Primary Aldosteronism & Implications for Primary Hypertension

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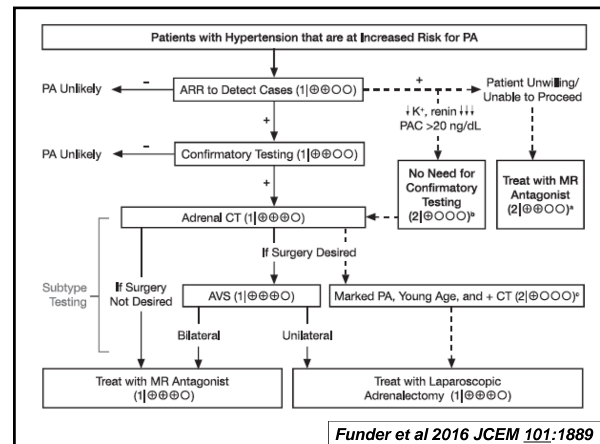
Disclosures

- Contracted Research
  - Millendo Therapeutics
  - Novartis Pharmaceuticals
  - Strongbridge Biopharma
- Consultant
  - Laboratory Corporation of America
  - Corcept Therapeutics
  - Janssen Pharmaceuticals
  - Novartis Pharmaceuticals
  - Tokai Pharmaceuticals
  - Innocrin Pharmaceuticals
  - Alder BioPharmaceuticals
  - Spruce Biosciences

Primary Aldosteronism

Key Points

- Most Common Cause of Secondary HTN
- High End-Organ Damage
- Curable or Targeted Therapy
- Low Rates of Screening & Diagnosis
  - Fear of Embarking On Workup
  - Confusion About Approach
  - <1% Ever Screened
- Syndrome With Many Etiologies



Funder et al 2016 JCEM 101:1889

Primary Aldosteronism

Whom To Screen?

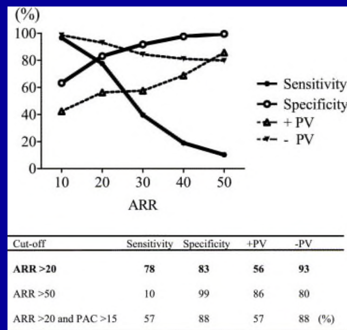
- HTN + Hypokalemia
- Patients With Resistant HTN
  - Or Controlled With 4 Drugs
- Patients With HTN At Age < 40
  - Or FH HTN or CVA Age <40
- Considering Secondary Causes
- Sustained BP >150/100
- HTN + Known Adrenal Mass or OSA
- HTN + First-Degree Relative With PA

Primary Aldosteronism

Screening Procedure: Stop Drugs?

- Most Drugs OK for Screening
  - Most Drugs ↑PRA & Aldo (β-Blockers ↓PRA)
  - *If PRA is Suppressed, Screen is Valid*
- Spironolactone, Eplerenone up to 4 wk
  - 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 (%)

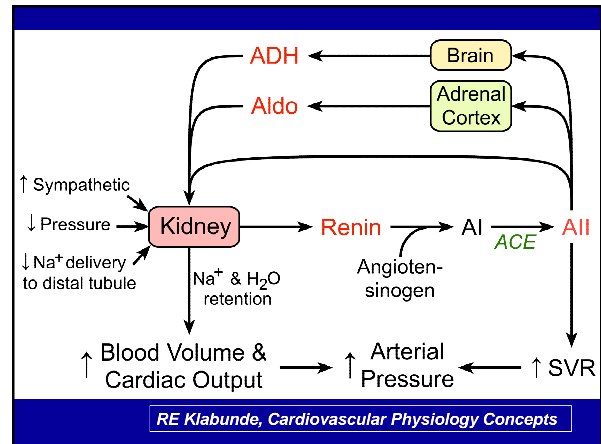
Nishizaka 2005 Am J Hypertens 18:805

Who Has Primary Aldo?

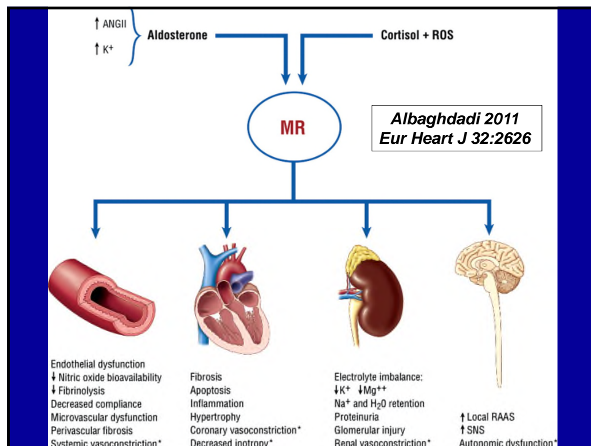
ARR Interpretation

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

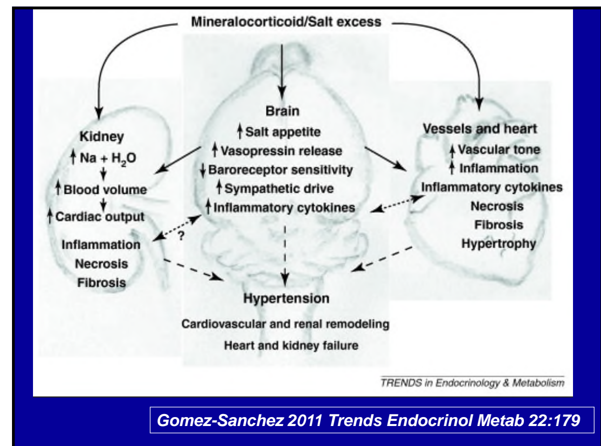
Why Do Patients With Primary Aldosteronism Have Hypertension?



RE Klabunde, Cardiovascular Physiology Concepts

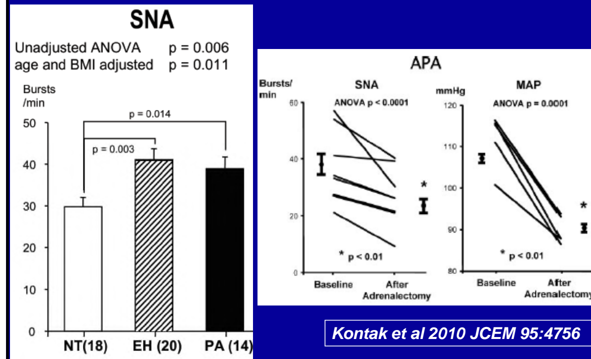


Albaghdadi 2011 Eur Heart J 32:2626



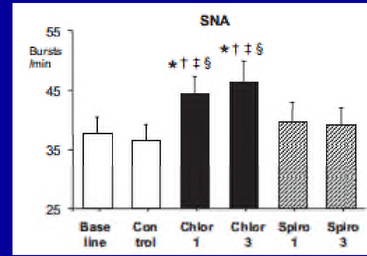
Gomez-Sanchez 2011 Trends Endocrinol Metab 22:179

SNA in Primary Aldosteronism



Kontak et al 2010 JCEM 95:4756

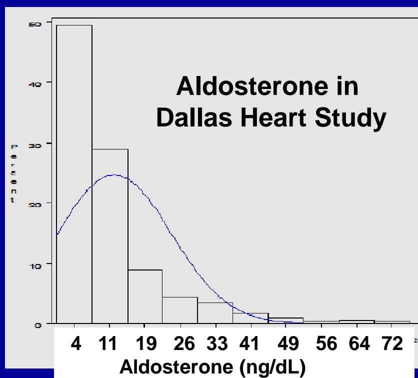
SNA & Spiro in Essential HTN



Spironolactone vs Chlorthalidone: Lowers BP
Reduces SNA
Lowers HOMA-IR

Menon et al 2009 JCEM 94:1361

Pathogenesis of PA



Eplerenone in Primary HTN

Dose (mg/d)	%DBP <90
50	44
100	61
200	80

--20% Nonresponders

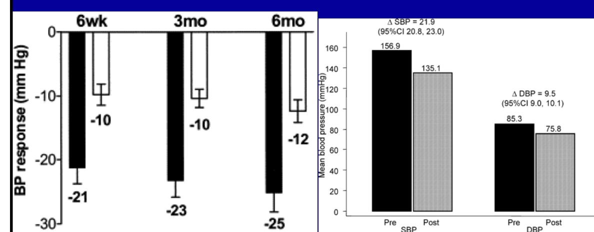
A Clinical Conundrum

Aldosterone and Primary Hypertension:

- Aldosterone implicated in ~10% of cases…BUT
- *Aldosterone antagonists* are effective
  - --In 60-80% of cases
  - --Independent of plasma aldosterone
  - --Particularly in resistant hypertension

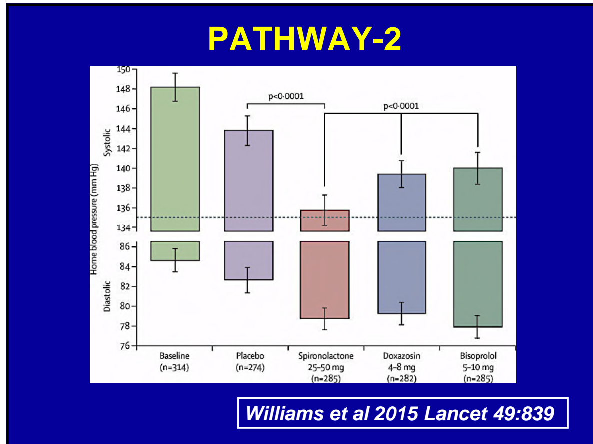
➢Either
- -Increased Sensitivity to Aldosterone
- -Some Other Steroid(s)

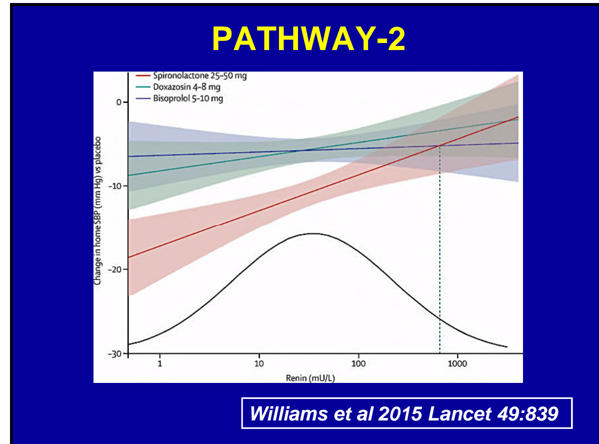
Spironolactone in Resistant HTN

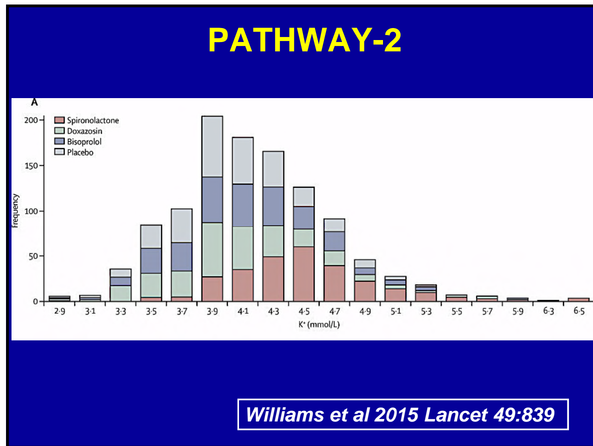


Nishizaka et al 2003 Am J Hypertens 16:925

Chapman et al 2007 Hypertension 49:839





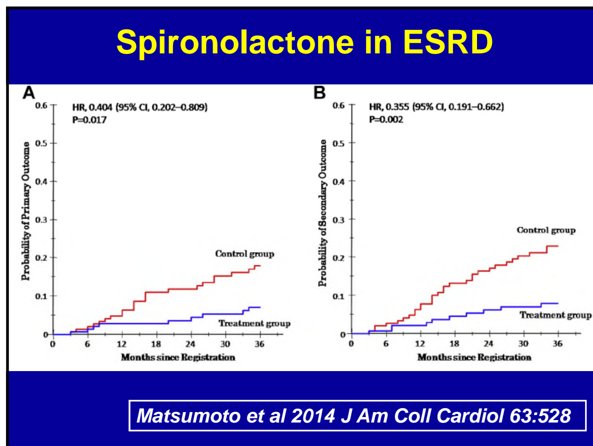


Spironolactone in ESRD

TABLE II. Change in Studied Variables After Intervention According to Study Group

	Spironolactone (n=100)	Placebo (n=98)
Mean number of antihypertensive drugs		
Baseline	4.52±1.88	4.97±2.85
2 years	3.29±1.51	5.36±2.44
Mean change from baseline vs placebo (95% CI)	−1.6 (−1.7 to −1.5)	–
P value	.041	–
Laboratory variables		
Mean plasma potassium		
Baseline	4.12±0.42	3.96±0.51
2 years	5.32±0.68	4.68±0.32
Mean change from baseline vs placebo (95% CI)	0.48 (0.42 to 0.54)	–
P value	.13	–
Mean BNP, pg/mL		
Baseline	77.32±21.72	74.85±19.27
2 years	75.38±19.47	81.69±17.41
Mean change from baseline vs placebo (95% CI)	−8.8 (−9.4 to −8.2)	–
P value	.07	–

Lin et al 2016 J Clin Hypertens 18:121

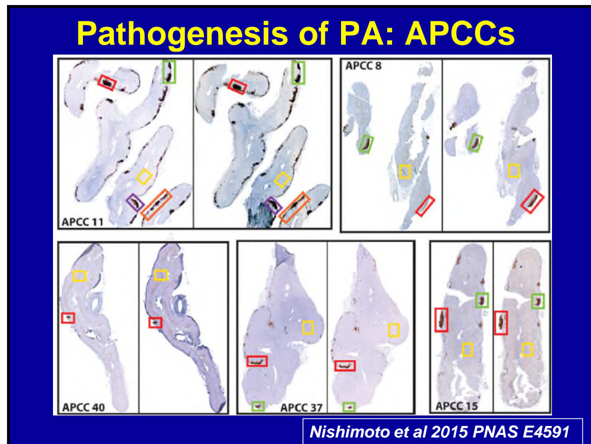


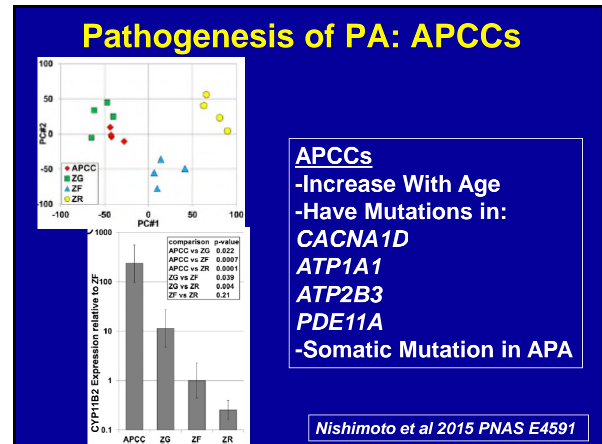
Primary Aldo Case

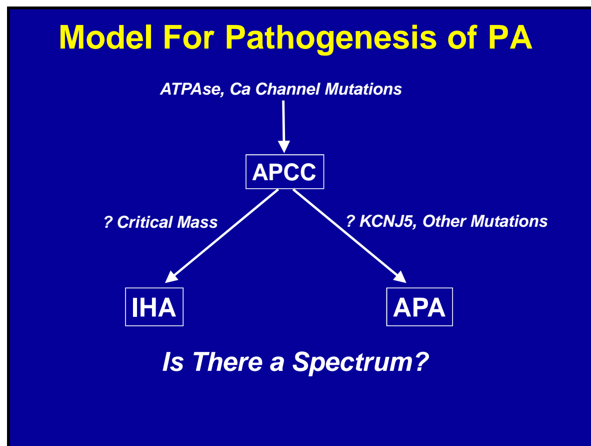
- 51 YO WM Reistant HTN, Low K
- Aldo 46, PRA 0.1, K 2.5-3.3
- CT: 1.5 cm R Adrenal Mass, Normal L
- AVS Pre-Post Cosyntropin:

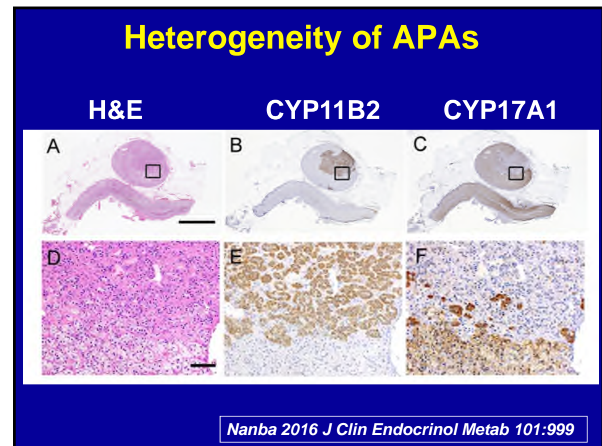
	Right Adrenal Vein			*Inf. Vena Cava*			*Left Adrenal Vein*			
Sample	Cort	Aldo	A/C	Cort	Aldo	A/C	Cort	Aldo	A/C	R/L
Basal	27.3	880	32.2	13.1	40.3	3.1	27.8	195	7.0	4.60
25 min	1478	>10,000	>6.76	27.6	94.5	3.4	1525	881	0.58	>11.7
35 min	1330	>10,000	>7.52	24.8	92.4	3.7	1200	809	0.67	>11.2
45 min	1036	>10,000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

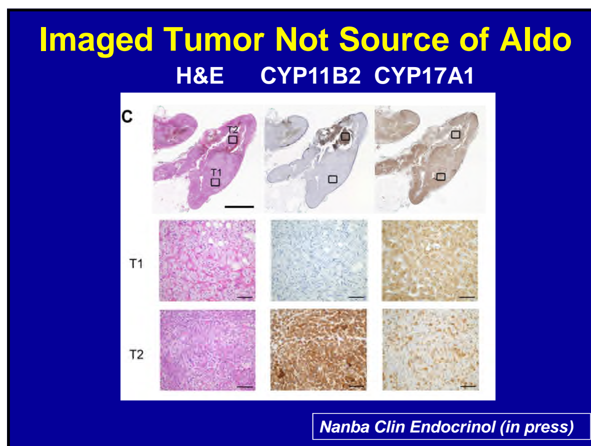
- After R ADX: Aldo 16, PRA 0.4, K 4.1











Primary Aldosteronism

Where Progress is Needed

- Getting Patients Screened
- Simplify Confirmatory Testing
- Secondary Criteria for AVS
- Other Ways to Identify Who Has Bilateral Disease & Does NOT Need CT & AVS
- Titrating Medical Therapy
- Dealing With The Heterogeneity of PA

PA & Essential HTN

In The Meantime

- Screen Appropriately for PA
- Use MR Antagonists!
- Third-Generation MR Antagonists
  - Finerenone, Less Hyperkalemia
  - CNS-Selectivity?
- Broader Indications
- Understanding Mechanisms of HTN

Everything Should Be Made As Simple As Possible

But Not Simpler

Albert Einstein