Primary Aldosteronism

Richard J. Auchus, MD, PhD, FACE
The James A. Shayman & Andrea S. Kevrick Professor of Translational Medicine
Division of Metabolism, Endocrinology & Diabetes
Departments of Internal Medicine & Pharmacology
University of Michigan & Ann Arbor VA Medical Center

Disclosures

- Contracted Research
  - Novartis Pharmaceuticals
  - Neurocrine Biosciences
  - Spruce Biosciences
  - Corcept Therapeutics
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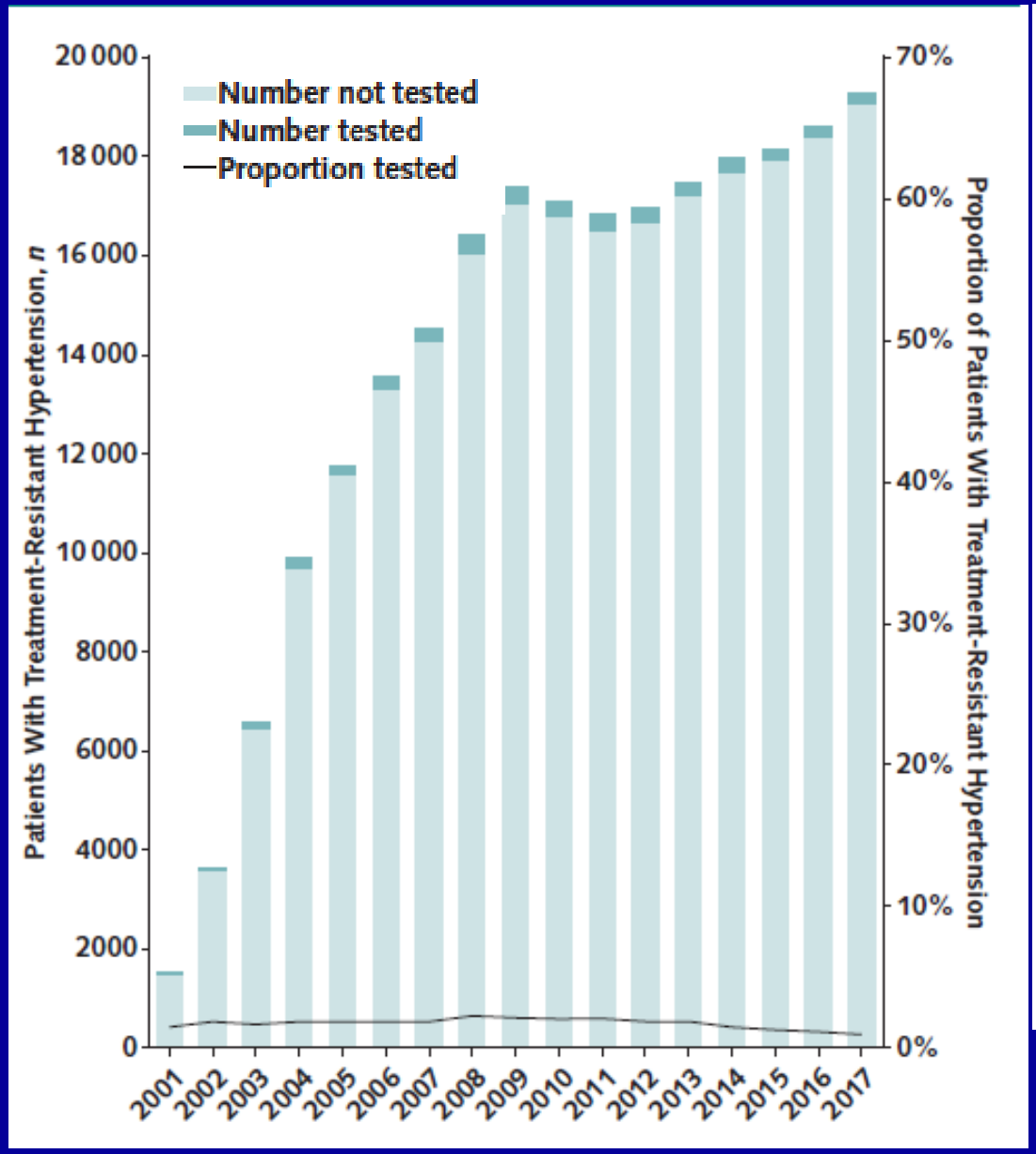
  - H Lundbeck A/S

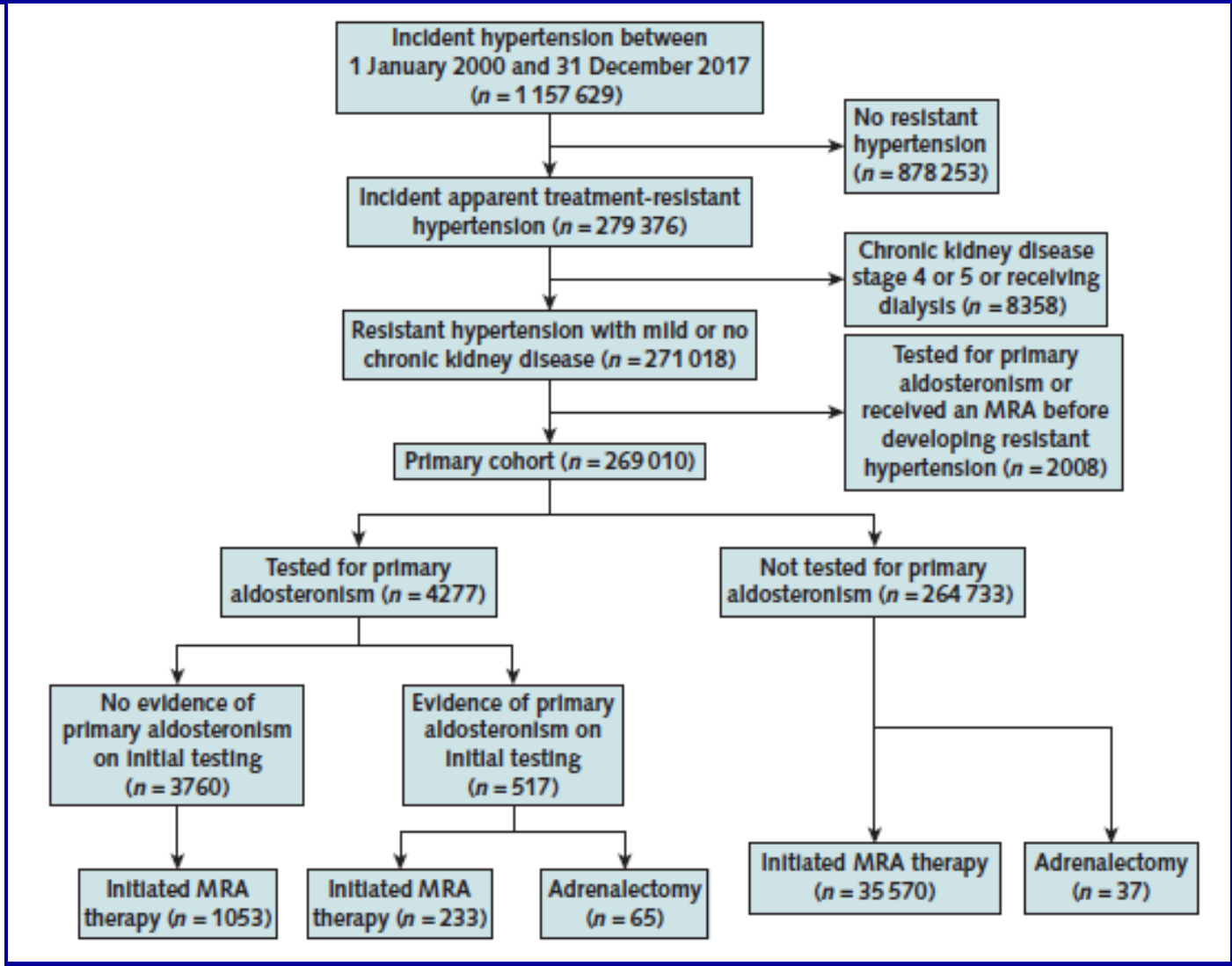
Screening

Subtyping

Tip of the Iceberg

Insufficient Screening for PA





Cohen et al Ann Intern Med 202;174:289

Screening is more about whether *renin* is *suppressed* than about whether aldosterone is high

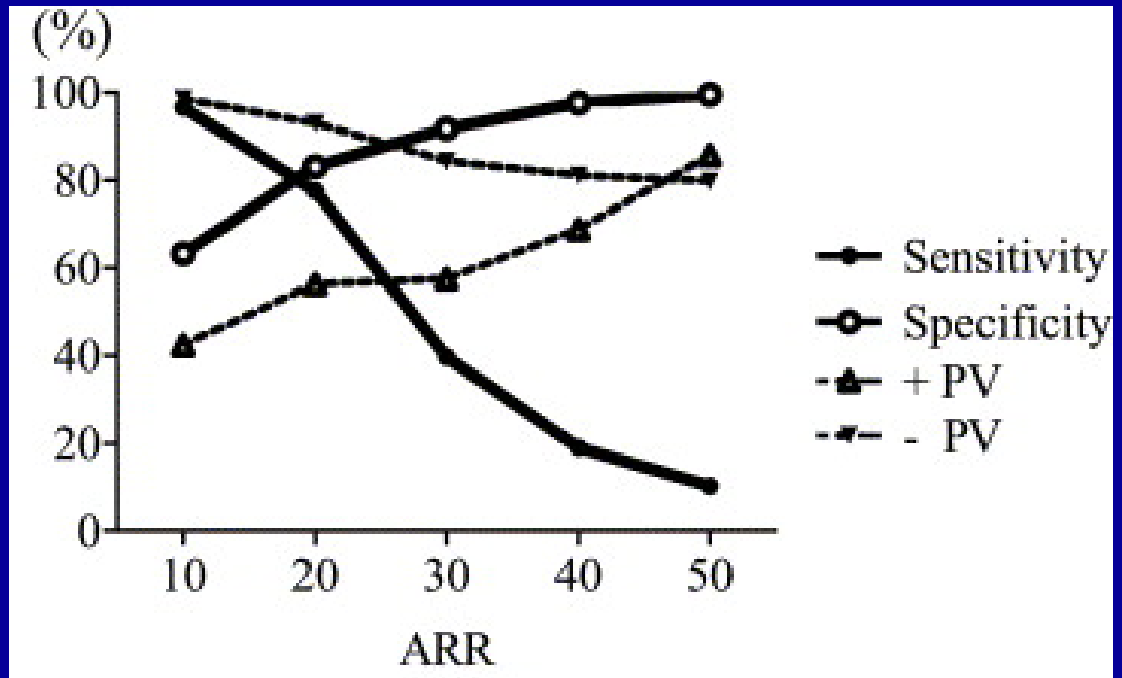
Auchus Rev Endocr Metab Disord 2011;12:37

Primary Aldosteronism

Screening ARR: Stop Drugs?

- Serum Aldosterone/Plasma Renin (ARR)
- Most Drugs OK for Screening
  - Most Drugs ↑PRA & Aldo (β-Blockers ↓PRA)
  - *If PRA is Suppressed, Screen is Valid*
- Up to 4 Wk: Spironolactone, Eplerenone
  - BUT STILL OK if PRA Suppressed
- Best: α_1-Blocker + Verapamil
- Can Always Rescreen After Off Drugs

ARR Sensitivity & Specificity



Cut-off	Sensitivity	Specificity	+PV	-PV
ARR >20	**78**	**83**	**56**	**93**
ARR >50	10	99	86	80
ARR >20 and PAC >15	57	88	57	88 (%)

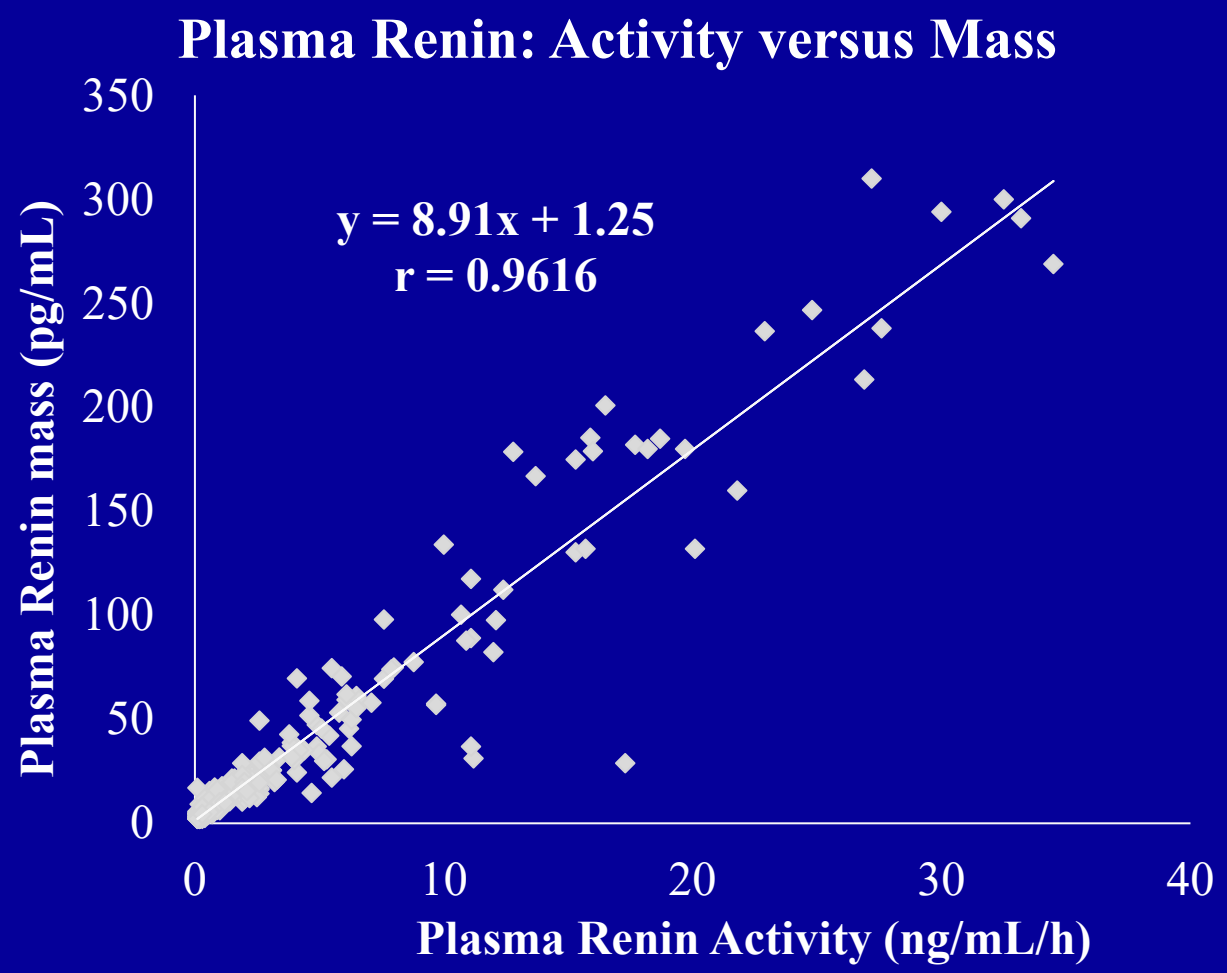
Nishizaka Am J Hypertens 2005;18:805

Who Has Primary Aldo?

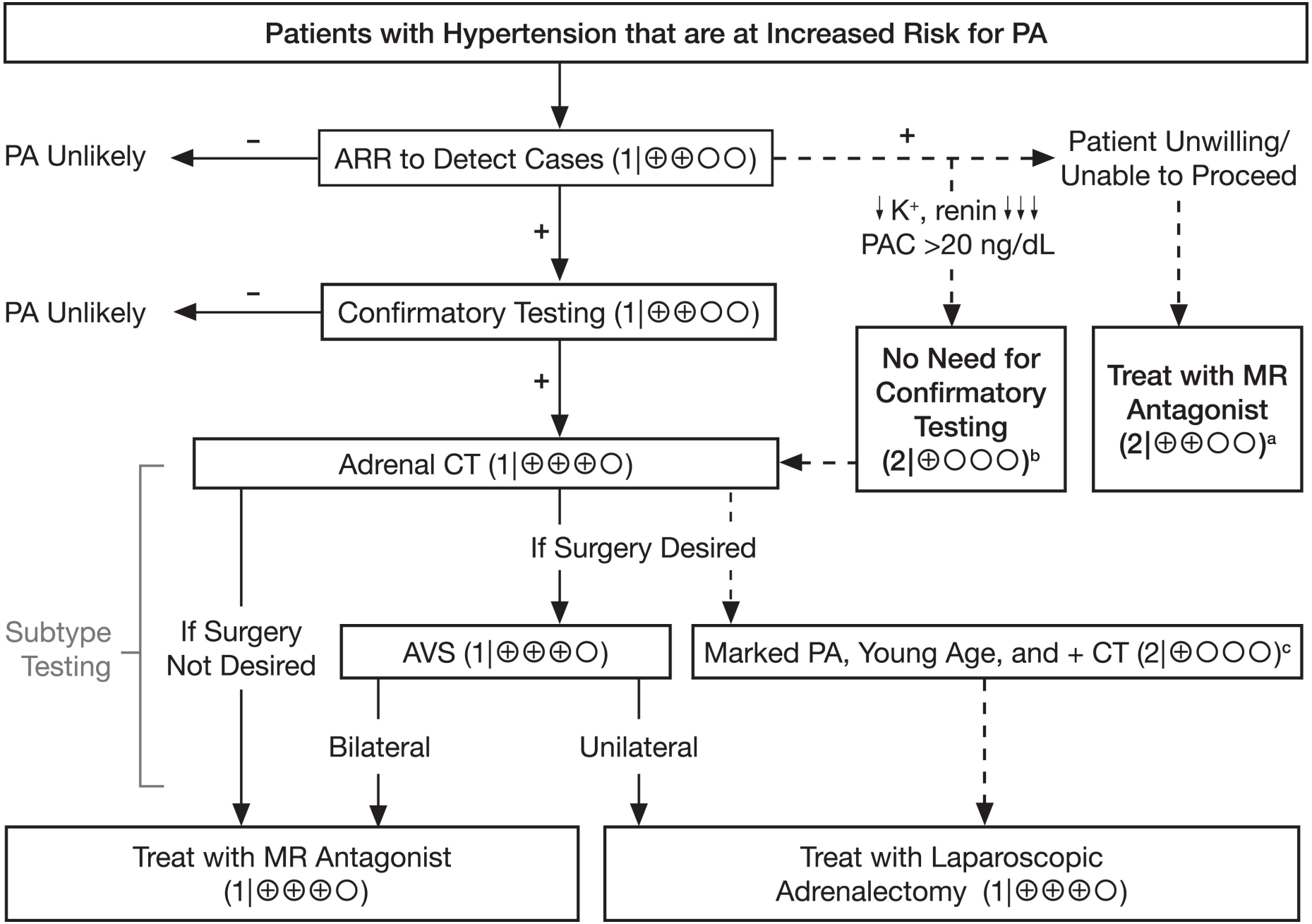
ARR Interpretation

Aldo (ng/dL)	PRA (ng/mL/hr)	ARR	Serum Potassium (meq/L)	Interpretation
6	3.2	2	4.4	Low ARR, not PA, stop
3	0.1	30	4.0	Low aldo, not PA, stop
18	0.6	30	3.5	Positive screen for PA, go to confirmatory testing
11	0.8	15	2.9	Probably PA, supplement K, rescreen
38	2.0	19	4.2	Probably PA, stop meds and rescreen

Direct Renin Conversion: PRA 1 = DRC 8-10 pg/mL


Plasma Renin: Activity versus Mass
y = 8.91x + 1.25
r = 0.9616
Plasma Renin mass (pg/mL)
350
300
250
200
150
100
50
0
0
10
20
30
40
Plasma Renin Activity (ng/mL/h)

Screen For Primary Aldo!!!



Funder et al J Clin Endocrinol Metab 2016;101:1889

That Part Was Easy

Now It Gets Hard

You Can Stop Here

PASO Criteria

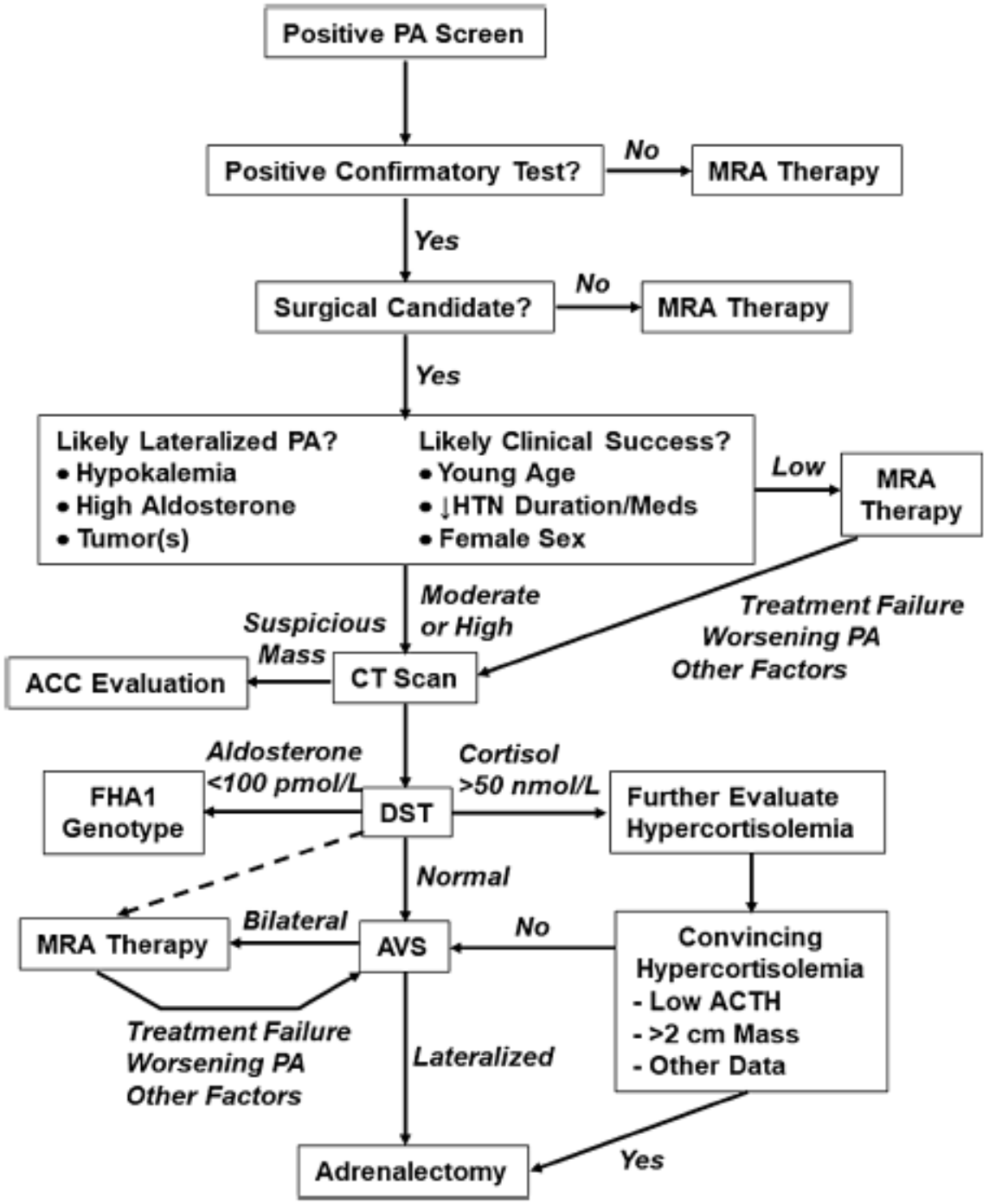
- Data on Success of Adrenalectomy Highly Variable
  - Success Varies with Criteria
- Criteria Consenses Using Delphi Method
  - Complete, Partial, & Absent Success
  - Clinical & Biochemical Outcomes
- 31 Experts, 28 Centers, 6 Surgeons
- Review of 705 Cases, 699 Biochemical

Williams et al Lancet Diabetes Endocrinol 2017;5:689

PASO Criteria: AVS-Guided ADX

- Biochemical Success Complete 94%
- Clinical Success Complete 37% (17-62)
- Clinical Success Partial 47% (35-66)
- Clinical Success More Likely
  - Female vs Male
  - Younger vs Older
- Clinical Success Less Likely
  - Higher Preoperative Meds, Older, Male
- Establishes Standardized Criteria for PA Management

Williams et al Lancet Diabetes Endocrinol 2017;5:689



Turcu & Auchus JCEM 2021;106:1195

Primary Aldosteronism

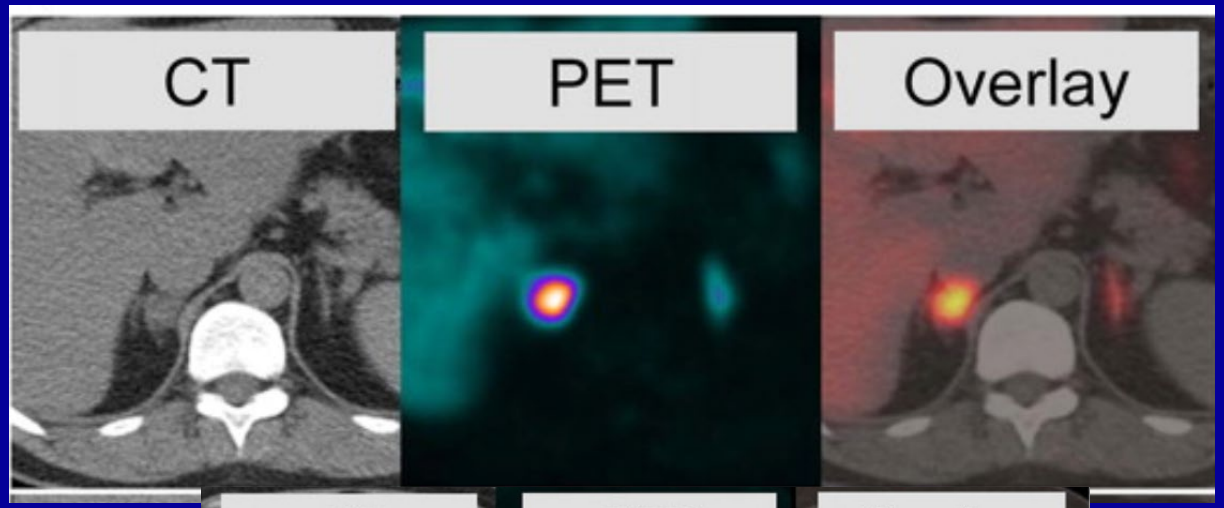
Subtype Determination

- CT is Too Sensitive: 5-10% of Adults Have Nodules
  - Accuracy = 53%!!!!
- >1 cm Nodule IF The Contralateral Gland Is Clearly Normal & <35-40 YO
- All Others Adrenal Vein Sampling
- Unfortunately, No Other Good Options – Yet
- Functional Imaging in Development

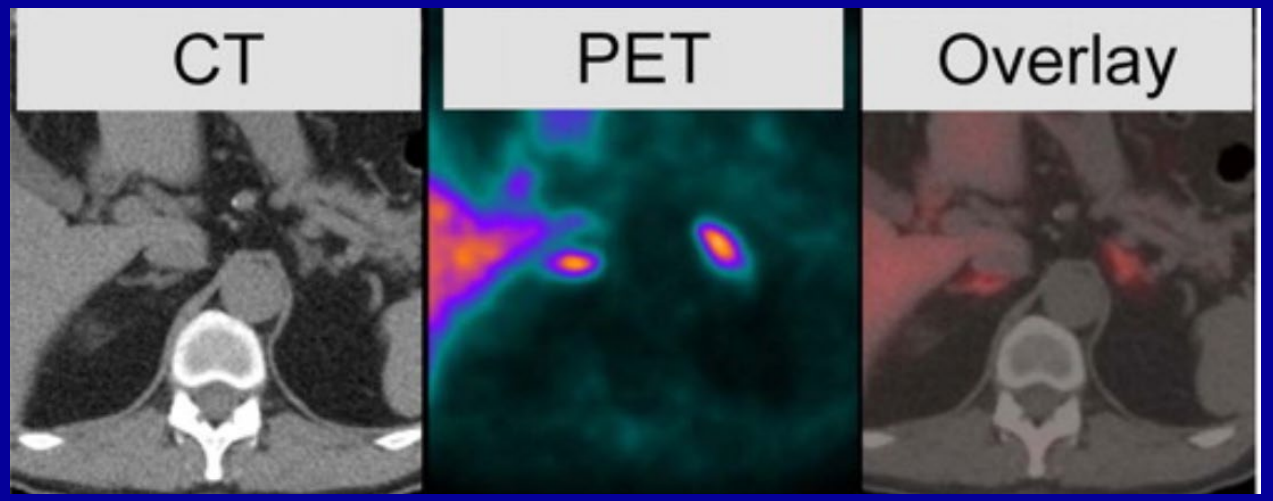
Young WF et al Surgery 2004;136:1227
Nwariaku FE et al Arch Surg 2006;141:497
Lim V et al J Clin Endocrinol Metab 2014;99:2712

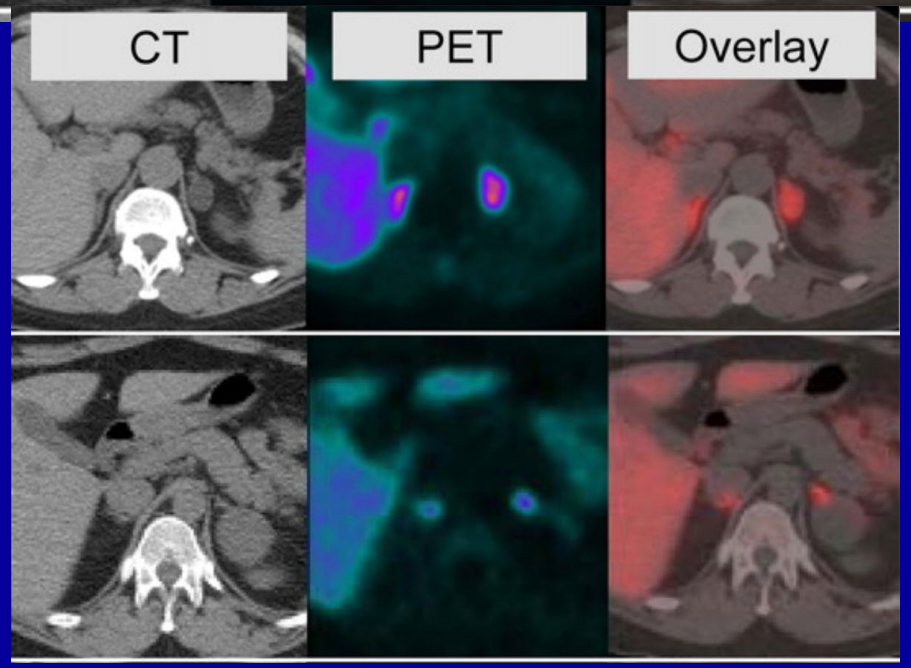
[^{11}C]-Metomidate in Primary Aldosteronism

Aldosterone-Producing Adenoma



Bilateral Hyperaldosteronism





Incidental Adenomas

Burton et al J Clin Endocrinol Metab 2012;97:100

Primary Aldosteronism

Case 1

- 42 yo HM, HTN x 5 yr
- BP 155/95; 3 Drugs ++KCl; Having Side Effects
- PRA 1, PAC 47, K now Normal, 18OHB 45
- 24 h Urine K 106, Na 385, Aldo 217
- Likely to Lateralize, Likely to Benefit From ADX
- Proceed to CT Scan: L 1.5 cm; 5 mm R Masses

CT Scan

Case 1

AVS Interpretation

- ✓ Mixed Venous Cortisol & Aldosterone
- RAV, LAV Cortisol = Selectivity Index (SI)
  - >2x IVC -Cosyntropin; >4x IVC +Cosyntropin
- A/C Gradients = Lateralization Index (LI)
  - >2 -Cosyntropin; >4 +Cosyntropin
  - Low Side < IVC = Contralateral Suppression
- Two Common Patterns (+Cosyntropin):

High AV	Low AV	IVC	Interpretation
4-50	0.5-1.5	1-5	Lateralized
2-4	2-4	1-2	Bilateral

AVS-Case 1

A 26,160
C 922
A/C 28.4

IVC:
A 39
C 19.3
A/C 2.02

A 2,131
C 1,264
A/C 1.79

Primary Aldosteronism: Case 2

- 69 YO WM HTN x 30 y, Low K
- Aldo 33, PRA 0.1, K 2.5-3.3
- CT: Normal Adrenal Glands

	Right Adrenal Vein			Inf. Vena Cava			Left Adrenal Vein			LI Gradient
Sample	Cort	Aldo	A/C	Cort	Aldo	A/C	Cort	Aldo	A/C	R/L
Basal	130.4	3390	112	9.6	33.8	3.52	22.8	41.5	1.82	61.3
Basal	235.0	5070	145	8.4	33.5	3.99	22.0	42.6	1.94	74.7
Basal	324.0	3720	155	7.8	33.6	4.31	24.1	42.7	1.77	87.6
Post-Cosyntropin										
5 min	1049	9400	8.96	10.8	38.5	3.56	1215	165	0.14	64.0
10 min	1001	8140	8.13	15.6	42.4	2.72	1038	173	0.17	47.8
20 min	1314	12700	9.67	15.2	47.6	3.13	1100	191	0.17	56.8

- Interpretation: Lateralized to Right
- After R ADX: K Normal, Normal BP on 2 Drugs

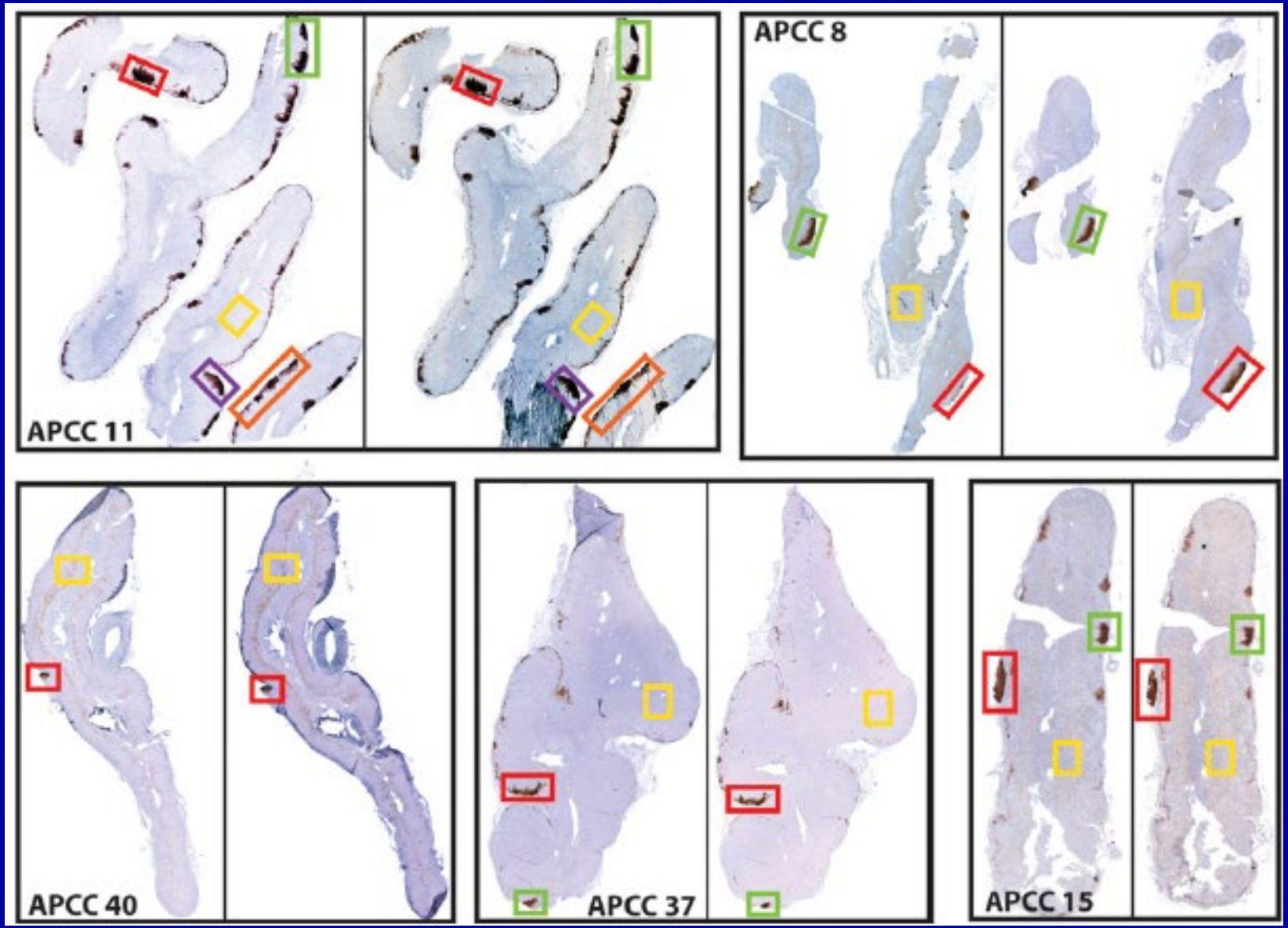
Primary Aldosteronism: Case 3

- 51 YO WM Reistant HTN, Low K
- Aldo 46, PRA 0.1, K 2.5-3.3
- CT: 1.5 cm R Adrenal Mass, Normal L

	Right Adrenal Vein			*Inf. Vena Cava*			*Left Adrenal Vein*			
Sample	Cort	Aldo	A/C	Cort	Aldo	A/C	Cort	Aldo	A/C	R/L
Basal	27.3	880	32.2	13.1	40.3	3.1	27.8	195	7.0	4.60
25 min	1478	>10,000	>6.76	27.6	94.5	3.4	1525	881	0.58	>11.7
35 min	1330	>10,000	>7.52	24.8	92.4	3.7	1200	809	0.67	>11.2
45 min	1036	>10,000	>9.66	28.6	126	4.4	1449	722	0.50	>19.3

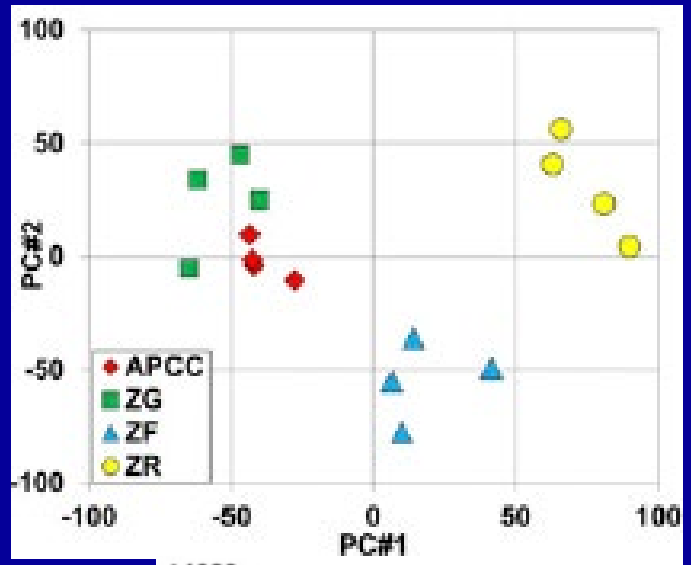
- After R ADX: Aldo 16, PRA 0.4, K 4.1
- BP Much Better, K Normal, 2 Drugs (MRA)

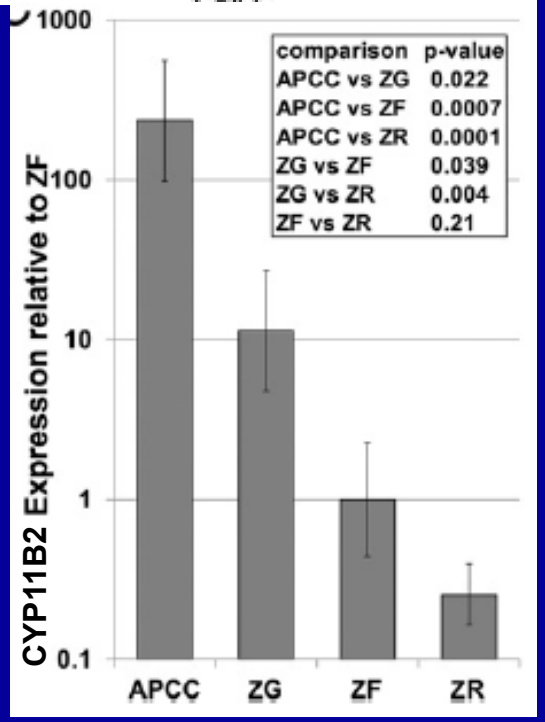
Pathogenesis of PA: APMNs



Nishimoto et al Proc Natl Acad Sci (USA) 2015;112:E4591

Pathogenesis of PA: APMNs





APMNs

-Increase With Age

-Have Mutations in:

CACNA1D

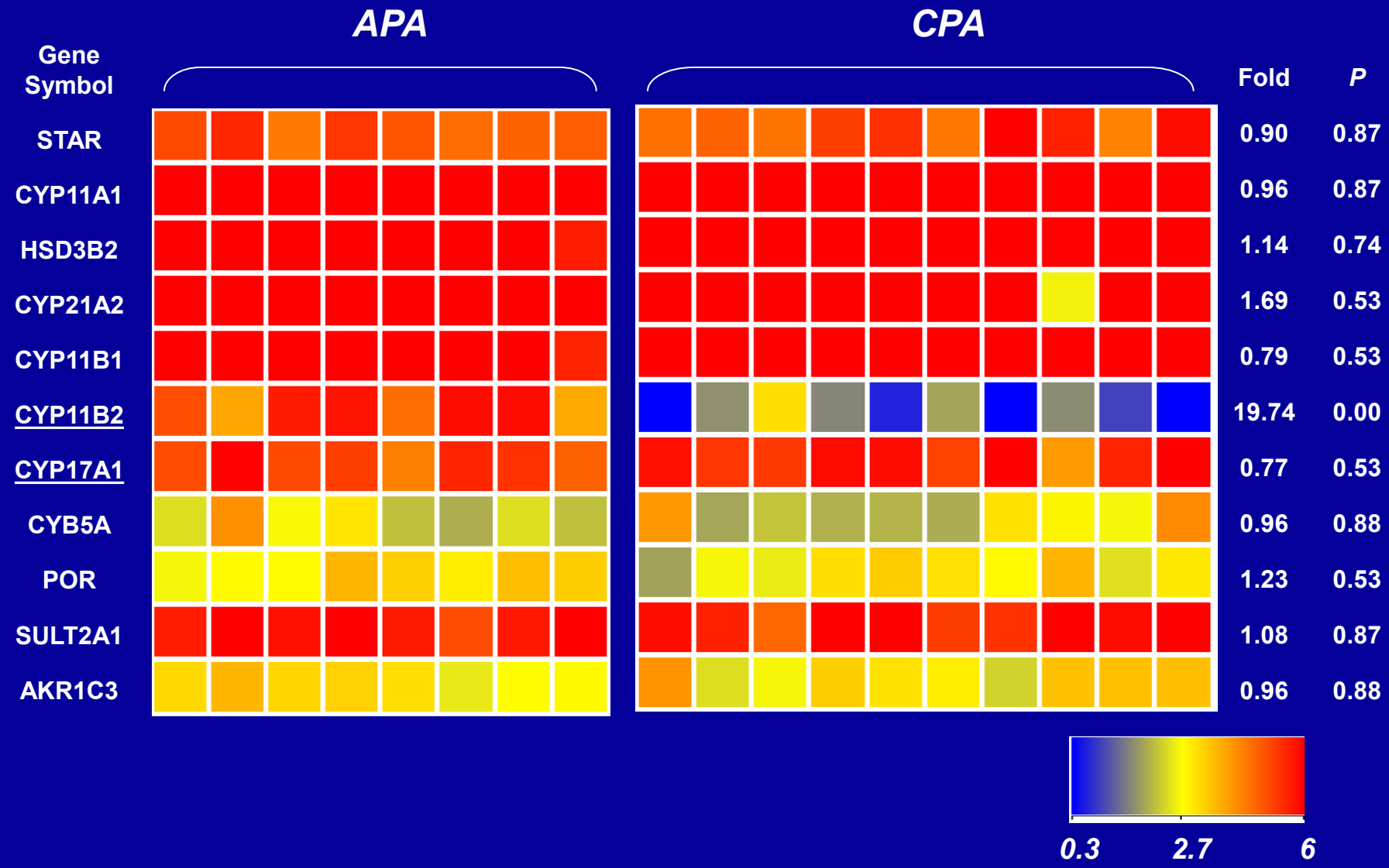
ATP1A1

ATP2B3

PDE11A

Nishimoto et al Proc Natl Acad Sci (USA) 2015;112:E4591

Gene Profiling APA vs CPA

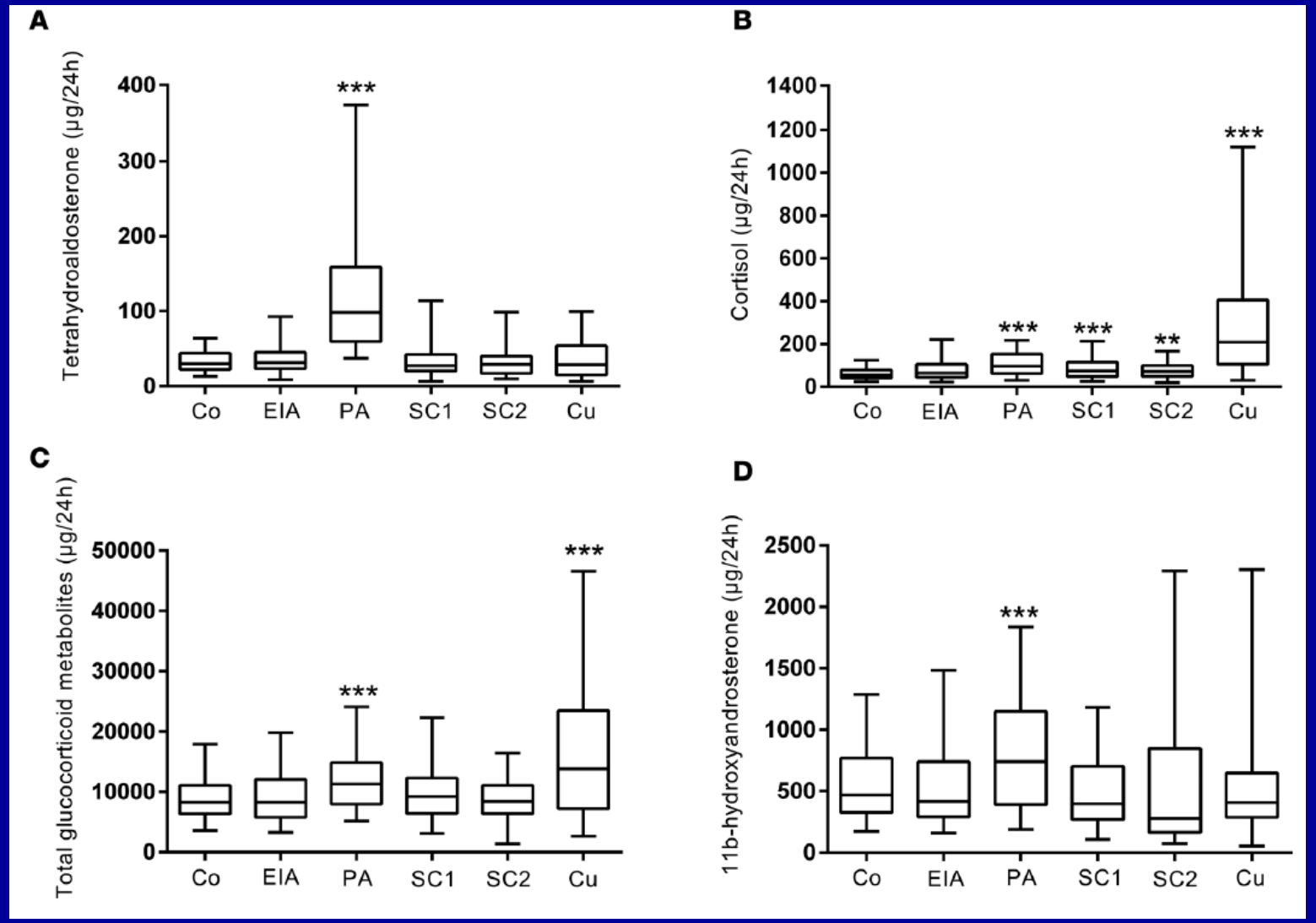


“Conn-Shing” Syndrome

- Large Adrenal Adenomas Sometimes Produce Both Aldosterone & Cortisol
- What About Small APA?
- 162 Healthy Controls; 174 PA (103 APA); 55+49 SCS; 47 Overt Adrenal Cushing
- Urine Metabolites of Aldosterone & Cortisol
- Found Elevated Cortisol Metabolites in APA That Resolved With Surgery

Arlt et al JCI Insight 2017;2:e93136

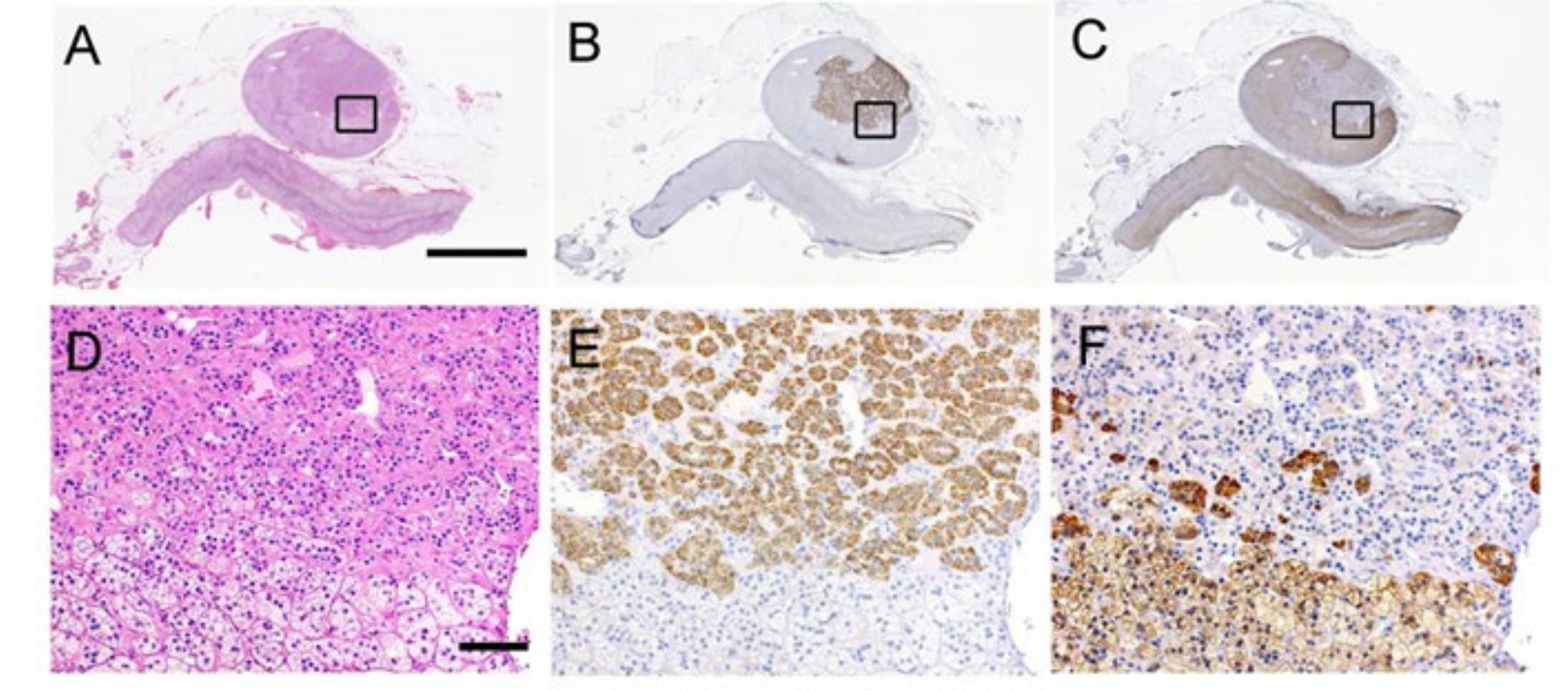
“Conn-Shing” Syndrome



Arlt et al JCI Insight 2017;2:e93136

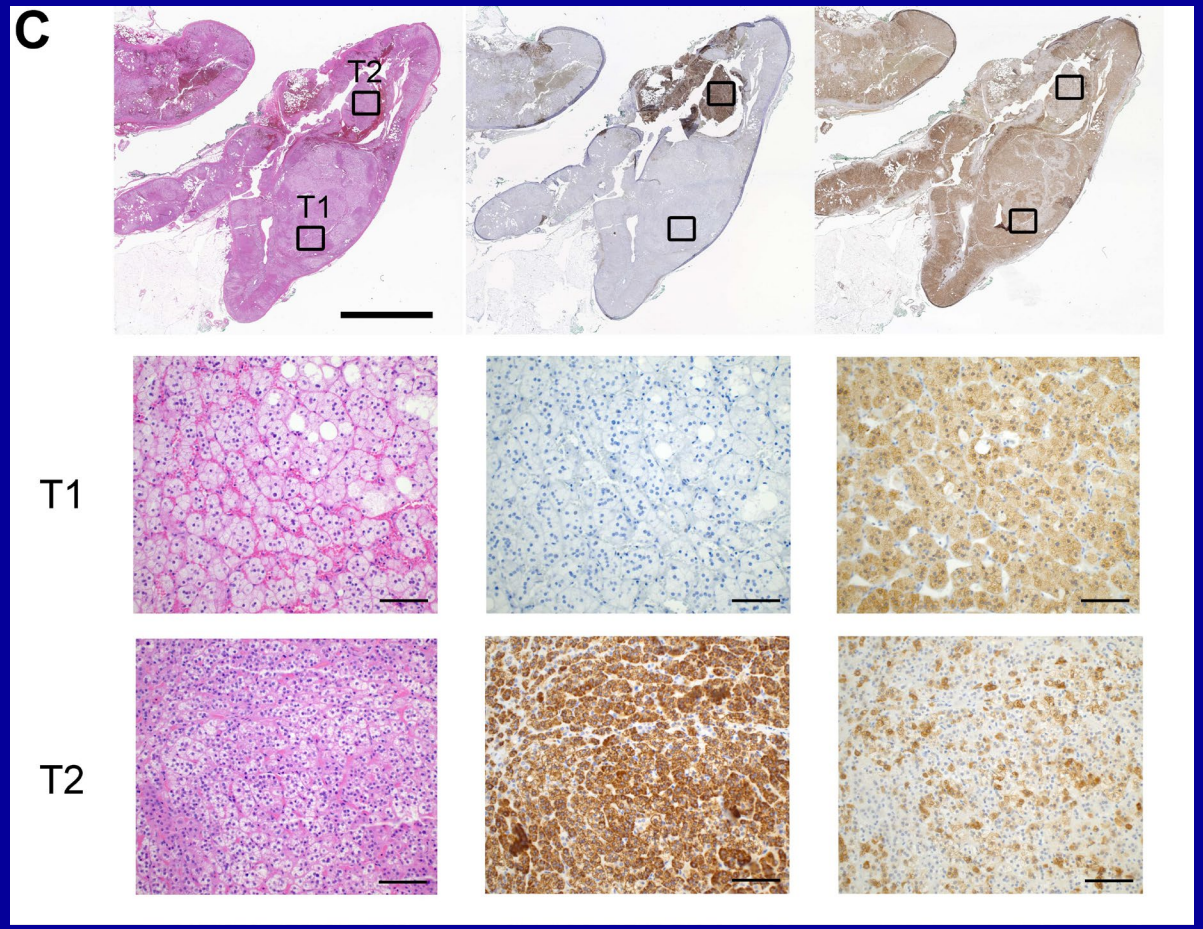
Heterogeneity of APAs

H&E P450 11B2 P450 17A1



Nanba J Clin Endocrinol Metab 2016;101:999

Imaged Tumor Not Source of Aldo!



Nanba J Clin Endocrinol Metab 2016;101:999

Primary Aldosteronism: Case 4

- 36 YO Vietnamese F
- Recurrent Pregnancy Losses
- Resistant HTN, Hypokalemia
- Labetolol, Amlodipine, KCl
- PRA 1 ng/mL/h; Aldo 21 ng/dL, K 3.0
- 24h U Aldo 17 μg Na 155 meq, K 197 meq
- CT: 3 cm R Adrenal Mass, L Poorly Seen

Primary Aldosteronism: Case 4

Primary Aldosteronism: Case 4 AVS

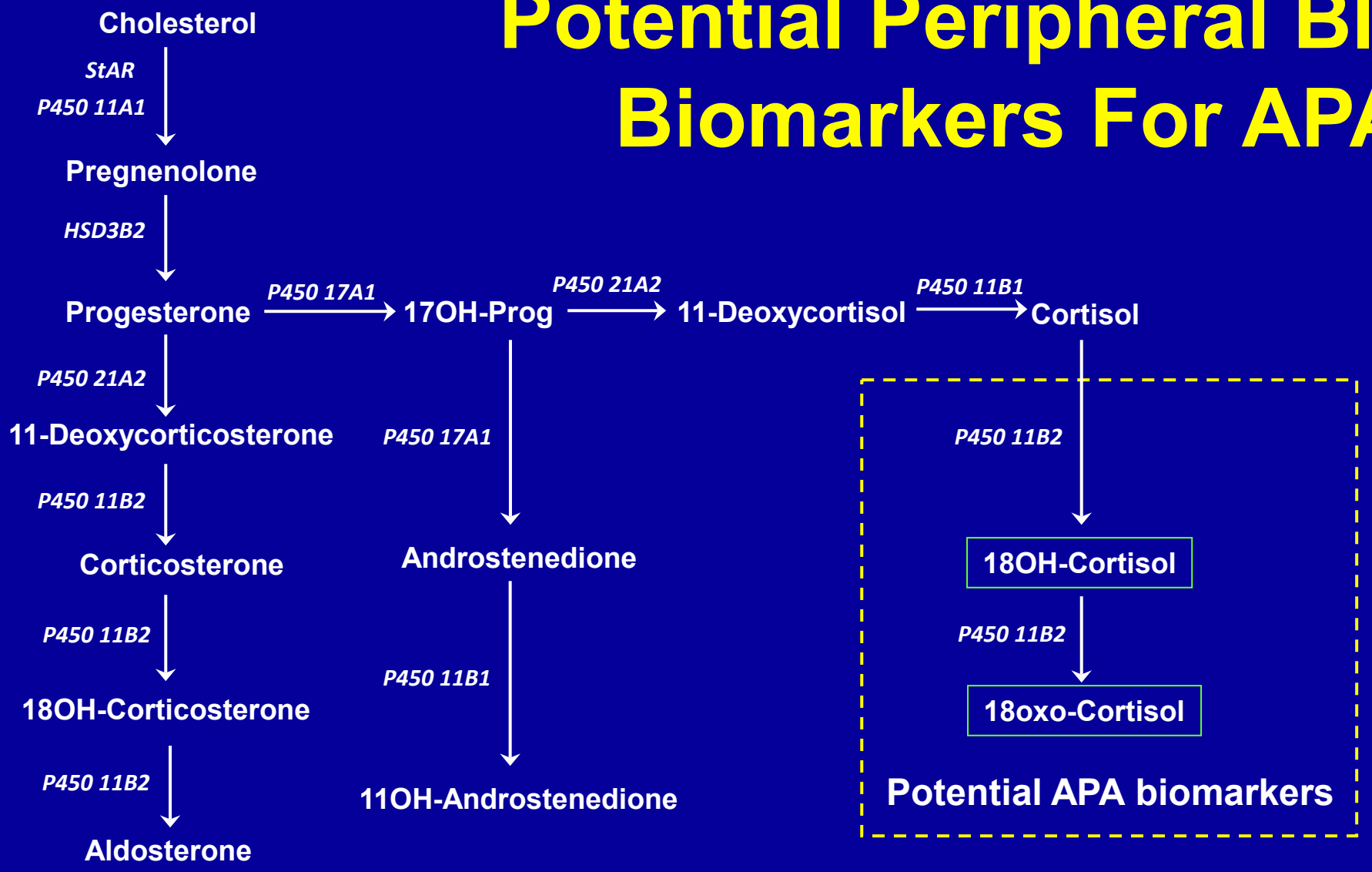
Site	Aldo	Cortisol	Ratio
RAV	6845	1382	5.0
LAV	2806	129	21
IVC	55	56	1.0
PV	49	37	1.3

What's Going On???

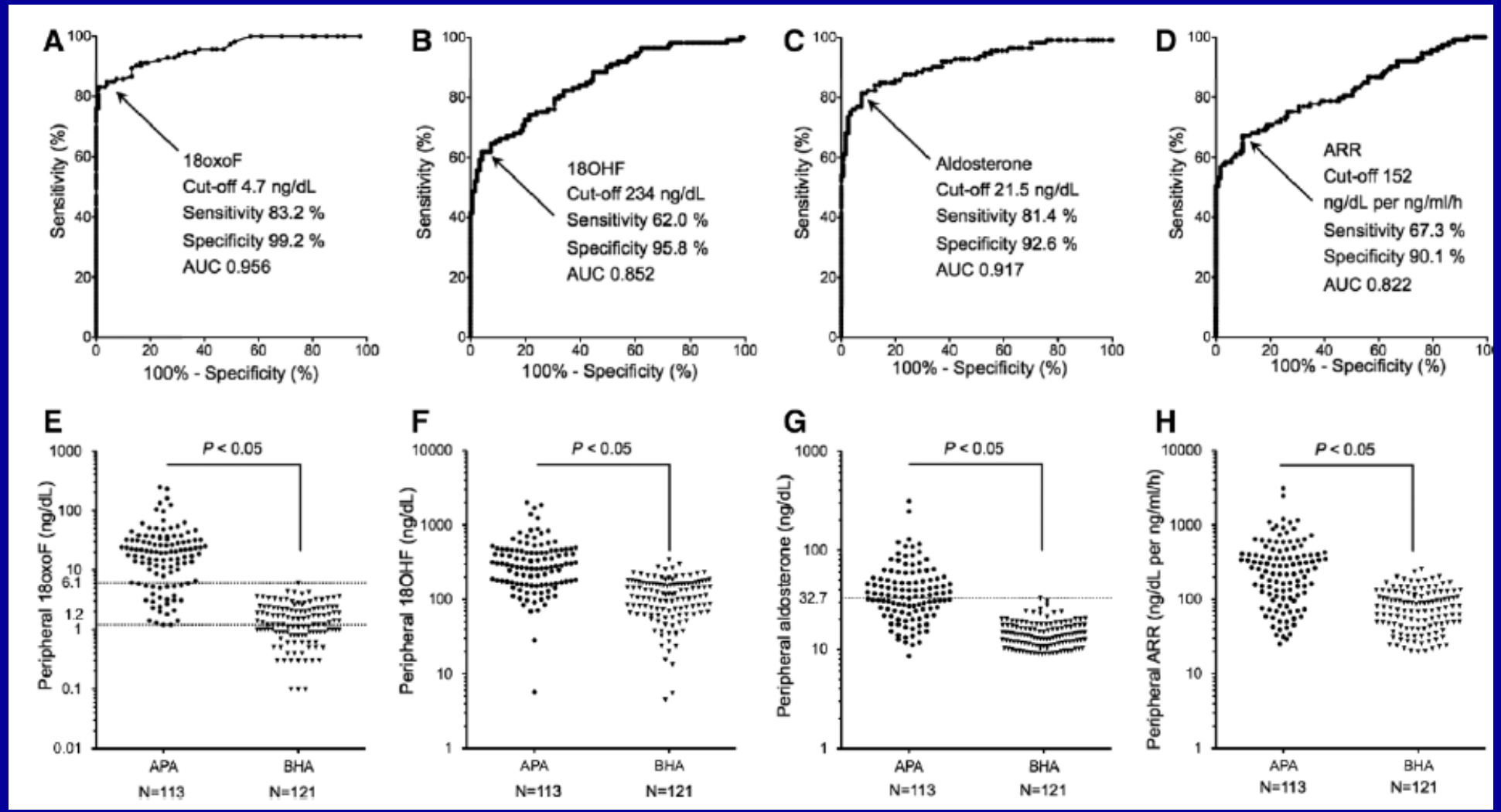
Primary Aldosteronism: Case 4

- Endo Referral
- ROS: Bruising, 10 lb Wt Gain, Depression
- Exam: Wt 103 lbs, BMI 24 kg/m^2, +Bruises, SC Fat Pads
- 24h UFC 260 μg
- ACTH <5 pg/mL
- DHEA-S 18 μg/dL
- AM Cortisol After 1 mg Dex 22.5 μg/dL

Potential Peripheral Blood Biomarkers For APA



18-Oxygenated Cortisol in PA



Satoh et al Hypertension 2015;65:1096

If Many APAs Make Cortisol, Why Use Cortisol To Normalize Aldo in AVS??

Improved Pre-Cosyntropin SI using Alternative Steroids

Pre-cosyntropin	Cortisol			
	SI < 2 (N=15)		SI < 3 (N=36)	
	Alternative Steroid SI			
Steroid / SI	≥2	≥3	≥3	≥4
11OHA4	14 (93%)	14 (93%)	35 (97%)	33 (92%)
DOC	11 (73%)	11 (73%)	32 (89%)	25 (69%)
11-Deoxycortisol	10 (67%)	10 (67%)	30 (83%)	26 (72%)
Corticosterone	10 (67%)	10 (67%)	29 (81%)	25 (69%)
A4	11 (73%)	11 (73%)	29 (81%)	20 (56%)
16OHProg	7 (47%)	7 (47%)	23 (64%)	19 (53%)
17OHProg	5 (33%)	5 (33%)	16 (44%)	14 (39%)

Turcu et al Hypertension 2020;75:183

Intermediate Lateralization Interpretation Using Alternative Steroids

Post-cosyn. Steroid ratios	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
	R/L	L/R	L/R	R/L	R/L	R/L
Clin Aldo/ Clin Cortisol	3.0	3.1	3.6	2.8	2.6	3.7
Aldo/18OHF	1.7	4.1	4.6	2.2	2.6	4.0
Aldo/18oxoF	0.9	2.2	1.9	1.1	0.6	5.3
Aldo/Cortisol	3.2	3.8	3.3	2.9	3.2	6.4
Aldo/11OHA4	4.5	2.6	3.5	2.9	3.4	7.1
Aldo/11dF	2.4	3.4	2.9	6.2	3.6	6.6
Aldo/Corticost	3.3	4.8	4.1	3.0	3.5	6.4
Aldo/16OHP	4.1	2.9	0.4	4.5	4.2	5.8
Aldo/17OHP	5.7	2.0	0.9	6.6	5.3	5.5
Aldo/A4	4.3	2.9	3.7	4.6	3.9	5.7
Aldo/DOC	2.3	3.1	2.9	5.5	3.8	5.4
Aldo/Prog	2.8	2.1	2.4	5.4	3.8	7.0

6/14 patients with intermediate lateralization could have been considered lateralized using other steroids for normalization

Turcu et al Hypertension 2020;75:183

AVS Quandary: MRA Interference?

Comparison of LI and CI between patients exposed & those not exposed to MRA at the time of AVS

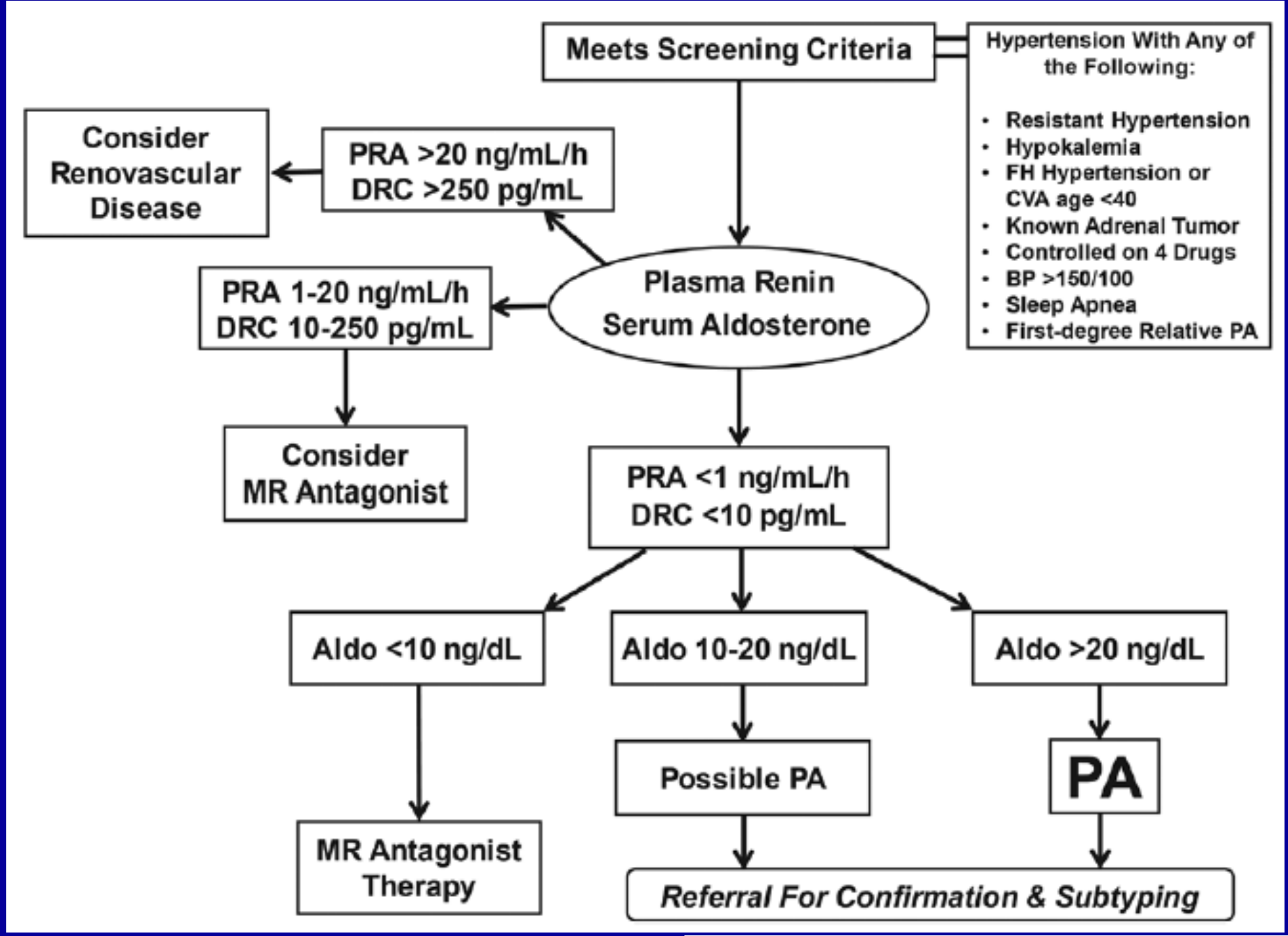
	MRA N=51		No MRA N=140		*p* value MRA *vs.* no MRA	
	Unilateral N=35	Bilateral N=13	Unilateral N=77	Bilateral N=53	Unilateral	Bilateral
LI	22.2 [8.2-49.8]	2.1 [1.5-2.5]	14.1 [8.0-25.1]	1.8 [1.1-2.6]	0.4	0.4
CI	0.2 [0.1-0.4]	0.7 [0.4-0.9]	0.2 [0.1-0.5]	1.1 [0.4-1.6]	0.3	0.08

Complete biochemical success:
+MRA: 22 (95.7%) No MRA: 37 (90.2%)

Lateralization in 35 patients taking MRA throughout PA diagnostic testing

	Unilateral, N=26			Bilateral, N=8	*p* value (Unilat *vs.* Bilat)
	Suppressed PRA N=24	PRA Not Suppressed N=2		Suppressed PRA N=8	
		Case 1	Case 2		
LI	14.4 [5.5-57.6]	46.0	88.2	1.9 [1.5-2.5]	<0.0001
CI	0.2 [0.1-0.5]	0.1	0.1	0.7 [0.4-0.8]	0.008
PAC (ng/dL)	40 [21-69]	31.2	98.3	35 [25-47]	>0.9
PRA (ng/mL/h)	0.2 [0.1-0.3]	1.4	6.4	0.5 [0.2-0.8]	0.07
Hypokalemia	83%	+	+	38%	0.02
DDD index	6.7 [4.8-9.2]	22.8	7.4	8.5 [4.9-12.1]	0.6
Spironolactone Dose (mg) (N)	25-400 (19)	200	200	25-300 (6)	
Eplerenone Dose (mg) (N)	50-100 (5)	-	-	50-300 (2)	

Nanba et al J Clin Endocrinol Metab 2019;104:487

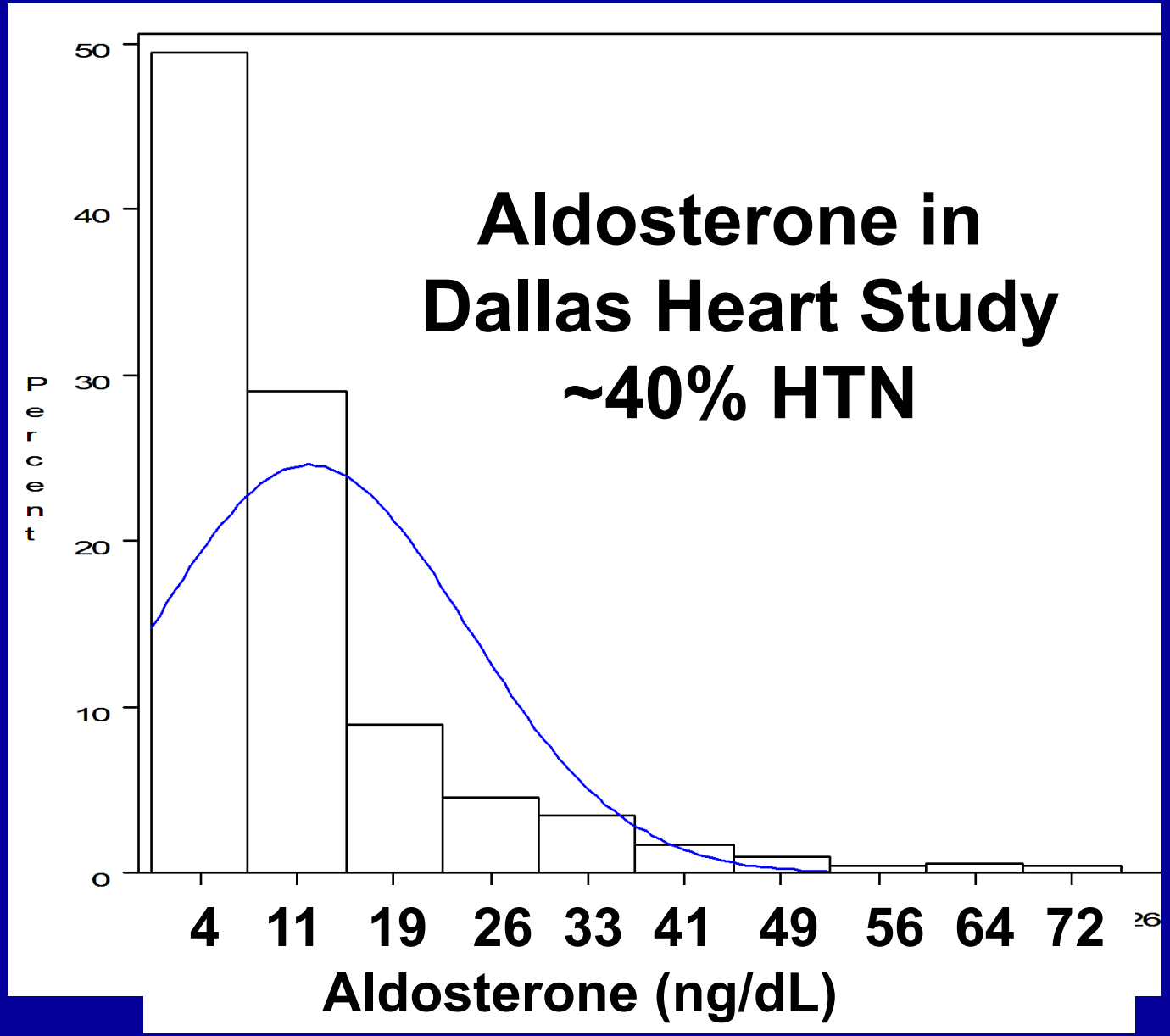


Byrd, Turcu, Auchus Circulation 2018;138:823

That Was Complicated Enough

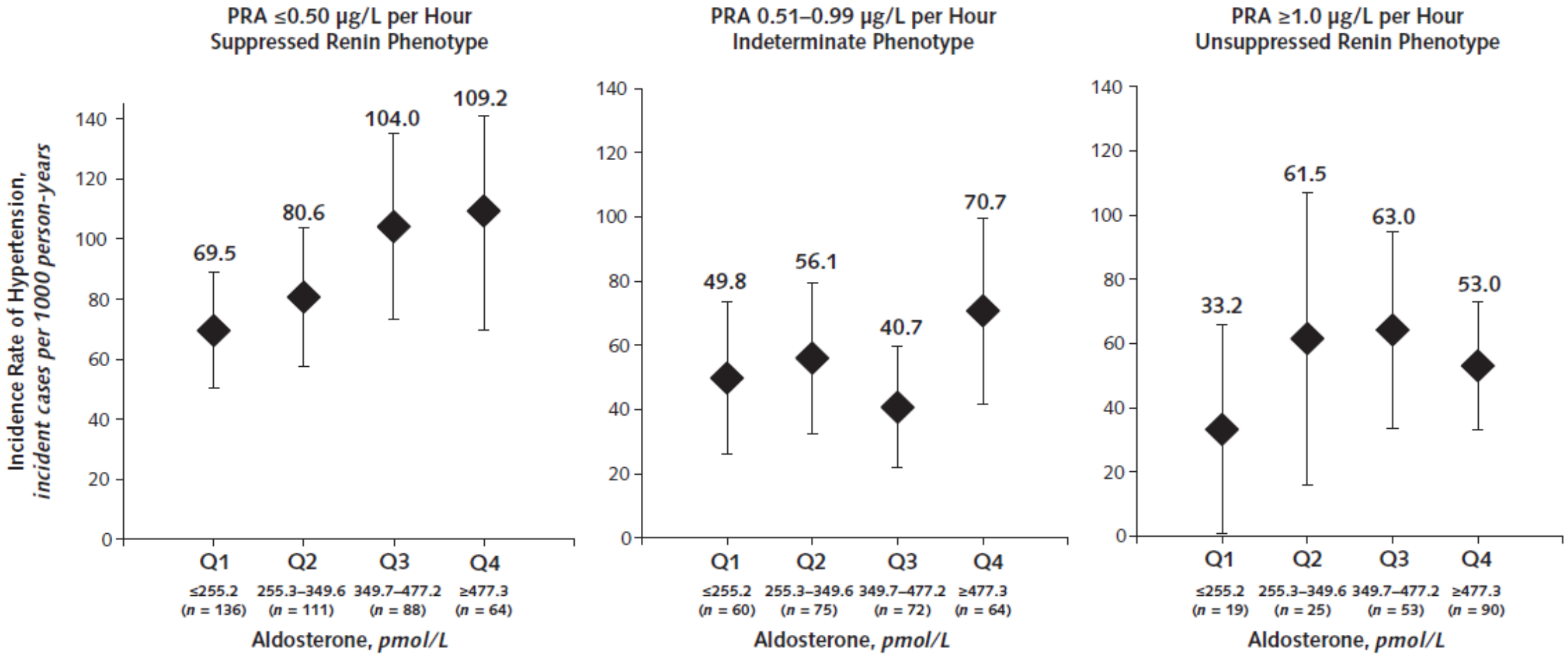
What About “Subclinical PA”?

Low-Renin HTN vs PA



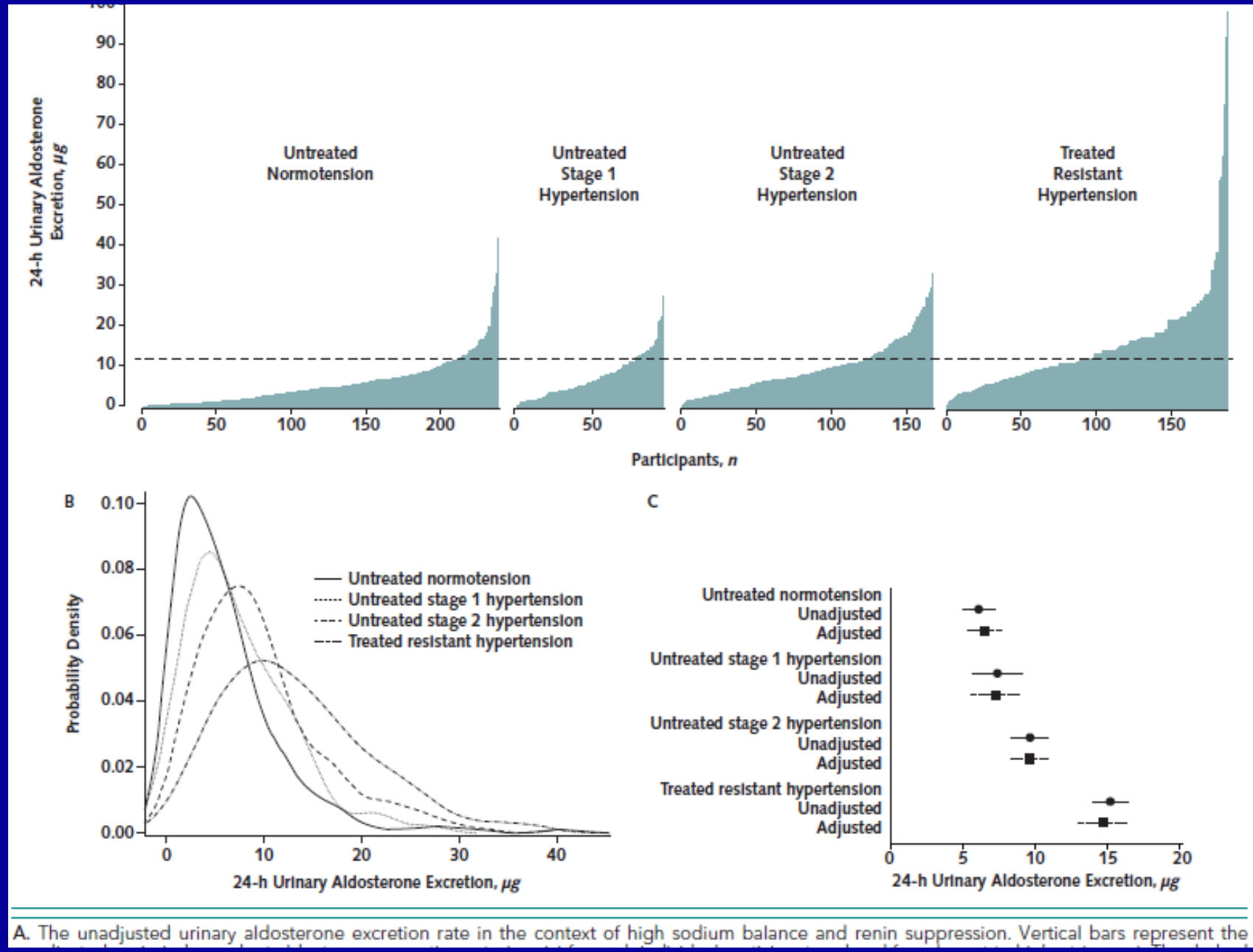
Who Has PA?

Figure 1. Renin-independent aldosteronism and the incidence rate of hypertension.



Brown et al Ann Intern Med 2017;167:630

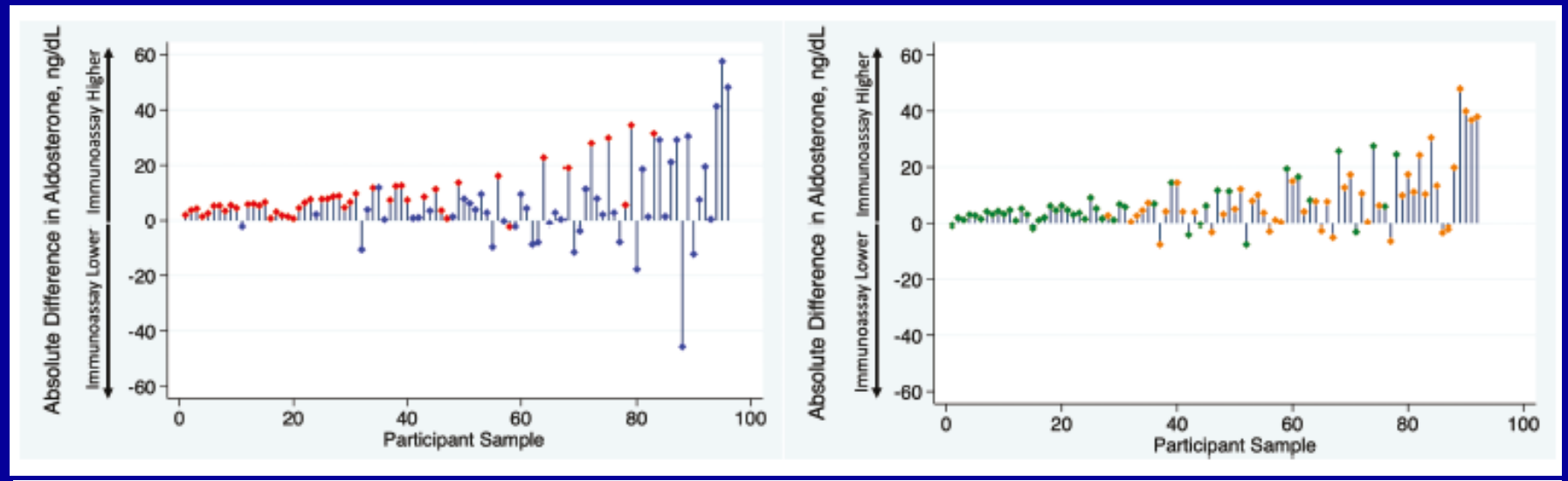
Occult PA

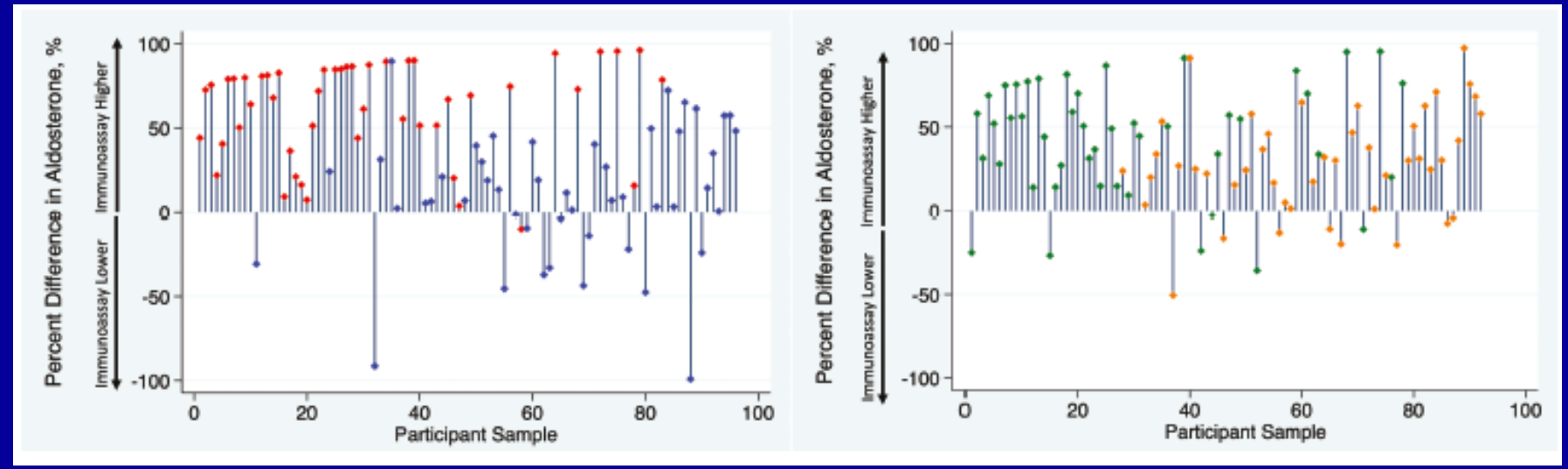


A. The unadjusted urinary aldosterone excretion rate in the context of high sodium balance and renin suppression. Vertical bars represent the

Brown et al Ann Intern Med 2020;173:10

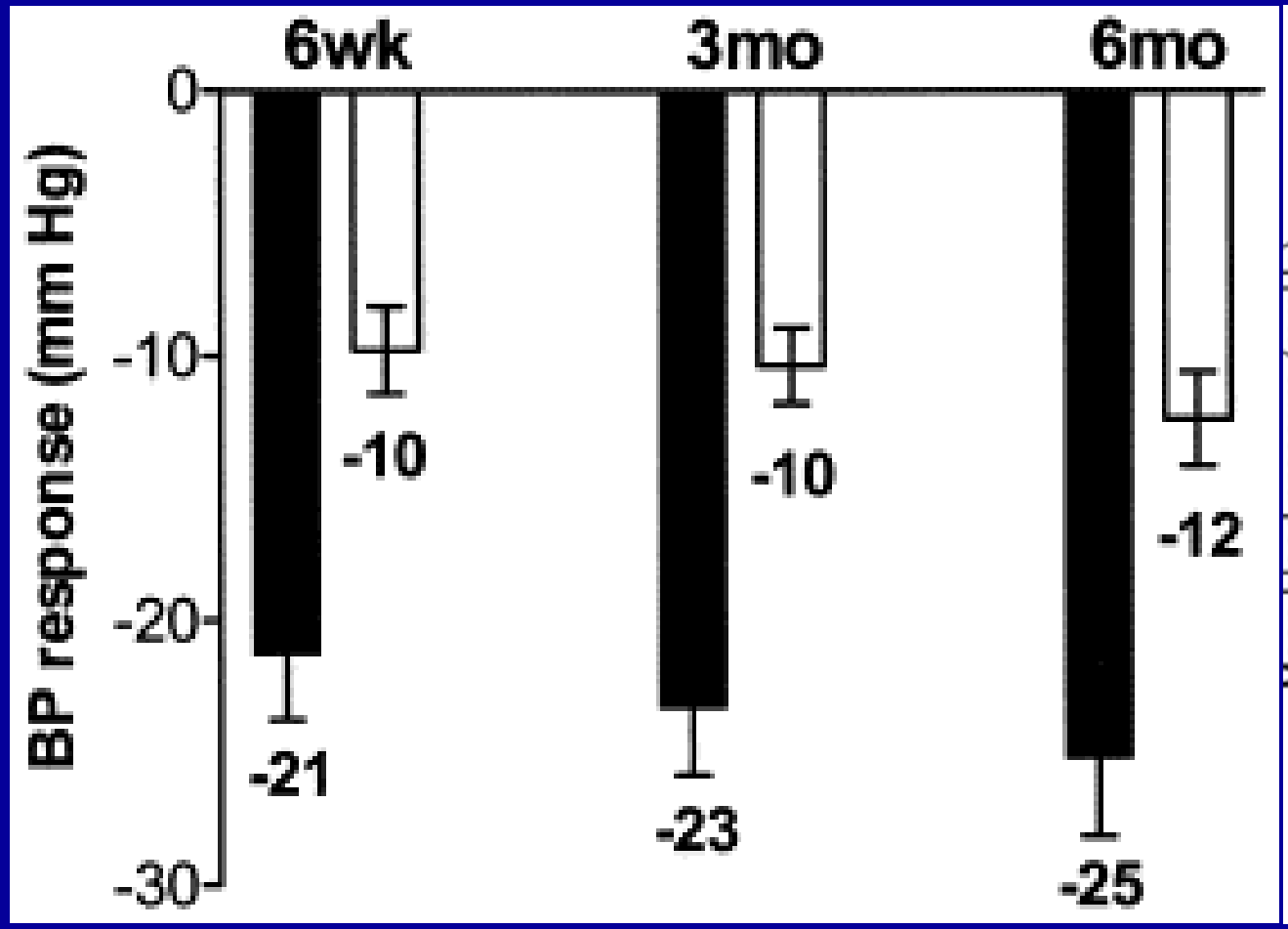
What is a Normal Aldosterone?

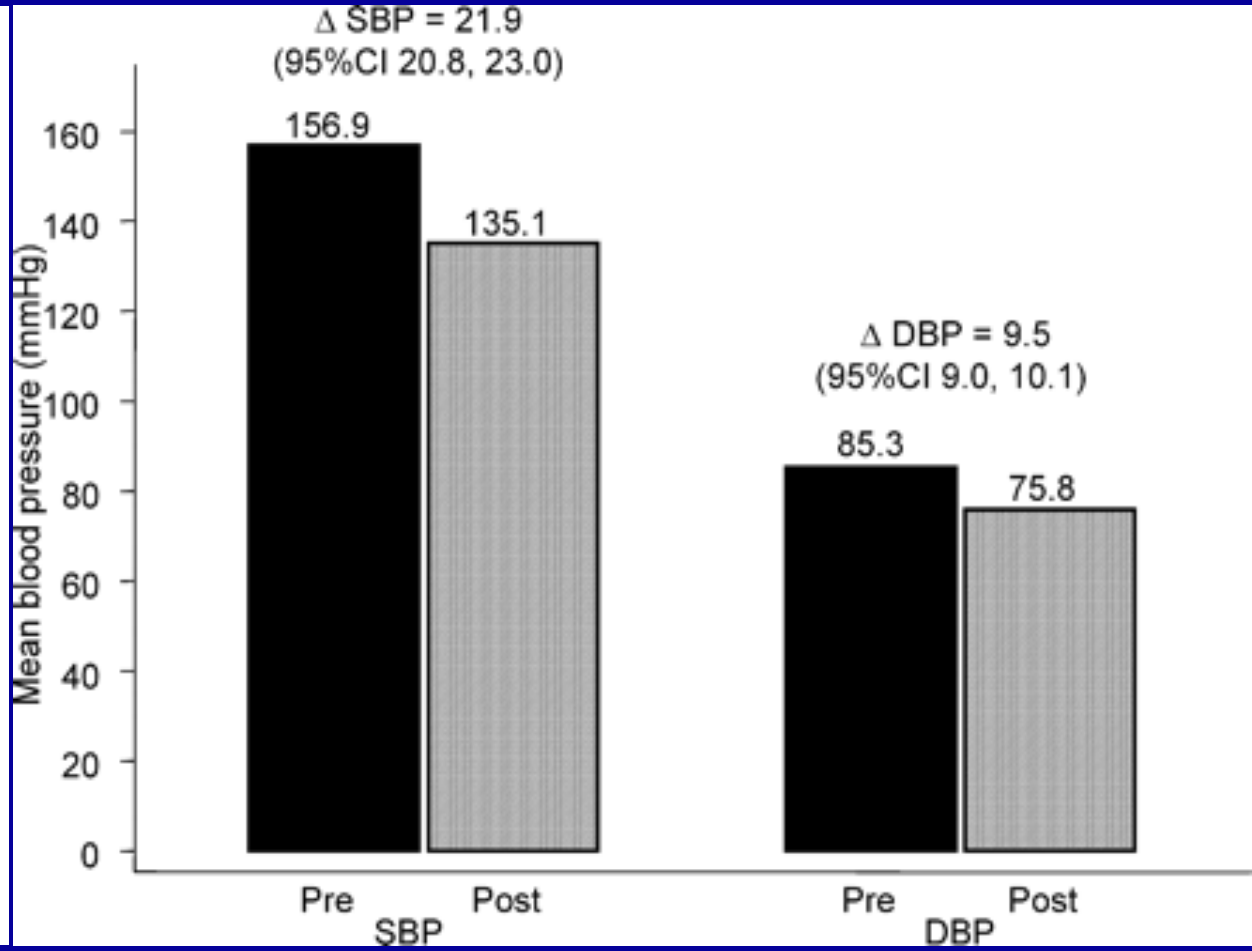




Brown et al J Endocr Soc 2022;6(6):bvac049

Spironolactone in Resistant HTN

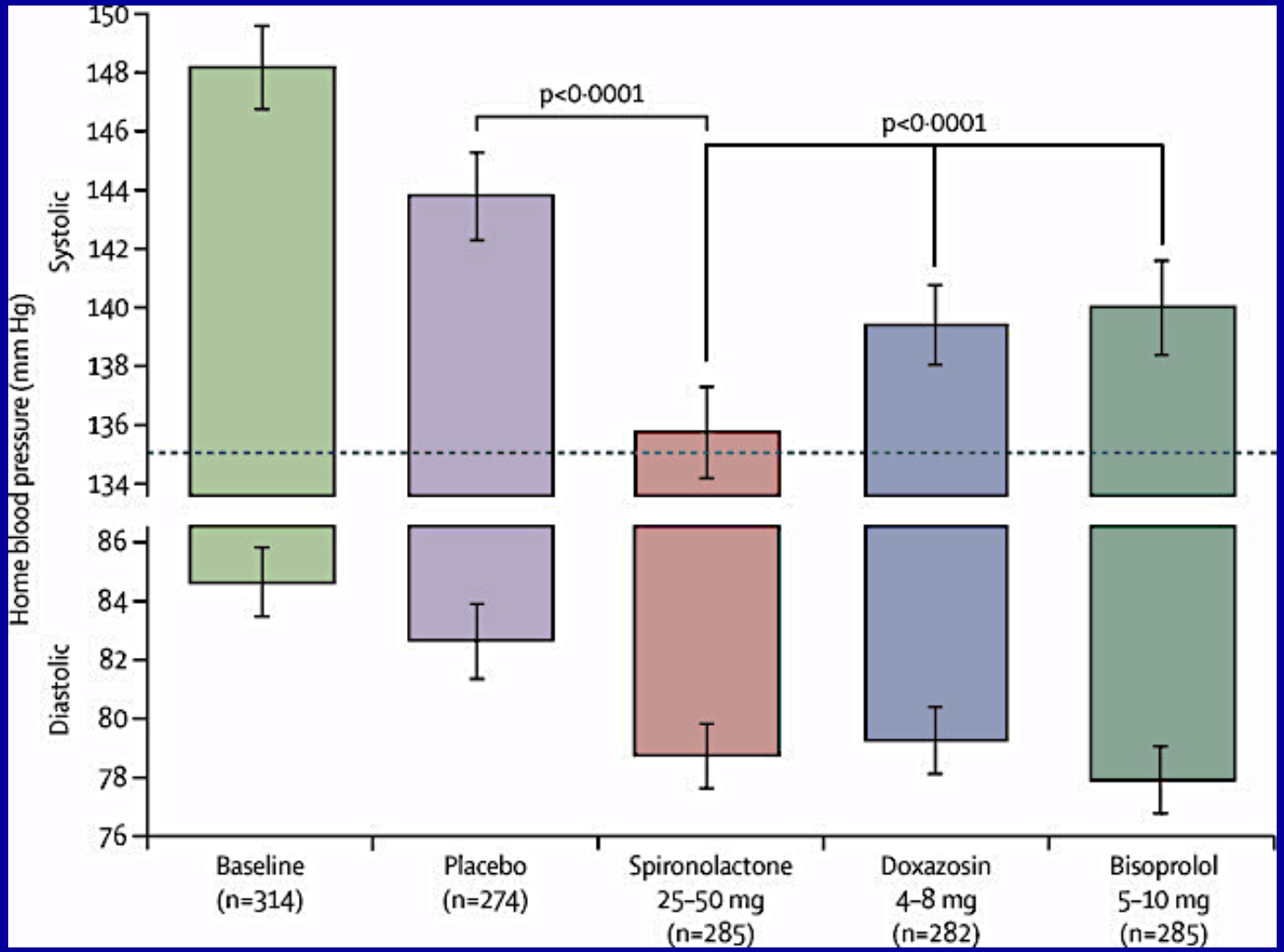




Nishizaka Am J Hypertens 2003;16:925

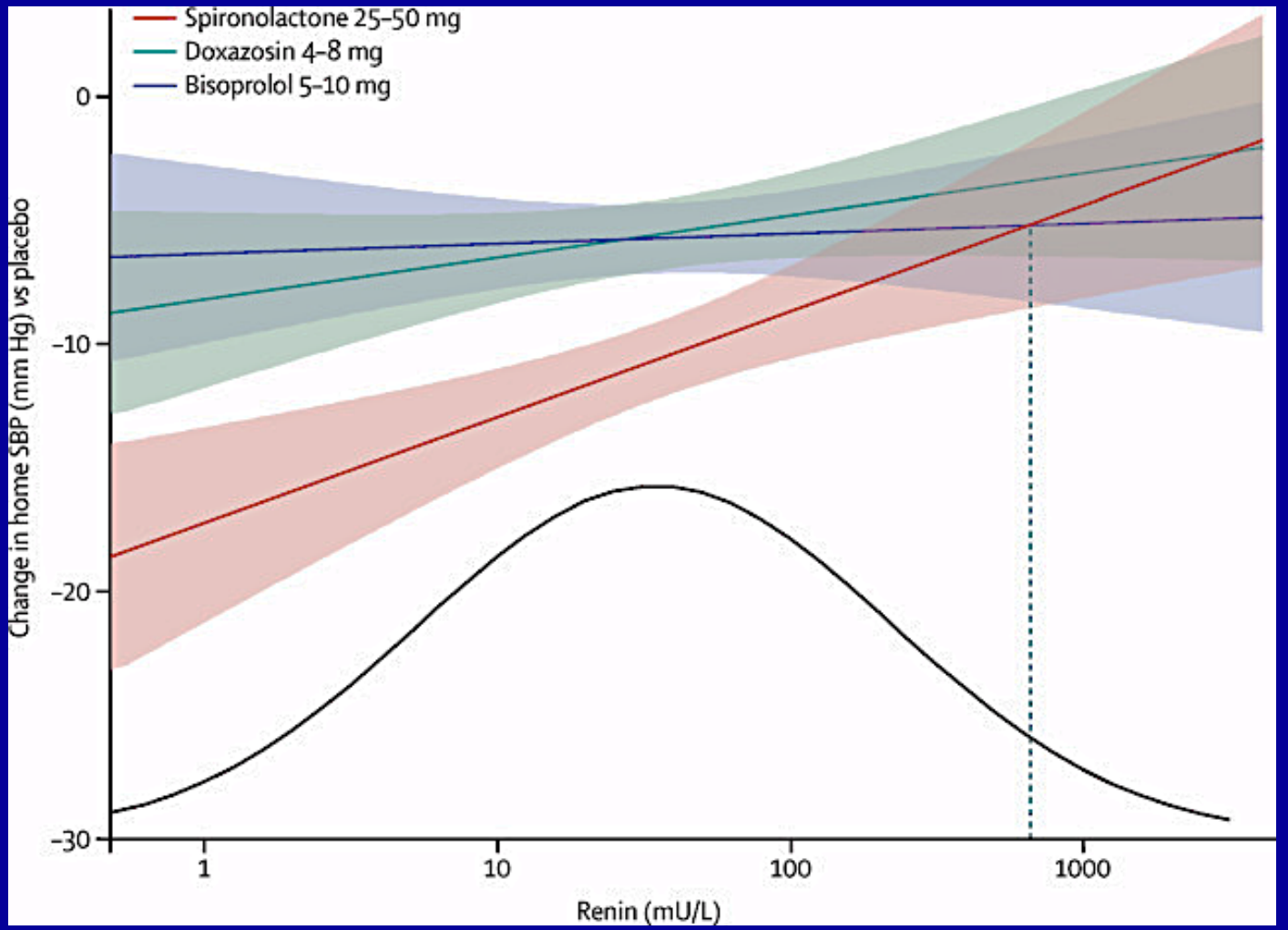
Chapman Hypertension 2007;49:839

PATHWAY-2



Williams et al Lancet 2015;49:839

PATHWAY-2



Williams et al Lancet 2015;49:839

Pearls to Using MRAs

- Start Low Go Slowly: Spiro 12.5-25 mg/d
  - Chemistries in 2 Weeks, 1 Week if CKD Stage 2-4
  - Do Not Up-Titrate for 4-6 Weeks
  - Double Dose & Iterate, Max ~400 mg/d
  - Goal: Normal BP & K, Non-Suppressed PRA Ideal
  - Consider Stopping Other Meds During Titration
  - Can Add Thiazide, Loop Diuretic For High K
  - Expect Rise in Cr; May Stop/Reduce Dose
- Switch to Eplerenone if Side Effects
  - Double Spiro Dose & Divide BID
- Amiloride an Alternative, Not Ideal

Primary Aldosteronism

Summary

- Screening is Easy But Under-utilized
- You Do Not Wake Up One Day With Primary Aldo
- Pathophysiology Explains High Prevalence
- Co-secretion of Cortisol is Common
- You Can Always Stop & Treat Medically
- MR Antagonists For Resistant Hypertension