Brigham and Women's Hospital
Founding Member, Mass General Brigham

Primary Aldosteronism

Anand Vaidya, MD MMSc
Chief, Division of Endocrinology, Diabetes & Metabolism, Mass General Brigham
Director, Center for Adrenal Disorders
George W. Thorn MD Endowed Chair in Endocrinology
Associate Professor of Medicine, Harvard Medical School

CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Training

- Harvard Medical School
- IM Residency @BWH
- Endocrinology Fellowship @BWH
- Cardiovascular Endocrinology Research Post-Doc @BWH

Positions

- Chief, Division of Endocrinology, and Metabolism @MGB
- Director, Center for Adrenal Disorders @BWH
- Associate Professor of Medicine @HMS
- Director, e-Learning Initiative @BWH/@NEJM

Disclosures

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Prior and Current Research Funding: National Institutes of Health, Doris Duke Charitable Foundation, Ventus Charitable Foundation

Key Learning Points

Essential hypertension is primarily aldosteronism

PARADIGM SHIFT

Primary aldosteronism is not a rare cause of "secondary HTN"; rather it is a highly prevalent and modifiable contributor to HTN and CVD

Aldosterone-mediated hypertension is very common

RISK FACTOR

HYPERTENSION

There are many reasonable and *individualized* pathways to achieve the clinical objectives for your patient within the context of your practice

There is no singular best practice

Perfect is the enemy of good

DESIRED OBJECTIVE

LOWER RISK FOR ADVERSE CARDIORENAL OUTCOMES

HYPERTENSION

No Testing – Just Control BP

Conventional Anti-HTNives

JUST TREAT THE BP!

1.3 BILLION people have hypertension worldwide

Hypertension is a **causal** risk factor for adverse cardiorenal outcomes; treating hypertension prevents these outcomes

Only ~20% have their BP adequately controlled

LOWER RISK FOR ADVERSE CARDIORENAL OUTCOMES

Adapted from:
Vaidya et al. NEJM 2025
Brown & Vaidya. JACC 2025

HYPERTENSION

No Testing -
Just Control BP

MR Antagonist

MR ANTAGONISTS

Lower BP in HTN & Resistant HTN

Lower BP and correct hypokalemia in Primary Aldosteronism

Especially effective at lowering BP when renin is low

Lower risk for adverse cardiorenal outcomes

Widely available, cheap, **under-utilized**

It is never wrong to start an MRA!

LOWER RISK FOR ADVERSE CARDIORENAL OUTCOMES

Adapted from:
Vaidya et al. NEJM 2025
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HYPERTENSION

No Testing –
Just Control BP

ALDOSTERONE SYNTHASE INHIBITOR

ALDOSTERONE SYNTHASE INHIBITORS

Lower Aldosterone & BP in Resistant and Uncontrolled HTN

Lower Aldosterone & BP in Primary Aldosteronism

Lower BP when renin is low

Lower BP when renin is not low

Enables simultaneous treatment of HTN and *unrecognized* PA

A NEW ERA: Medical Aldosterone-ectomy

The Future is Medical

LOWER RISK FOR ADVERSE CARDIORENAL OUTCOMES

Adapted from:
Vaidya et al. NEJM 2025
Brown & Vaidya. JACC 2025

HYPERTENSION

↓

TEST

NEW UPDATE

WHO:

ALL Patients with Hypertension

HOW:

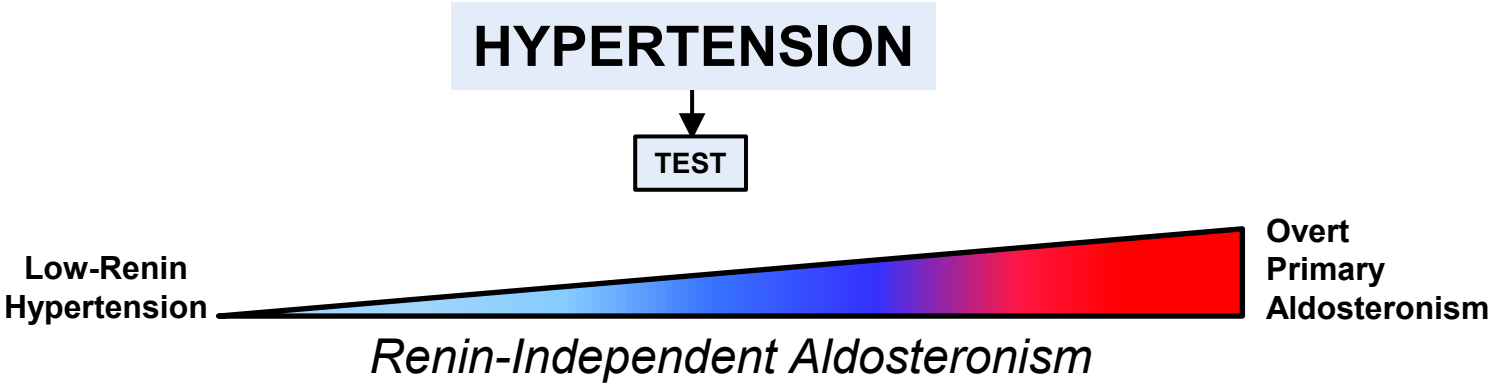
Plasma Aldosterone, Renin, and K^+

On antihypertensive medications (no washout)

Any time of day

LOWER RISK FOR ADVERSE CARDIORENAL OUTCOMES

Adapted from:
Vaidya et al. NEJM 2025
Brown & Vaidya. JACC 2025



There is no precise biochemical definition for PA

The diagnostic thresholds you use are designed to serve as practical guidelines, rather than definitive biological realities

LOWER RISK FOR ADVERSE CARDIORENAL OUTCOMES

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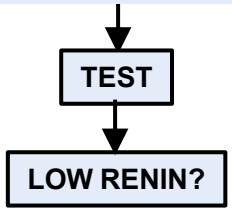
Vaidya et al. NEJM 2025
Brown & Vaidya. JACC 2025

HYPERTENSION



Majority PA pts have low renin
PRA < 1.0 ng/mL/h
PRC < 10 mU/L

The Value of Testing On Medications
If low renin despite
RAASi, Diuretic, MRA or ENaCi:

"PA until proven otherwise"

LOWER RISK FOR ADVERSE CARDIORENAL OUTCOMES

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Vaidya et al. NEJM 2025
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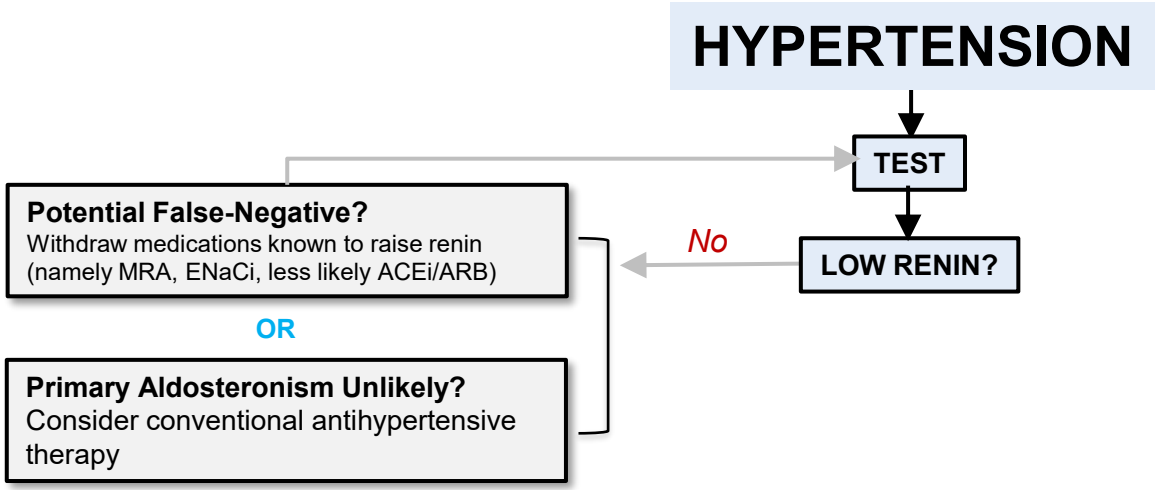

LOWER RISK FOR ADVERSE CARDIORENAL OUTCOMES

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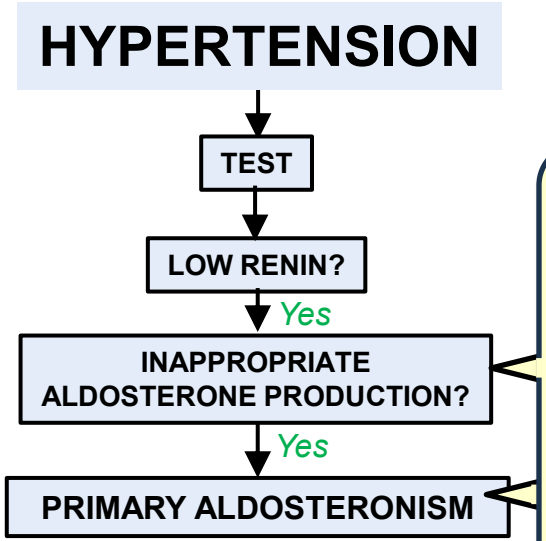
Brown & Vaidya. JACC 2025

CENTRAL DOGMA



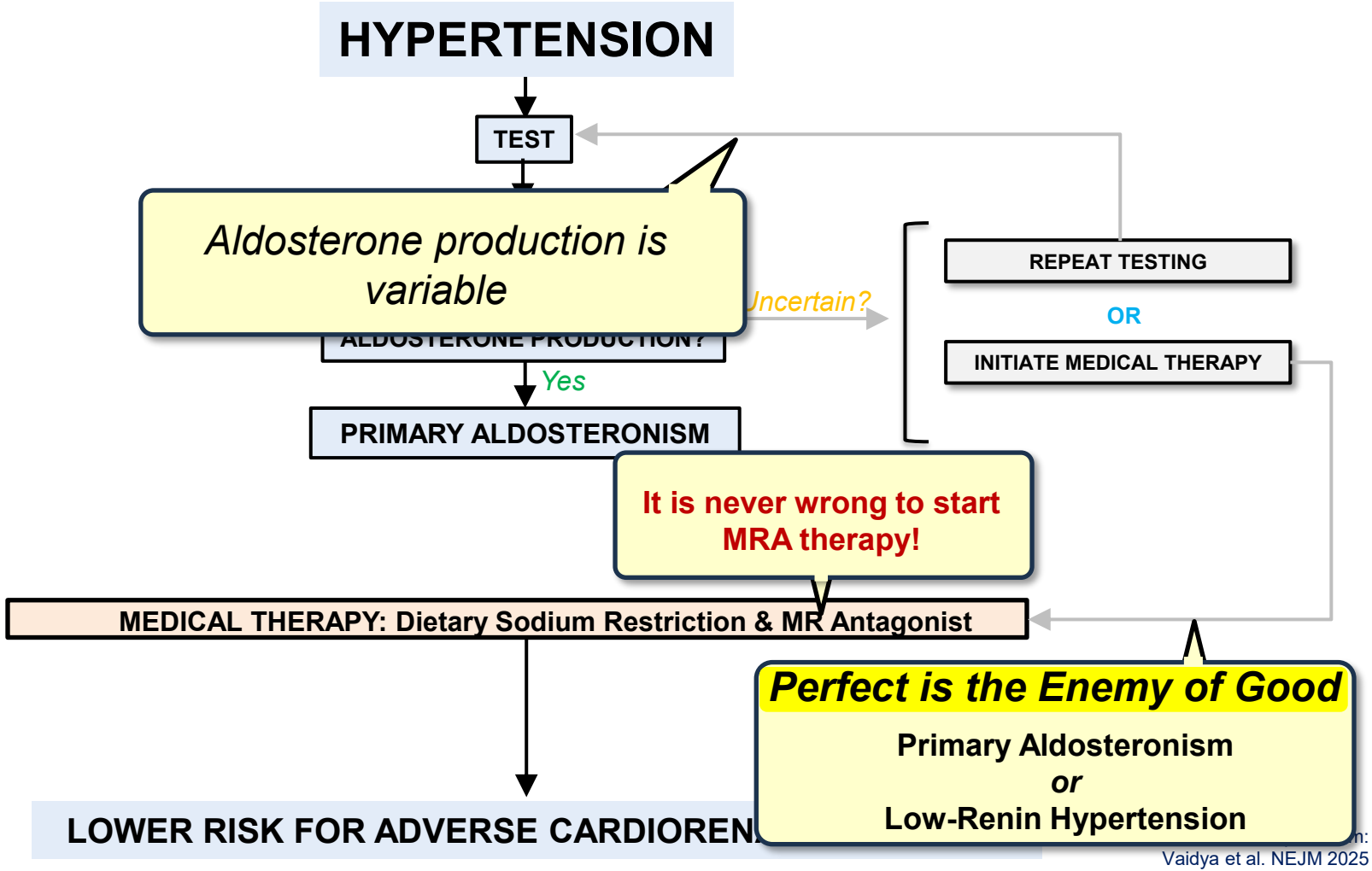
Continuum: *any aldosterone production when renin is low represents PA Pathophysiology amenable to targeted therapy*

Categorical: > 7.5 ng/dL (LC-MS/MS)
> 10 ng/dL (IA)

****If on ACEi/ARB (75-80%):*
"PA until proven otherwise"

1. **Liberally test (and/or treat) people with hypertension**
2. **Low or persistently suppressed renin is highly indicative**
3. **Any inappropriate aldosterone production when renin is low is either PA and/or amenable to aldosterone-directed therapy**

Adapted from:
Vaidya et al. NEJM 2025
Brown & Vaidya. JACC 2025



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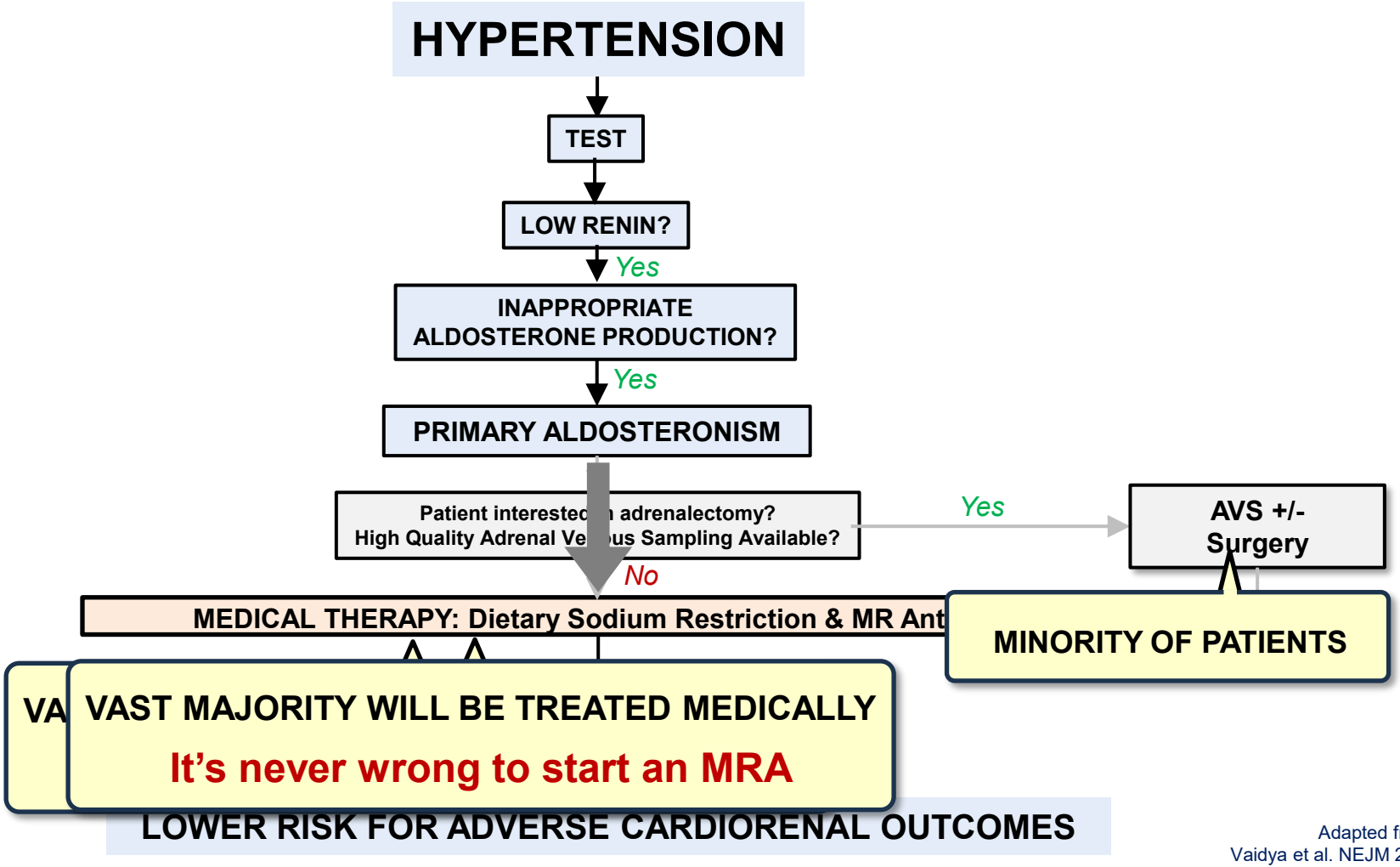

Adapted from:
Vaidya et al. NEJM 2025
Brown & Vaidya. JACC 2025

Case 1

38yoM referred for management of hypertension and cardiomyopathy

- Lives in a rural area, outdoorsman, has almost never sought medical care
- HTN diagnosed at ~28 years old, untreated for most part
- 160-180/100 mmHg
- Recurrent hypokalemia, as low as **3.1 mEq/L**
- Cardiac MRI with **hypertrophic cardiomyopathy** and **extensive late-gadolinium enhancement**

Age 38 (on **ACEi, TZ,** KCl)
PAC (LC-MS/MS): 25 ng/dL (693 pmol/L)
PRA 0.5 ng/mL/h
ARR 50 ng/dL per ng/mL/h
K 3.8 mEq/L

Case 1

POSITIVE/CONFIRMATORY TEST

Trust Yourself: **Low-Renin Hypertension + Renin-Independent Aldosterone production (*despite being on an ACEi + TZ*) => PA**

Trust the Experts: **ES Guidelines**

- ✓ **PRA ≤ 1.0 ng/mL/h *AND***
- ✓ **PAC ≥ 7.5 ng/dL (≥208 pmol/L) *AND***
- ✓ **ARR ≥ 15**

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and **extensive late-**

Age 38 (on **ACEi, TZ,** KCl)
PAC (LC-MS/MS): 25 ng/dL (693 pmol/L)
PRA 0.5 ng/mL/h
ARR 50 ng/dL per ng/mL/h
K 3.8 mEq/L

Case 1

CLINICAL PEARL

Renin-Independent Aldosterone Production despite the use of medications that should raise renin, and/or lower aldosterone, affirms PA

You don’t need to perform medication washouts or fancy maneuvers to diagnose PA

Case 1

Diagnosed with primary aldosteronism

BP controlled with 4 medications: ACEi, TZ, Alpha-blocker, Beta-blocker
K controlled with: KCl 40 mEq

Prognosis and all treatment options explained
Zero interest in pursuing invasive testing or treatment

TREATMENT PLAN:

- Aggressive dietary sodium restriction (<2g per day)
- Add eplerenone 25mg BID to current regimen
- Home BP monitoring and electronic reporting every 2 weeks

Dietary Na^+ Restriction in PA

	UNTREATED PA 1-week extreme dietary Na^+ restriction	
	~4,500 mg Na^+ per day	<1,000 mg Na^+ per day
SBP (mmHg)	160	134

CLINICAL PEARL

Dietary Na^+ Restriction can be as impactful, or more impactful, than pharmaceutical interventions

Dietary Na^+ Restriction provides synergistic benefits when combined with MR antagonist therapy

Baudrand et al. JCEM 2016; Schneider et al. JIM 2023

Case 1

	Pre-Targeted Therapy
	Lisinopril 40mg HCTZ 25mg Metoprolol 50mg Doxazosin 4mg KCL 40 mEq
K^+	3.9 mEq/L
Renin	<0.6 ng/mL/h
HOME BP	130/80

OPTIMIZED MEDICAL THERAPY

MR antagonists can be very effective

- ✓ **Normalization of BP!**
- ✓ **Reduction of polypharmacy**
- ✓ **Normalization of K^+ without supplementation**
- ✓ **Rise in renin**

6 MONTHS LATER:

On Eplerenone 75 mg BID, HCTZ 25mg QD, metoprolol
BP ~120/70 mmHg
K^+ 4.3 mEq/L
PRA 7.3 ng/mL/h (baseline 0.3-0.5 ng/mL/h)

LOWER RISK FOR ADVERSE CARDIORENAL OUTCOMES

Case 1

CLINICAL PEARL

MR antagonists are widely available, generic, relatively cheap, yet severely under-utilized

It is never wrong to start an MR antagonist

Case 1

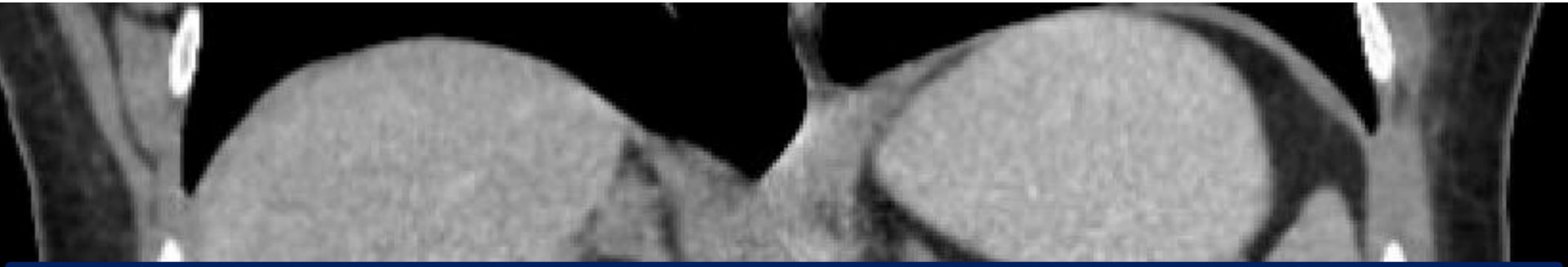
6 MONTHS LATER:

With a good medical outcome and increased trust:

Advised to consider AVS given young age, cardiovascular disease, and severity of PA

He agreed….

Case 1



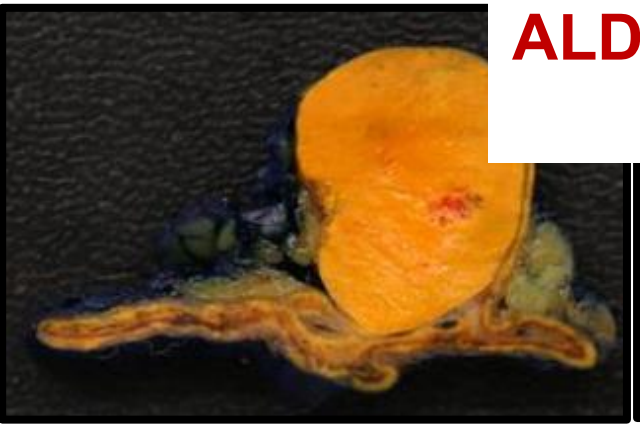
Adrenal Venous Sampling

Lateralization to the right adrenal with and without ACTH stimulation

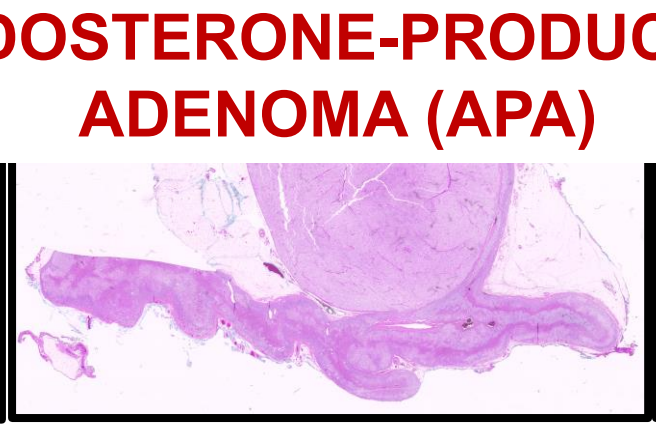
Relative suppression of aldosterone production from the left adrenal

What Causes PA?

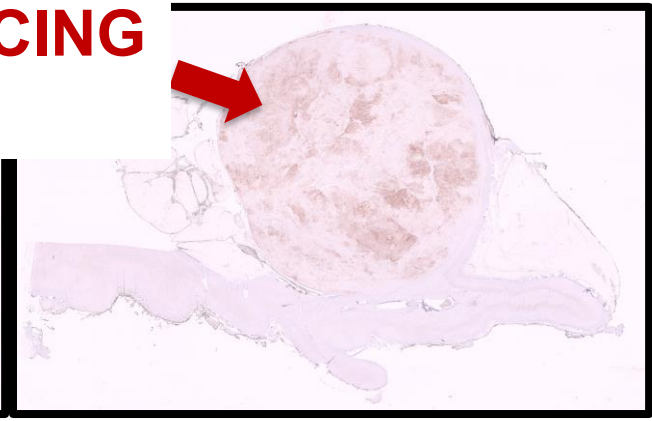
CYP11B2+ ALDOSTERONE-PRODUCING ADENOMA (APA)



Gross



H&E



IHC CYP11B2

A solitary APA expresses CYP11B2, an **NO CYP11B2 EXPRESSION IN THE ADJACENT CORTEX** in the adjacent adrenal cortex should endocrine physiology works!

This classic morphology is rare

Vaidya et al. NEJM 2025

CLINICAL PEARL

The underlying pathophysiology of most PA is multi-focal areas of pathologic aldosterone production that are not seen on standard imaging or histopathology, even in cases of severe, unilateral, PA

Parisien-La Salle et al. *Hypertension* 2026

Case 1

Post-op, on NO medications:

POD 1: PAC <4 ng/dL, PRA 2.1 ng/mL/h, K 4.3 mEq/L

POD 60: PAC 7.9 ng/dL, PRA 4.1 ng/mL/h, K 4.9 mEq/L
BP 140/70 mmHg => started on amlodipine 5 mg daily

POD 90: BP <120/80 mmHg on amlodipine 5 mg daily

LOWER RISK FOR ADVERSE CARDIORENAL OUTCOMES

Case 1 – Key Lessons

There are many individualized approaches to help your patient with PA

MR antagonists are very effective: It is never wrong to start an MRA!

Surgery is also very effective in unilateral PA (if you can offer it)

The underlying pathophysiology of most PA is multi-focal areas of pathologic aldosterone production, even in unilateral PA

Pathogenesis of PA

Key Point: The vast majority of primary aldosteronism is attributable to *diffuse and bilateral* foci of autonomous aldosterone production

Pathogenesis & Morphologies of PA

Early Life

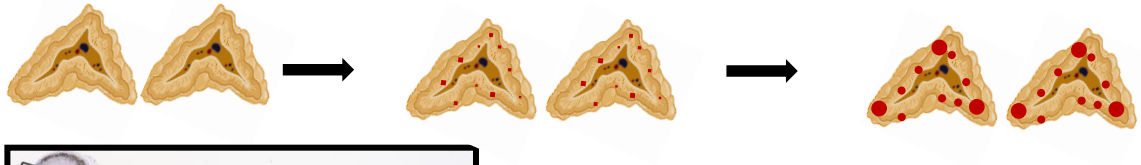
Normal Physiology & Structure

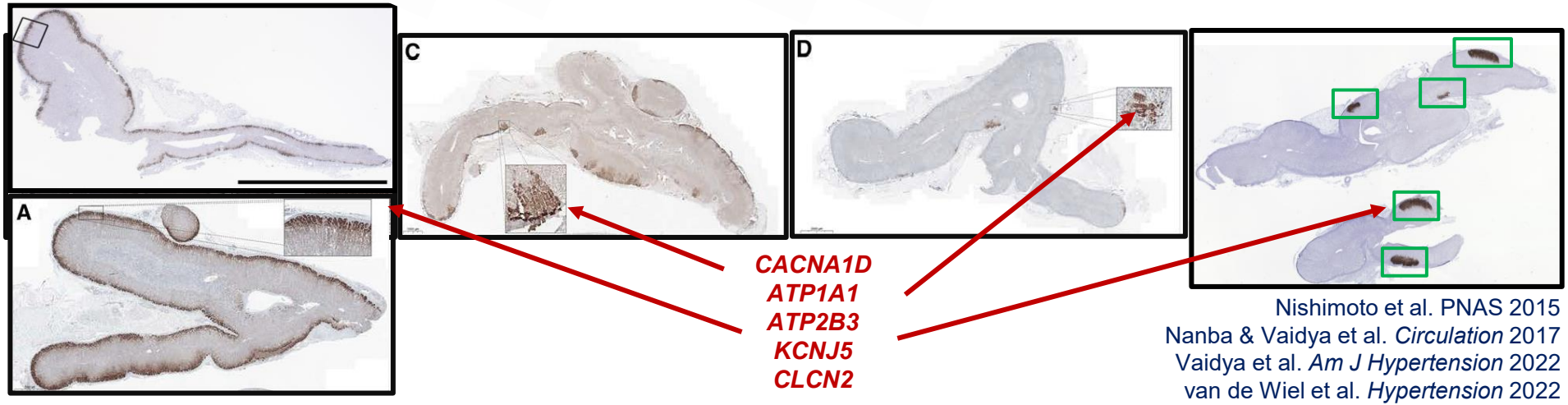
- Continuous CYP11B2 in ZG
- No neoplasia

Progressive Aging

Primary Aldosteronism with Morphologically Normal Adrenal Glands

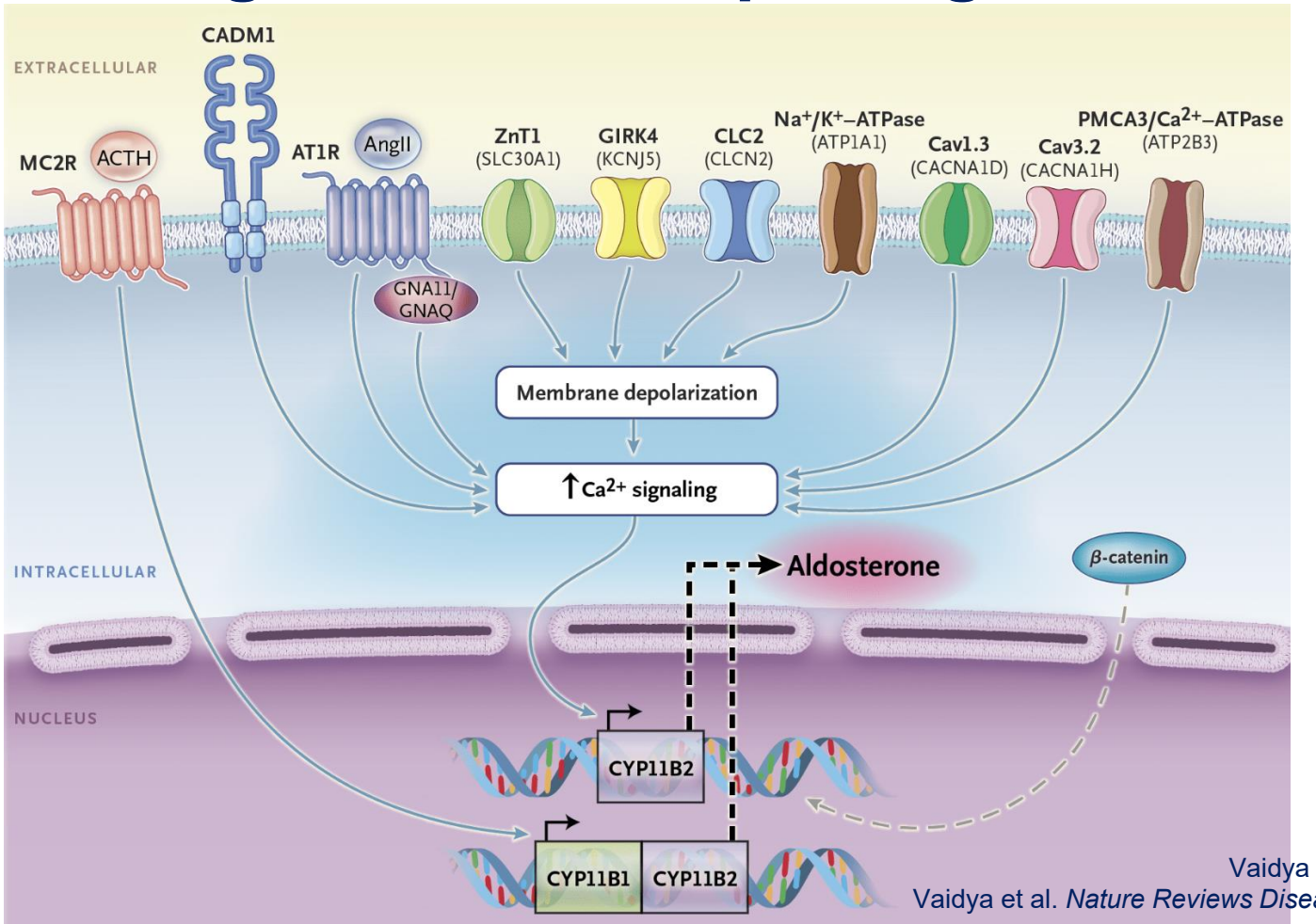
- Progressive loss of continuous ZG
- Emergence of Aldosterone Producing Cell Clusters
- Aldo-Driver somatic mutations within APCCs





Nishimoto et al. PNAS 2015
Nanba & Vaidya et al. *Circulation* 2017
Vaidya et al. *Am J Hypertension* 2022
van de Wiel et al. *Hypertension* 2022

Pathogenesis & Morphologies of PA



Vaidya et al. *NEJM* 2025
Vaidya et al. *Nature Reviews Disease Primers* 2026

Genetic Mutations Affecting *Zona Glomerulosa* Cells to Cause Primary Aldosteronism

Mutation		Inheritance		Consequences
Gene	Protein	Germline	Somatic	
CYP11B1/CYP11B2 hybrid	CYP11B1/CYP11B2 fusion	X		Fusion of *CYP11B1* promoter to the 5'-end of *CYP11B2* such that CYP11B2 expression is regulated by adrenocorticotropic hormone (ACTH). Cause of familial hyperaldosteronism type I.
CLCN2	CLC2	X	X	Increases chloride ion efflux, which results in a lower membrane depolarization threshold. Cause of familial hyperaldosteronism type II when germline variant.
KCNJ5	GIRK4	X	X	Permits sodium ion influx, which results in a lower membrane depolarization threshold. Cause of familial hyperaldosteronism type III when germline variant.
CACNA1D	Cav1.3	X	X	Increases calcium ion influx, which causes membrane depolarization. Cause of familial hyperaldosteronism type IV when germline variant.
ATP1A1	Na^+/K^+–ATPase		X	Increases influx of sodium and hydrogen ions, which results in a lower membrane depolarization threshold.
ATP2B3	PMCA3/Ca^{2+}–ATPase		X	Increases influx of sodium and calcium ions, which results in a lower membrane depolarization threshold.
CACNA1H	Cav3.2		X	Increases calcium ion influx, which causes membrane depolarization.
CTNNB1	β–catenin		X	Increases β–catenin signaling, which in concert with other genomic and nongenomic factors can synergize primary aldosteronism pathophysiology.
GNA11/GNAQ	GNA11/GNAQ		X	Increases G-protein signaling, which in turn increases intracellular calcium signaling.
CADM1	CADM1		X	Inhibits gap-junction permeability.
SLC30A1	ZnT1		X	Increases sodium ion influx, which results in a lower membrane depolarization threshold.

<<1% of all PA is due to inheritable/germline mutations

>95% of all unilateral APA surgical specimens harbor ***pathogenic somatic mutations***

~60% of all bilateral PA surgical specimens harbor ***pathogenic somatic mutation***

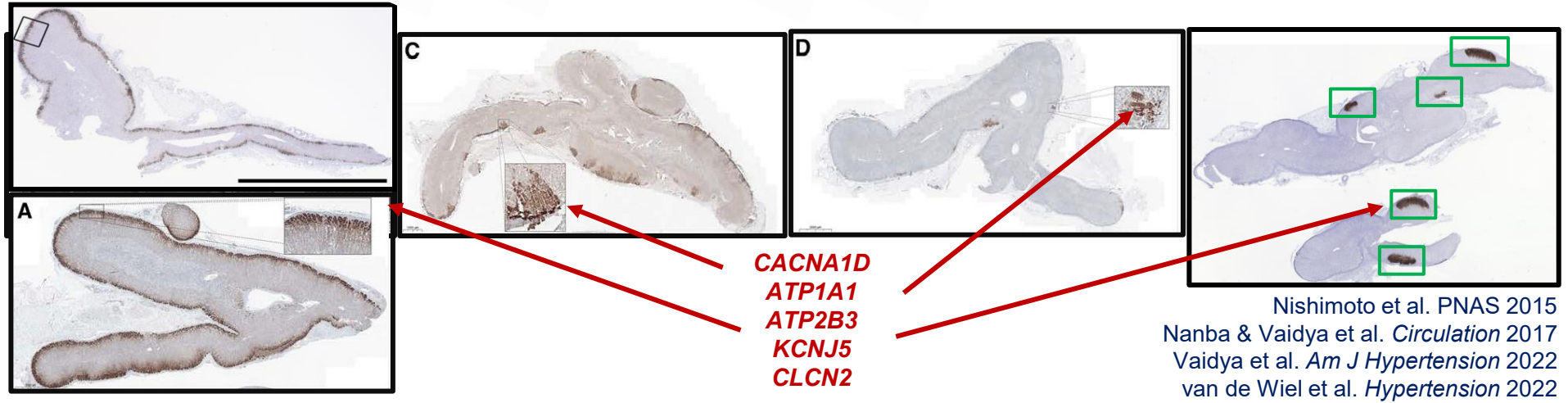
PA is largely a genetic disorder driven by somatic mutagenesis

Vaidya et al. NEJM 2025

Morphologically normal adrenals/no neoplasia

- Time/Age-dependent dysregulation CYP11B2 expression

  (loss of continuous ZG and emergence of APCCs)
- Enriched with Pathogenic Somatic Mutations in Aldosterone Driver Genes
- Bilateral process



Nishimoto et al. PNAS 2015
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Vaidya et al. *Am J Hypertension* 2022
van de Wiel et al. *Hypertension* 2022

Pathogenesis & Morphologies of PA

Early Life

Normal Physiology & Structure

- Continuous CYP11B2 in ZG
- No neoplasia

Progressive Aging

Primary Aldosteronism with Morphologically Normal Adrenal Glands

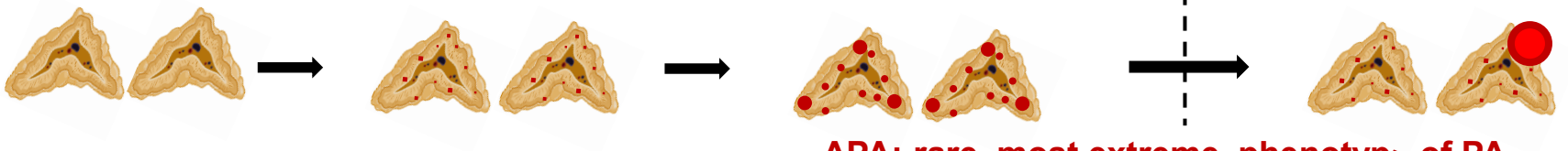
- Progressive loss of continuous ZG
- Emergence of Aldosterone Producing Cell Clusters
- Aldo-Driver somatic mutations within APCCs

Stochastic Collision/Co-Occurrence

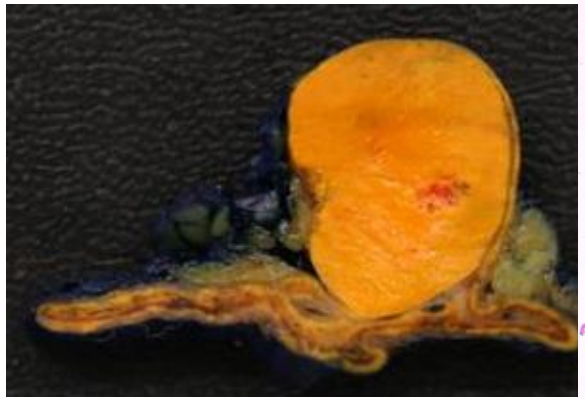
Neoplastic PA

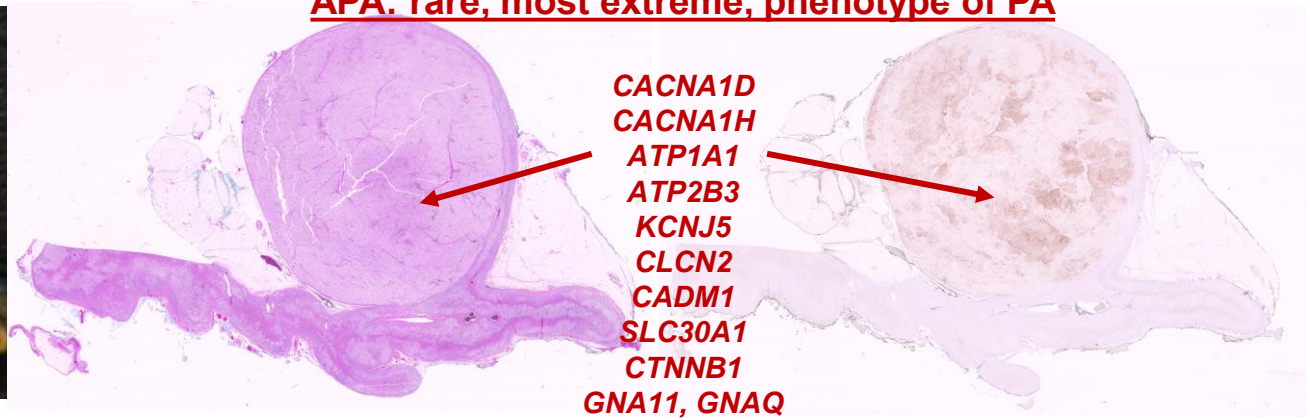
Overt Primary Aldosteronism with Aldosterone Producing Adenoma

- Aldo-Driver somatic mutations *within* adrenocortical neoplasia



APA: rare, most extreme, phenotype of PA



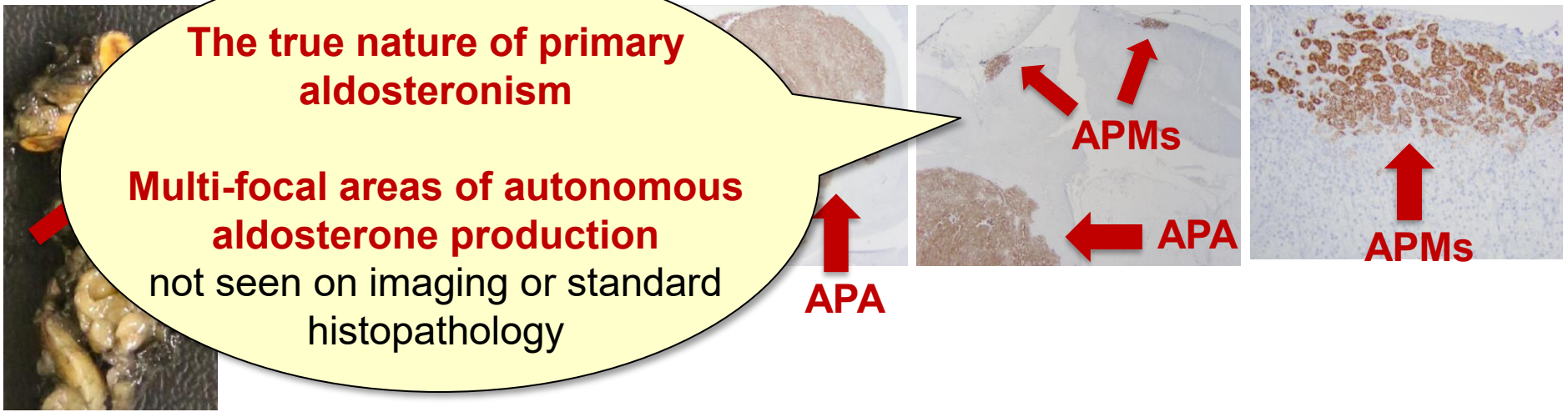


CACNA1D
CACNA1H
ATP1A1
ATP2B3
KCNJ5
CLCN2
CADM1
SLC30A1
CTNNB1
GNA11, GNAQ

Vaidya et al. *Am J Hypertension* 2022

The True Nature of Primary Aldosteronism

38yoM with severe, classic PA: rHTN (5 meds)+ hypokalemia
K 3.1 mEq/L; PRA 0.33 ng/mL/h, PAC 40 ng/dL
Preferred medical therapy: Eplerenone 75mg BID + HCTZ 25mg QD (2 meds)
(BP 120/70 mmHg, K 4.3 mEq/L)
Medical therapy (MRAs) can be very effective!



Vaidya et al. *NEJM* 2025
Parisien-La Salle et al. *Hypertension* 2026

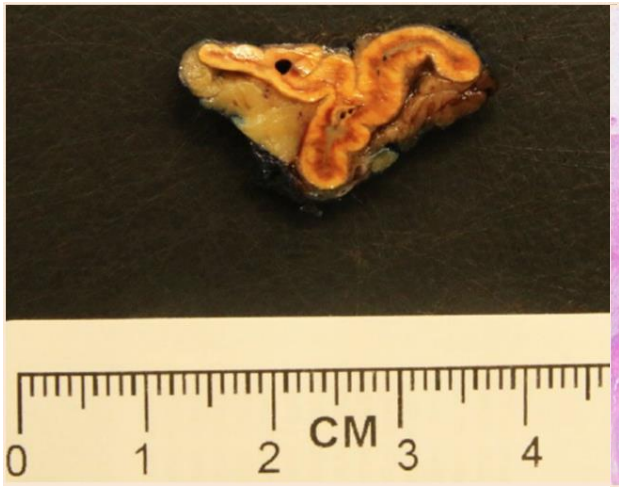
The True Nature of Primary Aldosteronism

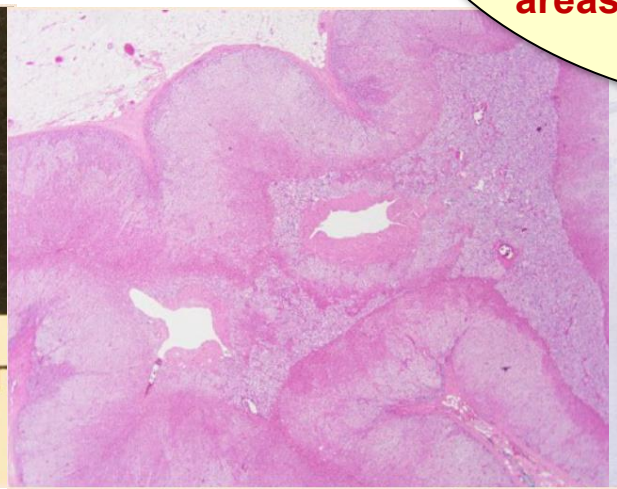
36yoF with HTN
No hypokalemia
No adrenal abnormalities on CT
PRA<0.6 ng/mL/h; Aldosterone 6.6-8.3 ng/dL (
AVS lateralized to the right
Right adrenalectomy
Post-op remission

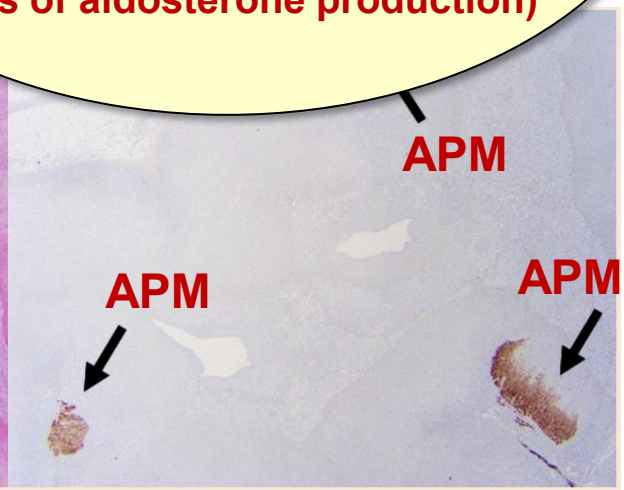
No hypokalemia?
No adrenal mass?
Aldosterone levels in single digits?

Is this Primary "Hyper"aldosteronism?

YES – this is the true nature of primary aldosteronism (renin-independent aldosterone production due to multi-focal areas of aldosterone production)







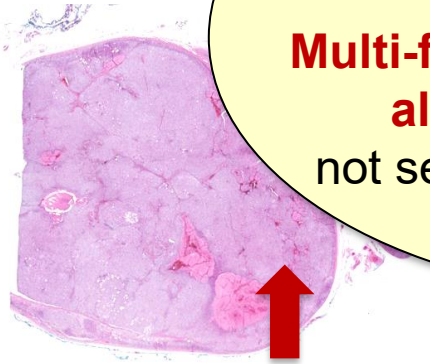
Vaidya et al. *NEJM* 2025
Parisien-La Salle et al. *Hypertension* 2026

The True Nature of Primary Aldosteronism

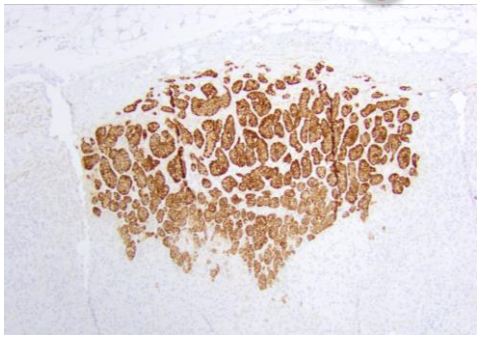
61yoF with R-HTN on 3 medications
Recurrent hypokalemia
PRA<0.6 ng/mL/h; Aldosterone 13-16 ng/dL (LC-MS/MS)
3.5 cm lipid-rich left adrenal mass
DST 1.7 mcg/dL
AVS lateralized to the l
Left adrenalectom
Post-op remiss

The true nature of primary aldosteronism

Multi-focal areas of autonomous aldosterone production
not seen on imaging or standard histopathology



Adenoma



CYP11B2 (-) Adenoma

Prevalence

Severity of Primary Aldosteronism

Early Life

Normal Physiology & Structure

- Continuous CYP11B2 in ZG
- No neoplasia

Progressive Aging

Primary Aldosteronism with Morphologically Normal Adrenal Glands

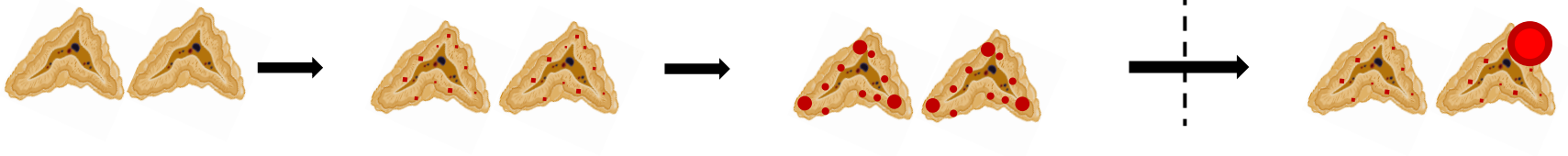
- Progressive loss of continuous ZG
- Emergence of Aldosterone Producing Cell Clusters
- Aldo-Driver somatic mutations within APCCs

Stochastic Collision/Co-Occurrence

Neoplastic PA

Overt Primary Aldosteronism with Aldosterone Producing Adenoma

- Aldo-Driver somatic mutations *within* adrenocortical neoplasia



Vaidya et al. *Am J Hypertension* 2022

Pathogenesis & Morphology of PA

Nearly all PA is caused by *pathogenic somatic mutations* resulting in foci of autonomous aldosterone production

These foci of aldosterone production generally arise *diffusely and bilaterally*, accumulate with age, usually not neoplasia/adenomas, and not seen on standard histopathology (requires IHC for CYP11B2)

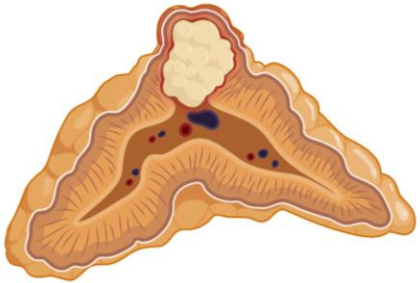
PA manifests as renin-independent aldosterone production, but can be further modified by aberrantly expressed GPCRs and their ligands, contributing to variability of the phenotype

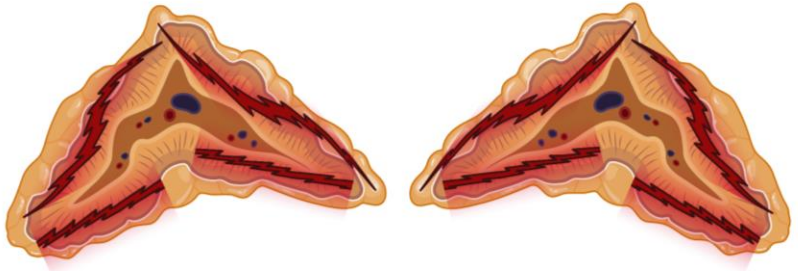
The absence of an adrenal mass does not exclude the possibility of PA; the presence of an adrenal mass(es) does not imply that it is the source of PA

Cortisol co-production from adrenal adenomas can occur in PA; all adrenal adenomas should be screened for hypercortisolism

Lateralizing PA (better term than "unilateral") does not exclude the possibility of contralateral aldosterone producing foci that may contribute to recurrent, residual, and/or persistent PA following unilateral adrenalectomy

Seeing is Believing





"Unilateral"
"Aldosterone-producing adenoma"

vs.

"Bilateral"
"Adrenal Hyperplasia"

The majority of primary aldosteronism is attributable to diffuse, bilateral, microscopic foci of aldosterone production

Diagnostic Testing Complexity

Key Point: The landscape of PA testing is dominated by *relatively arbitrary* and *unnecessarily complex* practices that rely on *unvalidated* diagnostic thresholds

Diagnostic Testing

There is no reference/gold-standard diagnostic
Diagnostic thresholds are relatively arbitrary and not rigorously validated

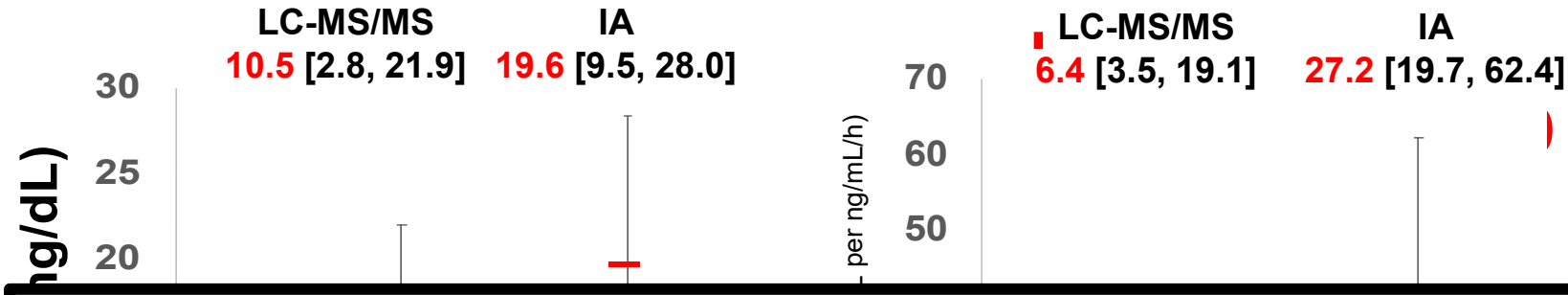
ARR ➡ **Relatively Arbitrary Thresholds**
30, 25, 20, etc.

Aldosterone ➡ **Relatively Arbitrary Thresholds**
20, 15, 10 ng/dL, etc.

Aldosterone Suppression Tests ➡ **Multiple Protocols**
Arbitrary Thresholds

Aldosterone Assays

Immunoassay → LC-MS/MS

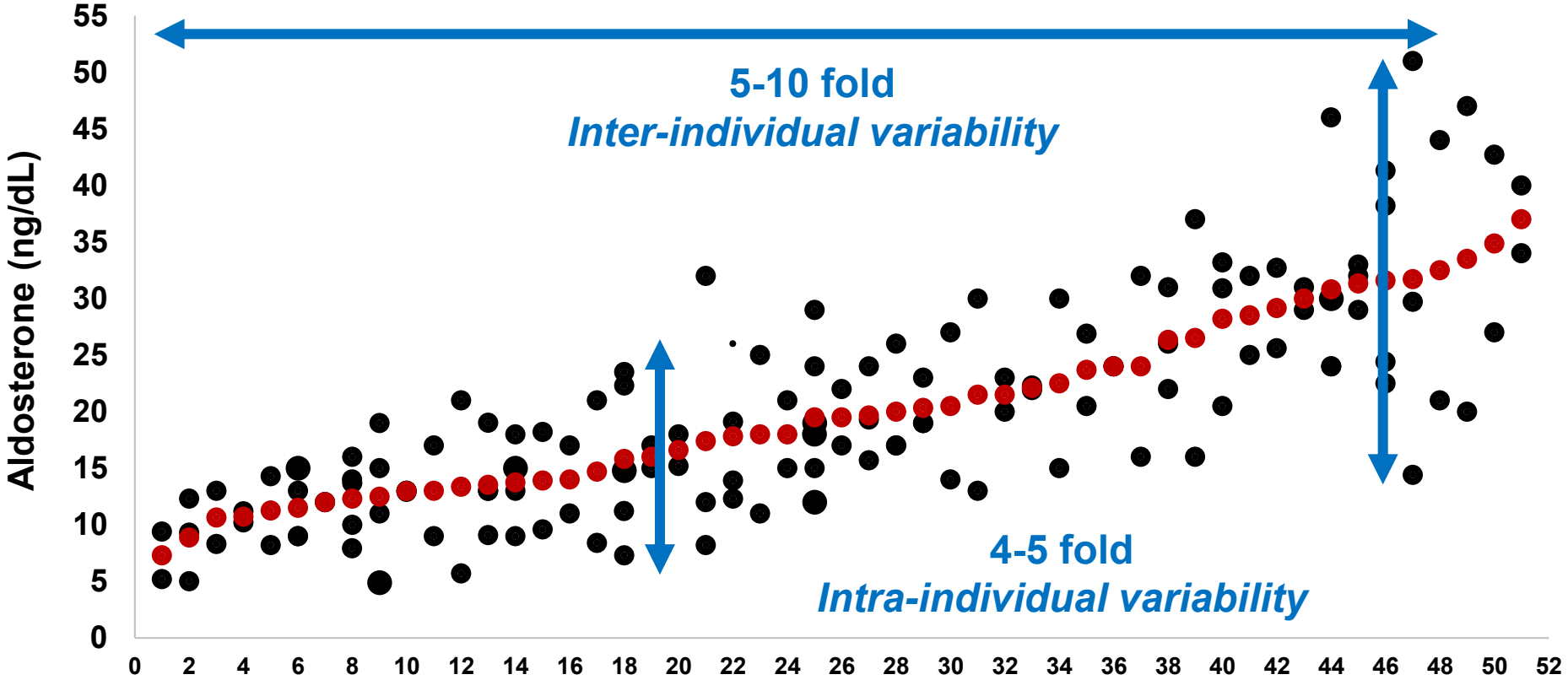


LC-MS/MS aldosterone assays require you to re-calibrate your expectations and interpretations

Brown et al. Journal of the Endocrine Soc 2022

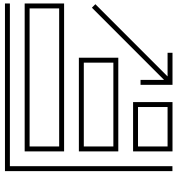
Variability of Aldosterone Production

Variability of Aldosterone Production



Yozamp et al. Hypertension 2021

Variability of Aldosterone Production



ALDO Thresholds

< 15 ng/dL: **49%**

< 10 ng/dL: **29%**

A single aldosterone measurement should not be used to confidently *exclude* the possibility of PA when the pre-test probability is high

Yozamp et al. Hypertension 2021

Over-Reliance on “Confirmatory” Testing

BETTER TERMINOLOGY

“Aldosterone Suppression Tests”

Aldosterone Suppression Tests

1. Oral sodium suppression test
2. Supine Saline suppression test
3. Seated Saline suppression test
4. Captopril challenge test
5. Fludrocortisone suppression test
6. Losartan suppression test
7. Dex-captopril-valsartan suppression test
8. IV Furosemide challenge test
9. Oral furosemide challenge test
10. Upright Posture test
11. ….

Continuum of Primary Aldosteronism

Arbitrary/conventional diagnostic thresholds aside

How common is "*inappropriate, non-suppressible, renin-independent aldosterone production*"
(aka *Primary Aldosteronism Pathophysiology*)?

Aldosterone Suppression Test → **Visualize the spectrum of PA**
(agnostic of conventional thresholds)

Continuum of Primary Aldosteronism

Oral Sodium Suppression Test

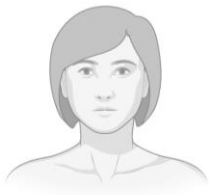
Brown et al. *Annals of Int Med* 2020

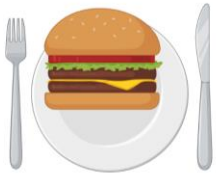
Continuum of Primary Aldosteronism

Oral Sodium Suppression Test

Supplemental Na^+ Intake

~2-4 g/d x 3-4 days





+

Mean U.S. Dietary Na^+ Intake

~3.5 g/d

Net Summary

~4-6 g/d Na^+ x 3-4d
~1.5 L/d H_2O/NS x 3-4d

Physiologic Expectations

ECV/IVV Expansion
↓Renin
↓AngII
↓**Aldosterone**

Brown et al. *Annals of Int Med* 2020

Continuum of Primary Aldosteronism

CONTINUUM: severity spectrum of non-suppressible, renin/AngII-independent aldosterone production

This is physiologic

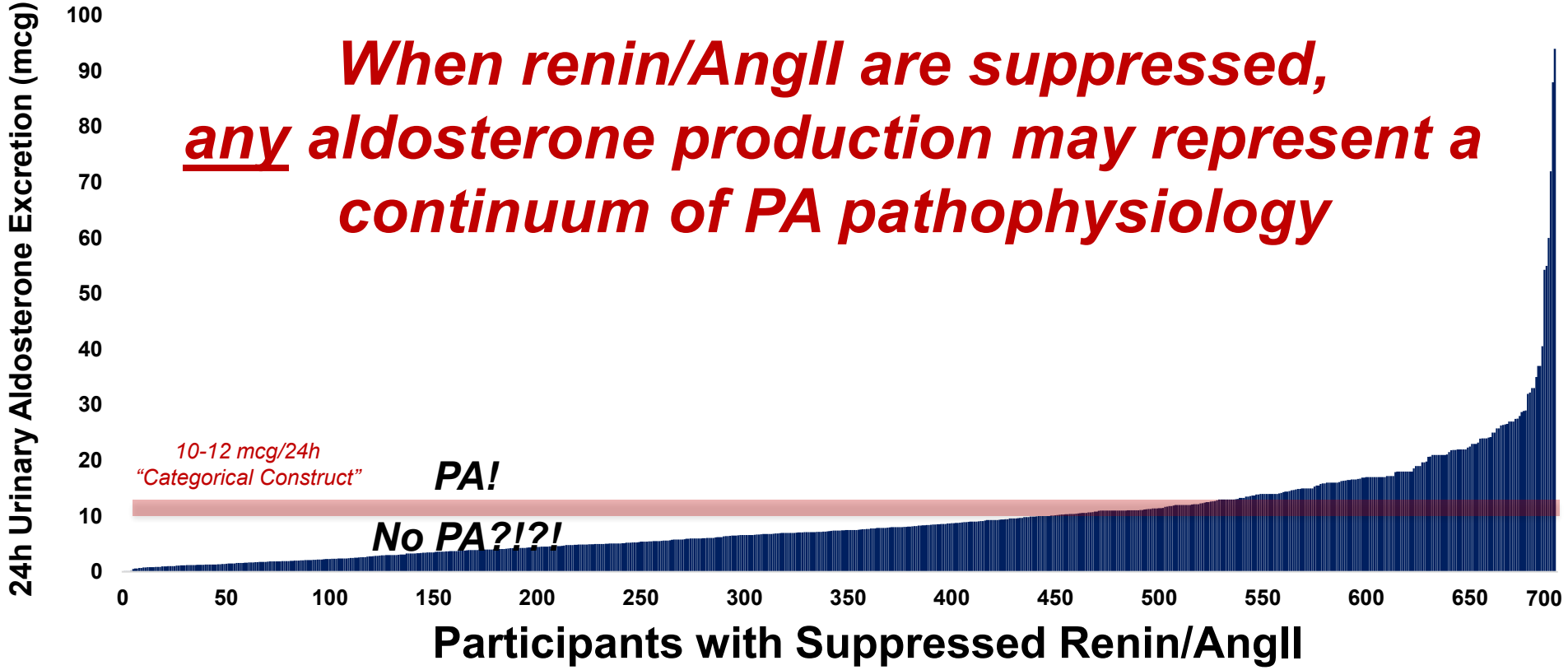
When does physiology end?
When does pathophysiology begin?

This is pathophysiologic (aka overt PA)

Number of Participants with Suppressed Renin/AngII

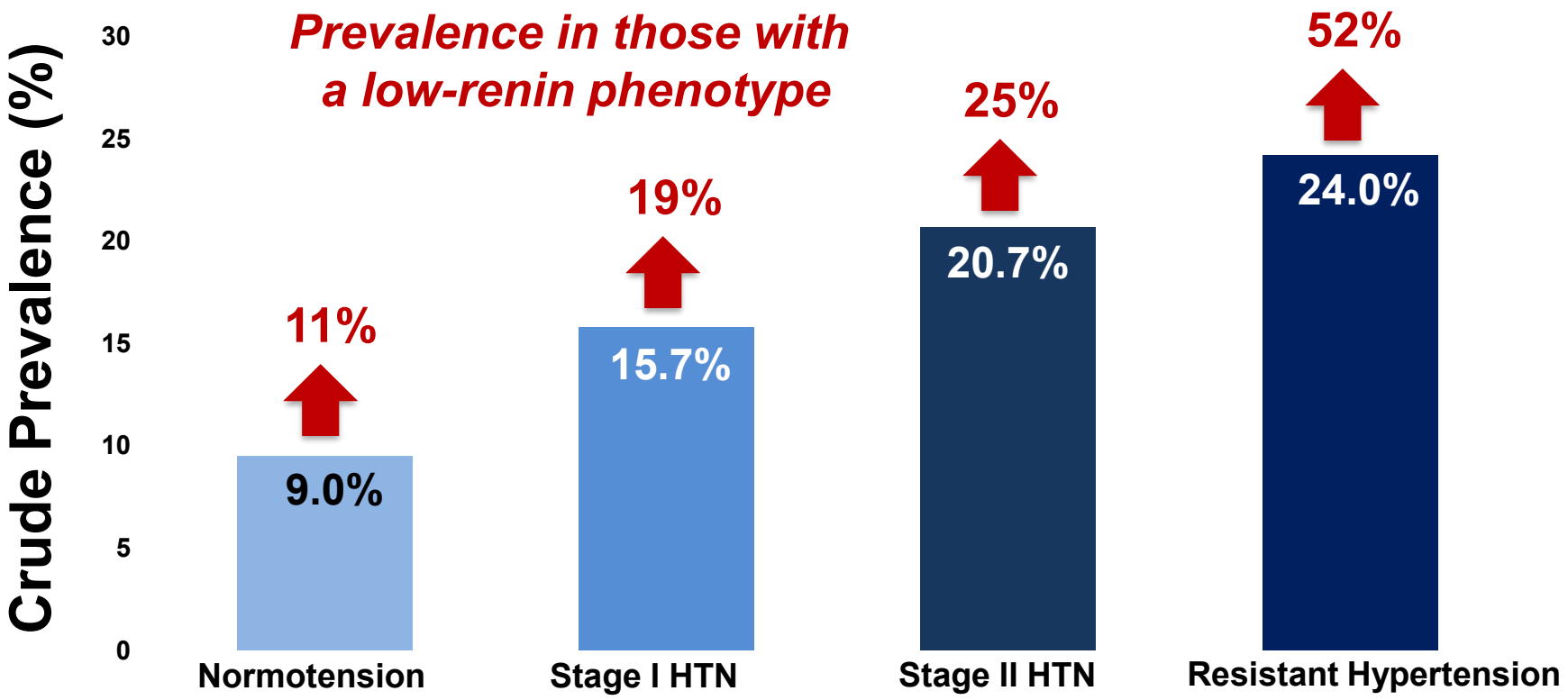
Brown et al. *Annals of Int Med* 2020

Continuum of Primary Aldosteronism



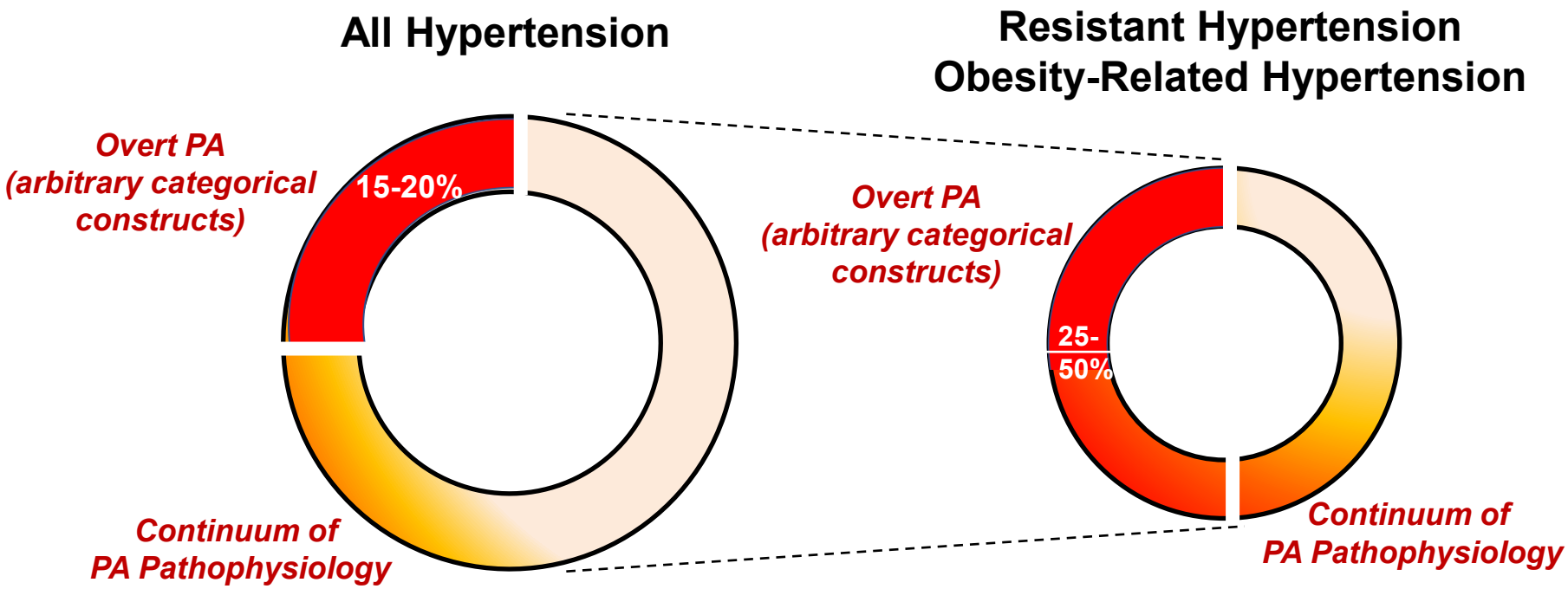
Brown et al. *Annals of Int Med* 2020

The Prevalence of Primary Aldosteronism



Brown et al. *Annals of Int Med* 2020

The Prevalence of Primary Aldosteronism

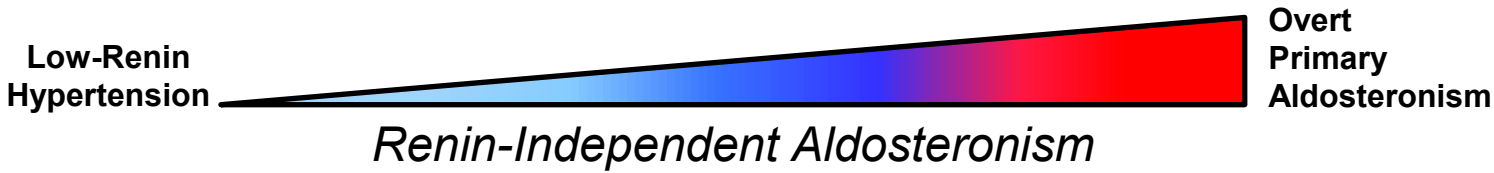


Vaidya et al. *Am J Hypertension* 2022
Tsai et al. *Circulation* 2026
Parisien-La Salle et al. *JACC BTS* 2026

Confirmatory Testing is No Longer Recommended for Diagnosing PA

For decades, diagnosing PA *required* the use of one of many different confirmatory tests, each with their own unique protocol, labor, resources, expenses, and each with their own relatively arbitrary interpretation schemes

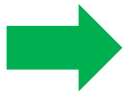
Yet...there is no official biochemical definition for PA



Confirmatory Testing is No Longer Recommended for Diagnosing PA

Eminence-Based Medicine

Well-intended approaches for PA determined largely based on expert assessments of evidence and personal opinions and experiences



Evidence-Based Medicine

Approaches for PA determined following independent, unbiased, and systematic assessments for the presence, or absence, of evidence, and reflecting the quality of evidence

Confirmatory Testing is No Longer Recommended for Diagnosing PA

Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline

Gail K. Adler,[1] Michael Stowasser,[2] Ricardo R. Correa,[3] Nadia Khan,[4] Gregory Kline,[5] Michael J. McGowan,[6] Paolo Mulatero,[7] M. Hassan Murad,[8] Rhian M. Touyz,[9] Anand Vaidya,[1] Tracy A. Williams,[10] Jun Yang,[11,12] William F. Young,[8] Maria-Christina Zennaro,[13,14] and Juan P. Brito[8,15]

A Systematic Review Supporting the Endocrine Society Clinical Practice Guideline on Management of Primary Aldosteronism

Magdoleen H. Farah,[1,2] Moustafa Hegazi,[1,2] Mohammed Firwana,[1,2] Mohamed Abusalih,[1,2] Samer Saadi,[1,2] Mohammad Al-Kordi,[1,2] Arwa Elsheikh,[3] Zhen Wang,[1,2] Leslie Hassett,[4] Irina Bancos,[5] and M. Hassan Murad[1,2,6]

ES Guidelines: Adler et al. JCEM 2025
ES Guideline Evidence Assessment: Farah et al. JCEM 2025

Confirmatory Testing is No Longer Recommended for Diagnosing PA

NEW UPDATE

Medical Reversal / PROGRESS

Confirmatory testing is no longer recommended to diagnose or exclude PA

ES Guidelines: Adler et al. JCEM 2025

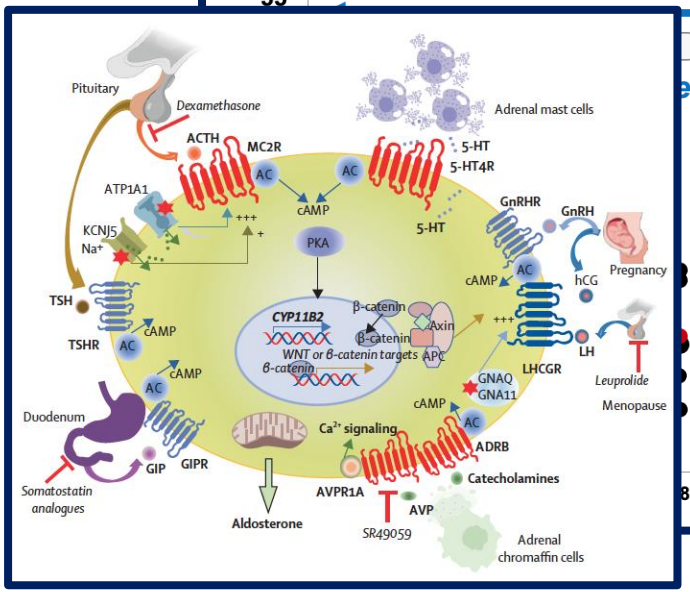
ES Guideline Evidence Assessment: Farah et al. JCEM 2025

Why Are Suppression Tests Unreliable?

Lack of validated thresholds to define pathophysiology

Variability & imprecision of aldosterone levels

Non-RAS **duction**



et al. *Lancet D&E* 2024
m J Hypertension 2025
Parksook et al. *Eur J Endo* 2025

“Confirmatory” Tests

Are better described as “aldosterone suppression tests”

Are not validated or calibrated or reproducible…

They are not accurate diagnostic tests…

They are not accurate at predicting lateralization…

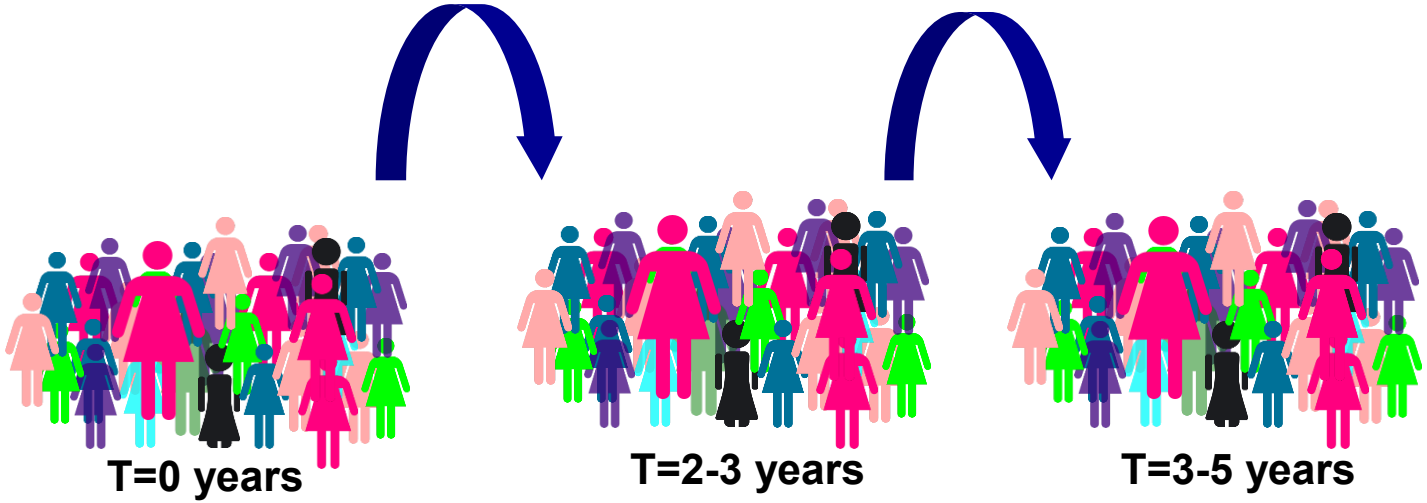
Are labor and resource intensive…

Add little PPV, but contribute to false-negative case detection...

Are NOT necessary or supported by the evidence

Is the continuum of Primary Aldosteronism Pathophysiology clinically relevant?

Prospective Cohort Studies



Normotensive Cohort Studies

Normotensive

Magnitude of Aldosterone Production when Renin Suppressed

→

Arterial Stiffness
Incident Hypertension
Subclinical Structural CVD
Atrial Fibrillation
MACE

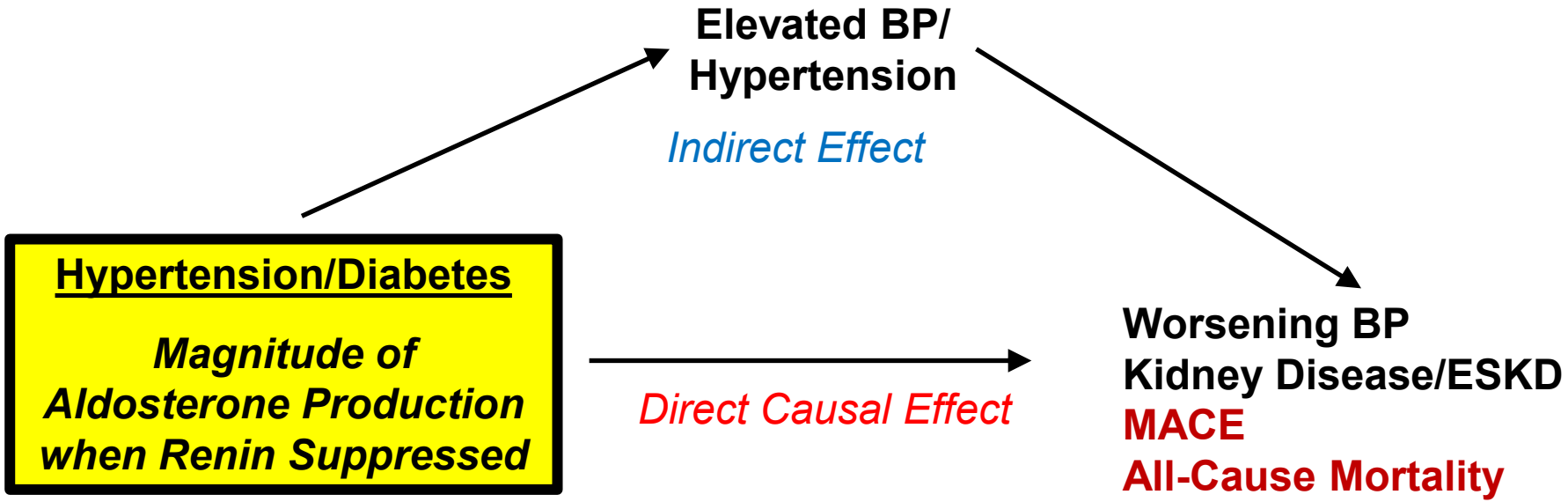
RAINE	MESA	FHS	JHS	ARIC	CARTaGENE
Young	*Multi-ethnic*	*White (mostly)*	*Black*	*Nationwide*	*Quebec*
Perth, Australia	*Nationwide*	*Framingham, MA*	*Jackson, MS*	*USA*	*Canada*

Brown et al. *Annals of Internal Medicine* 2017
Brown et al. *Hypertension* 2022

Vasan et al. *NEJM* 2004
Newton-Cheh et al. *Hypertension* 2007

Joseph et al. *Circulation* 2021
Hundemer et al. *Circulation* 2023
Goupil et al. *Circulation* 2025

Hypertensive Cohort Studies



FHS
White (mostly)
Framingham, MA

MESA
Multi-ethnic
USA

JHS
Black
Jackson, MS

CONPASS
Chinese
Chongqing, China

EIMDS
Chinese
Chongqing, China

UK BIOBANK
Nationwide
UK

ARIC
Nationwide
USA

CRIC
Nationwide
USA

CARTaGENE
Quebec
Canada

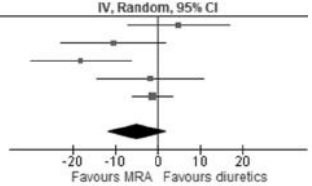
Brown et al. *Annals Int Med* 2017; Inoue et al. *Hypertension* 2020; Joseph et al. *Circulation* 2021; Hu et al. *JAHA* 2021; Brown et al. *Hypertension* 2022; Verma et al *Eur Heart J* 2022; Hu et al Metabolism 2023; Hundemer et al. 2023, Goupil et al. *Circulation* 2025

Meta-Analysis of RCTs in LRH

MRA vs Thiazides (- 4.8 mmHg)

Study or Subgroup	MRA Mean [mmHg]	MRA SD [mmHg]	MRA Total	Diuretic Mean [mmHg]	Diuretic SD [mmHg]	Diuretic Total	Weight	Mean Difference IV, Random, 95% CI	Year
Adlin	-24	15.8	18	-29	15.1	10	17.8%	5.00 [-6.87, 16.87]	1972
Vaughan	-28.3	17.8	21	-17.9	19.7	16	17.2%	-10.40 [-22.69, 1.89]	1973
Spark	-32	11.4	10	-13.9	15.3	10	17.9%	-18.10 [-29.93, -6.27]	1974
Ferguson	-13.1	15.1	11	-11.4	15.1	11	16.8%	-1.70 [-14.32, 10.92]	1977
Hood (bendroflumethiazide)	-11.6	13.8	51	-10.5	10.4	51	30.3%	-1.10 [-5.84, 3.64]	2007
Total (95% CI)			111			98	100.0%	-4.75 [-11.91, 2.40]	

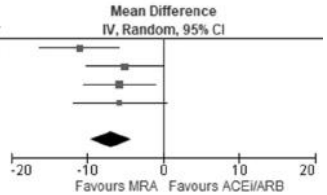
Heterogeneity: Tau² = 38.05; Chi² = 10.05, df = 4 (P = 0.04); I² = 60%
Test for overall effect: Z = 1.30 (P = 0.19)



MRA vs ACEi/ARB (- 6.8 mmHg)

Study or Subgroup	MRA Mean [mmHg]	MRA SD [mmHg]	MRA Total	ACEi/ARB Mean [mmHg]	ACEi/ARB SD [mmHg]	ACEi/ARB Total	Weight	Mean Difference IV, Random, 95% CI	Year
Flack 2003	-16	15.5	60	-5	14.2	62	24.7%	-11.00 [-16.28, -5.72]	2003
Williams 2004	-15.3	15.7	67	-10.3	16	82	26.3%	-5.00 [-10.11, 0.11]	2004
Weinberger 2005	-15.8	15.8	86	-10.1	15.4	82	30.4%	-5.70 [-10.42, -0.98]	2005
Hood 2007 (losartan)	-11.6	13.8	51	-5.9	17.7	51	18.5%	-5.70 [-11.86, 0.46]	2007
Total (95% CI)			264			277	100.0%	-6.83 [-9.56, -4.10]	

Heterogeneity: Tau² = 0.58; Chi² = 3.24, df = 3 (P = 0.36); I² = 7%
Test for overall effect: Z = 4.90 (P < 0.00001)



MRA vs β-blocker (- 4.5 mmHg)
MRA vs α-blocker (- 4.0 mmHg)

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial


ESC European Heart Journal - Cardiovascular Pharmacotherapy ORIGINAL ARTICLE

Spironolactone effect on the blood pressure of patients at risk of developing heart failure: an analysis from the HOMAGE trial

João Pedro Ferreira, Timothy Collier, Andrew L. Clark, Mamas A. Mamas, Hans-Peter Brunner-La Rocca, Stephane Heymans, Arantxa González, Fozia Z. Ahmed, Johannes Petutschnigg, Blerim Mujaj, Joe Cuthbert, Philippe Rouet, Pierpaolo Pellicori, Beatrice Mariottoni, Franco Cosmi, Frank Edelmann, Lutgarde Thijs, Jan A. Staessen, Mark Hazebroek, Job Verdonschot, Patrick Rossignol, Nicolas Girerd, John G. Cleland, and Faiez Zannad

Williams et al. Lancet 2015; Shah et al. JHH 2024

KEY CONCEPT

Greater aldosterone production in the context of a low-renin phenotype is associated with progressive risk for CV and kidney disease and responds preferentially to MRA therapy

PA Pathophysiology is *any* aldosterone production when renin is low; there is no lower limit of aldosterone that confidently excludes PA

ASIs appear to be a new anti-HTN class, highly effective at lowering aldosterone, and BP in R-HTN, uncontrolled HTN, and PA

They affirm that a large proportion of essential/idiopathic HTN is aldosterone-mediated

"Medical Aldosterone-ectomy" may be the treatment of the future

Key Learning Points

Essential hypertension is primarily aldosteronism

PARADIGM SHIFT

Primary aldosteronism is not a rare cause of "secondary HTN"; rather it is a highly prevalent and modifiable contributor to HTN and CVD

Aldosterone-mediated hypertension is very common

Key Resources

Vaidya A et al. *New England Journal of Medicine* 2025; 392(4): e14

Vaidya et al. *Nature Reviews Disease Primers* 2026