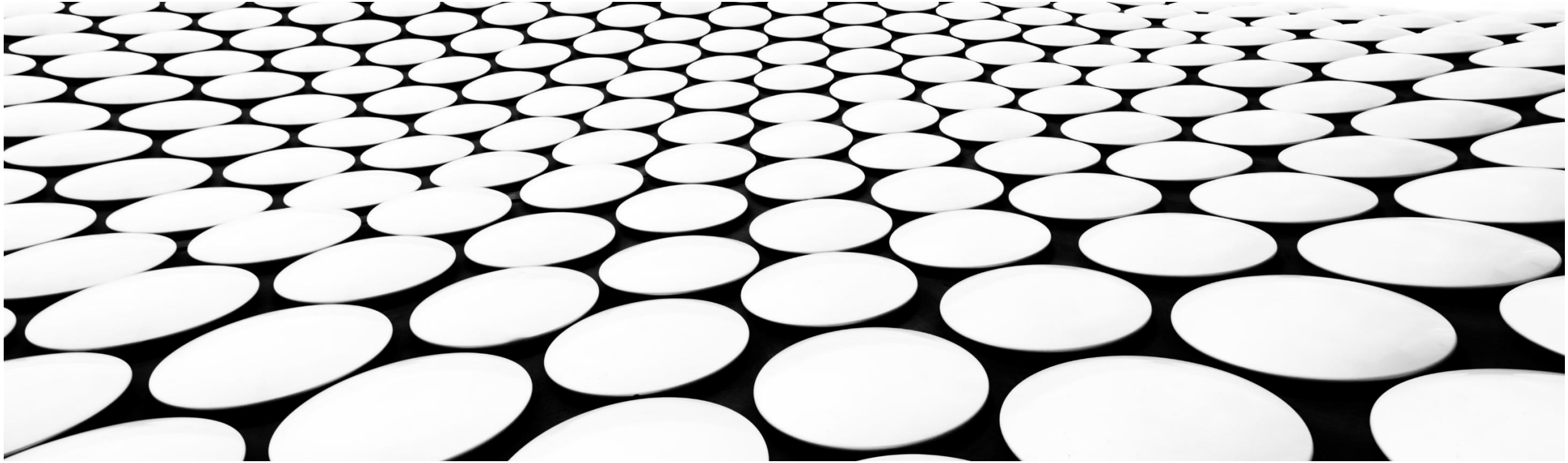
ALDOSTERONE DYSREGULATION: WHERE DO WE STAND

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

PROF BELEN PONTE - RESPONSABLE DE L'UNITÉ D'HYPERTENSION

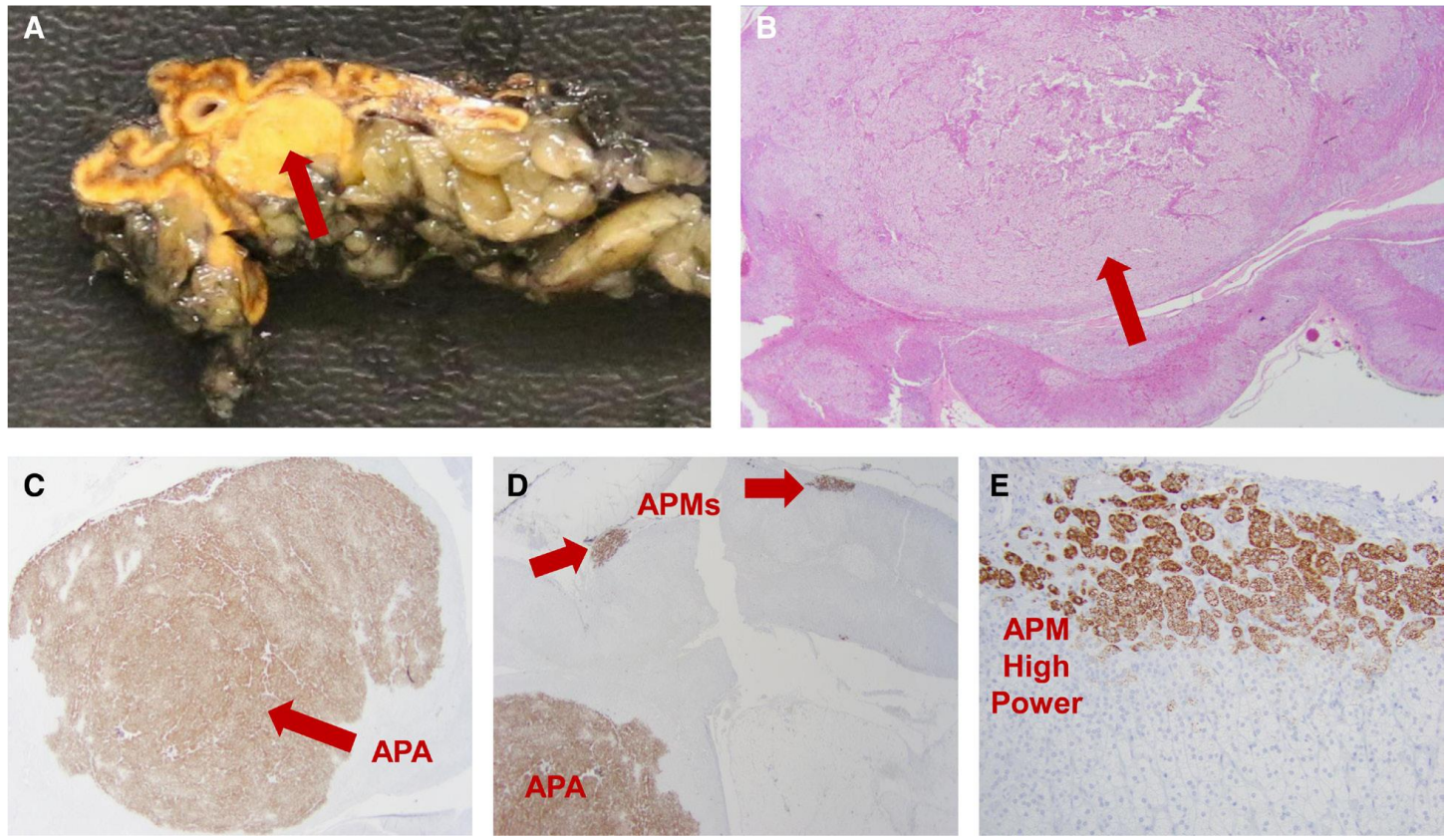
SERVICE DE NEPHROLOGIE ET HYPERTENSION

HUG



CONFLICTS OF INTEREST FOR THIS PRESENTATION

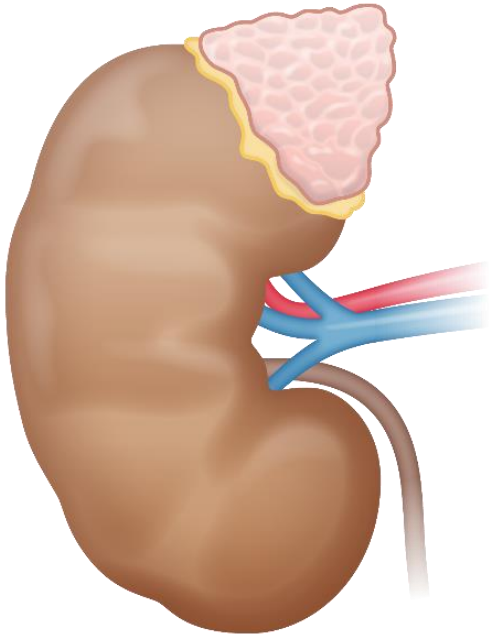
- Fees to our division for SSMI 2026 symposium and Think Aldo project



Parisien-La Salle S et al. Hypertension 2026

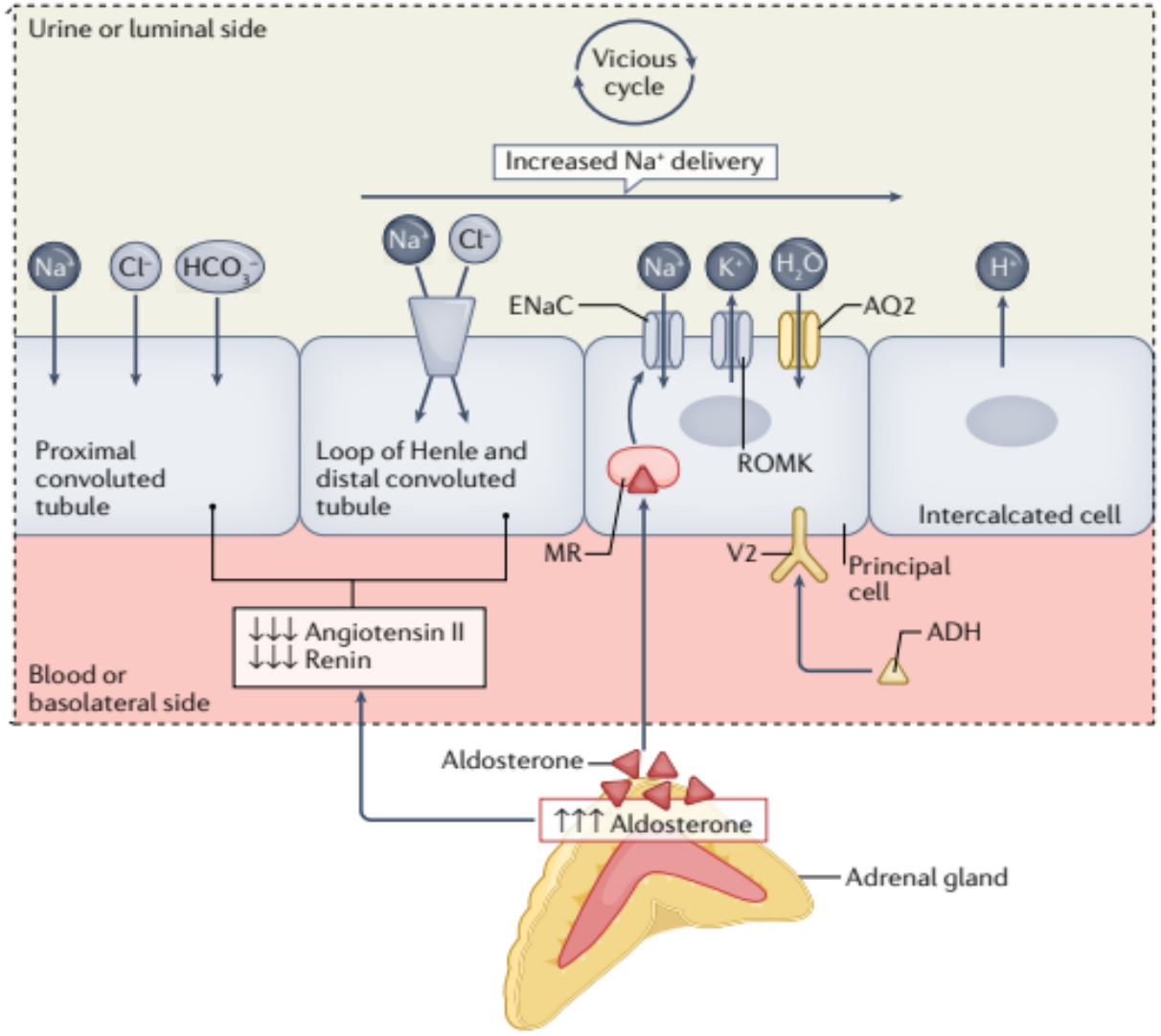
PLAN

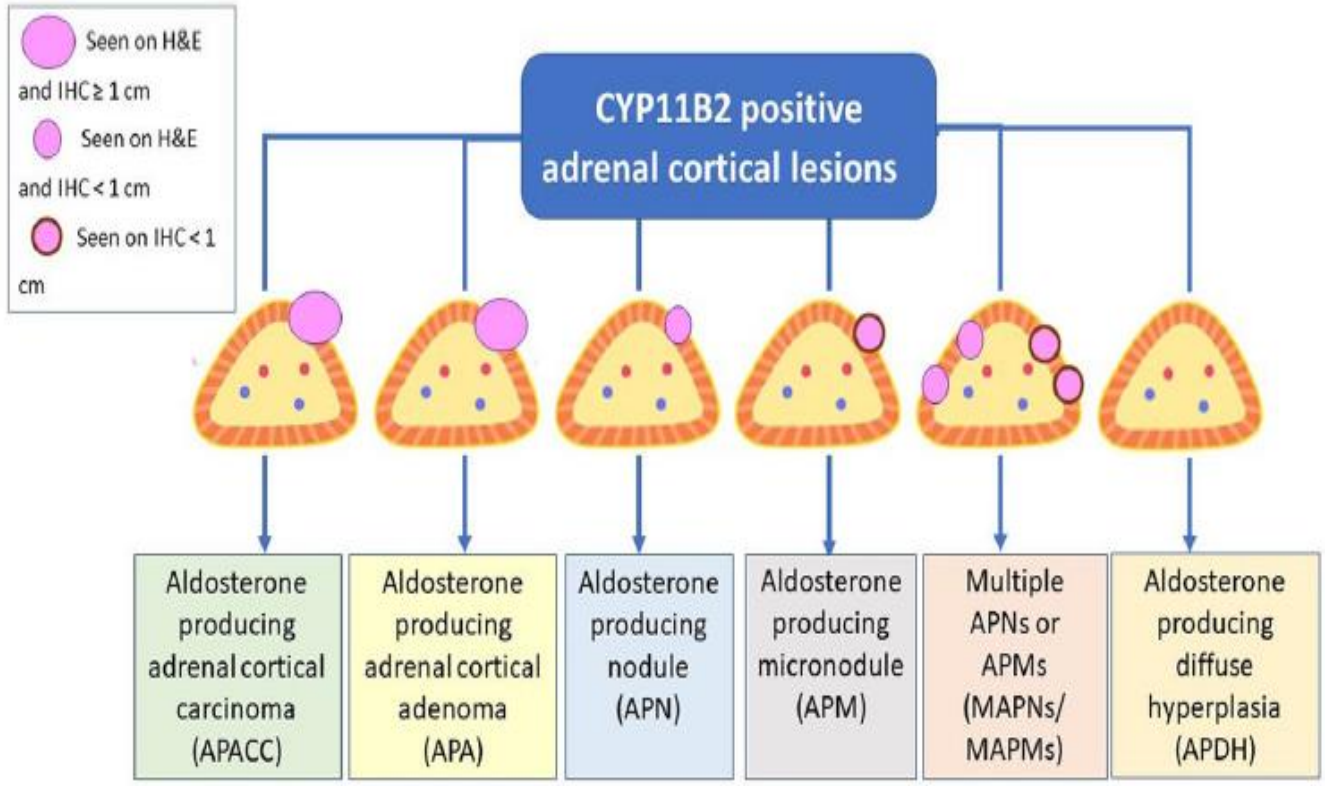
- PRIMARY ALDOSTERONISM (PA): EPIDEMIOLOGY and SPECTRUM
- WHO and HOW TO SCREEN ?
- WHY DOES IT MATTER ?
  - Cardio-kidney-metabolic risk
  - Specific treatments
- TAKE HOME MESSAGES



Turcu et al. Nat rev Endocrinol 2022
O. Mete, et al. Endocr. Pathol 2022.

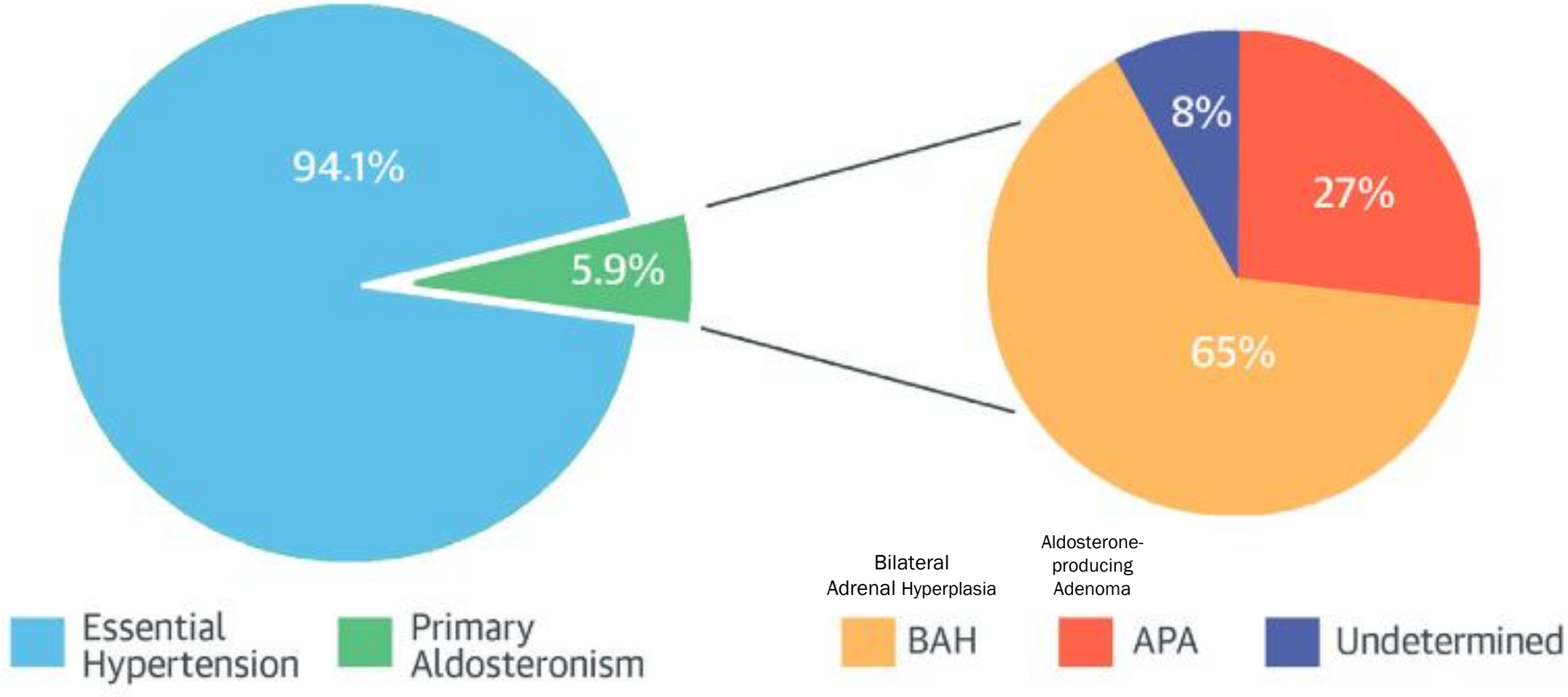
PA: FROM PHYSIOPATHOLOGY TO EPIDEMIOLOGY





PA EPIDEMIOLOGY: FROM RARE TO COMMON DISEASE

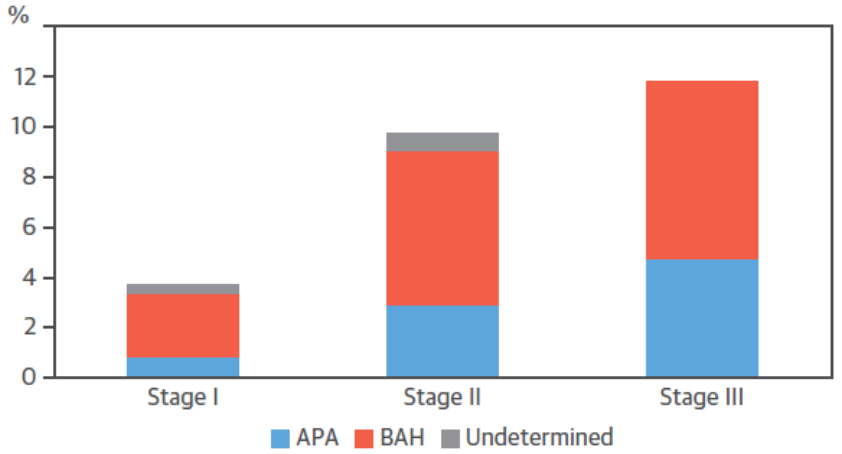
1672 HT patients in primary care practice(Torino, Italy)
screening according to ESH criteria



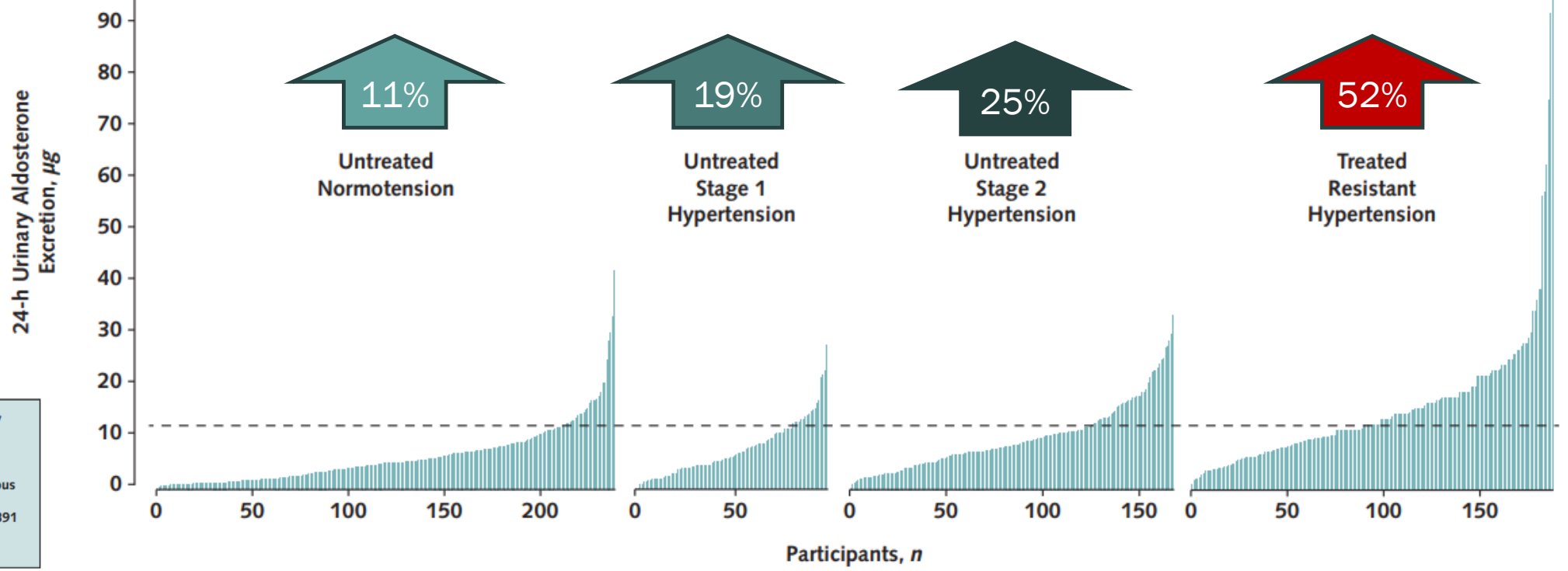
Monticone S, J Am Coll Cardiol 2017;69(14):1811-20
ADLER GK et al. JCEM 2025

PA PREVALENCE: DEPENDS ON THE SETTING

- Most common cause of secondary hypertension.
- But <2% eligible patients are screened



	Setting	Prevalence
	Hypertension in Primary Care	5.9% (range, 3.2-14.0)
	Hypertension in referral centers	7.2% (range, 0.7-21.9)
*	Hypertension in young adults (ages 18-40 years)	16.2%
	[a]Grade 1 hypertension	3.9%-15.7%
	[a]Grade 2 hypertension	9.7%-21.6%
	[a]Grade 3 hypertension	11.9%-19%
*	Resistant hypertension	11.3%-29.1%
*	Hypertension and hypokalemia	28.1%
	Hypertension and adrenal incidentaloma	4.4% (range, 0.4-24.6%)
*	Hypertension and atrial fibrillation[b]	42.5%
	Hypertension and type 2 diabetes mellitus	11.3%-19.1%

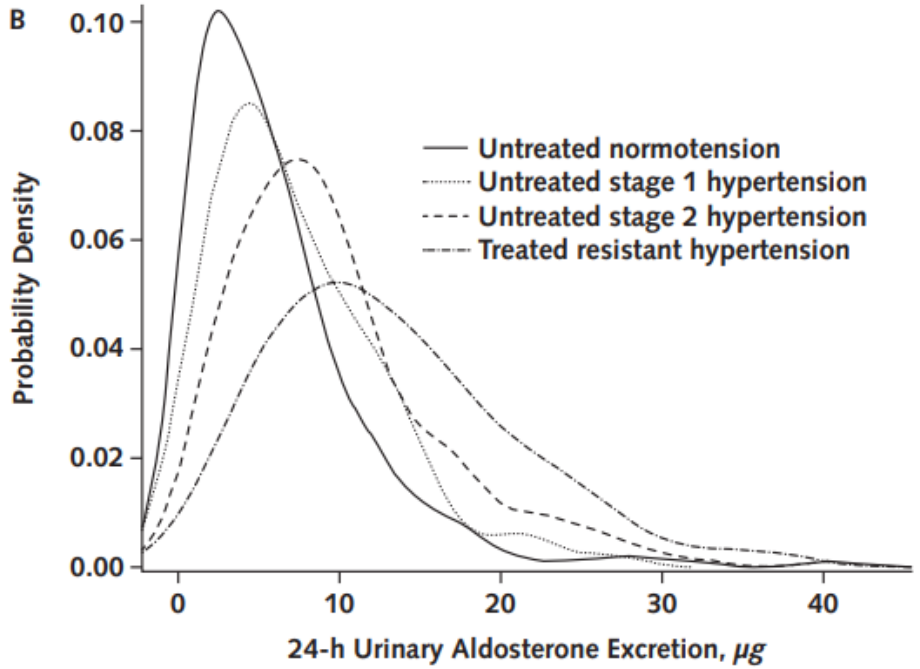


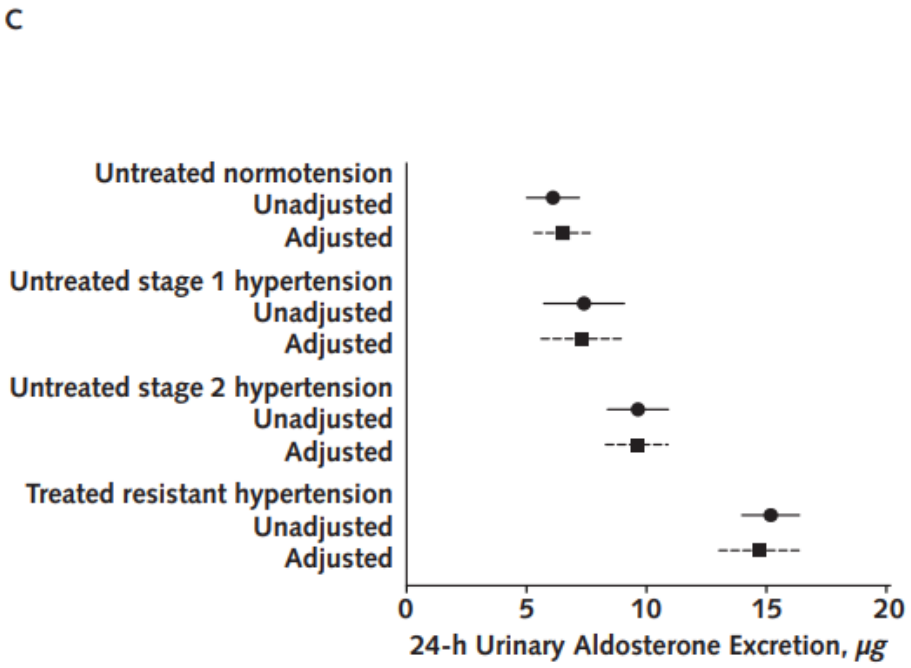
Participants with complete data for aldosterone, renin, and urinary sodium ($n = 1846$)
- Charlottesville, Virginia: Salt Sensitivity of Blood Pressure protocol: 93
- Boston, Massachusetts: Prospective Phenotyping of Autonomous Aldosterone Secretion protocol: 45
- Boston, Massachusetts: Hypertensive Pathotype Consortium: 391
- Salt Lake City, Utah: Hypertensive Pathotype Consortium: 243
- Birmingham, Alabama: Resistant Hypertension Clinic: 1074

→ Excluded for inadequate 24-h urinary sodium excretion on oral sodium suppression test ($n = 831$)*

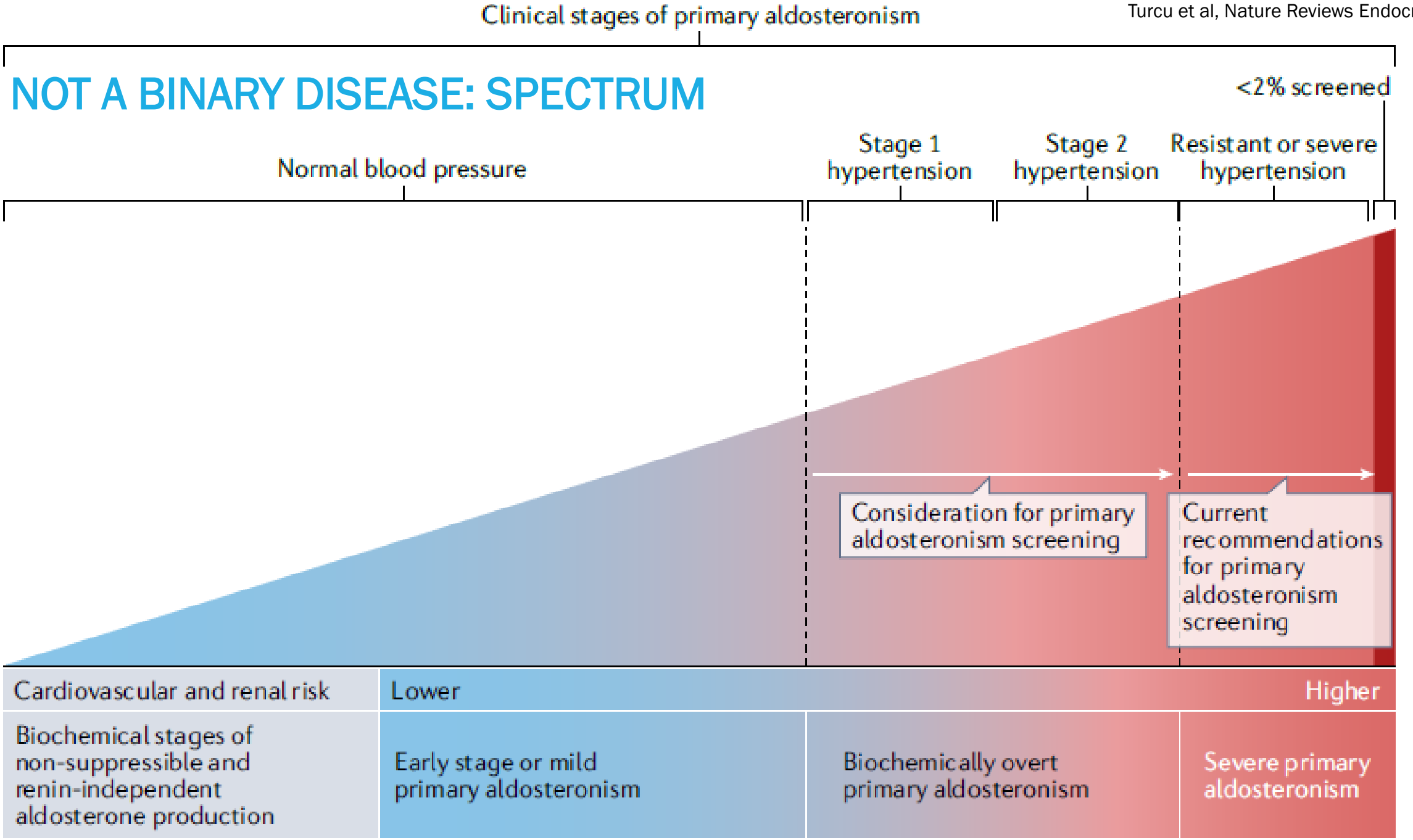
Eligible study population: participants in high sodium balance ($n = 1015$)
- Charlottesville: Salt Sensitivity of Blood Pressure protocol: 93
- Boston: Prospective Phenotyping of Autonomous Aldosterone Secretion protocol: 32
- Boston: Hypertensive Pathotype Consortium: 308
- Salt Lake City: Hypertensive Pathotype Consortium: 174
- Birmingham: Resistant Hypertension Clinic: 408

Assessment of renin-independent aldosterone production: participants with high sodium balance *and* suppressed renin activity ($n = 691$)†
- Charlottesville: Salt Sensitivity of Blood Pressure protocol: 80
- Boston: Prospective Phenotyping of Autonomous Aldosterone Secretion protocol: 25
- Boston: Hypertensive Pathotype Consortium: 261
- Salt Lake City: Hypertensive Pathotype Consortium: 137
- Birmingham: Resistant Hypertension Clinic: 188





NOT A BINARY DISEASE: SPECTRUM



Turcu et al, Nature Reviews Endocr, 2022

SCREENING RECOMMANDATIONS: BROADER INDICATIONS

Guideline	Who to Screen	Class/Strength of Recommendation	Distinctive Features
AHA/ACC 2025 [9]	• All adults with resistant HTN, regardless of potassium • Stage 2 HTN (≥140/90 mm Hg) – new, expanded population • Clinical suspicion of secondary causes	• Class 1: Screen resistant HTN regardless of hypokalemia • Class 2b: *Consider* screening all adults with stage 2 HTN	• Aligns with ESC 2024 on broadening screening • Allows continuation of most antihypertensive medications (except MRAs) before ARR testing to reduce barriers
ESC 2024 [10]	• All adults with confirmed HTN (≥140/90 mm Hg) • Any degree of hypertension with suggestive features (resistant HTN, hypokalemia, adrenal incidentaloma, family history)	• Class IIa (*should be considered*): Screen all adults with confirmed HTN	• Endorsed by the European Society of Endocrinology • Shifts from case-finding to near-universal screening among hypertensive adults
Endocrine Society 2025 [8]	• All individuals with HTN, regardless of severity or potassium level	• Conditional (*moderate certainty*): Suggest screening all adults with HTN	• Most detailed diagnostic algorithm (ARR → confirmatory testing → lateralization) • Integrates evidence on PA continuum[19] and renin-guided MRA titration

ESH 2023 not large screening!

Adler GK et al. Endocrine Society Clinical Practice Guideline. JCEM 2025

DIAGNOSTIC TESTS : NEW CRITERIA

New renin suppression criterion

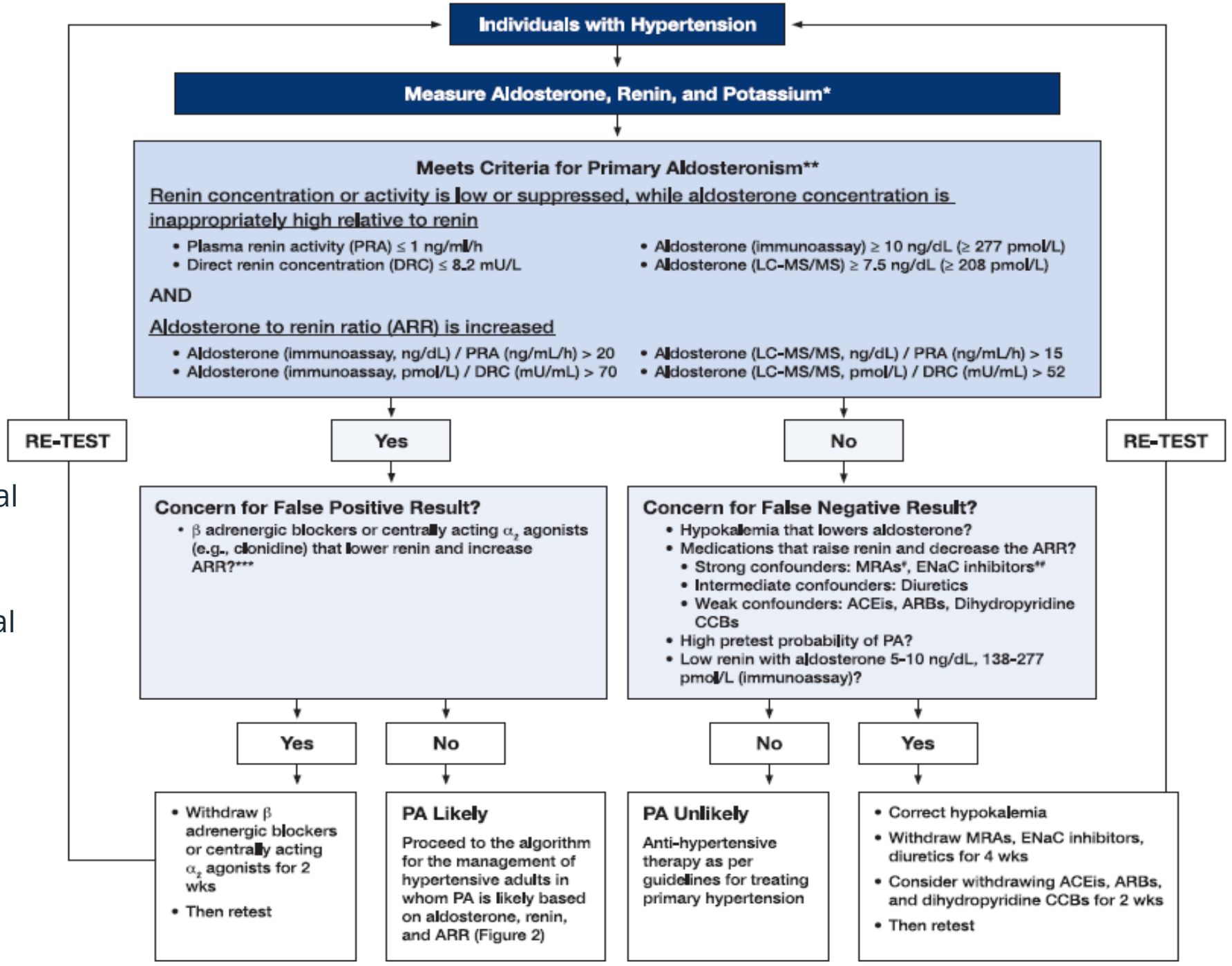
Lower aldosterone requirement

Aldosterone to renin ratio still central

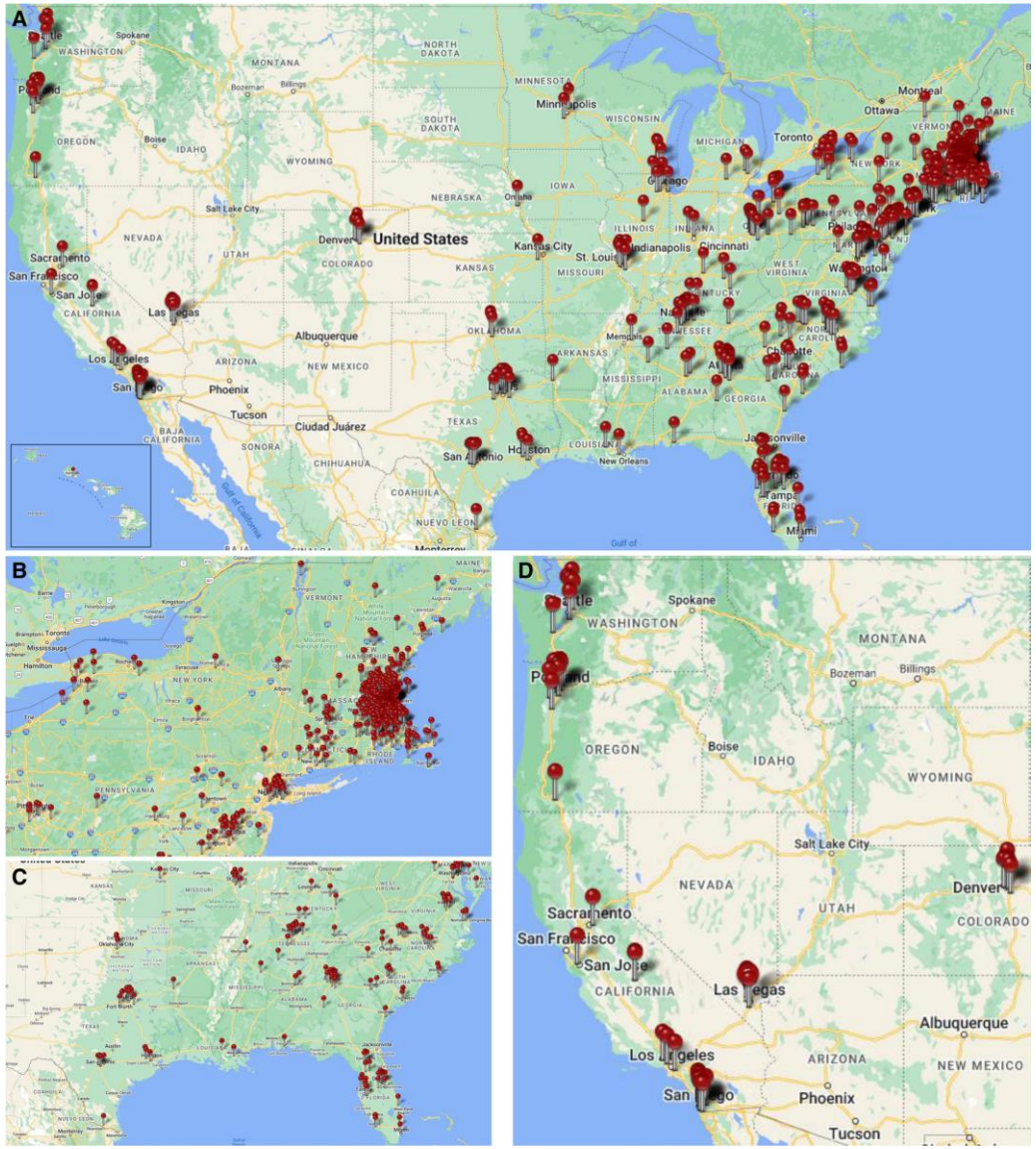
! Laboratory thresholds are essential

Broader initial screening

Less confirmatory tests



DIRECT-TO-PATIENT PA TESTING PROGRAM



Reached by Study Advertising (n=623,330+)
Facebook/Meta (608,860)
Research Match (6,594)
MGB Patient Portal (7,483)
Other (393+)

Screened for Eligibility (n=910):
Facebook/Meta (329)
Research Match (210)
MGB Patient Portal (256)
Other (115)

→ Participant did not meet inclusion criteria or withdrew prior to consent.

Enrolled (n=742):
Facebook/Meta (264)
Research Match (184)
MGB Patient Portal (218)
Other (76)

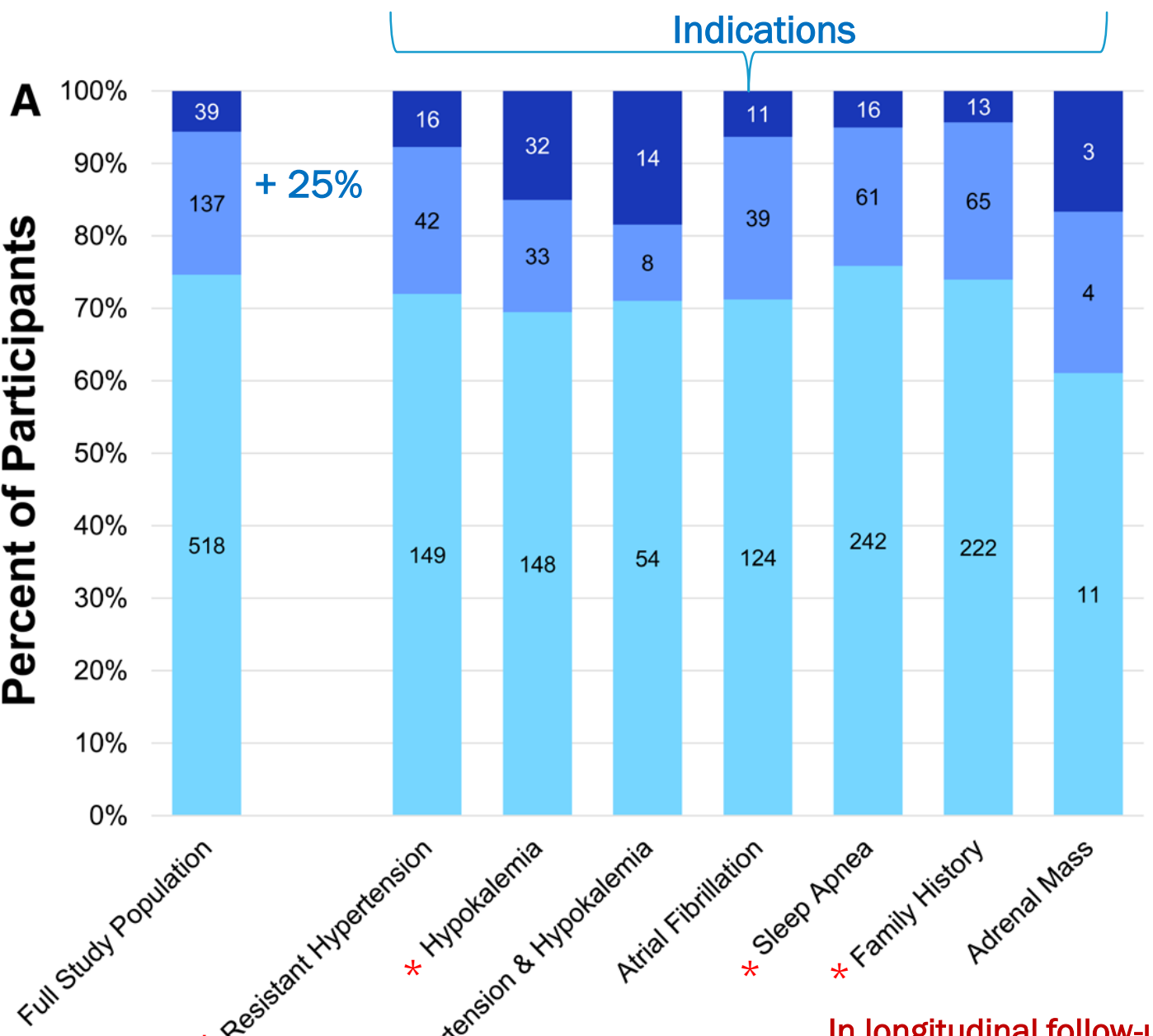
→ Participant opted to withdraw or did not keep appointment for lab draw.

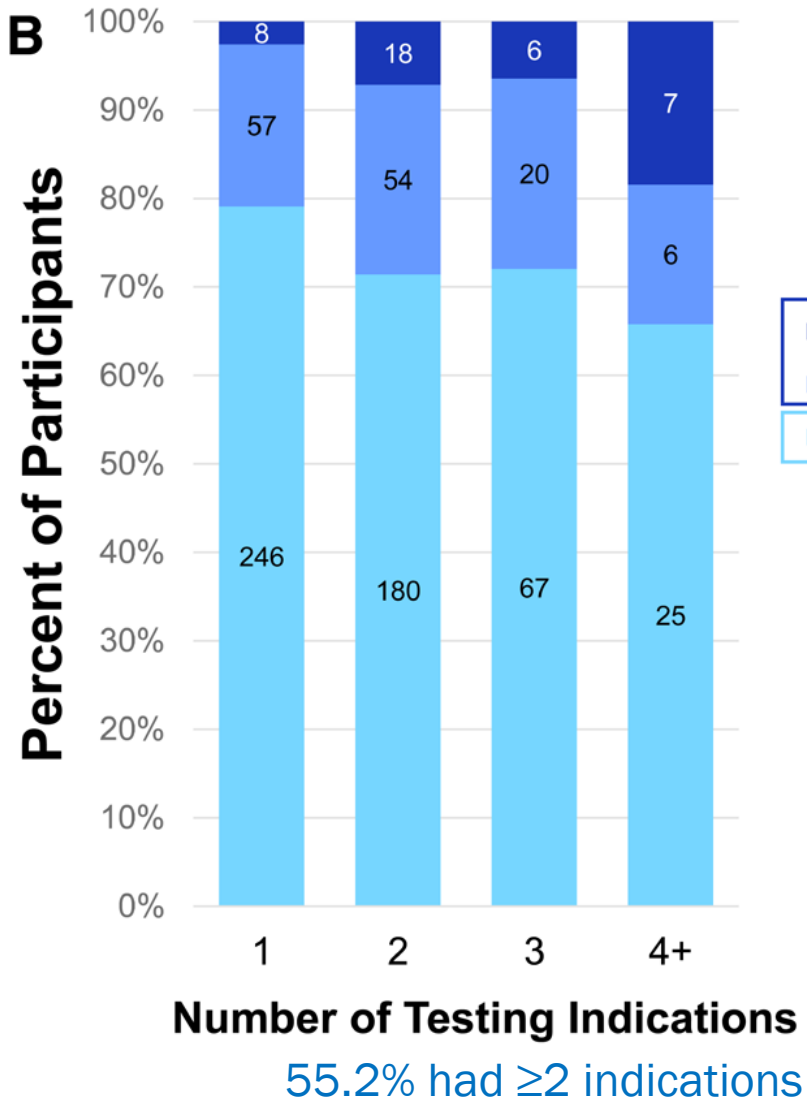
Completed Blood Draw (n=699)

→ One or more laboratory test did not result due to technical failure.

Final Study Population with Interpretable Results (n=694)

Responded to 6- to 12-Month Follow-Up Survey (n=433)



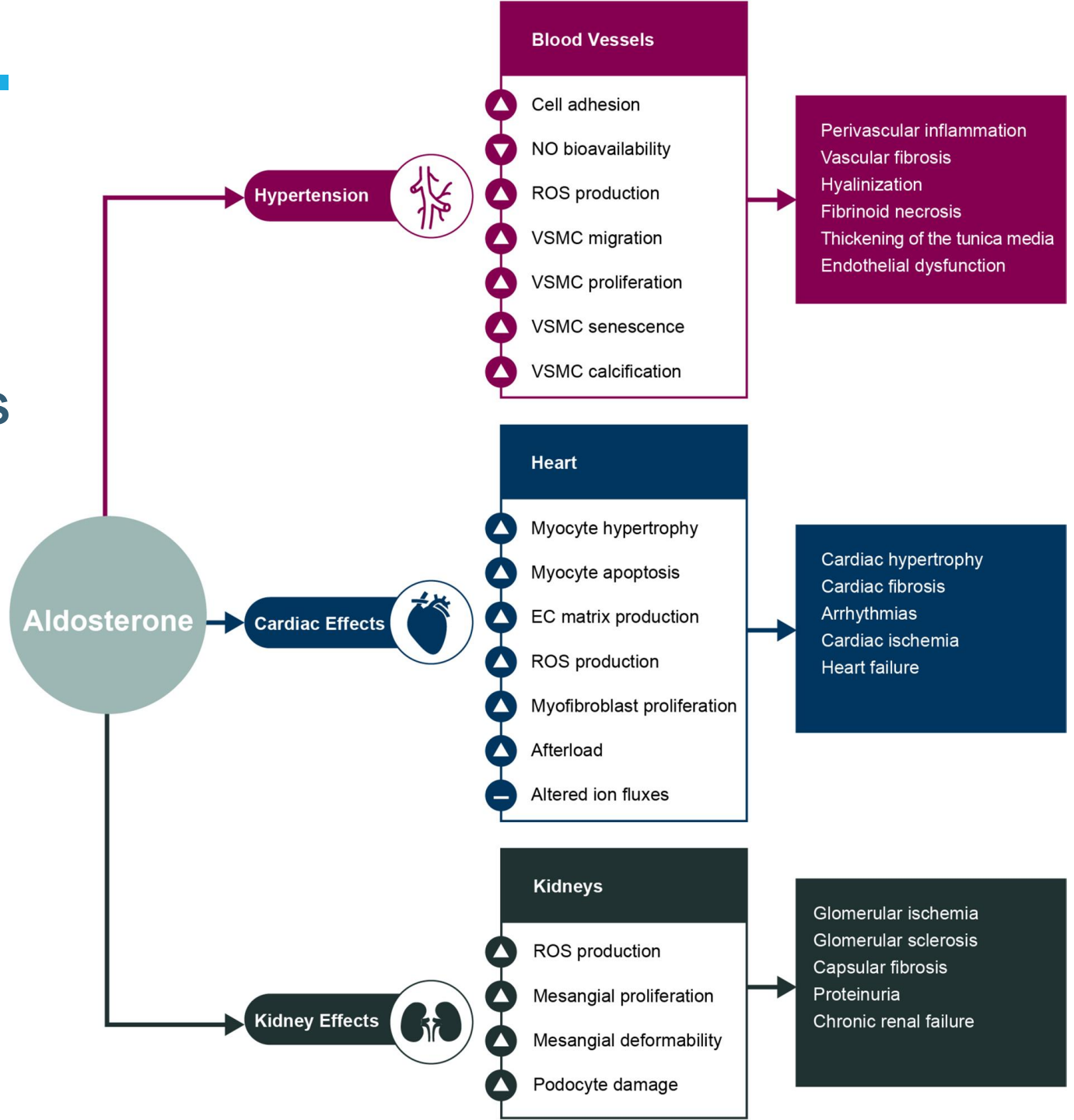


In longitudinal follow-up - 12months:

- 25.5% had additional testing
- 13.7% were started on aldosterone-targeted therapy (MRA or adrenalectomy)
- 24.5% reported improved blood pressure control.

WHY DETECTING PA MATTERS?

- CV and target organ complications
- Specific treatment targeting aldosterone



Monticone S et al. Lancet Diab Endoc 2018. Monticone S et al. J Hypertension 2019. Rossi GP, Hypertension 2006;48(2):232

PA IS ASSOCIATED WITH HIGHER CV RISK THAN PRIMARY HT

PA REMAINED AT HIGHER RISK OF HF, AF AND STROKE EVEN AFTER CORRECTION FOR SIMILAR BP

Meta-Analysis of 31 observational studies (N=12'122)		
	OR (95%CI) PA vs primary HT	OR (95%CI) PA vs primary HT *Matching for blood pressure*
Coronary Heart Disease	1.77 (1.10-2.83)	1.82 (0.94-3.52)
Heart Failure	2.05 (1.11-3.78)	**3.39 (1.79-6.41)**
Atrial Fibrillation	3.52 (2.06-5.99)	**4.00 (1.83-8.76)**
Stroke	2.58 (1.83-3.45)	**2.63 (1.76-3.94)**

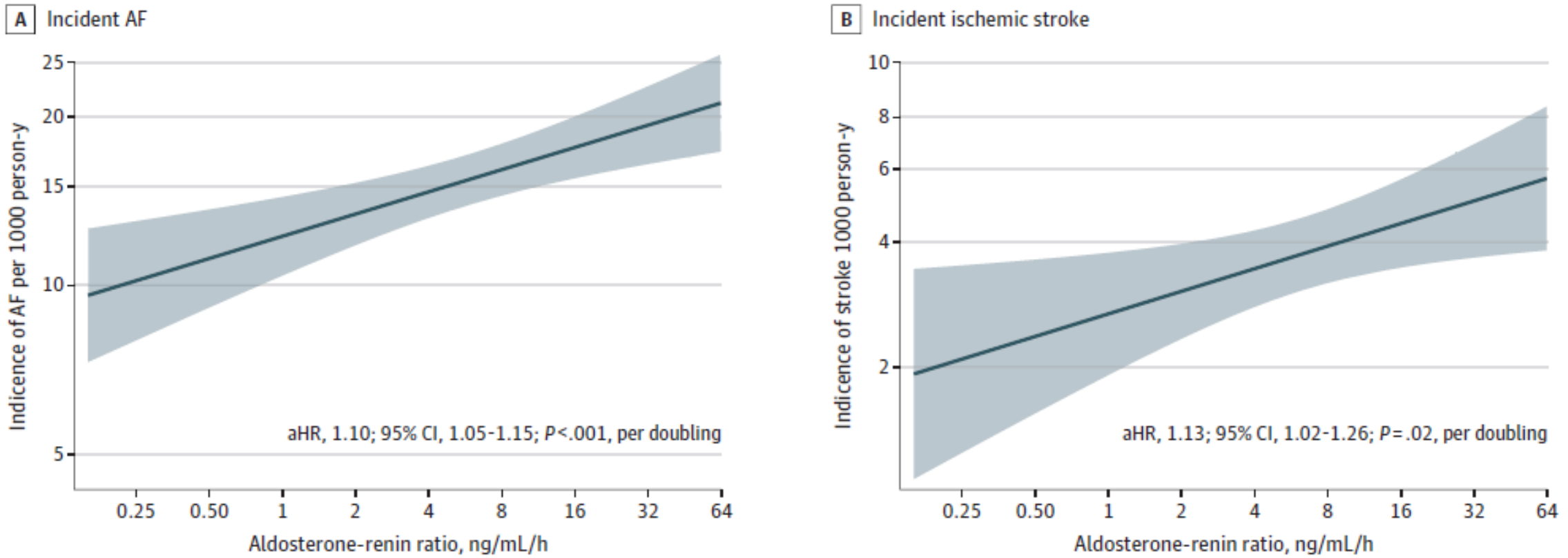
! Also increased in albuminuria: OR 2.09 (1.40-3.12) and proteinuria OR 2.68 (1.89-3.79)

BIOLOGICAL SEVERITY IS ASSOCIATED WITH CV EVENTS

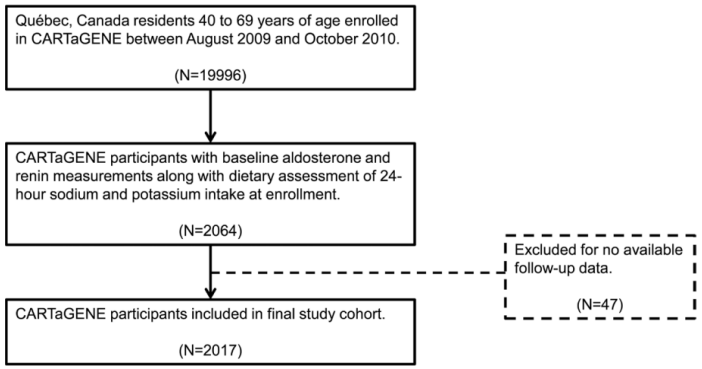
ARIC study (n=3477): mean 74.8 [4.9] years during 9 years

Higher ARR associate with Atrial Fibrillation, Stroke but not Heart Failure, nor Myocardial Infarct

Figure 2. Restricted Cubic Splines Displaying Associations Between Aldosterone-Renin Ratio and Risk of Cardiovascular Outcomes



SUBCLINAL PA IS ALSO ASSOCIATED WITH MAJOR ADVERSE CV EVENTS



Variable*	Crude HR (95% CI) for MACEs	Adjusted HR (95% CI) for MACEs†
Aldosterone concentration, pmol/L	1.33 (0.38–4.70)	1.57 (0.42–5.90)
Renin concentration, ng/L‡	0.42 (0.21–0.85)	0.45 (0.21–0.98)
ARR, pmol/L per ng/L‡	2.49 (1.25–4.96)	2.43 (1.15–5.12)

Mean age 56 (8) years
Mean BP 129 (15)/76(10)
Hypertension 27%

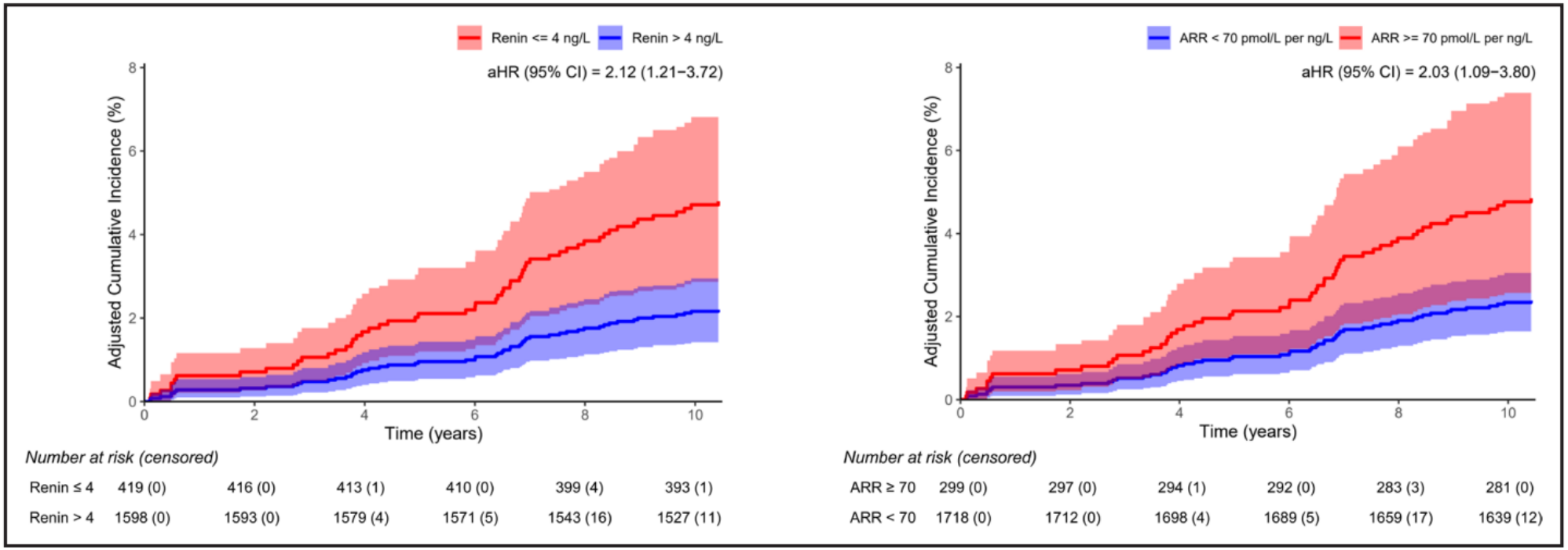
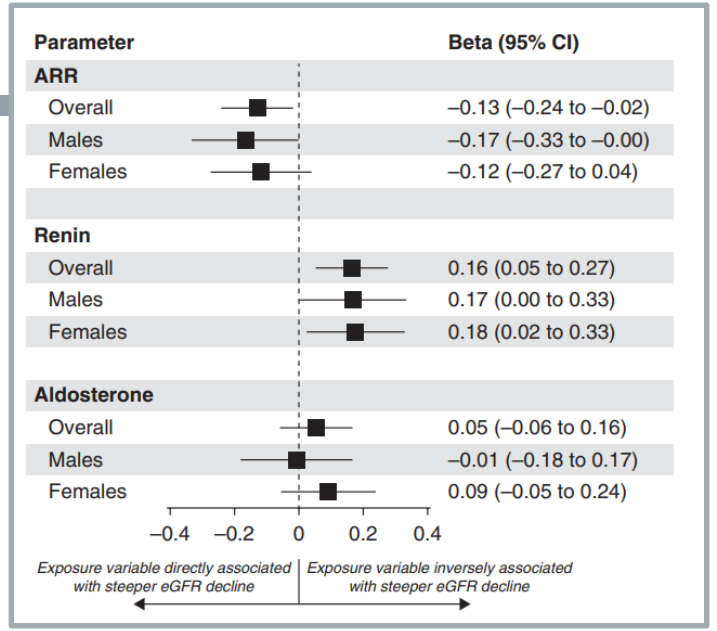


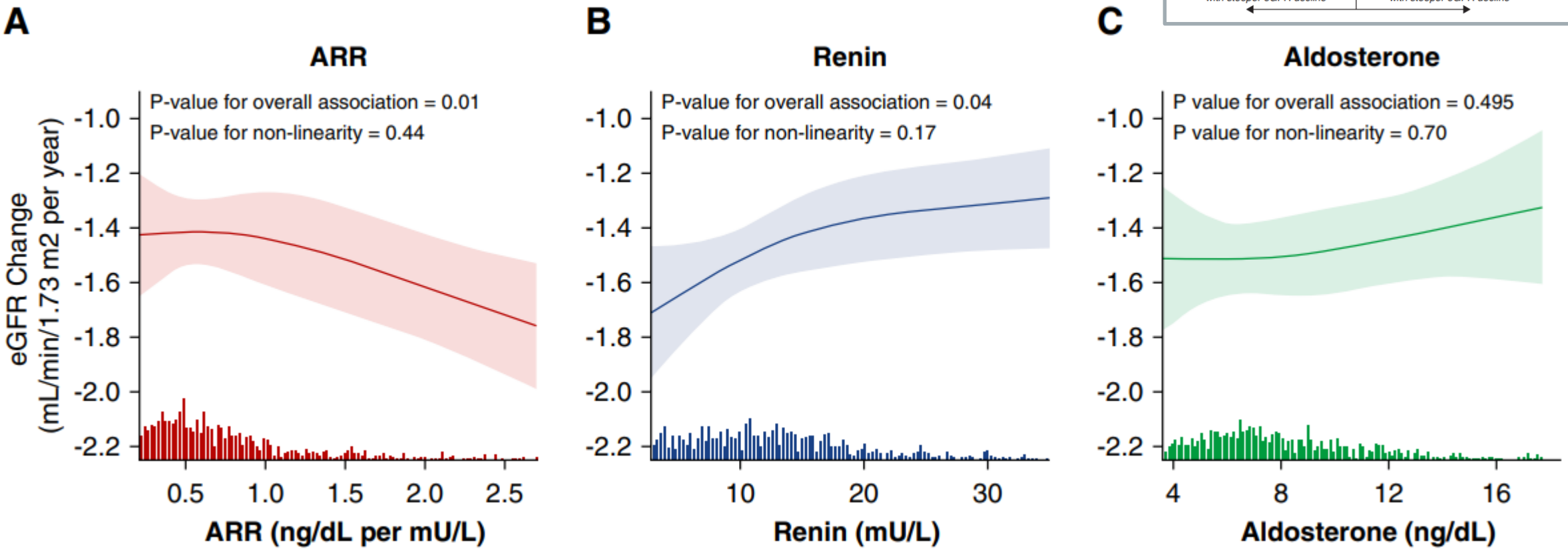
Figure 3. Adjusted cumulative incidence curves using outcome-derived thresholds for increased risk of major adverse cardiovascular events in subclinical primary aldosteronism.

SUBCLINICAL PA AND RENAL FUNCTION DECLINE

CARTAGENE STUDY SUBGROUP (N=976) - 11% HT STAGE 1 NOT TREATED

↑ ARR AND ↓ RENINE ARE ASSOCIATED WITH STEEPER DECLINE IN GFR (11% AND 16%) - INDEPENDENT OF BLOOD PRESSURE





WHY SCREENING? ALSO BECAUSE THERE ARE SPECIFIC TREATMENTS

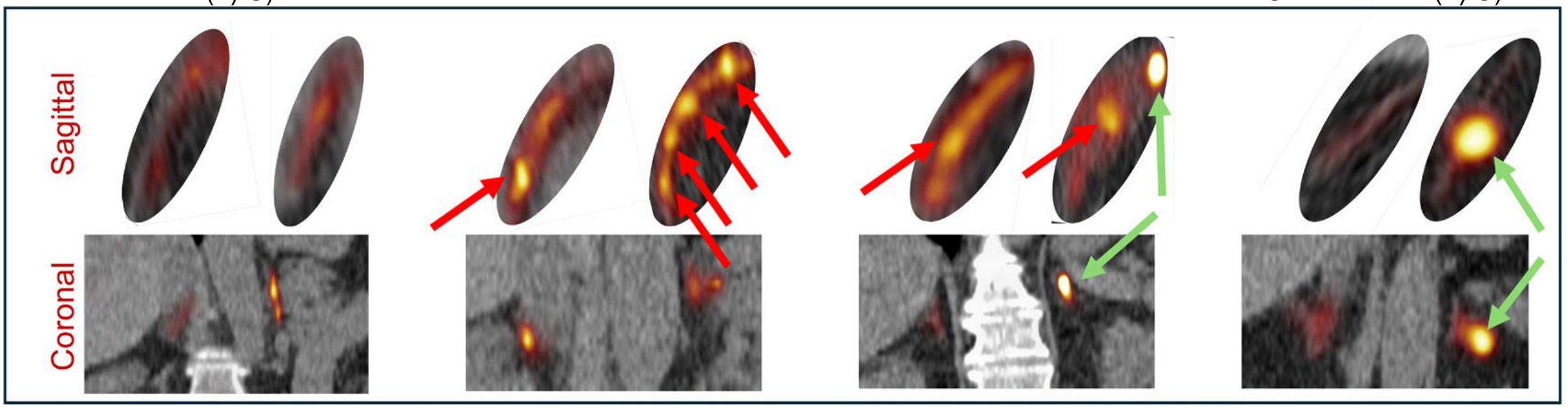
BILATERAL (2/3)

UNILATERAL (1/3)

PET/CT

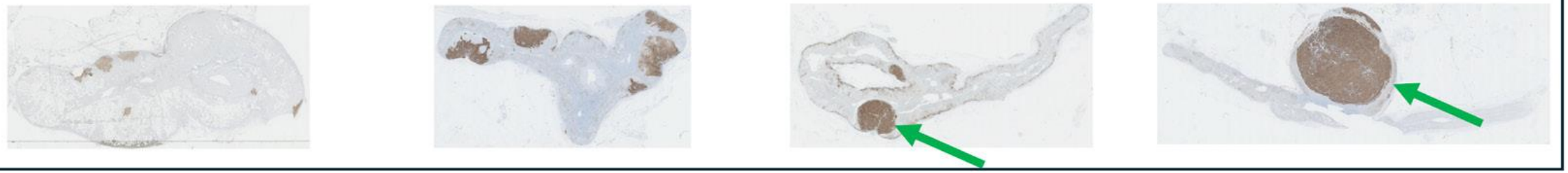
Sagittal

Coronal



Medical Therapy → TTT or Surgery

IHC



Hundmer GL et al. Lancet Diab Endo, 2018
Sho Katsuragawa et al. Lancet Diabetes Endocrinol 2025

HIGH RENIN IN TREATED PA IMPROVES OUTCOME

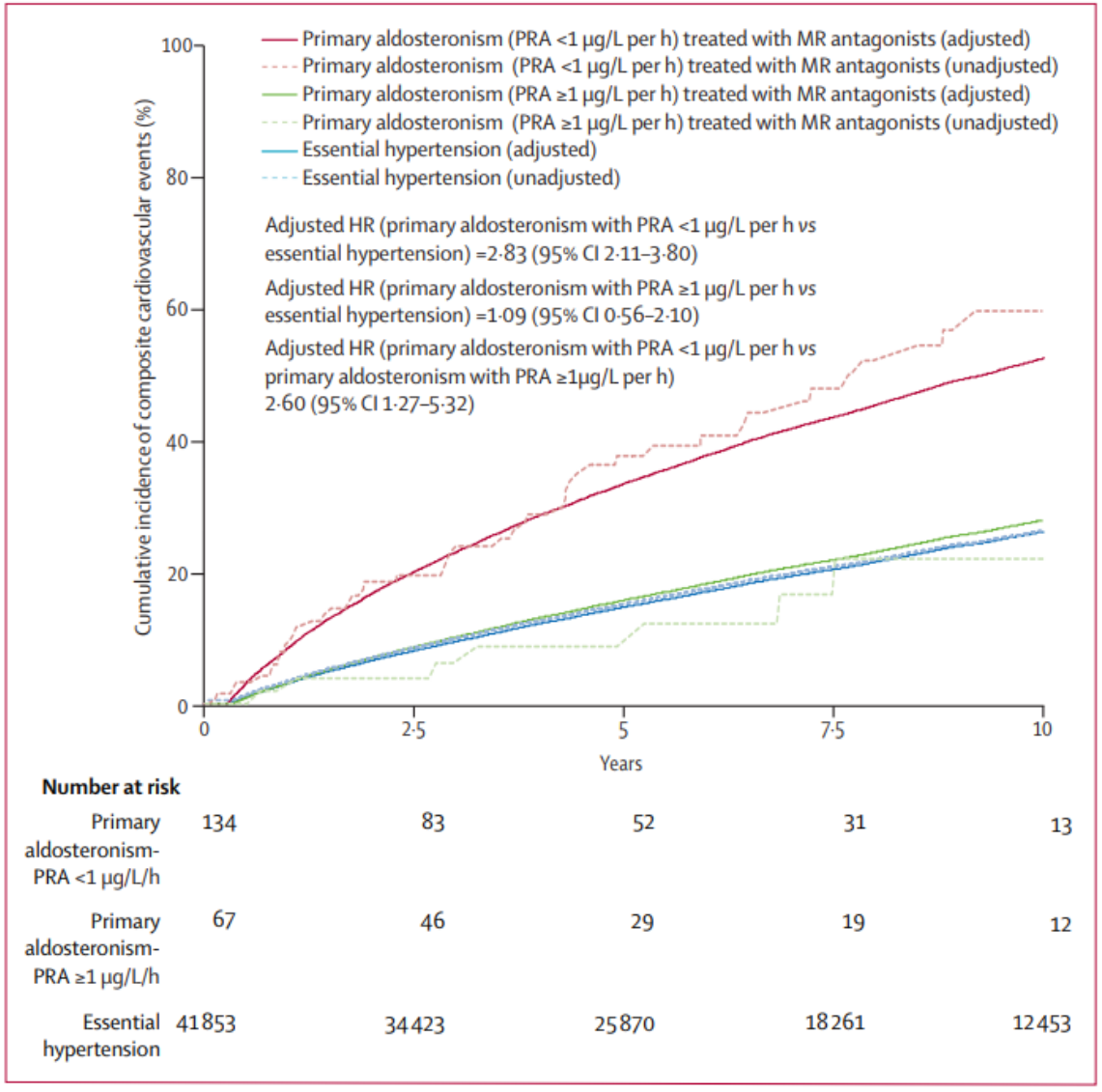


Figure 3: **Standardised cumulative incidence curve of composite cardiovascular outcomes stratified by plasma renin activity**

Better CV outcome when renin is unsuppressed
With MRA treatment.
→ Outcome similar to primary HT

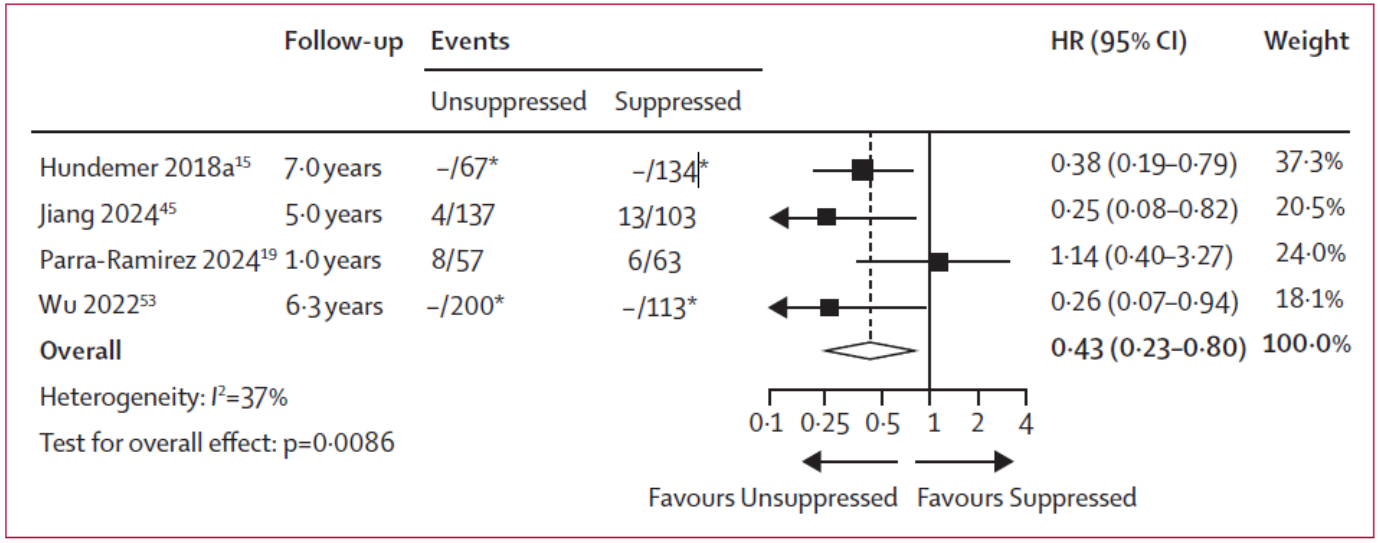
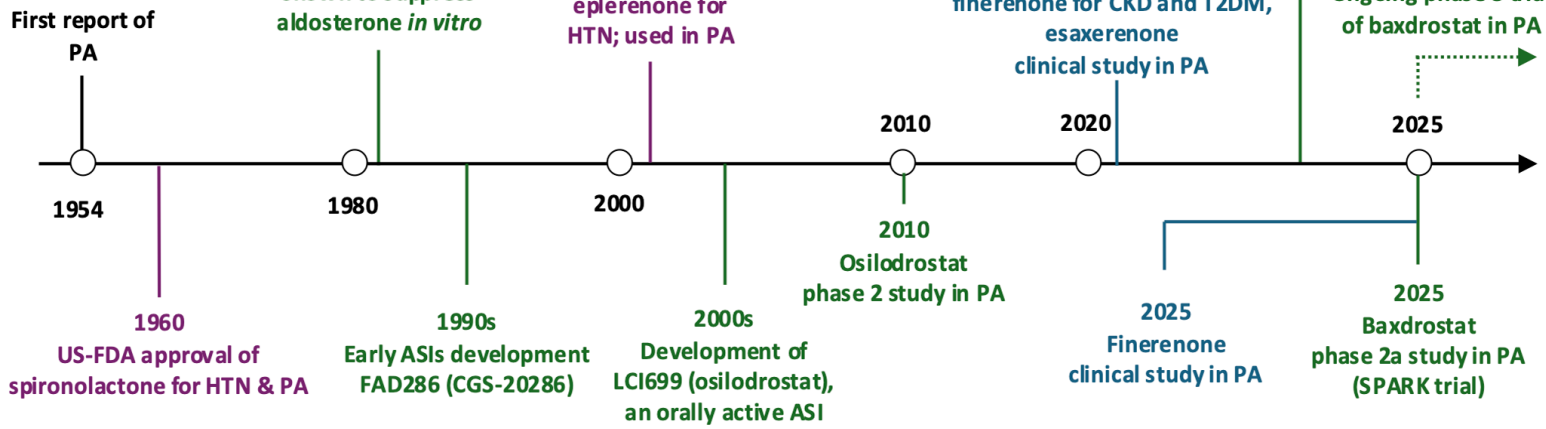
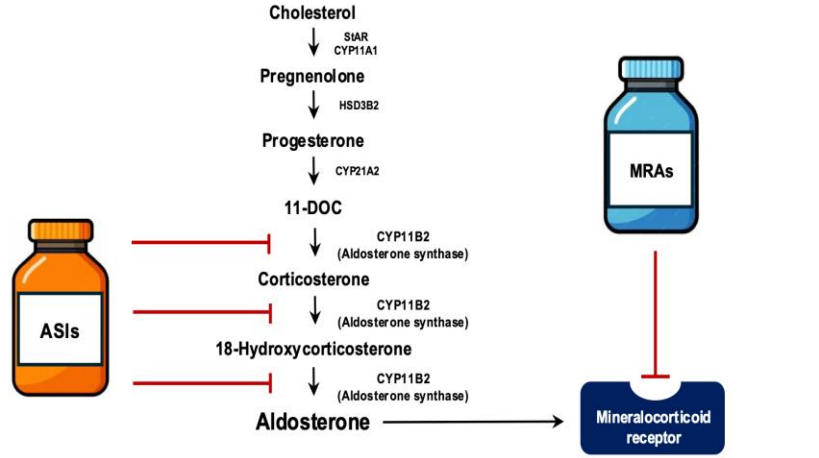
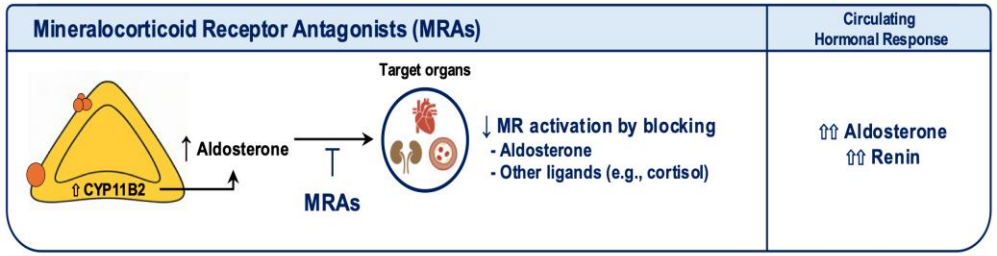


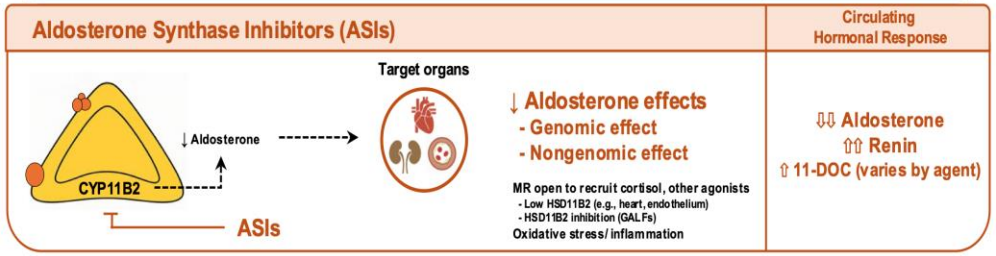
Figure 2: **Forest plot for the association between post-treatment renin status and the incidence of cardiovascular events**
HR=hazard ratio. *The number of events in each group were not reported.

MEDICAL TREATMENT: ONGOING AND FUTURE









TAKE HOME MESSAGES

- PA PREVALENCE IS UNDERESTIMATED. NOT A BINARY DISEASE BUT A SPECTRUM.

- HIGHER CV-RENAL-METABOLIC RISK COMPARED TO PRIMARY HT.

- SPECIFIC TREATMENT EXISTS.
- OUTCOME IMPROVEMENT INDEPENDENT OF BP REDUCTION.
- ROLE OF LOW RENIN?

- EARLY IDENTIFICATION = EARLY TREATMENT.
- NO PA NOW IS NOT PA NEVER

→ **SCREEN MORE TO REDUCE RISKS**

	Normal BP	Hypertension	Overt PA
Renin	Low	Low	Low
BP Phenotype	High-Normal BP ↑Incident Hypertension	Stage I/II HTN	Resistant HTN
Evidence of MR Activation	Normokalemia Mild Kaliuresis		High risk for Hypokalemia Increased Kaliuresis
Response to MR Antagonists	Not Tested	Enhanced	Proven Superior
Cardiovascular-Renal-Metabolic Risk	Lower		Higher
Renin/AngII-Independent Aldosterone Production	Progressively non-suppressible aldosterone after volume expansion		
ACTH-Mediated Aldosterone Production	Progressively non-suppressible aldosterone after dexamethasone Increasing aldosterone stimulation by ACTH		
Dysregulated CYP11B2 Activity	Progressively increasing 18OHF and 18oxoF production		
Histopathologic Abnormalities	APM/APN		APA
Lateralization	Non-Lateralizing		Lateralizing

European Society of Hypertension

THANK YOU!

SHG SSI SSH