Hypertension –

Using the rare to deal with the common:

Conn's syndrome

Roger Foo

Cardiac long noncoding RNA

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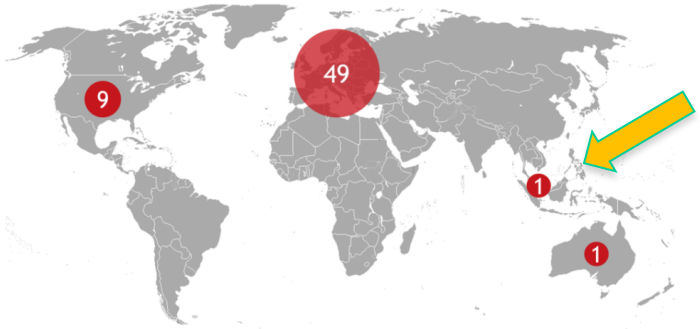
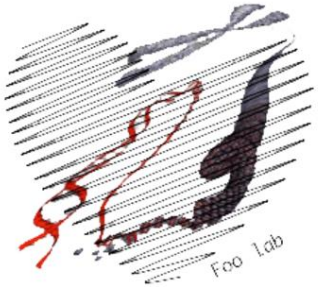


Genome Institute of Singapore

National University of Singapore

Cardiovascular Research Institute

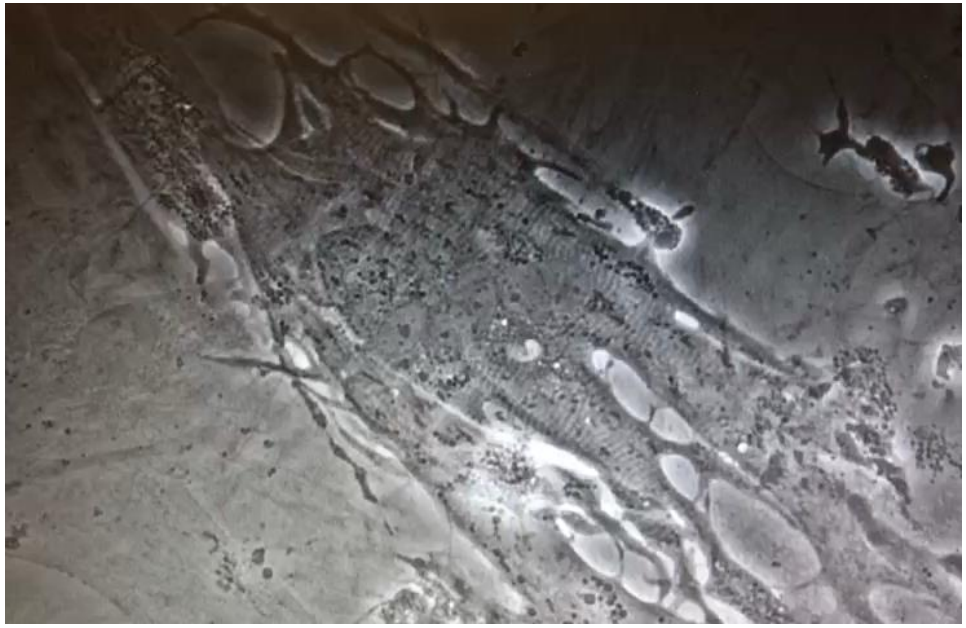


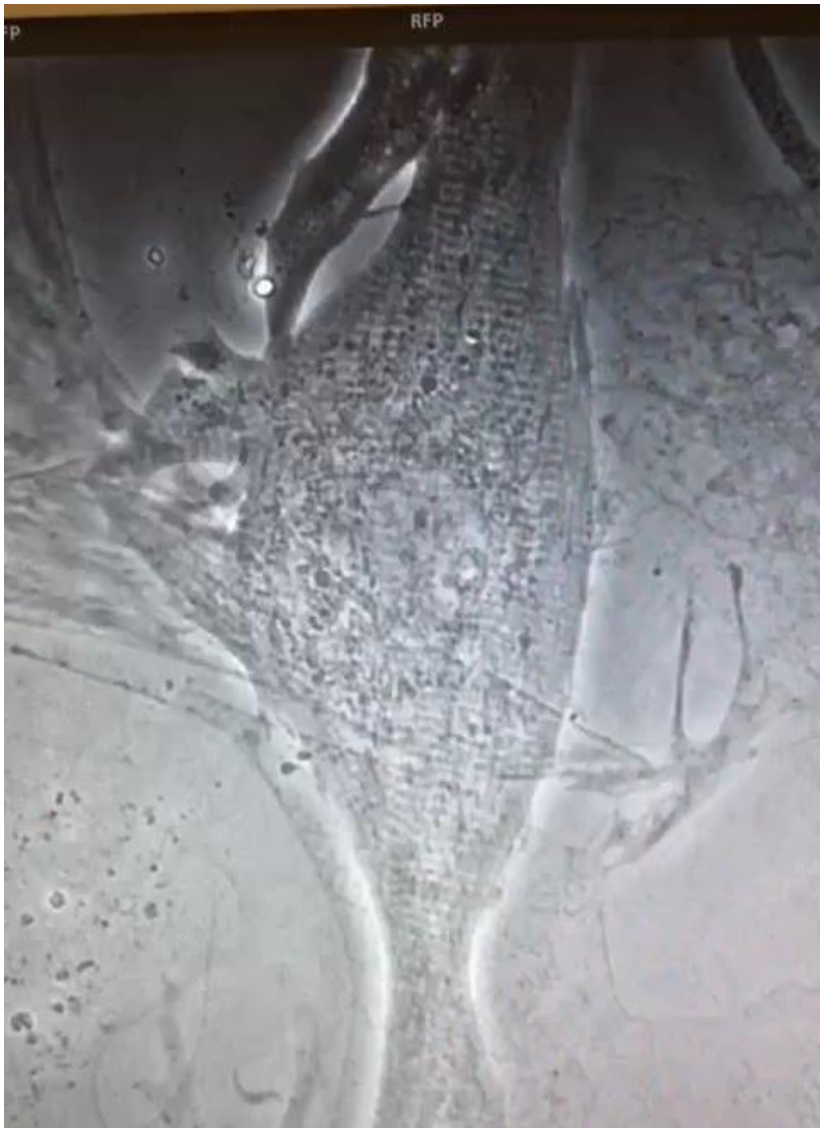
Lab of Cardiac Epigenomics, and molecular epigenetics

www.Foo-lab.com

A*STAR Genome Institute of Singapore

NUS National University of Singapore





Transdifferentiated cardiomyocytes

Fibroblasts → cardiomyocytes

Rare disease genomics

Solving genetics for undiagnosed diseases

@Genetics, KKH / NUH

Tracking mutated genes that wreak havoc

Special test called exome sequencing, done with help from A*Star scientists, helps save kids' lives

Kash Cheong

When Mrs Evelyn Lim's four-month-old son Jason (not their real names) had a lung infection, his constant crying was not the worst of her nightmares.

Doctors found something more shocking – that Jason, who was born smaller than other babies, had an extremely low platelet count. While a normal count is 150,000 blood or more, slightly more tha

BAFFLING DISEASES

Some illnesses are ultra-rare. We might have read of cases in textbooks and

(From left) Dr Saumya Jamuar and Dr Angeline Lai from KK Women's and Children's Hospital; Associate Professor Roger Foo from A*Star's Genome Institute of Singapore; and Dr Bruno Reversade from A*Star's Institute of Medical Biology. So far, A*Star has sequenced samples from 159 families at KKH since 2013 and found gene mutation in about one in three cases. The test is also available through the National University Hospital. ST PHOTO: CHEW SENG KIM

Singapore Childhood Genetic Diseases

rdss.org.sg/patient-stories

Chloe Mah

16/04/2014

Jarren Ng

16/04/2014

Issac Tan

16/04/2014

Clinic screens patients for genetic heart problems

By LINETTE LAI

RETAIL assistant Aziz Marjan, 54, has a rare heart condition, one which took the lives of his son, brother and niece.

It has little to do with lifestyle or age. His 23-year-old daughter, Wardah, has it too.

Instead, it is caused by a gene mutation that is inherited, causing sufferers to have cardiomyopathy where heart muscles are abnormal, rendering the heart unable to pump blood efficiently.

He might not have found out if he had not been referred last November to the inherited cardiac conditions clinic, the only one here that screens patients for genetic heart problems.

The relatives of those who tested positive may also be asked to go for screenings. Mr Aziz's daughter, who te positive.

Set up nearly two years the clinic housed at the Nat al University Heart Centre gapore (NUHCS) has seen a 190 patients so far. The c hopes to expand the servi the National Heart Centre Si pore next, said Associate Pr sor Roger Foo of NUHCS' c ology department at a n

Prof Roger Foo (right) with (from left) Ms Wardah Aziz, 23, her mother Abibah Wahab, 53, and father Aziz Marjan, 54. Genetic testing helped Mr Aziz and his daughter discover that they have a rare heart condition. ST PHOTO: AZIZ HUSSIN

Inherited heart conditions

HCM, DCM, Brugada, LQT, Marfan &c

@NUH & CGH

Please refer

NMRC National Medical Research Council
Singapore

Centre Grant (CG)

August 2016 Grant Call

Grant Application Form

Treating Hypertension in Singapore

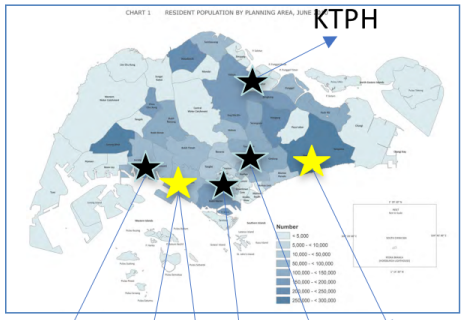
Governance for this CG grant

PI: Roger Foo; Co-PIs: Troy Puar, Ronald Lee

Seeding funds for HTN research

Research personnel / Cores

Admin Core
- Manager



CORE 1: PA-OSA @NUH, including imaging @CIRC/NUS

CORE 2: PA-OSA @CGH

Admin support staff x1, 0.5FTE @CGH

Admin support staff x1, 0.5FTE @NUH

Theme 1
low renin and primary aldosteronism
(**PA-CURE** study)
Leader: Troy Puar (CGH)

Theme 2
Obstructive sleep apnoea
(MOSAIC HT study)
Le

Resistant Hypertension Clinic

@NUH & CGH

Please refer

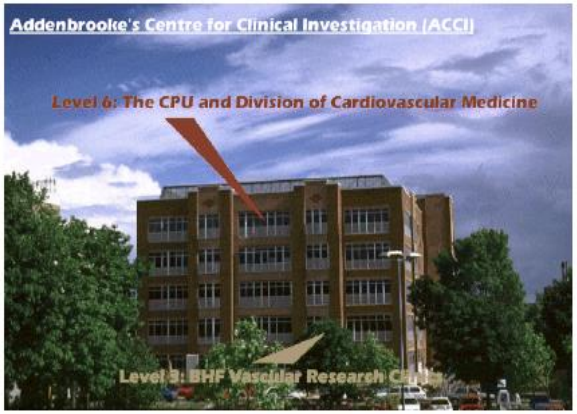
Lead Centres:
Resistant hypertension clinics: CGH, NUH

Collaborating Centres:
Endocrine: SGH, TTSH, KTPH, JGH
Hypertension: TTSH

UNIVERSITY OF CAMBRIDGE
800 YEARS
1209 - 2009

Cambridge University Hospitals NHS
NHS Foundation Trust

Guidelines for the Management of Hypertension



Clinical Pharmacology Unit

Genome Institute of Singapore

60 years of Conn's Syndrome:

Impact of molecular analysis and imaging on detection and understanding of a common, curable cause of Hypertension

Time : 2pm – 3pm
Date : Monday, 4 July 2016
Venue : GIS Seminar Area, Level 2

PROFESSOR MORRIS J BROWN

MD FRCP FMedSci
Professor of Endocrinology Hypertension
The Barts Heart Centre
Queen Mary University of London

ABSTRACT :

Aldosterone-producing adenomas (APA) of the adrenal gland are the commonest single cause of Hypertension. Most have gain-of-function somatic mutations, first reported in KCNJ5 (Science 2011), and then in CACNA1D, ATP1A1, ATP2B3 and CTNNB1 (Nat Gen 2013, NEJM 2015).[1-4] A clear genotype:phenotype relation became apparent between the KCNJ5 and other mutations, with the former arising in 'classical Conn's tumours' which paradoxically resemble cortisol-secreting cells in adrenal zona fasciculata (ZF), and the newer somatic mutations unmasking a more frequent, but smaller, adenoma resembling the aldosterone-secreting cells of the normal adrenal zona glomerulosa (ZG). These are now detectable using a PET radiotracer, 11C-metomidate, which targets aldosterone synthase. The principal clinical challenge is how to recognise the minority of patients with APAs whose hypertension can be completely cured by adrenalectomy. The discovery of three patients with APAs unmasked by pregnancy (or menopause), shows how 'sleeper' mutations (e.g. in **b**-catenin) can cause explosive onset of PA, followed by complete cure.[5]

1. Choi, M. et al. K^+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. *Science* **331**, 768-772 (2011).
2. Azizan, E.A. et al. Somatic mutations in ATP1A1 and CACNA1D underlie a common subtype of adrenal hypertension. *Nat Genet* **45**, 1055-1060 (2013).
3. Beuschlein, F. et al. Somatic mutations in ATP1A1 and ATP2B3 lead to aldosterone-producing adenomas and secondary hypertension. *Nat Genet* **45**, 440-444 (2013).
4. Teo, A.E. et al. Pregnancy, Primary Aldosteronism, and Adrenal CTNNB1 Mutations. *N Engl J Med* **373**, 1429-1436 (2015).
5. Teo, A.E. & Brown, M.J. Pregnancy, Primary Aldosteronism, and Somatic CTNNB1 Mutations. *N Engl J Med* **374**, 1494 (2016).

BIOGRAPHY:

By being among the youngest in living memory to be appointed into a Professorial Chair at Cambridge (aged 34), and moving up from Hammersmith Hospital, Morris founded the Clinical Pharmacology Unit at Cambridge in 1985. From there, he has taught, instructed and mentored a generation of Cambridge medical students - no medical graduate of Cambridge would have gone untrained by Professor Brown's Clinical Pharmacology wisdom, and his inimitable textbook appropriately called "Clinical Pharmacology" (Publisher: Elsevier), and generations of Clinical Pharmacologists, Clinician Scientists, Registrars and Consultants, who today are scattered across the world far and wide.

From the Clinical Pharmacology Unit in Cambridge also, Morris founded the AB/CD rule of hypertension treatment which today underpins guidelines set forth by the British Hypertension Society, of which he was also its one-time President (2005-2007). He is also renowned for leading multi-centre blood pressure trials including: INSIGHT (Lancet 2000), ACCELERATE (Lancet 2011) and the recent PATHWAY programme (Lancet 2015), among others.

He is the writer of the section on Secondary Hypertension in the Oxford Textbook of Medicine, and most recently made the groundbreaking discovery of somatic mutations in small but pathologically significant adrenal adenomas, leading to the understanding of the molecular and genetic basis for what is an important cause for hypertension that easily goes unnoticed (Nat Gen 2013).

After 30 years in Cambridge, Morris has moved to a new Chair in Endocrine Hypertension at Barts and the London Medical School, from where he received this year's Royal College of Physicians/Lancet award for translating outstanding research into clinical care. His connection with Singapore is as firm as ever, and most recently the ASTAR MB/PhD scholar Ada Teo who was first author on their recent publications in the N Engl J Med (2015 & 2016).

Content

1. Low-renin hypertension→NASSH (normo-aldo Spiro-sensitive HTN)→Conn's
2. Clinical vignettes
3. PHARst study
4. Cambridge → UK AB/CD rule for hypertension management
5. ^{11}C-metomidate PET-CT for adrenal adenomas
6. Singapore PA-CURE study
7. **Renin for hypertension stratification**

N.A.S.S.H.

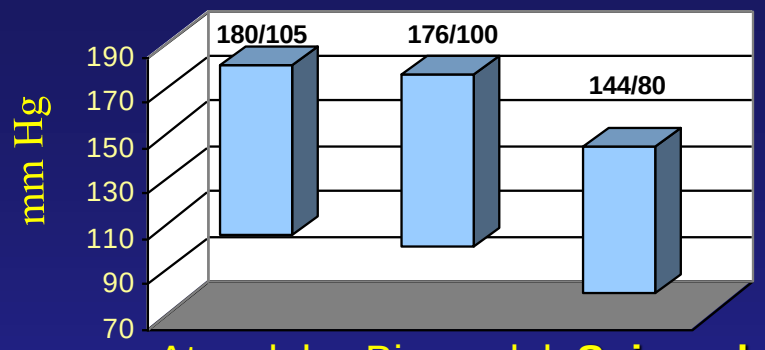
Normo-aldosterone Spironolactone-sensitive Hypertension

October 2000

Grand Staff Round
University of Cambridge School of Medicine

Clinical Vignettes

A

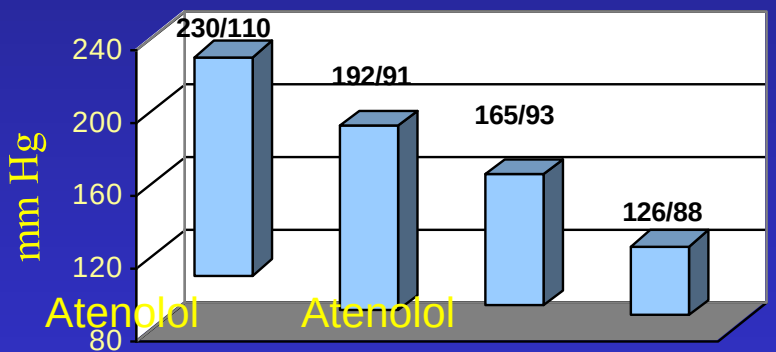


Atenolol
Lisinopril
Doxazosin

Bisoprolol
Irbesartan
Doxazosin

Spironolactone

B



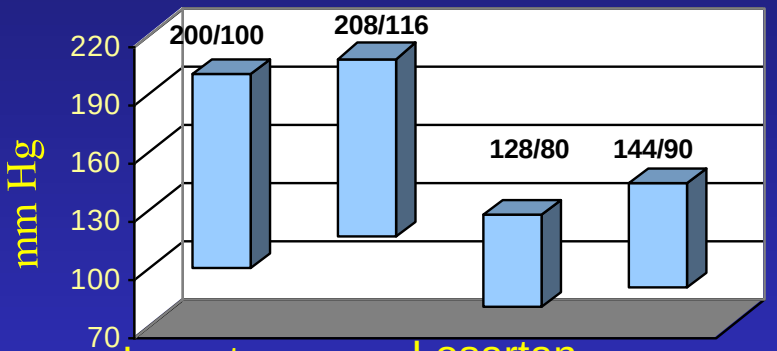
Atenolol
Enalapril
BFZ
Indoramin
Lacidipine
Clonidine
Hydralazine

Atenolol
Enalapril
BFZ
Indoramin
Amlodipine
Hydralazine

Atenolol
Co-amilozide

Spironolactone

c

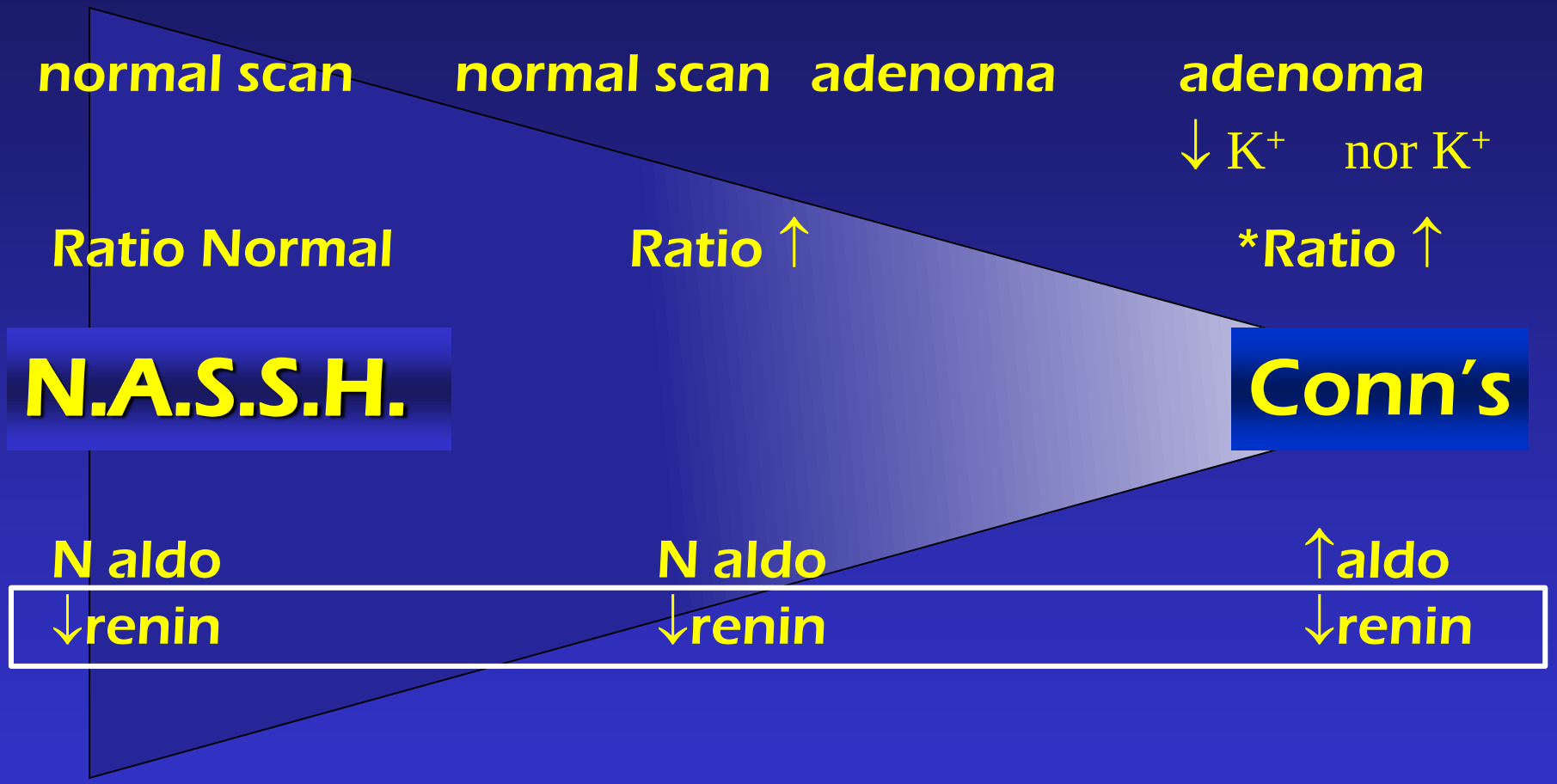


Losartan
Bisoprolol

Losartan
Bisoprolol
Spironolactone

Spironolactone

Spironolactone-sensitive hypertension

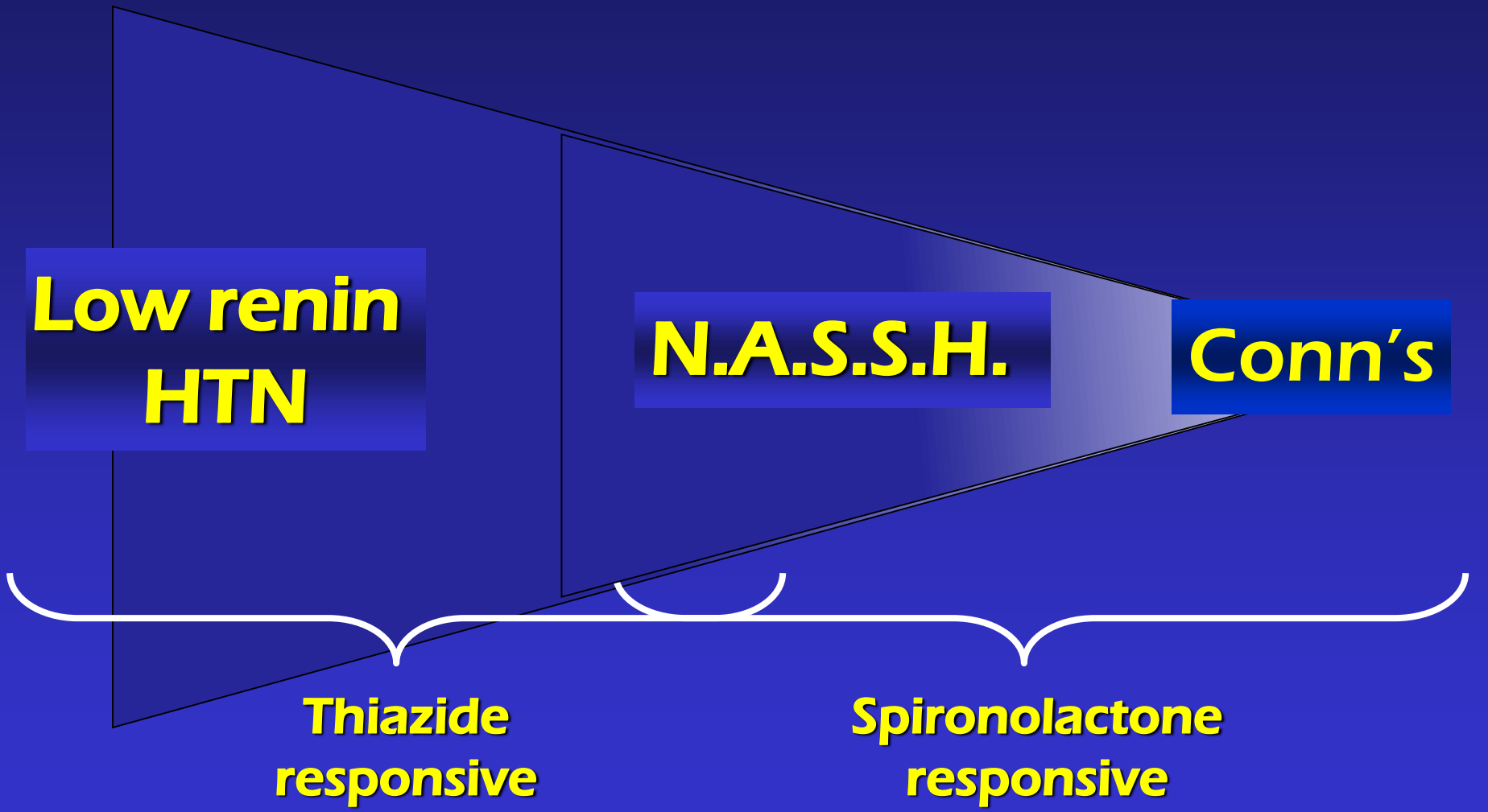


*ratio=aldo/renin

Normo-aldosterone Spironolactone-sensitive hypertension [N.A.S.S.H.]

	age	Pre-BP	aldo	renin	AR ratio	CT/ MRI	Present Meds	Present BP
KB	55 Γ	186/92	210	0.5	**420**	normal	**Spironolactone 25bd** Doxazosin 8bd Irbesartan 300od	146/80
SW	48 E	164/96	170	0.7	**243**	normal	**Spironolactone 25bd** Irbesartan 300od	128/88
JG	63 E	180/104	160	0.6	**266**	*pending*	**Spironolactone 50bd**	164/78
IZ	58 E	210/104	260	0.6	**433**	*pending*	**Spironolactone 25bd** Irbesartan 300od	180/84
AS	64 E	150/95	230	0.3	**767**	normal	**Spironolactone 25bd**	124/80
CA	62 Γ	200/100	220	0.2	**1100**	*pending*	**Spironolactone 75od** Enalapril 10od	144/80
GK	54 E	205/90	240	0.2	**1200**	*pending*	**Spironolactone 25bd** Doxazosin 2od	130/80
MB	66 Γ	180/102	280	0.2	**1400**	normal	**Spironolactone 25bd** Amlodipine 10od	148/98
JG	53 Γ	198/120	360	0.2	**1800**	*pending*	**Spironolactone 25bd**	147/90

Low-renin hypertension



The Red House Surgery, Cambridge

Mr WI

Hx - 64 M
- referred from The Red House Surgery
- HT >30yrs, "difficult to treat" HT

P/Hx - out-of-hospital cardiac arrest
- further episodes of VT
→ automated cardiac defib

smoking ^{0}, alcohol ^{0}

Rx

Atenolol 100mg od, Lisinopril 20mg bd

O/E

170/100 mmHg
fundi normal

Heart/lungs clear
urine dipstix normal

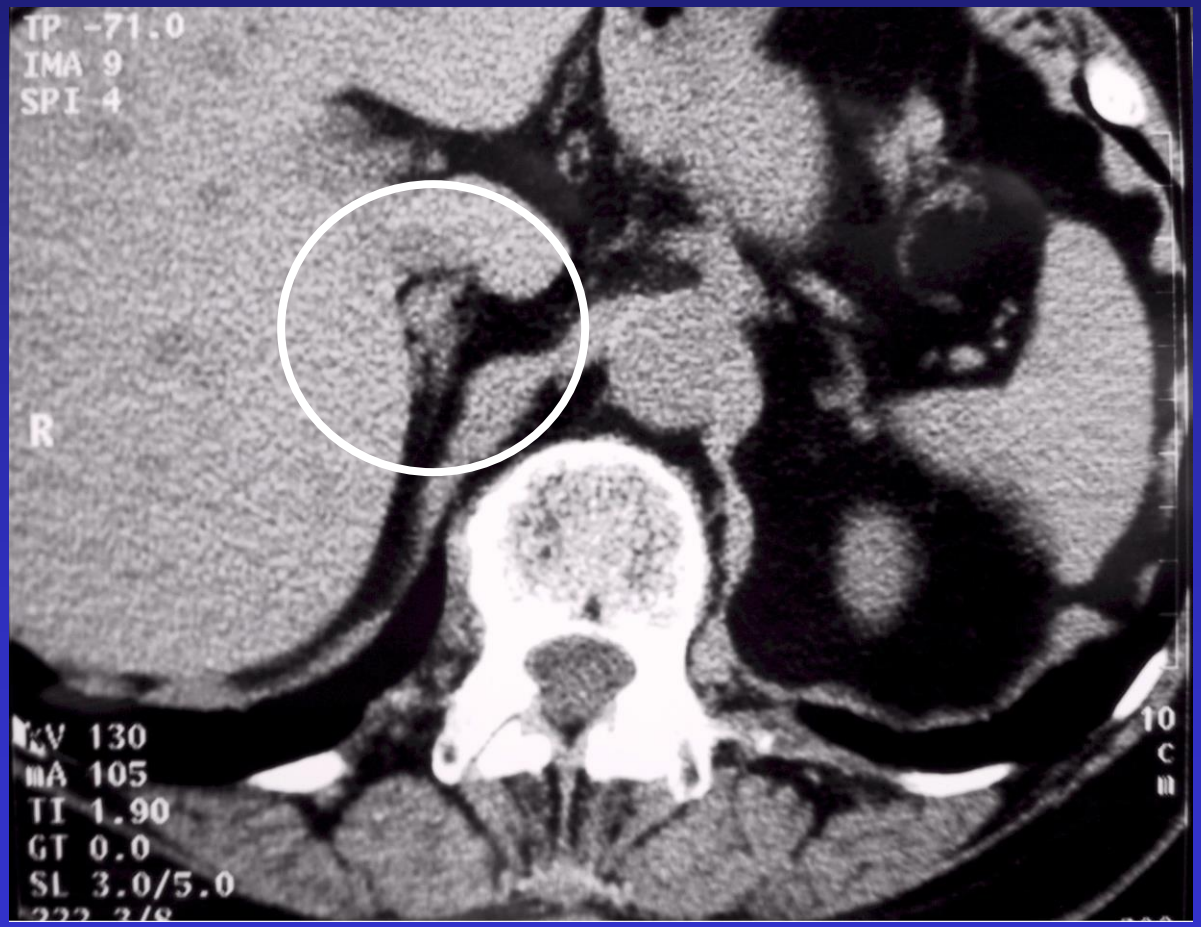
Mr WI

K^+	3.2		
Other electrolytes normal			
aldosterone	850	↑	(100-450 pmol/l)
renin (PRA)	0.2	↓	(0.5-3.1 pmol/ml/hour)
AR ratio	4250	↑↑	(<750 units)

CT adrenal glands

Mr WI

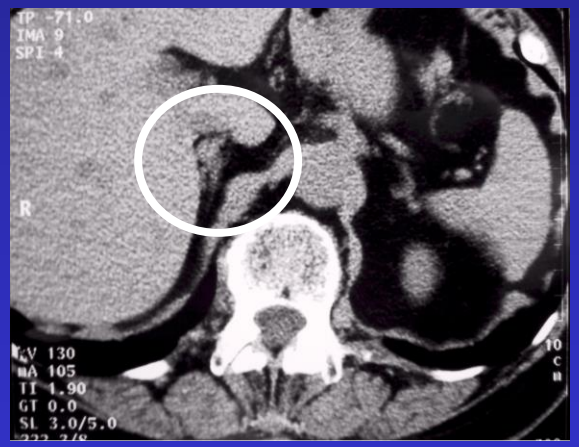
normal left adrenal gland,
1cm nodule on anterior aspect of the right gland

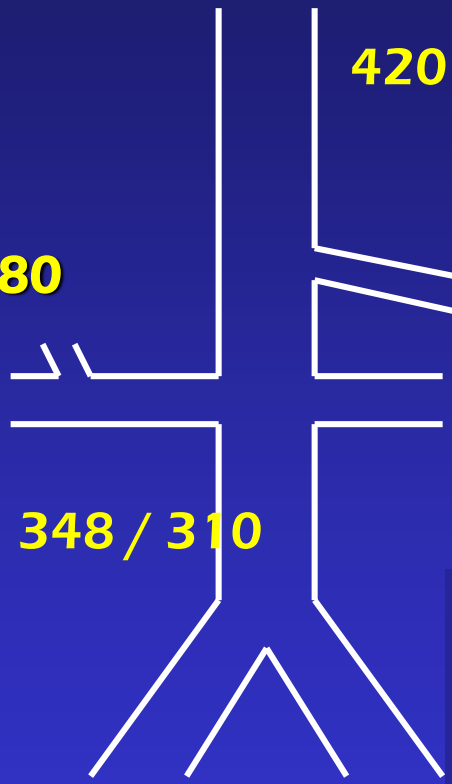


Mr WI

Adrenal venous sampling

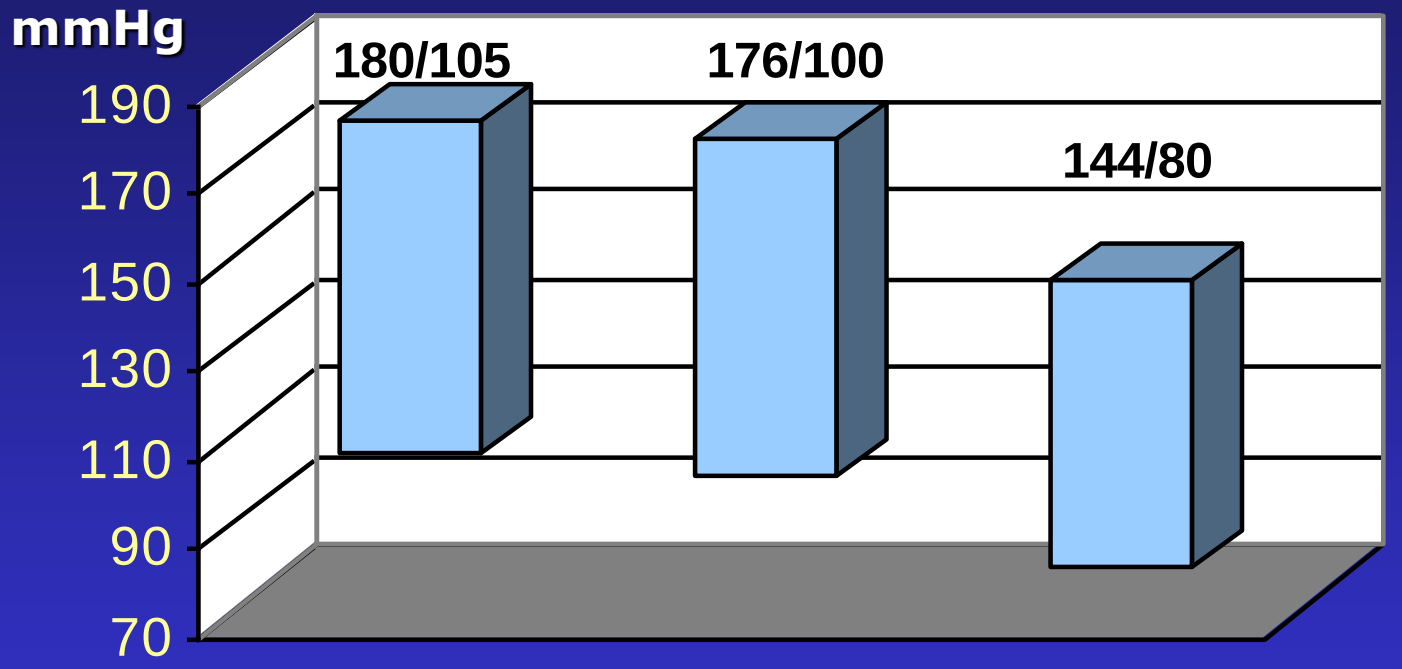
aldosterone / cortisol
(280-650 nmol/l)





- Normalised ratio
unilat: 3x contralat
contralat: suppressed
(suprarenal IVC)
- Confirm catheter position
cortisol: 2x suprarenal IVC
right hepatic tributaries

Mr WI



Atenolol
Lisinopril

Bisoprolol
Irbesartan
Amlodipine

Spironolactone

Mrs DB

Hx 68 F
HT >20yrs, resistant to therapy
No cardiovascular symptoms

P/Hx nil of note
F/Hx brother HT
smoking ^{0}, alcohol ^{0}

Rx
Atenolol 100mg, Enalapril 20mg, bendrofluazide 2.5mg, indoramin 12.5mg, lacidipine 60mg, hydralazine 50mg bd, clonidine 75ug bd

O/E 230/110 mmHg
fundi normal
Heart/lungs clear
urine dipstix trace protein

Mrs DB

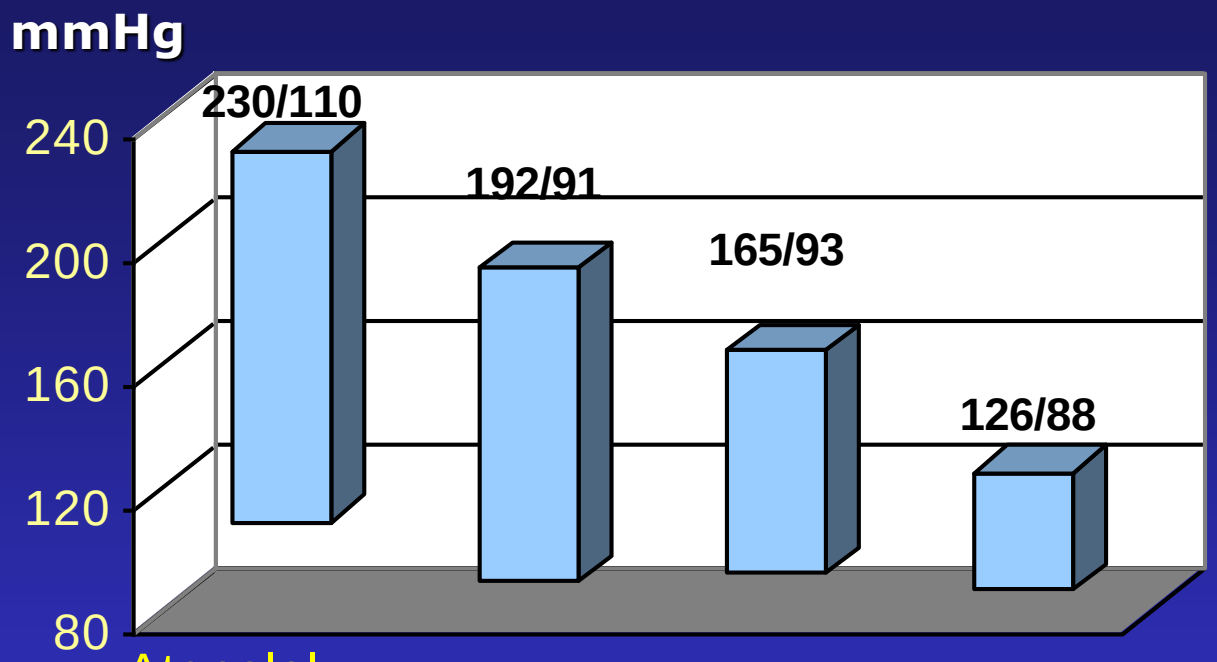
K^+ 3.5

Other electrolytes normal

aldosterone	290	N	(100-450 pmol/l)
renin (PRA)	< 0.2	↓	(0.5-3.1 pmol/ml/hour)
AR ratio	1450	↑↑	(<750 units)

CT adrenal glands – normal

Mrs DB



Atenolol
Enalapril
BFZ
Indoramin
Lacidipine
Clonidine
Hydralazine

Atenolol
Enalapril
BFZ
Indoramin
Amlodipine
Hydralazine

Atenolol
Co-amilozide
Spironolactone

Mr PR

Hx 57 M
6-year history of uncontrolled hypertension
No cardiovascular symptoms

P/Hx nil of note
F/Hx smoking ^{0}, alcohol ^{0}

Rx Bisoprolol 5mg, Losartan 100mg

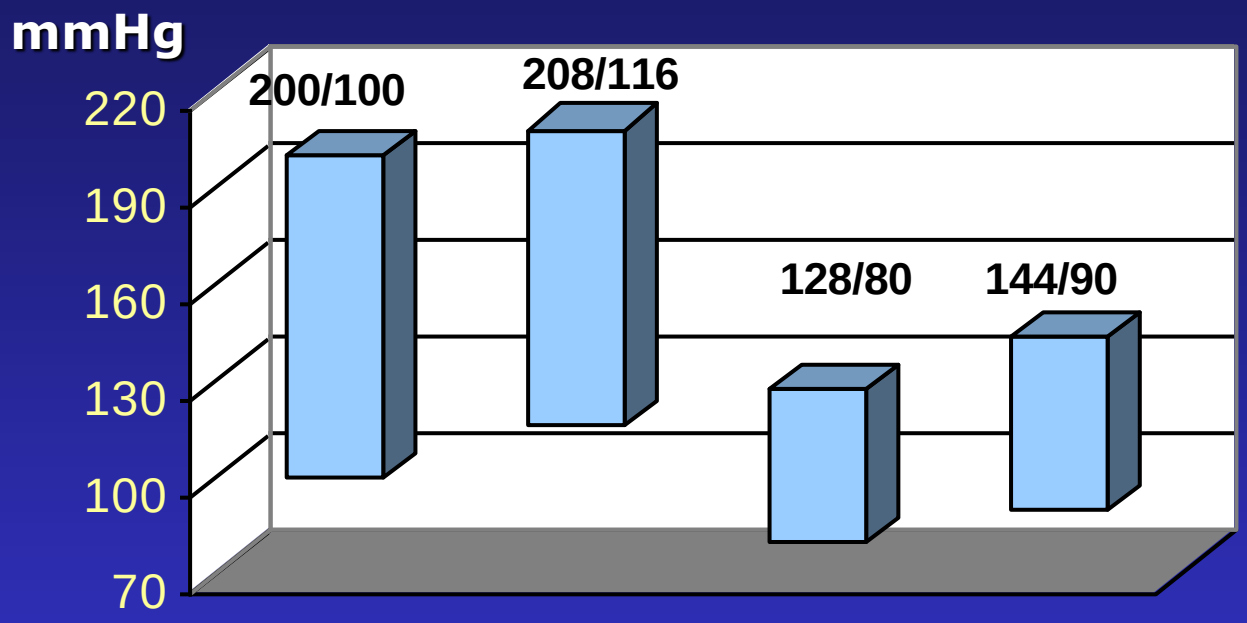
O/E 220/116 mmHg
fundi normal
Heart/lungs clear
urine dipstix normal

Mr PR

Electrolytes normal

Aldosterone	190	N	(100-450 pmol/l)
renin (PRA)	0.4	↓	(0.5-3.1 pmol/ml/hour)
AR ratio	475	N	(<750 units)

Mr PR



Losartan
Bisoprolol

Losartan
Bisoprolol
Spironolactone

Spironolactone

CT adrenal glands – normal

Prevalence of Primary Hyperaldosteronism measured by Aldosterone to Renin ratio and Spironolactone Testing (PHArst) study

Sue Hood, John Cannon, Roger Foo, Michael Scanlon, Morris Brown

Clinical Pharmacology Unit, Addenbrooke's Hospital

Background

- Gordon RD *et al*. Evidence that primary aldosteronism may not be uncommon: 12% incidence among antihypertensive drug trial volunteers. *Clin.Exp.Pharmacol.Physiol* 1993;20:296-298.
- Lim *et al*. Potentially high prevalence of primary aldosteronism in a primary-care population (14.4%: 18/125) (versus: 16% in resistant HTN clinic) *Lancet* 1999;353:40.
- Lim PO, Jung RT, MacDonald TM. Raised aldosterone to renin ratio predicts antihypertensive efficacy of spironolactone. *Br J Clin Pharmacol*. 1999;48:756-60.

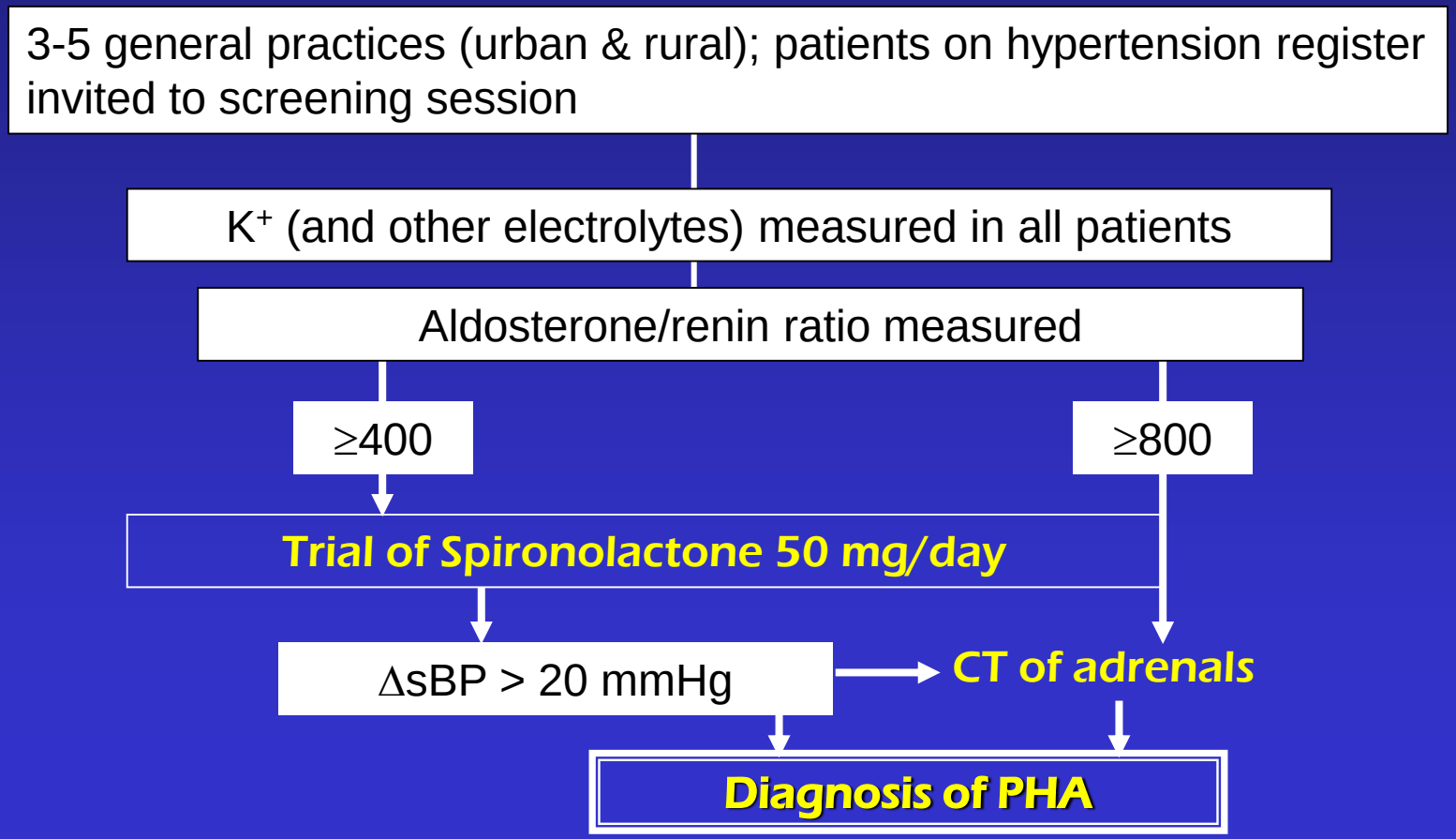
ORIGINAL PAPERS

Prevalence of primary hyperaldosteronism assessed by aldosterone/renin ratio and spironolactone testing

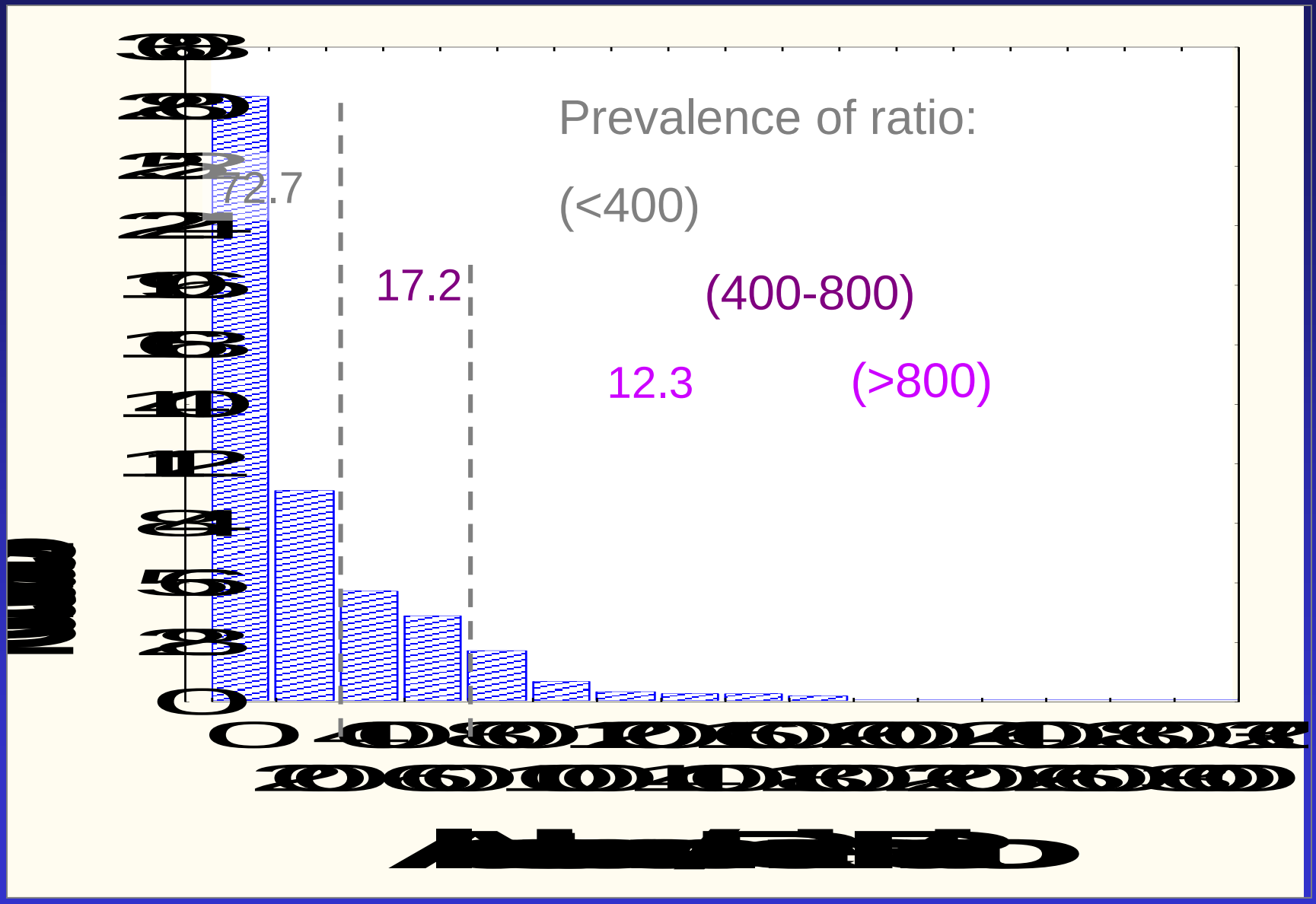
Sue Hood, John Cannon, Roger Foo and Morris Brown

Clin Med, 2005

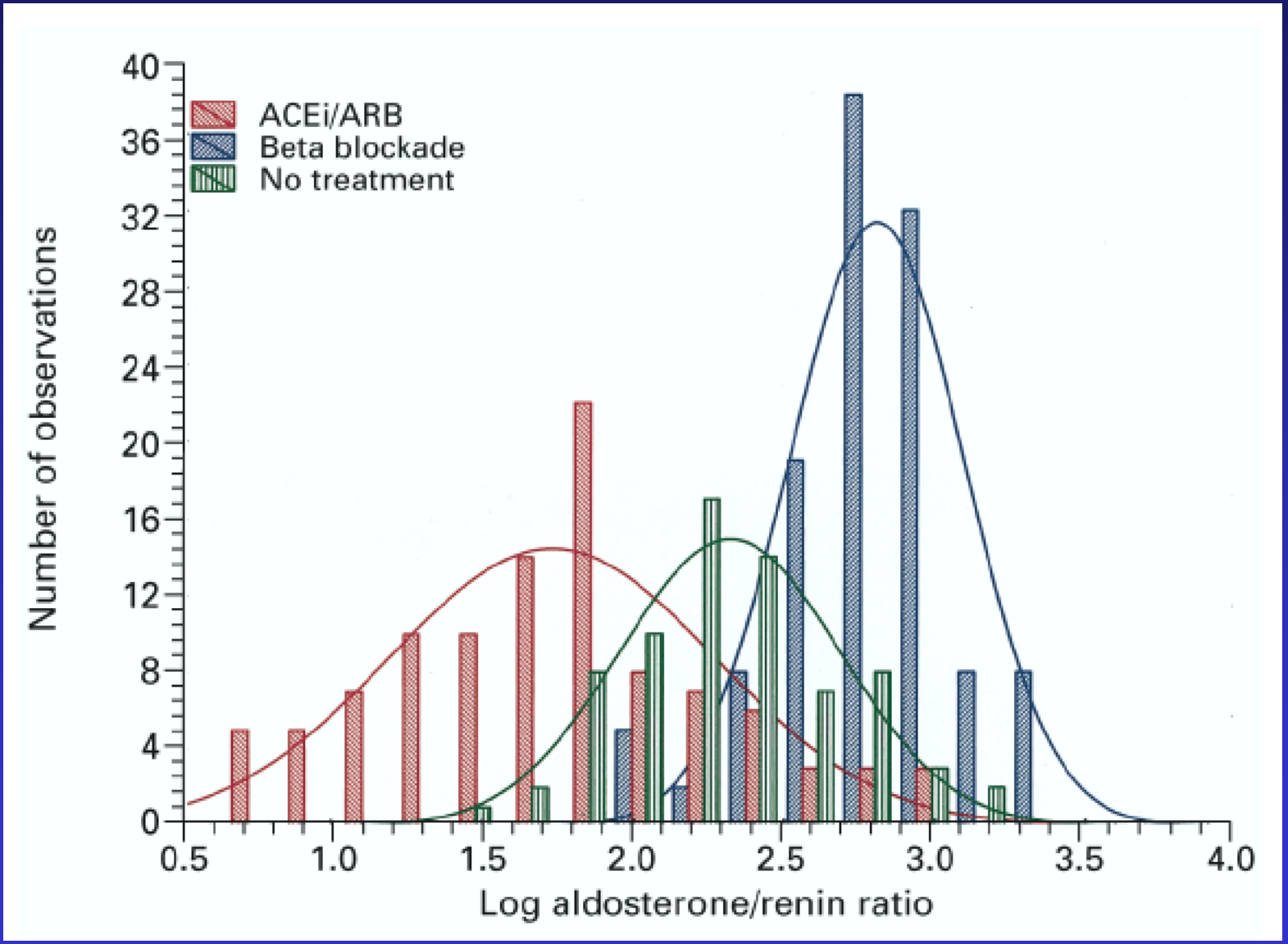
Study Plan



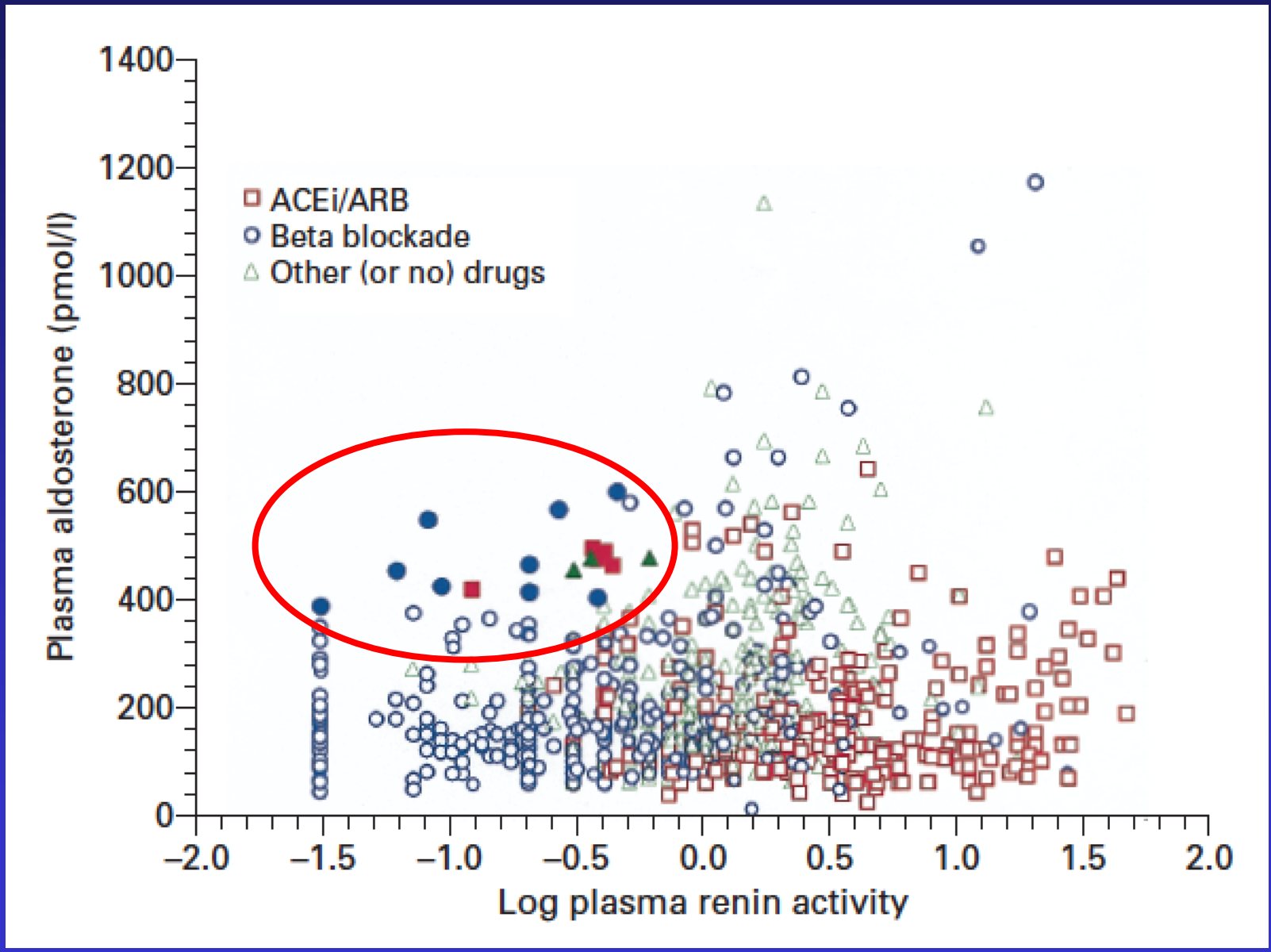
Distribution of aldosterone/renin ratio



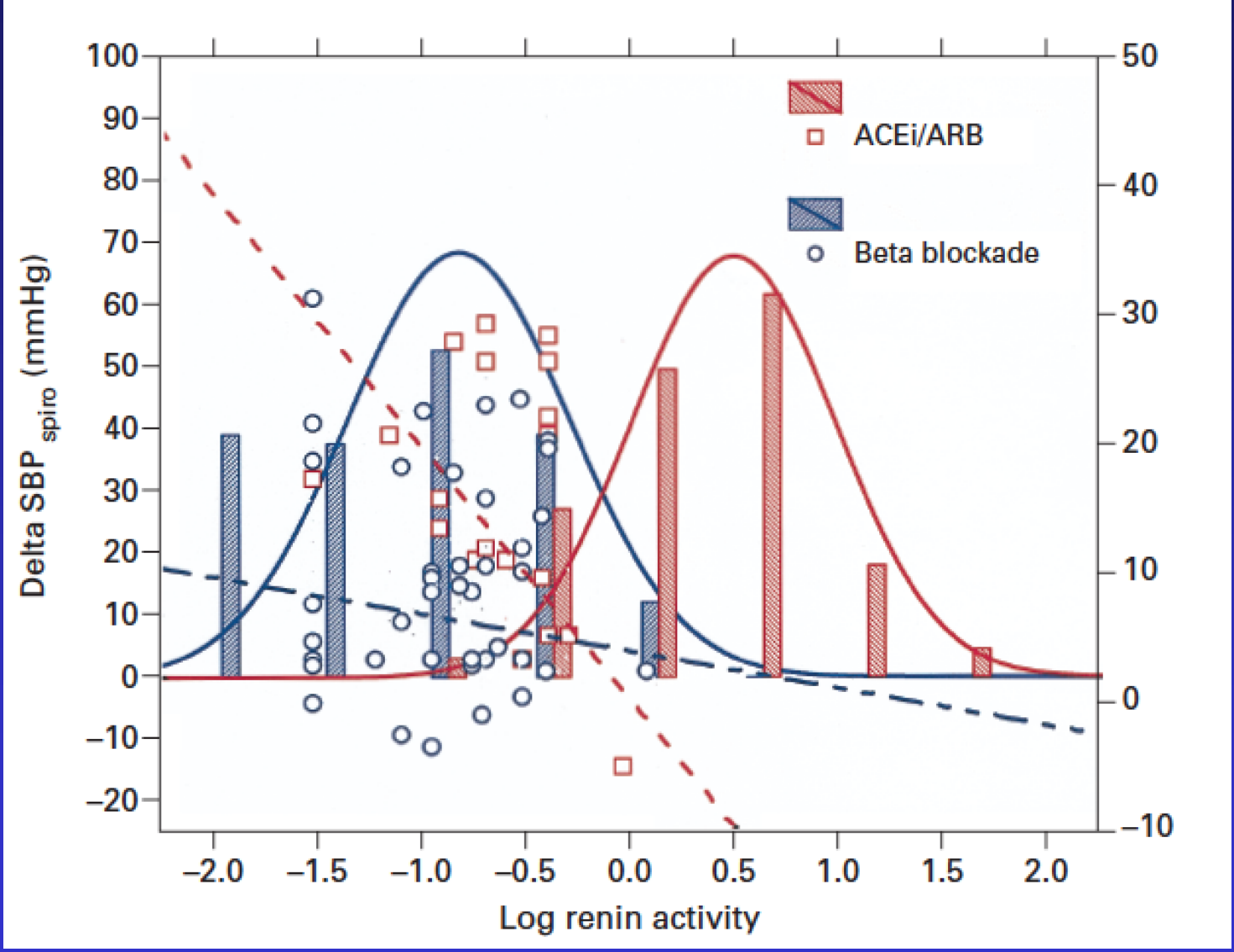
Beta-blockers but not other Rx affect aldo/renin ratio



Scattergram of aldosterone and renin levels



Plasma renin predicts response to spironolactone (excluding patients on BB)



Conclusions

Low-renin HTN !!!

A much commoner syndrome is that of low-renin resistant hypertension, which responds to spironolactone when other drugs (including thiazide diuretics) have apparently been ineffective

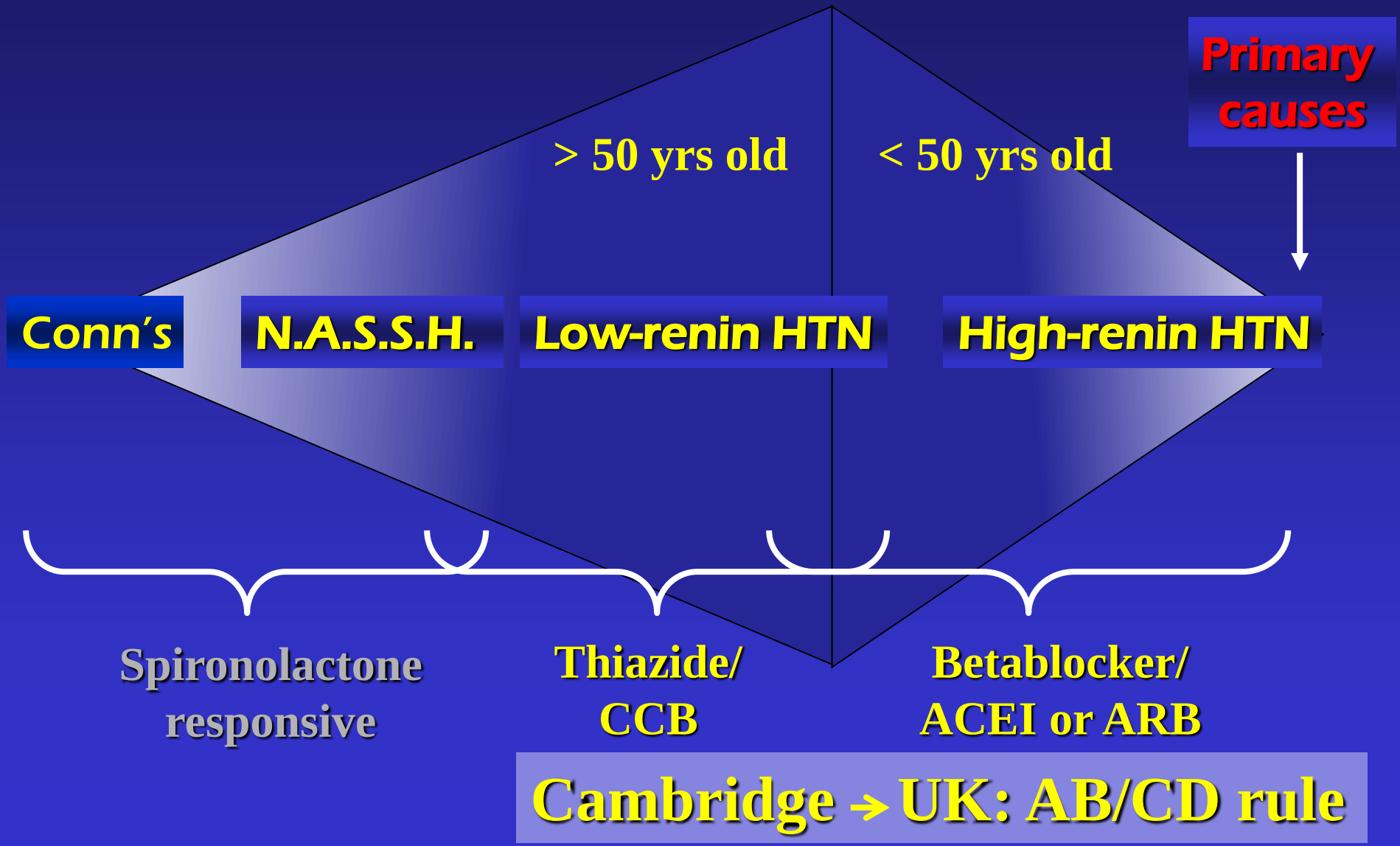
A recently introduced immunochemiluminometric assay for plasma renin mass provides a cheap and quick method for detecting both of the above syndromes, whereas the current manual assay for aldosterone can be reserved for patients with low plasma renin and hypokalaemia

Both renin and aldosterone measurements are open to confounding by commonly used antihypertensive drugs. β blockers work by suppressing renin secretion, and cause false-positive elevation of the aldosterone/renin ratio. Calcium blockers can suppress aldosterone secretion, as does hypokalaemia of any cause

Primary hyperaldosteronism is most likely when a high Na^+, low K^+, low renin and high aldosterone are found despite treatment with an ACE inhibitor or angiotensin blocker

Low-dose thiazide-induced hypokalaemia is a reason for considering, not rejecting, the diagnosis of primary hyperaldosteronism

Renin and hypertension

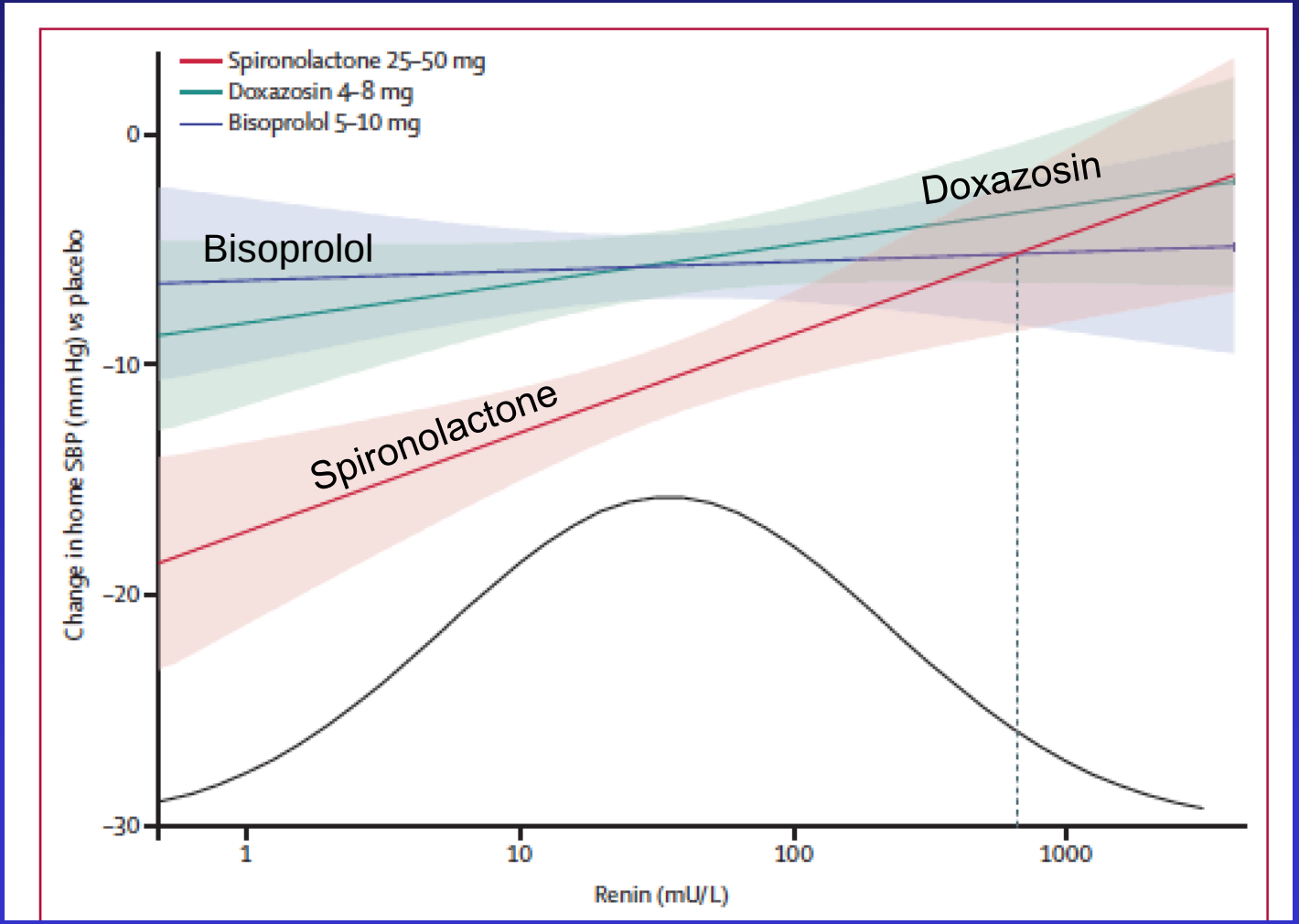


Cambridge → UK: AB/CD rule

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

*Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon Mcinnes, Ian Ford, J Kennedy Cruickshank, Mark J Caulfield, Jackie Salsbury, Isla Mackenzie, Sandosh Padmanabhan, Morris J Brown, for The British Hypertension Society's PATHWAY Studies Group**

- Clear inverse relation between BP fall with **Spironolactone** and plasma renin
- BP response was superior to **Bisoprolol** or **Doxazosin** across most plasma renin distribution

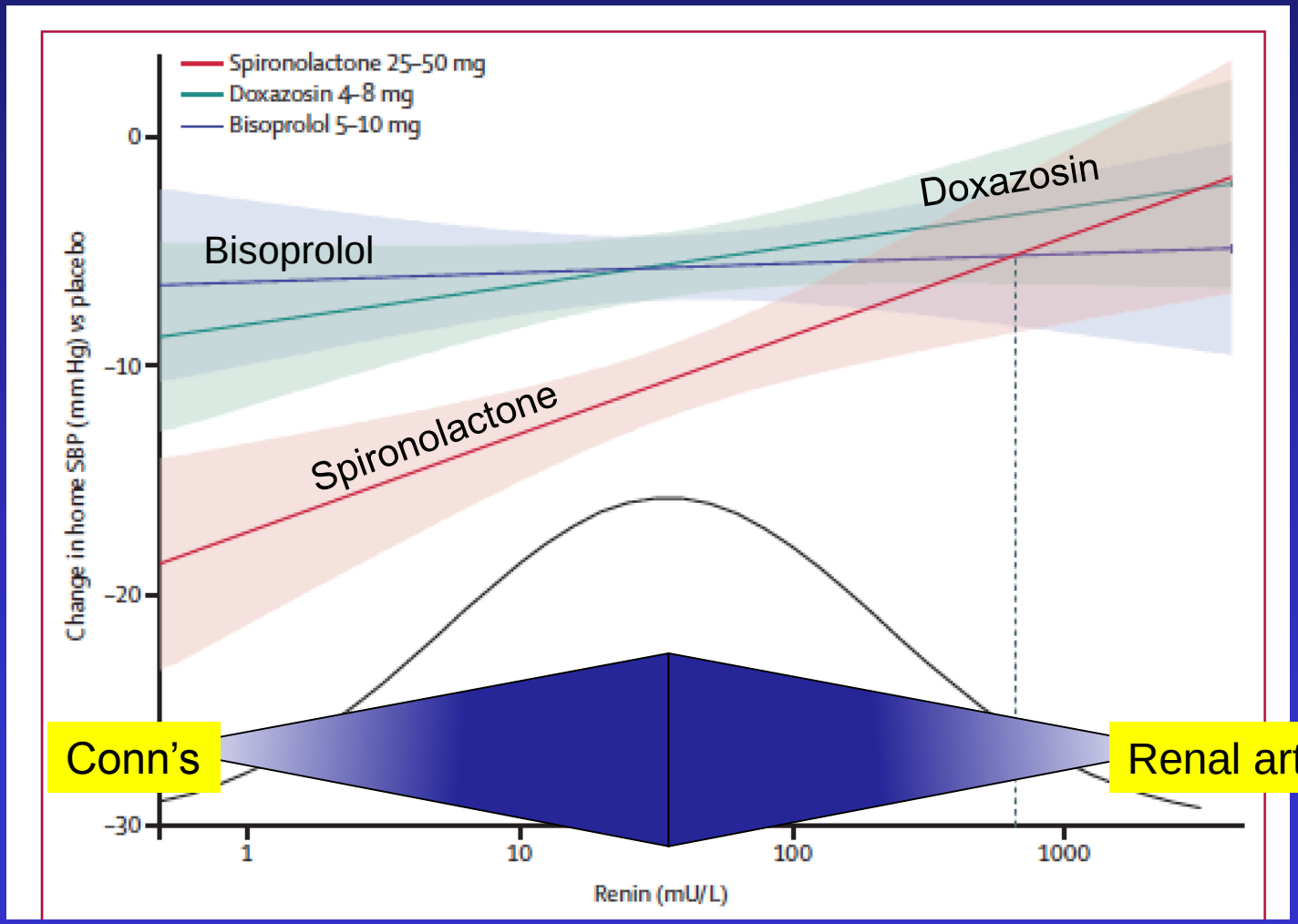


Lancet 2015

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

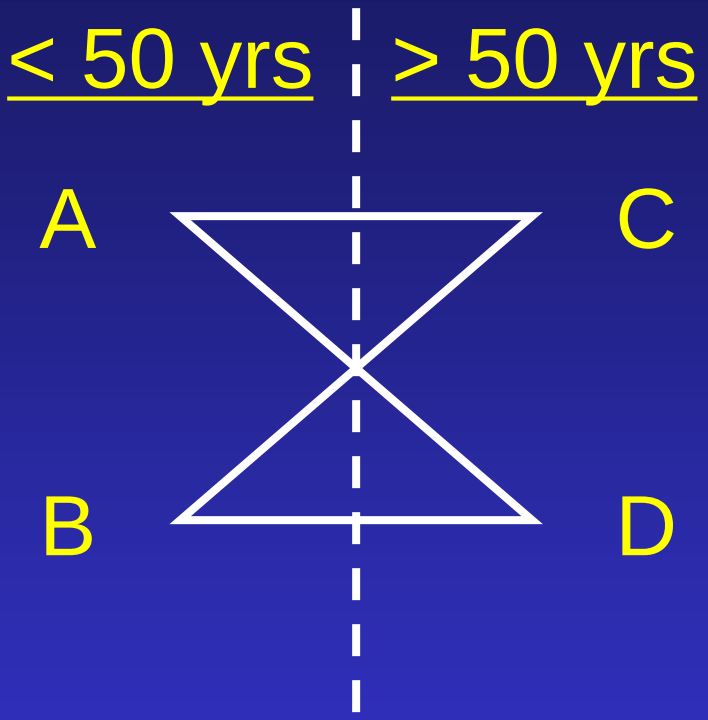
*Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon Mcinnes, Ian Ford, J Kennedy Cruickshank, Mark J Caulfield, Jackie Salsbury, Isla Mackenzie, Sandosh Padmanabhan, Morris J Brown, for The British Hypertension Society's PATHWAY Studies Group**

- Clear inverse relation between BP fall with **Spironolactone** and plasma renin
- BP response was superior to **Bisoprolol** or **Doxazosin** across most plasma renin distribution

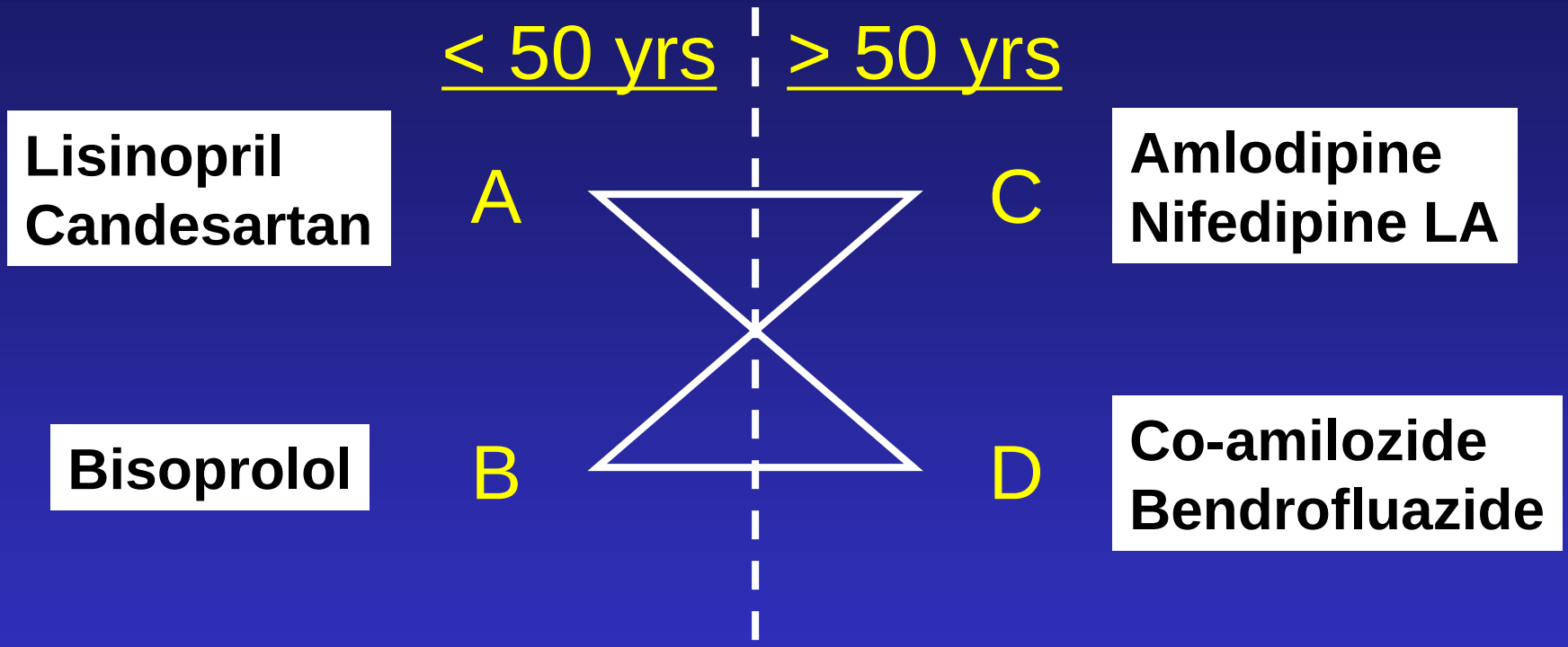


Lancet 2015

Cambridge ABCD rule



Cambridge ABCD rule



α1- blockers - Doxazosin

Centrally acting - Moxonidine

Potent vasodilators - Minoxidil

Cambridge Hypertension Clinic Protocol

Clinical examination

- primary causes: RAS, Cushing's, renal disease
- target organ damage: fundoscopy, urinstix

Routine investigations

- U+E+Cr
- cholesterol
- random glucose
- ECG
- 24h ur VMA

- renin (aldosterone)
- echocardiogram

Primary causes: suspect in young HT
primary hyperaldosteronism and others

Cambridge Hypertension Clinic Protocol

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Captopril Mag3
Plasma catecholamines
Renal angiography

Primary causes: suspect in young HT
primary hyperaldosteronism and others

Renin based proforma for treating resistant hypertension

Incorporated into the BHS IV guidelines (2004)

1 **ACEi + {Thiazide or CCB}**

Measure **Renin**

2 Add **CCB or Thiazide**

3

Low

Thiazide → + ACEi Spironolactone

Normal/High

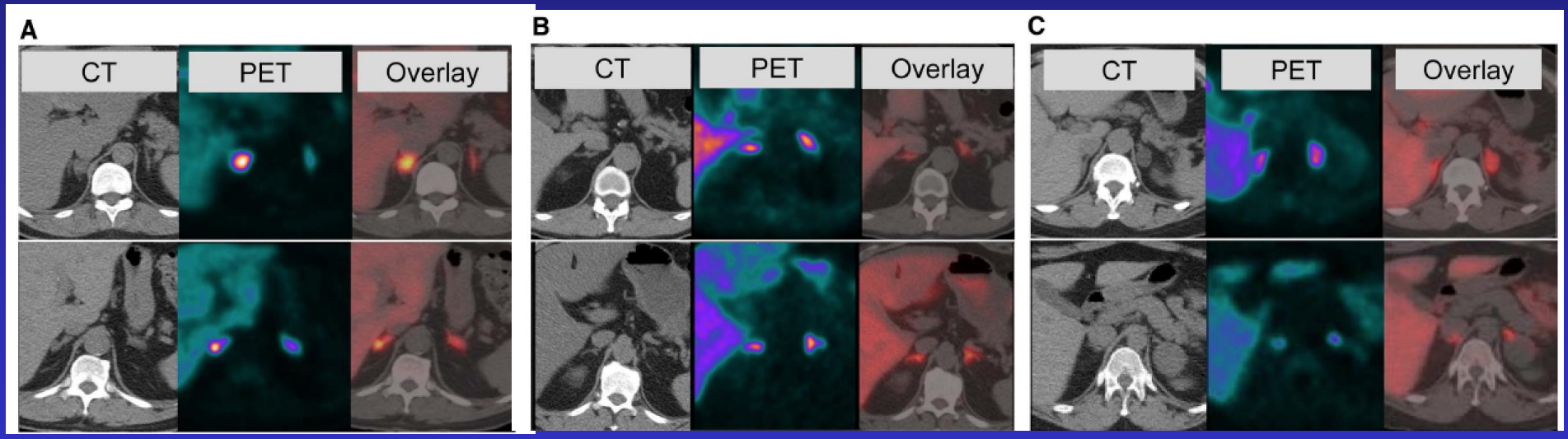
ACEi → Sartan & βblocker

4 Spironolactone + Sartan

5 Add **long-acting α -blocker**

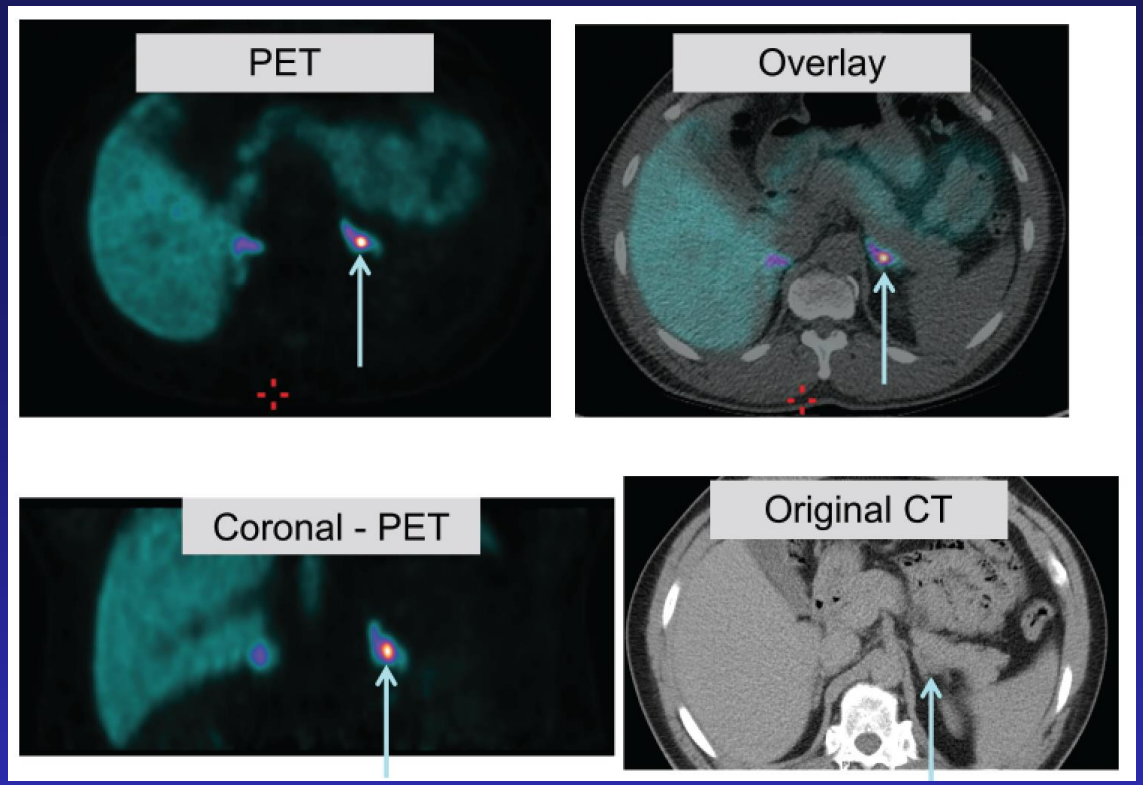
Evaluation of the Sensitivity and Specificity of ^{11}C-Metomidate Positron Emission Tomography (PET)-CT for Lateralizing Aldosterone Secretion by Conn's Adenomas

Timothy J. Burton, Isla S. Mackenzie, Kottekkattu Balan, Brendan Koo, Nick Bird, Dmitri V. Soloviev, Elena A. B. Azizan, Franklin Aigbirhio, Mark Gurnell, and Morris J. Brown



Unilateral APA	Bilateral APA	Negative

J Clin Endocrin Metab 2012



48 yo Afrocaribbean poorly controlled HTN on 5 drugs. Plasma renin 0.3pmol/ml/h off BB.

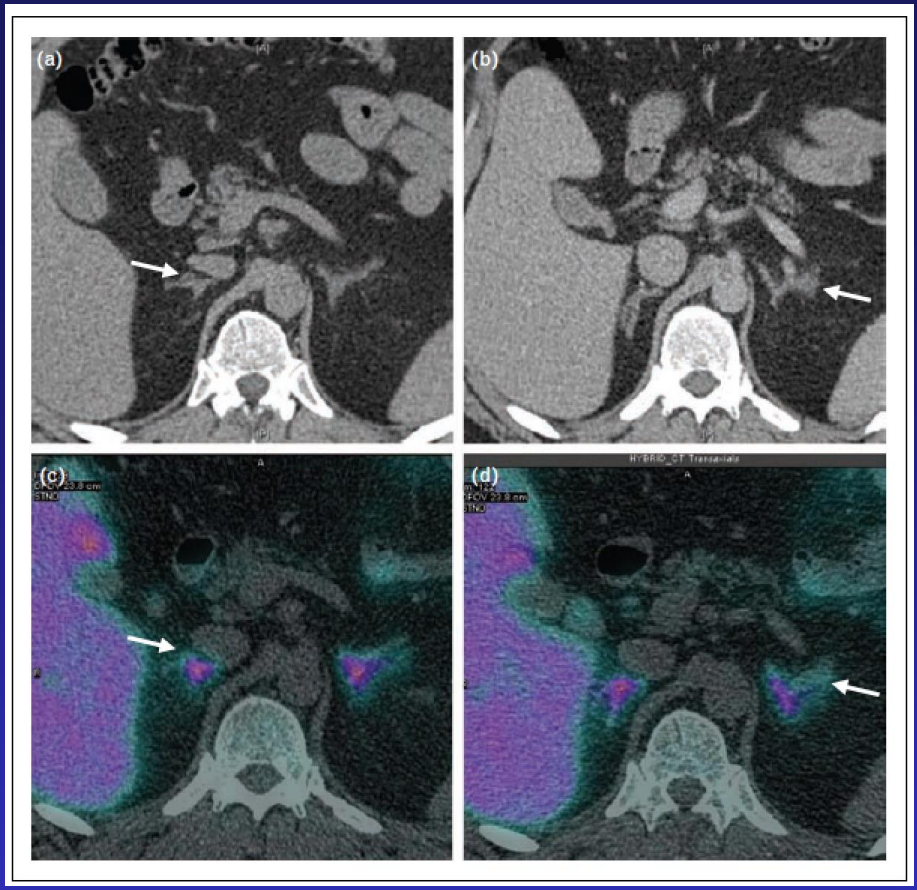
Multiple CT adrenal over several years, reported variably as thickened left adrenal/small adenoma.

^{11}C-PET CT showed clear, 6mm adenoma in left APA, visible on CT in retrospect.

Surgical adrenalectomy. Normotensive.

= Functional and anatomical diagnosis

J Clin Endocrin Metab 2012



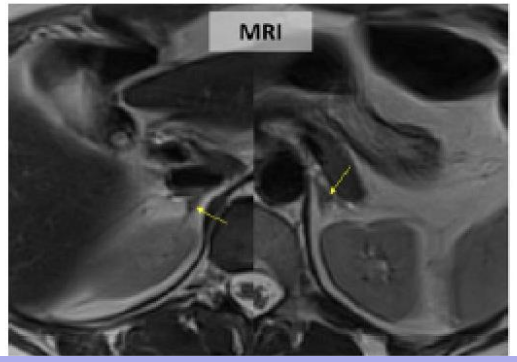
52 yo man found to have primary aldosteronism. CT: 7mm right and 16mm left adrenal adenomas, no lateralization on AVS.

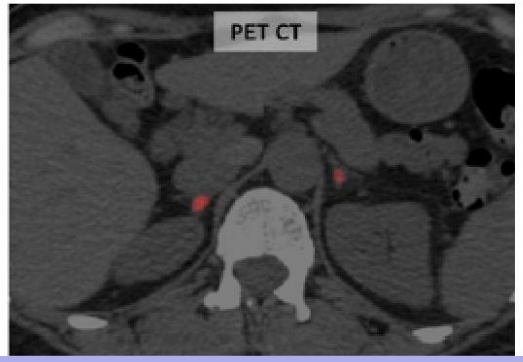
^{11}C-PET CT: boyth adenomas relatively cold. Not suggestive of surgically-remeadiable unilateral cause.

BP controlled by triple therapy: Losartan, amlodipine, BFZ + Eplerenone/amiloride.

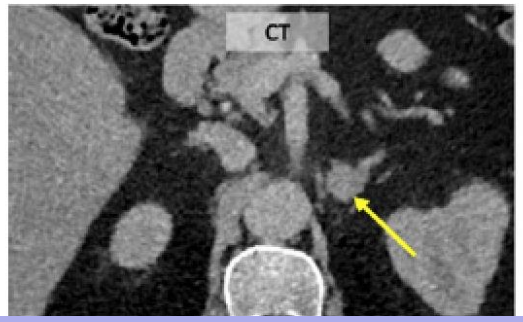
= Distinguish between APA and incidentalomas

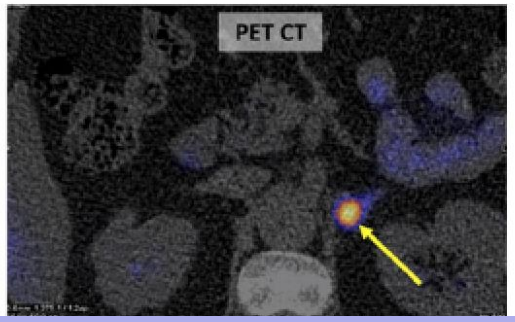
Curr Opin Endocrinol Diabetes Obes, 2015



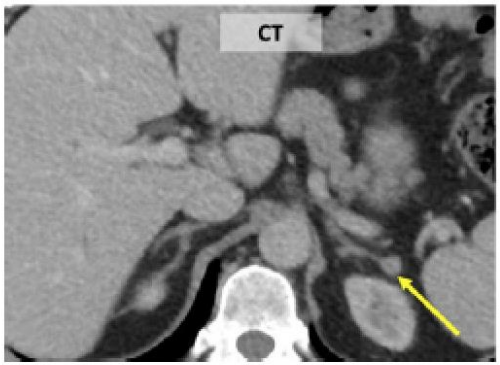


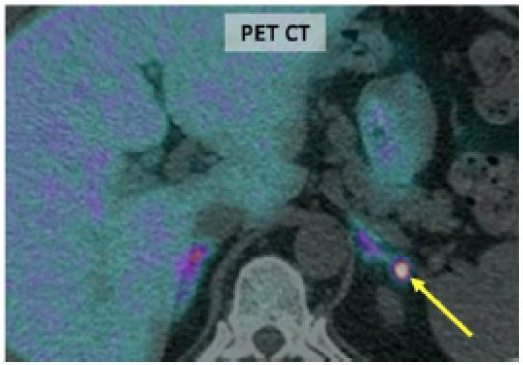
Bilateral APAs: not suspected on original MRI, but apparent in retrospect





Obvious left adrenal adenoma on CT, but AVS technically unsuccessful

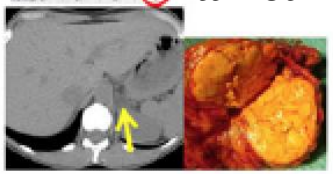




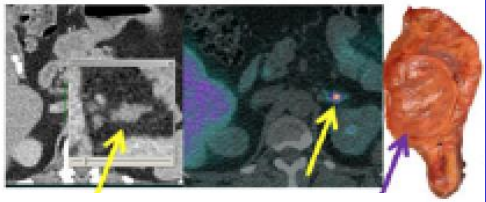
Small is beautiful: sub-cm APA caused BP 240/140 mmHg despite 5 drugs

Aldo-Producing Adenomas

Conn's original tumour >4cm



~2cm APA



Sub-cm micro APA

Clin Endocrin 2015

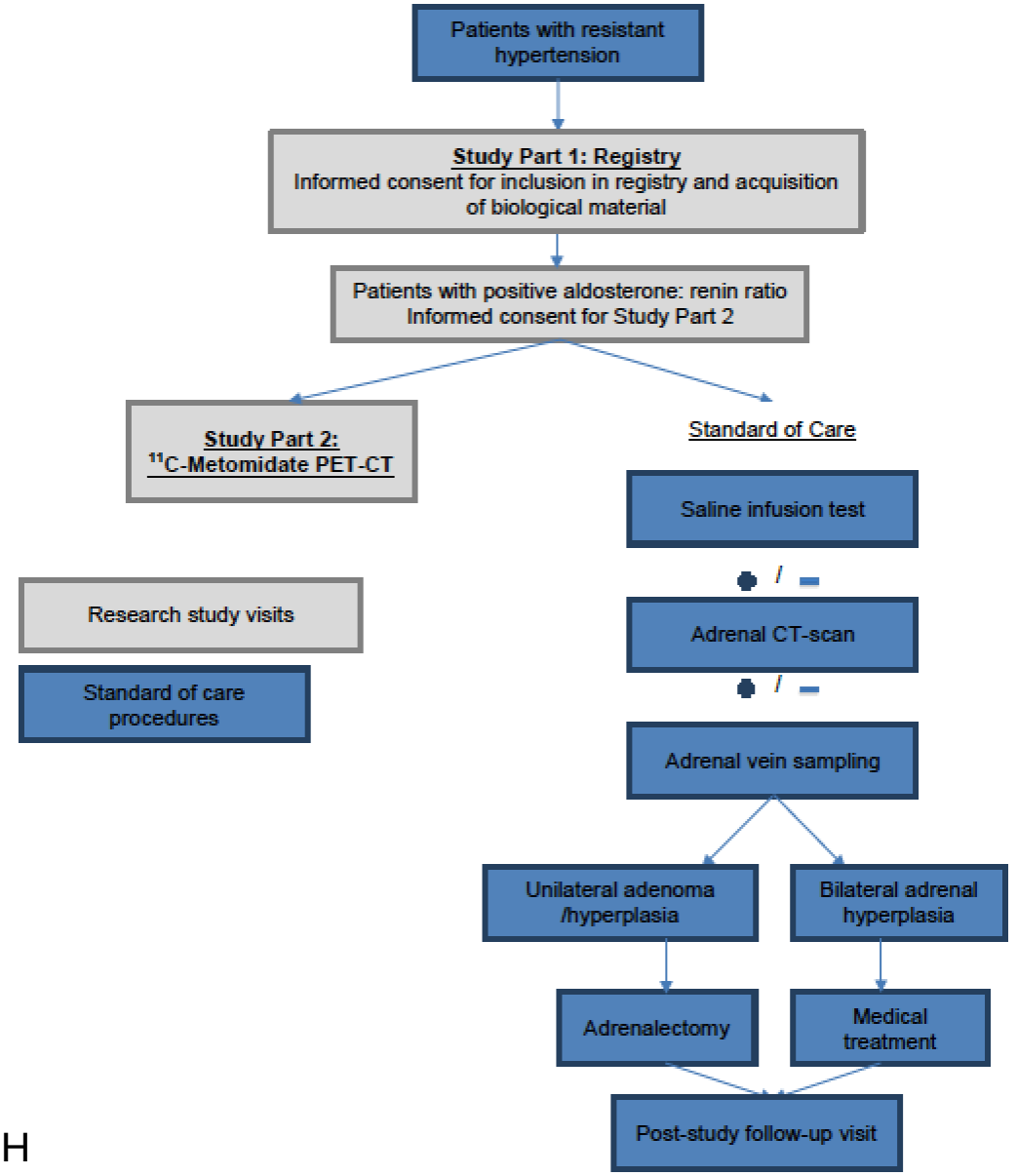
PA-CURE Study

1. The use of ^{11}C-metomidate PET-CT in Sg
2. Prevalence of low renin HTN

Audrey Wong,
Consultant Physician, NUH

Troy Puar,
Consultant Endocrinologist, CGH

Figure 2: PA-CURE Study Workflow (Theme 1)

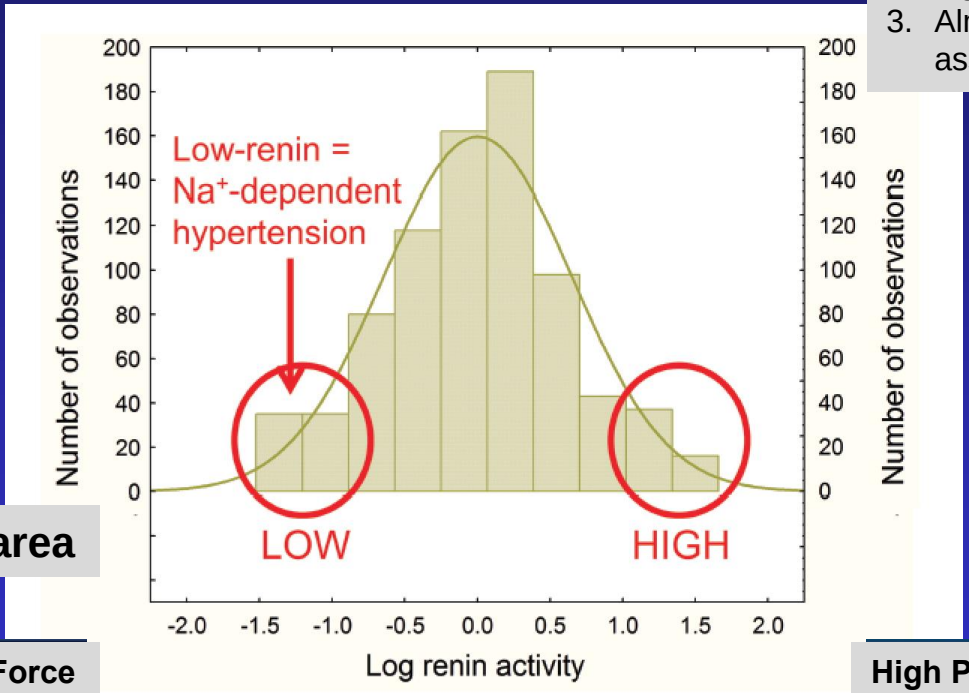


Clinical Value of Plasma Renin Estimation in the Management of Hypertension

Morris J. Brown[1]

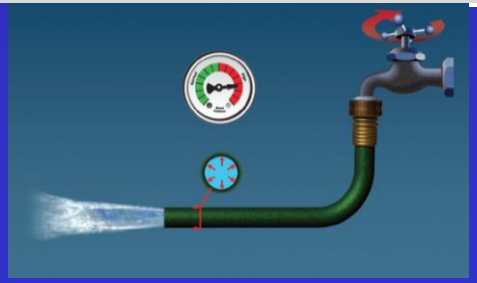
Am J Hypertens 2014

1. However complex and continuous the spectrum, **the rainbow reminds us that there are just 2 ends to a spectrum** and some remarkable distinct patterns in between.
2. Much broader spread than single log unit of most hormones
3. Almost an entire log unit can be assigned high-renin and low-renin



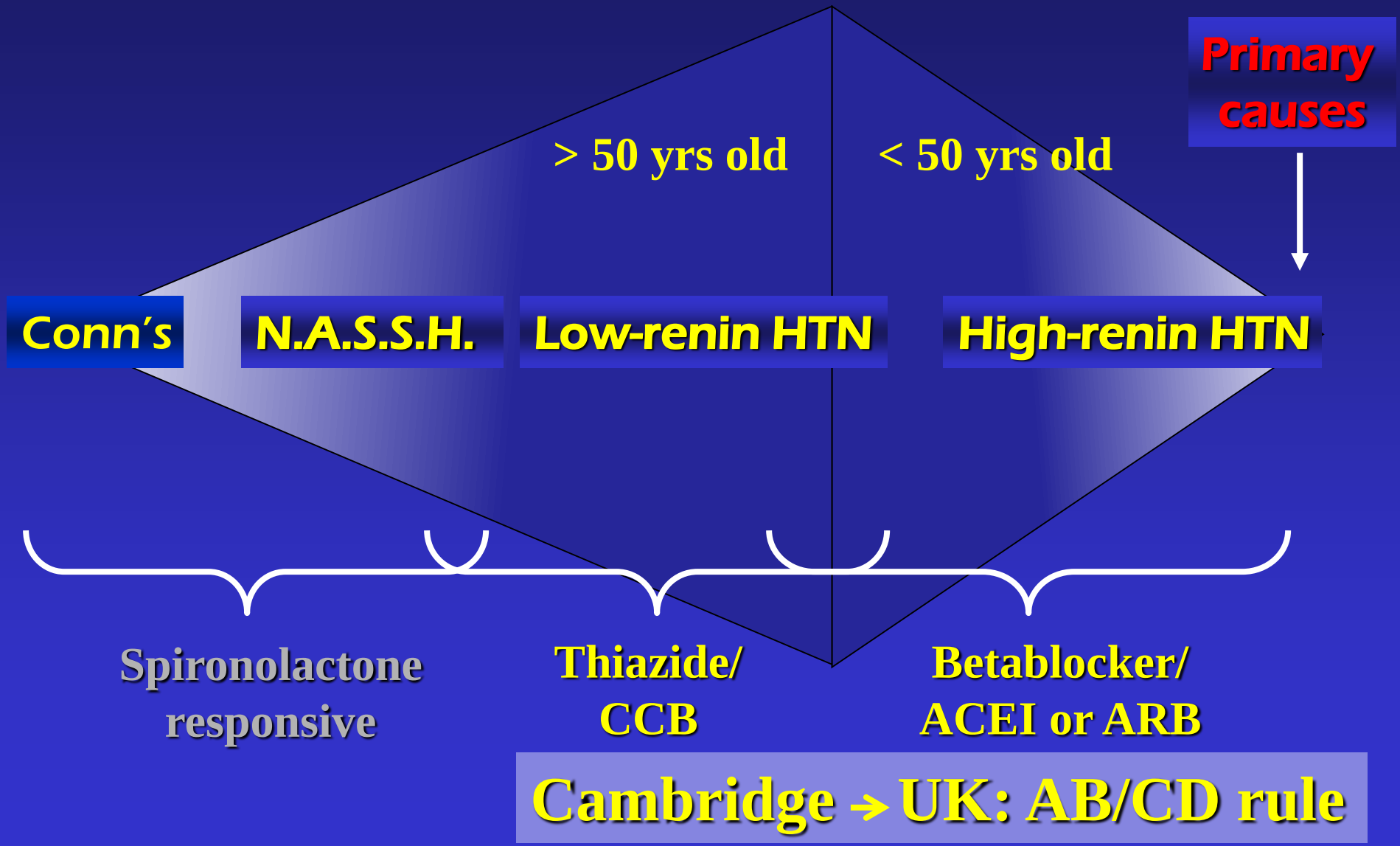
Pressure = Force / area

High Pressure due to ↑ Force



High Pressure due to ↓ Area

Renin and hypertension

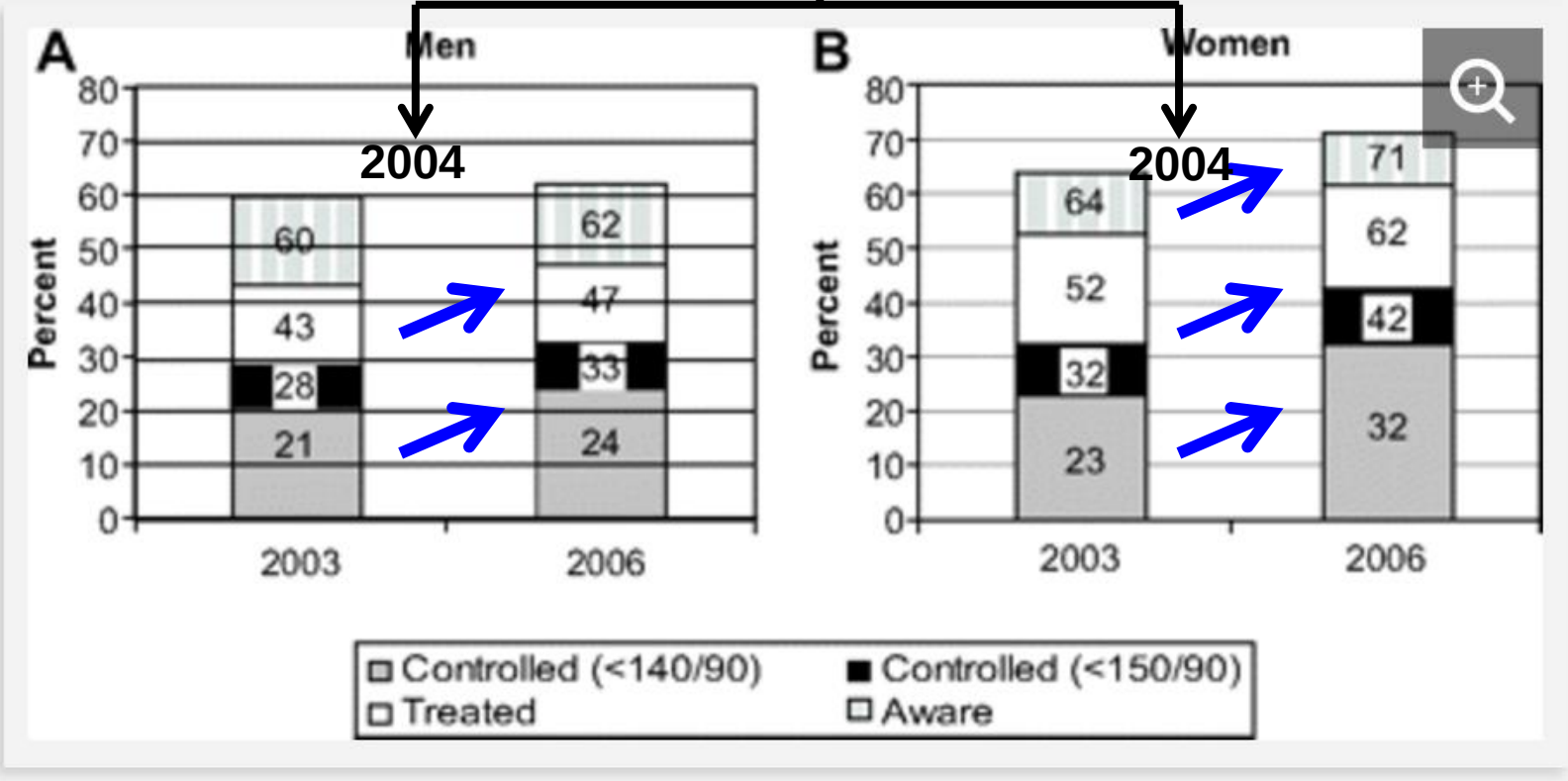


Cambridge → UK: AB/CD rule

AB/CD rule
and improvement in UK BP control

British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary AB/CD rule

Bryan Williams, Neil R Poulter, Morris J Brown, Mark Davis, Gordon T McInnes, John F Potter, Peter S Sever and Simon McG Thom



Hypertension, 2009

Thank you