Best Therapy for Resistant Hypertension: The PATHWAY-2 Study

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Conflict of interest concerning this presentation: None

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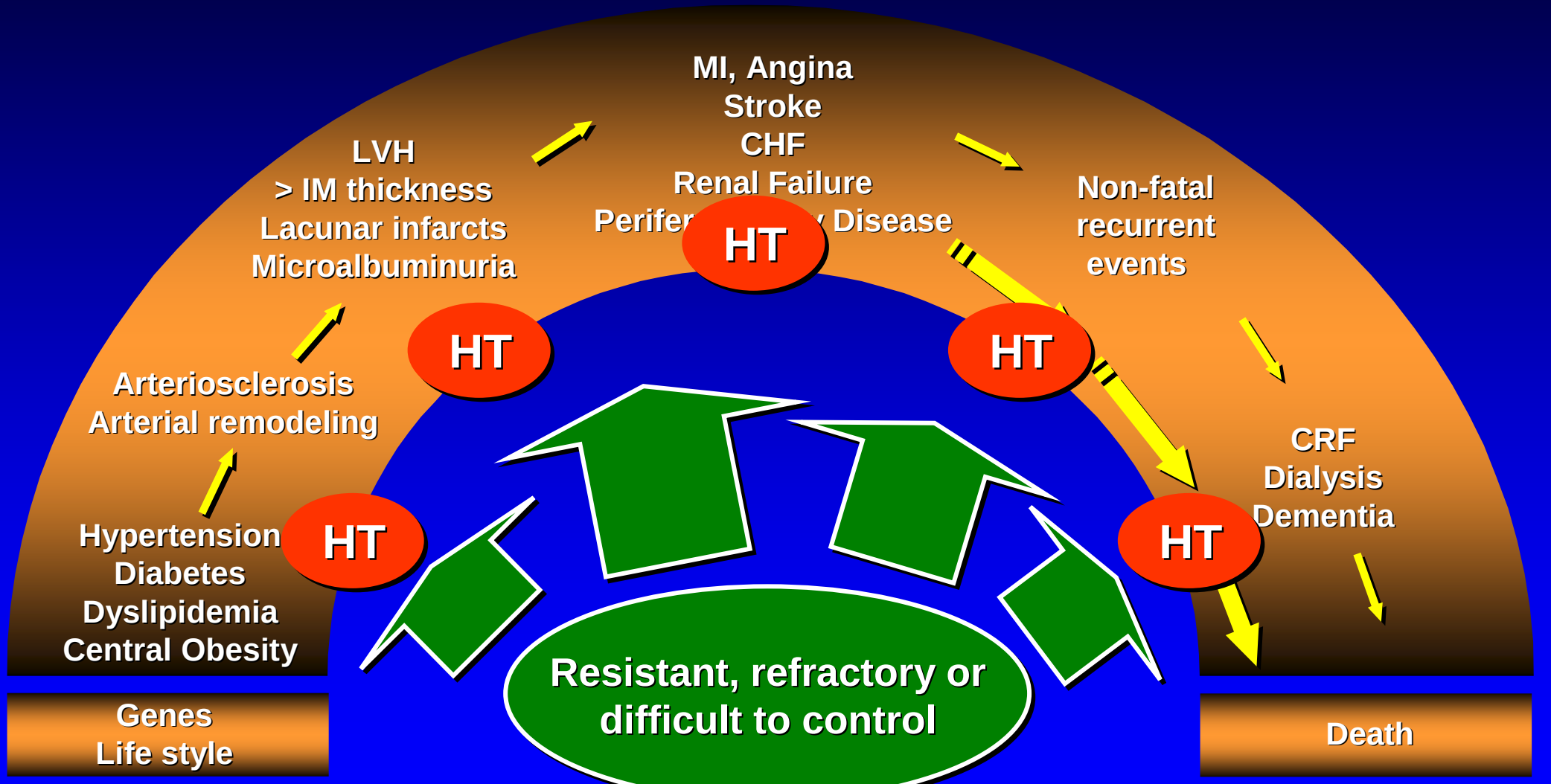
Natural History of Cardiovascular Disease



Definition of Resistant Hypertension

BP > 140/90 mmHg despite:

- Attention to lifestyle measures
- Treatment with 3 antihypertensive drugs in adequate doses (including a diuretic)

2013 ESH/ESC Guidelines. J Hypertens 2013; 31: 1281–1357
2013 ESH/ESC Guidelines. Eur Heart J 2013; 34: 2159-2219

BP < 140/90 mmHg

- Requiring 4 or more antihypertensive drugs

AHA 2008. Calhoun et al. Circulation 2008; 117: e510-e516

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Prevalence of Resistant Hypertension

- The prevalence is unknown. Most data come from observational studies and retrospective analyses of clinical trials on prevention of morbidity and mortality

- Resistant hypertension is not synonymous with uncontrolled hypertension (which includes all patients not at BP goal independently of the cause and type of treatment)

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Persell SD. Hypertension 2011;57:1076-1080

Estimated Prevalence of Resistant Hypertension in Trials on Prevention of Morbidity and Mortality

Study	Uncontrolled patients (%)	Patients with ≥3 drugs (%)	Estimated prevalence (%)
ALLHAT	34%	27%	15%
CONVINCE	33%	18%	12%
VALUE	40%	15%	10%

Epstein M. J Clin Hypertens 2007; 9 (Suppl 1): 2 -6

Prevalence of Resistant Hypertension

Data from the US National Health and Nutrition Examination Survey from 2003 – 2008 including 15,968 adults with BP≥ 140/90

- **Resistant Hypertension: BP ≥ 140/90 despite using 3 different antihypertensive drug classes or using ≥ 4 drugs regardless of BP**
- **539 patients (12.8% of drug treated patients) met criteria for resistant hypertension**

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Persell SD. Hypertension 2011;57:1076-1080

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal (2013) **34**, 1204–1214
doi:10.1093/eurheartj/ehs368

CLINICAL RESEARCH
Hypertension

Resistant hypertension: a frequent and ominous finding among hypertensive patients with atherothrombosis

Dharam J. Kumbhani[1], P. Gabriel Steg[2,3,4], Christopher P. Cannon[1,5], Kim A. Eagle[6], Sidney C. Smith Jr[7], Kevin Crowley[5], Shinya Goto[8], E. Magnus Ohman[9], George L. Bakris[10], Todd S. Perlstein[1], Scott Kinlay[1,11], and Deepak L. Bhatt[1,5,11]*, on Behalf of the REACH Registry Investigators†

- **The REACH registry is an international cohort of 53,530 patients with clinical atherosclerosis (5,587 physicians from 44 countries)**
- **The prevalence of resistant hypertension is estimated at 12.7% (6.2 treated with 3 drugs, 4.6% with 4 and 1.9% with ≥ 5 drugs)**

Kumbhani et al. Eur Heart J 2013; 34; 1204-1214

Prevalence of Resistant Hypertension

Summary

- Accepting the reported prevalence of patients uncontrolled despite treatment with ≥ 3 antihypertensives of about 12.5% (RHT)
- Assuming that no more than 10% of all evaluated patients with apparent RHT have “true essential resistant HT”
- Hypertensive patients with true essential resistant HT represent no more than 1% of all hypertensive patients
- Therefore, RHT may be considered an “infrequent” clinical condition

Jung et al. J Hypertens 2013; 31: 766-774
Kumbhani et al. Eur Heart J 2013; 34; 1204-1214
Egan BM et al. Circulation 2011;124:1046-1058
Garg et al. Am J Hypertens 2005; 18: 619-626

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Causes of Resistant Hypertension

- **Apparently Resistant Hypertension**
  - Non compliance with treatment
  - White coat hypertension
  - Pseudohypertension
- **True Resistant Hypertension**
  - Medications and illicit drug use
    - Drugs (weight loss medicines..)
    - Herbal medicines
    - Illicit drugs (cocaine,..)
  - Associated clinical factors
    - Excessive salt and alcohol consumption
    - Obesity
    - Obstructive sleep apnea

Resistant Hypertension due to incorrect diagnosis or inadequate treatment

- Identifiable causes
  - Primary aldosteronism
  - Renovascular disease
  - Chronic kidney disease
  - Pheochromocytoma, Cushing's
  - Aortic coarctation

- **No identifiable causes**
  - **"Essential" Resistant Hypertension**

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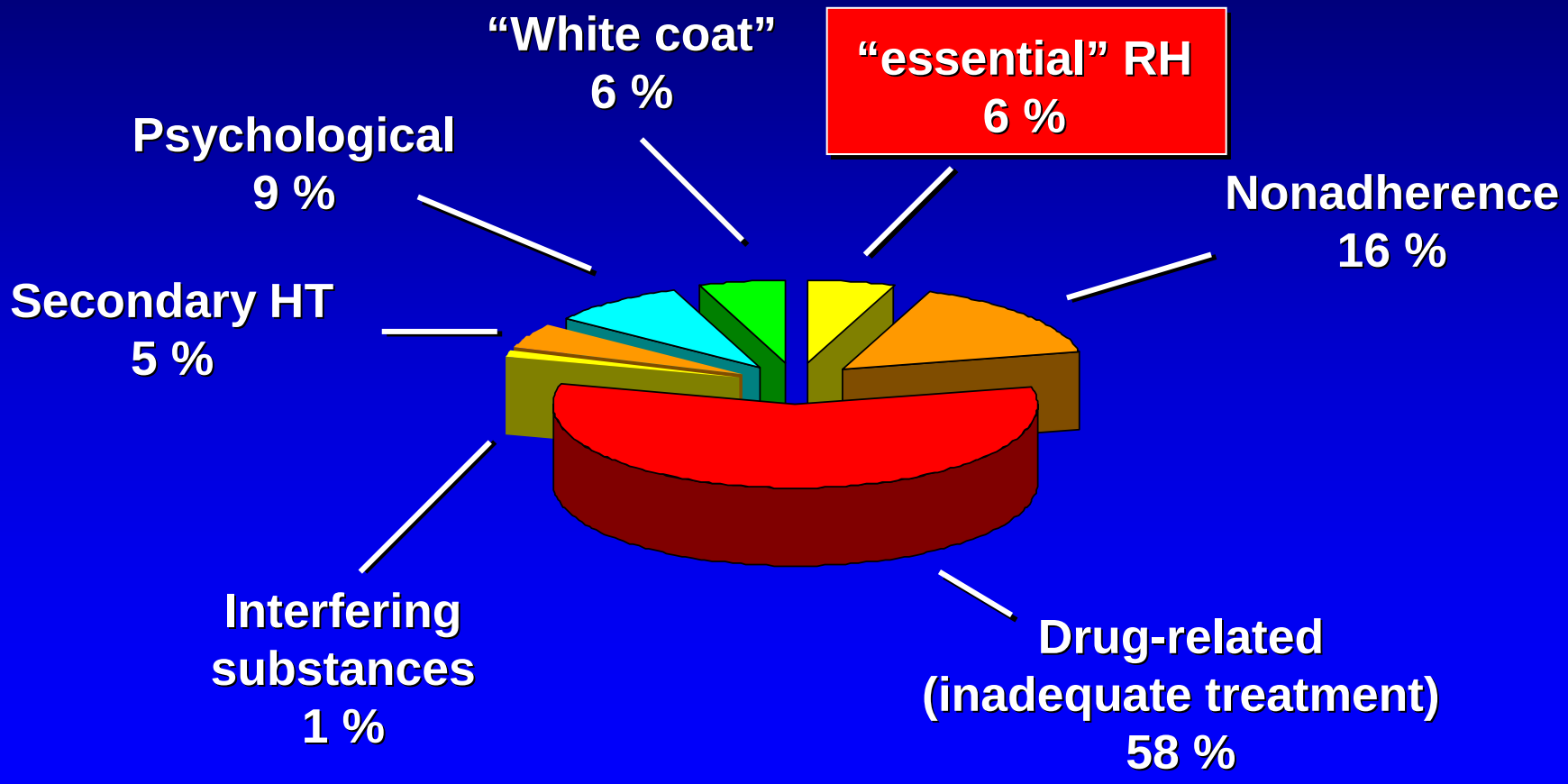
Coca A. Resistant HT In: Parra Ed. Hipertension 2n Ed. 2013; 241-259

Causes of Resistant Hypertension

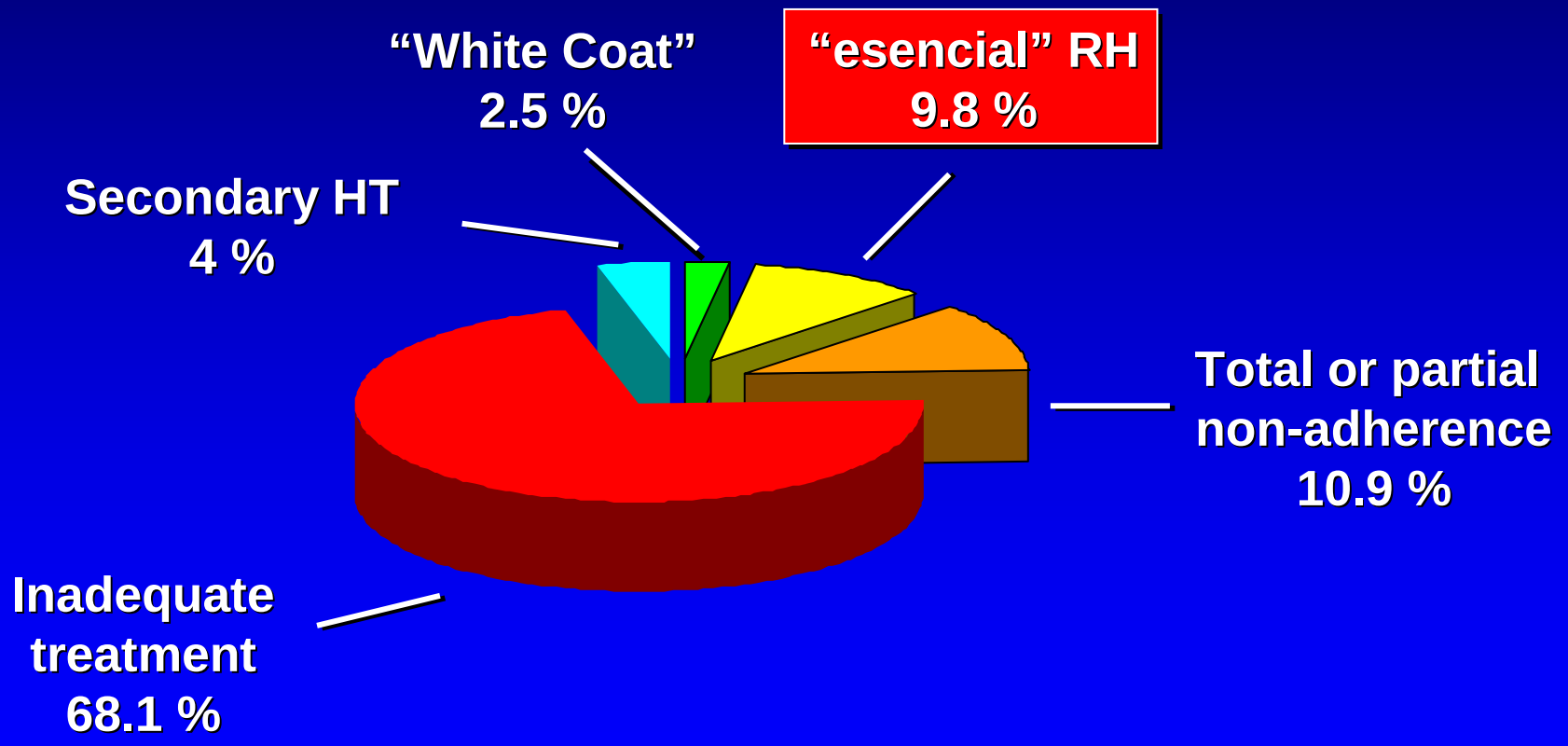
141 patients (11%) with RH out of 1281 HT attended by the Hypertension Unit, RUSH University (Chicago) between 1993 and 2001



Garg et al. Am J Hypertens 2005; 18: 619-626

Causes of Resistant Hypertension

375 patients referred to the Hypertension Unit of Goethe University Hospital (Frankfurt) between January 2004 and December 2011

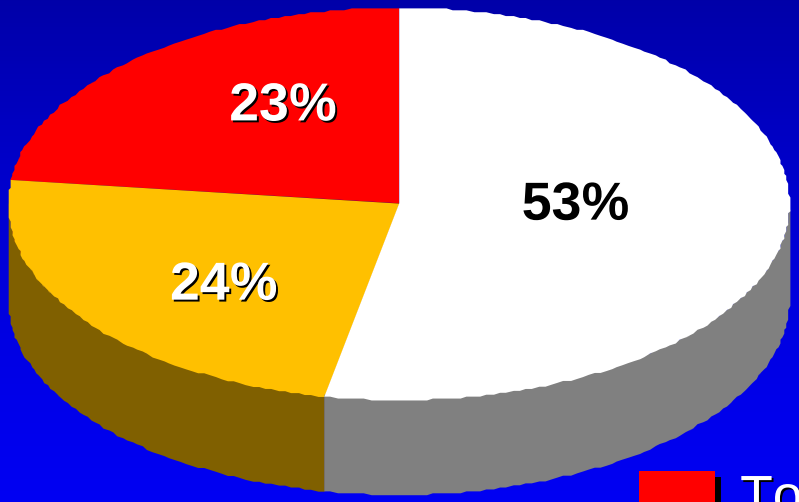


Jung et al. J Hypertens 2013; 31: 766-774

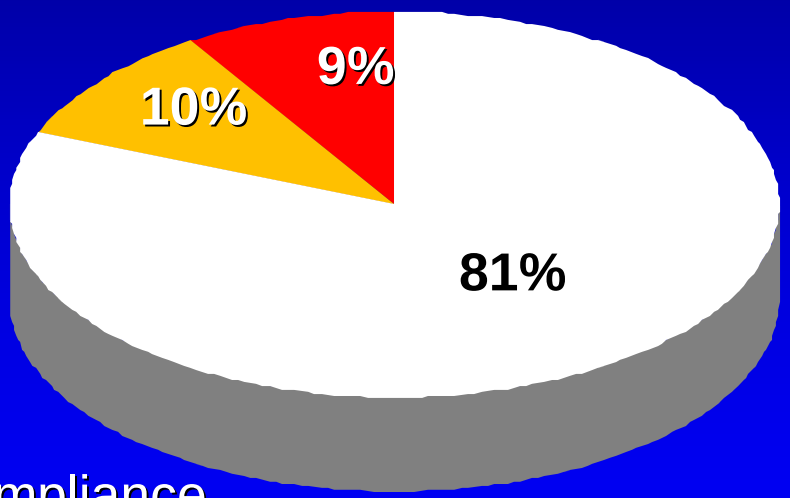
Compliance with Antihypertensive Treatment in Resistant Hypertensive Patients

Compliance assessed by unplanned blood sampling for measurement of serum antihypertensive drug concentrations in all patients

163 men with RHT investigated for first time in the Out-patients Clinic



176 men with RHT admitted for hospitalization to exclude secondary HT



Total noncompliance
Partial noncompliance
Full compliance

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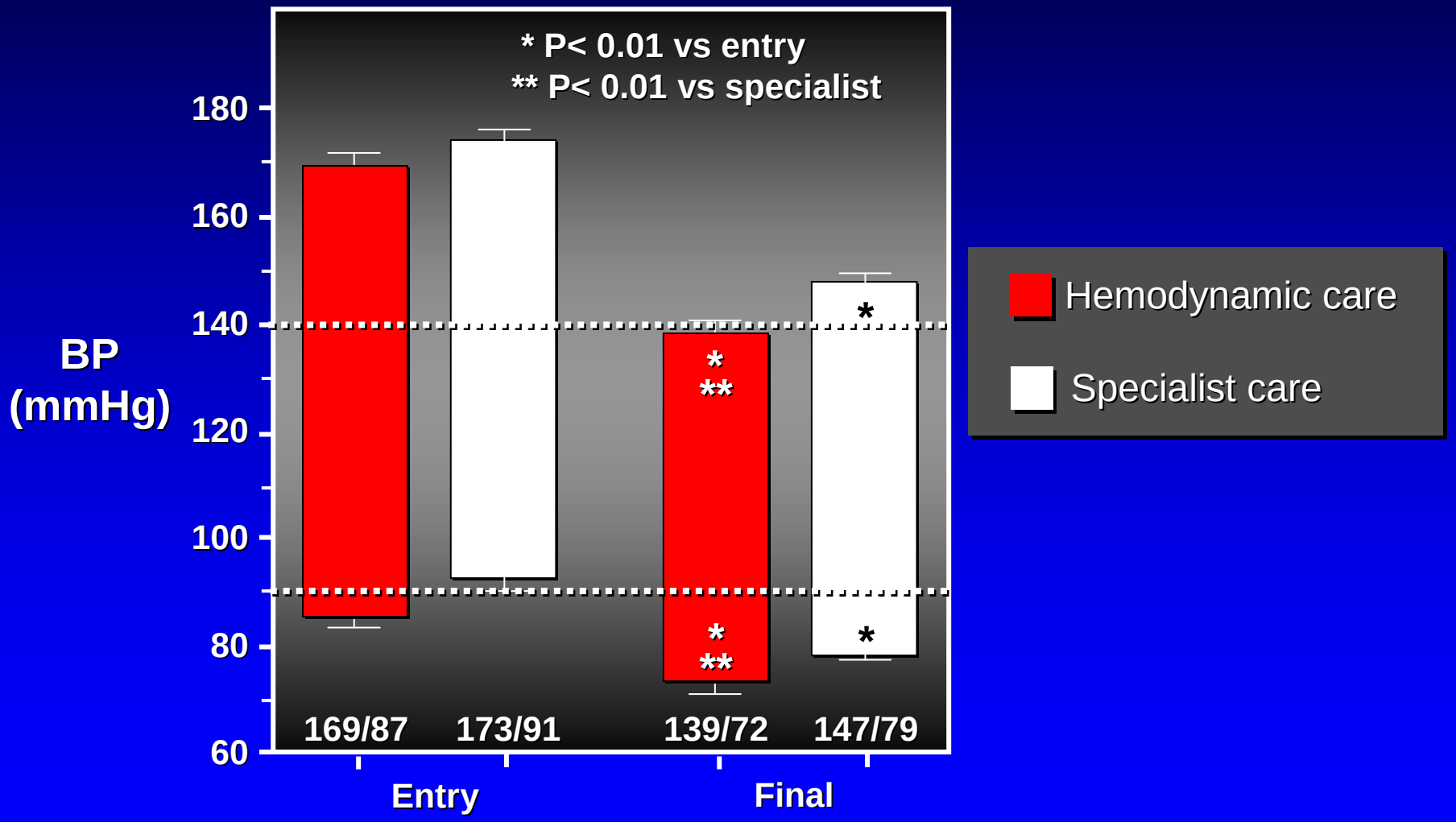
Strauch et al. J Hypertens 2013; 31: 2455-2461

Hemodynamic Treatment of Resistant Hypertension



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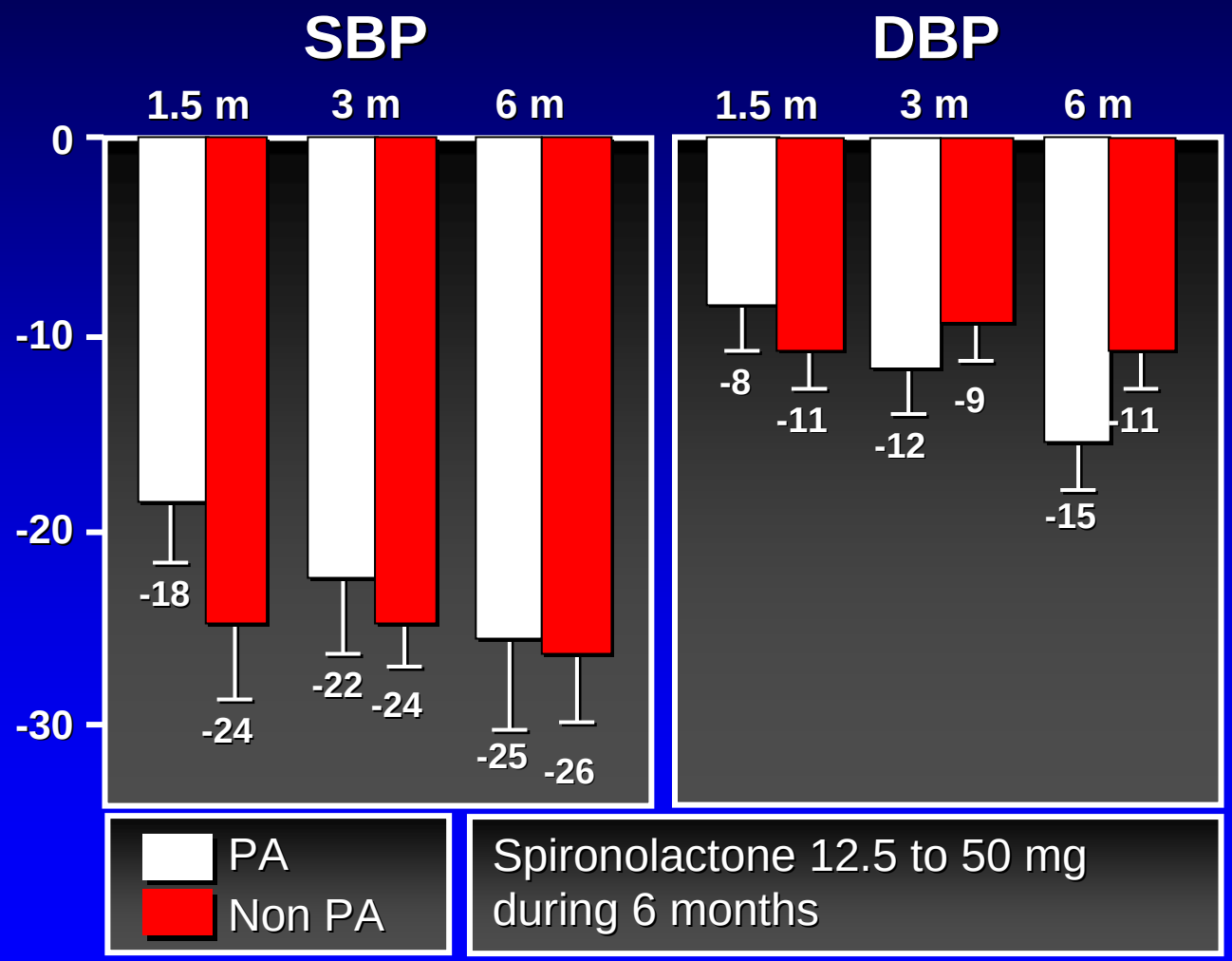
Taler et al. Hypertension 2002; 39: 982-988

Low-dose Spironolactone in the Management of Resistant Hypertension



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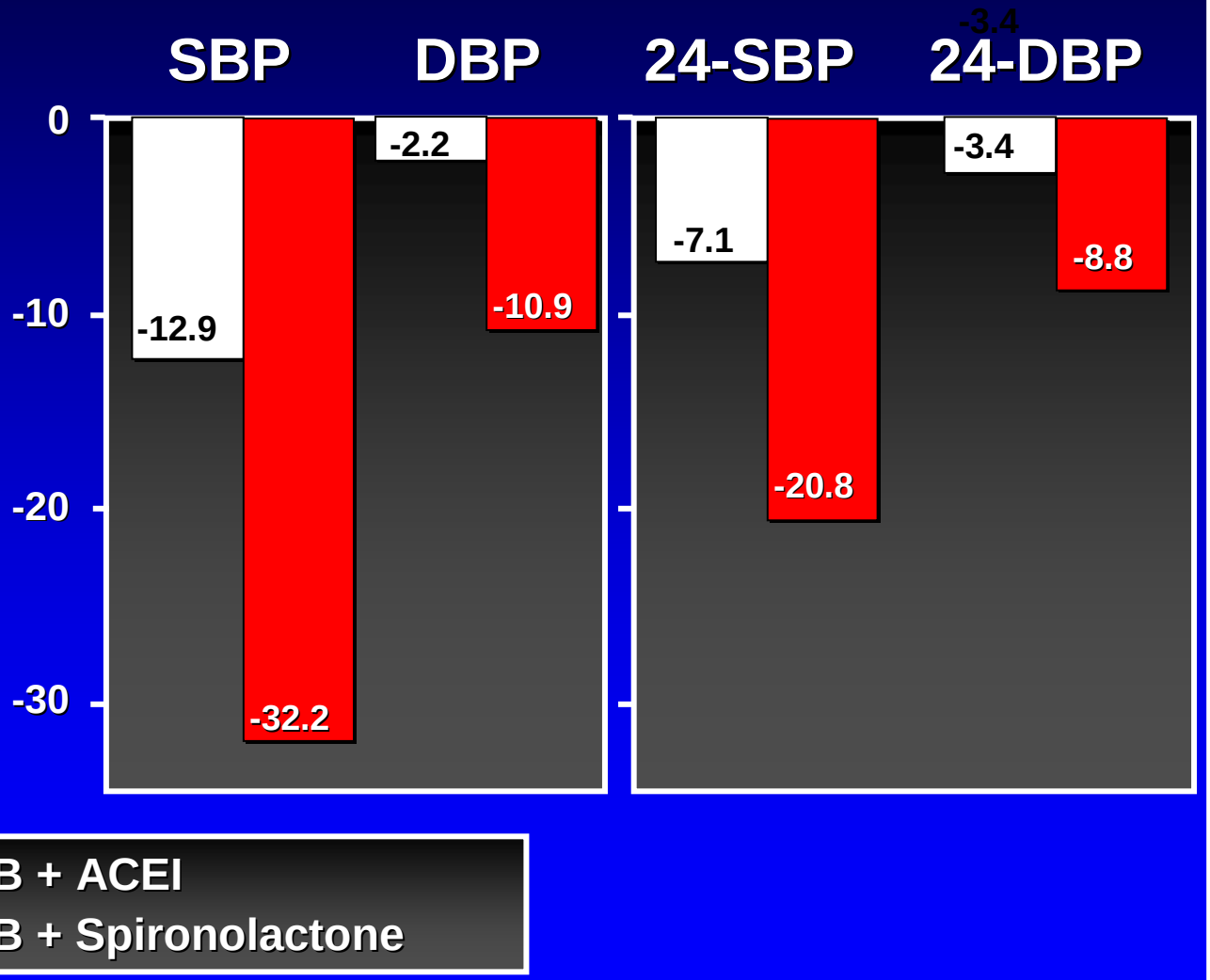
Nishizaba et al. Am J Hypertens 2003; 16: 925-930

Spironolactone vs. dual RAS Blockade in the Management of Resistant HT

- 42 patients with true Resistant hypertension
- Prospective, open-label, crossover design, with two treatment strategies:
- Phase 1: ARB + ACEI for 12 w
- Wash-out: 4 w
- Phase 2: ARB + Spironolactone 25- 50 mg for 12 w
- Mean age: 67 ± 9
- Gender: 50% male
- Baseline office SBP: 158.4 ± 15.3
- Baseline office DBP: 80.4 ± 11.4



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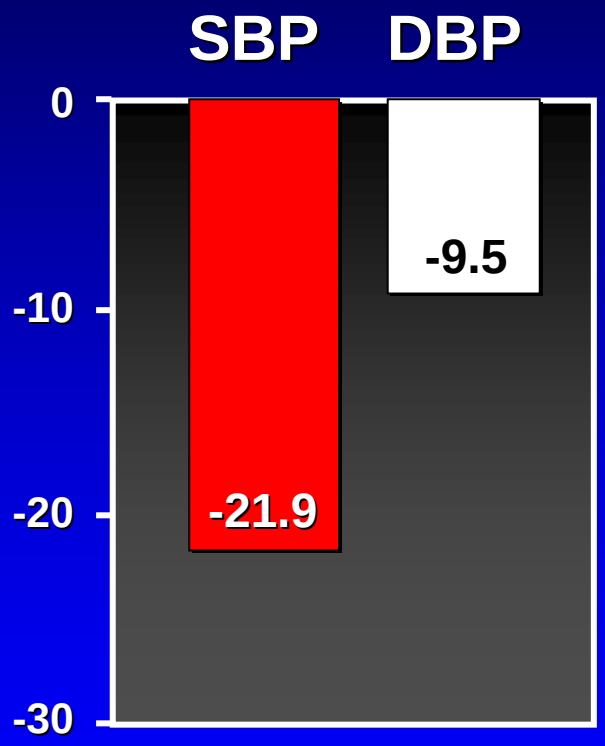
Alvarez et al. J Hypertens 2010; 28: 2329-2335

Spironolactone in the Management of Resistant Hypertension: ASCOT Study

- Prospective, open, randomized, two treatment groups:
- Group 1: AML 5-10 + PERIND 4-8 + DOXAZ 4-8
- Group 2: ATL 50-100 + DIU 1.2-2.5 + DOXAZ 4-8
- 1411 uncontrolled patients out of 19257 (7%) received 25-50 mg/d of spironolactone
- Mean age: 63 ± 8 years
- 40% with type 2 Diabetes
- Baseline BP 156.9 ± 18 / 85.3 ± 11.5



- K^+: ↑ 0.41 mmol/L
- 4% K^+ > 5.5 mmol/L
- 2% K^+ > 6.0 mmol/L
- Cr: ↑ 0.1 mg/dL
- Side effects 6%
- Final mean dose of spironolactone 41 mg
- Follow-up 1.3 years (0.6-2.6)

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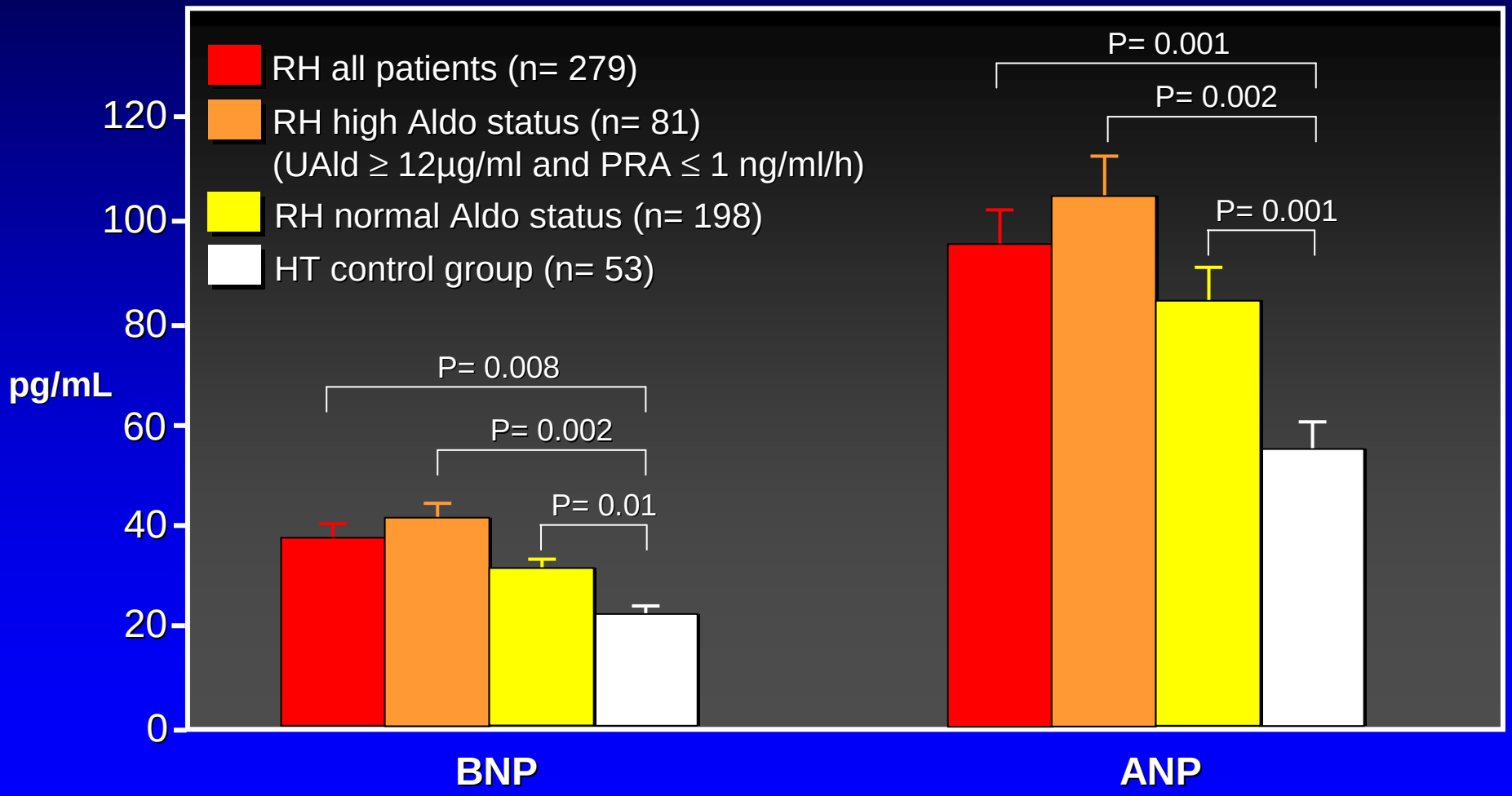
Chapman et al. Hypertens 2007; 49: 839-845

Resistant Hypertension, Aldosterone, and Intravascular Volume Expansion



Gaddam KK et al. Arch Intern Med 2008; 168: 1159-1164

PATHWAY
Clinical Trials in Hypertension

The **P**revention **A**nd **T**reatment of **H**ypertension **W**ith **A**lgorithm based therap**Y**
PATHWAY

Optimal Treatment of Drug Resistant Hypertension
PATHWAY-2

Principal Results

Bryan Williams, Tom MacDonald and Morris Brown
on behalf of the PATHWAY Investigators

Williams B, et al. Lancet 2015; 386: 2059-2068

British Heart Foundation

BHS British Hypertension Society

NHS National Institute for Health Research

Background

- The optimal drug treatment of resistant hypertension remains undefined
- Recent meta-analysis, 3 small RCTs, and several open/observational studies suggests that spironolactone is an effective treatment versus placebo
- There have been no RCTs directly comparing spironolactone with other BP-lowering drugs to determine whether spironolactone is the most effective treatment for resistant hypertension

Dahal K, et al. Am J Hypertens, 2015

Hypothesis

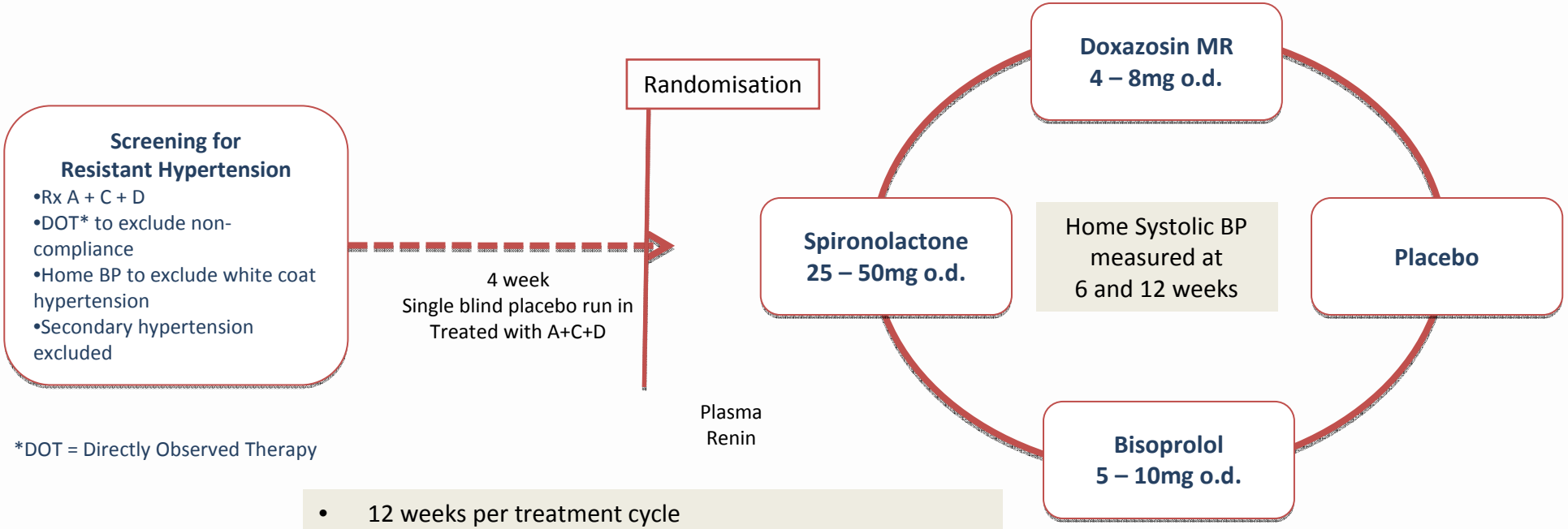
- Resistant hypertension is a sodium retaining state that is characterised by an inappropriately low plasma renin level despite treatment with a RAS-blocker + CCB + Thiazide Diuretic
- Further diuretic therapy with spironolactone will be more effective at lowering BP than alternative treatments, targeting different mechanisms, i.e. bisoprolol (β-sympathetic blockade and renin suppression) or doxazosin MR (α-sympathetic blockade and vasodilatation)
- Plasma renin level will be inversely related to the response to spironolactone

Williams B, et al. Lancet 2015; 386: 2059-2068

PATHWAY-2
Clinical Trials in Hypertension

PATHWAY-2 Study Design

Double blind, Randomised, Placebo-Controlled, Cross-over Study



*DOT = Directly Observed Therapy

- 12 weeks per treatment cycle
- Forced titration; lower to higher dose at 6 weeks
- No washout period between cycles

Williams B, et al. Lancet 2015; 386: 2059-2068

Primary outcome measures

Hierarchical Primary End-point:

1) Difference in average home systolic BP (HSBP) between spironolactone and placebo

followed, if significant by;

2) HSBP difference between spironolactone and the average of the other two active drugs (bisoprolol and doxazosin MR)

followed, if significant by;

3) HSBP difference between spironolactone and each of the other two active drugs

Williams B, et al. Lancet 2015; 386: 2059-2068

PATHWAY 2
Clinical Trials in Hypertension

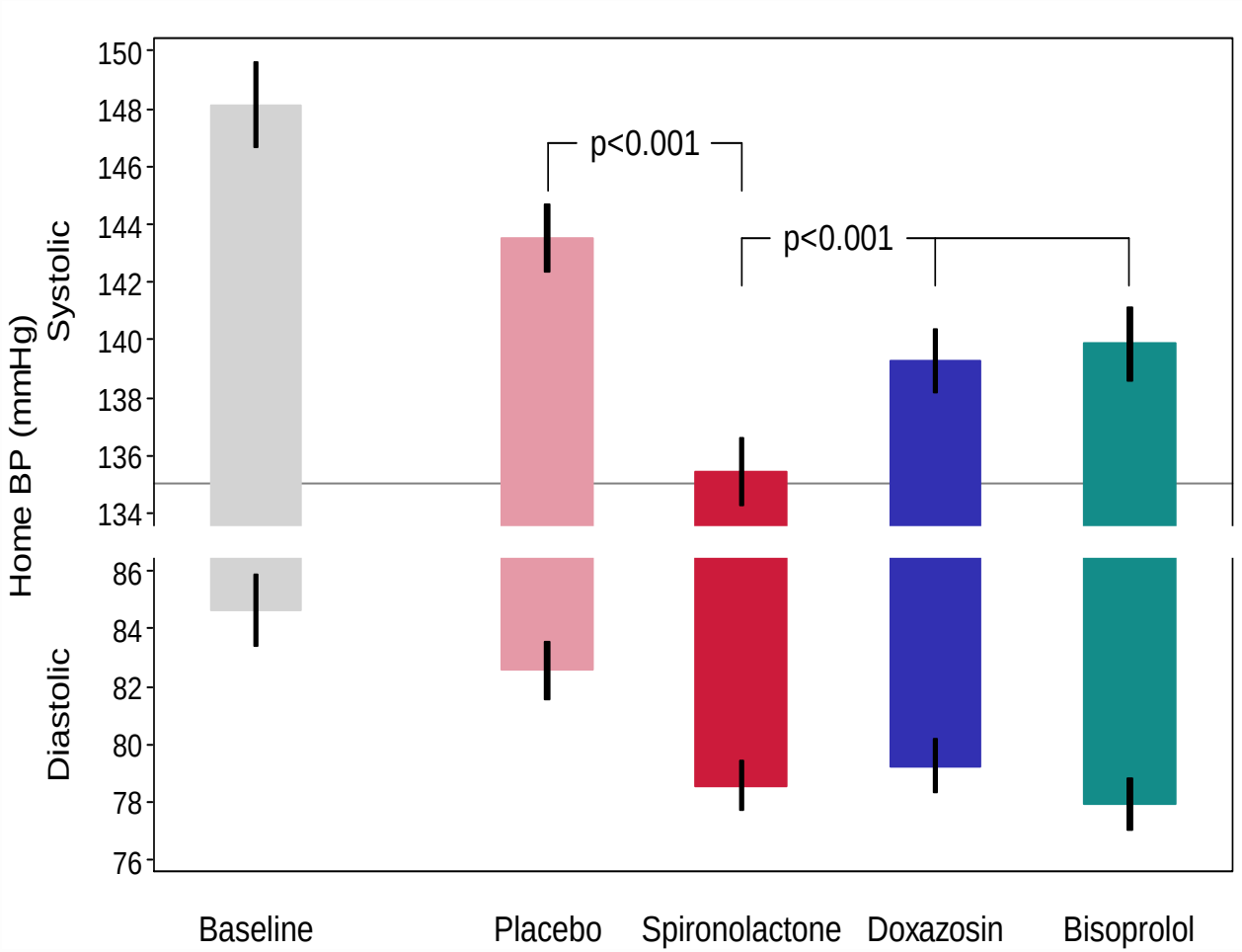
Primary Outcome

Comparators (N=314)	Home Systolic BP difference (mmHg)	p value
Spironolactone vs placebo	-8.70 (-9.72,-7.69)	<0.001
Spironolactone vs mean Bisoprolol/Doxazosin	-4.26 (-5.13,-3.38)	<0.001
Spironolactone vs Doxazosin	-4.03 (-5.04,-3.02)	<0.001
Spironolactone vs Bisoprolol	-4.48 (-5.50,3.46)	<0.001

Treatments	Home Systolic BP (mmHg)	Change from baseline
Spironolactone	134.9 (134.0,135.9)	-12.8 (-13.8,-11.8)
Doxazosin	139.0 (138.0,140.0)	-8.7 (-9.7,-7.7)
Bisoprolol	139.4 (138.4,140.4)	-8.3 (-9.3,-7.3)
Placebo	143.6 (142.6,144.6)	-4.1 (-5.1,-3.1)

Williams B, et al. Lancet 2015; 386: 2059-2068

Primary Outcome



Williams B, et al. Lancet 2015; 386: 2059-2068

PATHWAY 2
Clinical Trials in Hypertension

BP Control Rates

	Home Systolic BP (mmHg)		Patients	Met target		Least Squares Estimates	Odds ratio	p value
	Baseline	Final	(n)	(r)	r/n (%)			
Spironolactone	148.3	133.9	282	163	57.8	58.0 (52.0,63.7)		
Doxazosin	147.8	138.9	276	115	41.7	41.5 (35.8,46.5)	0.52 (0.37,0.73)	<0.001
Bisoprolol	147.7	139.6	280	122	43.6	43.3 (37.5,49.2)	0.55 (0.39,0.78)	<0.001
Placebo	147.8	143.5	270	66	24.4	23.9 (19.1,29.4)	0.23 (0.16,0.33)	<0.001

BP control rates refer to patients achieving a home systolic BP of <135mmHg.
Odds ratios from logistic regression models adjusted for baseline.

Williams B, et al. Lancet 2015; 386: 2059-2068

PATHWAY 2
Clinical Trials in Hypertension

Serious Adverse Events and Withdrawals

	Bisoprolol	Spironolactone	Doxazosin	Placebo	p value
Serious adverse events	8 (2.6%)	7 (2.3%)	5 (1.7%)	5 (1.7%)	0.831
Any adverse event	68 (11.3%)	67 (10.4%)	58 (10.1%)	42 (9.1%)	0.711
Withdrawals for adverse events	2 (2.9%)	3 (3.4%)	8 (10.0%)	2 (2.6%)	0.084

p values for Fisher's exact test

Williams B, et al. Lancet 2015; 386: 2059-2068

PATHWAY 2
Implications for Clinical Practice

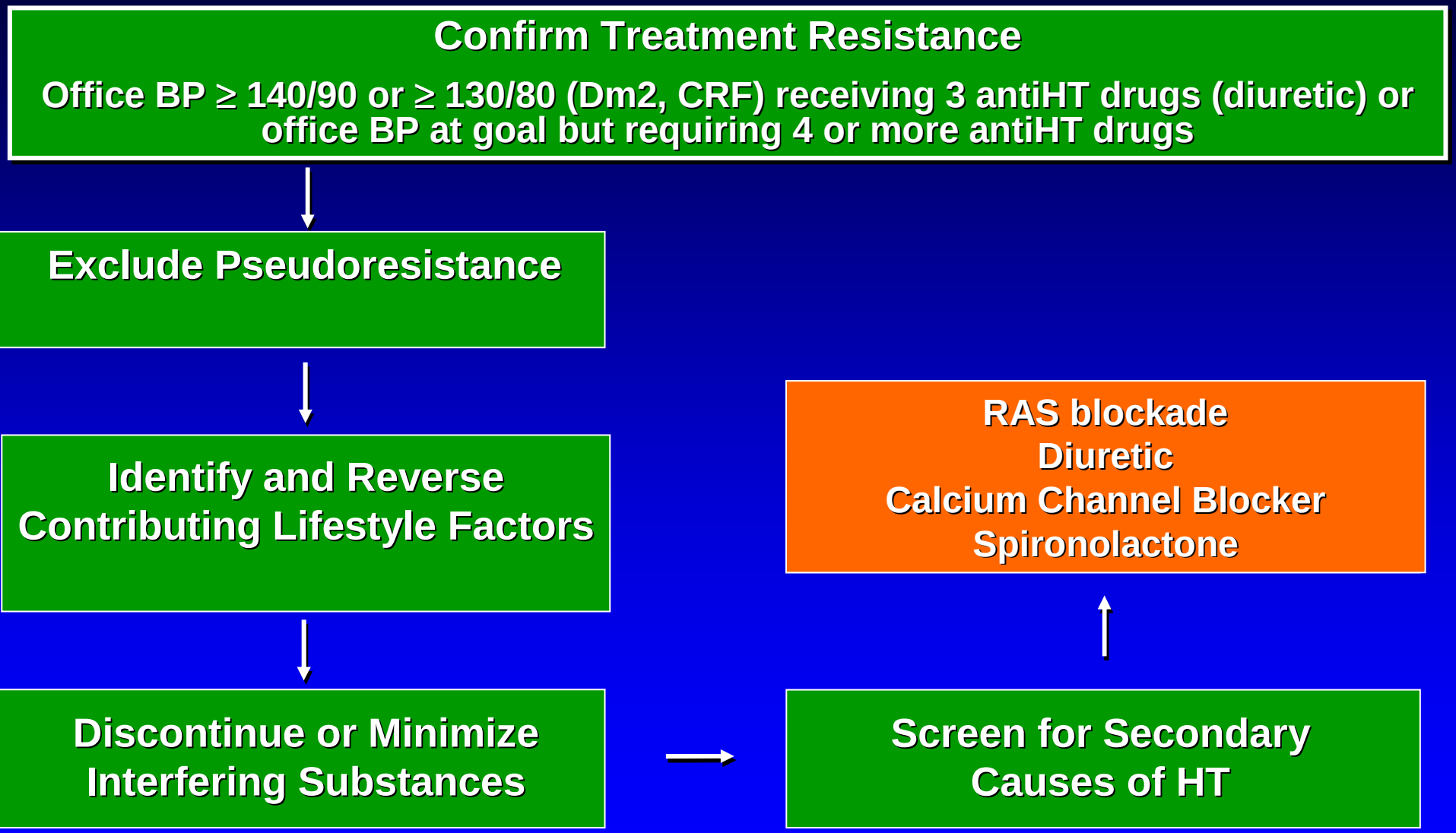
- PATHWAY-2 is the first RCT to directly compare spironolactone with other active BP-lowering treatments in patients with well characterised resistant hypertension

- The result in favor of spironolactone is unequivocal – Spironolactone is the most effective treatment for resistant hypertension, and these results should influence treatment guidelines globally

- Patients should not be defined as resistant hypertension unless their BP remains uncontrolled on spironolactone

Williams B, et al. Lancet 2015; 386: 2059-2068

How to Manage Resistant Hypertension



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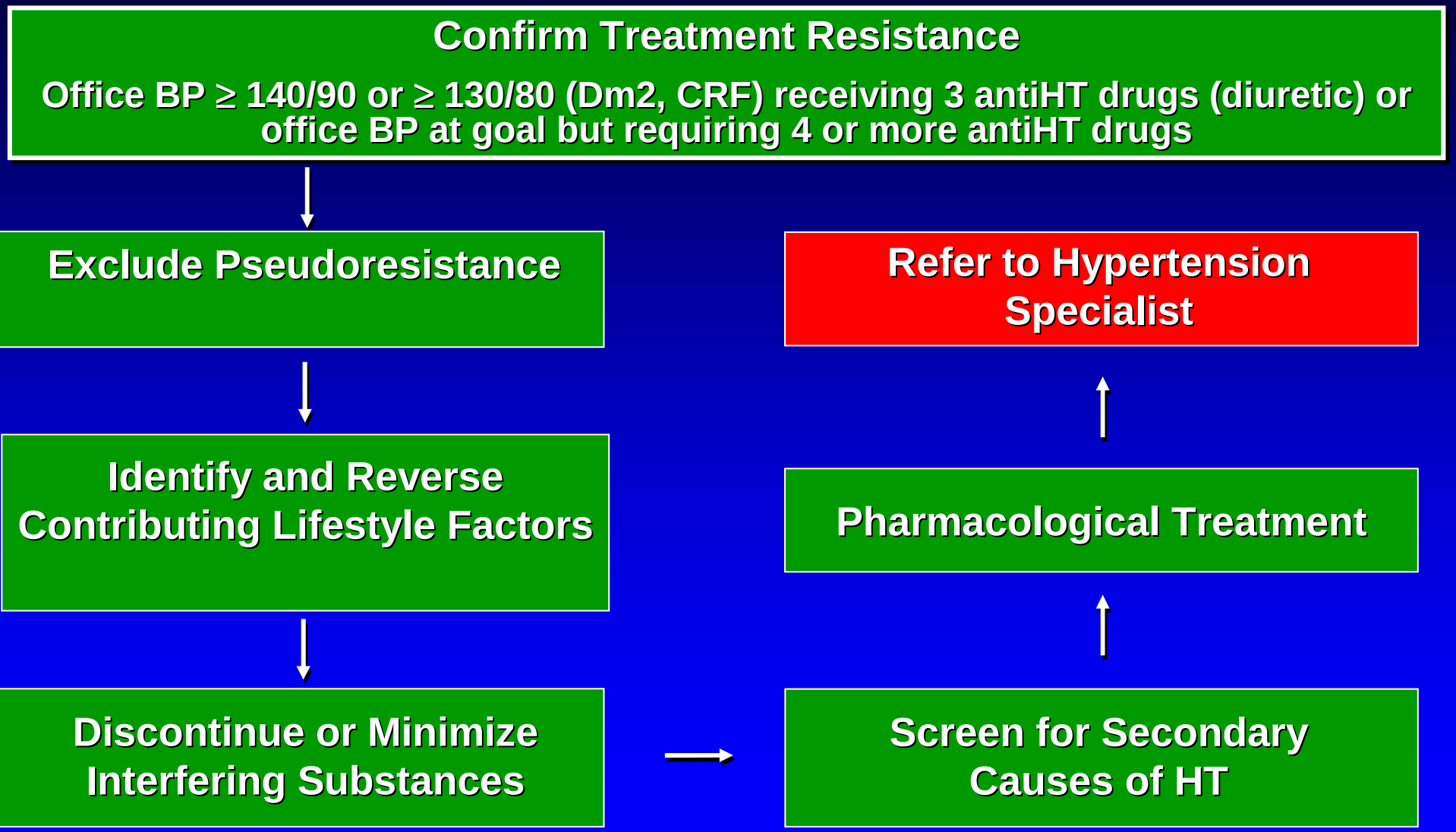
How to Manage Resistant Hypertension



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