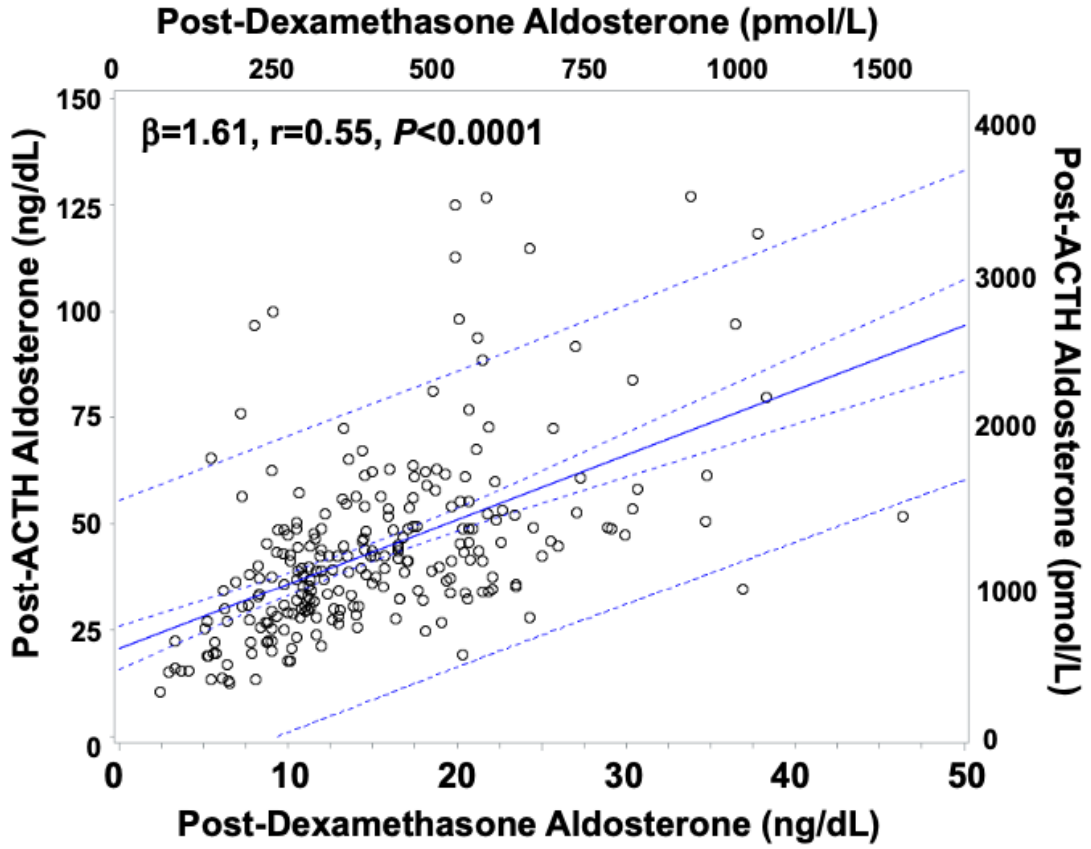
SST can falsely exclude PA, even in **those with overt PA and lateralizing PA**.



Parksook WW et al. J Clin Endocrinol Metab 2024. PMID: 38450549.

Interrogation of ACTH-Mediated Aldosterone Production

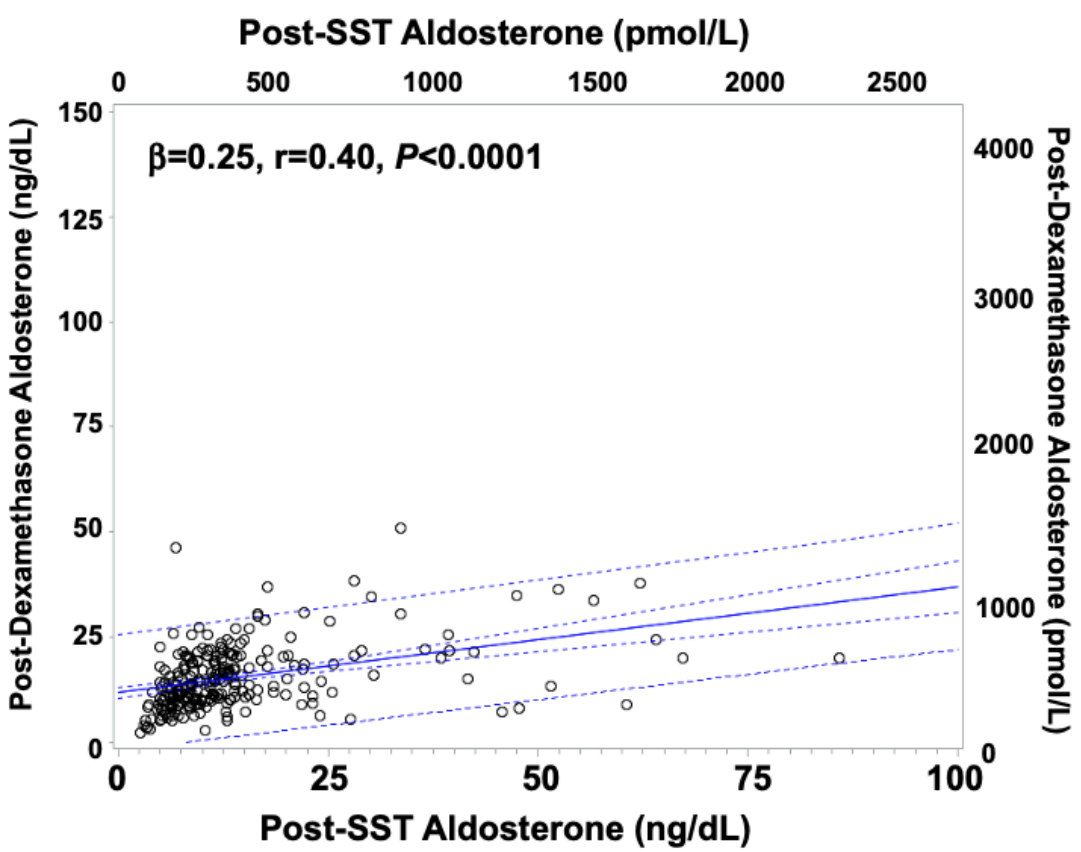


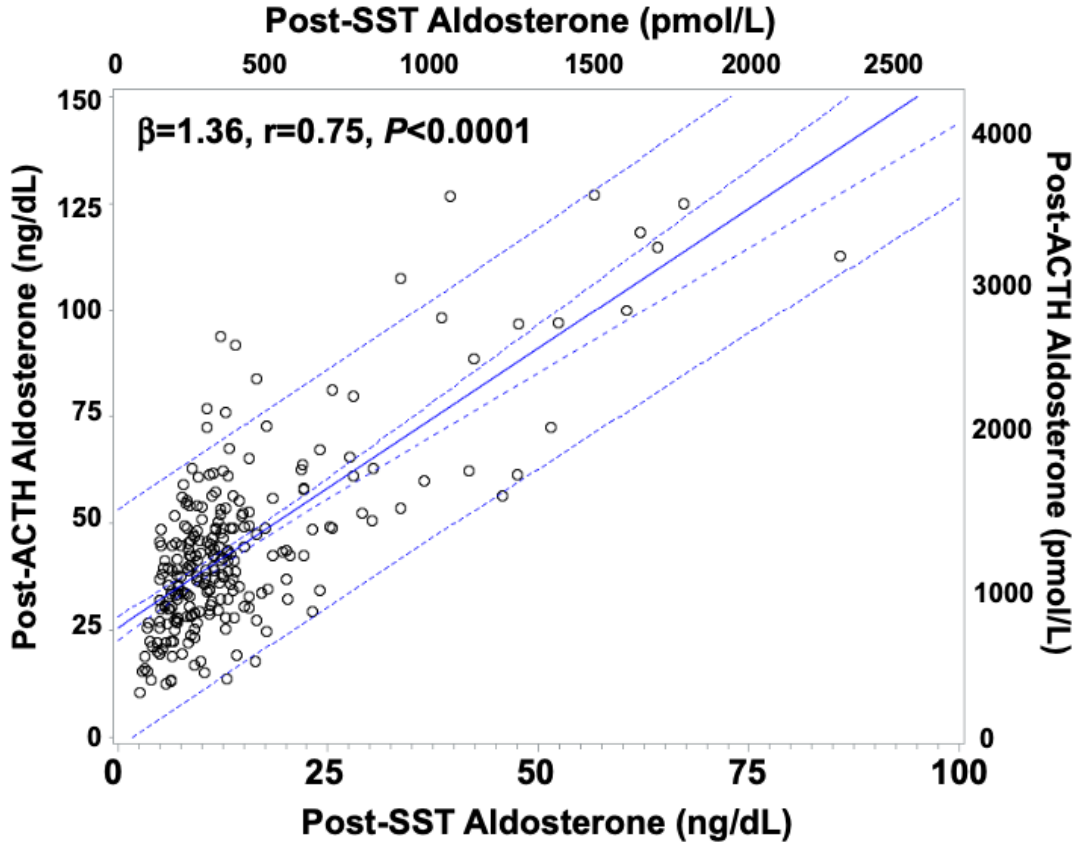


Shown are the mean regression line with the 95% CI

Parksook WW et al. J Clin Endocrinol Metab 2024. PMID: 38450549.

Correlation Between Renin- and ANGII-Independent Aldosterone Production and ACTH-Mediated Aldosterone Production





Shown are the mean regression line with the 95% CI

Parksook WW et al. J Clin Endocrinol Metab 2024. PMID: 38450549.

There is a **correlation** between the **magnitude of renin-independent aldosteronism and ACTH-mediated aldosterone production**, highlighting the synchronous roles of angiotensin II and ACTH in determining aldosterone dysregulation.

Intra/interindividual variability of aldosterone could be influenced by ACTH, which is **not adequately captured in clinical practice**.

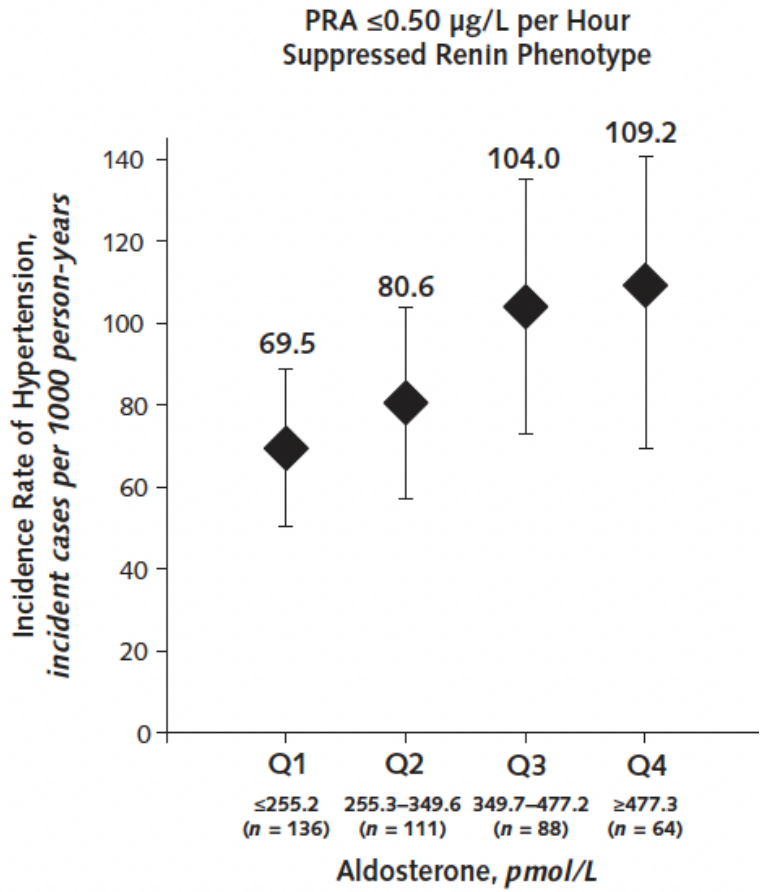
Clinical Relevance in Prospective Studies of Participants WITHOUT Overt PA

Overt PA

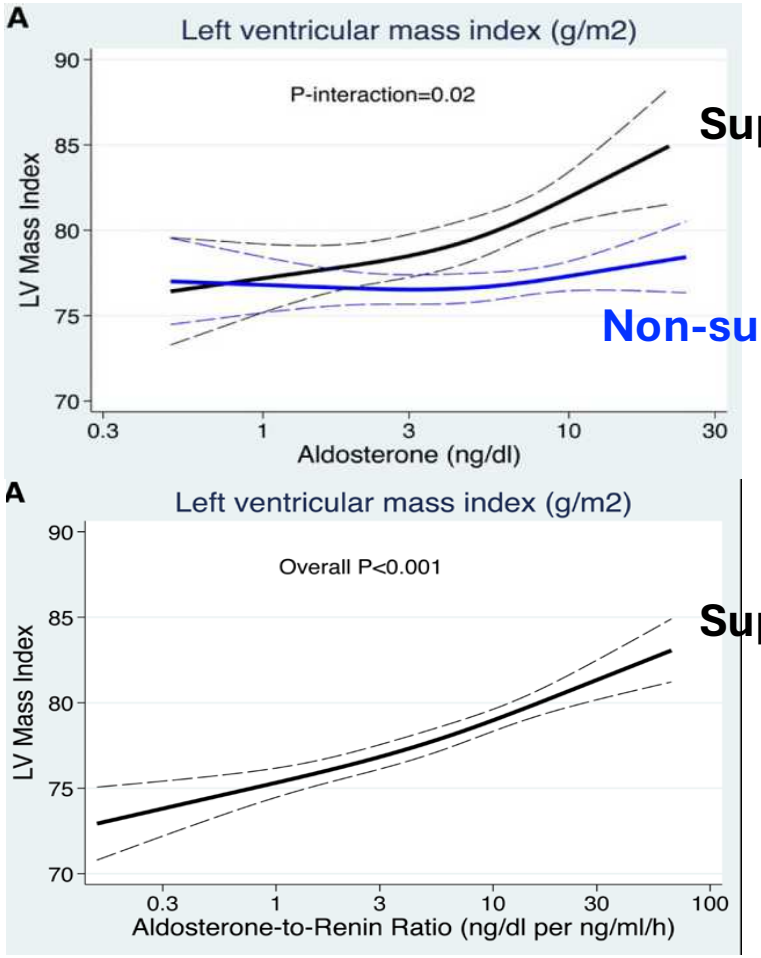
DIAGNOSTIC THRESHOLDS

No PA

Continuum of Primary Aldosteronism in Prospective Studies



Normotensives from MESA (N= 850)
(Multi-Ethnic Study of Atherosclerosis), USA



Suppressed renin

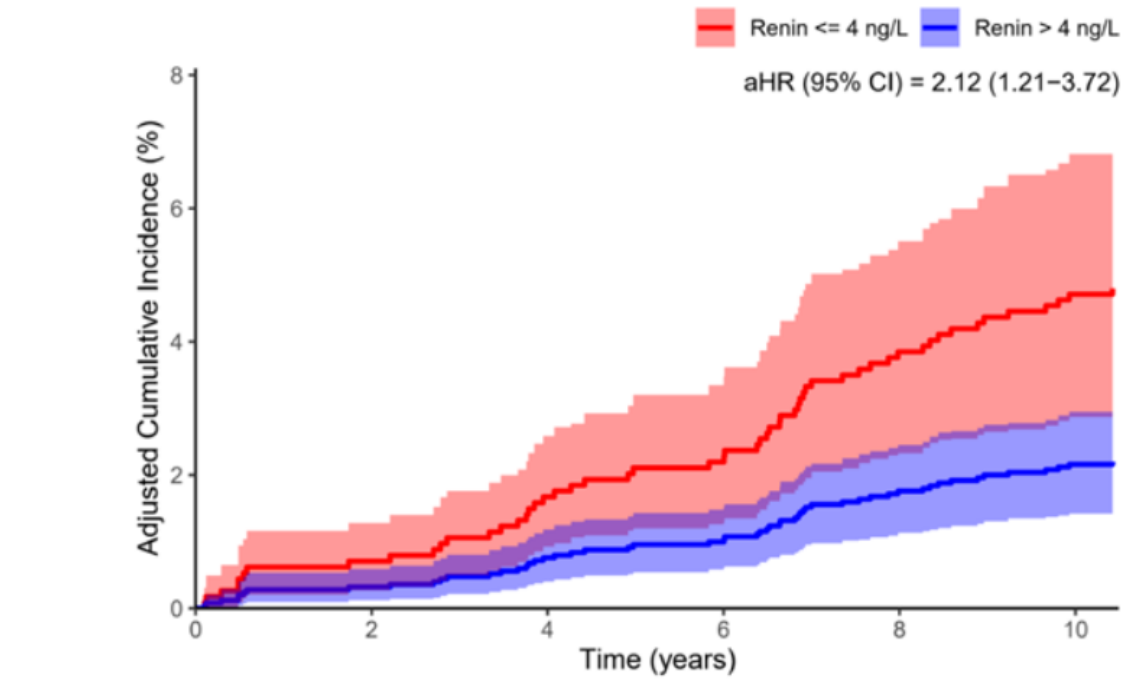
Non-suppressed renin

Suppressed renin

Participants from ARIC (N= 4547)
(Atherosclerotic Risk Communities), Nationwide USA

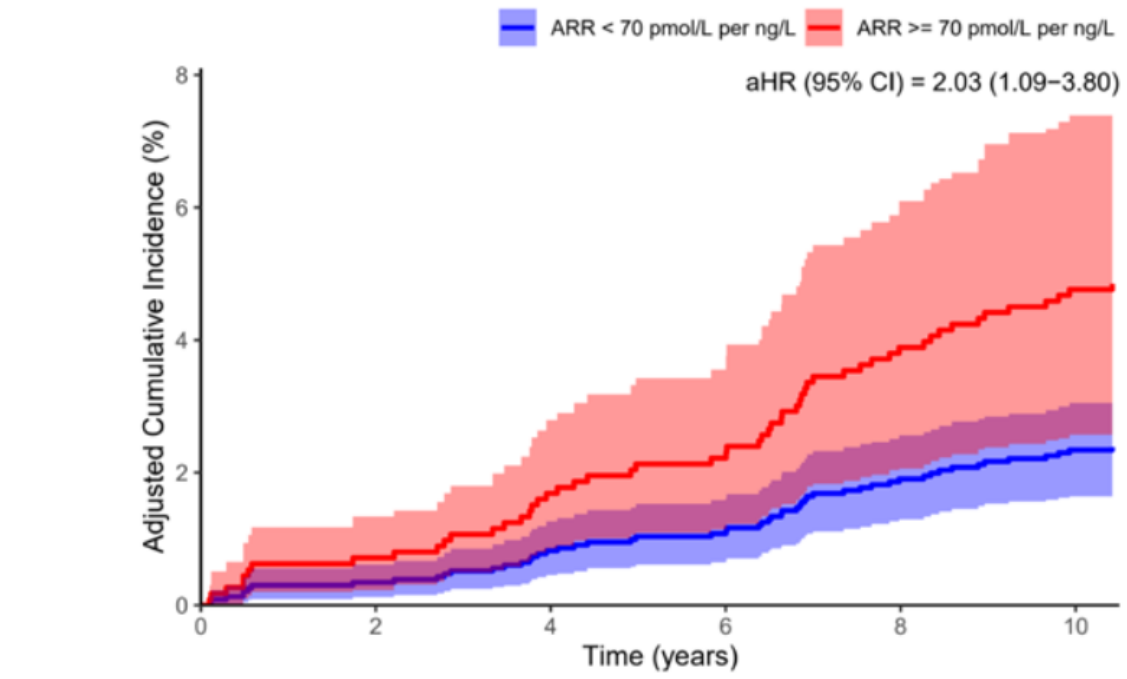
1. Brown JM et al. Ann Intern Med 2017. PMID: 29052707; 2. Brown JM, et al. Hypertension 2022. PMID: 35582954.

Increased MACE in the Population-Based Cohort Study



Number at risk (censored)

Renin ≤ 4	419 (0)	416 (0)	413 (1)	410 (0)	399 (4)	393 (1)
Renin > 4	1598 (0)	1593 (0)	1579 (4)	1571 (5)	1543 (16)	1527 (11)



Number at risk (censored)

ARR ≥ 70	299 (0)	297 (0)	294 (1)	292 (0)	283 (3)	281 (0)
ARR < 70	1718 (0)	1712 (0)	1698 (4)	1689 (5)	1659 (17)	1639 (12)

N= 2017
Median follow-up time = 10.8 years

Goupil R et al. Circulation 2025. PMID: 40631720.

Wrap Up #2

- Results from multiple cohorts support the consequences of this pathophysiology
  - Worsening BP, increased incidence of hypertension
  - Structural cardiovascular disease, MACE
  - Increased risk of kidney disease/end-stage kidney disease
  - Increase in 18-hybrid steroids and blunted stimulation of NT-proBNP

Framingham Study (MA, USA), ARIC (Nationwide, USA), MESA (Nationwide, USA), CRIC (Nationwide, USA), CONPASS (China), Jackson Heart Study (African descent, Jackson, MS), CARTaGENE (Quebec, Canada)

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