Hypertension Excellence Centre
of the European Society of Hypertension

Università degli Studi Di Torino
Scuola di Medicina

Dipartimento di
Scienze Mediche

SIIA - Sezione Regionale
Piemonte, Liguria e Valle d'Aosta

To What Extent is Low-renin Hypertension a Manifestation of PA?

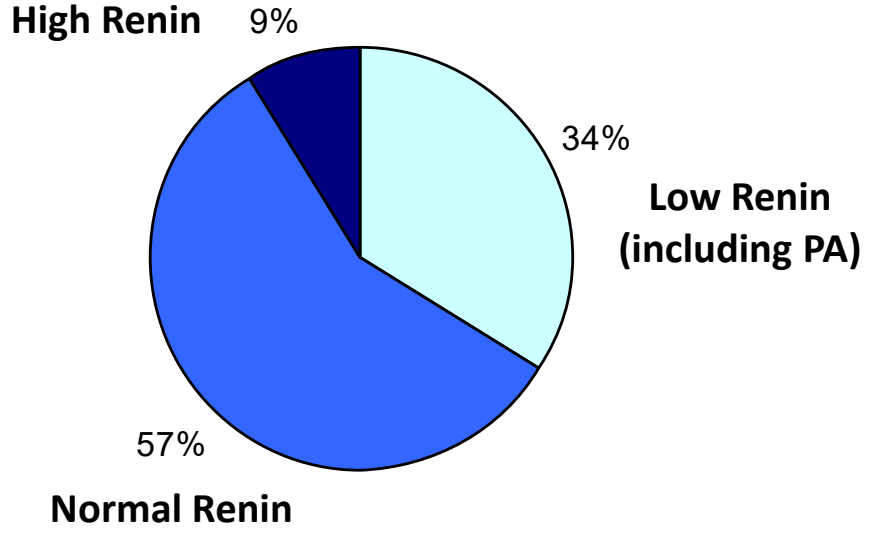
Paolo Mulatero

Division of Internal Medicine and Hypertension
University of Torino - Italy

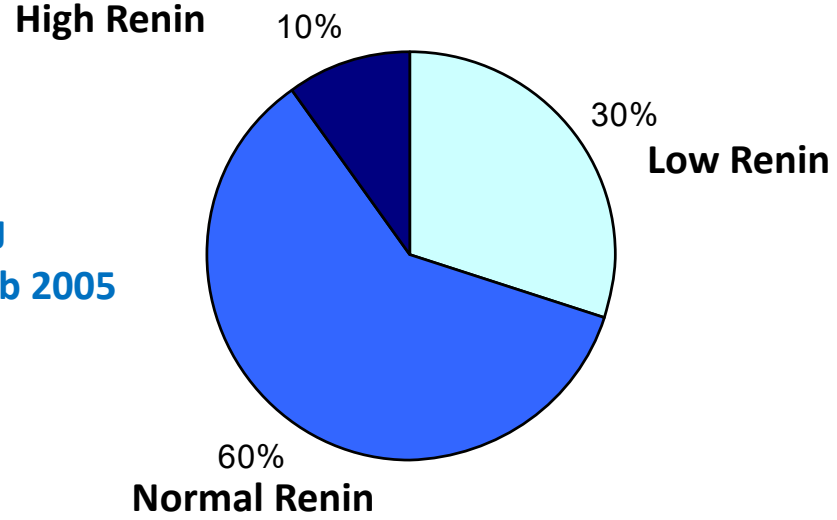
感谢台湾之友的邀请

Prevalence of Different Renin Phenotypes

PATO Study
Monticone S et al.
J Am Coll Cardiol 2017



Sealey J & Laragh J
Trends Endocrinol Metab 2005



Rates of BP progression and incident hypertension among non-hypertensive subjects

Vasan RS,
N Engl J Med 2004

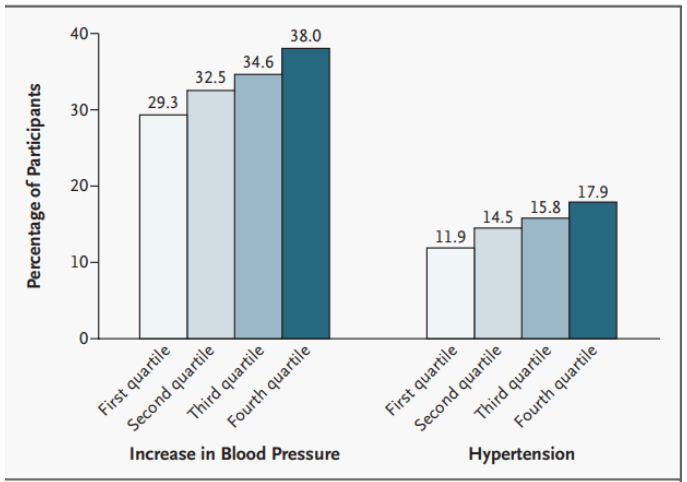
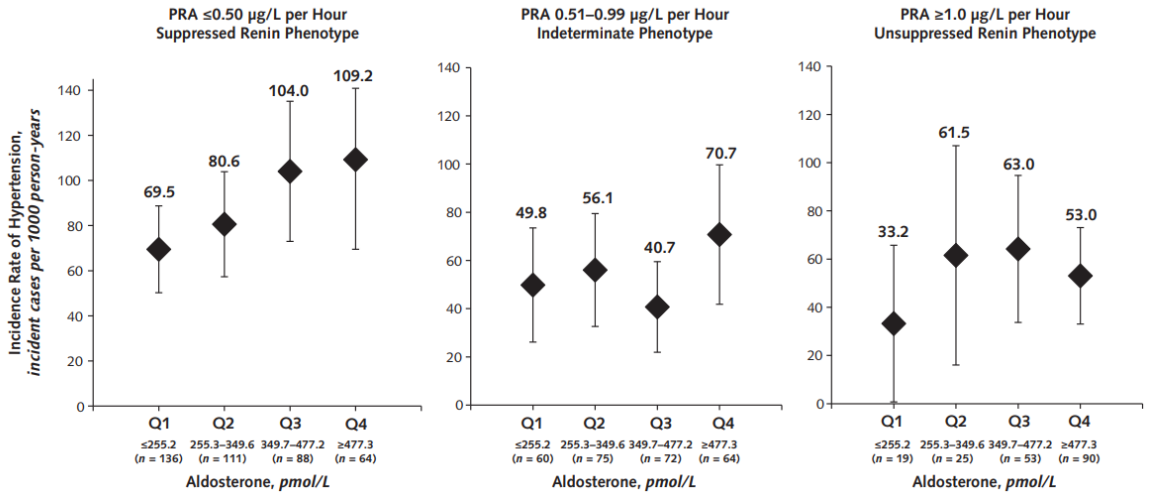


Figure 1. Age- and Sex-Adjusted Rates of Blood-Pressure Outcomes at Four Years According to Quartile of Serum Aldosterone Level.

An increase in blood pressure was defined as an increment of at least one category according to the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive medications.



Brown JM,
Ann Int Med 2017

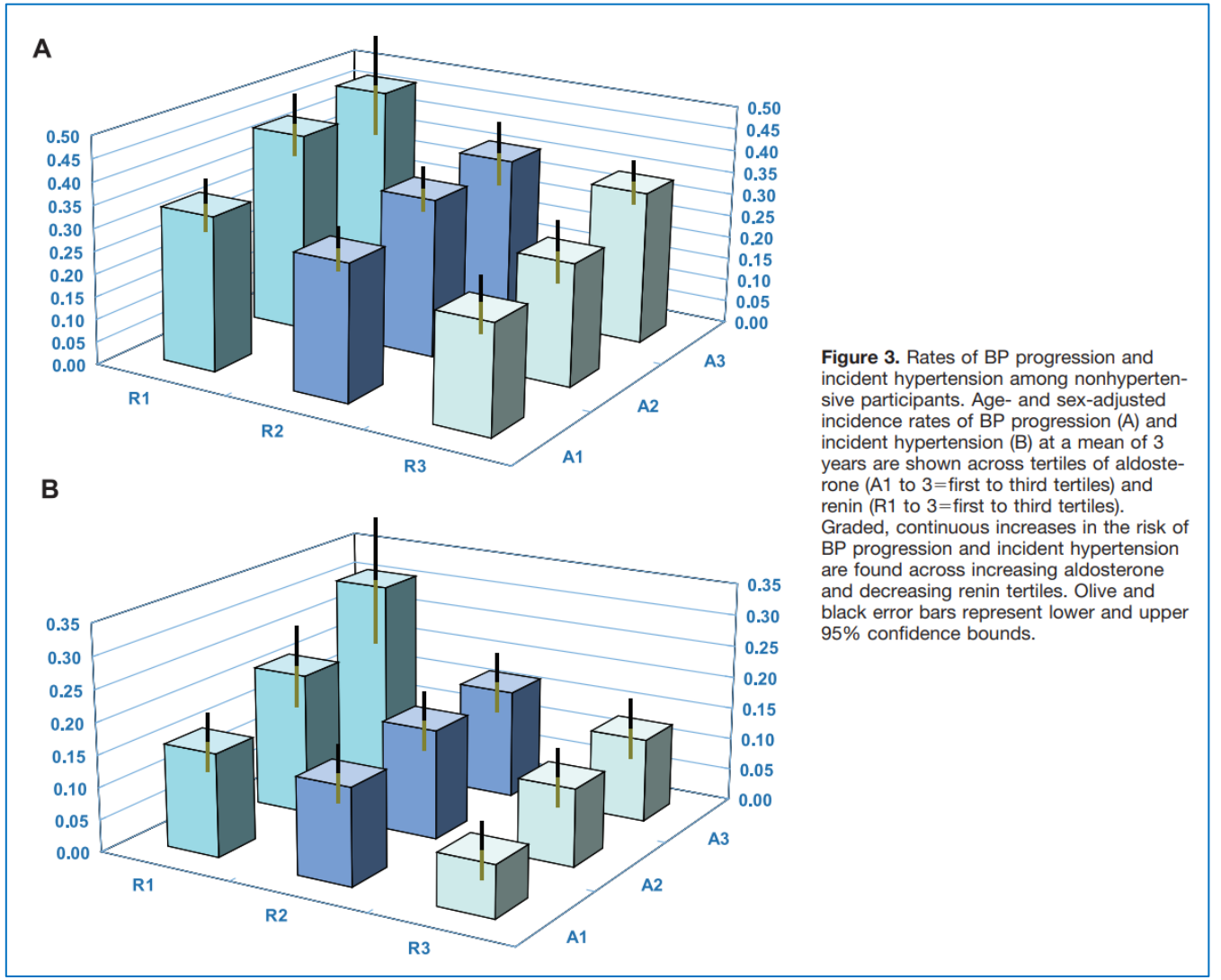
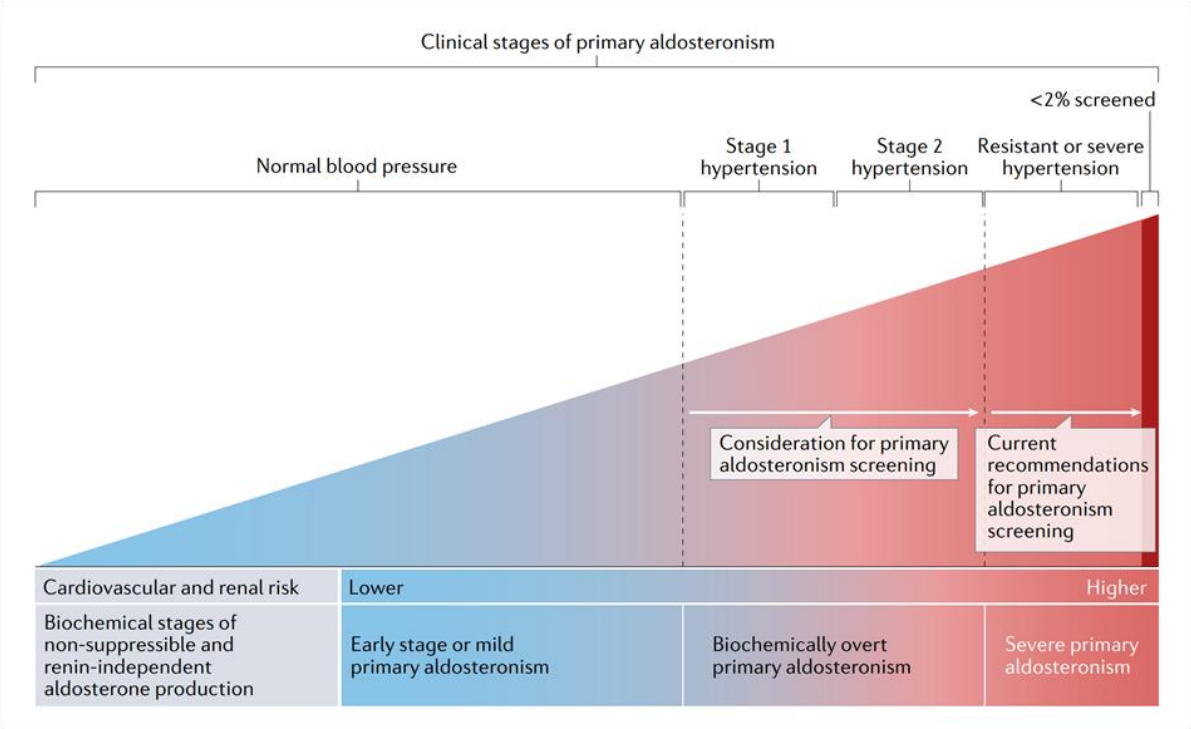


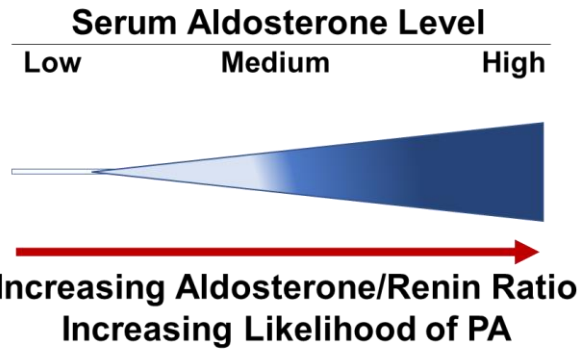
Figure 3. Rates of BP progression and incident hypertension among nonhypertensive participants. Age- and sex-adjusted incidence rates of BP progression (A) and incident hypertension (B) at a mean of 3 years are shown across tertiles of aldosterone (A1 to 3=first to third tertiles) and renin (R1 to 3=first to third tertiles). Graded, continuous increases in the risk of BP progression and incident hypertension are found across increasing aldosterone and decreasing renin tertiles. Olive and black error bars represent lower and upper 95% confidence bounds.

Newton-Cheh C,
Hypertension 2007

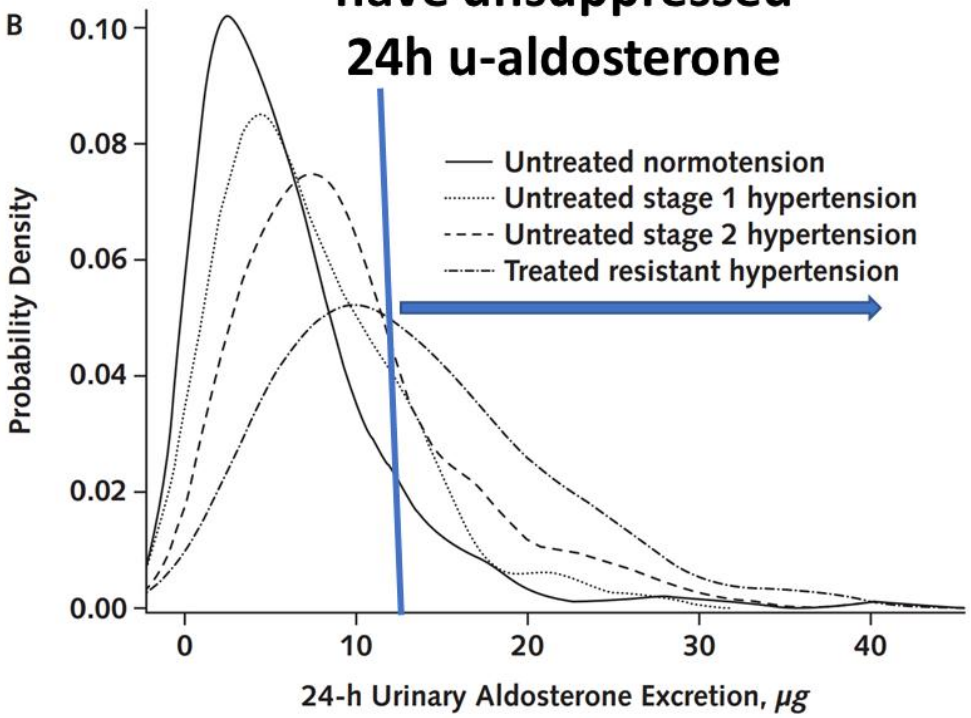
Continuum of Aldosterone Secretion



IN PATIENTS WITH HYPERTENSION
AND SUPPRESSED RENIN



~ 15-22% of hypertensives have unsuppressed 24h u-aldosterone



Brown JM. Ann Intern Med 2020

ARR Correlates with Vascular Stiffness

The Framingham Heart Study

Table 3. Association of the Entire Biomarker Panel and of Individual Biomarkers With Measures of Arterial Stiffness

Characteristics and Biomarkers†	Model R^2	Partial R^2	Global P*	β‡	P
Central pulse pressure, mm Hg	0.2683	0.0158	<0.0001	...	...
BNP	...	...	...	0.80±0.37	0.03
ARR	...	...	...	1.54±0.33	<0.0001
PAI-1	...	...	...	1.24±0.39	0.001
Fibrin	...	...	...	0.74±0.35	0.04
Carotid-femoral PWV, m/s	0.4665	0.006	0.0025	...	...
CRP	...	...	...	0.14±0.07	0.048
ARR	...	...	...	0.20±0.06	0.001
Mean arterial pressure, mm Hg	0.2075	0.0328	<0.0001	...	...
ARR	...	...	...	2.11±0.26	<0.0001
PAI-1	...	...	...	0.89±0.30	0.003
Forward pressure wave, mm Hg	0.2301	0.0103	0.0004	...	...
ARR	...	...	...	1.00±0.27	0.0002
PAI-1	...	...	...	0.80±0.31	0.01
Augmented pressure, mm Hg	0.2695	0.0119	<0.0001	...	...
CRP	...	...	...	0.62±0.17	0.0003
ARR	...	...	...	0.49±0.16	0.002

*A test of whether any of the biomarkers differed with respect to arterial stiffness–dependent measures. Covariates in the multivariable models included age, age squared, sex, heart rate, height, weight, ratio of total to high-density lipoprotein cholesterol, blood glucose, diabetes mellitus, smoking, prevalent cardiovascular disease, hormone replacement therapy, hypertension treatment, aspirin (≥3 d/wk), and lipid-lowering medication.

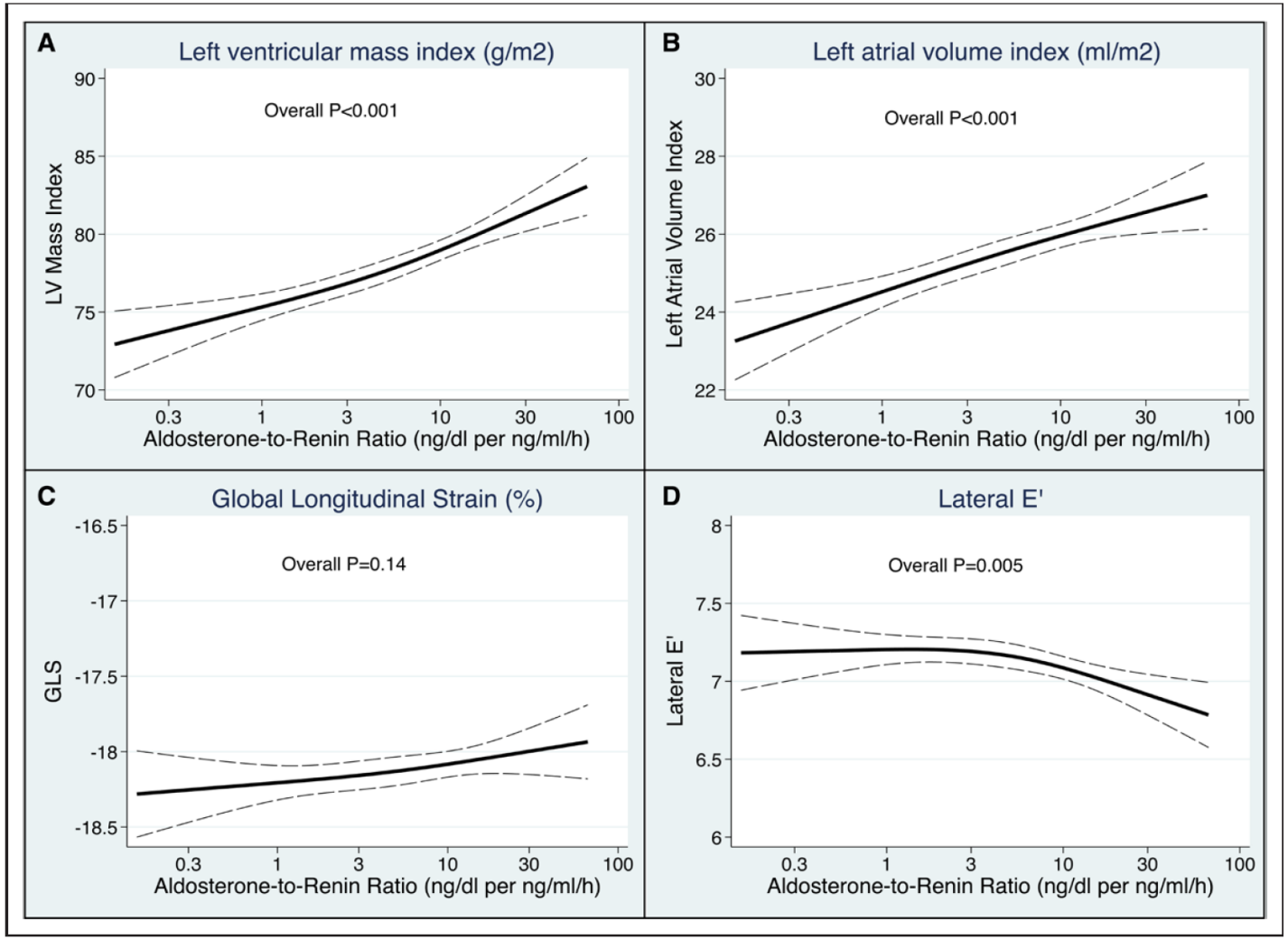
†For tonometry measures with a global $P<0.01$, individual biomarkers related ($P<0.05$) to vascular function measures after backward elimination are displayed.

‡β, the regression coefficient, shows a change in vascular function measure per 1-SD increment in log marker. Thus, an e^{SD}-fold increase in BNP (original units) results in an increase of 0.80 mm Hg in central pulse pressure.

Lieb W, Circulation 2009

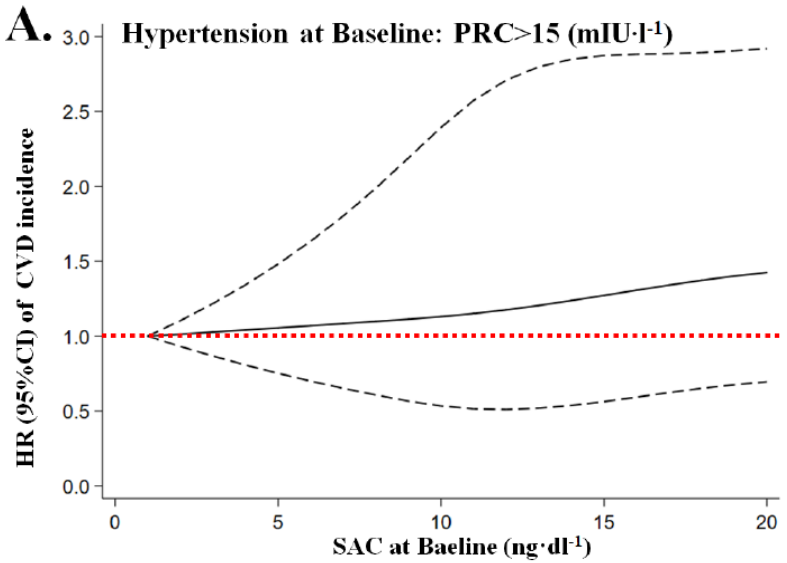
Association between ARR and cardiac structure and function

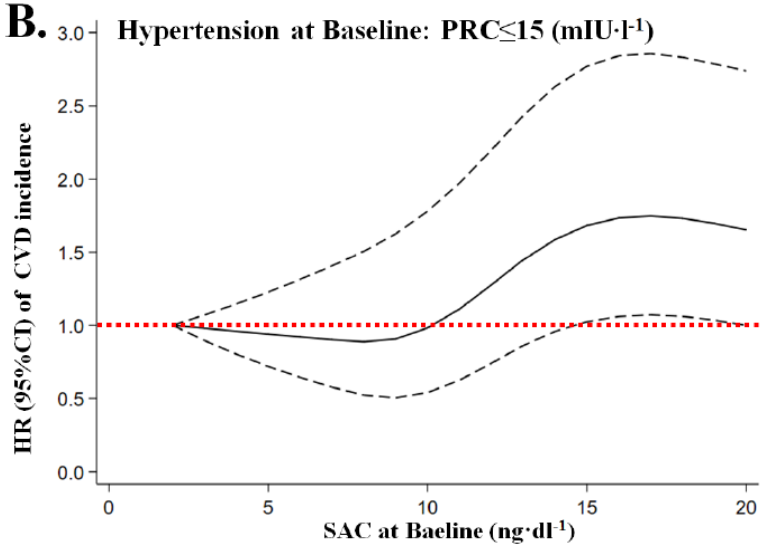
The ARIC Study



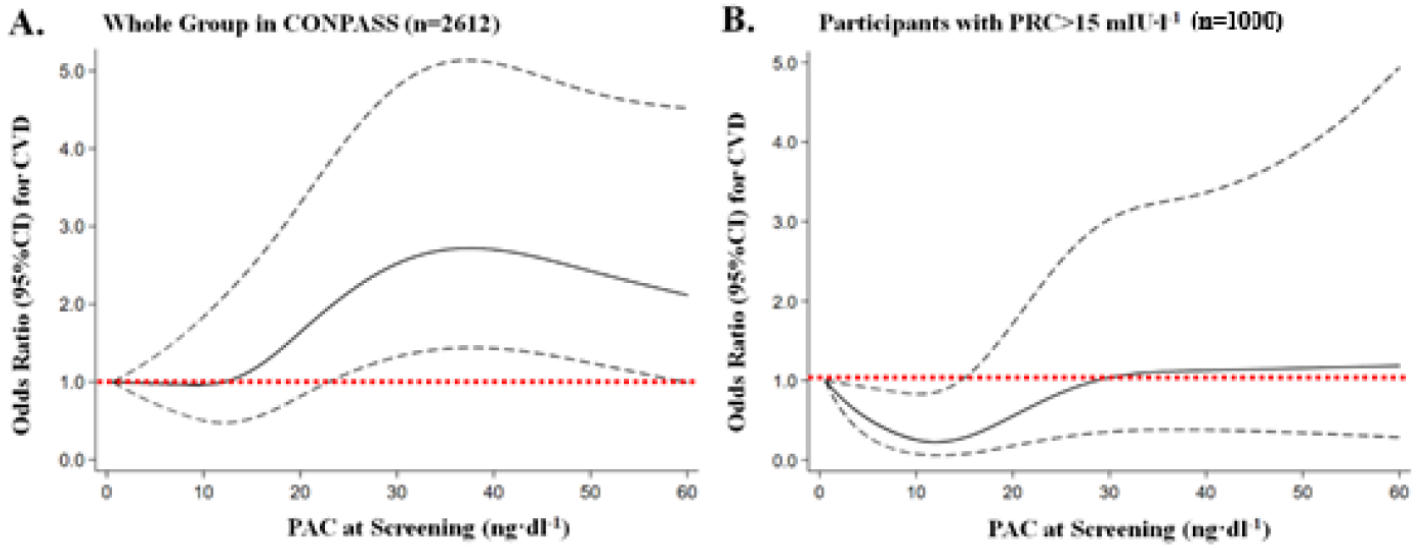
Brown J, Hypertension 2022

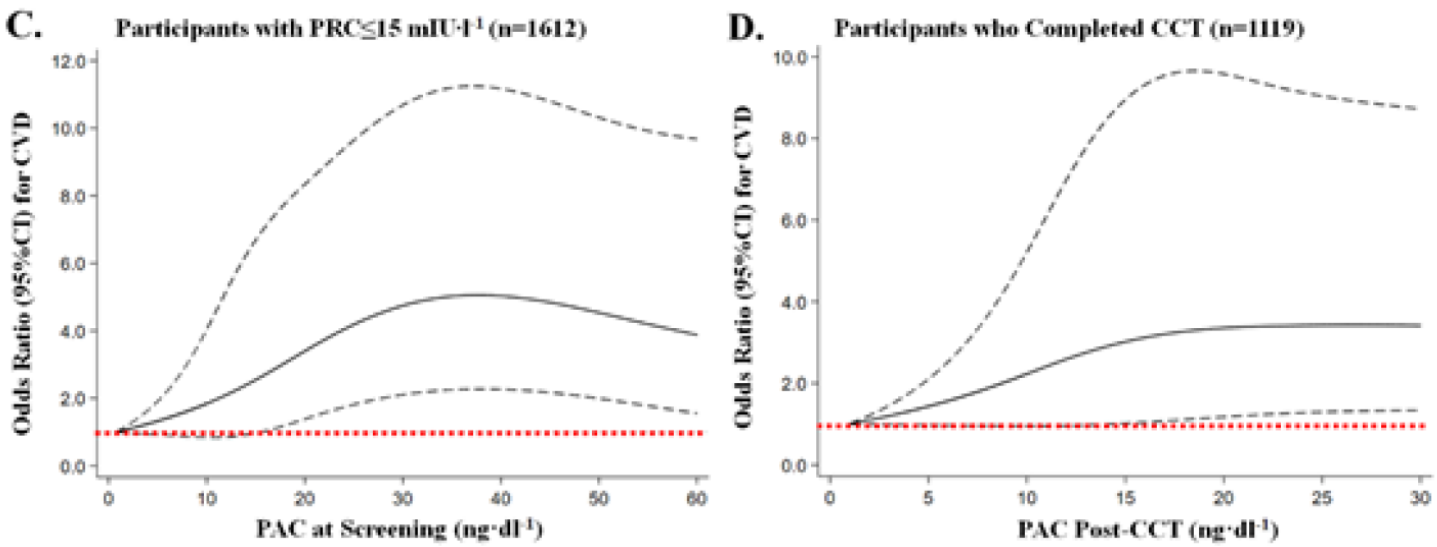
Framingham Offspring Study





COMPASS Study





Hu J, JAHA 2021

Subclinical Primary Aldosteronism and Major Adverse Cardiovascular Events: A Longitudinal Population-Based Cohort Study

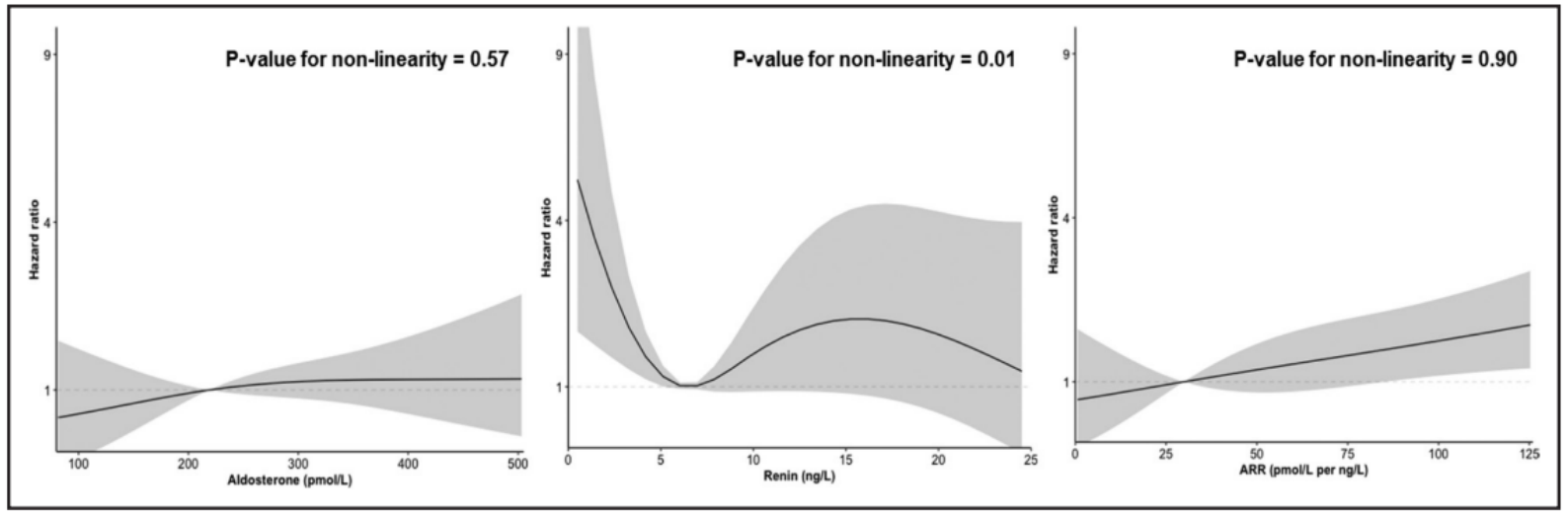


Figure 2. Assessment for nonlinear associations of aldosterone, renin, and aldosterone-to-renin ratio with major adverse cardiovascular events.

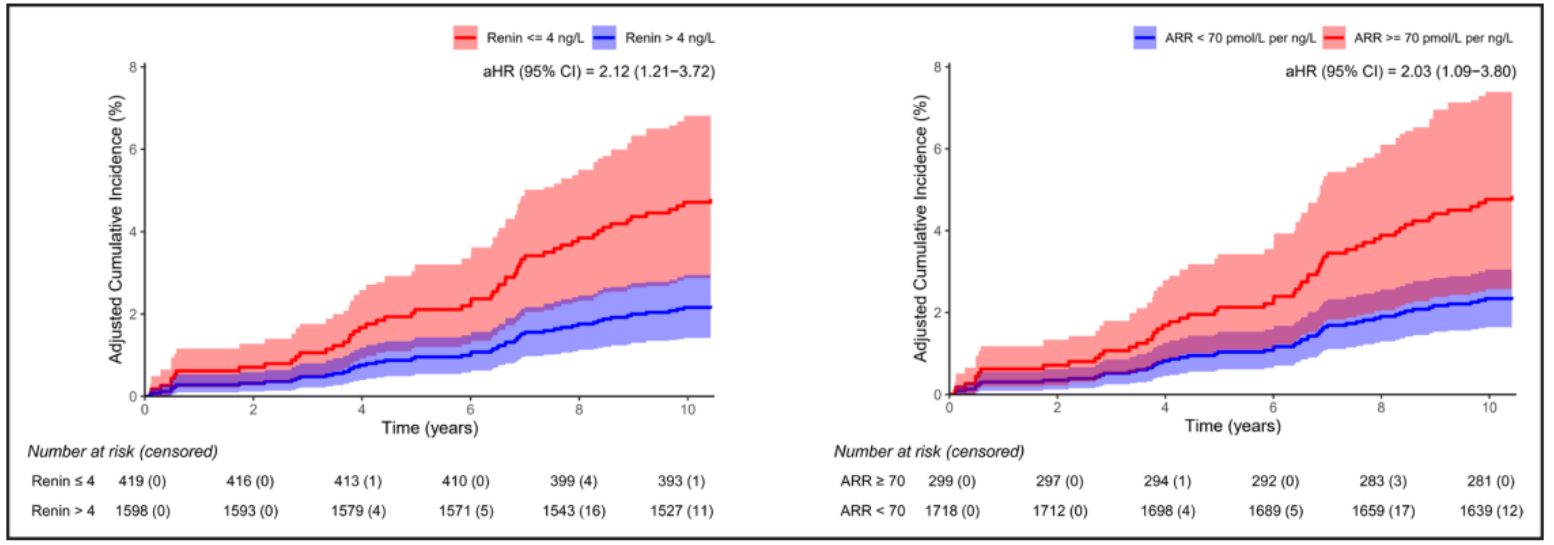
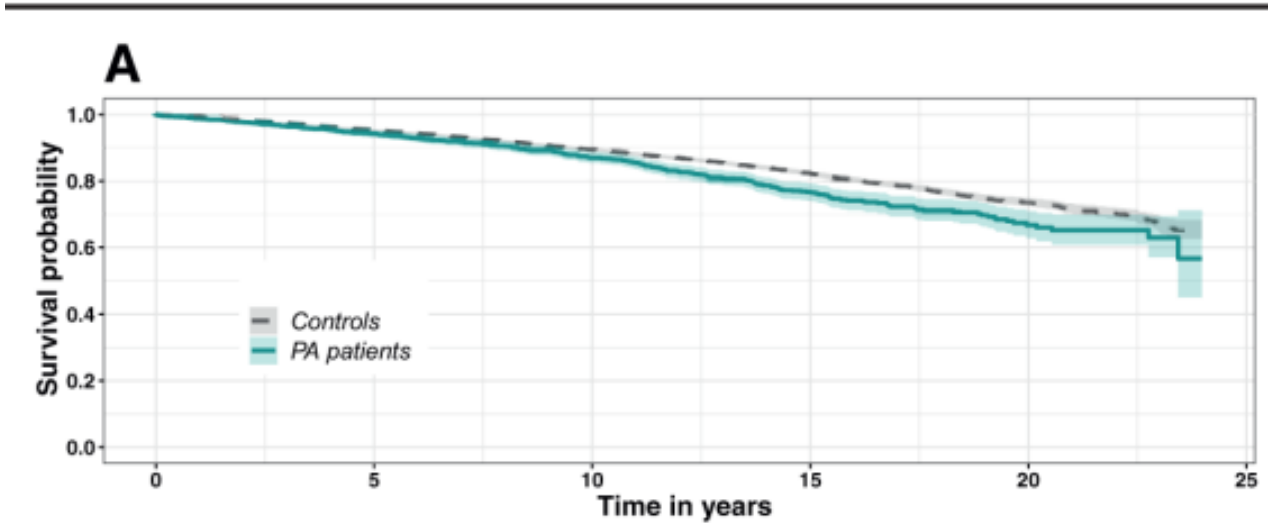


Figure 3. Adjusted cumulative incidence curves using outcome-derived thresholds for increased risk of major adverse cardiovascular events in subclinical primary aldosteronism.

Goupil R,
Circulation 2025

Mortality in Patients With Primary Aldosteronism: A Swedish Nationwide Study

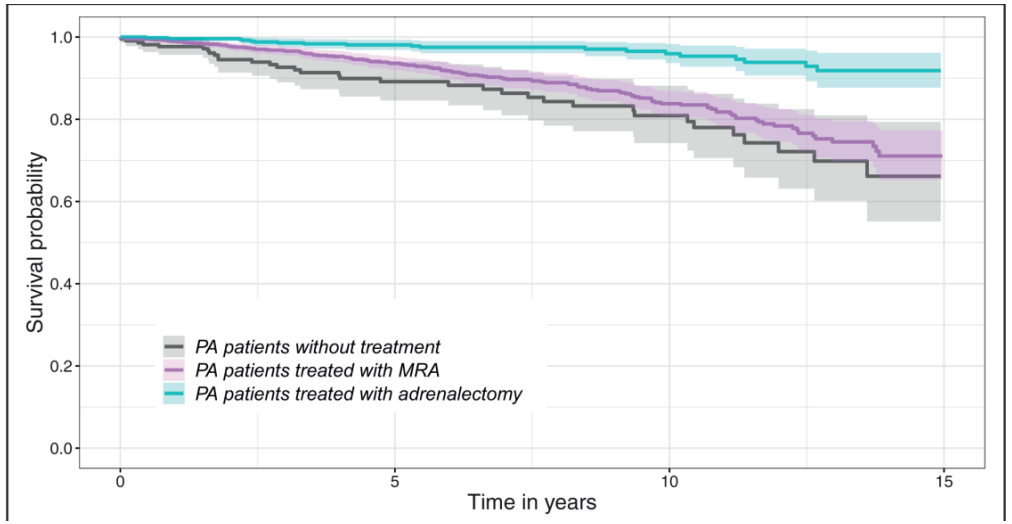


(HR 1.23 [95% CI 1.10–1.38]; P=0.0004)

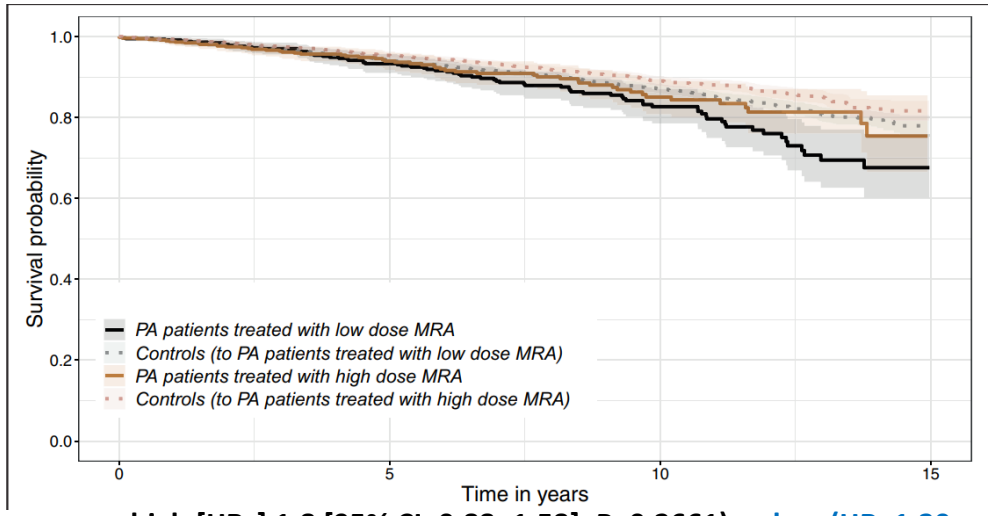
Table 2. All-Cause and Cause-Specific Mortality in Patients With PA and Controls Matched for Age, Gender, and County of Residence

Outcome	No. (%) of deaths in PA	No. (%) of deaths in controls	Model 1, HR (95% CI)*	P	Model 2, HR (95% CI)†	*P* value
All-cause mortality	346 (14.3)	2736 (11.3)	1.36 (1.21–1.52)	<0.0001	1.23 (1.10–1.38)	0.0004
Cause-specific mortality‡						
Cardiovascular death	134 (5.5)	851 (3.5)	1.71 (1.43–2.05)	<0.0001	1.57 (1.30–1.89)	<0.0001
Coronary heart disease	49 (2.0)	368 (1.5)	1.43 (1.06–1.92)	0.0199	1.27 (0.93–1.72)	0.1334
Stroke	23 (1.0)	118 (0.5)	2.14 (1.37–3.35)	0.0008	1.85 (1.16–2.93)	0.0094
Other	212 (8.8)	1885 (7.8)	1.20 (1.04–1.38)	0.0121	1.08 (0.94–1.25)	0.2858

Gkaniatsa E, Hypertension 2023



patients with PA treated with adrenalectomy [HRs], 1.04 [95% CI, 0.77–1.42]; P=0.7850), mineralocorticoid receptor antagonists (MRA; HR, 1.23 [95% CI, 1.02–1.496]; P=0.0278), or neither adrenalectomy nor MRA (HR, 2.51 [95% CI, 1.72–3.67]; P<0.0001)



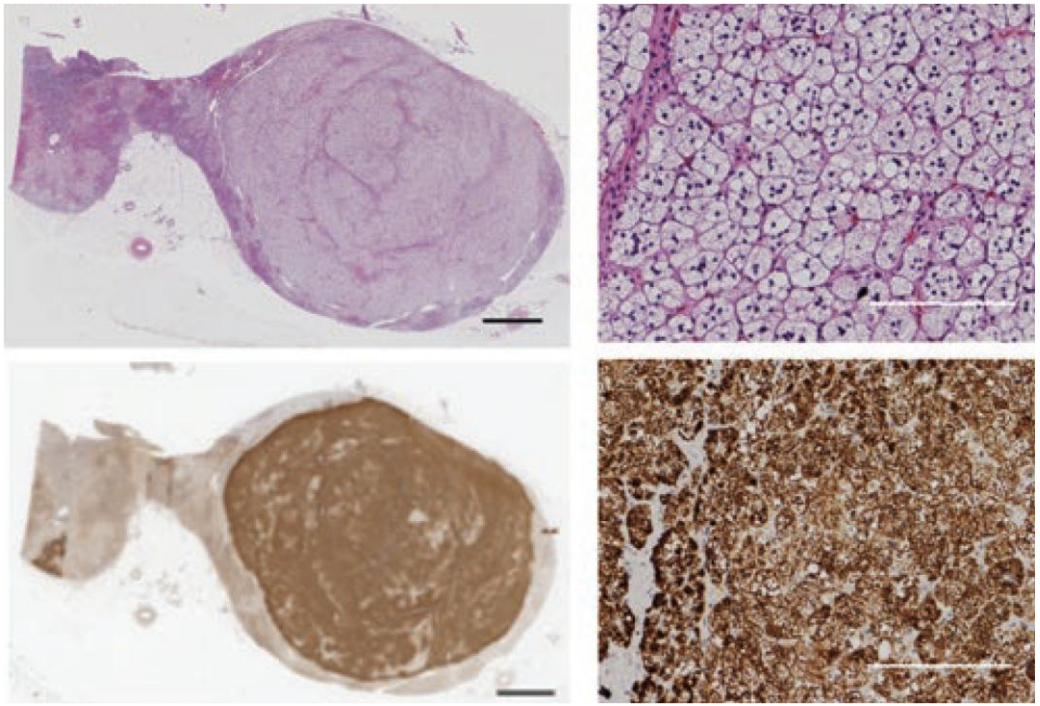
high [HRs] 1.8 [95% CI, 0.88–1.58]; P=0.2661) or low (HR, 1.30 [95% CI, 1.02–1.66]; P=0.0365) doses of MRA and their matched controls.

HISTALDO consensus

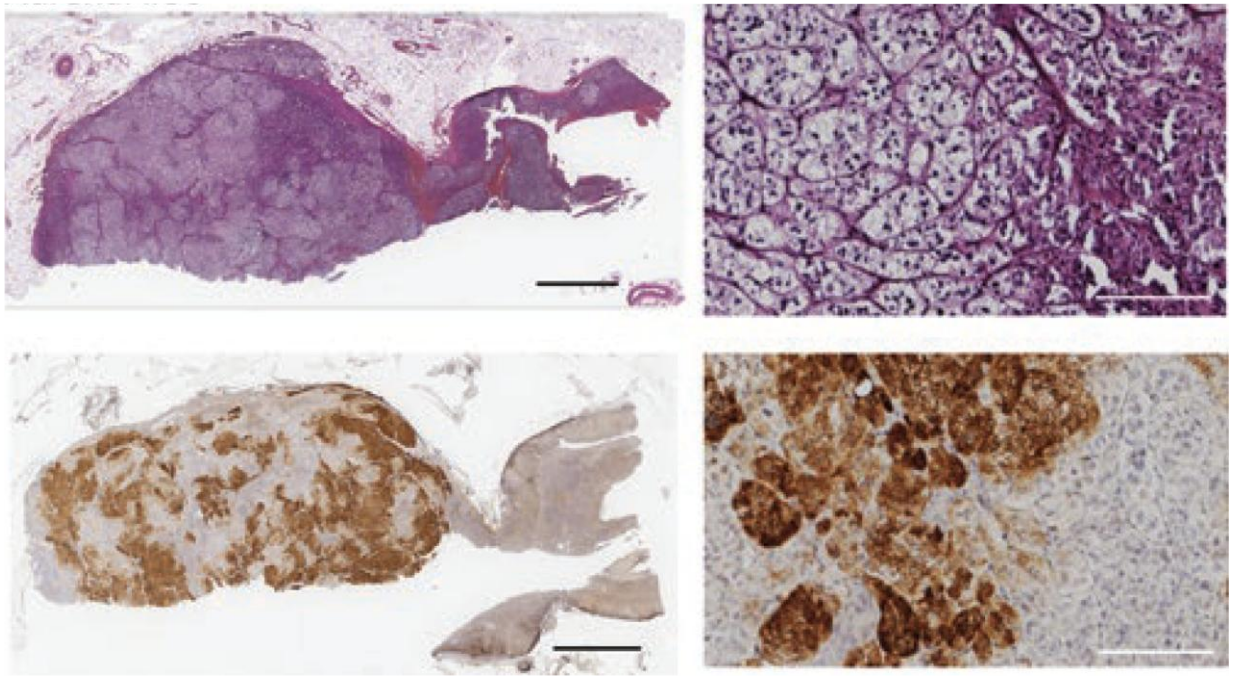
Classical	Aldosterone-producing adenoma	APA	Well circumscribed CYP11B2[a]-positive solitary neoplasm (≥ 10 mm diameter) composed of clear or compact eosinophilic cells or both cell types.
	Aldosterone-producing nodule	APN	CYP11B2-positive lesion (<10 mm diameter)[b] morphologically visible with hematoxylin-eosin staining. An APN often displays a gradient of CYP11B2 immunostaining decreasing in intensity from the outer to the inner part of the lesion.
Non- Classical	Aldosterone-producing micronodule (formally known as aldosterone-producing cell cluster)	APM	CYP11B2-positive lesion (<10 mm diameter)[b] composed of zona glomerulosa cells located beneath adrenal capsule that do not differ in morphology from adjacent adrenocortical cells by hematoxylin-eosin staining. An APM often displays a gradient of CYP11B2 immunostaining decreasing in intensity from the outer to the inner part of the lesion.
	Multiple aldosterone-producing nodules or multiple aldosterone-producing micronodules (formally known as micronodular hyperplasia)	MAPN or MAPM	Multiple APN or multiple APM located beneath the adrenal capsule with intermittent regions of normal zona glomerulosa. MAPN and MAPM can coexist in the same adrenal.
	Aldosterone-producing diffuse hyperplasia	APDH	Relatively broad and uninterrupted strip of zona glomerulosa cells with more than half of these cells displaying CYP11B2-positive immunostaining.

Williams TA, J Clin Endocrinol Metab 2021

Classical histopathology of unilateral PA



Biochemical success: complete

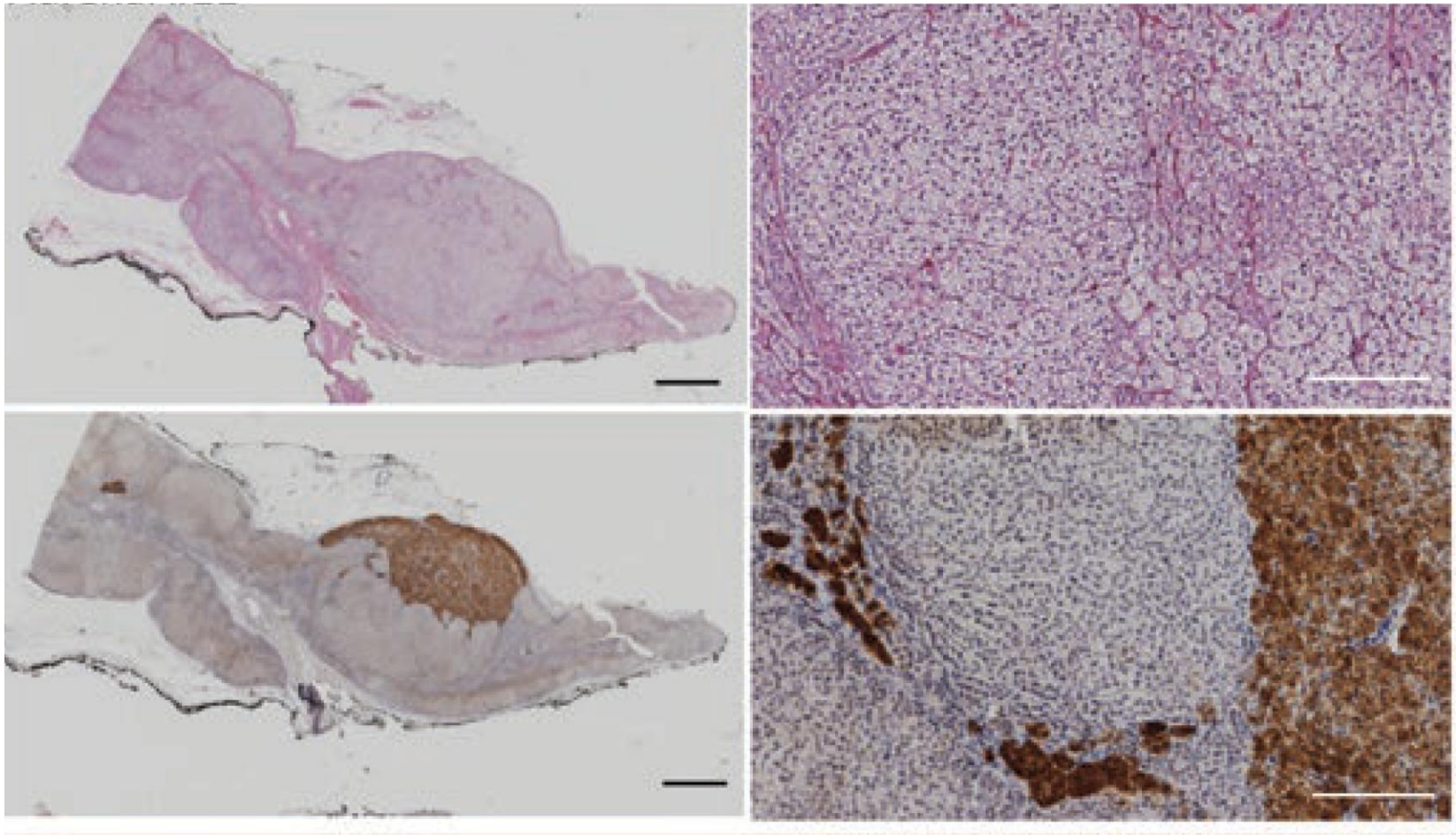


Biochemical success: complete

Aldosterone-producing Adenoma (APA)

Well circumscribed CYP11B2-positive solitary neoplasm (≥ 10 mm diameter)
composed of clear or compact eosinophilic cells or both cell types

Classical histopathology of unilateral PA

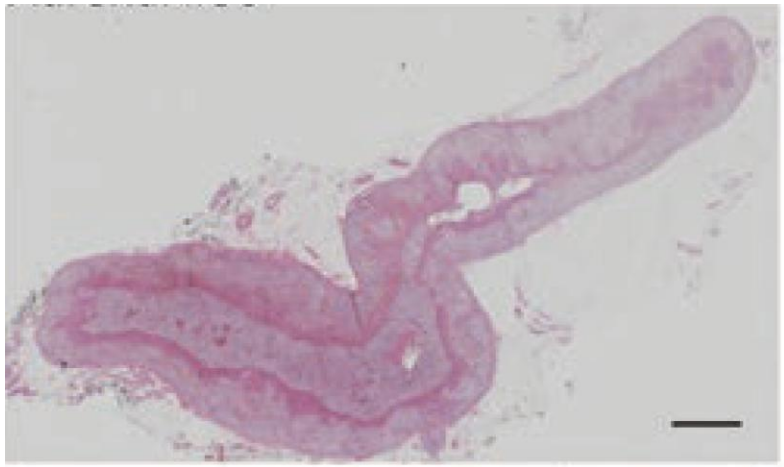


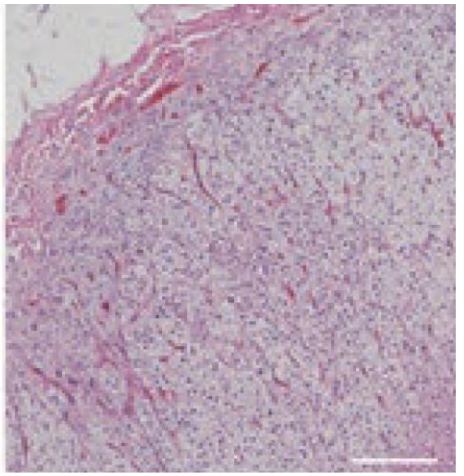
Biochemical success: complete

Aldosterone-producing nodule (APN)

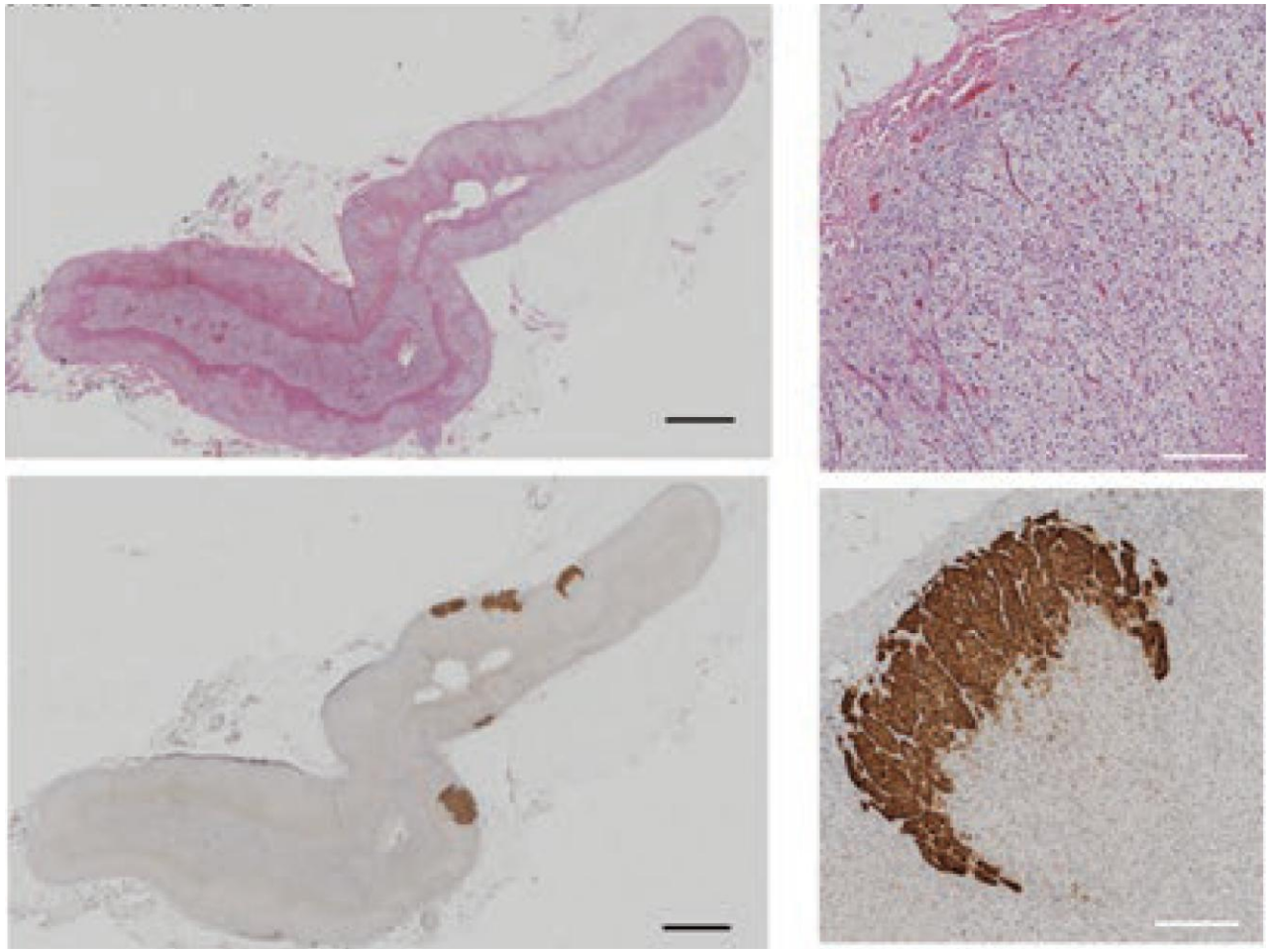
CYP11B2-positive lesion (<10 mm diameter) morphologically visible with hematoxylin-eosin staining.
An APN often displays a gradient of CYP11B2 immunostaining decreasing in intensity from the outer to the inner part of the lesion.

Nonclassical histopathology of unilateral PA





Nonclassical histopathology of unilateral PA



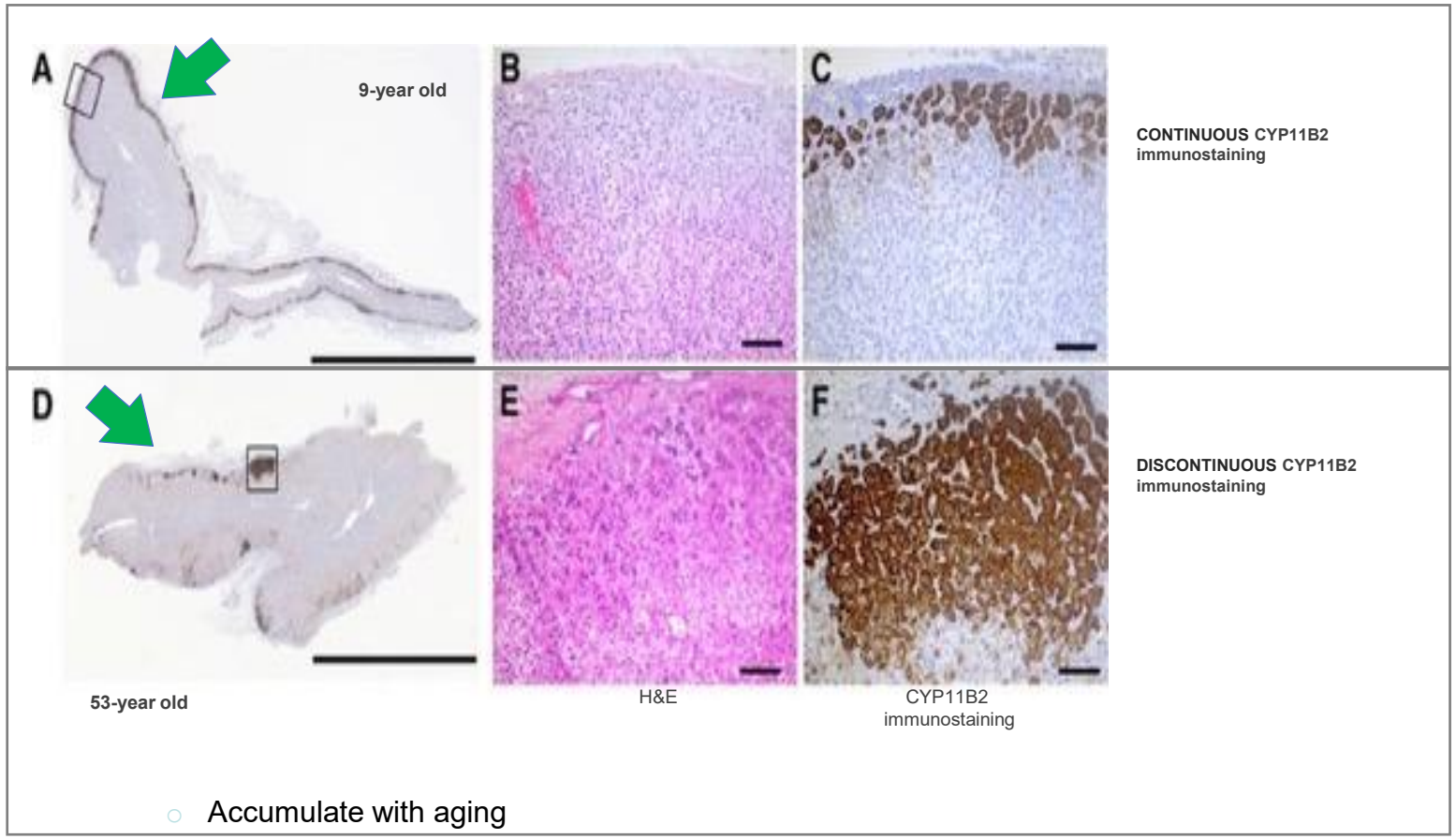
Biochemical success: complete

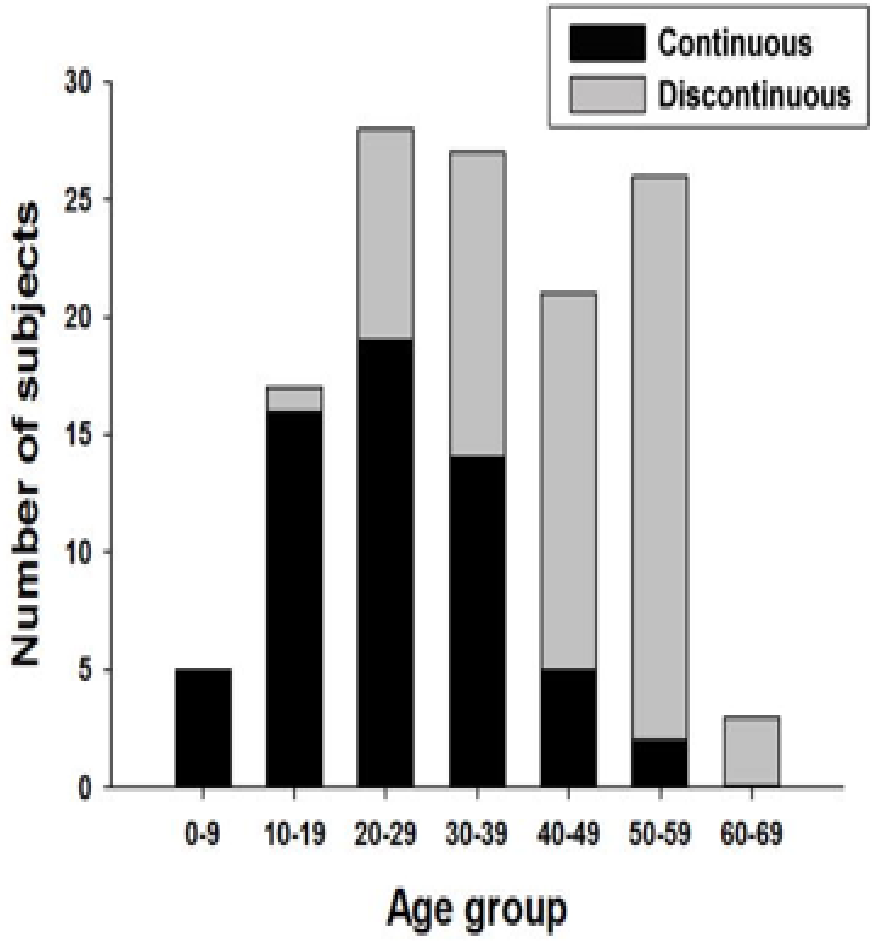
Aldosterone-producing micronodule (APM) (formally known as aldosterone-producing cell cluster)
CYP11B2-positive lesion (<10 mm diameter) composed of zona glomerulosa cells located beneath adrenal capsule that do not differ in morphology from adjacent adrenocortical cells by hematoxylin-eosin staining.
An APM often displays a gradient of CYP11B2 immunostaining decreasing in intensity from the outer to the inner part of the lesion.

Aldosterone-Producing Micronodules

aka APCCs (aldosterone-producing cell clusters)

In normal human adrenal glands



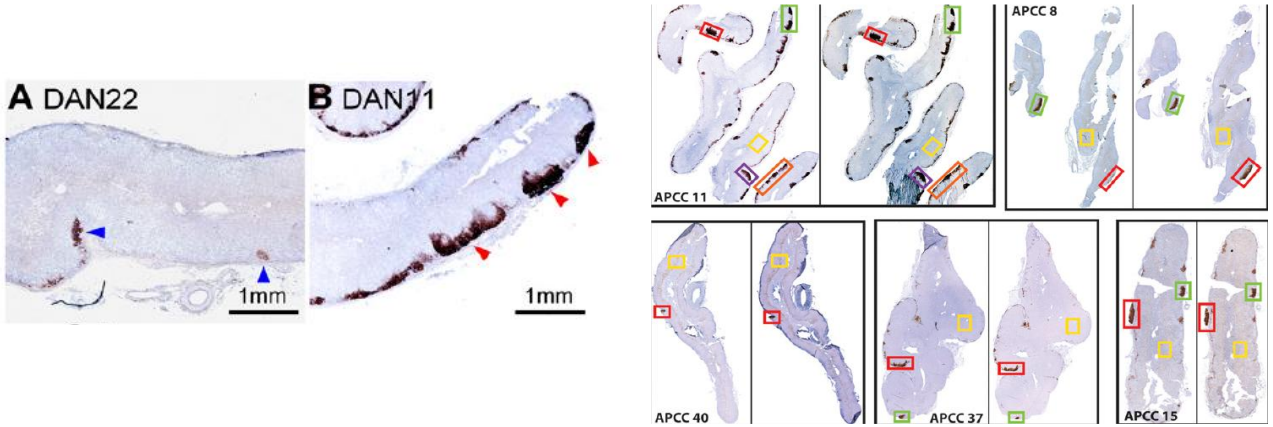


- Accumulate with aging
- Potential source of age-related abnormal aldosterone physiology

Nanba K, Circulation 2017

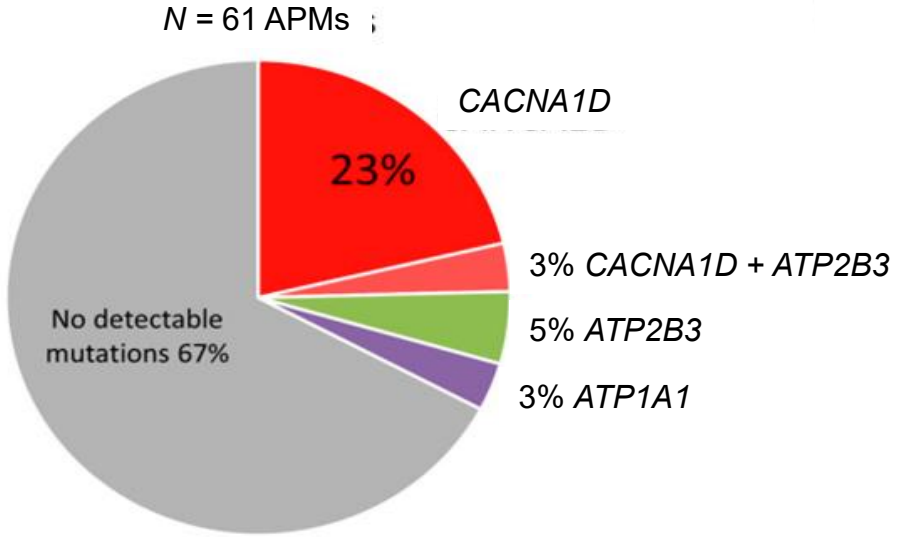
Aldosterone-producing micronodules

- APMs (aka APCC) common in normal human adrenals
- Carry aldosterone-driver mutations (35% of 23 APMs)
- Somatic mutations in KCNJ5 were not identified in APMs



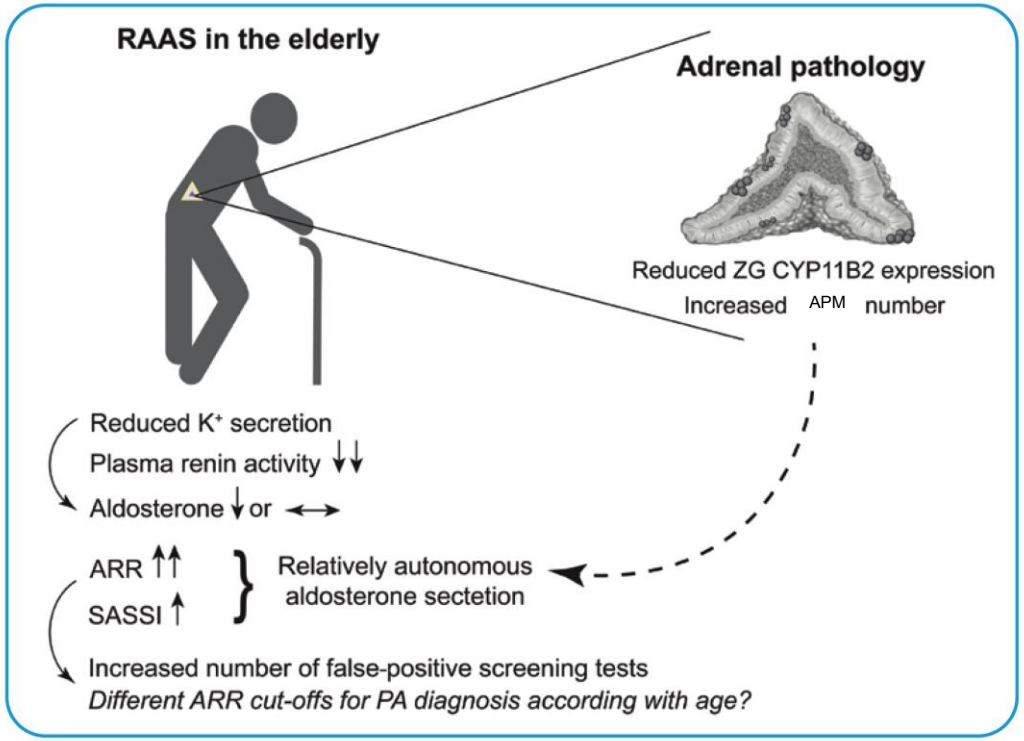
Nishimoto K et al., PNAS 2015

Normal human adrenals



Omata K et al., J Endocr Soc. 2017

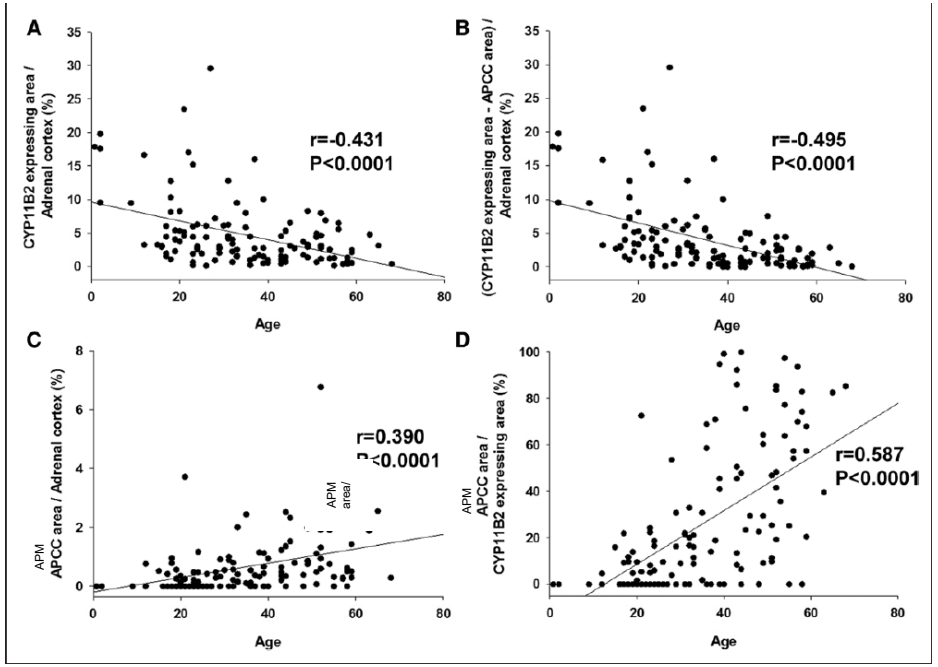
Renin-angiotensin-aldosterone system pathophysiology in the elderly



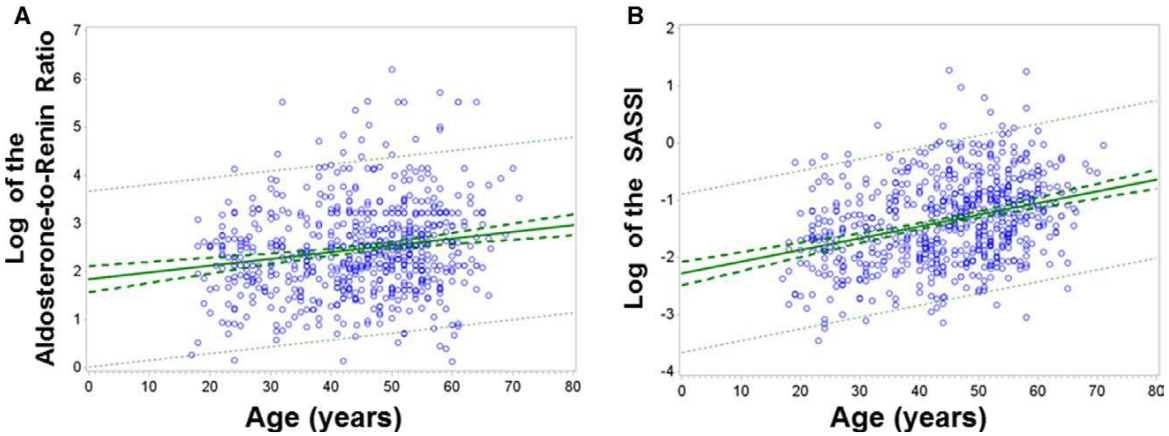
SASSI is calculated by dividing s-aldosterone under Na+load (maximally suppressed aldo) by the s-aldosterone under Na+restricted conditions (maximally stimulated aldo).
A lower SASSI suggests normal aldo physiology
a higher SASSI indicates abnormal aldo physiology

Mulatero P, J Clin Endocrinol Metab 2020

CYP11B2 expression patterns in normal human adrenals across aging



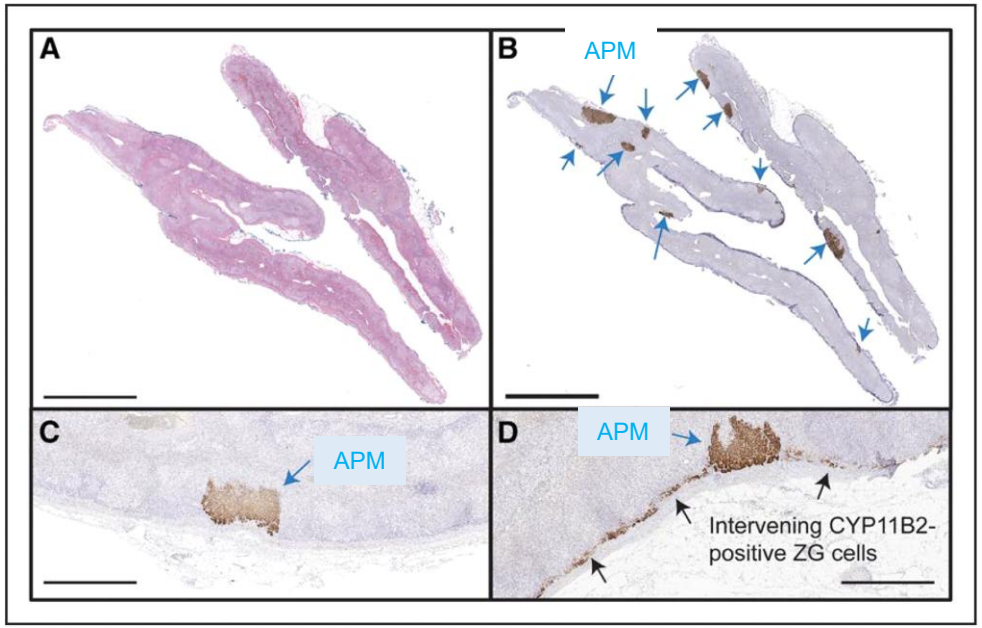
Age and aldosterone dysregulation

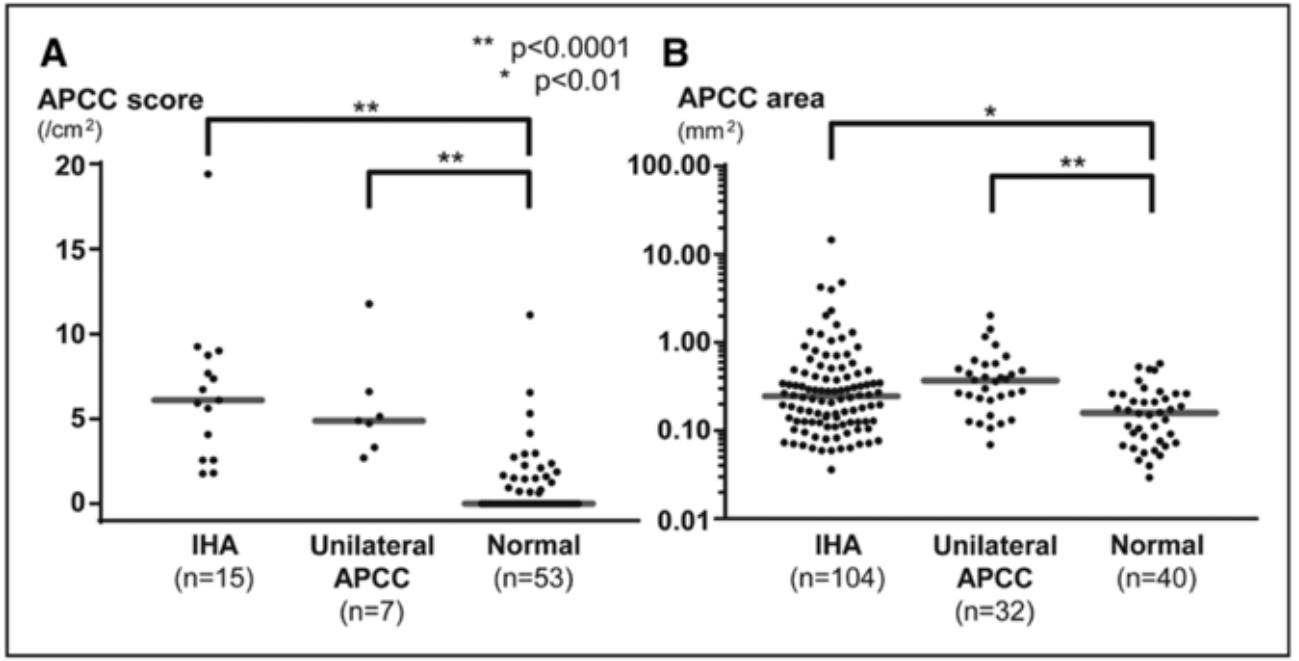


Nanba K, Circulation 2017

Aldosterone-Producing Micronodules and Idiopathic Hyperaldosteronism (Bilateral PA)

CYP11B2 immunohistochemistry and NGS of CT-undetectable adrenals from surgically-treated patients for bilateral PA



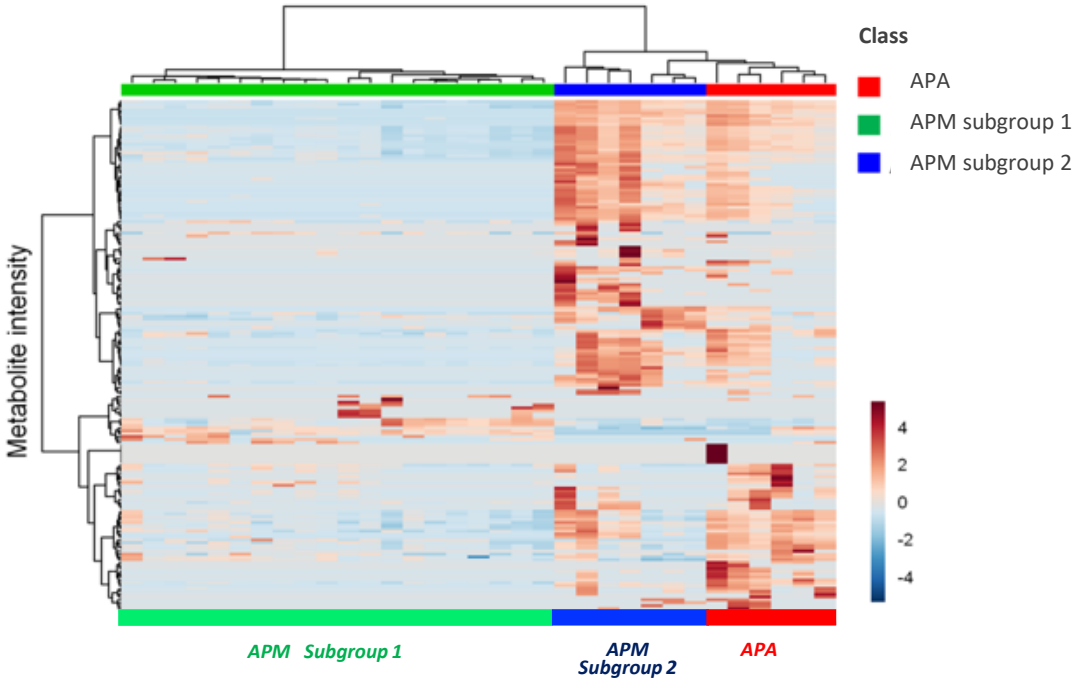


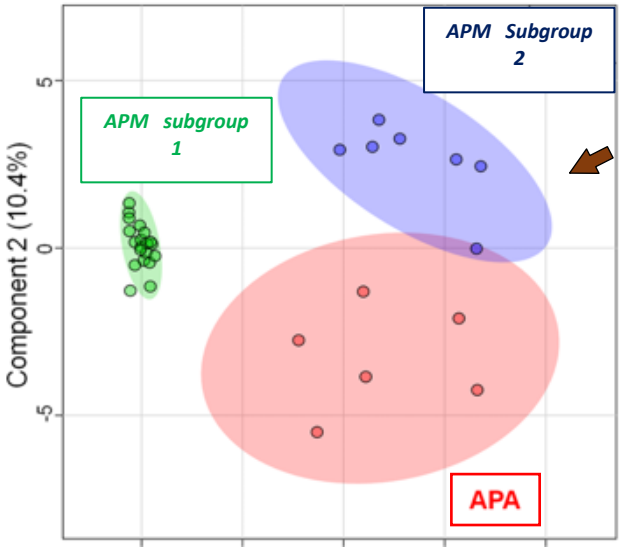
- **Non-nodular hyperplasia** in 4 of 15 adrenals
- All 15 adrenals displayed aldosterone-producing micronodules

- Number of APMs and lesion area higher in IHA adrenals than normal adrenals
- Higher prevalence of aldosterone-driver mutations in APMs of IHA adrenals *versus* normal adrenals (57% *versus* 35%)

Omata K, Hypertension 2018

In situ MALDI-MSI identifies 2 distinct subgroups of aldosterone-producing micronodules



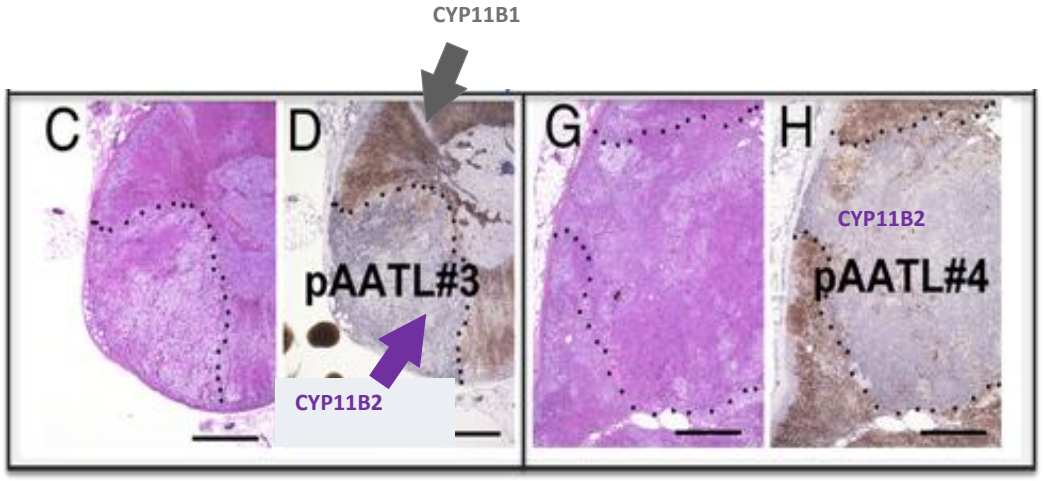


Enriched for pathways associated with cell proliferation

APM, aldosterone-producing micronodule (aka APCC);
APA, aldosterone-producing adenoma

Sun N et al, Hypertension 2020

Aldosterone-Producing Micronodule/Adenoma Hybrid Lesions



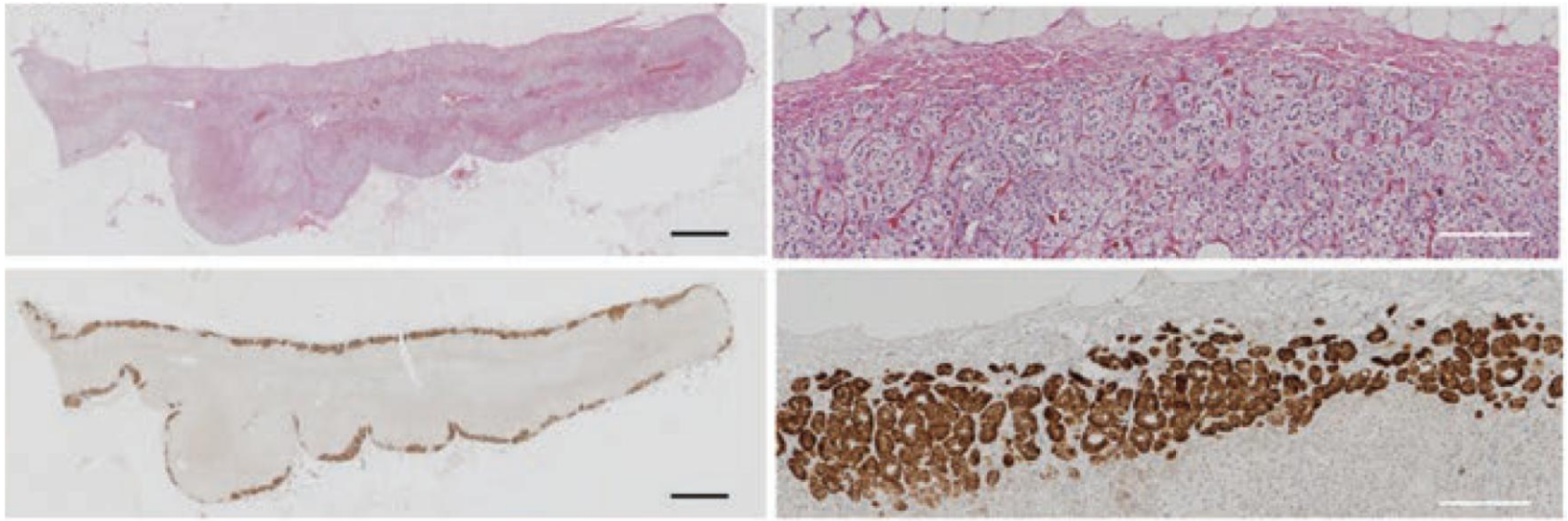
pAATL (**p**ossible APM-to-APA **T**ransitional **L**esions)

CYP11B2-positive lesions with histologic features characteristic of both APMs and APAs

- Subcapsular zona glomerulosa cells
- Inner zona fasciculata cells
- Interpreted as APMs transitioning to APAs

Nishimoto K et al., J Clin Endocrinol Metab. 2016

Nonclassical histopathology of unilateral PA



Biochemical success: partial

Aldosterone-producing diffuse hyperplasia (APDH)

Relatively broad and uninterrupted strip of zona glomerulosa cells with more than half of these cells displaying CYP11B2-positive immunostaining.

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]

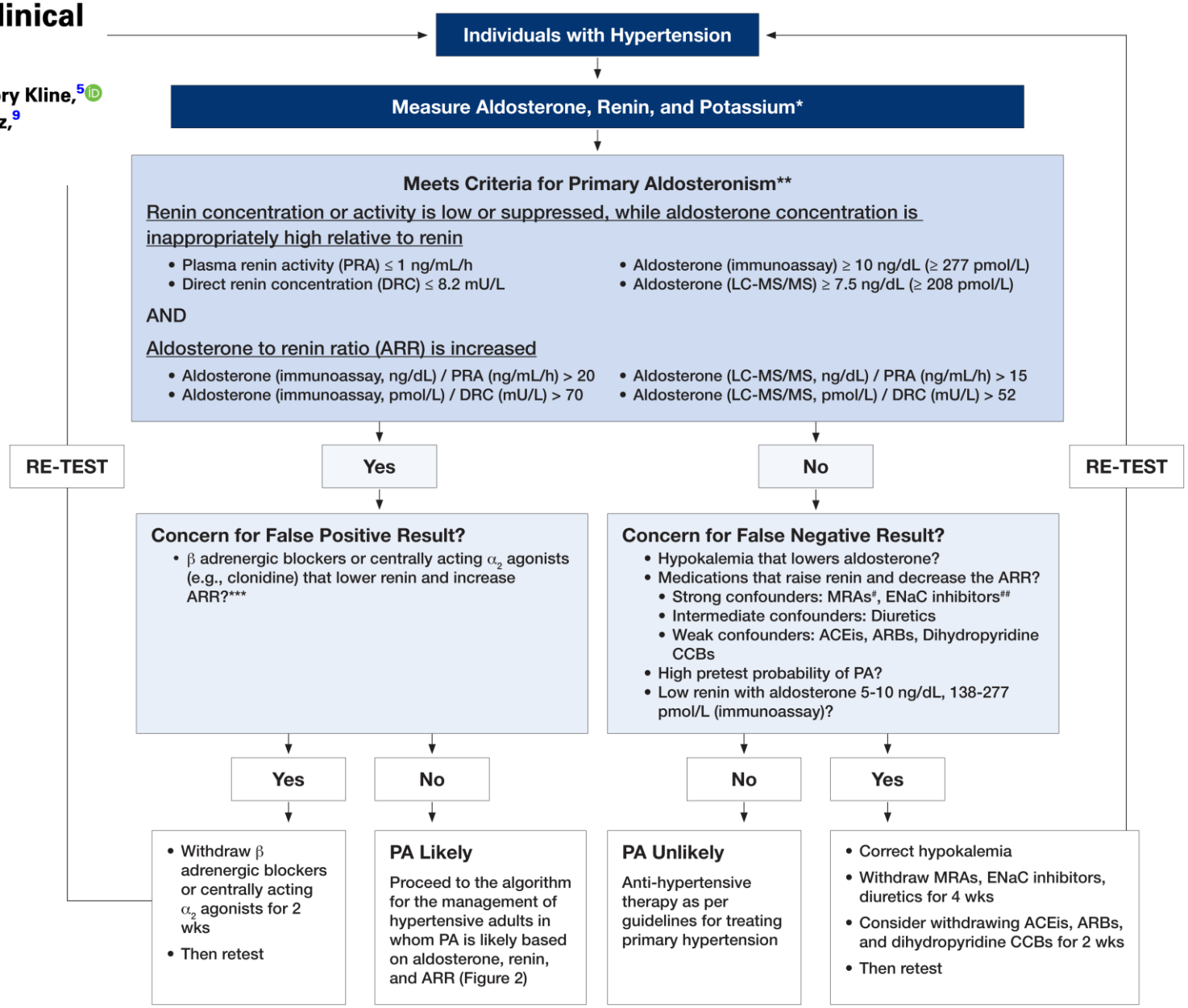
The Journal of Clinical Endocrinology & Metabolism, 2025
https://doi.org/10.1210/clinem/dgaf284
Advance access publication 14 July 2025
Clinical Practice Guideline

Recommendation 1

In all individuals with hypertension, we suggest screening for primary aldosteronism (PA) (2 | ⊕⊕OO).

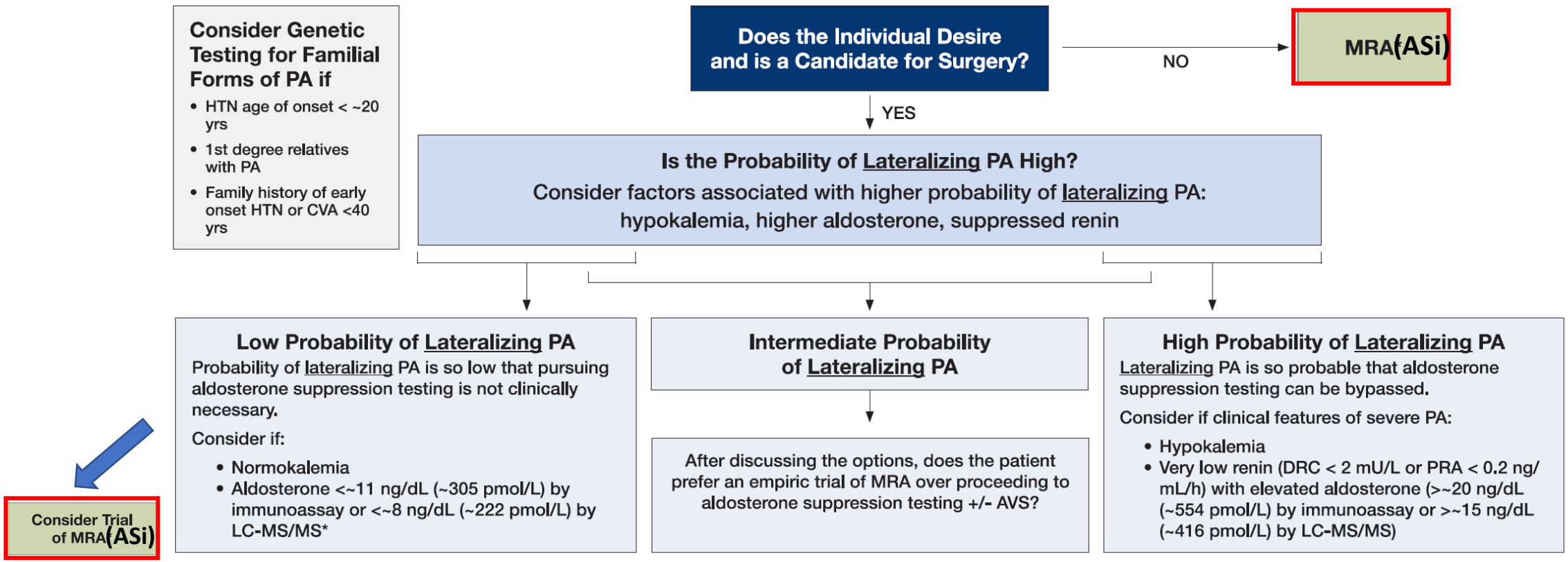
Recommendation 3

In individuals with hypertension, we suggest primary aldosteronism (PA) screening with serum/plasma aldosterone concentration and plasma renin (concentration or activity) (2 | ⊕⊕OO).



Recommendation 4

In individuals who screen positive for primary aldosteronism (PA), we suggest aldosterone suppression testing in situations when screening results suggest an intermediate probability for lateralizing PA and individualized decision making confirms a desire to pursue eligibility for surgical therapy (2 | ⊕OOO).



ES PA Guideline: Adler G, Stowasser M et al, J Clin Endocrinol Metab. 2025

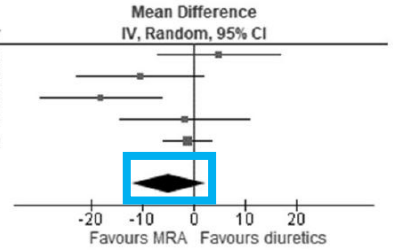
Mineralocorticoid Receptor Antagonists for the Treatment of Low-Renin Hypertension

MRAs vs Diuretics

A

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)



B

Study or Subgroup	MRA Mean [mmHg]	MRA SD [mmHg]	MRA Total	Diuretics Mean [mmHg]	Diuretics SD [mmHg]	Diuretics Total	Weight	Mean Difference IV, Random, 95% CI	Year
Adlin	-11	9.4	18	-16	8.9	10	20.4%	5.00 [-2.02, 12.02]	1972
Vaughan	-18.1	12.4	21	-16.4	11	16	19.5%	-1.70 [-9.26, 5.86]	1973
Spark	-25	10.3	10	-8	12.1	10	16.1%	-17.00 [-26.85, -7.15]	1974
Ferguson	-4.3	10.8	11	-7.1	9.5	11	18.1%	2.80 [-5.70, 11.30]	1977
Hood (bendroflumethiazide)	-1.3	9.1	51	-4	8.2	51	26.0%	2.70 [-0.66, 6.06]	2007
Total (95% CI)			111			98	100.0%	-0.84 [-6.85, 5.17]	

Heterogeneity: Tau² = 33.27; Chi² = 15.71, df = 4 (P = 0.003); I² = 75%
Test for overall effect: Z = 0.27 (P = 0.78)

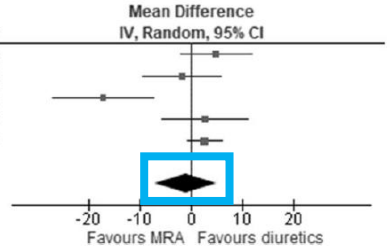


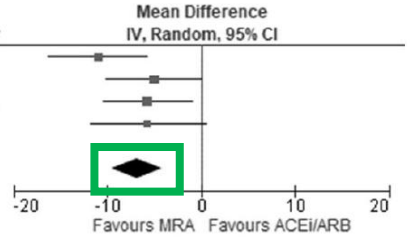
Fig. 2 Meta-analysis of blood pressure lowering effect with mineralocorticoid receptor antagonists (MRA) versus diuretics. A systolic blood pressure; **B** diastolic blood pressure.

MRAs vs ACE.Is/ARBs

A

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)



B

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	-13	7.7	60	-6.2	6.3	62	26.2%	-6.80 [-9.30, -4.30]	2003
Williams 2004	-11.1	8.4	67	-9	8.7	82	25.5%	-2.10 [-4.86, 0.66]	2004
Weinberger 2005	-9.3	8.9	86	-6.7	8.7	82	25.8%	-2.60 [-5.26, 0.06]	2005
Hood 2007 (losartan)	-1.3	9.1	51	-3.7	10	51	22.5%	2.40 [-1.31, 6.11]	2007
Total (95% CI)			264			277	100.0%	-2.45 [-5.90, 1.00]	

Heterogeneity: Tau² = 10.18; Chi² = 17.49, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 1.39 (P = 0.16)

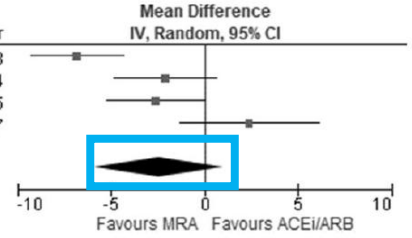


Fig. 3 Meta-analysis of blood pressure lowering effect with mineralocorticoid receptor antagonists (MRA) versus angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB). A systolic blood pressure; **B** diastolic blood pressure.

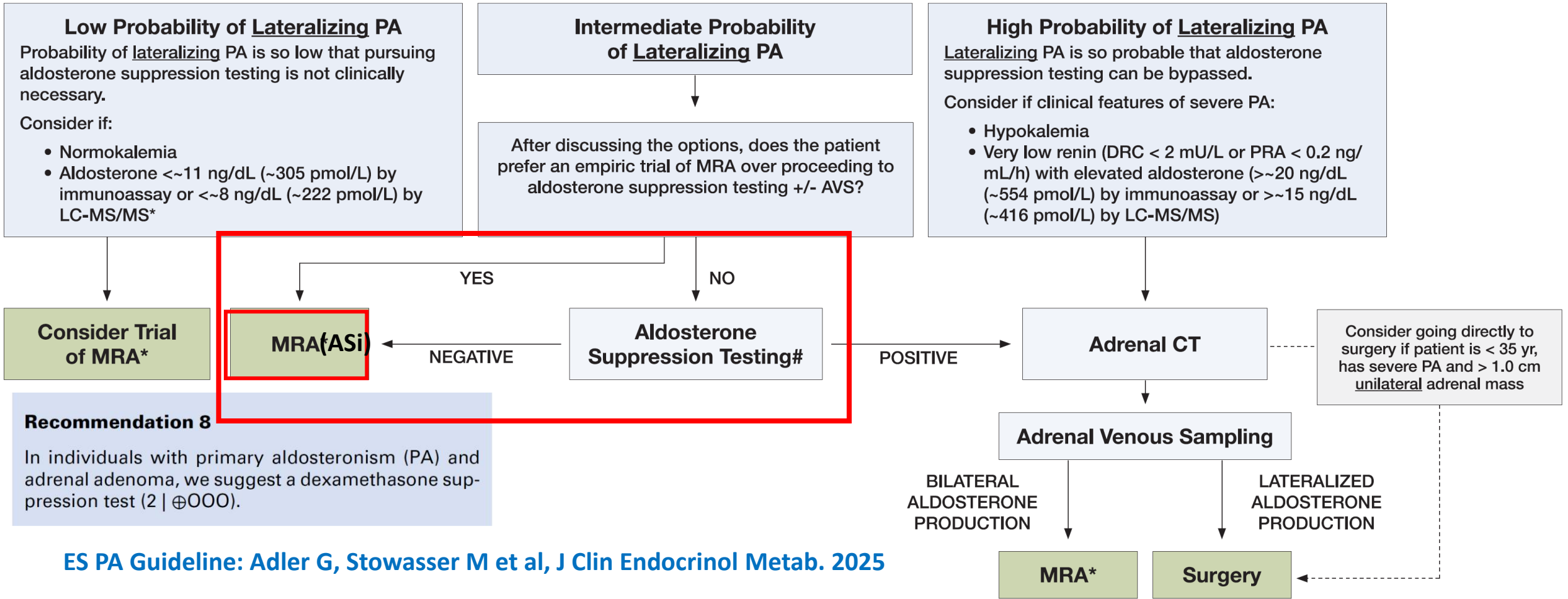
Shah SS,
J Hum Hypertens 2024

Recommendation 5

In individuals with primary aldosteronism (PA), we suggest medical therapy or surgical therapy with the choice of therapy based on lateralization of aldosterone hypersecretion and candidacy for surgery (2 | ⊕OOO).

Recommendation 6

In individuals with primary aldosteronism (PA) considering surgery, we suggest adrenal lateralization with computed tomography (CT) scanning and adrenal venous sampling (AVS) prior to deciding the treatment approach (medical or surgical) (2 | ⊕⊕OO).

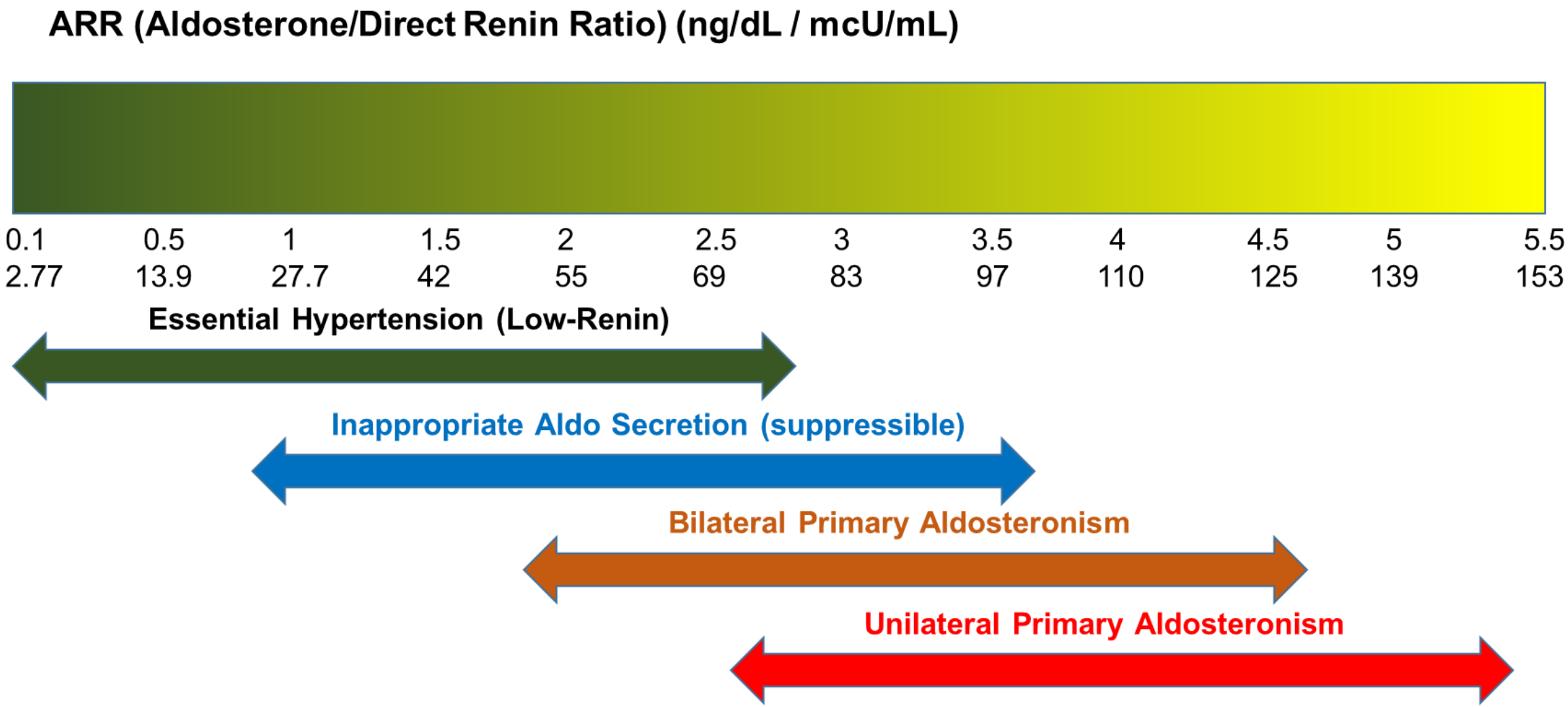


Recommendation 8

In individuals with primary aldosteronism (PA) and adrenal adenoma, we suggest a dexamethasone suppression test (2 | ⊕OOO).

ES PA Guideline: Adler G, Stowasser M et al, J Clin Endocrinol Metab. 2025

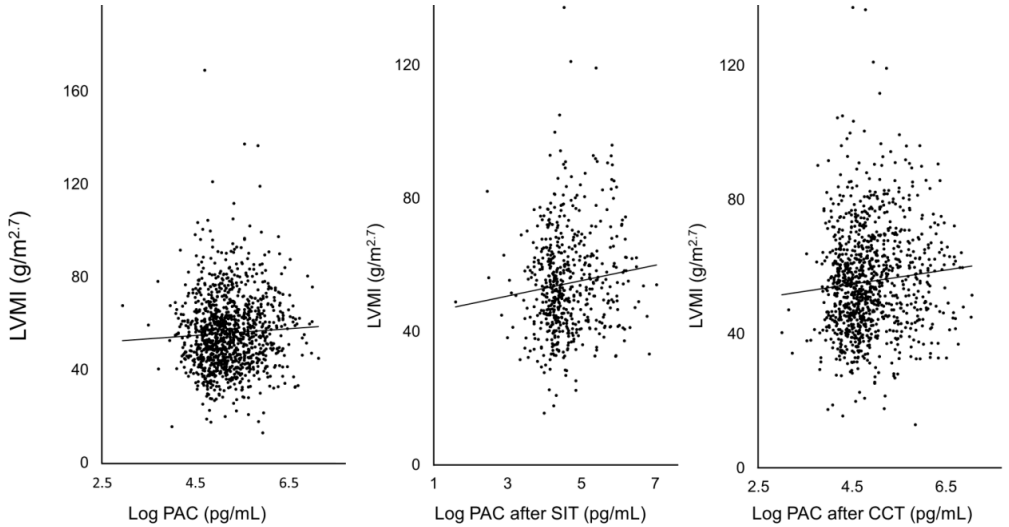
Confirmatory/Suppression tests



Aldosterone Levels After Confirmatory Tests Are Correlated With LV Mass in Primary Aldosteronism

Table 3. Correlation Between Left Ventricular Mass Index and Each Parameter in Single Regression Analyses

Parameter	Coefficient	SE	*P* Value	95% CI
Serum K^+, mEq/L	–4.067	0.874	<0.001*	–5.783 to –2.352
Hypokalemia, %	5.260	0.937	<0.001*	3.422 to 7.098
Log ARR, pg/mL per ng/(mL·h)	0.674	0.516	0.192	–0.339 to 1.687
Log plasma renin activity, ng/(mL·h)	–0.176	0.618	0.776	–1.390 to 1.037
Log PAC, pg/mL	1.446	0.812	0.075	–0.147 to 3.039
Log PAC after CCT, pg/mL	2.112	0.726	0.004*	0.688 to 3.536
Log PAC after SIT, pg/mL	2.319	0.892	0.010*	0.567 to 4.070
Unilateral subtype, %	3.280	1.115	0.003*	1.093 to 5.468



Ohno Y, Hypertension 2020

Long-Term Follow-Up of Patients With Elevated ARR but Negative Confirmatory Test: The Progression of Primary Aldosteronism Phenotypes

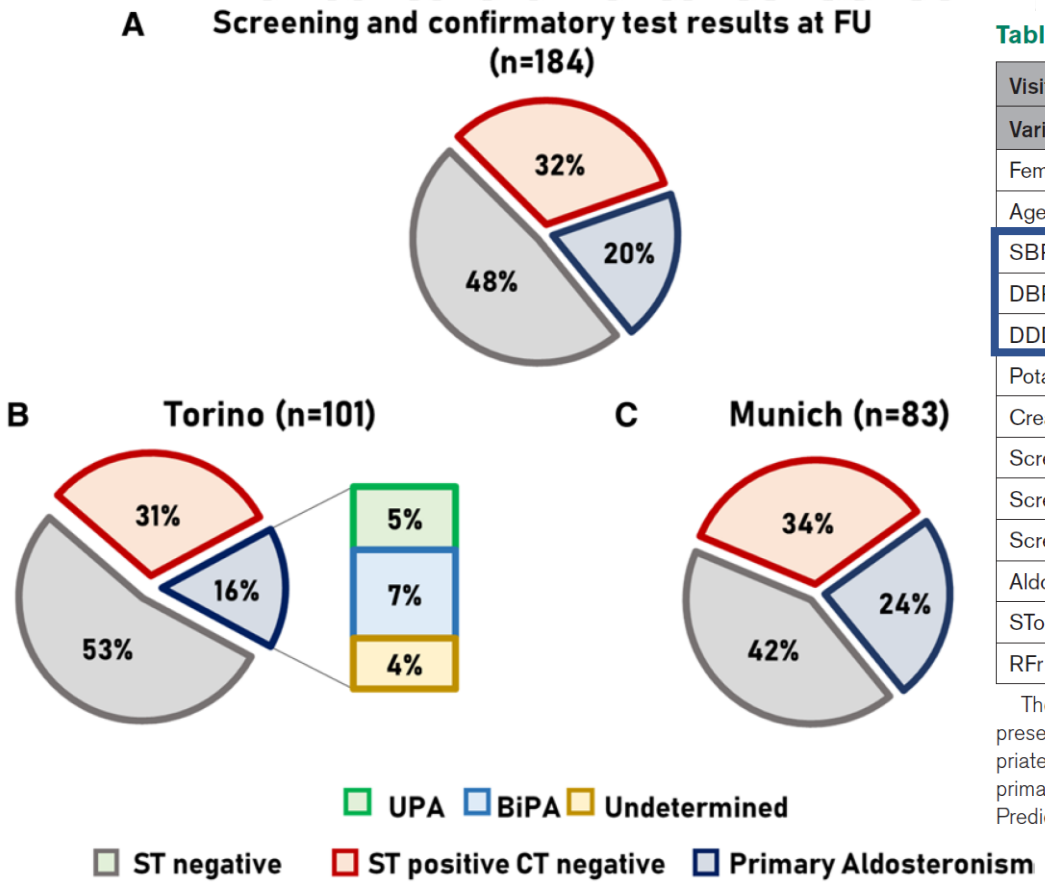


Table 2. Comparison of Patients With PA Diagnosis at Follow-Up and Patients Without PA

Visit	First visit			Second visit		
Variables	Non-PA (n=148)	PA (n=36)	*P* value	Non-PA (n=148)	PA (n=36)	*P* value
Female sex, n (%)	90 (60.8%)	23 (63.9%)	0.734	…	…	…
Age, y	47±10	46±8	0.645	52±10	51±8	0.483
SBP, mm Hg	146±15	147±18	0.343	133±12	142±17	0.005*
DBP, mm Hg	93±11	94±10	0.243	85±9	89±8	0.007*
DDD	1.00 (0.00–2.50)	1.58 (0.81–3.00)	0.122	2.00 (1.00–3.46)	2.13 (0.81–3.00)	0.941
Potassium, mmol L^{-1}	4.1±0.4	4.0±0.3	0.373	4.1±0.4	4.0±0.4	0.195
Creatinine, mg dL^{-1}	0.84±0.21	0.82±0.16	0.538	0.86±0.19	0.85±0.15	0.385
Screening test PRA, ng mL^{-1} h^{-1}†	0.30 (0.20–0.42)	0.25 (0.12–0.49)	0.405	0.72 (0.25–1.51)	0.30 (0.24–0.46)	0.023*
Screening test renin, μU mL^{-1}‡	3.7 (2.0–6.1)	3.2 (2.0–5.1)	0.422	7.0 (3.0–12.9)	4.8 (2.1–7.4)	0.013*
Screening test aldosterone, ng dL^{-1}	16.5 (9.4–24.4)	12.9 (8.4–26.6)	0.366	13.9 (6.7–19.7)	17.8 (12.6–26.7)	<0.001*
Aldosterone post-SSIT, ng dL^{-1}§	3.3 (2.5–4.6)	3.9 (3.1–5.0)	0.035*	4.6 (3.5–5.5)	8.1 (7.0–10.1)	<0.001*
SToP-PA score	8.5 (6.0–10.5)	9.5 (6.5–11.0)	0.229	8.5 (6.0–10.5)	10.0 (7.0–11.5)	0.046*
RFr coefficient	0.26 (0.00–0.45)	0.32 (0.25–0.44)	0.183	0.30 (0.25–0.44)	0.35 (0.26–0.56)	0.019*

The comparison of clinical and biochemical characteristics of patients without PA (n=148) and with confirmed PA (n=36). The first visit was performed before the present study while the second visit was part of the present study. Variables are reported as mean±SD, median (interquartile range), or absolute number (%), as appropriated. DDD: average maintenance dose per day for a drug used for its main indication in adults. DBP indicates diastolic blood pressure; DDD, defined daily dose; PA, primary aldosteronism; PRA, plasma renin activity; RFr, random forest regressor; SBP, systolic blood pressure; SSIT, seated saline infusion test; and SToP-PA, Score To Predict Primary Aldosteronism.

Buffolo F, Hypertension 2024

Table 8. Description of the most commonly used aldosterone suppression tests

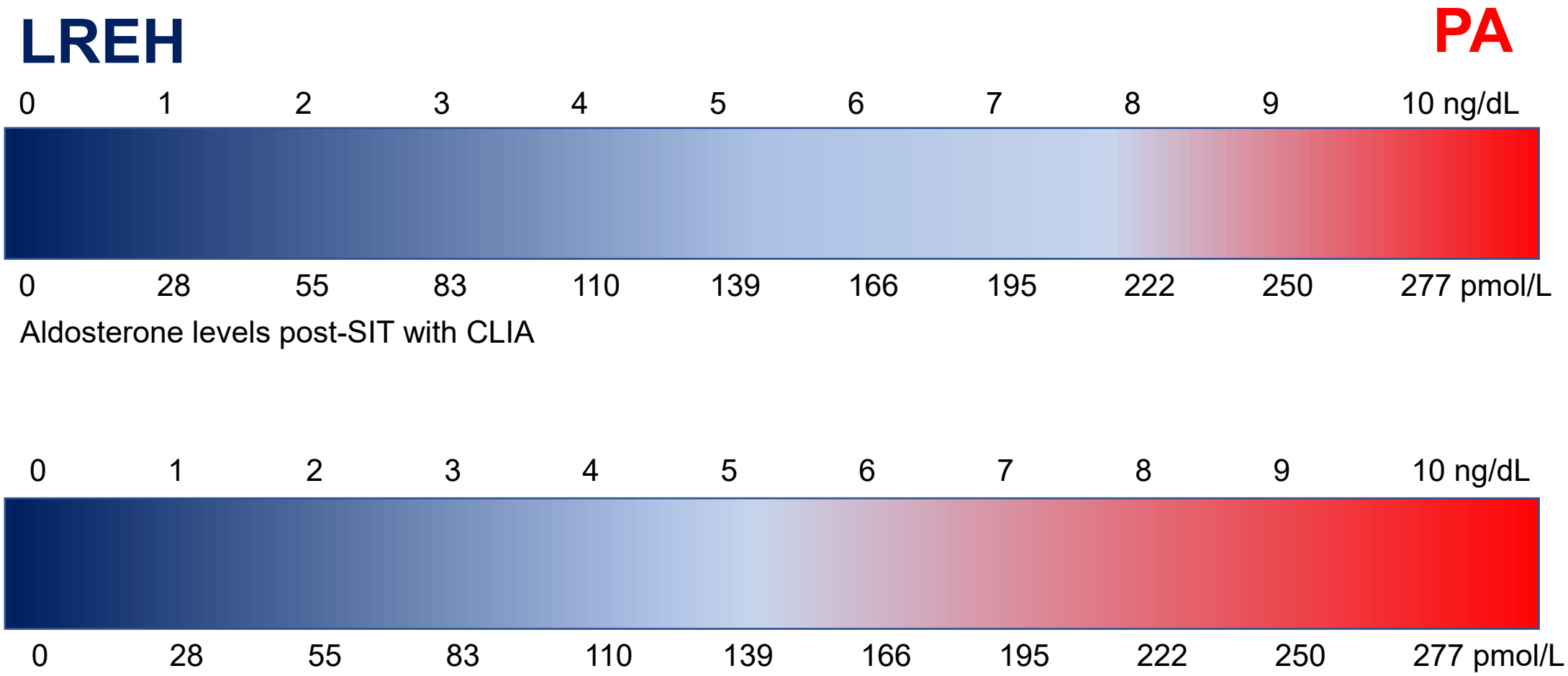
Aldosterone suppression test	Resource requirements	Protocol	Metrics	Interpretations	Comments
Oral sodium suppression test	Low	Individuals are instructed to consume 4-5 g of sodium per day for 3-4 days Collect 24-h urine collection on final day of high sodium intake	Measure urinary aldosterone, sodium, creatinine	24-h urine sodium should ideally be >200 mEq/24 hours 24-h urine creatinine is used to assess adequacy of urine collection 24-h urine aldosterone <10 mcg/nmol/24 hours makes PA unlikely (84)	Oral sodium can be consumed via sodium chloride tablets or sodium rich foods Because hypokalemia may cause false-negative interpretations, serum potassium should be normalized before the study protocol Interpretation of results is probabilistic and lacks evidence to recommend a precise diagnostic threshold (23) Protocol can be conducted in the ambulatory setting
Captopril challenge test	Moderate	After sitting for 1 hour, blood is drawn to mark t = 0 Individuals are then given 50 mg of captopril and remain seated for 2 hours following administration Blood should be drawn at t = 2 hours to complete the study	Measure plasma aldosterone and renin at t = 0 and t = 2h	In the context of a post-captopril suppressed renin (<1.0 ng/mL/h or <10 mU/L), a 2-h post-captopril plasma aldosterone level <277 pmol/L (10 ng/dL) by immunoassay or <203 pmol/L (7.5 ng/dL) by LC-MS/MS makes PA unlikely (84) (112)	Many individuals with hypertension are actively treated with ACE inhibitors or ARBs; plasma aldosterone and renin values measured after taking these routinely prescribed medications may serve as a proxy for the captopril challenge test Interpretation of results should be considered to be probabilistic as the evidence to support a singular diagnostic threshold is not firm (26) Protocol requires an in-person visit and space and staff to accommodate the procedures
Saline suppression test	Moderate	After sitting for 1 hour, blood should be drawn to mark t = 0 Two liters of normal saline are infused over 4 hours (500 mL/h for 4 hours), while maintaining a seated position, after which blood should be drawn	Measure plasma aldosterone and serum potassium at t = 0 and t = 4 hours	Plasma aldosterone <162 pmol/L (5.8 ng/dL) via LC-MS/MS assay makes PA unlikely Plasma aldosterone <217 pmol/L (7.8 ng/dL) via immunoassay assay makes PA unlikely (84, 100, 102, 113)	Because hypokalemia may cause false-negative interpretations, serum potassium should be normalized before the study protocol Interpretation of results should be considered to be probabilistic as the evidence to support a singular diagnostic threshold is not firm (25) Protocol requires an in-person visit, space and staff to accommodate the procedures, and IV infusion of saline Protocol should not be performed if baseline BP is uncontrolled, or in patients at high risk for pulmonary edema (such as in heart failure or advanced chronic kidney disease)

Captopril Challenge Test
post-CCT PAC level
<10 ng/dL makes PA unlikely

Seated Saline Suppression
post-SST PAC level
<7.8 ng/dL makes PA unlikely

ES PA Guideline: Adler G, Stowasser M et al, J Clin Endocrinol Metab. 2025

Cut-off Levels for Confirmatory SIT

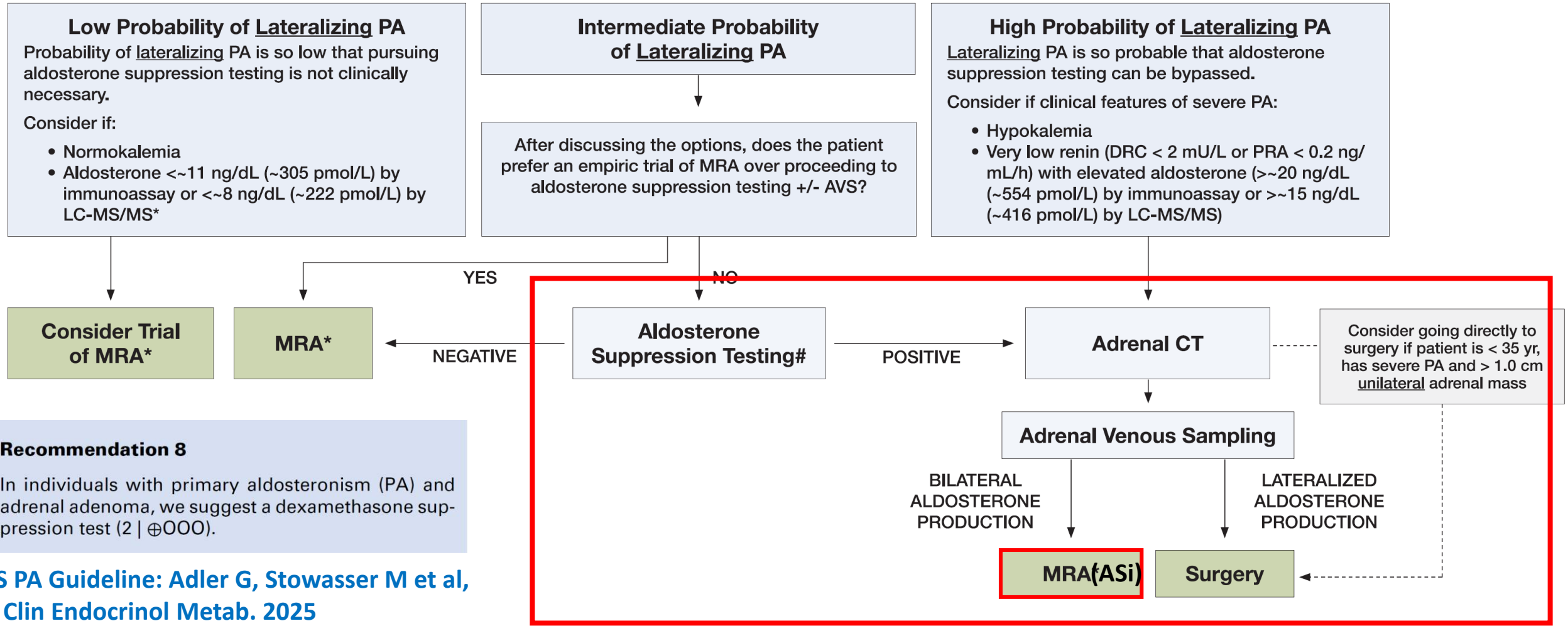


Recommendation 5

In individuals with primary aldosteronism (PA), we suggest medical therapy or surgical therapy with the choice of therapy based on lateralization of aldosterone hypersecretion and candidacy for surgery (2 | ⊕OOO).

Recommendation 6

In individuals with primary aldosteronism (PA) considering surgery, we suggest adrenal lateralization with computed tomography (CT) scanning and adrenal venous sampling (AVS) prior to deciding the treatment approach (medical or surgical) (2 | ⊕⊕OO).



Recommendation 8

In individuals with primary aldosteronism (PA) and adrenal adenoma, we suggest a dexamethasone suppression test (2 | ⊕OOO).

ES PA Guideline: Adler G, Stowasser M et al, J Clin Endocrinol Metab. 2025

Consequences of skipping suppression test

-ALL patients with positive ARR are considered PA (which cut-off?) → with liberal cut-offs 20-30% of patients with hypertension (and more than 5% of healthy subjects)

Consequences

-ALL patients with «liberal PA diagnosis» should udergo subtype diagnosis, including AVS: NOT feasable! → AVS limited availability, unilateral PA a minority

-ALL patients with «liberal PA diagnosis» should be treated with MRA/Asi/ENaCi

Patients with a «traditional PA» display an increased CV risk that is reduced by MRA/surgery

Unknown if patients with «liberal PA diagnosis» are at increased risk

Unknown if MRA/Asi/ENaCi reduce CV risk in patients with «liberal PA diagnosis»

Diagnostic approach to low-renin hypertension

Silvia Monticone | Isabel Losano | Martina Tetti | Fabrizio Buffolo | Franco Veglio | Paolo Mulatero

Clin Endocrinol 2018

Syndrome	Inheritance	Gene(s) involved, chromosome	Protein	Therapy
FH-I	AD	Hybrid *CYP11B1/ CYP11B2* Chr. 8q24.3	Cytochrome P450 family 11 subfamily B member 1 (11-beta-hydroxylase)/ cytochrome P450 family 11 subfamily B member 2 (aldosterone synthase)	Dexamethasone
FH-II	AD, incomplete penetrance	*CLCN2* Chr. 3q27.1	Chloride voltage-gated channel 2	MR-antagonists
FH-III	AD	*KCNJ5* Chr. 11q24.3	G protein-activated inward rectifier potassium channel 4, GIRK4	MR-antagonists, bilateral adrenalectomy
FH-IV	AD, incomplete penetrance	*CACNA1H* Chr. 16p13.3	Calcium voltage-gated channel subunit alpha1H, $Ca_v3.2$	MR-antagonists
PASNA syndrome	n.a.	*CACNA1D* Chr. 3p21.3	Calcium voltage-gated channel subunit alpha1D, $Ca_v1.3$	MR-antagonists, CCBs
Liddle syndrome	AD	*SCNN1A*, Chr. 12p13.3 *SCNN1B*, Chr. 16p12.2 *SCNN1G*, Chr. 16p12.2	Sodium channel epithelial 1 alpha subunit, Sodium channel epithelial 1 beta-subunit, Sodium channel epithelial 1 gamma-subunit	ENaC inhibitors (amiloride and triamterene)
AME syndrome	AR	*HSD11B2* Chr. 16q22.1	Hydroxysteroid 11-beta-dehydrogenase 2	Dexamethasone MR-antagonists
CYP11B1 deficiency	AR	*CYP11B1* Chr. 8q24.3	Cytochrome P450 family 11 subfamily B member 1 (11-beta-hydroxylase)	Hydrocortisone (in children) Dexamethasone
CYP17 deficiency	AR	*CYP17A1* Chr. 10q24.3	Cytochrome P450 family 17 subfamily A member 1 (17α-hydroxylase)	Hydrocortisone (in children) Dexamethasone
Glucocorticoid resistance syndrome	AR	*NR3C1* Chr. 5q31.3	Nuclear receptor subfamily 3 group C member 1 (glucocorticoid receptor)	Dexamethasone
MR-activating mutation	AD	*NR3C2* Chr. 4q31.2	Nuclear receptor subfamily 3 group C member 2 (mineralocorticoid receptor)	ENaC inhibitors (amiloride and triamterene)
Gordon syndrome (familial hyperkalemic hypertension, pseudohypoaldosteronism type 2)	AD or AR	*WNK1*, Chr.12p12.3 *WNK4*, Chr. 17q21.2 *CUL3*, Chr. 2q36.2 *KLHL3*, Chr.5q31.2	WNK lysine-deficient protein kinase 1 WNK lysine-deficient protein kinase 4 Cullin 3 Kelch-like family member 3	NCC inhibitors (thiazide diuretics)

Diagnostic approach to low-renin hypertension

Silvia Monticone | Isabel Losano | Martina Tetti | Fabrizio Buffolo | Franco Veglio | Paolo Mulatero

Clin Endocrinol 2018

Syndrome	Inheritance	Gene(s) involved, chromosome	Protein	Therapy
FH-I	AD	Hybrid *CYP11B1/ CYP11B2* Chr. 8q24.3	Cytochrome P450 family 11 subfamily B member 1 (11-beta-hydroxylase)/ cytochrome P450 family 11 subfamily B member 2 (aldosterone synthase)	Dexamethasone
FH-II	AD, incomplete penetrance	*CLCN2* Chr. 3q27.1	Chloride voltage-gated channel 2	MR-antagonists
FH-III	AD	*KCNJ5* Chr. 11q24.3	G protein-activated inward rectifier potassium channel 4, GIRK4	MR-antagonists, bilateral adrenalectomy
FH-IV	AD, incomplete penetrance	*CACNA1H* Chr. 16p13.3	Calcium voltage-gated channel subunit alpha1H, $Ca_v3.2$	MR-antagonists
PASNA syndrome	n.a.	*CACNA1D* Chr. 3p21.3	Calcium voltage-gated channel subunit alpha1D, $Ca_v1.3$	MR-antagonists, CCBs
Liddle syndrome	AD	*SCNN1A*, Chr. 12p13.3 *SCNN1B*, Chr. 16p12.2 *SCNN1G*, Chr. 16p12.2	Sodium channel epithelial 1 alpha subunit, Sodium channel epithelial 1 beta-subunit, Sodium channel epithelial 1 gamma-subunit	ENaC inhibitors (amiloride and triamterene)
AME syndrome	AR	*HSD11B2* Chr. 16q22.1	Hydroxysteroid 11-beta-dehydrogenase 2	Dexamethasone MR-antagonists
CYP11B1 deficiency	AR	*CYP11B1* Chr. 8q24.3	Cytochrome P450 family 11 subfamily B member 1 (11-beta-hydroxylase)	Hydrocortisone (in children) Dexamethasone
CYP17 deficiency	AR	*CYP17A1* Chr. 10q24.3	Cytochrome P450 family 17 subfamily A member 1 (17α-hydroxylase)	Hydrocortisone (in children) Dexamethasone
Glucocorticoid resistance syndrome	AR	*NR3C1* Chr. 5q31.3	Nuclear receptor subfamily 3 group C member 1 (glucocorticoid receptor)	Dexamethasone
MR-activating mutation	AD	*NR3C2* Chr. 4q31.2	Nuclear receptor subfamily 3 group C member 2 (mineralocorticoid receptor)	ENaC inhibitors (amiloride and triamterene)
Gordon syndrome (familial hyperkalemic hypertension, pseudohypoaldosteronism type 2)	AD or AR	*WNK1*, Chr.12p12.3 *WNK4*, Chr. 17q21.2 *CUL3*, Chr. 2q36.2 *KLHL3*, Chr.5q31.2	WNK lysine-deficient protein kinase 1 WNK lysine-deficient protein kinase 4 Cullin 3 Kelch-like family member 3	NCC inhibitors (thiazide diuretics)

Diagnostic approach to low-renin hypertension

Silvia Monticone | Isabel Losano | Martina Tetti | Fabrizio Buffolo | Franco Veglio | Paolo Mulatero

Clin Endocrinol 2018

Syndrome	Inheritance	Gene(s) involved, chromosome	Protein	Therapy
FH-I	AD	Hybrid *CYP11B1/ CYP11B2* Chr. 8q24.3	Cytochrome P450 family 11 subfamily B member 1 (11-beta-hydroxylase)/ cytochrome P450 family 11 subfamily B member 2 (aldosterone synthase)	Dexamethasone
FH-II	AD, incomplete penetrance	*CLCN2* Chr. 3q27.1	Chloride voltage-gated channel 2	MR-antagonists
FH-III	AD	*KCNJ5* Chr. 11q24.3	G protein-activated inward rectifier potassium channel 4, GIRK4	MR-antagonists, bilateral adrenalectomy
FH-IV	AD, incomplete penetrance	*CACNA1H* Chr. 16p13.3	Calcium voltage-gated channel subunit alpha1H, $Ca_v3.2$	MR-antagonists
PASNA syndrome	n.a.	*CACNA1D* Chr. 3p21.3	Calcium voltage-gated channel subunit alpha1D, $Ca_v1.3$	MR-antagonists, CCBs
Liddle syndrome	AD	*SCNN1A*, Chr. 12p13.3 *SCNN1B*, Chr. 16p12.2 *SCNN1G*, Chr. 16p12.2	Sodium channel epithelial 1 alpha subunit, Sodium channel epithelial 1 beta-subunit, Sodium channel epithelial 1 gamma-subunit	ENaC inhibitors (amiloride and triamterene)
AME syndrome	AR	*HSD11B2* Chr. 16q22.1	Hydroxysteroid 11-beta-dehydrogenase 2	Dexamethasone MR-antagonists
CYP11B1 deficiency	AR	*CYP11B1* Chr. 8q24.3	Cytochrome P450 family 11 subfamily B member 1 (11-beta-hydroxylase)	Hydrocortisone (in children) Dexamethasone
CYP17 deficiency	AR	*CYP17A1* Chr. 10q24.3	Cytochrome P450 family 17 subfamily A member 1 (17α-hydroxylase)	Hydrocortisone (in children) Dexamethasone
Glucocorticoid resistance syndrome	AR	*NR3C1* Chr. 5q31.3	Nuclear receptor subfamily 3 group C member 1 (glucocorticoid receptor)	Dexamethasone
MR-activating mutation	AD	*NR3C2* Chr. 4q31.2	Nuclear receptor subfamily 3 group C member 2 (mineralocorticoid receptor)	ENaC inhibitors (amiloride and triamterene)
Gordon syndrome (familial hyperkalemic hypertension, pseudohypoaldosteronism type 2)	AD or AR	*WNK1*, Chr.12p12.3 *WNK4*, Chr. 17q21.2 *CUL3*, Chr. 2q36.2 *KLHL3*, Chr.5q31.2	WNK lysine-deficient protein kinase 1 WNK lysine-deficient protein kinase 4 Cullin 3 Kelch-like family member 3	NCC inhibitors (thiazide diuretics)

Diagnostic approach to low-renin hypertension

Silvia Monticone | Isabel Losano | Martina Tetti | Fabrizio Buffolo | Franco Veglio | Paolo Mulatero

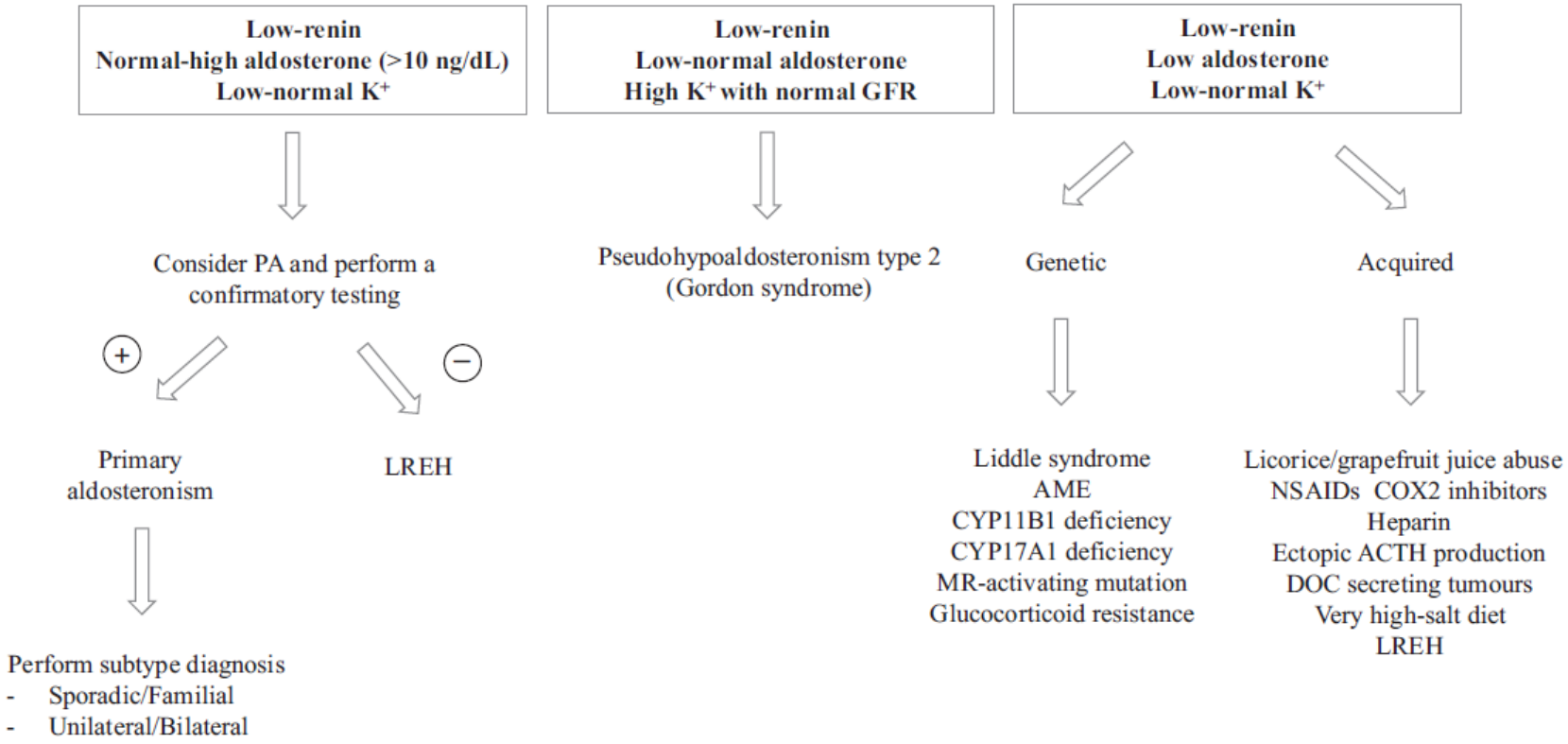
Clin Endocrinol 2018

Syndrome	Inheritance	Gene(s) involved, chromosome	Protein	Therapy
FH-I	AD	Hybrid *CYP11B1/ CYP11B2* Chr. 8q24.3	Cytochrome P450 family 11 subfamily B member 1 (11-beta-hydroxylase)/ cytochrome P450 family 11 subfamily B member 2 (aldosterone synthase)	Dexamethasone
FH-II	AD, incomplete penetrance	*CLCN2* Chr. 3q27.1	Chloride voltage-gated channel 2	MR-antagonists
FH-III	AD	*KCNJ5* Chr. 11q24.3	G protein-activated inward rectifier potassium channel 4, GIRK4	MR-antagonists, bilateral adrenalectomy
FH-IV	AD, incomplete penetrance	*CACNA1H* Chr. 16p13.3	Calcium voltage-gated channel subunit alpha1H, $Ca_v3.2$	MR-antagonists
PASNA syndrome	n.a.	*CACNA1D* Chr. 3p21.3	Calcium voltage-gated channel subunit alpha1D, $Ca_v1.3$	MR-antagonists, CCBs
Liddle syndrome	AD	*SCNN1A*, Chr. 12p13.3 *SCNN1B*, Chr. 16p12.2 *SCNN1G*, Chr. 16p12.2	Sodium channel epithelial 1 alpha subunit, Sodium channel epithelial 1 beta-subunit, Sodium channel epithelial 1 gamma-subunit	ENaC inhibitors (amiloride and triamterene)
AME syndrome	AR	*HSD11B2* Chr. 16q22.1	Hydroxysteroid 11-beta-dehydrogenase 2	Dexamethasone MR-antagonists
CYP11B1 deficiency	AR	*CYP11B1* Chr. 8q24.3	Cytochrome P450 family 11 subfamily B member 1 (11-beta-hydroxylase)	Hydrocortisone (in children) Dexamethasone
CYP17 deficiency	AR	*CYP17A1* Chr. 10q24.3	Cytochrome P450 family 17 subfamily A member 1 (17α-hydroxylase)	Hydrocortisone (in children) Dexamethasone
Glucocorticoid resistance syndrome	AR	*NR3C1* Chr. 5q31.3	Nuclear receptor subfamily 3 group C member 1 (glucocorticoid receptor)	Dexamethasone
MR-activating mutation	AD	*NR3C2* Chr. 4q31.2	Nuclear receptor subfamily 3 group C member 2 (mineralocorticoid receptor)	ENaC inhibitors (amiloride and triamterene)
Gordon syndrome (familial hyperkalemic hypertension, pseudohypoaldosteronism type 2)	AD or AR	*WNK1*, Chr.12p12.3 *WNK4*, Chr. 17q21.2 *CUL3*, Chr. 2q36.2 *KLHL3*, Chr.5q31.2	WNK lysine-deficient protein kinase 1 WNK lysine-deficient protein kinase 4 Cullin 3 Kelch-like family member 3	NCC inhibitors (thiazide diuretics)

Diagnostic approach to low-renin hypertension

Silvia Monticone | Isabel Losano | Martina Tetti | Fabrizio Buffolo | Franco Veglio | Paolo Mulatero

Clin Endocrinol 2018



UNIVERSITÀ DI TORINO

Hypertension Excellence Centre of the European Society of Hypertension

Medicina Interna 4 1988-2023

Medicina Interna 3 2024-2025

非常感谢您的关注