The Evolution of Primary Aldosteronism

Dr. Greg Hundemer

BCRenal
Provincial Health Services Authority

Territorial Acknowledgement

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

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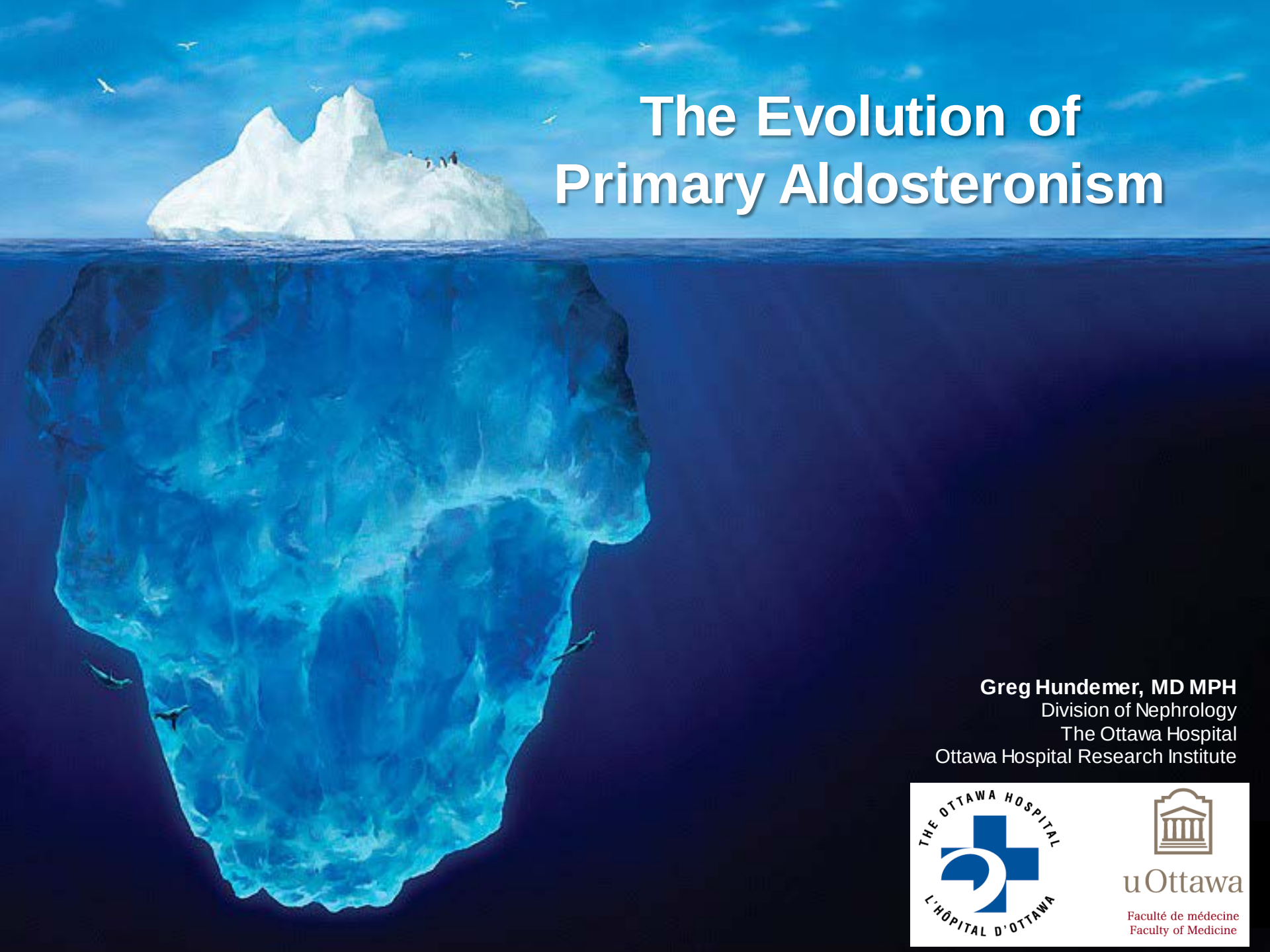

The Evolution of Primary Aldosteronism

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Disclosures

None

Objectives

Primary Aldosteronism

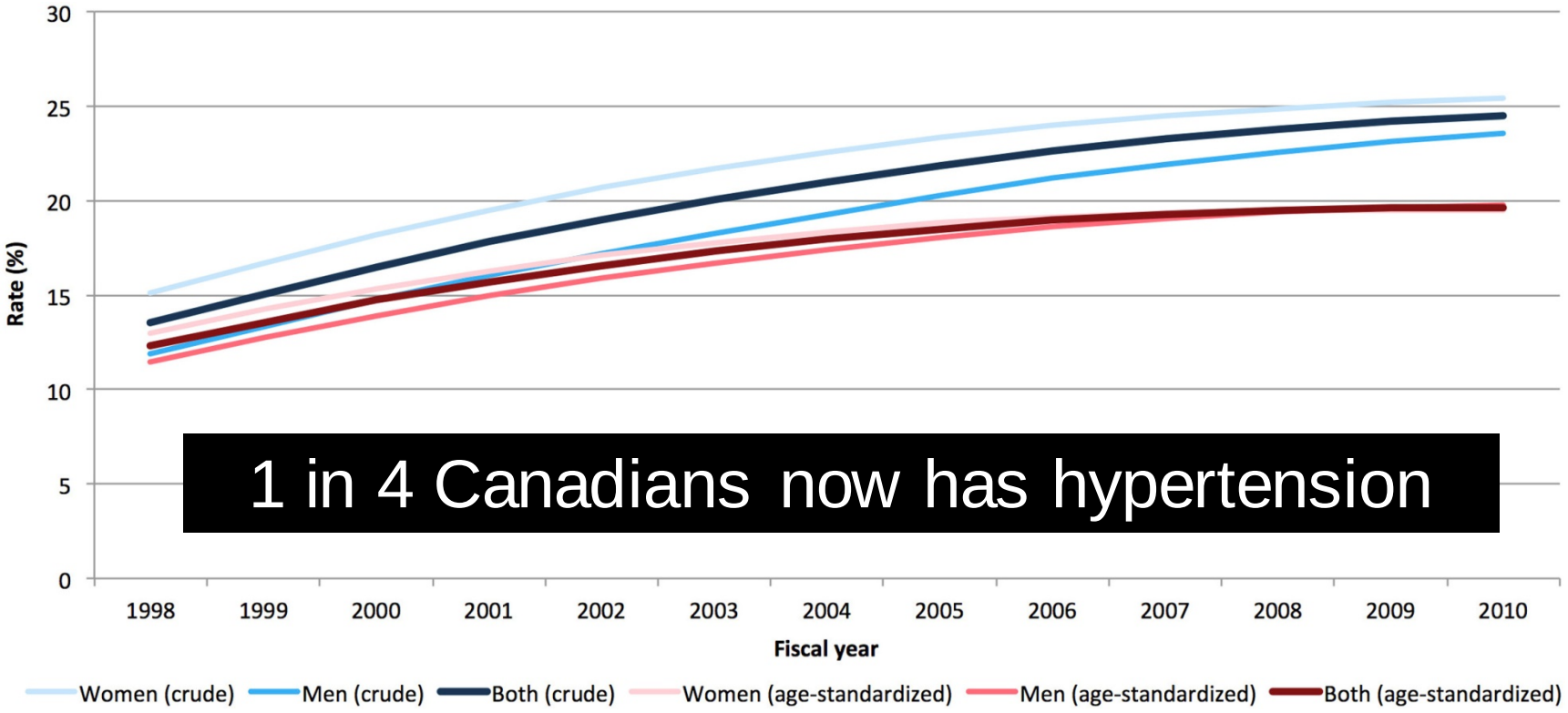
1. **What is Primary Aldosteronism?**

2. **Is There an Unrecognized Spectrum of Primary Aldosteronism?**

3. **How Should Primary Aldosteronism be Treated?**

Hypertension

- Definition
  - Blood pressure ≥ 140/90 mmHg
  - Drug treatment for high blood pressure

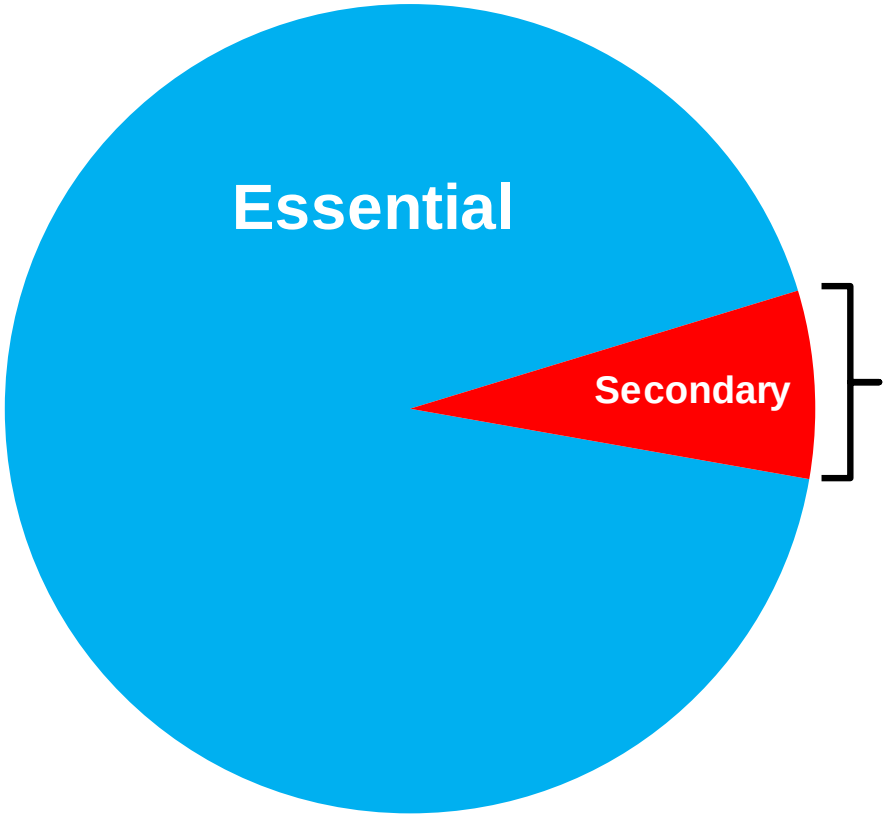


1 in 4 Canadians now has hypertension

Leung et al, Can J Cardiol 2016

What we're taught in Med School

Hypertension

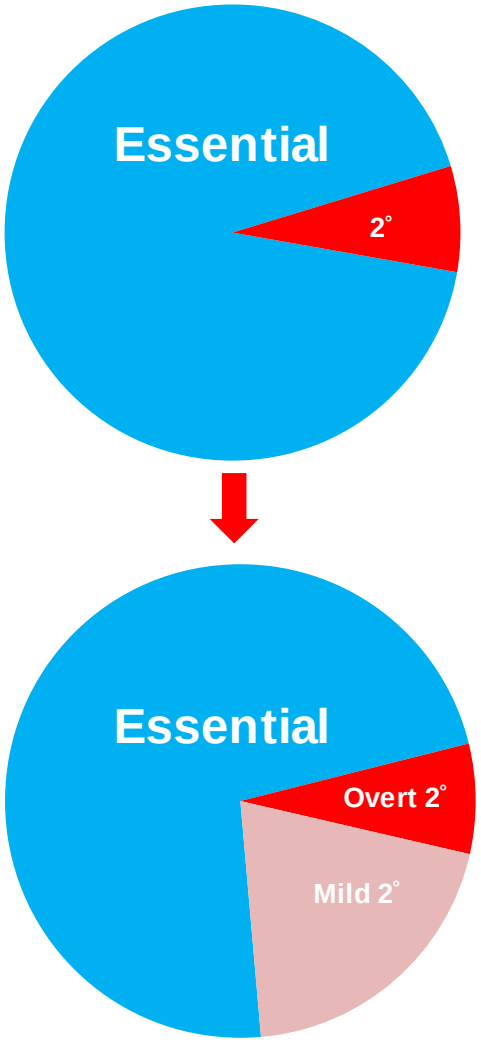


Primary Aldosteronism

Cushing's Syndrome
Pheochromocytoma
Renal Artery Stenosis
Kidney Parenchymal Disease
Sleep Apnea
Oral Contraceptives

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

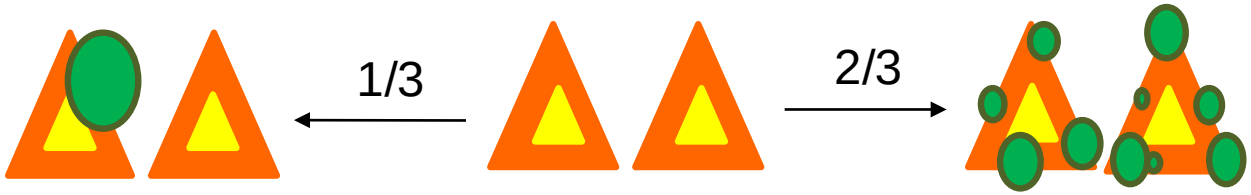
- Also known as:
  - Primary Hyperaldosteronism
  - Conn's Syndrome

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)

Diagnosing Primary Aldosteronism

SCREENING TEST: ARR=aldosterone-to-renin ratio

- Positive Screen:
  - ARR that is >1~~44~~ or **>~~192~~**

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

	PRA, ng/mL/h	PRA, pmol/L/min	DRC, mU/L[a]	DRC, ng/L[a]
PAC (as ng/dL)	20	1.6	2.4	3.8
	30[b]	2.5	3.7	5.7
	40	3.1	4.9	7.7
PAC (as pmol/L)	750[b]	60	91	144
	1000	80	122	192

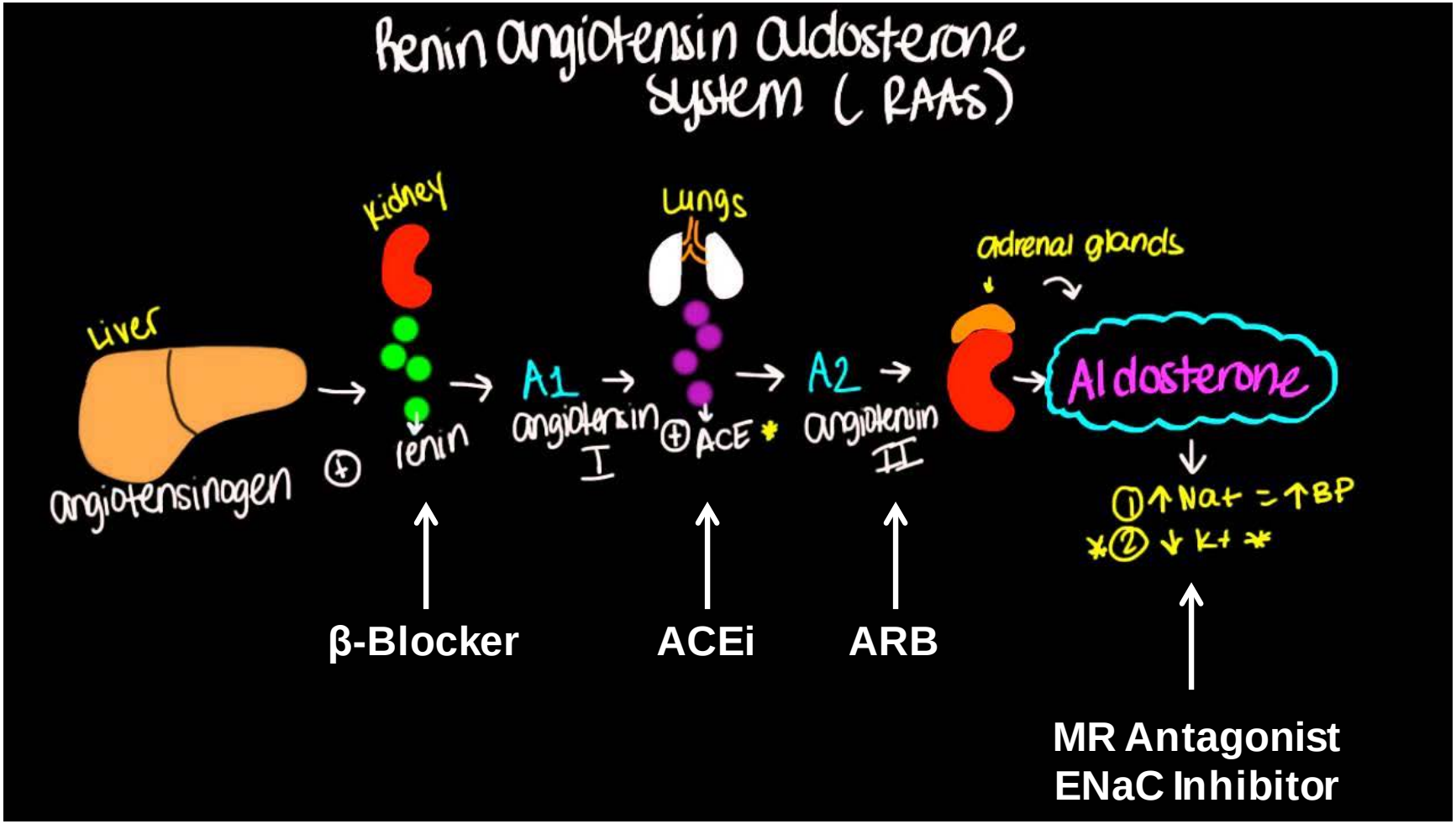
  - Renin **must** be suppressed (DRC <10 ng/L; PRA <1 ng/mL/h)
  - Sufficiently elevated aldosterone (>2~~80~~, **>~~320~~** pmol/L)

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

TES: Funder et al. JCEM 2016

AACE: Vaidya et al. Endocr Pract 2017

How BP Meds Affect the ARR



How BP Meds Affect the ARR

Main Concern: False Negatives

	Renin	Aldosterone
ACE Inhibitors/ ARBs	↑	↓
MR Antagonists/ ENaC Inhibitors	↑	↑
Beta Blockers	↓	↓

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

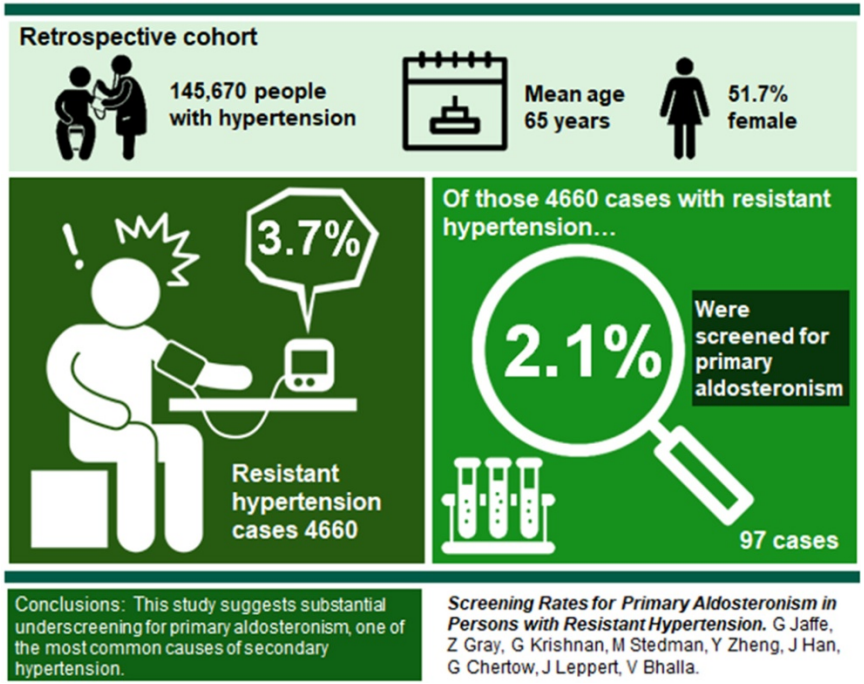
I will typically initially measure the ARR even if a patient is on an MR antagonist or ENaC inhibitor
- **if Renin suppressed -> ARR still valid**
- **if Renin not suppressed -> Hold MRA/ENaCi 4-6 weeks and repeat ARR**

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

What are the screening rates for primary aldosteronism among persons with resistant hypertension?

Hypertension



Conclusions: This study suggests substantial underscreening for primary aldosteronism, one of the most common causes of secondary hypertension.

Screening Rates for Primary Aldosteronism in Persons with Resistant Hypertension. G Jaffe, Z Gray, G Krishnan, M Stedman, Y Zheng, J Han, G Chertow, J Leppert, V Bhalla.

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

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

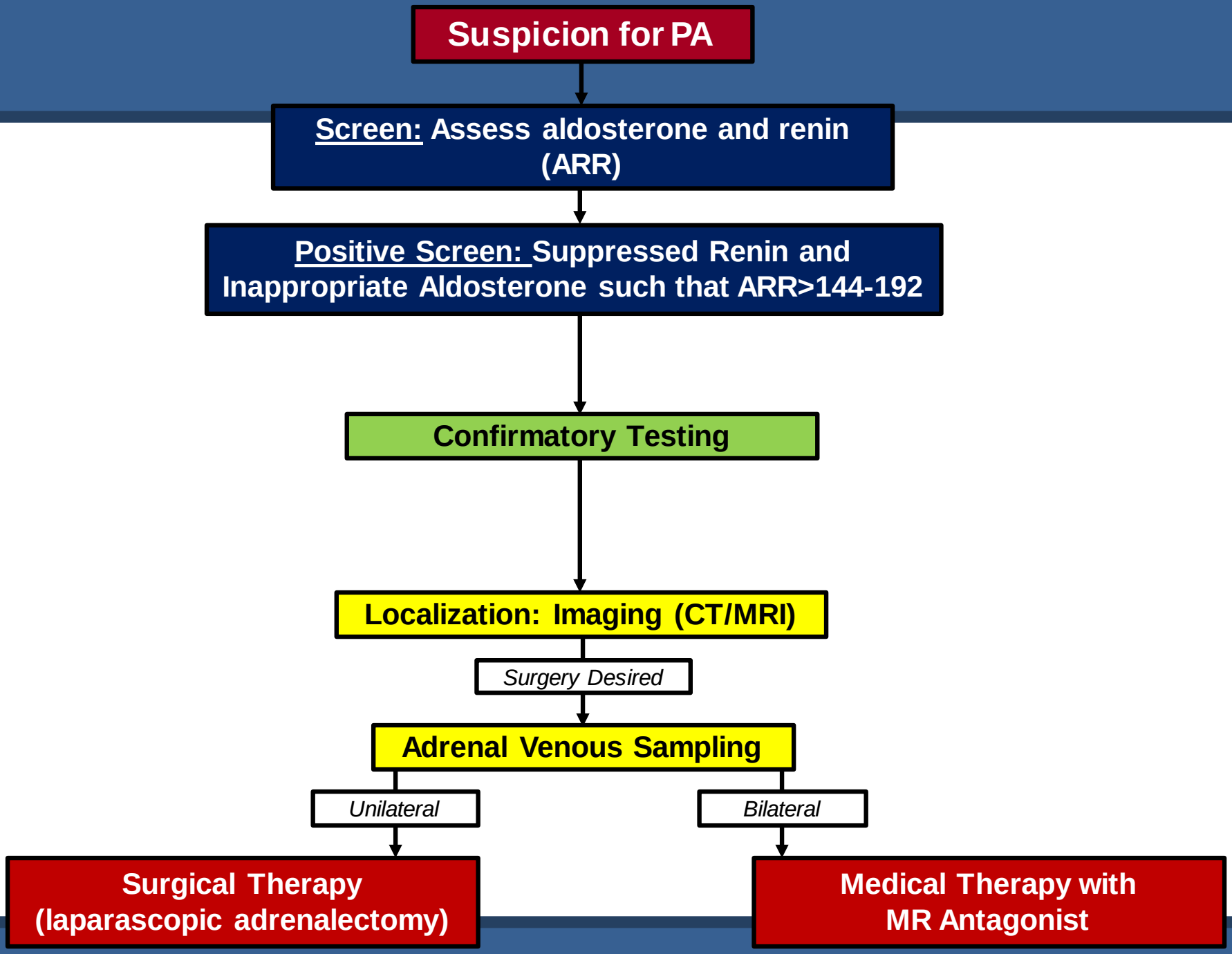
Results: Of nearly 37,000 patients with hypertension and hypokalemia, only 2.7% were ever screened for primary aldosteronism. Most opportunities for case detection were during inpatient hospitalizations, yet in this setting, patients were less likely than clinic patients be screened. Similarly, 3.0% 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[a], Toni Beninato, MD, MS[b], Thomas J. Fahey III, MD[b,*]

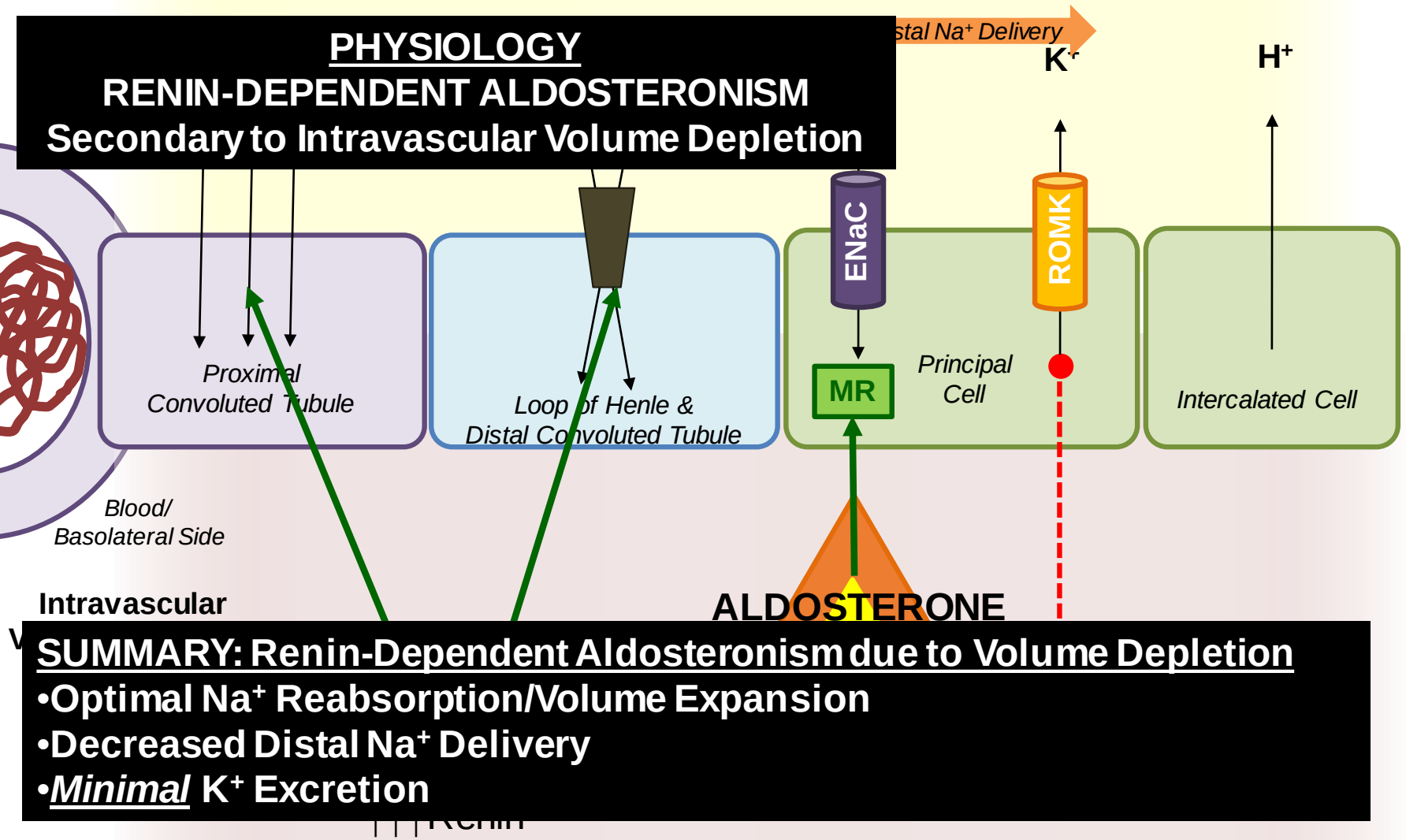
Table II
Frequency rates of criteria from the Endocrine Society 2016 clinical practice guidelines for case-detection of PA

Criteria	Patients	
	Yes (%)	No (%)
Sustained BP above 150/100 mm Hg on each of 3 measurements obtained on different days	199 (2.92)	6,610 (97.08)
Hypertension (BP >140/90 mm Hg) resistant to 3 conventional antihypertensive drugs (including a diuretic)	17 (0.25)	6,792 (99.75)
Controlled BP (<140/90 mm Hg) on ≥4 antihypertensive drugs	2 (0.03)	6,807 (99.97)
Hypertension and hypokalemia		
Spontaneous	6,227 (91.45)	582 (8.55)
Diuretic-induced	107 (1.57)	6,702 (98.43)
Hypertension and adrenal incidentaloma	77 (1.13)	6,732 (98.87)
Hypertension and sleep apnea	745 (10.94)	6,064 (89.06)
Hypertension and a family history of early onset (<40 y)		
Hypertension	183 (2.69)	6,626 (97.31)
Cerebrovascular accident	10 (0.15)	6,799 (99.85)
All hypertensive first-degree relative of patients with PA		



Funder et al. JCEM 2016

Not All Hyperaldosteronism is the Same



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

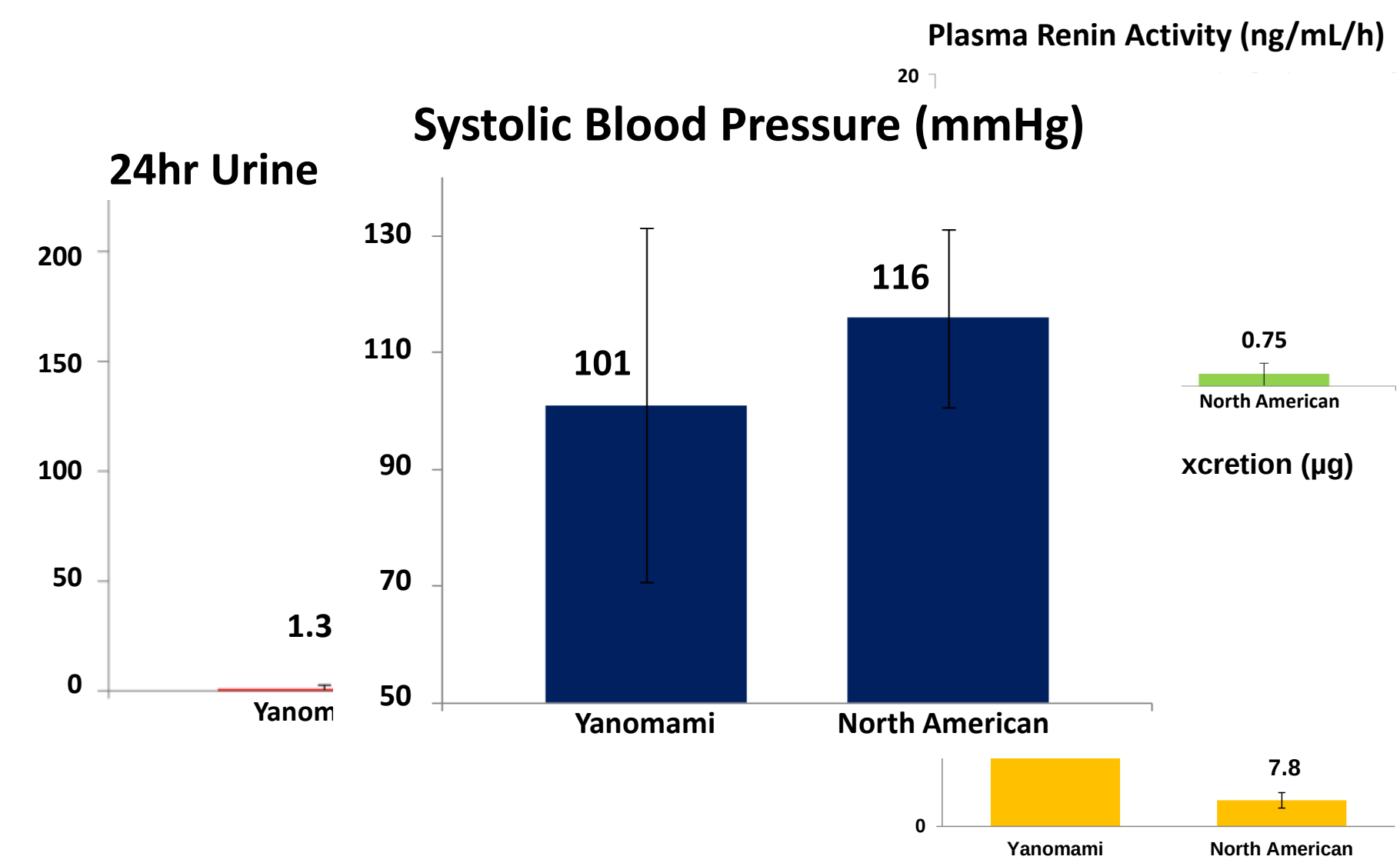
PHYSIOLOGY
Renin-Dependent Aldosterone Regulation

Yanomami People

PHYSIOLOGY

Renin-Dependent Aldosterone Regulation

Yanomami People vs. Normotensive North Americans (MESA)



Oliver et al. Circulation 1975

PHYSIOLOGY
Renin-Dependent Aldosterone Regulation

Brazilian Pit Viper
(*Bothrops jararaca*)

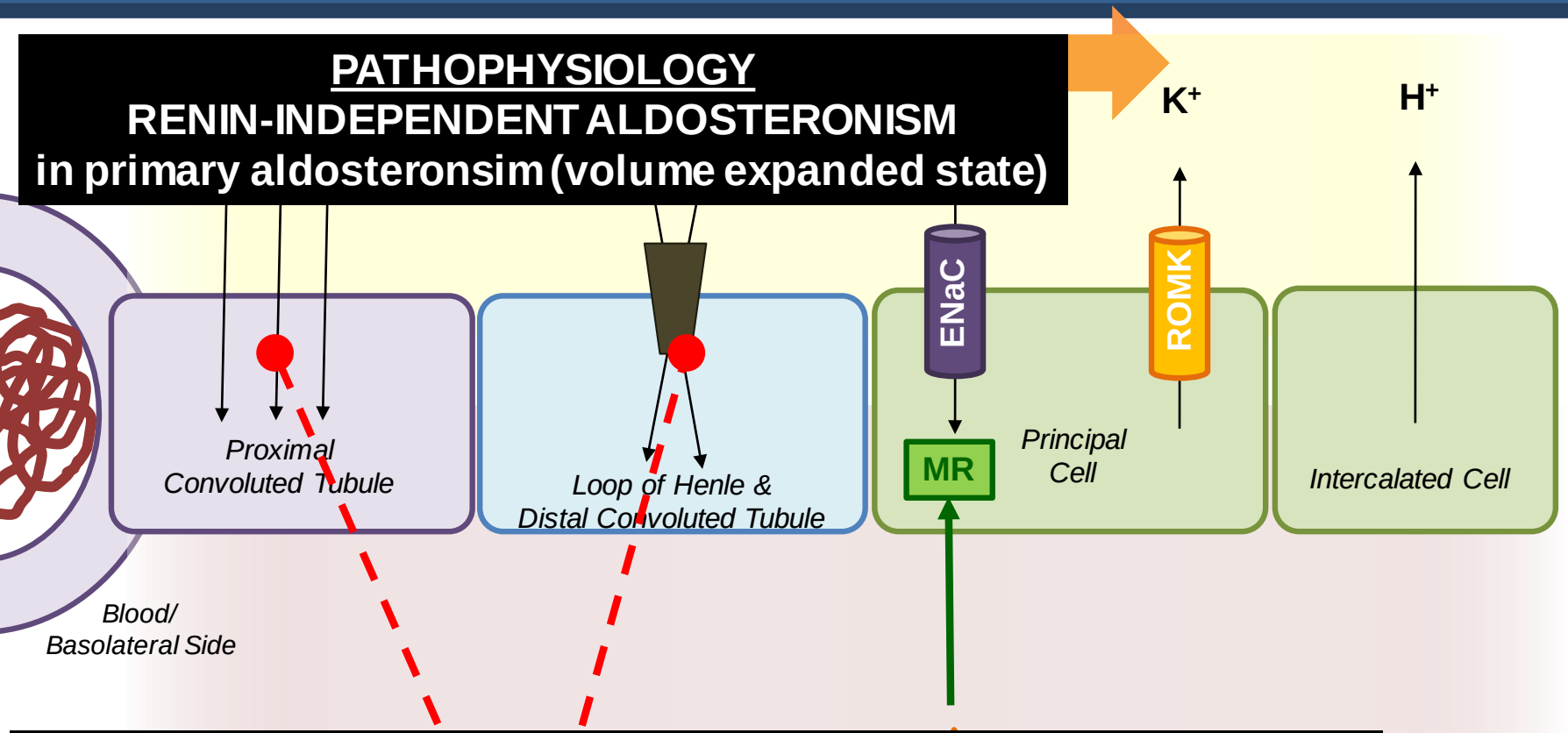
www.faunaparaguay.com

"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."

Bomback et al. JRAAS 2007
Ciolek et al. PNAS 2017

Pathophysiology: Primary Aldosteronism

PATHOPHYSIOLOGY
RENIN-INDEPENDENT ALDOSTERONISM
in primary aldosteronsim (volume expanded state)



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

Health Outcomes in PA PRE-Targeted Therapy

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

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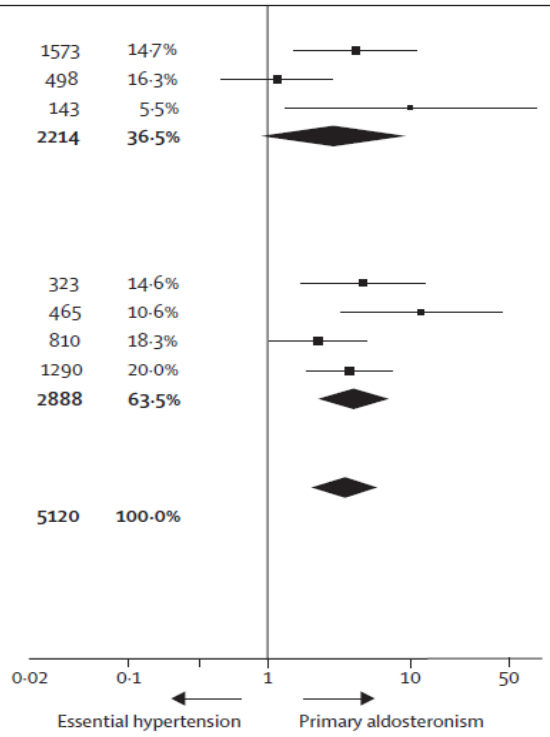
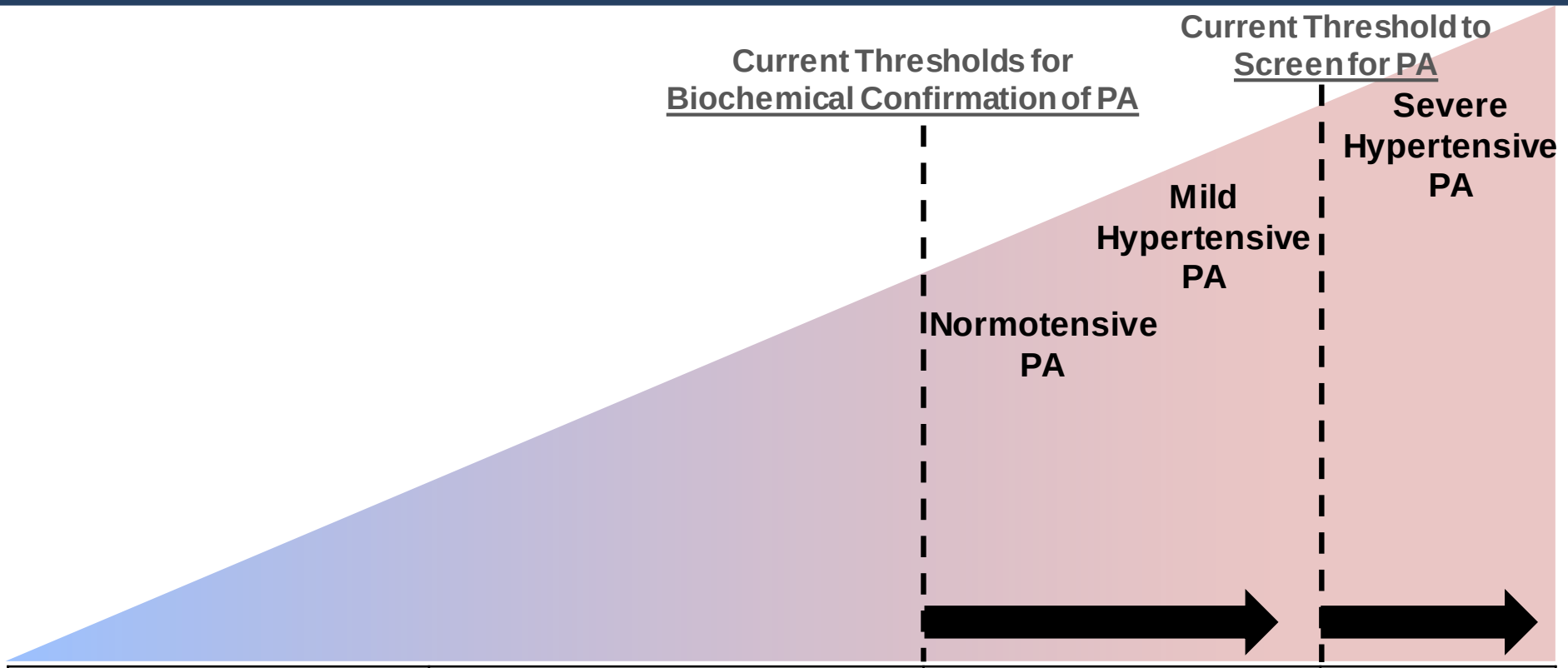
	Primary aldosteronism		Essential hypertension			OR (95% CI)
	Events	Total	Events	Total	Weight	
Not matched studies						
Monticone et al (2017)[21]	5	99	20	1573	14·7%	4·13 (1·52–11·25)
Murata et al (2017)[22]	8	292	12	498	16·3%	1·14 (0·46–2·82)
Rossi et al (2013)[26]	12	180	1	143	5·5%	10·13 (1·30–78·96)
Subtotal (95% CI)		**571**		**2214**	**36·5%**	**2·93 (0·91–9·47)**
Total events	25		33			
Heterogeneity: τ^2=0·66; χ^2=5·61, df=1 (p=0·06); I^2=64%						
Test for overall effect: Z=1·80 (p=0·07)						
Matched studies						
Catena et al (2008)[23]	7	54	10	323	14·6%	4·66 (1·69–12·84)
Milliez et al (2015)[24]	9	124	3	465	10·6%	12·05 (3·21–45·23)
Mulatero et al (2013)[14]	11	270	15	810	18·3%	2·25 (1·02–4·96)
Savard et al (2013)[12]	18	459	14	1290	20·0%	3·72 (1·83–7·54)
Subtotal (95% CI)		**907**		**2888**	**63·5%**	**4·01 (2·25–7·12)**
Total events	45		42			
Heterogeneity: τ^2=0·13; χ^2=4·77, df=3 (p=0·19); I^2=37%						
Test for overall effect: Z=4·72 (p<0·00001)			132			**3·52 (2·06–5·99)**
Total (95% CI)		**1478**		**5120**	**100·0%**	
Total events	70		75			
Heterogeneity: τ^2=0·24; χ^2=11·75, df=6 (p=0·07); I^2=49%						
Test for overall effect: Z=6·43 (p<0·00001)						
Test for subgroup differences: χ^2=0·22, df=1 (p=0·64); I^2=0%						



Monticone et al. Lancet D&E 2018; Savard et al. Hypertension 2013; Milliez et al. JACC 2005; Rossi et al. Hypertension 2006

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

Severity Spectrum of Primary Aldosteronism



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

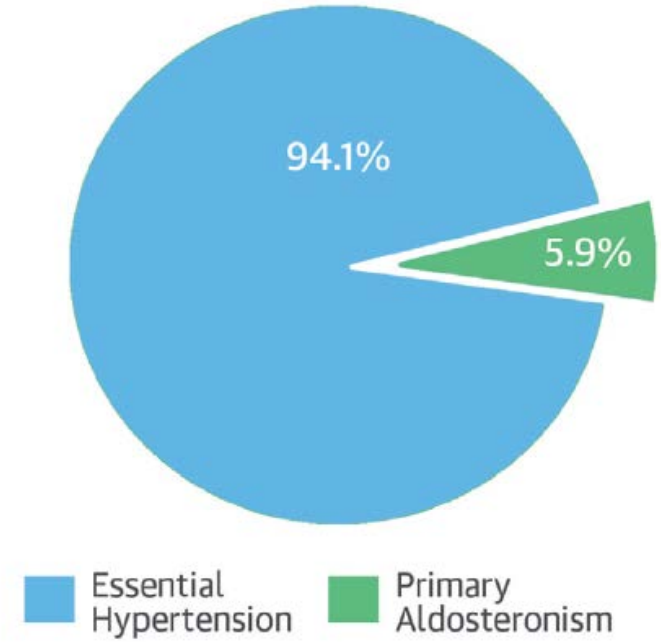
1672 consecutive Italian primary care HTNives on NO medications

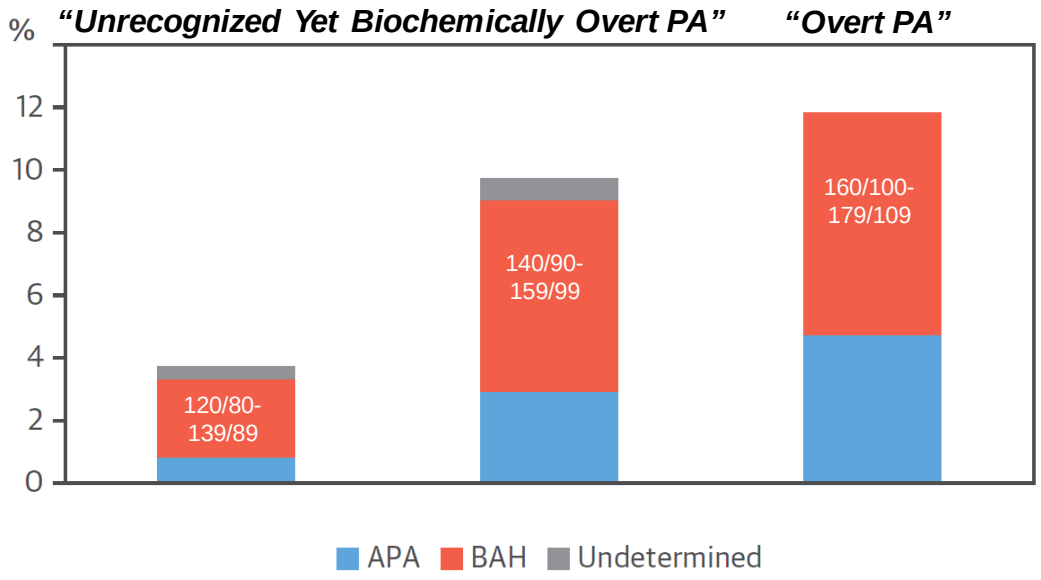
PA Screen

232 with positive PA screen

Confirmatory Testing

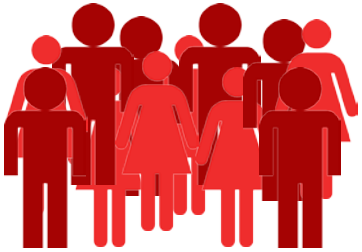
99 with confirmed PA





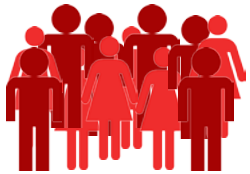
Monticone et al. JACC 2017

Unrecognized Yet Biochemically Overt Primary Aldosteronism



609 Chilean HTNives

PA Screen

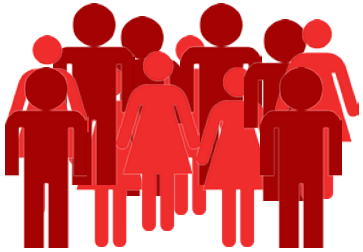


63 with positive PA screen

Confirmatory Testing

37 with confirmed PA
6.1% TOTAL
2% Stage I
8% stage II
13% Stage III

Mosso et al. Hypertension 2003



241 American <u>STAGE 1 HTNives</u> on NO treatment

PA Screen

79 with positive PA screen

Confirmatory Testing

48 with confirmed PA
19% TOTAL

Baudrand et al. JCEM 2016

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

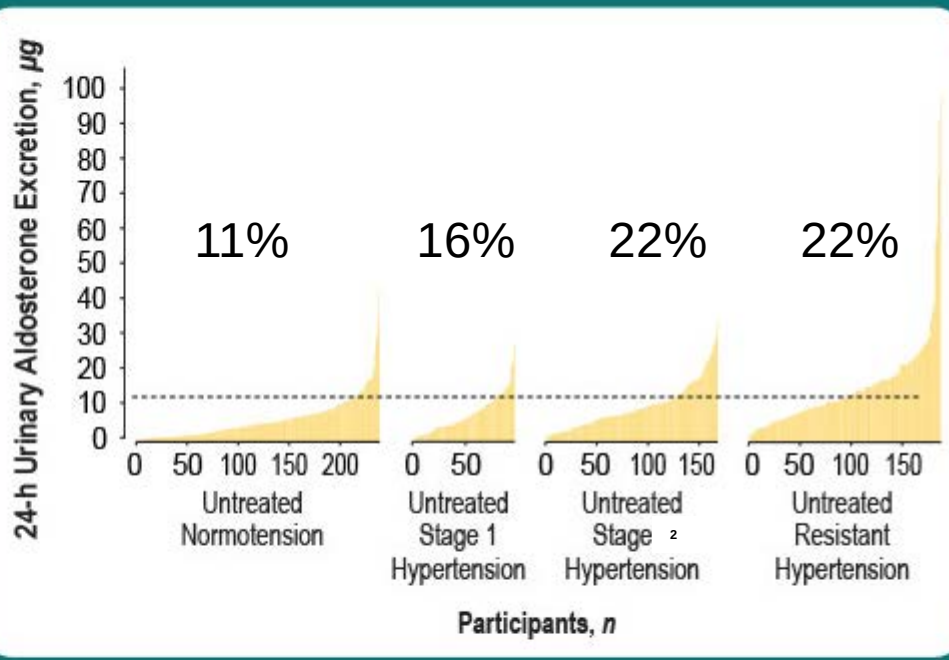
OR=18.4 (3.7, 90.1)

Markou et al. JCEM 2013

Unrecognized Prevalence of Primary Aldosteronism

n=1015 participants completed an oral sodium suppression test

Magnitude of renin-independent aldosterone production

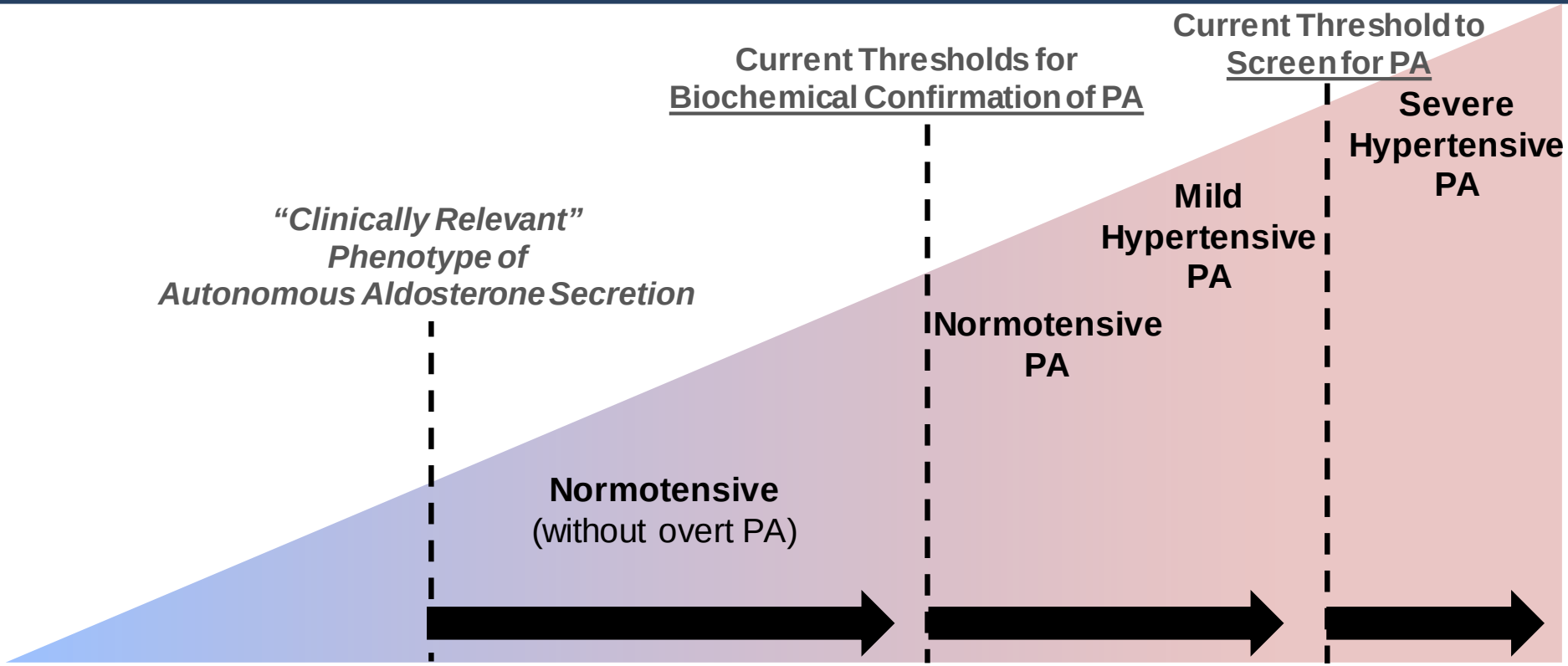


- Continuum of renin-independent aldosterone production parallels blood pressure severity
- Primary aldosteronism prevalence is high

Sensitivity of the ARR was poor at detecting biochemically overt PA

Brown et al. Annals of Int Med 2020

Severity Spectrum of Primary Aldosteronism

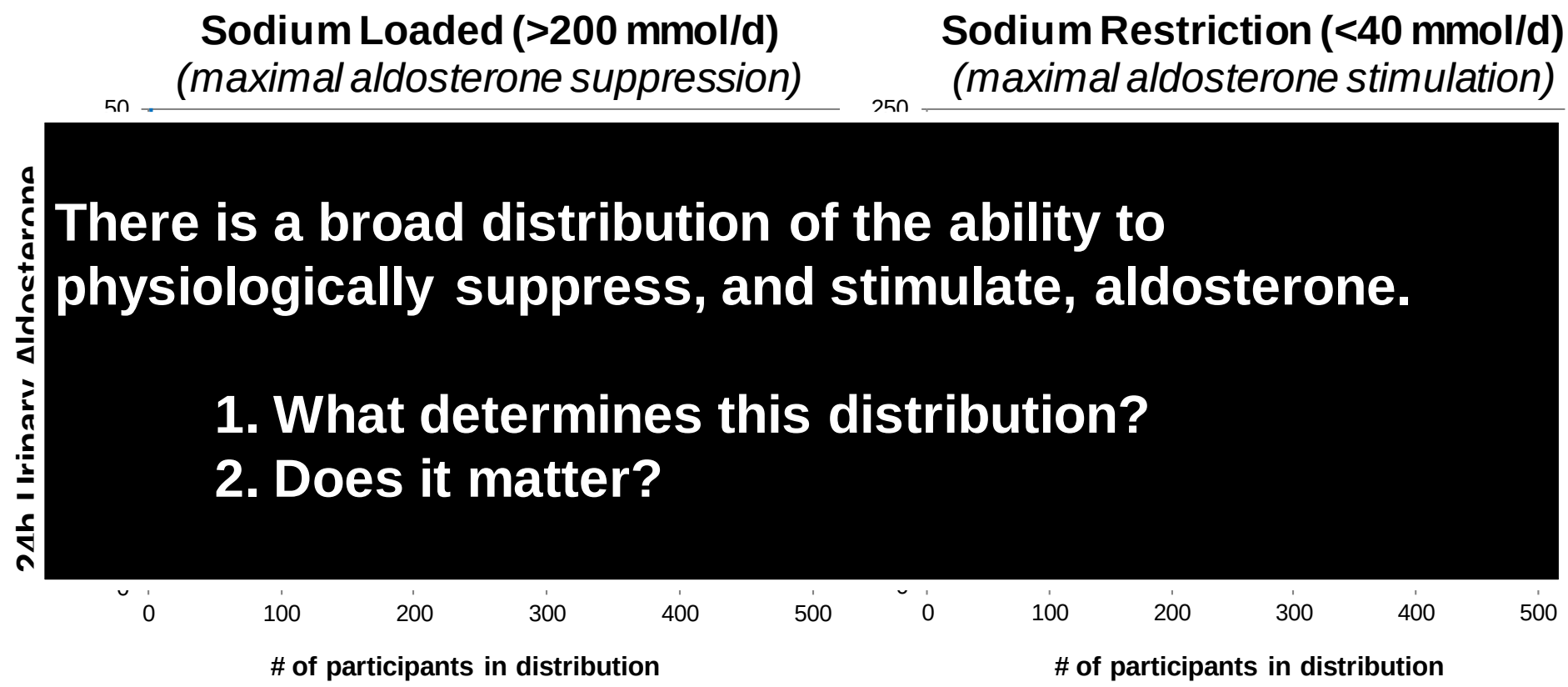


DISEASE		Unrecognized Yet Biochemically Overt PA	Overt PA
Obvious Clinical Syndrome of Excessive MR Activation?		NO	YES
Biochemical Confirmation of PA		YES	YES
Cardiovascular Risk			*Highest*

Brown et al. *Annals of Internal Medicine* 2017

Inappropriate/Dysregulated Secretion of Aldosterone

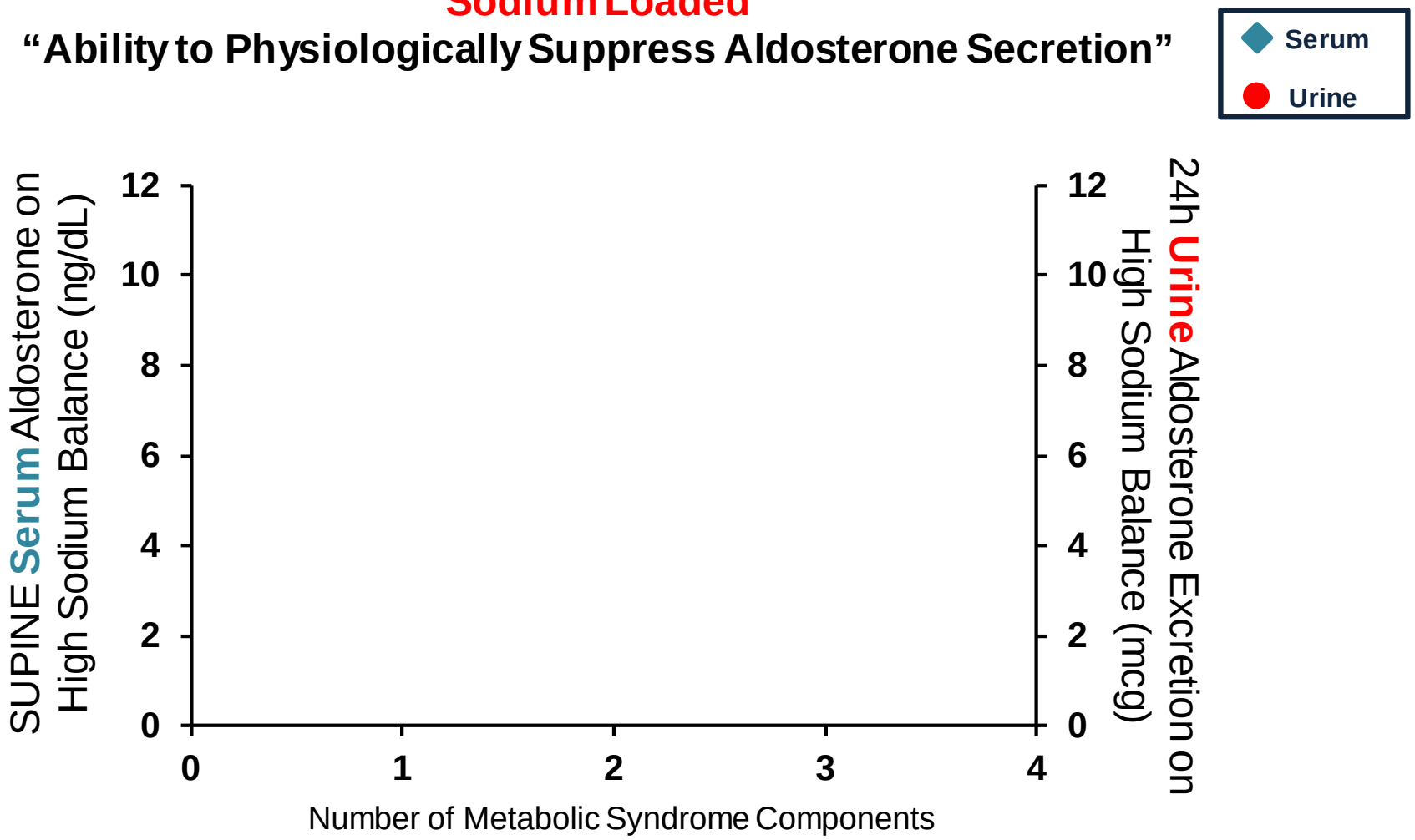
Aldosterone Dysregulation



There is a broad distribution of the ability to physiologically suppress, and stimulate, aldosterone.

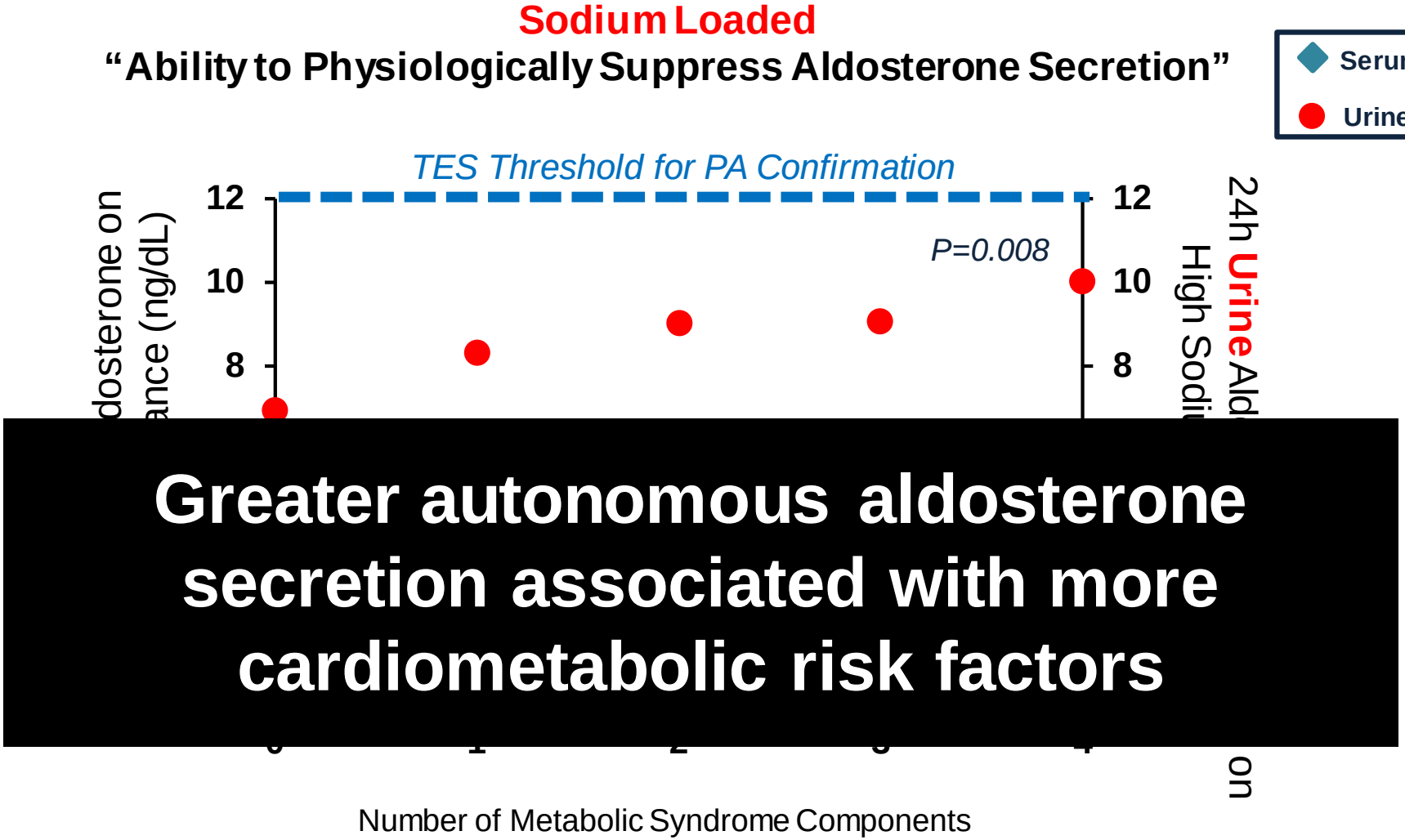
1. **What determines this distribution?**
2. **Does it matter?**

Aldosterone Dysregulation



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

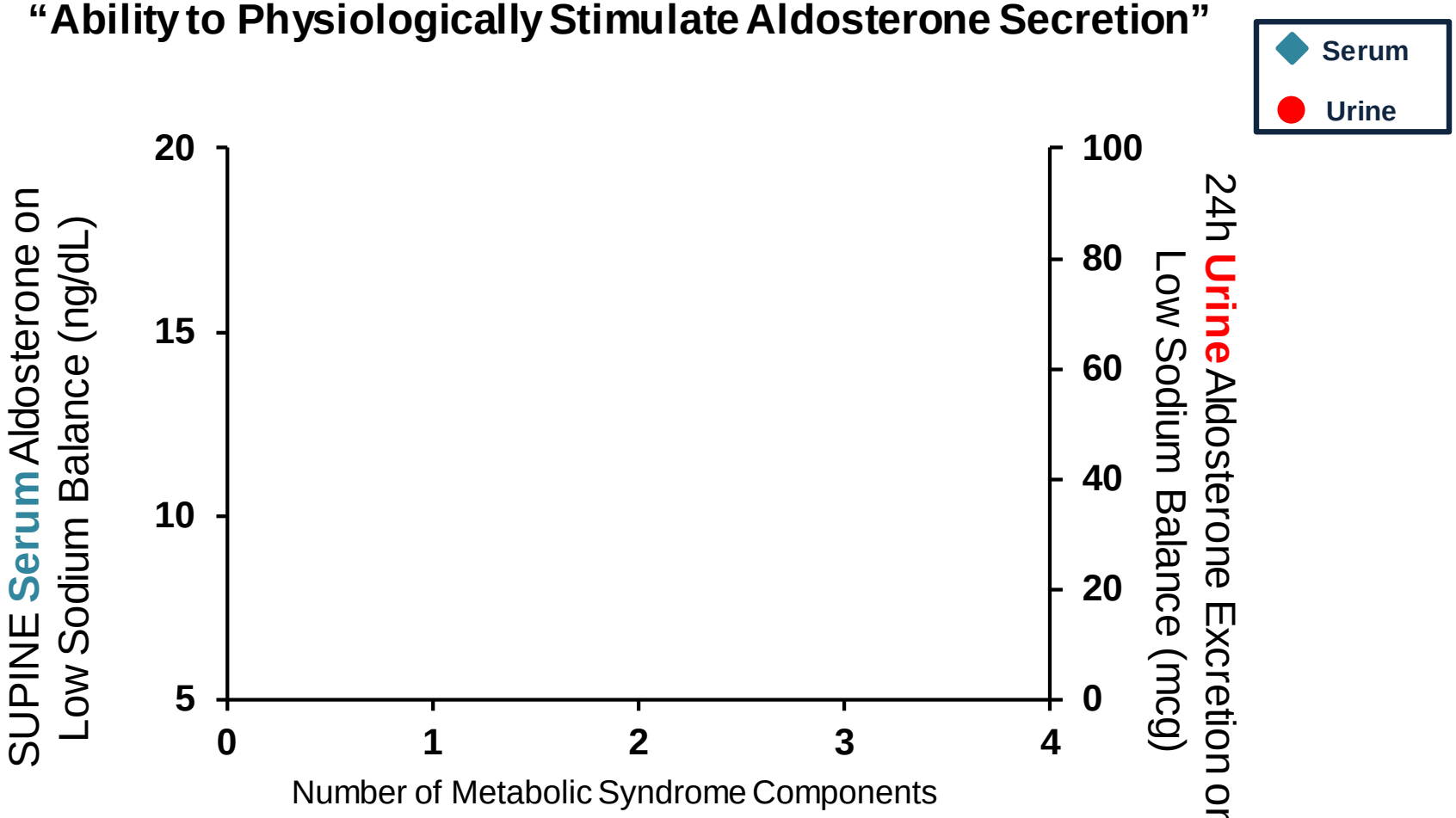
Aldosterone Dysregulation



Greater autonomous aldosterone secretion associated with more cardiometabolic risk factors

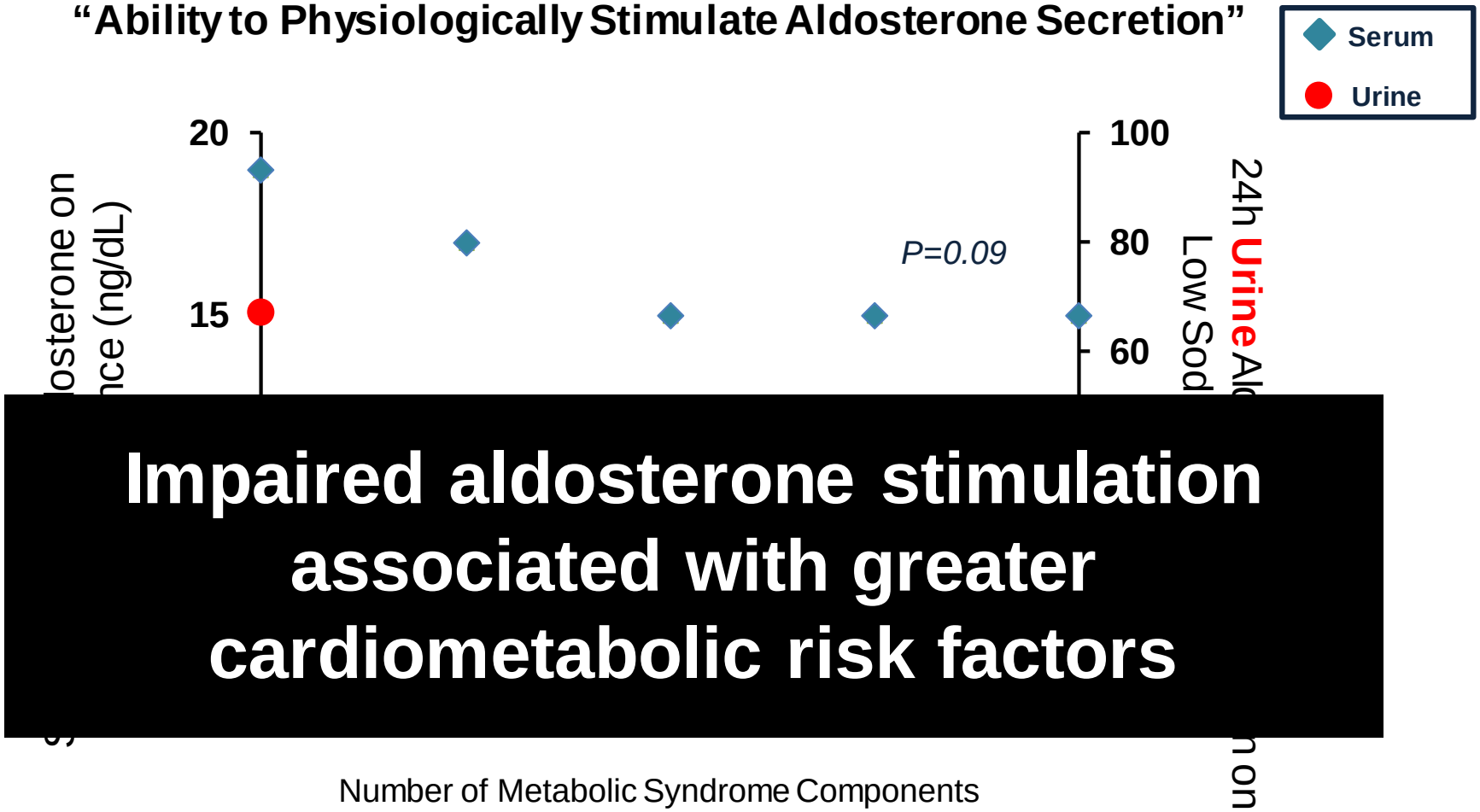
Vaidya et al. Hypertension 2013
Brown et al. Hypertension 2014

Aldosterone Dysregulation



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

Aldosterone Dysregulation



Impaired aldosterone stimulation associated with greater cardiometabolic risk factors

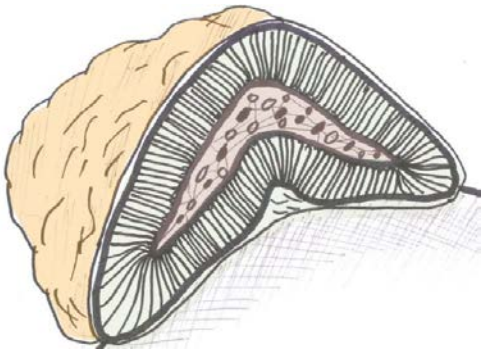
Vaidya et al. Hypertension 2013
Brown et al. Hypertension 2014

Aldosterone Dysregulation

Suppressibility when Sodium Loaded

ABNORMAL

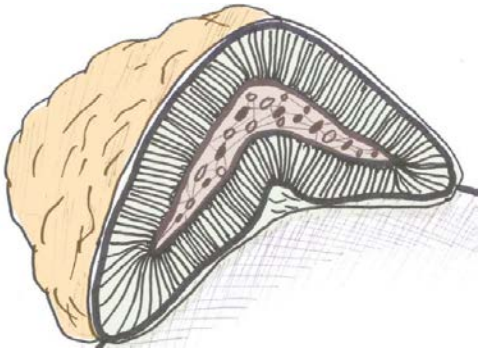
PHYSIOLOGIC



Stimulation when Sodium Restricted

PHYSIOLOGIC

ABNORMAL



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

Renin Suppression:
A Biomarker for MR Activity

Renin Suppression: A Crude 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"

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Temple University,
Philadelphia,
Pennsylvania 19140,
U.S.A.

E. VICTOR ADLIN.

Renin Suppression: A Crude Biomarker for MR Activity

PLASMA-RENIN AND BLOOD-PRESSURE

THE LANCET, MARCH 22, 1975

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

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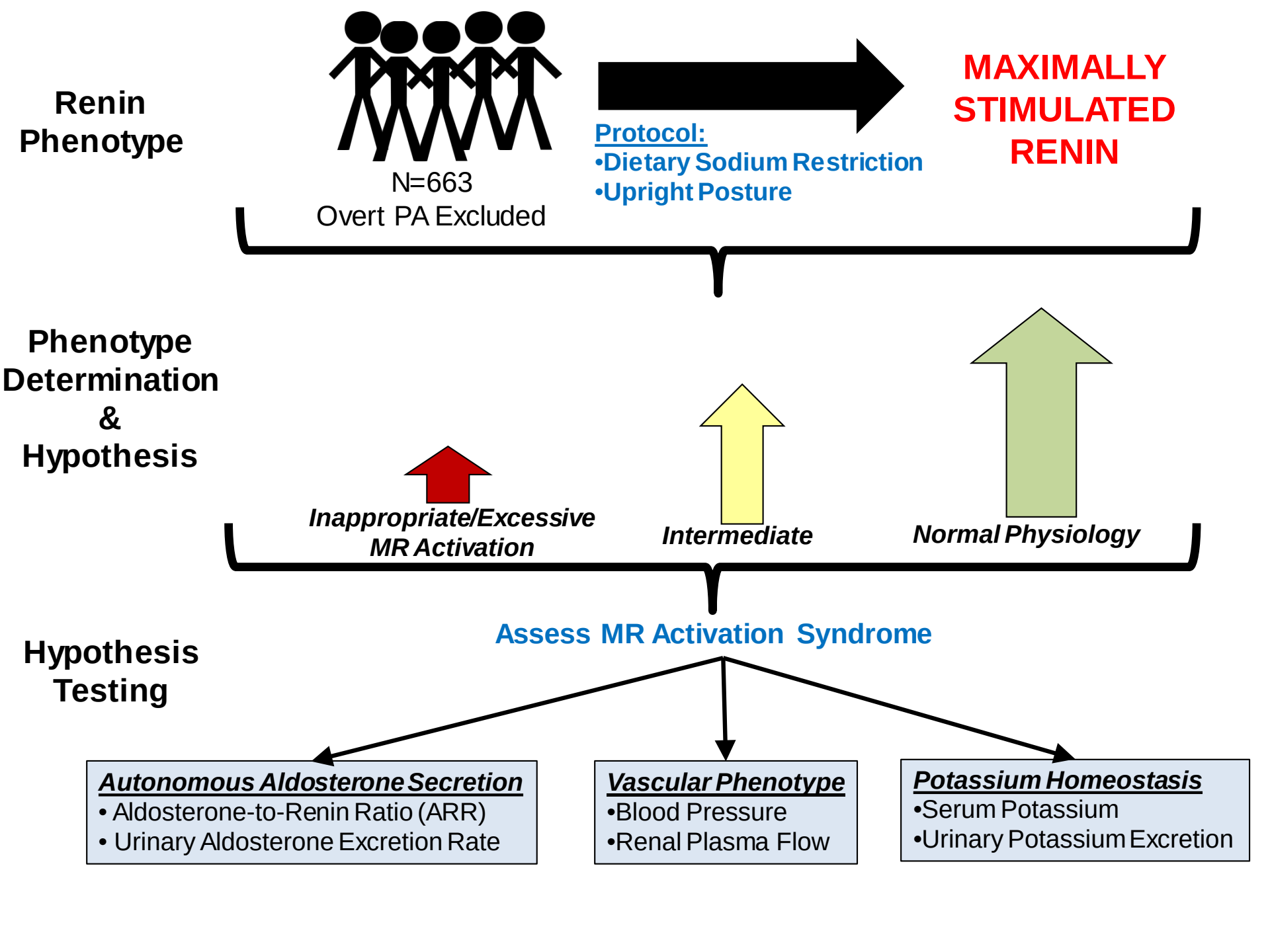
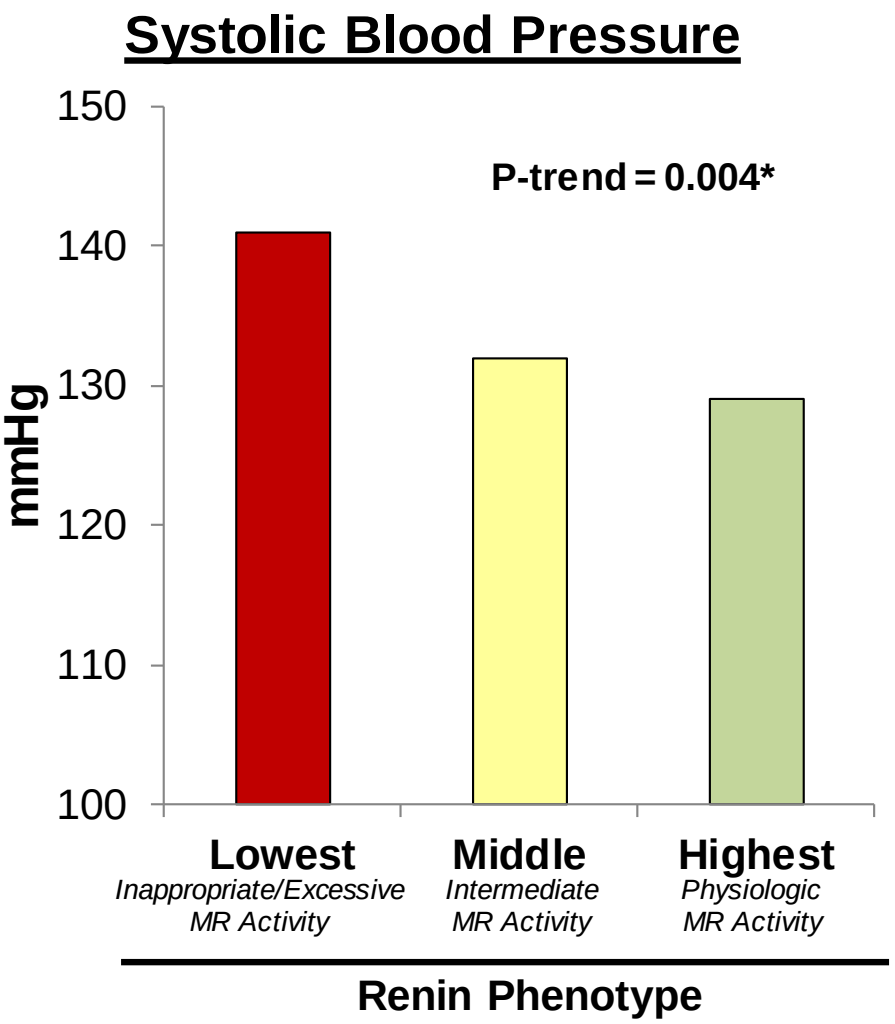
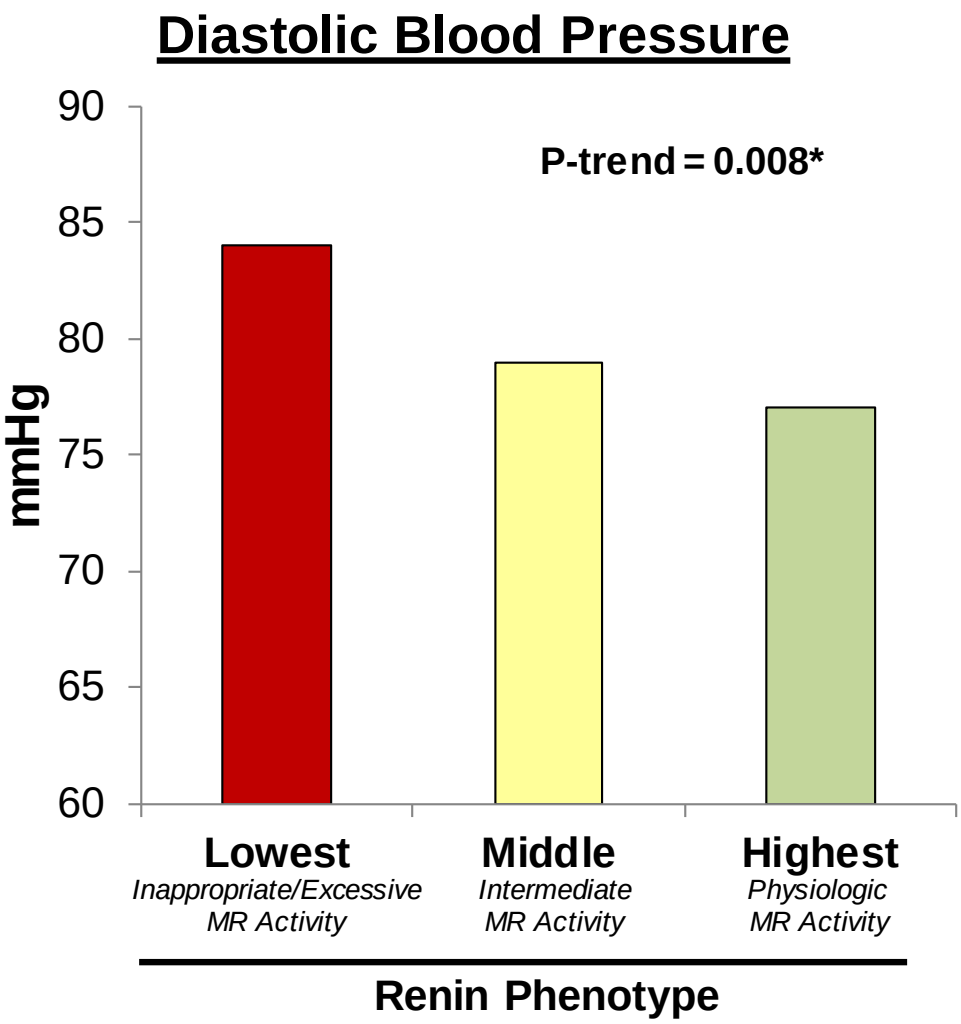

Renin Phenotype
N=663
Overt PA Excluded
Protocol:
•Dietary Sodium Restriction
•Upright Posture
MAXIMALLY STIMULATED RENIN
Phenotype Determination & Hypothesis
Inappropriate/Excessive MR Activation
Intermediate
Normal Physiology
Hypothesis Testing
Assess MR Activation Syndrome
Autonomous Aldosterone Secretion
• Aldosterone-to-Renin Ratio (ARR)
• Urinary Aldosterone Excretion Rate
Vascular Phenotype
•Blood Pressure
•Renal Plasma Flow
Potassium Homeostasis
•Serum Potassium
•Urinary Potassium Excretion

Renin Suppression: A Biomarker for MR Activity

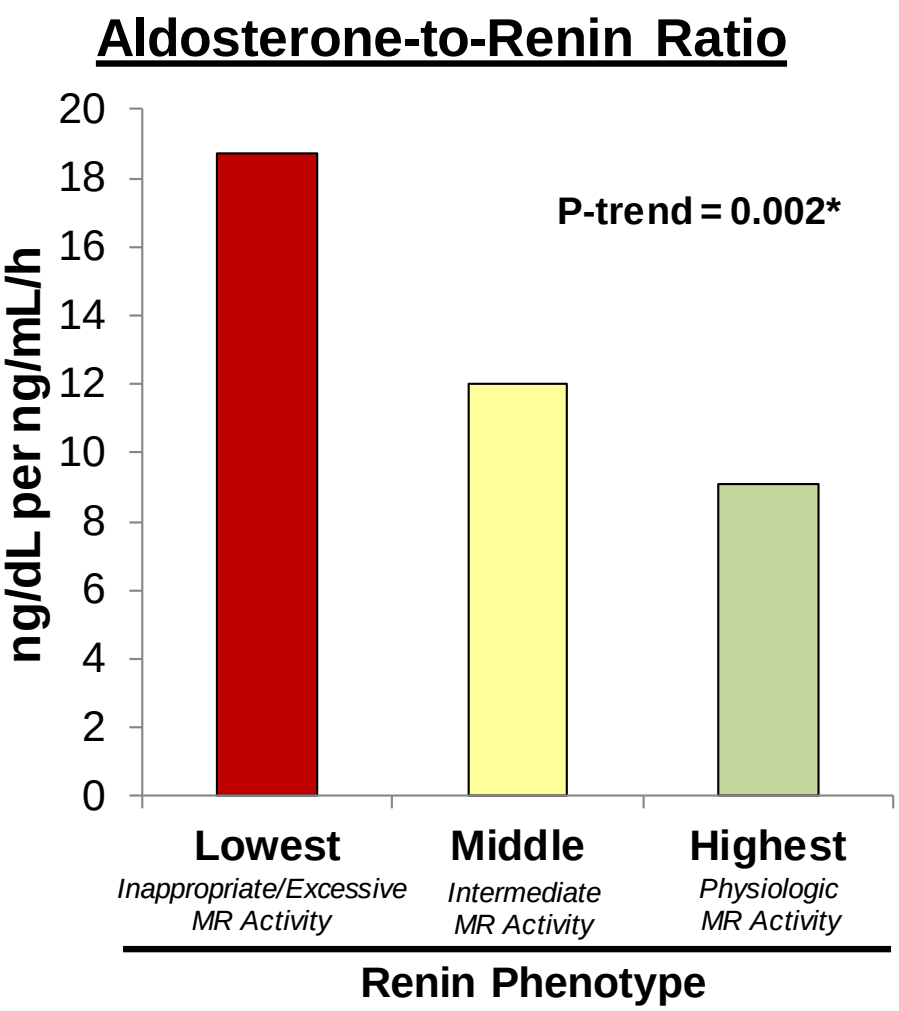


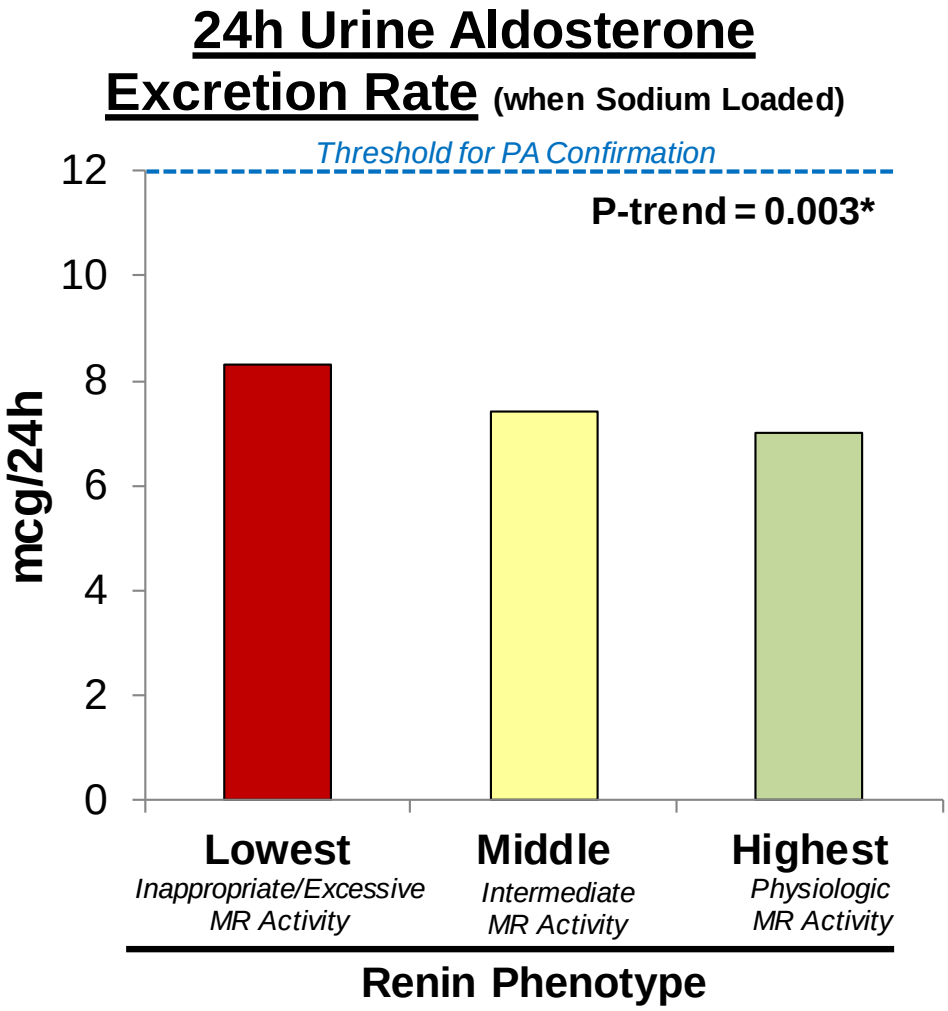


*Adjusted for age, sex, race, BMI, diabetes mellitus, Cr and 24hr U_{Na}

Hundemer et al. JCEM 2017

Renin Suppression: A Biomarker for MR Activity

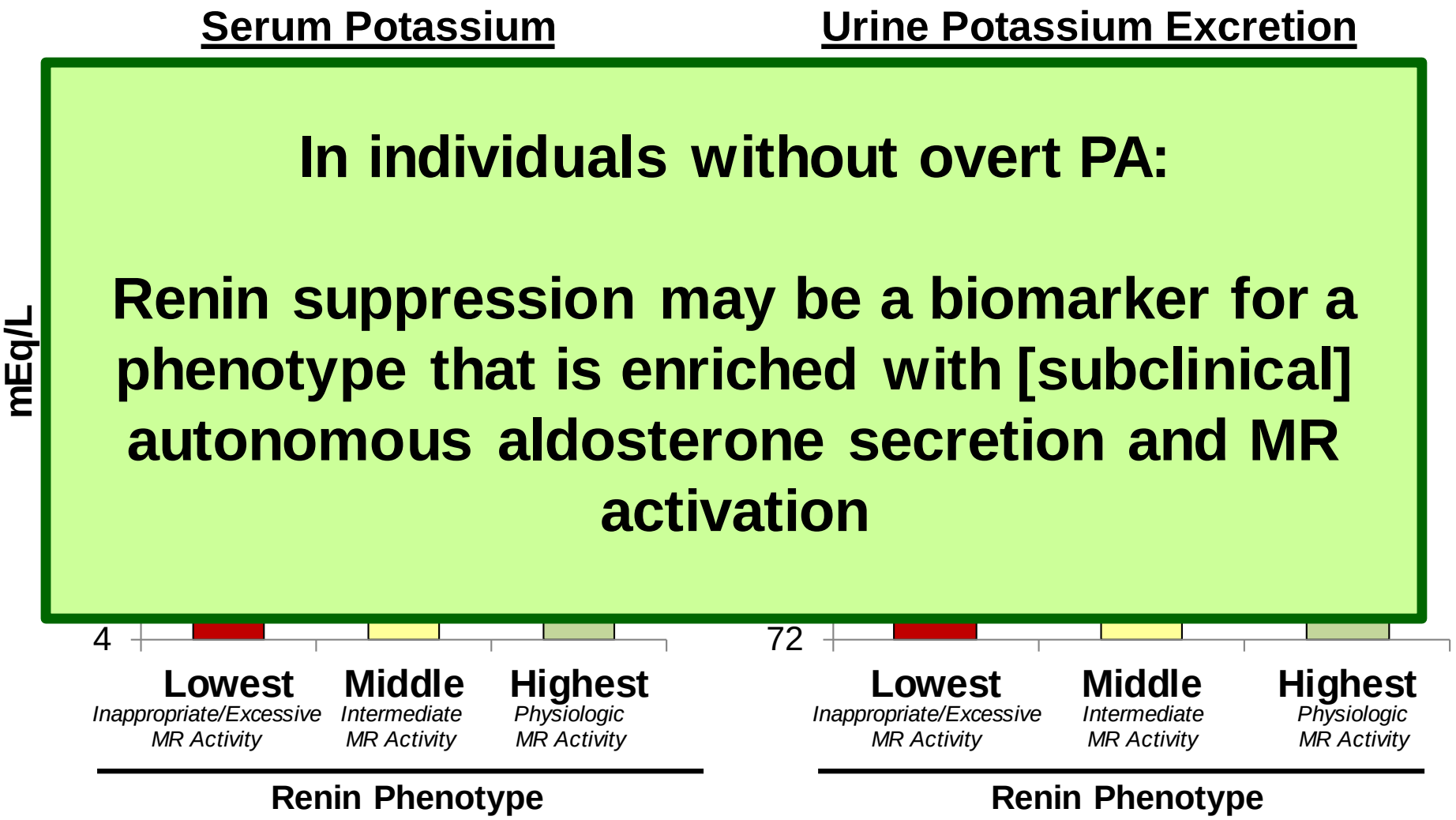




*Adjusted for age, sex, race, BMI, diabetes mellitus, Cr and 24hr U_{Na}

Hundemer et al. JCEM 2017

Renin Suppression: A Biomarker for MR Activity



*Adjusted for age, sex, race, BMI, diabetes mellitus, Cr and 24hr U_{Na}

Renin Suppression: A Crude Biomarker for MR Activity

PLASMA RENIN AND BLOOD PRESSURE

fe
or
m
ar
su

bl
interest.

Continuum of Renin-Independent Aldosteronism in Normotension

Is this a continuum of physiology or pathophysiology?

What is the relevance to human health?

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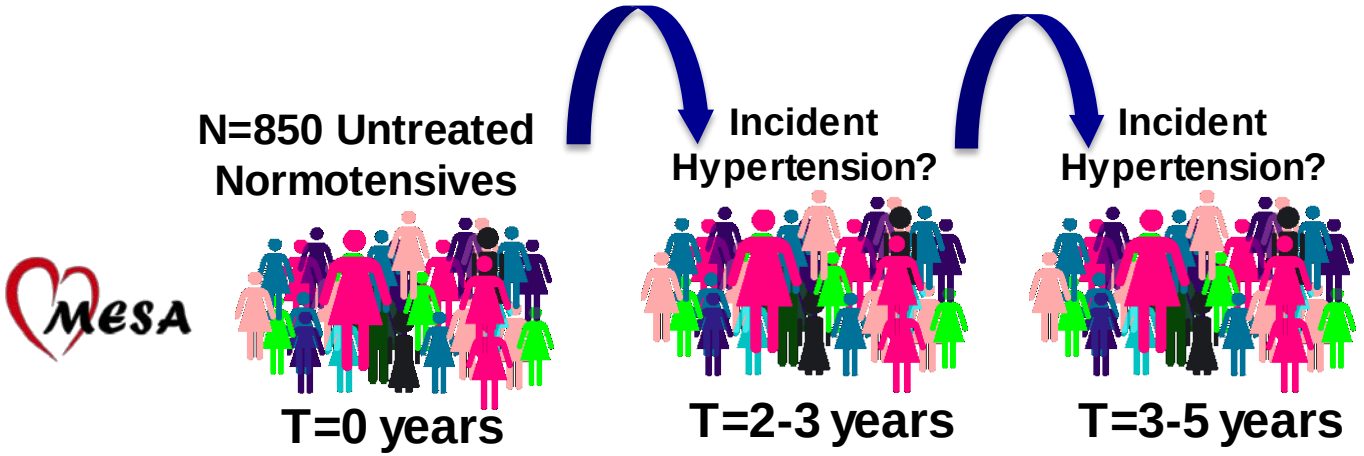
Longitudinal Cohort Study

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??

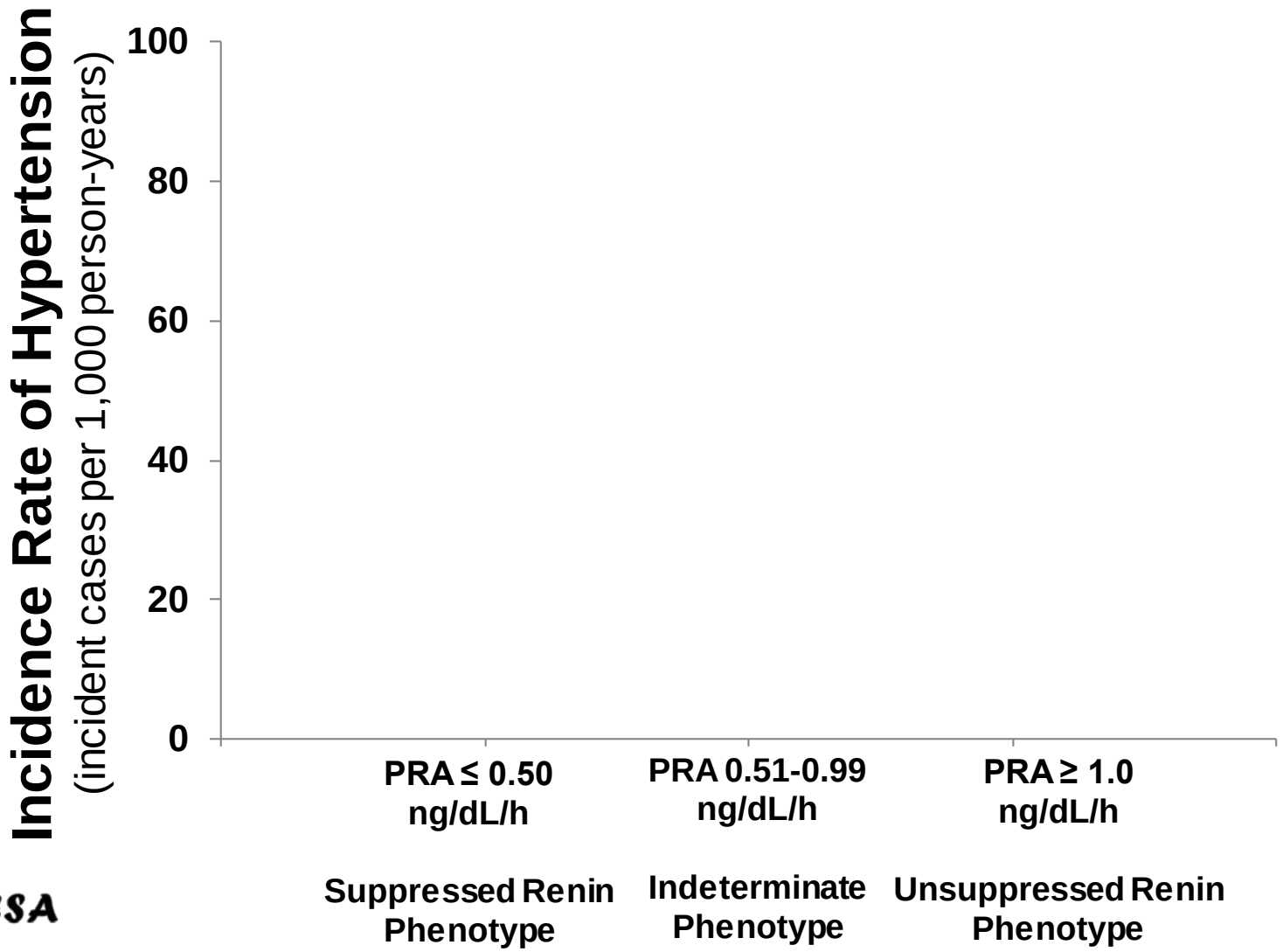
Indeterminate Renin Phenotype: PRA 0.51-0.99 ng/dL/h

Unsuppressed Renin Phenotype: PRA ≥ 1.0 ng/dL/h

- Enriched with Renin-Dependent Aldosterone Secretion and Physiologic MR Activity??

Brown et al. *Annals of Internal Medicine* 2017

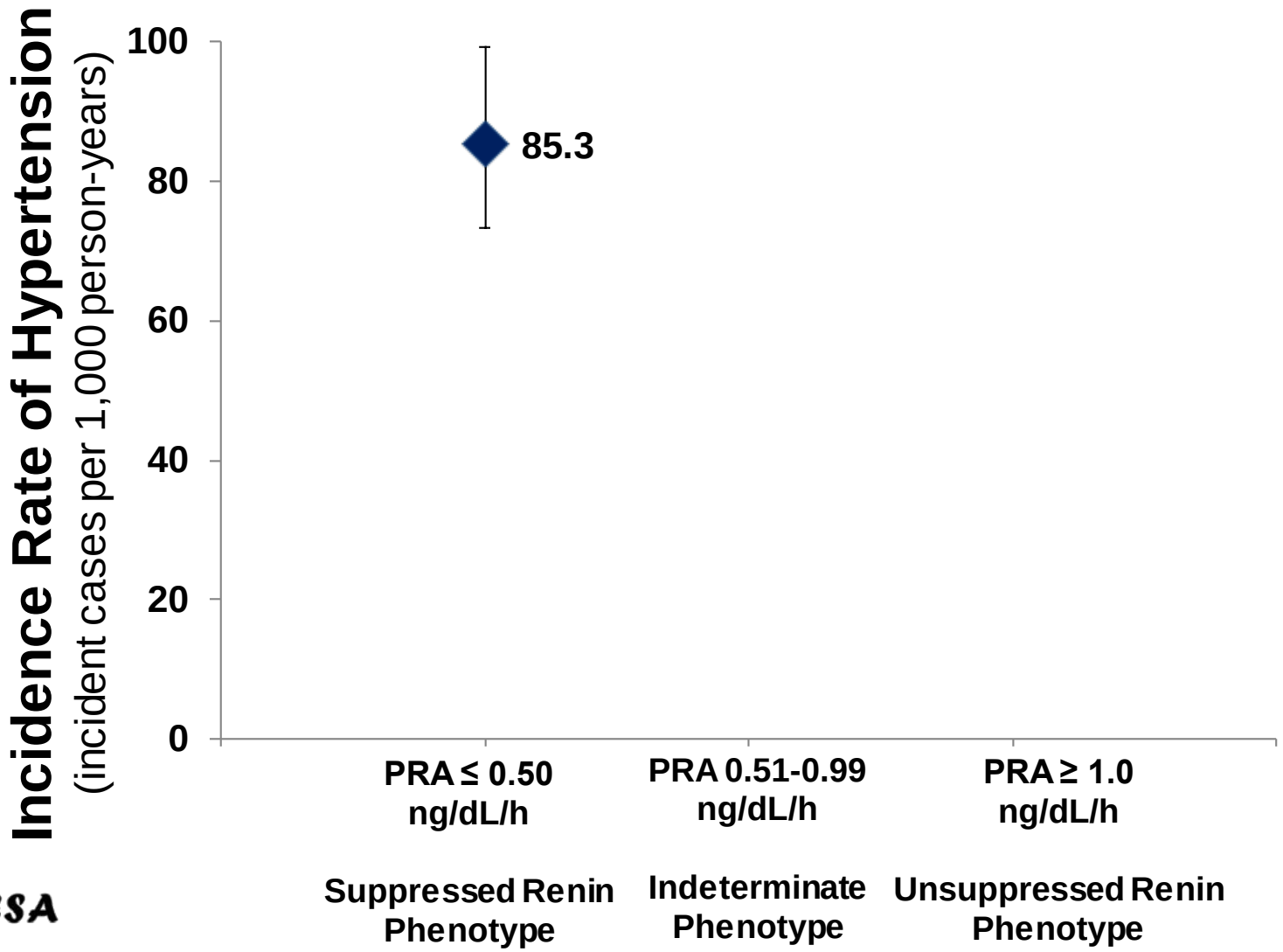
Renin Phenotype and Incident Hypertension



MESA

Brown et al. *Annals of Internal Medicine* 2017

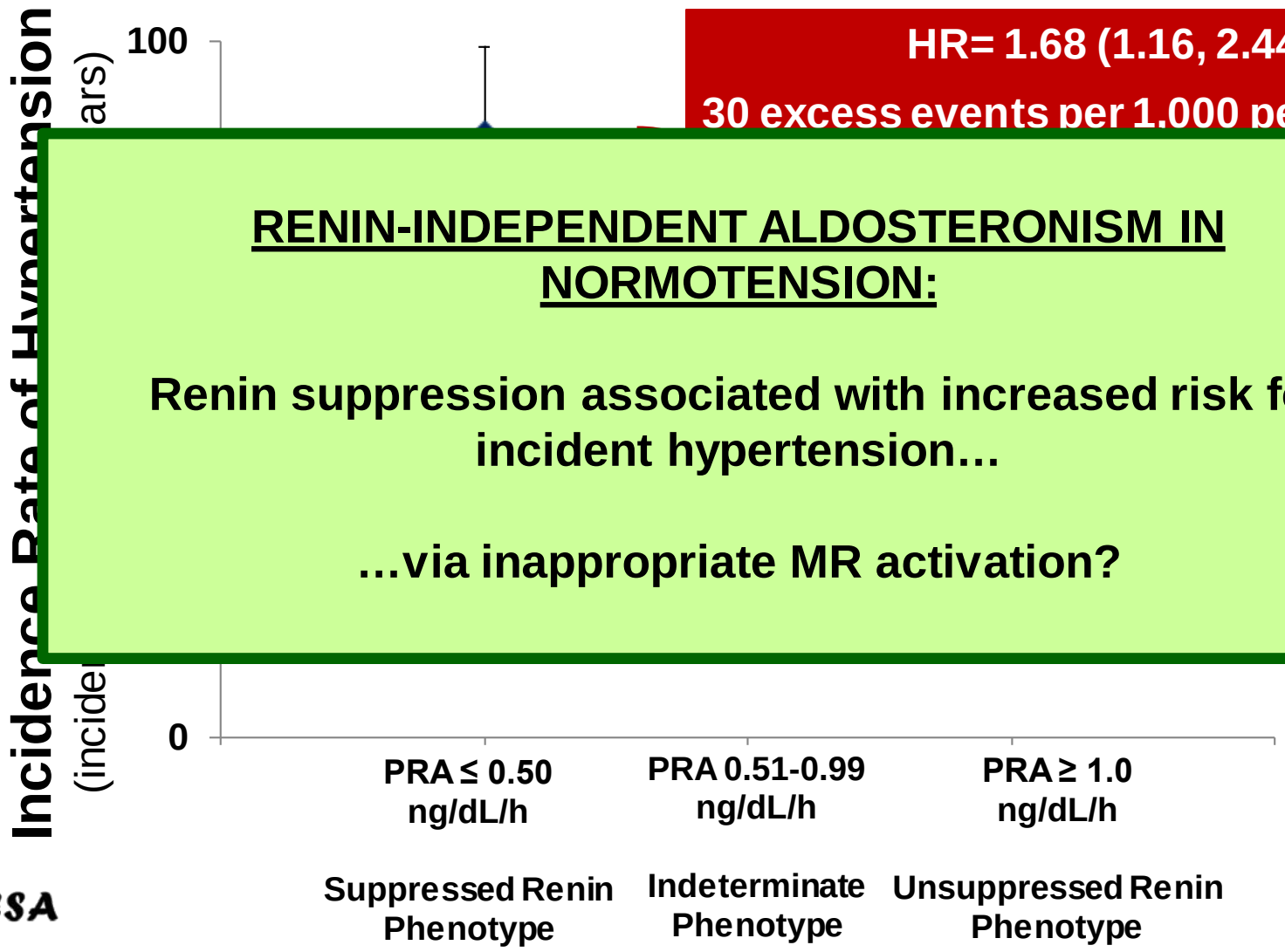
Renin Phenotype and Incident Hypertension



MESA

Brown et al. *Annals of Internal Medicine* 2017

Renin Phenotype and Incident Hypertension



RENIN-INDEPENDENT ALDOSTERONISM IN NORMOTENSION:

Renin suppression associated with increased risk for incident hypertension…

…via inappropriate MR activation?

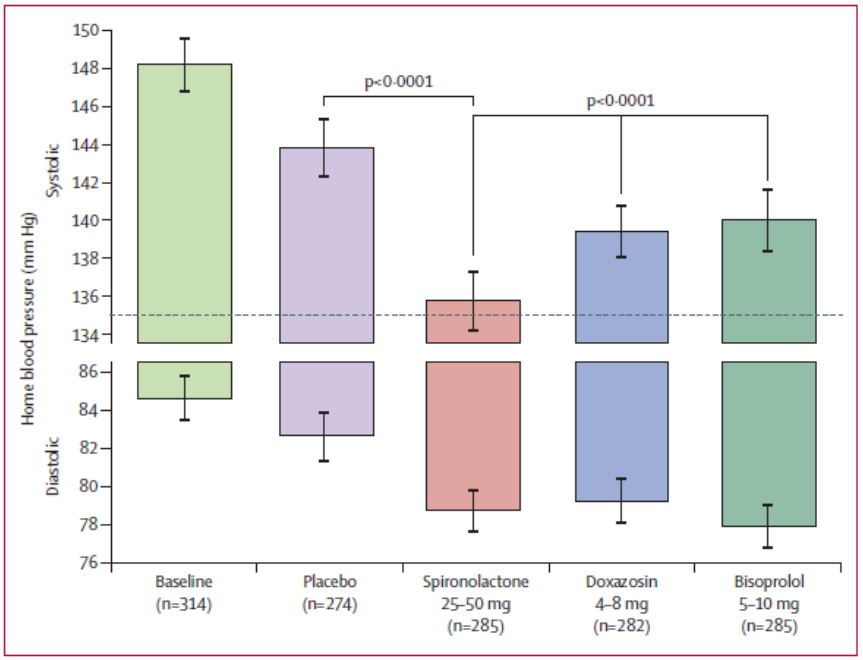
MESA

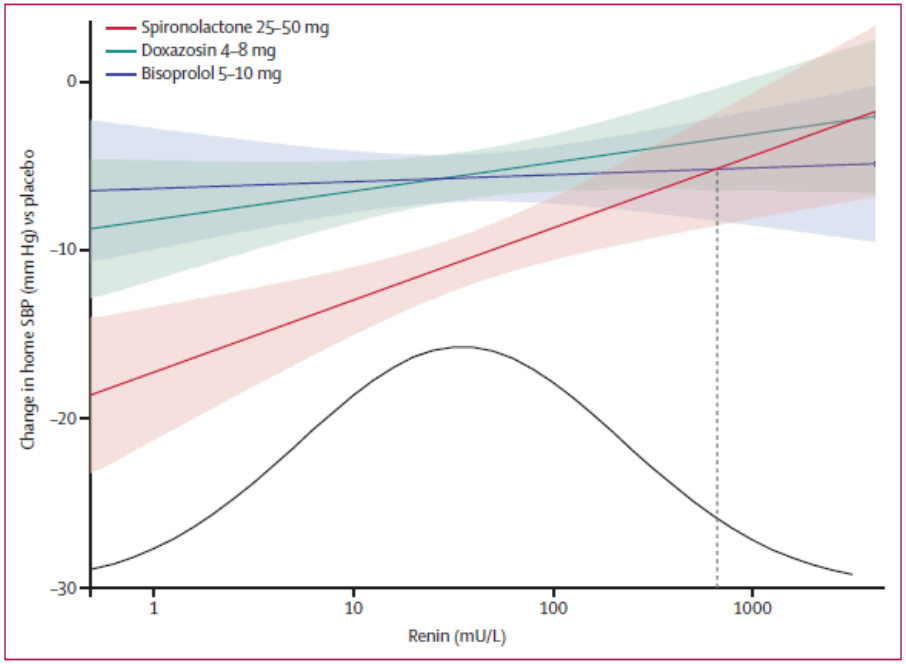
Brown et al. *Annals of Internal Medicine* 2017

MR-Mediated Hypertension

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?

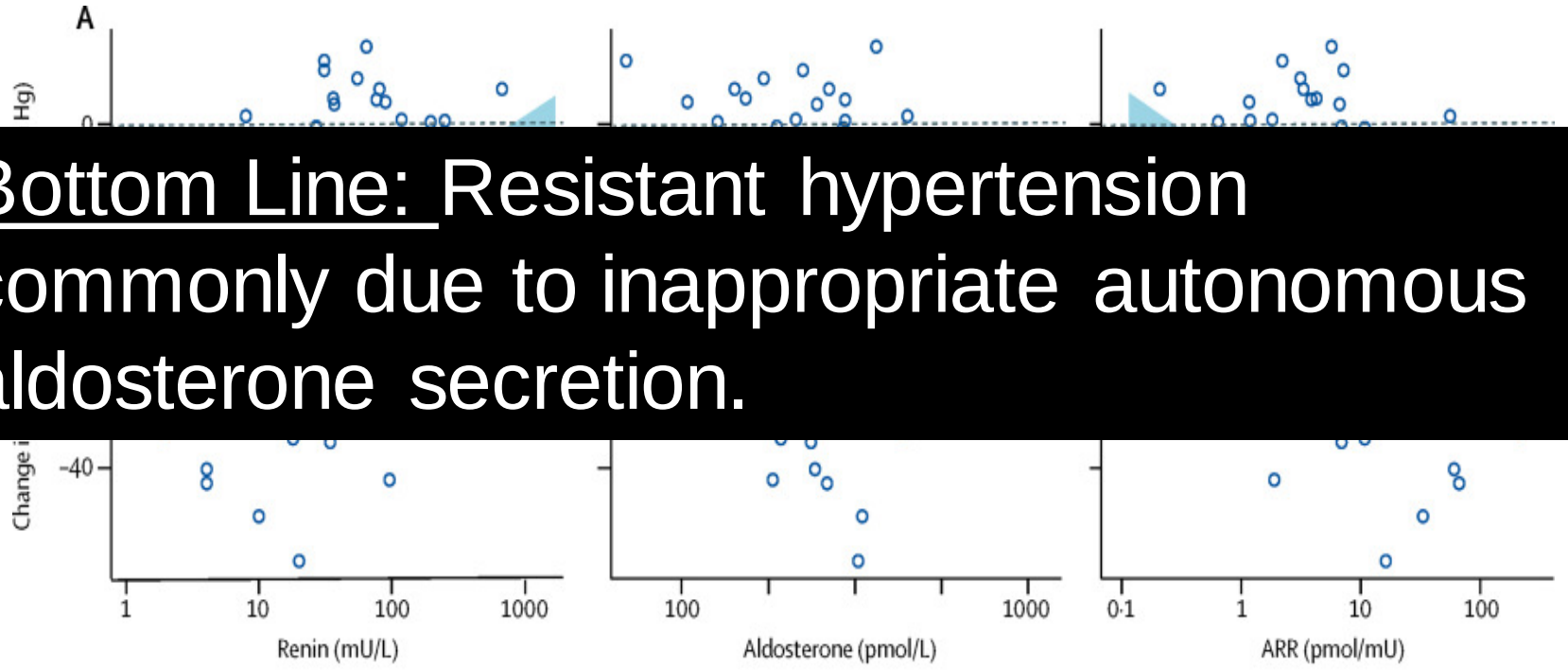




Williams et al. Lancet 2015

PATHWAY-2 Trial

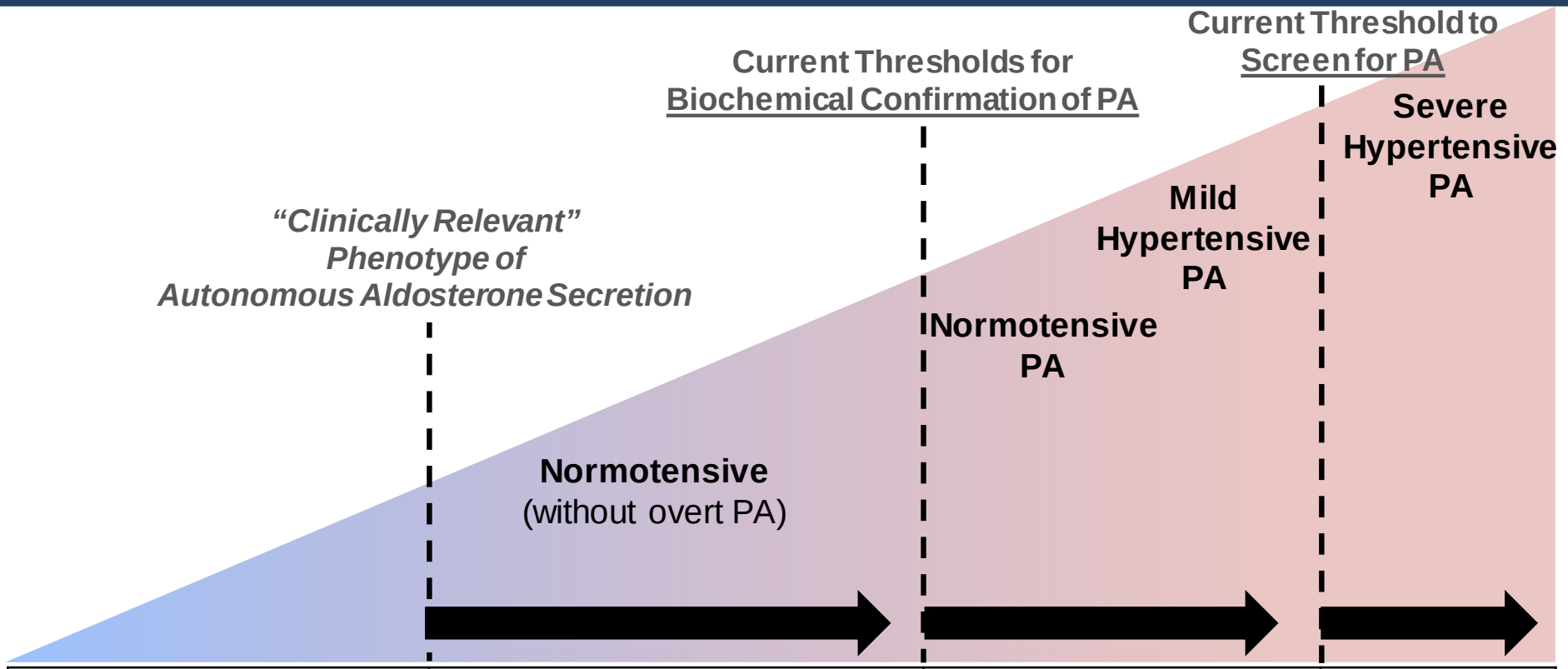
Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies



Bottom Line: Resistant hypertension commonly due to inappropriate autonomous aldosterone secretion.

Williams et al. Lancet D+E 2018

Severity Spectrum of Primary Aldosteronism



DISEASE	Subclinical Primary Aldosteronism	Unrecognized Yet Biochemically Overt PA	Overt PA
Obvious Clinical Syndrome of Excessive MR Activation?	NO	NO	YES
Biochemical Confirmation of PA	NO	YES	YES
Cardiovascular Risk	????		*Highest*

Brown et al. *Annals of Internal Medicine* 2017

Part 3: How Should Primary Aldosteronism Be Treated?

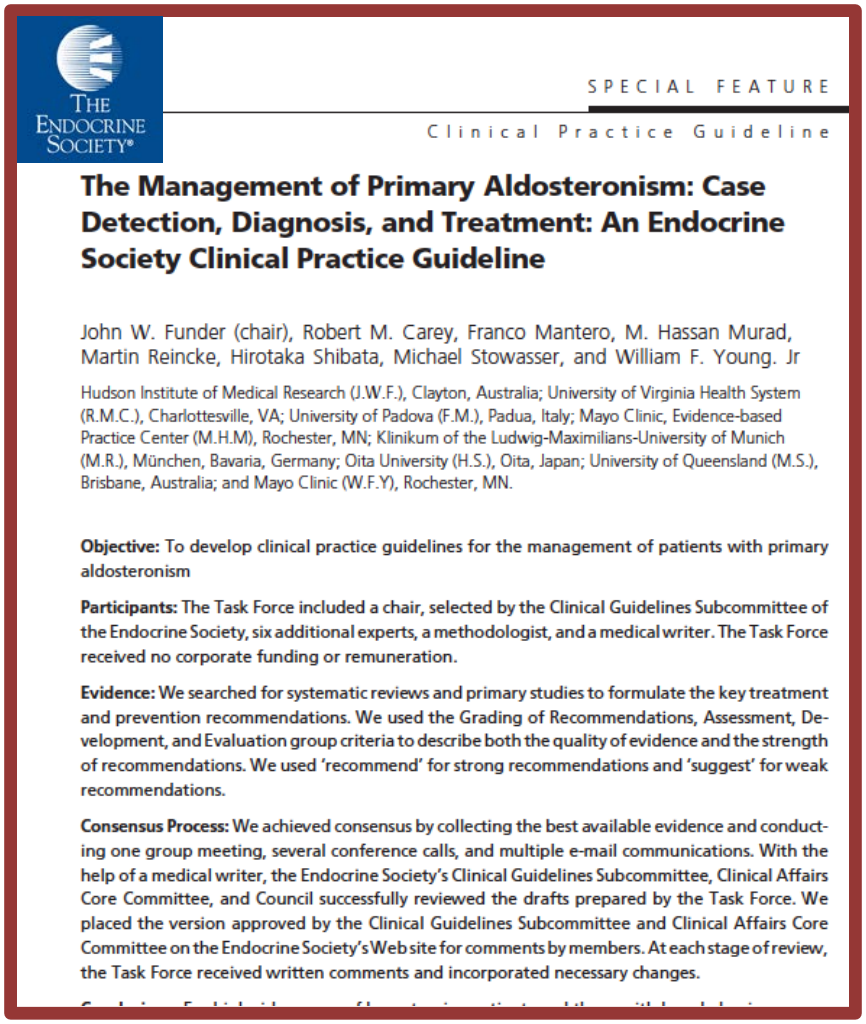
How Should Primary Aldosteronism Be Treated?

CLINICAL VIGNETTE

- **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?**

How Should Primary Aldosteronism Be Treated?



THE ENDOCRINE SOCIETY®

SPECIAL FEATURE

Clinical Practice Guideline

The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline

John W. Funder (chair), Robert M. Carey, Franco Mantero, M. Hassan Murad, Martin Reincke, Hirotaka Shibata, Michael Stowasser, and William F. Young. Jr

Hudson Institute of Medical Research (J.W.F.), Clayton, Australia; University of Virginia Health System (R.M.C.), Charlottesville, VA; University of Padova (F.M.), Padua, Italy; Mayo Clinic, Evidence-based Practice Center (M.H.M), Rochester, MN; Klinikum of the Ludwig-Maximilians-University of Munich (M.R.), München, Bavaria, Germany; Oita University (H.S.), Oita, Japan; University of Queensland (M.S.), Brisbane, Australia; and Mayo Clinic (W.F.Y), Rochester, MN.

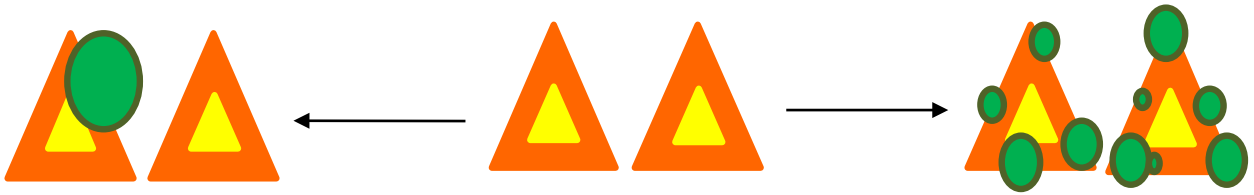
Objective: To develop clinical practice guidelines for the management of patients with primary aldosteronism

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

Treatment
1) Na^+ Restriction AND
2) Lifelong Mineralocorticoid Receptor Antagonist to normalize BP and K^+

***Level 1 evidence lacking**

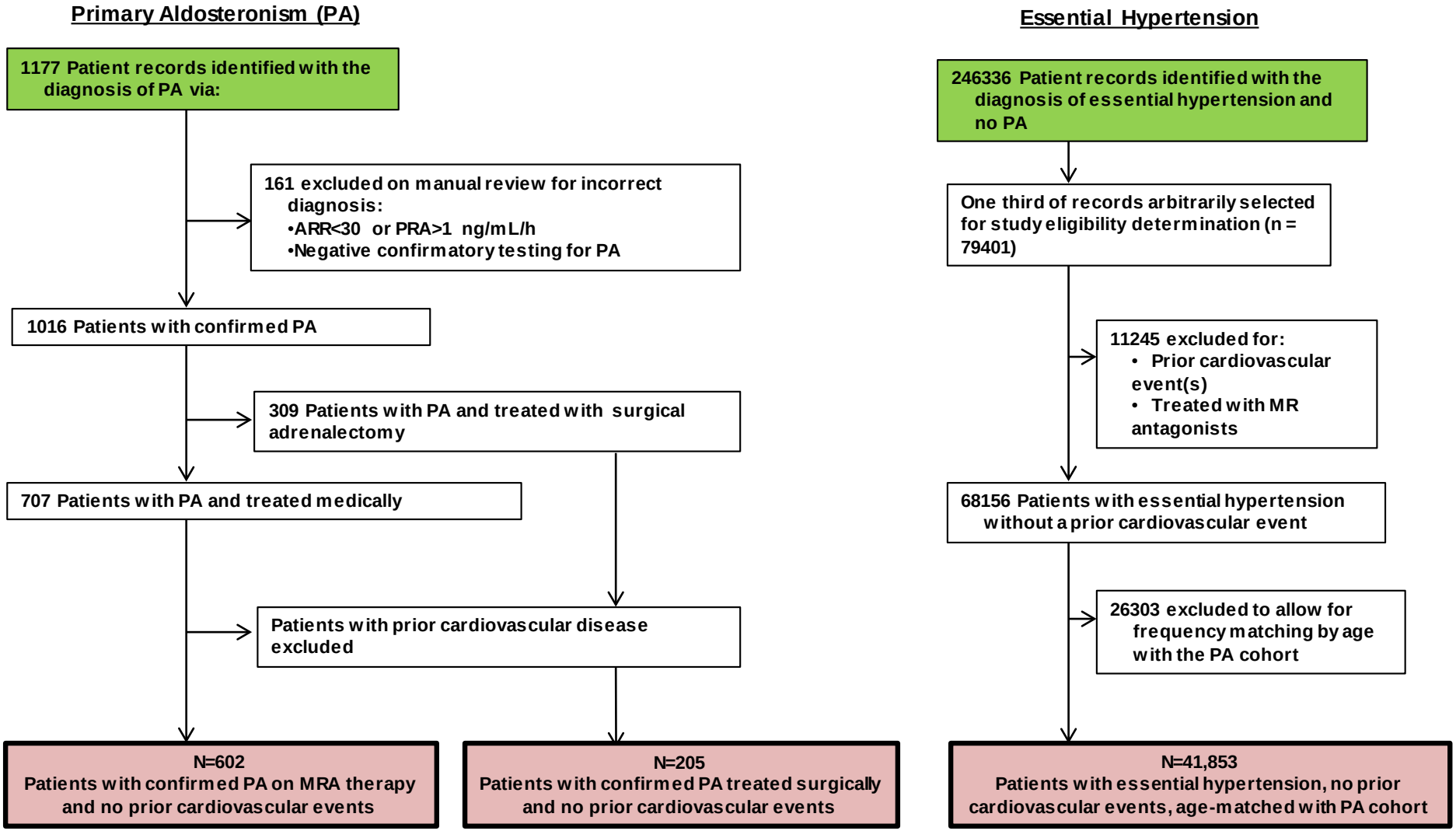
Our Recent Studies Evaluating the Efficacy of PA Therapies

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?

Study Cohort Derivation



Medical Therapy for PA and Incident Outcomes

	PA on MRA (N=602)	Essential HTN (N=41,853)
Age (years)	58 (12)	57 (12)
BMI (kg/m²)	31.1 (6.0)	29.8 (6.4)
Serum Potassium	3.6 (0.5)	4.1 (0.5)
SBP at Study Entry	137 (19)	135 (18)
DBP at Study Entry	81 (13)	80 (11)
Mean Anti-HTNive medications (non-MRAs)	2.9 (1.4)	2.7 (1.4)
Other CV Risk Factors (aspirin, statin, LDL, A1c, eGFR, smoking)	No difference	

Hundemer et al, The Lancet D&E 2018

Cardiovascular Events

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)

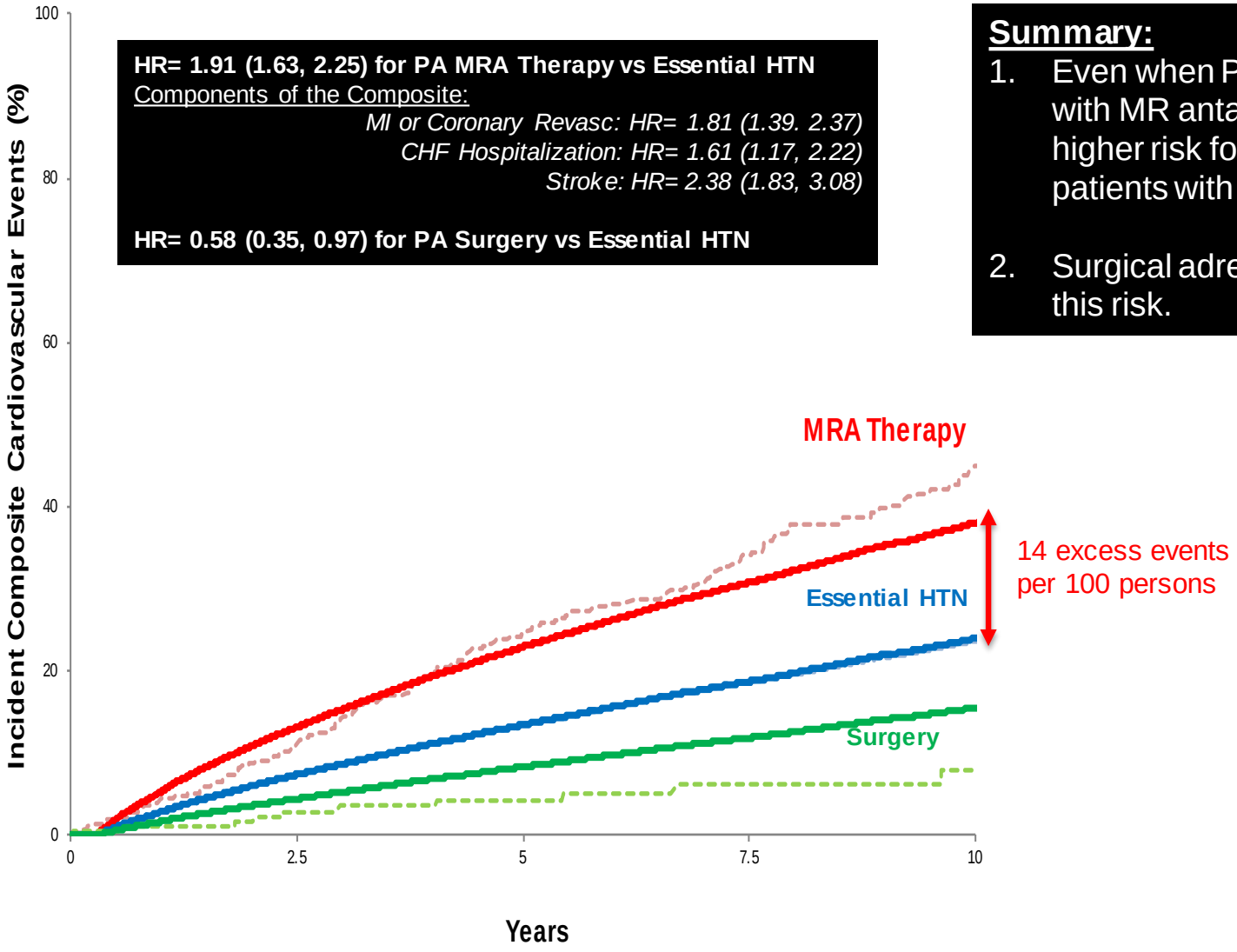
CHF Hospitalization: HR= 1.61 (1.17, 2.22)

Stroke: HR= 2.38 (1.83, 3.08)

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

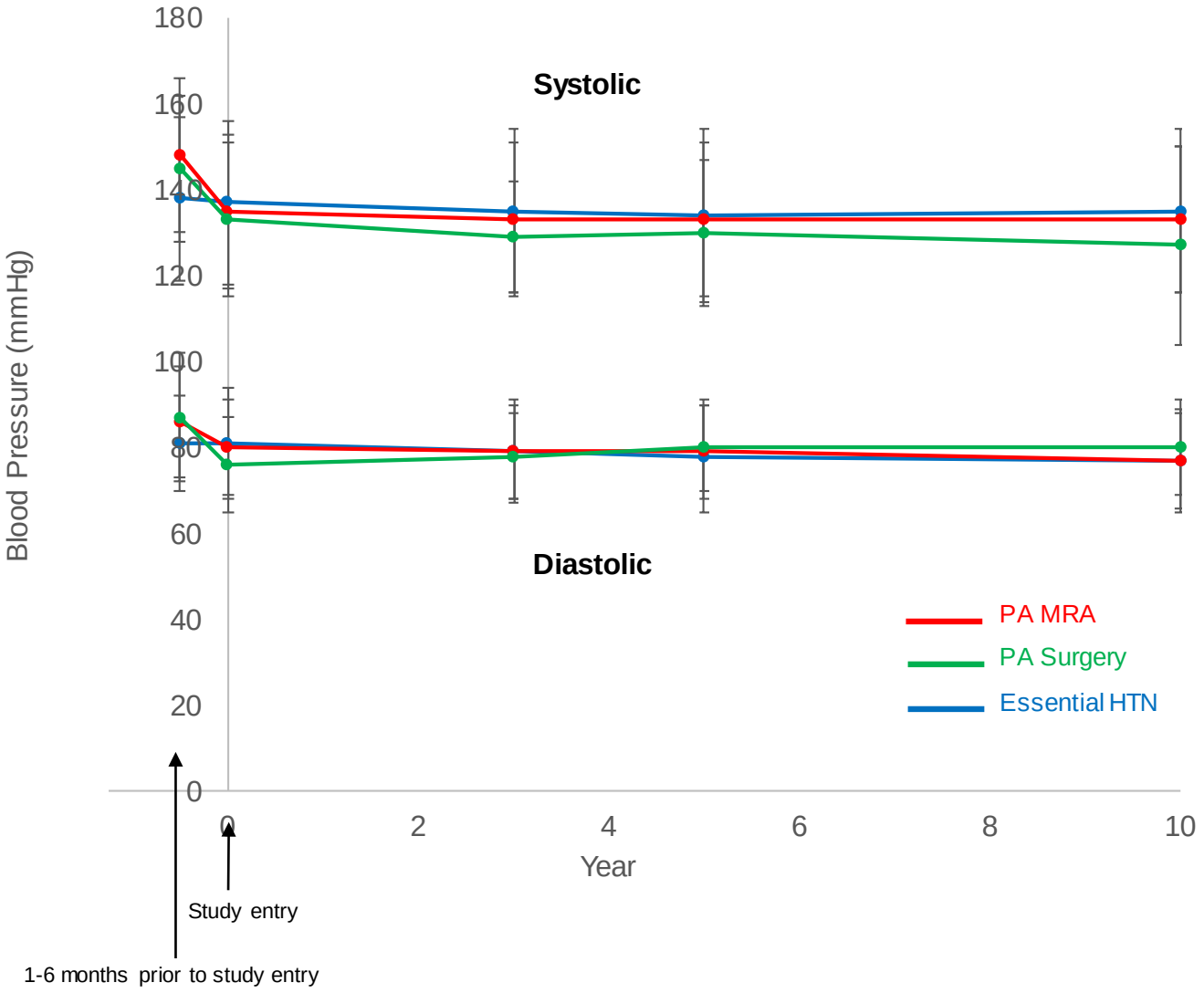
Summary:

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.

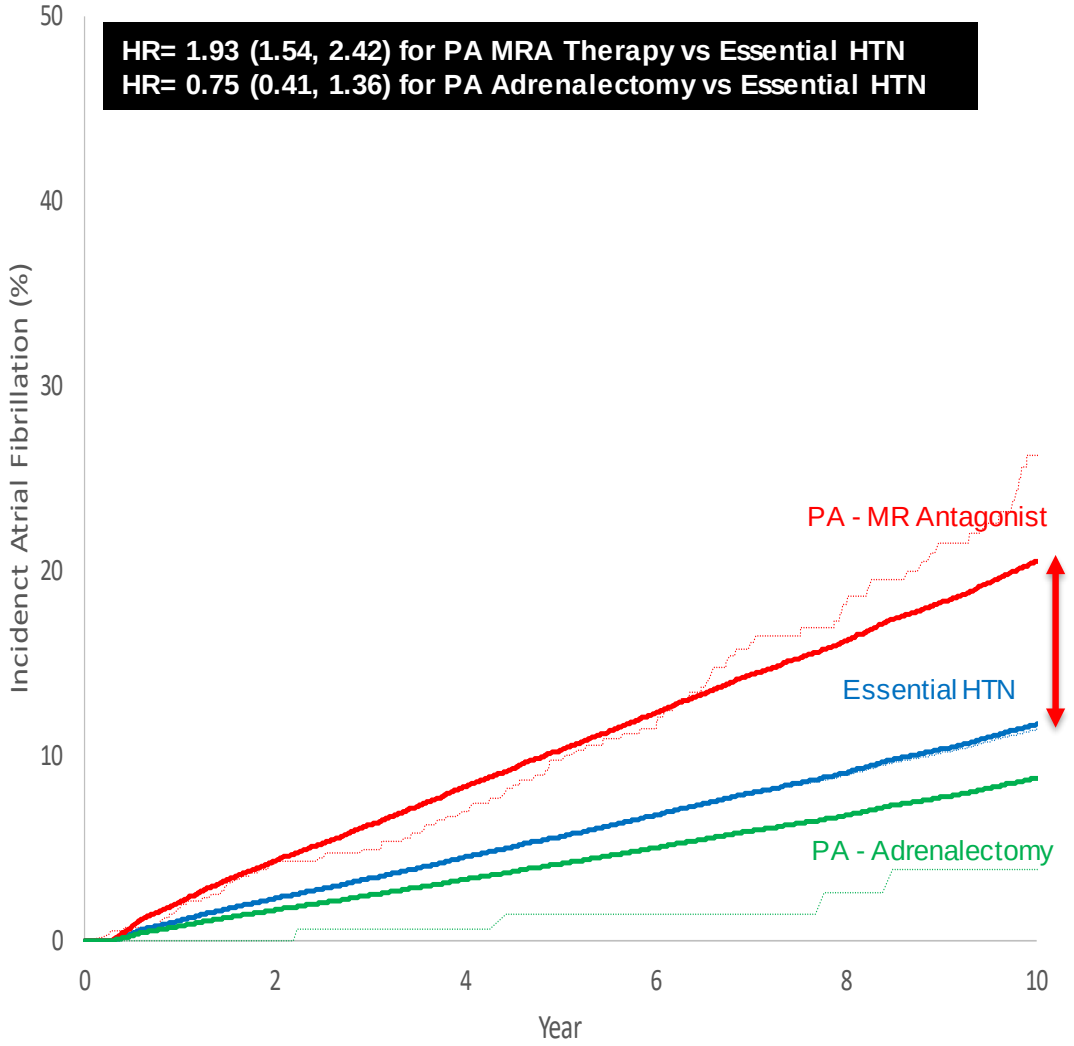


Hundemer et al, The Lancet D&E 2018

Blood Pressure Trends in Study Cohort



Atrial Fibrillation



Summary:

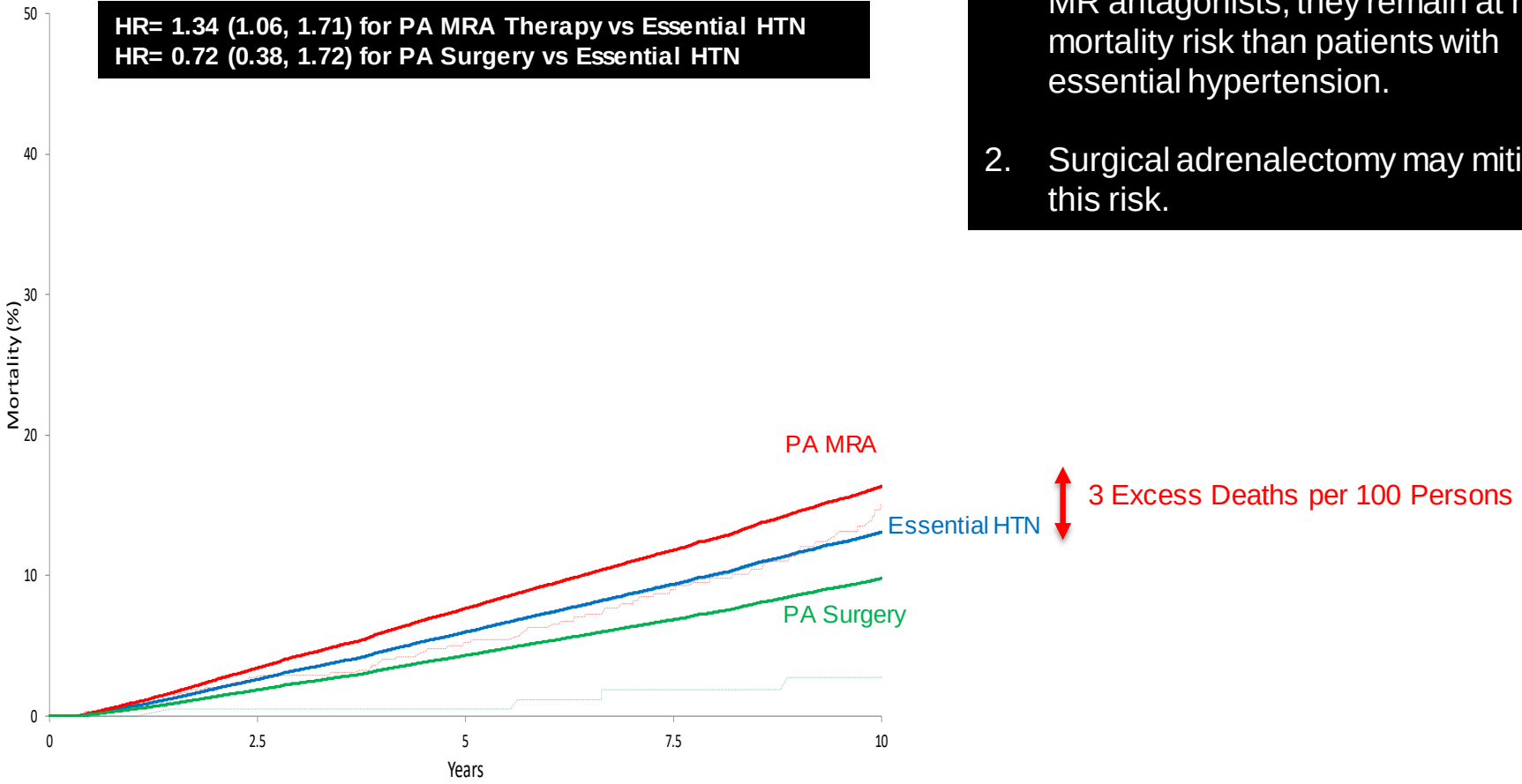
1. Even when PA patients are treated with MR antagonists, they remain at higher risk for atrial fibrillation than patients with essential hypertension.

2. Surgical adrenalectomy may mitigate this risk.

Hundemer et al, JAMA Cardiology 2018

Mortality

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.

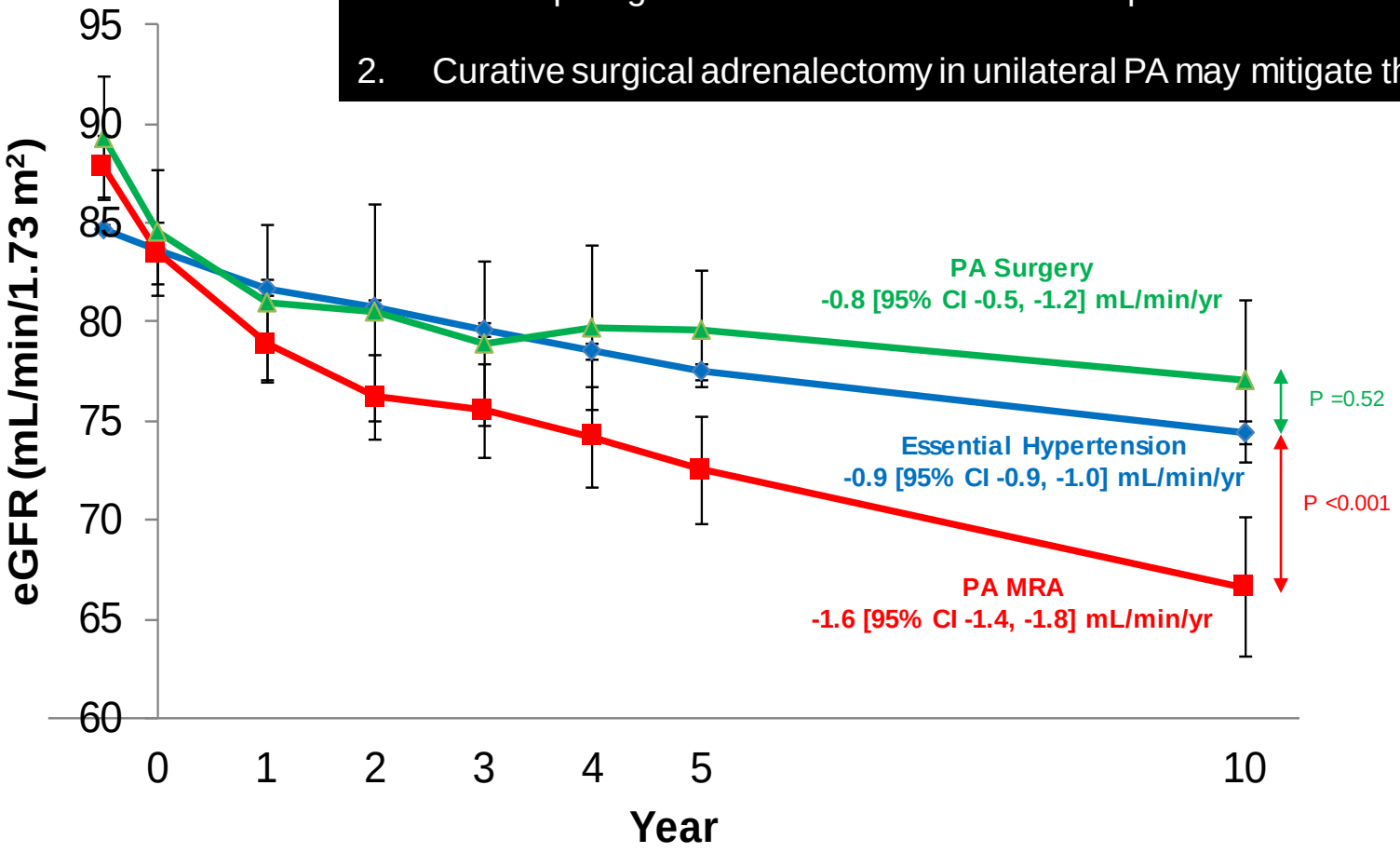
Hundemer et al, Lancet D&E 2018

Longitudinal eGFR Decline

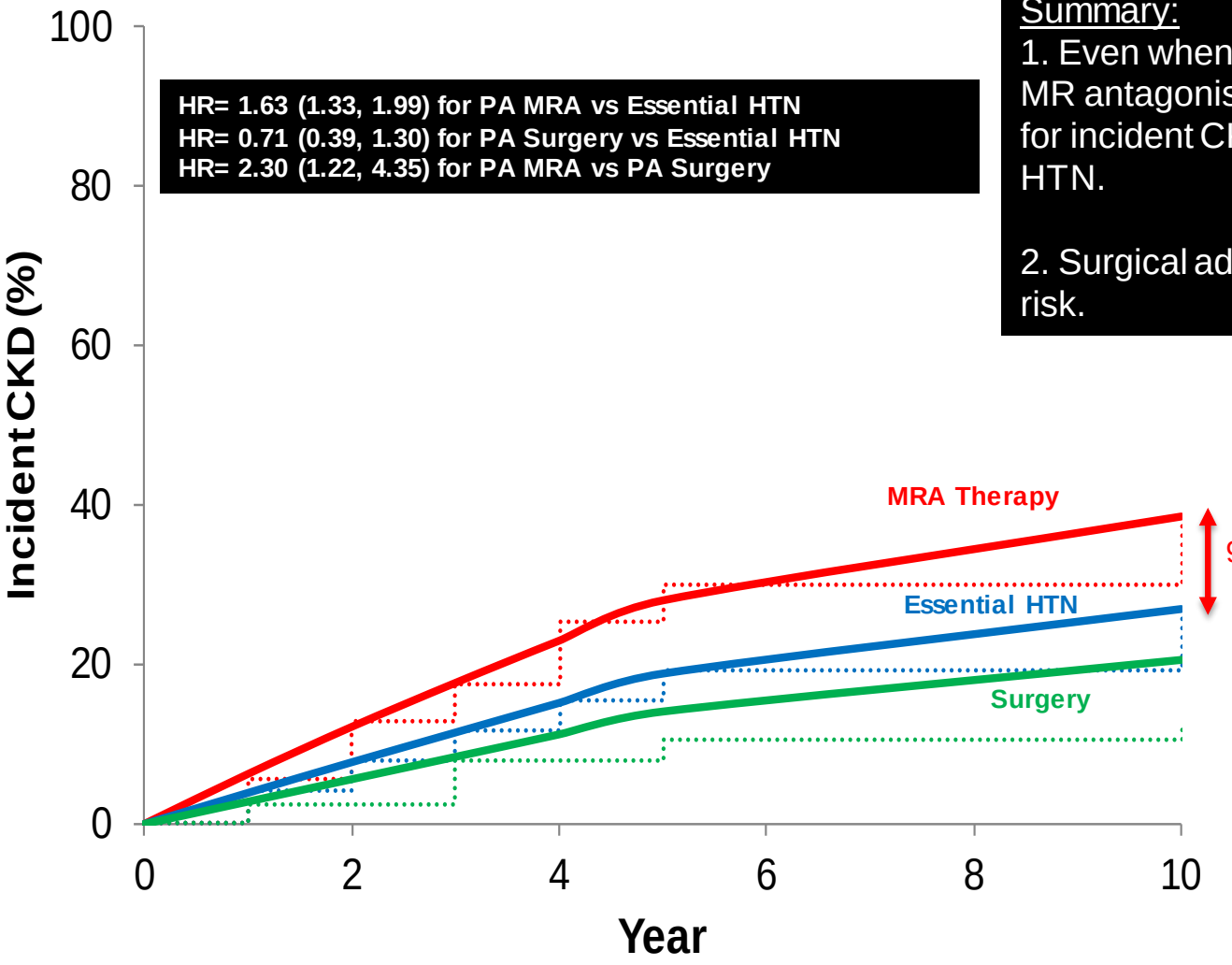
Summary:

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



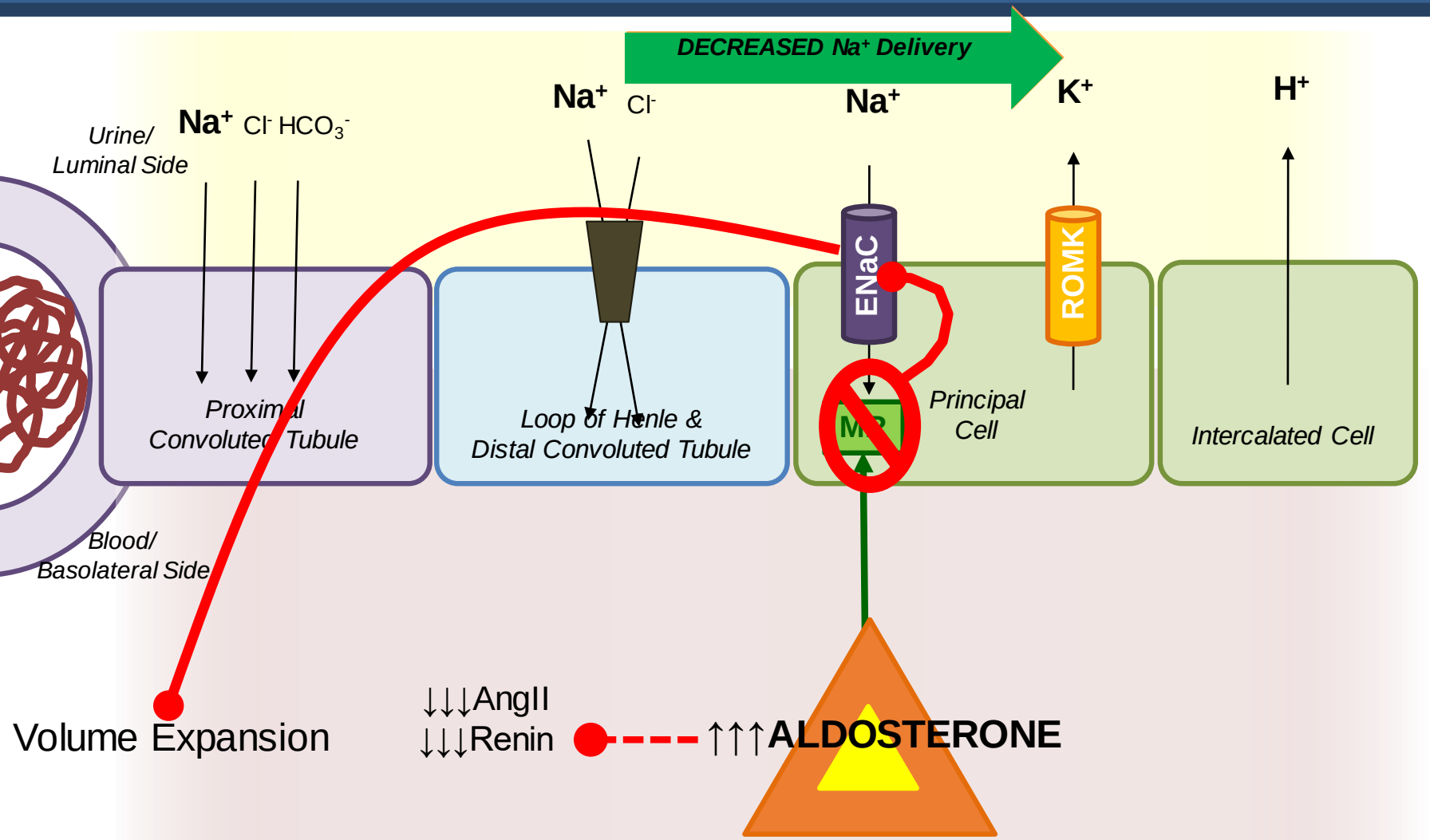
Summary:

1. Even when PA patients are treated with MR antagonists, they remain at higher risk for incident CKD than patients with essential HTN.

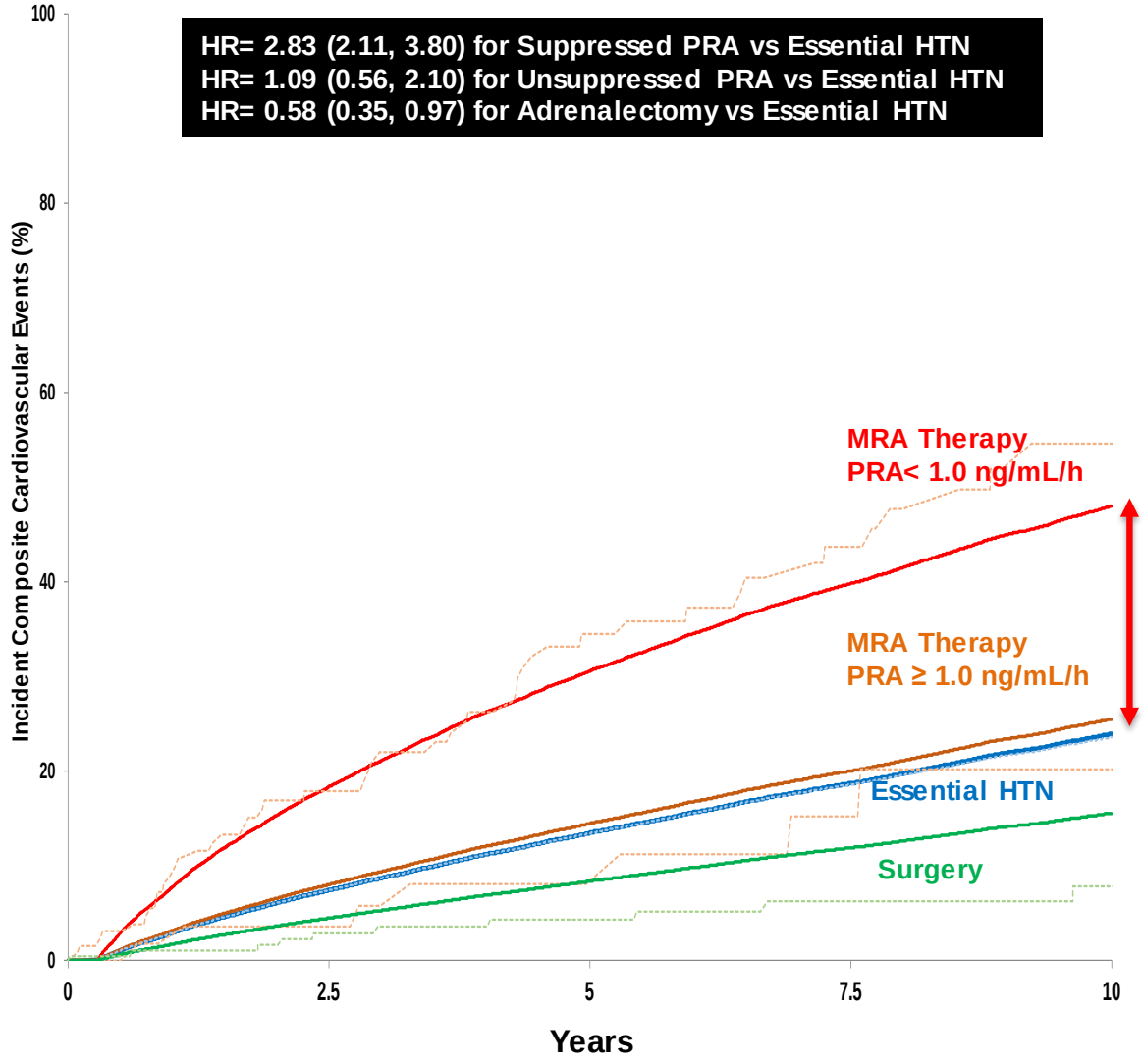
2. Surgical adrenalectomy may mitigate this risk.

Hundemer et al. Hypertension, 2018

Biomarkers of MR Antagonism



Risk for Incident Composite Cardiovascular Events



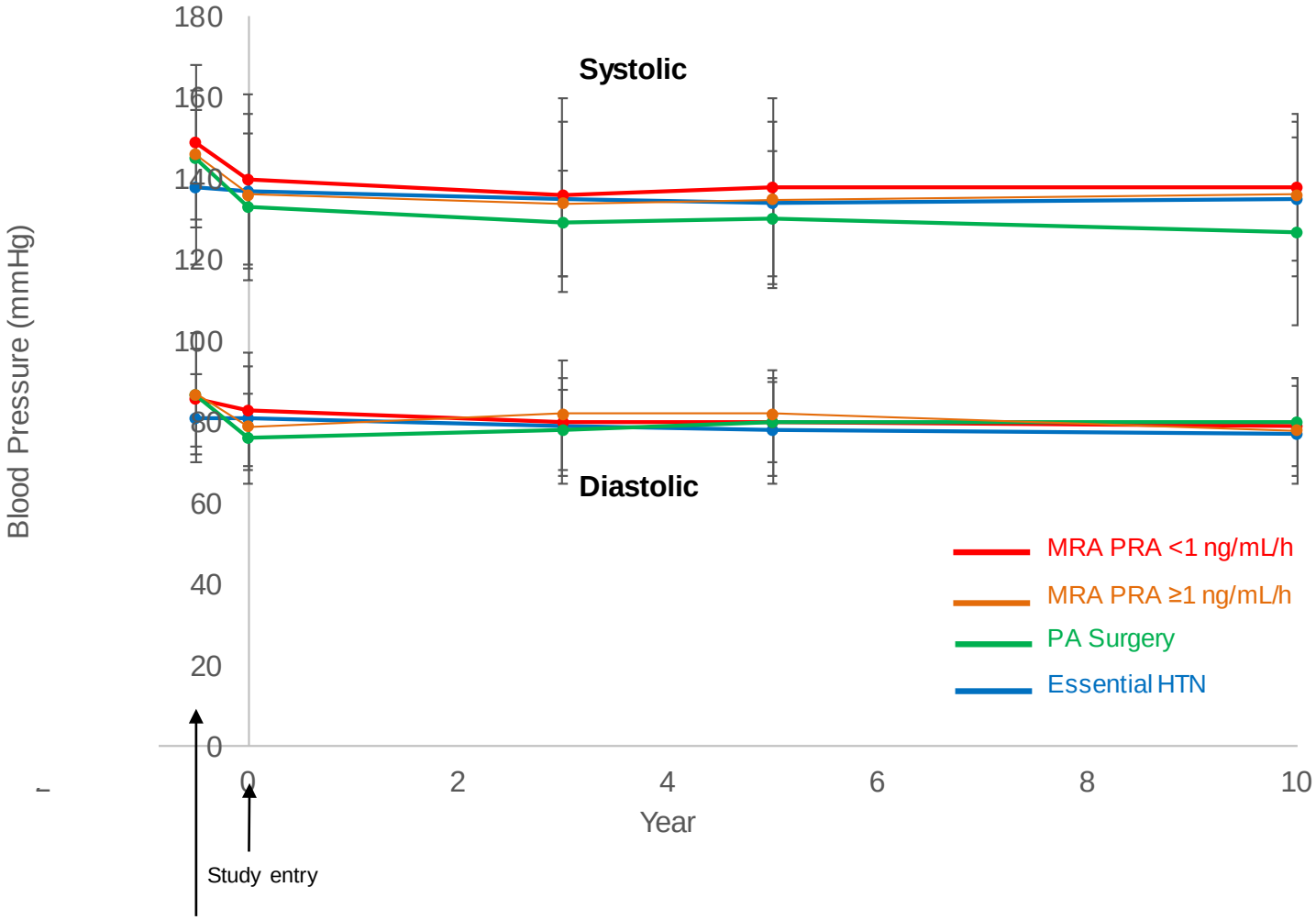
Summary:

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

Hundemer et al, The Lancet D&E 2018

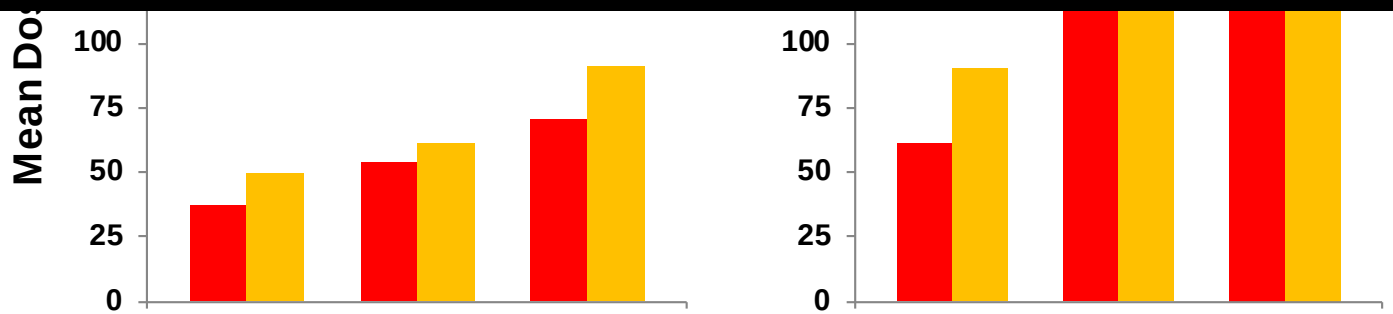
Blood Pressure Trends in Study Cohort



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

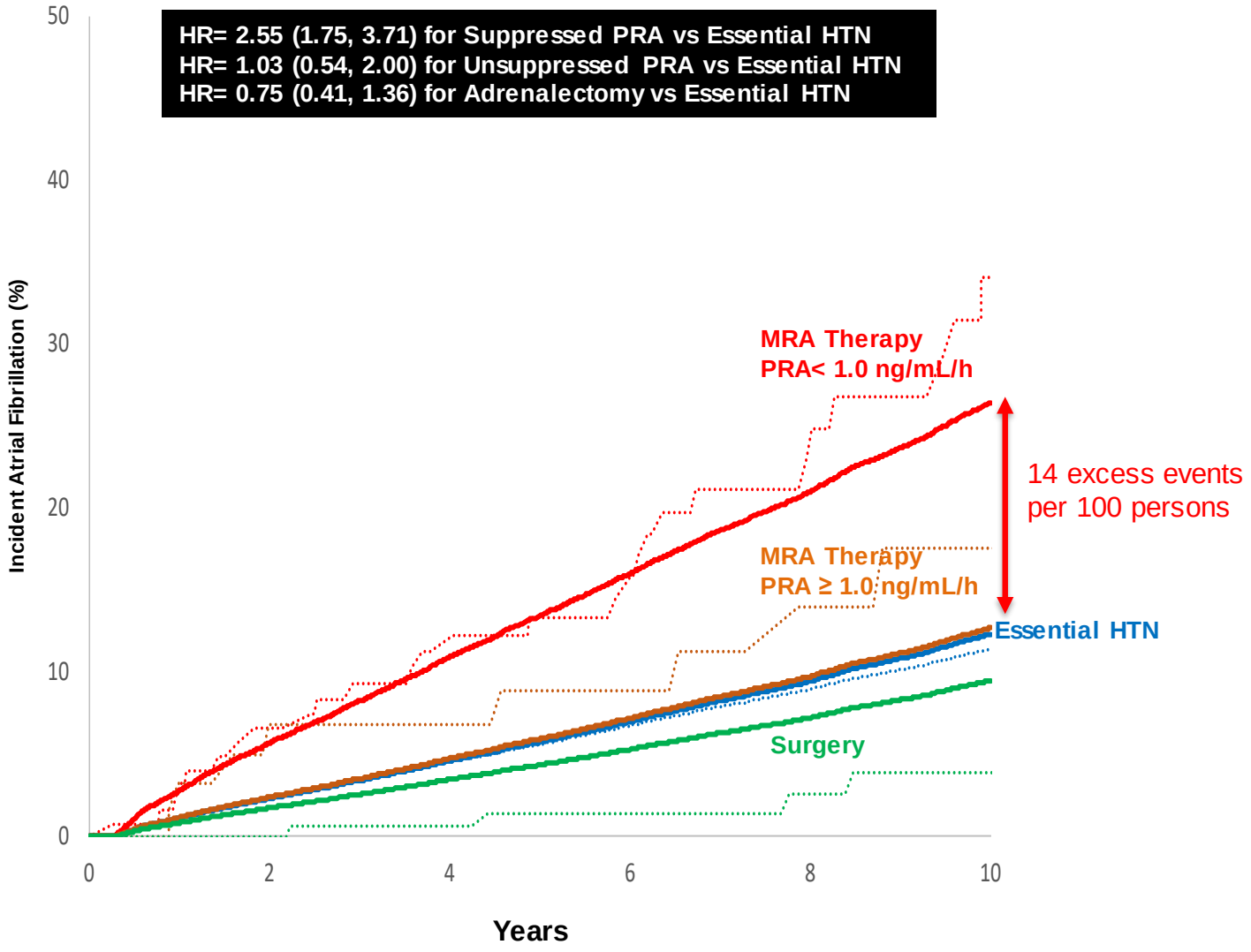


PRA < 1.0 ng/mL/h on MRA

PRA ≥ 1.0 ng/mL/h on MRA

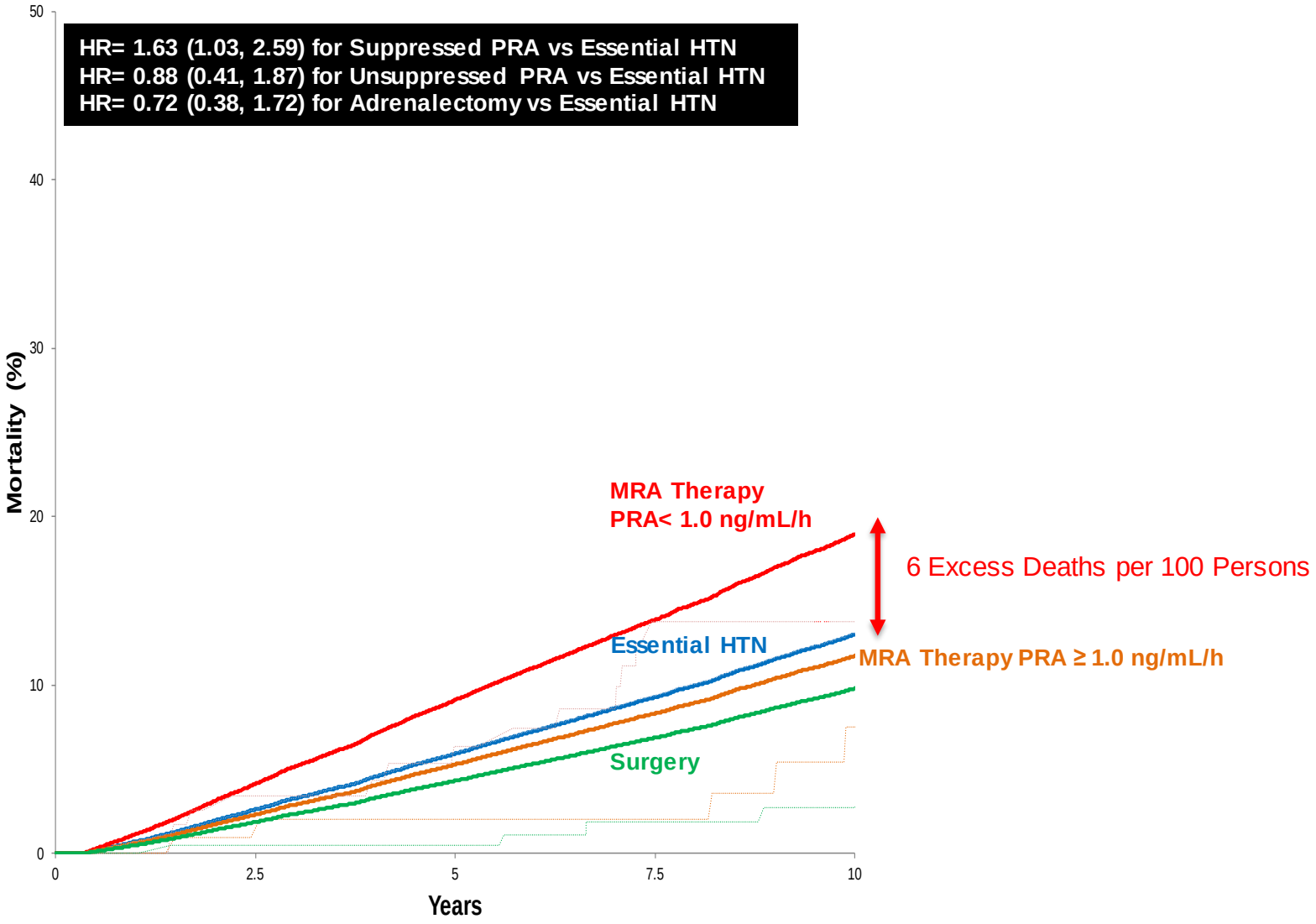
Hundemer et al, The Lancet D&E 2018

Risk for Incident Atrial Fibrillation



Hundemer et al, JAMA Cardiology 2018

Risk for Mortality



Hundemer et al, Lancet D&E 2018

Treatment Summary

The current (recommended) practice of lifelong MR antagonist therapy in PA:

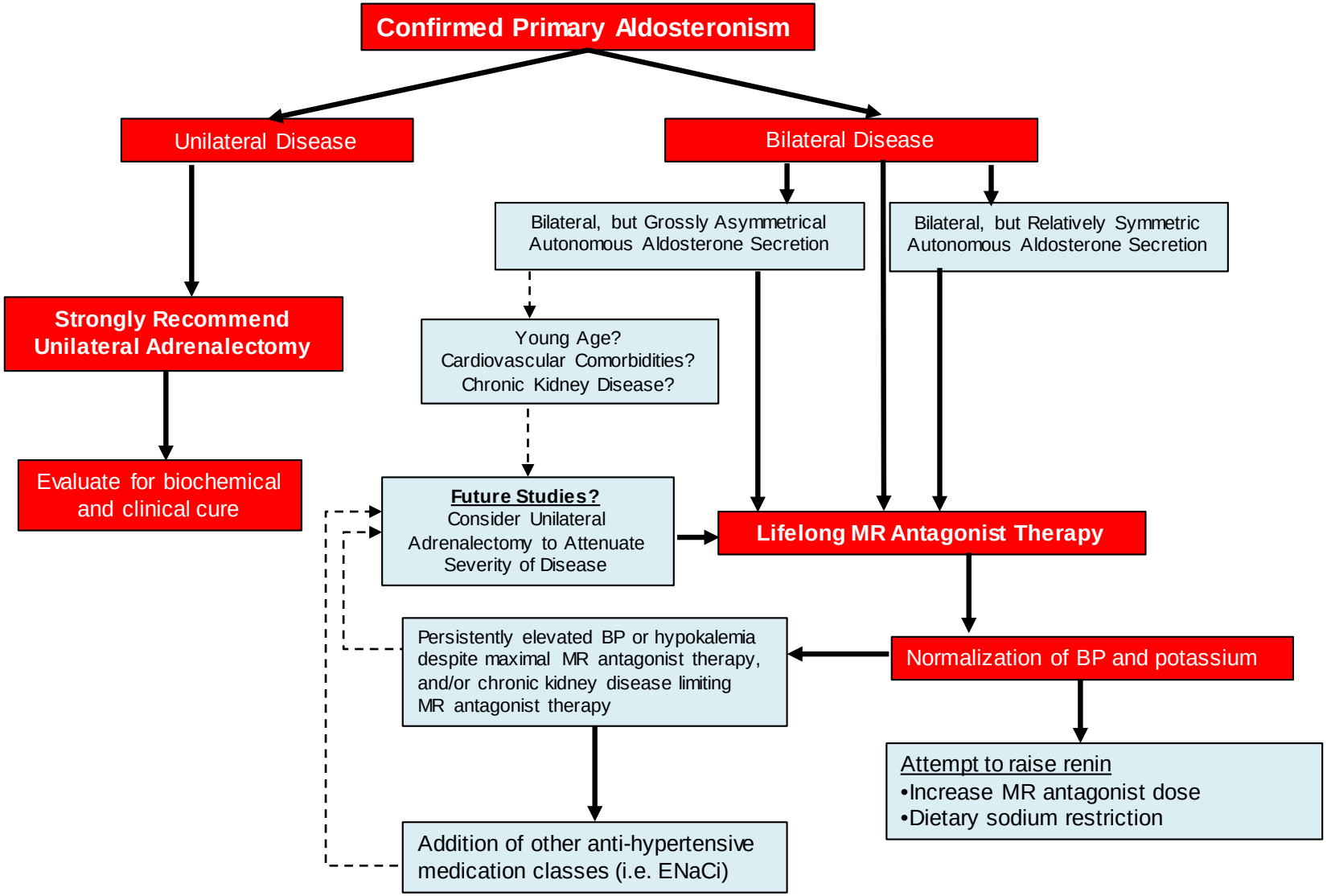
- **Associated with a significantly higher risk for incident cardiovascular disease, renal disease & death, *independent of blood pressure control***
- **Intensification of MR antagonist therapy to raise renin, as a proxy for optimal MR antagonism, may mitigate these risks.**
  - Not always possible!!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

Surgical therapy, to cure primary aldosteronism, mitigates these risks

<u>MORE QUESTIONS:</u>

- **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



QUESTIONS?