The Evolution of Primary Aldosteronism

Dr. Greg Hundemer
We are hosting this session on the unceded and ancestral territory of the Coast Salish peoples, including the territories of the Musqueam, Squamish, Tsleil-Waututh Nations, and the Métis Chartered Community of the Lower Mainland Region.
Learning Objectives

1. To review the pathophysiology of primary aldosteronism.
2. To explore the under-recognized prevalence of primary aldosteronism.
3. To discuss emerging data on optimal treatment strategies for primary aldosteronism.
None
Objectives

Primary Aldosteronism

1. What is Primary Aldosteronism?

2. Is There an Unrecognized Spectrum of Primary Aldosteronism?

3. How Should Primary Aldosteronism be Treated?
Hypertension

- Definition
  - Blood pressure $\geq 140/90$ mmHg
  - Drug treatment for high blood pressure

1 in 4 Canadians now has hypertension
What we’re taught in Med School

Hypertension

Essential

Primary Aldosteronism
- Cushing’s Syndrome
- Pheochromocytoma
- Renal Artery Stenosis
- Kidney Parenchymal Disease
- Sleep Apnea
- Oral Contraceptives

Secondary
What we’re taught in Med School

Hypertension

When/who to screen for secondary HTN?
- Drug-Resistant HTN
- Malignant HTN w/end organ damage
- Onset at young age
- Other clinical clues: hypokalemia, response to specific BP medications

Problems with this approach?
- Missing milder forms of these secondary causes?
  - Misclassification as “Essential” HTN
  - Identify patients late in disease course
  - Missed opportunities for early targeted interventions
  - Can’t tailor treatment to individual patients
Part 1: What is Primary Aldosteronism?
Primary Aldosteronism

- Also known as:
  - Primary Hyperaldosteronism
  - Conn’s Syndrome
Primary Aldosteronism

• Discovered in 1954 by Jerome Conn (U of Michigan)
  – 34yoF patient
    • Episodic weakness of the legs (near paralysis)
    • Periodic muscle spasms/cramps in the hands
    • Severe, resistant HTN
    • Severe hypokalemia
    • Metabolic alkalosis
  – Hospitalized for 8 months
  – Found to have high urinary aldosterone levels
  – Underwent exploratory surgery to assess adrenal glands
  – Found to have adrenal adenoma
  – HTN/hypokalemia resolved with adenoma removal
  – Soon many additional cases identified
Primary Aldosteronism

• Most common endocrine cause of HTN but massively underdiagnosed
• Etiology: Autonomous hypersecretion of aldosterone from adrenal glands

- Worse prognostically than other causes of HTN (independent of BP)
- Clinical clues:
  - Severe/resistant HTN
  - Hypokalemia
  - Metabolic alkalosis
  - Adrenal nodule
- Different 1st line therapies than other forms of HTN
CLINICAL VIGNETTE

• 37 year old man diagnosed with HTN
  • Treated with diuretic and calcium-channel blocker

• At age 39, BP 138/92 mmHg on 2 medications
  • Serum Aldosterone: 240 pmol/L
  • Direct Renin Concentration: 2 ng/L
  • Aldosterone-to-Renin Ratio: 120
  • K+ 3.7 mmol/L

Does he have primary aldosteronism?
When/Who to Screen for PA?

- Severe or Resistant Hypertension
  - BP >150/100 mmHg x3; or >140/90 mmHg on 3 medications; or <140/90 mmHg on 4+ medications

- HTN + spontaneous or diuretic-induced hypokalemia

- HTN + adrenal mass

- HTN + sleep apnea

- HTN + family member with PA

- HTN + Family history of early-onset HTN or cerebrovascular accident (<40yrs)

Funder et al. JCEM 2016
**SCREENING TEST:** ARR = aldosterone-to-renin ratio

- **Positive Screen:**
  - ARR that is >144 or >192
  - Renin **must** be suppressed (DRC <10 ng/L; PRA <1 ng/mL/h)
  - Sufficiently elevated aldosterone (>280, >420 pmol/L)

- “Renin-Independent Aldosteronism”
  1. Suppressed Renin
  2. Inappropriately/Dysregulated aldosterone secretion (?)

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**Table 6.** ARR Cutoff Values, Depending on Assay and Based on Whether PAC, PRA, and DRC Are Measured in Conventional or Système International (SI) Units

<table>
<thead>
<tr>
<th>PAC (as ng/dL)</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>60</th>
<th>91</th>
<th>144</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA (ng/mL/h)</td>
<td>1.6</td>
<td>2.5</td>
<td>4.9</td>
<td>7.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA (pmol/L/min)</td>
<td>2.4</td>
<td>3.7</td>
<td>5.7</td>
<td>7.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRC (mU/L)</td>
<td>2.4</td>
<td>3.7</td>
<td>5.7</td>
<td>7.7</td>
<td>144</td>
<td>192</td>
</tr>
<tr>
<td>DRC (ng/L)</td>
<td></td>
<td></td>
<td></td>
<td>144</td>
<td>192</td>
<td></td>
</tr>
</tbody>
</table>

TES: Funder et al. JCEM 2016
AACE: Vaidya et al. Endocr Pract 2017
How BP Meds Affect the ARR

- **β-Blocker**
- **ACEi**
- **ARB**
- **MR Antagonist**
- **ENaC Inhibitor**
How BP Meds Affect the ARR

Main Concern: False Negatives

<table>
<thead>
<tr>
<th></th>
<th>Renin</th>
<th>Aldosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors/ ARBs</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>MR Antagonists/ ENaC Inhibitors</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

The main issue is with MR antagonists and ENaC inhibitors; the other BP meds will not have a major effect when aldosterone is autonomously secreted as with Primary Aldosteronism.

I will typically initially measure the ARR even if a patient is on an MR antagonist or ENaC inhibitor. If Renin suppressed -> ARR still valid. If Renin not suppressed -> Hold MRA/ENaCi 4-6 weeks and repeat ARR.

If a patient is on an ACEi/ARB/MRA/ENaC Inhibitor and their renin is still suppressed, that is highly suspicious for Primary Aldosteronism.
We Are Not Good at Screening for PA

Keeping primary aldosteronism in mind: Deficiencies in screening at-risk hypertensives

Brian C. Ruhle, MD, Michael G. White, MD, MS, Salman Alsafran, MD, Edwin L. Kaplan, MD, Peter Angelos, MD, PhD, Raymon H. Grogan, MD, MS

Results: Of nearly 37,000 patients with hypertension and hypokalemia, only 2.7% were ever screened for primary aldosteronism. Most opportunities for case detection were during hospitalizations, yet in this setting, patients were less likely to clinic patients be screened. Similarly, 3.0% of hypertensive patients with sleep apnea were screened since the inclusion of this group in case detection recommendations.

Adherence to consensus guidelines for screening of primary aldosteronism in an urban healthcare system

Maheshwaran Sivarajah, MD, MSc, Toni Beninato, MD, MS, Thomas J. Fahey III, MD

<table>
<thead>
<tr>
<th>Table II</th>
<th>Frequency rates of criteria from the Endocrine Society 2016 clinical practice guidelines for case-detection of PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Yes (%)</td>
</tr>
<tr>
<td>Sustained BP above 150/100 mm Hg on each of 3 measurements obtained on different days</td>
<td>199 (2.92)</td>
</tr>
<tr>
<td>Hypertension (BP &gt;140/90 mm Hg) resistant to 3 conventional antihypertensive drugs (including a diuretic)</td>
<td>17 (0.25)</td>
</tr>
<tr>
<td>Controlled BP (&lt;140/90 mm Hg) on ≥4 antihypertensive drugs</td>
<td>2 (0.03)</td>
</tr>
<tr>
<td>Hypertension and hypokalemia</td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>6,227 (91.45)</td>
</tr>
<tr>
<td>Diuretic-induced</td>
<td>107 (1.57)</td>
</tr>
<tr>
<td>Hypertension and adrenal incidentaloma</td>
<td>77 (1.13)</td>
</tr>
<tr>
<td>Hypertension and sleep apnea</td>
<td>745 (10.94)</td>
</tr>
<tr>
<td>Hypertension and a family history of early onset (&lt;40 y) hypertension</td>
<td>183 (2.69)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>10 (0.15)</td>
</tr>
<tr>
<td>All hypertensive first-degree relative of patients with PA</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: This study suggests substantial under screening for primary aldosteronism, one of the most common causes of secondary hypertension.
Suspicion for PA

Screen: Assess aldosterone and renin (ARR)

Positive Screen: Suppressed Renin and Inappropriate Aldosterone such that ARR>144-192

Confirmatory Testing

Localization: Imaging (CT/MRI)

Surgery Desired

Adrenal Venous Sampling

Unilateral

Surgical Therapy (laparoscopic adrenalectomy)

Bilateral

Medical Therapy with MR Antagonist

Funder et al. JCEM 2016
Not All Hyperaldosteronism is the Same

**SUMMARY: Renin-Dependent Aldosteronism due to Volume Depletion**
- Optimal \(\text{Na}^+\) Reabsorption/Volume Expansion
- Decreased Distal \(\text{Na}^+\) Delivery
- *Minimal* \(\text{K}^+\) Excretion

**PHYSIOLOGY**

RENIN-DEPENDENT ALDOSTERONISM
Secondary to Intravascular Volume Depletion

- Proximal Convoluted Tubule
- Loop of Henle & Distal Convoluted Tubule
- Blood/ Basolateral Side
- Intravascular

**ENaC**

**ROMK**

**MR**

**K**

**H**

**ALDOSTERONE**

**Kamel et al. Kidney Int 2017; Palmer, B. CJASN 2015**
PHYSIOLOGY

Renin-Dependent Aldosterone Regulation

Yanomami People
“Over thousands of years, the same environmental pressures that forced Yanomami and other terrestrial animals to evolve a hyperactive RAAS, also led Bothrops jararaca to conserve an efficient killing mechanism that targeted its enemies’ haemodynamic vulnerabilities. The bradykinin-potentiating peptides that would become the first ACEi’s were, in essence, the viper’s weapon of choice in a predator-prey arms race.”
**Pathophysiology: Primary Aldosteronism**

**Summary:** Vicious cycle that leads to CV and kidney disease

- ↑↑↑ Distal Na⁺ Delivery
- ↑↑↑ Na⁺ Reabsorption/Volume Expansion/Blood Pressure
- ↑↑↑ K⁺/H⁺ Excretion
- CV and kidney disease
Independent of Blood Pressure, MR activation in PA increases risk for:

- CV Disease: CAD, Stroke, CHF, AFib
- Kidney Disease: CKD, Albuminuria

Therefore, early recognition and treatment is indicated.

Part 2: Is There an Unrecognized Spectrum of Primary Aldosteronism?
Severe Hypertensive PA

Mild Hypertensive PA

Normotensive PA

Current Thresholds for Biochemical Confirmation of PA

Current Threshold to Screen for PA

DISEASE

Obvious Clinical Syndrome of Excessive MR Activation?

Biochemical Confirmation of PA

Cardiovascular Risk

Highest

Brown et al. Annals of Internal Medicine 2017
Unrecognized Yet Biochemically Overt Primary Aldosteronism

1672 consecutive Italian primary care HTNives on NO medications

PA Screen
232 with positive PA screen

Confirmatory Testing
99 with confirmed PA

94.1%
5.9%

“Unrecognized Yet Biochemically Overt PA”
“Overt PA”

Monticone et al. JACC 2017
Unrecognized Yet Biochemically Overt Primary Aldosteronism

Mosso et al. Hypertension 2003

- 609 Chilean HTNives
  - PA Screen: 63 with positive PA screen
  - Confirmatory Testing: 37 with confirmed PA
    - 6.1% TOTAL
    - 2% Stage I
    - 8% stage II
    - 13% Stage III

Baudrand et al. JCEM 2016

- 241 American STAGE 1 HTNives on NO treatment
  - PA Screen: 79 with positive PA screen
  - Confirmatory Testing: 48 with confirmed PA
    - 19% TOTAL
Unrecognized Yet Biochemically Overt Primary Aldosteronism

210 American Normotensives With PRA<1 ng/mL/h

Confirmatory Testing

29 with confirmed PA (14%)

13/210 (6%) also had ARR>144

Baudrand et al. Hypertension 2017

100 Greek Normotensives

Confirmatory Testing

13 with confirmed PA (13%)

5 years follow-up

11/13 (85%) with PA developed HTN

20/87 (23%) without PA developed HTN

OR=18.4 (3.7, 90.1)

Markou et al. JCEM 2013
Unrecognized Prevalence of Primary Aldosteronism

Magnitude of renin-independent aldosterone production

n=1015 participants completed an oral sodium suppression test

Continuum of renin-independent aldosterone production parallels blood pressure severity

Primary aldosteronism prevalence is high

Sensitivity of the ARR was poor at detecting biochemically overt PA

Severe Hypertensive PA

Mild Hypertensive PA

Normotensive PA

“Clinically Relevant” Phenotype of Autonomous Aldosterone Secretion

Normotensive (without overt PA)

Current Thresholds for Biochemical Confirmation of PA

Current Threshold to Screen for PA

Biochemically Overt PA

Unrecognized Yet Biochemically Overt PA

Overt PA

Obvious Clinical Syndrome of Excessive MR Activation?

Biochemical Confirmation of PA

Cardiovascular Risk

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<td>Obvious Clinical Syndrome of Excessive MR Activation?</td>
<td>NO</td>
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<td>Cardiovascular Risk</td>
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<td>Highest</td>
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Inappropriate/Dysregulated Secretion of Aldosterone
There is a broad distribution of the ability to physiologically suppress, and stimulate, aldosterone.

1. What determines this distribution?
2. Does it matter?
Sodium Loaded
“Ability to Physiologically Suppress Aldosterone Secretion”

SUPINE Serum Aldosterone on High Sodium Balance (ng/dL)

24h Urine Aldosterone Excretion on High Sodium Balance (mcg)
Greater autonomous aldosterone secretion associated with more cardiometabolic risk factors

Sodium Loaded
“Ability to Physiologically Suppress Aldosterone Secretion”

TES Threshold for PA Confirmation

P=0.008

Vaidya et al. Hypertension 2013
Brown et al. Hypertension 2014
Aldosterone Dysregulation

Sodium Restriction
“Ability to Physiologically Stimulate Aldosterone Secretion”

SUPINE Serum Aldosterone on Low Sodium Balance (ng/dL)

24h Urine Aldosterone Excretion on Low Sodium Balance (mcg)

Number of Metabolic Syndrome Components

Vaidya et al. Hypertension 2013
Brown et al. Hypertension 2014
Aldosterone Dysregulation

Sodium Restriction
“Ability to Physiologically Stimulate Aldosterone Secretion”

Impaired aldosterone stimulation associated with greater cardiometabolic risk factors

Vaidya et al. Hypertension 2013
Brown et al. Hypertension 2014

Number of Metabolic Syndrome Components
Aldosterone Dysregulation

Suppressibility when Sodium Loaded

ABNORMAL

PHYSIOLOGIC

Stimulation when Sodium Restricted

PHYSIOLOGIC

ABNORMAL

Vaidya et al. Hypertension 2013
Brown et al. Hypertension 2014
Renin Suppression: A Biomarker for MR Activity
PLASMA-RENIN AND BLOOD-PRESSURE
THE LANCET, MARCH 22, 1975

healthy normotensive medical students, nurses, and laboratory technicians were studied while they ate their customary unrestricted diet. 42 of these subjects were also studied after they had consumed a 10 meq. sodium diet for 3 days. Blood for P.R.A. was drawn at noon after 4 hours’ ambulation.

“MAXIMALLY STIMULATED RENIN”

Section of Endocrinology,
Department of Medicine,
Temple University,
Philadelphia,
Pennsylvania 19140,
U.S.A.

E. VICTOR ADLIN.
Renin activity after sodium restriction, a more sensitive indicator of renin suppression, did show a significant negative correlation with blood pressure.

Section of Endocrinology, Department of Medicine, Temple University, Philadelphia, Pennsylvania 19140, U.S.A.

E. Victor Adlin.
Assess MR Activation Syndrome

N=663
Overt PA Excluded

Renin Phenotype

Phenotype Determination & Hypothesis

Inappropriate/Excessive MR Activation Normal Physiology

Autonomous Aldosterone Secretion
- Aldosterone-to-Renin Ratio (ARR)
- Urinary Aldosterone Excretion Rate

Vascular Phenotype
- Blood Pressure
- Renal Plasma Flow

Potassium Homeostasis
- Serum Potassium
- Urinary Potassium Excretion

Hypothesis Testing

Protocol:
- Dietary Sodium Restriction
- Upright Posture

MAXIMALLY STIMULATED RENIN
**Renin Suppression: A Biomarker for MR Activity**

**Systolic Blood Pressure**
- Lowest: Inappropriate/Excessive MR Activity
- Middle: Intermediate MR Activity
- Highest: Physiologic MR Activity

P-trend = 0.004*

**Diastolic Blood Pressure**
- Lowest: Inappropriate/Excessive MR Activity
- Middle: Intermediate MR Activity
- Highest: Physiologic MR Activity

P-trend = 0.008*

*Adjusted for age, sex, race, BMI, diabetes mellitus, Cr and 24hr U$_{\text{Na}}$
Renin Suppression: A Biomarker for MR Activity

Aldosterone-to-Renin Ratio

- Lowest: Inappropriate/Excessive MR Activity
- Middle: Intermediate MR Activity
- Highest: Physiologic MR Activity

P-trend = 0.002*

24h Urine Aldosterone Excretion Rate (when Sodium Loaded)

- Lowest: Inappropriate/Excessive MR Activity
- Middle: Intermediate MR Activity
- Highest: Physiologic MR Activity

P-trend = 0.003*

*Adjusted for age, sex, race, BMI, diabetes mellitus, Cr and 24hr UNa

Hundemer et al. JCEM 2017
In individuals without overt PA:

Renin suppression may be a biomarker for a phenotype that is enriched with [subclinical] autonomous aldosterone secretion and MR activation.

*Adjusted for age, sex, race, BMI, diabetes mellitus, Cr and 24hr U$_{Na}$
Continuum of Renin-Independent Aldosteronism in Normotension

Is this a continuum of physiology or pathophysiology?

What is the relevance to human health?

Section of Endocrinology, Department of Medicine, Temple University, Philadelphia, Pennsylvania 19140, U.S.A.

E. Victor Adlin.
Hypothesis:
• A suppressed renin phenotype in normotension increases the risk for incident hypertension (MR-mediated)

Hypothesized Phenotypes:

Suppressed Renin Phenotype: PRA ≤ 0.50 ng/dL/h
  • Enriched with Renin-Independent Aldosterone Secretion and High MR Activity??

Indeterminate Renin Phenotype: PRA 0.51-0.99 ng/dL/h

Unsuppressed Renin Phenotype: PRA ≥ 1.0 ng/dL/h
  • Enriched with Renin-Dependent Aldosterone Secretion and Physiologic MR Activity??
Renin Phenotype and Incident Hypertension

Incidence Rate of Hypertension

(incident cases per 1,000 person-years)

- PRA ≤ 0.50 ng/dL/h: Suppressed Renin Phenotype
- PRA 0.51-0.99 ng/dL/h: Indeterminate Phenotype
- PRA ≥ 1.0 ng/dL/h: Unsuppressed Renin Phenotype

Brown et al. *Annals of Internal Medicine* 2017
Renin Phenotype and Incident Hypertension

Intricate details to be clarified in the image.
RENIN-INDEPENDENT ALDOSTERONISM IN NORMOTENSION:

Renin suppression associated with increased risk for incident hypertension…

…via inappropriate MR activation?

HR = 1.68 (1.16, 2.44)
30 excess events per 1,000 person-years
Among Resistant Hypertensives, add-on therapy with spironolactone is most effective, AND those with the lowest Renin responded most.

Do a substantial proportion of Resistant HTNives have MR-mediated HTN?
Bottom Line: Resistant hypertension commonly due to inappropriate autonomous aldosterone secretion.
Severity Spectrum of Primary Aldosteronism

“Clinically Relevant” Phenotype of Autonomous Aldosterone Secretion

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>Subclinical Primary Aldosteronism</th>
<th>Unrecognized Yet Biochemically Overt PA</th>
<th>Overt PA</th>
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</thead>
<tbody>
<tr>
<td>Obvious Clinical Syndrome of Excessive MR Activation?</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
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<tr>
<td>Biochemical Confirmation of PA</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
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<tr>
<td>Cardiovascular Risk</td>
<td>????</td>
<td></td>
<td>Highest</td>
</tr>
</tbody>
</table>

Current Thresholds for Biochemical Confirmation of PA

Cardiovascular Risk: Highest

Brown et al. Annals of Internal Medicine 2017
Part 3: How Should Primary Aldosteronism Be Treated?
CLINICAL VIGNETTE

• 56 year old woman with worsening blood pressure (170/100 mmHg)
• Serum Aldosterone: 600 pmol/L, DRC 1 ng/L, ARR 600, K+=2.9 mEq/L
• Confirmatory Testing (oral salt loading): Positive for PA
• Adrenal vein sampling performed -> no lateralization
• Started on spironolactone 50mg daily

1 year later in follow-up:
• BP= 135/85 mmHg on spironolactone 50mg daily, amlodipine 10mg daily
• Aldosterone=500 pmol/L, DRC 2.4 ng/L, K=3.7 mmol/L

Is medical treatment optimized?
Will we reduce the risk for adverse outcomes?

*What is the goal of medical therapy for PA?*

• BP normalization?
• K⁺ normalization?
• Efficient MR blockade/renin elevation?**
The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline

Objective: To develop clinical practice guidelines for the management of patients with primary aldosteronism.

Participants: The Task Force included a chair, selected by the Clinical Guidelines Subcommittee of the Endocrine Society, six additional experts, a methodologist, and a medical writer. The Task Force received no corporate funding or remuneration.

Evidence: We searched for systematic reviews and primary studies to formulate the key treatment and prevention recommendations. We used the Grading of Recommendations Assessment, Development, and Evaluation group criteria to describe both the quality of evidence and the strength of recommendations. We used ‘recommend’ for strong recommendations and ‘suggest’ for weak recommendations.

Consensus Process: We achieved consensus by collecting the best available evidence and conducting one group meeting, several conference calls, and multiple e-mail communications. With the help of a medical writer, the Endocrine Society’s Clinical Guidelines Subcommittee, Clinical Affairs Core Committee, and Council successfully reviewed the drafts prepared by the Task Force. We placed the version approved by the Clinical Guidelines Subcommittee and Clinical Affairs Core Committee on the Endocrine Society’s Web site for comments by members. At each stage of review, the Task Force received written comments and incorporated necessary changes.

Traditional Treatment Dogma

UNILATERAL PA Adenoma (Conn’s Tumor) → "Normal" → BILATERAL PA Macro or micro nodular, hyperplasia

**Treatment**
- Surgery for Cure
- 1) Na⁺ Restriction AND
- 2) Lifelong Mineralocorticoid Receptor Antagonist to normalize BP and K⁺

*Level 1 evidence lacking*
Objectives:

1. Do MR antagonists and surgical adrenalectomy adequately prevent adverse outcomes?

2. Does renin serve as a clinically useful biomarker of adequate MR blockade?
Primary Aldosteronism (PA)

1177 Patient records identified with the diagnosis of PA via:

- 161 excluded on manual review for incorrect diagnosis:
  - ARR<30 or PRA>1 ng/mL/h
  - Negative confirmatory testing for PA

1016 Patients with confirmed PA

- 309 Patients with PA and treated with surgical adrenalectomy
- 707 Patients with PA and treated medically

Patients with prior cardiovascular disease excluded

N=602
Patients with confirmed PA on MRA therapy and no prior cardiovascular events

Essential Hypertension

246336 Patient records identified with the diagnosis of essential hypertension and no PA

One third of records arbitrarily selected for study eligibility determination (n = 79401)

11245 excluded for:
- Prior cardiovascular event(s)
- Treated with MR antagonists

68156 Patients with essential hypertension without a prior cardiovascular event

26303 excluded to allow for frequency matching by age with the PA cohort

N=41,853
Patients with essential hypertension, no prior cardiovascular events, age-matched with PA cohort
## Medical Therapy for PA and Incident Outcomes

<table>
<thead>
<tr>
<th></th>
<th>PA on MRA (N=602)</th>
<th>Essential HTN (N=41,853)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>58 (12)</td>
<td>57 (12)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>31.1 (6.0)</td>
<td>29.8 (6.4)</td>
</tr>
<tr>
<td><strong>Serum Potassium</strong></td>
<td>3.6 (0.5)</td>
<td>4.1 (0.5)</td>
</tr>
<tr>
<td><strong>SBP at Study Entry</strong></td>
<td>137 (19)</td>
<td>135 (18)</td>
</tr>
<tr>
<td><strong>DBP at Study Entry</strong></td>
<td>81 (13)</td>
<td>80 (11)</td>
</tr>
<tr>
<td><strong>Mean Anti-HTNive medications (non-MRAs)</strong></td>
<td>2.9 (1.4)</td>
<td>2.7 (1.4)</td>
</tr>
<tr>
<td><strong>Other CV Risk Factors</strong> (aspirin, statin, LDL, A1c, eGFR, smoking)</td>
<td>No difference</td>
<td></td>
</tr>
</tbody>
</table>
Summary:
1. Even when PA patients are treated with MR antagonists, they remain at higher risk for CV events than patients with essential hypertension.
2. Surgical adrenalectomy may mitigate this risk.

HR = 1.91 (1.63, 2.25) for PA MRA Therapy vs Essential HTN

Components of the Composite:
- MI or Coronary Revasc: HR = 1.81 (1.39, 2.37)
- CHF Hospitalization: HR = 1.61 (1.17, 2.22)
- Stroke: HR = 2.38 (1.83, 3.08)

HR = 0.58 (0.35, 0.97) for PA Surgery vs Essential HTN

14 excess events per 100 persons
Atrial Fibrillation

HR = 1.93 (1.54, 2.42) for PA MRA Therapy vs Essential HTN
HR = 0.75 (0.41, 1.36) for PA Adrenalectomy vs Essential HTN

Summary:
1. Even when PA patients are treated with MR antagonists, they remain at higher risk for atrial fibrillation than patients with essential hypertension.
2. Surgical adrenalectomy may mitigate this risk.
HR = 1.34 (1.06, 1.71) for PA MRA Therapy vs Essential HTN
HR = 0.72 (0.38, 1.72) for PA Surgery vs Essential HTN

Summary:
1. Even when PA patients are treated with MR antagonists, they remain at higher mortality risk than patients with essential hypertension.
2. Surgical adrenalectomy may mitigate this risk.
Summary:
1. Even when PA patients are treated with MR antagonists, they have a more rapid age-related decline in eGFR than patients with essential HTN.
2. Curative surgical adrenalectomy in unilateral PA may mitigate this risk.
Incident Chronic Kidney Disease

Summary:
1. Even when PA patients are treated with MR antagonists, they remain at higher risk for incident CKD than patients with essential HTN.
2. Surgical adrenalectomy may mitigate this risk.

MRA Therapy
Essential HTN
Surgery

HR= 1.63 (1.33, 1.99) for PA MRA vs Essential HTN
HR= 0.71 (0.39, 1.30) for PA Surgery vs Essential HTN
HR= 2.30 (1.22, 4.35) for PA MRA vs PA Surgery

9 Excess Events per 100 Persons

Hundemer et al. Hypertension, 2018
Biomarkers of MR Antagonism

**Increased Na⁺ Delivery**

Principal Cell Loop of Henle & Distal Convoluted Tubule

Intercalated Cell

Proximal Convoluted Tubule

Blood/Basolateral Side

Urine/Luminal Side

Na⁺ Cl⁻ HCO₃⁻

Na⁺ Cl⁻

ENaC

ROMK

Principal Cell

Intercalated Cell

**DECREASED Na⁺ Delivery**

**Volume Expansion**

↓↓↓ AngII

↓↓↓ Renin

ALDOSTERONE

**Volume Contraction**

↑↑ Renin

↑↑↑ ALDOSTERONE

↓↓↓ AngII

↓↓↓ Renin

Volume Expansion

Volume Contraction
Risk for Incident Composite Cardiovascular Events

Summary:
1. The increased risk for CV disease in PA treated with MR antagonists is limited to those whose renin remains suppressed.

2. PA patients whose renin substantially rose with MR antagonists had a risk for CV disease comparable to:
   - Essential hypertension AND
   - Unilateral PA treated with adrenalectomy

HR= 2.83 (2.11, 3.80) for Suppressed PRA vs Essential HTN
HR= 1.09 (0.56, 2.10) for Unsuppressed PRA vs Essential HTN
HR= 0.58 (0.35, 0.97) for Adrenalectomy vs Essential HTN

Hundemer et al, The Lancet D&E 2018
Blood Pressure Trends in Study Cohort

Blood Pressure (mmHg) vs Year

- Systolic Blood Pressure
- Diastolic Blood Pressure

Legend:
- Red: MRA PRA <1 ng/mL/h
- Orange: MRA PRA ≥1 ng/mL/h
- Green: PA Surgery
- Blue: Essential HTN

Study entry
1-6 months prior to study entry
Summary:

Independent of BP, higher MR antagonist dose and a substantial increase in renin activity are associated with a lower risk of incident CV outcomes.
Risk for Incident Atrial Fibrillation

HR = 2.55 (1.75, 3.71) for Suppressed PRA vs Essential HTN
HR = 1.03 (0.54, 2.00) for Unsuppressed PRA vs Essential HTN
HR = 0.75 (0.41, 1.36) for Adrenalectomy vs Essential HTN

Hundemer et al, JAMA Cardiology 2018
HR = 1.63 (1.03, 2.59) for Suppressed PRA vs Essential HTN
HR = 0.88 (0.41, 1.87) for Unsuppressed PRA vs Essential HTN
HR = 0.72 (0.38, 1.72) for Adrenalectomy vs Essential HTN

6 Excess Deaths per 100 Persons
The current (recommended) practice of lifelong MR antagonist therapy in PA:

- Associated with a significantly higher risk for incident cardiovascular disease, renal disease & death, *independent of blood pressure control*
- Intensification of MR antagonist therapy to raise renin, as a proxy for optimal MR antagonism, may mitigate these risks.
  - Not always possible!! (adverse effects of MRA, CKD/hyperkalemia)

Surgical therapy, to cure primary aldosteronism, mitigates these risks

MORE QUESTIONS:

- How to candidly counsel PA patients who receive lifelong MR antagonist therapy about the efficacy and future risk associated with this decision?
- Is the current treatment dogma still appropriate?
- Should surgical adrenalectomy be considered more frequently?
Future Areas to Consider for Treating Primary Aldosteronism

Confirmed Primary Aldosteronism

- **Unilateral Disease**
  - Strongly Recommend Unilateral Adrenalectomy
  - Evaluate for biochemical and clinical cure

- **Bilateral Disease**
  - Bilateral, but Grossly Asymmetrical Autonomous Aldosterone Secretion
    - Young Age? Cardiovascular Comorbidities? Chronic Kidney Disease?
    - Future Studies?
      - Consider Unilateral Adrenalectomy to Attenuate Severity of Disease
  - Bilateral, but Relatively Symmetric Autonomous Aldosterone Secretion

- Life-long MR Antagonist Therapy
  - Persistently elevated BP or hypokalemia despite maximal MR antagonist therapy, and/or chronic kidney disease limiting MR antagonist therapy
  - Attempt to raise renin
    - Increase MR antagonist dose
    - Dietary sodium restriction
  - Addition of other anti-hypertensive medication classes (i.e. ENaC)
QUESTIONS?