Resistant Hypertension

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TUMS

NRC

Learning objectives

- To understand the definition, prevalence and prognosis of resistant hypertension.
- To describe the methods for effective diagnosis of resistant hypertension.
- To review the treatment options for resistant hypertension, including lifestyle advice, pharmacological treatment and surgical intervention.

Definition

RH defined by ACC-AHA as “BLOOD PRESSURE ABOVE THE GOAL” despite the patient is on maximally dose of at least 3 anti hypertension medication including a diuretic.

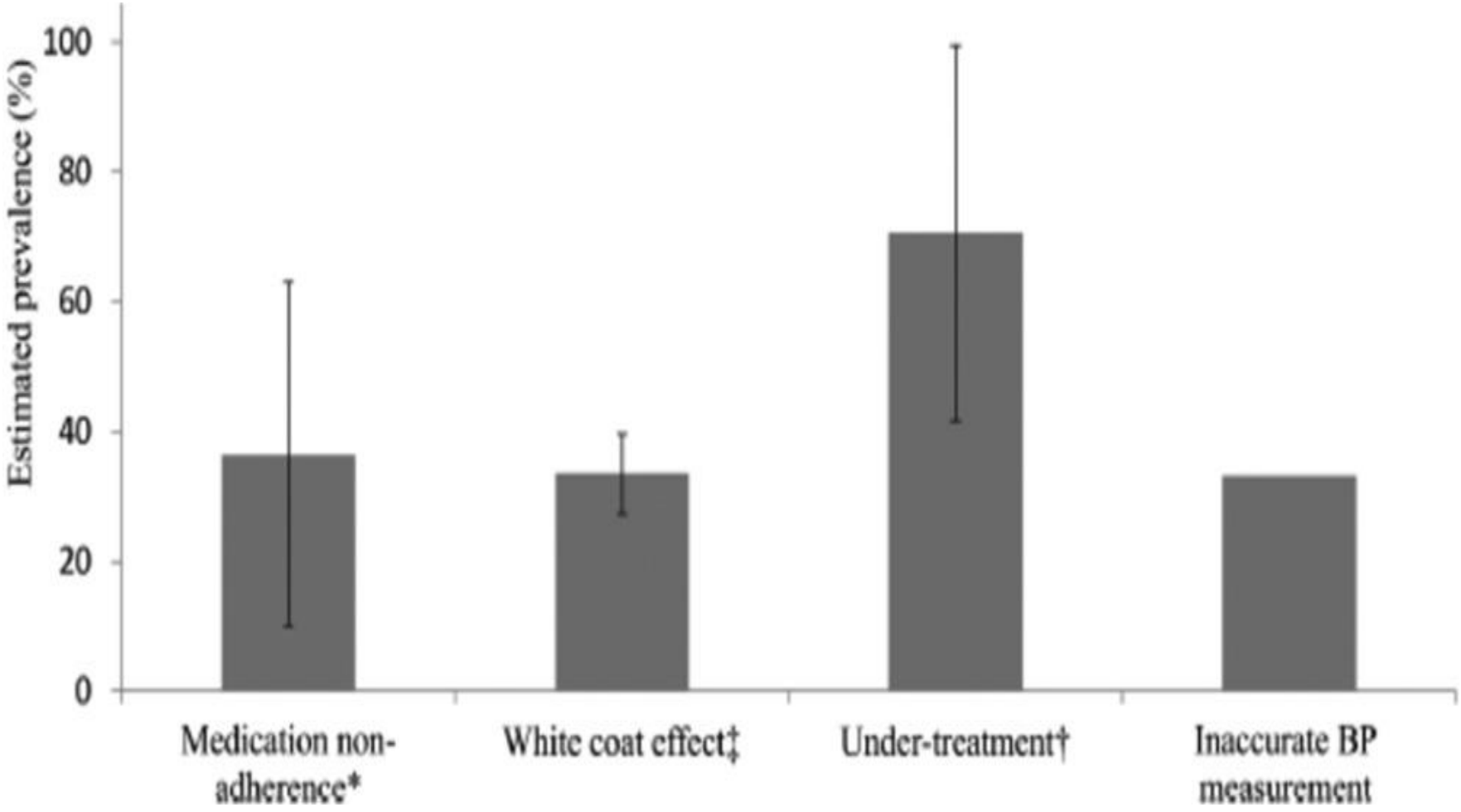
Controlled RH is defined as controlled BP with 4 medications.

Pseudo-RH defined as sub optimal BP control secondary to medication non adherence.

Apparent RH is uncontrolled BP unverified adherence or medication dosing or not undergone out-of-office BP monitoring to rule out white-coat effect.

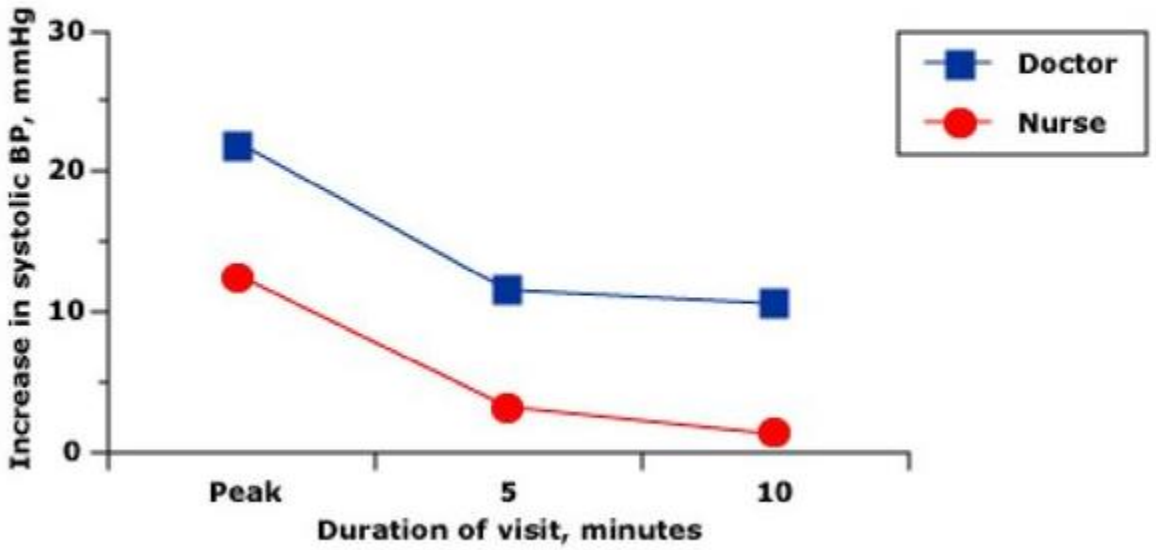
Table 1 Studies examining the prevalence of resistant hypertension

Study	Country	Study type	Population	Total population	Definition of resistant hypertension	Prevalence
Chia and Ching[7]	Malaysia	Routine medical records	All patients with hypertension	1217	BP=140/90 mm Hg on=3 drugs (including a thiazide diuretic)	8.8% (95% CI 7.3 to 10.5)
Persell[8]	USA	Routine medical records	Non-pregnant adults with hypertension	5230	BP>140/90 mm Hg on 3 drugs or any level of BP>4 drugs	8.9% (95% CI 7.7 to 10.1)
McAdam-Marx *et al*[9]	USA	Routine medical records	Adults with hypertension	29474	BP=140/90 mm Hg (=130/80 mm Hg for those with diabetes & CKD) and on =3 drugs (including a thiazide)	9.1% (95% CI 8.7 to 9.4)
Egan *et al*[10]	USA	Routine medical records	Adults with hypertension	3555	BP >140/90 mm Hg on >3 drugs or any level of BP on >4 drugs	11.8% (95% CI 10.7 to 12.9)
Sim *et al*[11]	USA	Routine medical records	Adults with hypertension	470386	BP >140/90 mm Hg on >3 drugs or any level of BP on >4 drugs	12.8% (95% CI 12.7 to 12.9)
de la Sierra *et al*[12]	Spain	ABPM registry	Treated adults with hypertension	68045	BP=140/90 mm Hg on=3 drugs (including a thiazide diuretic)	12.2% (95% CI 11.9 to 12.4)
Egan *et al*[13]	USA	Routine medical records	Adults with hypertension with =2 clinical visits and =1 medication prescribed	468877	BP>140/90 mm Hg on>3 drugs or any level of BP on >4 drugs	18.0% (95% CI 17.8 to 18.1)



Prevalence of pseudo resistant hypertension

Effect of physician and nurse measurement of blood pressure during an office visit



Specific Clinical Issues Associated With Treatment Resistance

Issue Associated With Treatment Resistance	Management Consideration(s)
Volume control, edema resolution	Thiazide→chlorthalidone→loop diuretic
Heart rate control inadequate	β-Blocker, α,β-blocker, verapamil, diltiazem
Renin and aldosterone levels low	Low-salt diet, avoid nighttime shift work, amiloride
Renin low, aldosterone normal to high normal	Mineralocorticoid receptor antagonist
Would split dosing of medications improve control?	Evaluate BP pattern according to home and ambulatory BP monitoring
Medication adherence questionable	Initiate indirect or direct methods to detect nonadherence; if nonadherence is documented (partial or complete), discuss frankly, nonjudgmentally with patient and family
Pattern of BP response to medications outside clinician visit times unknown	Identify meal effects on BP, duration of medication effect, relationship of BP to side effects using out-of-office BP monitoring
Sleep disordered breathing; significant anxiety associated with highly variable hypertension	Initiate nondrug strategies concurrently with or separately from antihypertensive drug therapy

Most prevalent causes of secondary hypertension

Chronic kidney disease
Renovascular disease
Obstructive sleep apnoea
Coarcation of the aorta
Pheochromocytoma
Primary hyperaldosteronism
Cushing's syndrome
Thyroid disease
Intracranial mass

Suspected secondary hypertension
Hypertension with target-organ damage
eGFR <30ml/min/1.73m^2
eGFR decline of 15% within 3 months
Proteinuria >1g/day
Requiring >4 medications for pressure control [10,40]

Other Endocrine Causes of Secondary Hypertension

Disorder	Major Clinical Findings	Physical Examination	Screening Tests	Additional/Confirmatory Tests
Hypothyroidism	Dry skin; cold intolerance; constipation; hoarseness; weight gain	Delayed ankle reflex; periorbital puffiness; coarse skin; cold skin; slow movement; goiter	High TSH; low or normal fT4	
Hyperthyroidism	Warm, moist skin; heat intolerance; nervousness; tremulousness; insomnia; weight loss; diarrhea; proximal muscle weakness	Lid lag; fine tremor of the outstretched hands; warm, moist skin	Low TSH; high or normal fT4 and T3	Radioactive iodine uptake and scan
Hypercalcemia and primary hyperparathyroidism	Hypercalcemia	Usually none	Serum calcium	Serum parathyroid hormone
Congenital adrenal hyperplasia (excess DOC)	Hypertension and hypokalemia; virilization (11-β-OH deficiency); incomplete masculinization in males and primary amenorrhea in females (17-α-OH deficiency)	Signs of virilization (11β) or incomplete masculinization (17α)	Hypertension and hypokalemia with low or normal aldosterone and renin	11-β-OH: elevated DOC, 11-deoxycortisol and androgens; 17-α-OH: decreased androgens and estrogen; elevated DOC and corticosterone
Other mineralocorticoid excess syndromes caused by DOC	Early-onset hypertension, hypokalemia	Arrhythmias (with hypokalemia)	Low aldosterone and renin	DOC; urinary cortisol metabolites; genetic testing
Acromegaly	Acral features; enlarging shoe, glove, or hat size; headache; visual disturbances; diabetes mellitus	Acral features; large hands and feet; frontal bossing	Serum growth hormone ≥1 ng/mL during oral glucose load	Elevated age- and sex-matched IGF-1 level; MRI scan of the pituitary

Drugs and Other Substances With Potential to Induce or Exacerbate Elevated BP and Hypertension

NSAIDs

Oral contraceptives

Sympathomimetic

Cyclosporine, tacrolimus

Erythropoietin

Glucocorticoids, mineralocorticoids

VEGF inhibitors

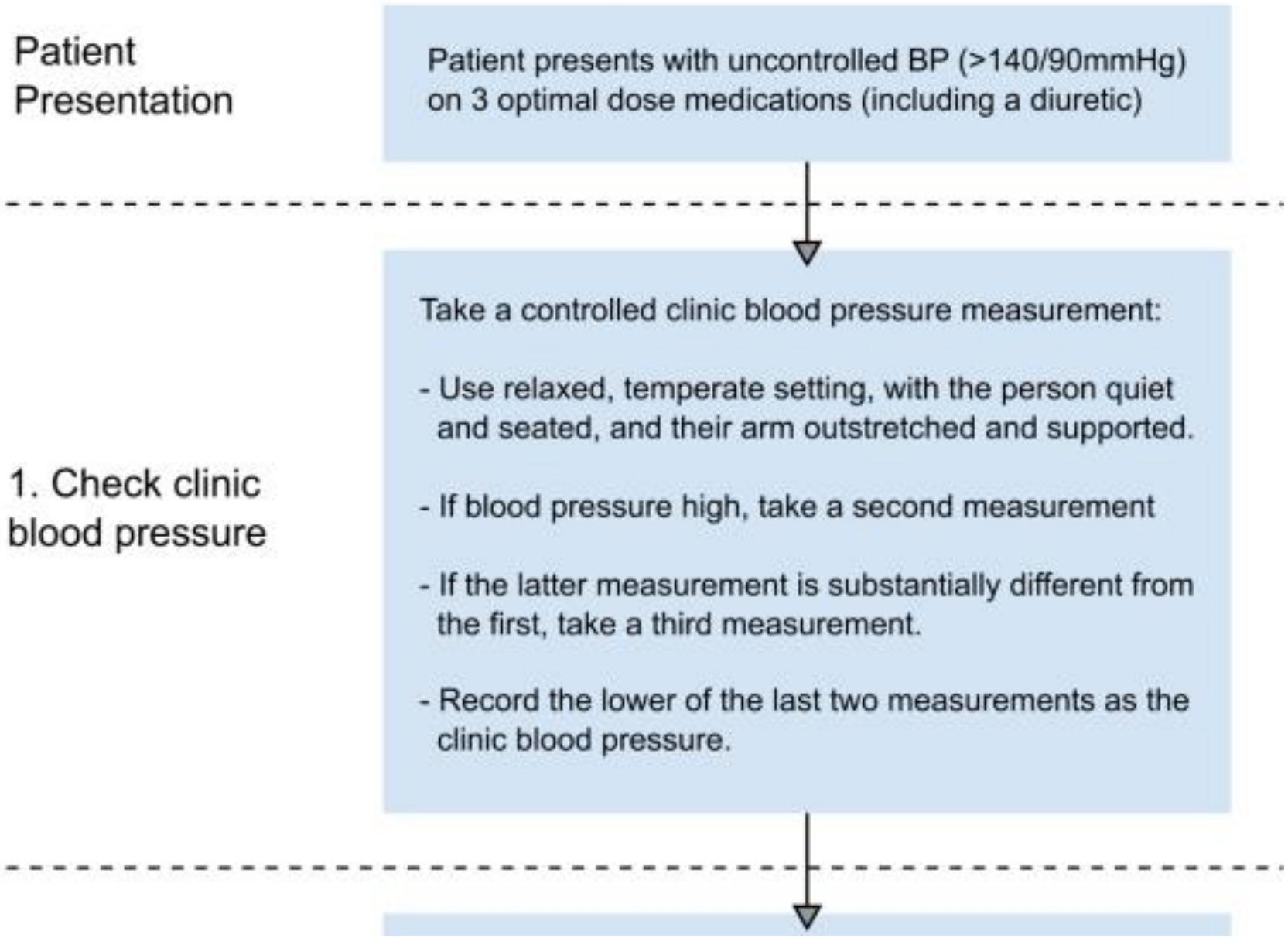
Alcohol

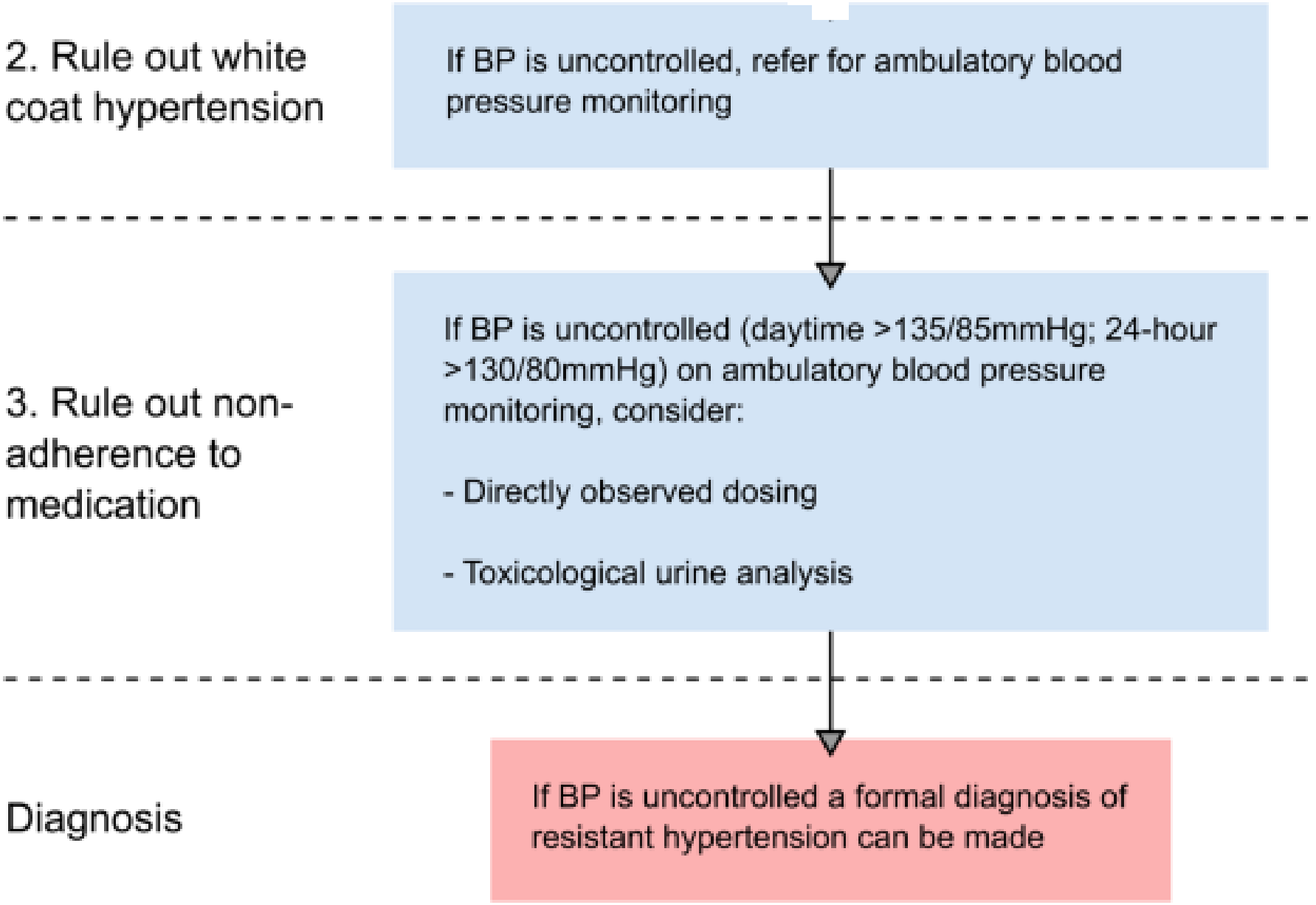
Cocaine

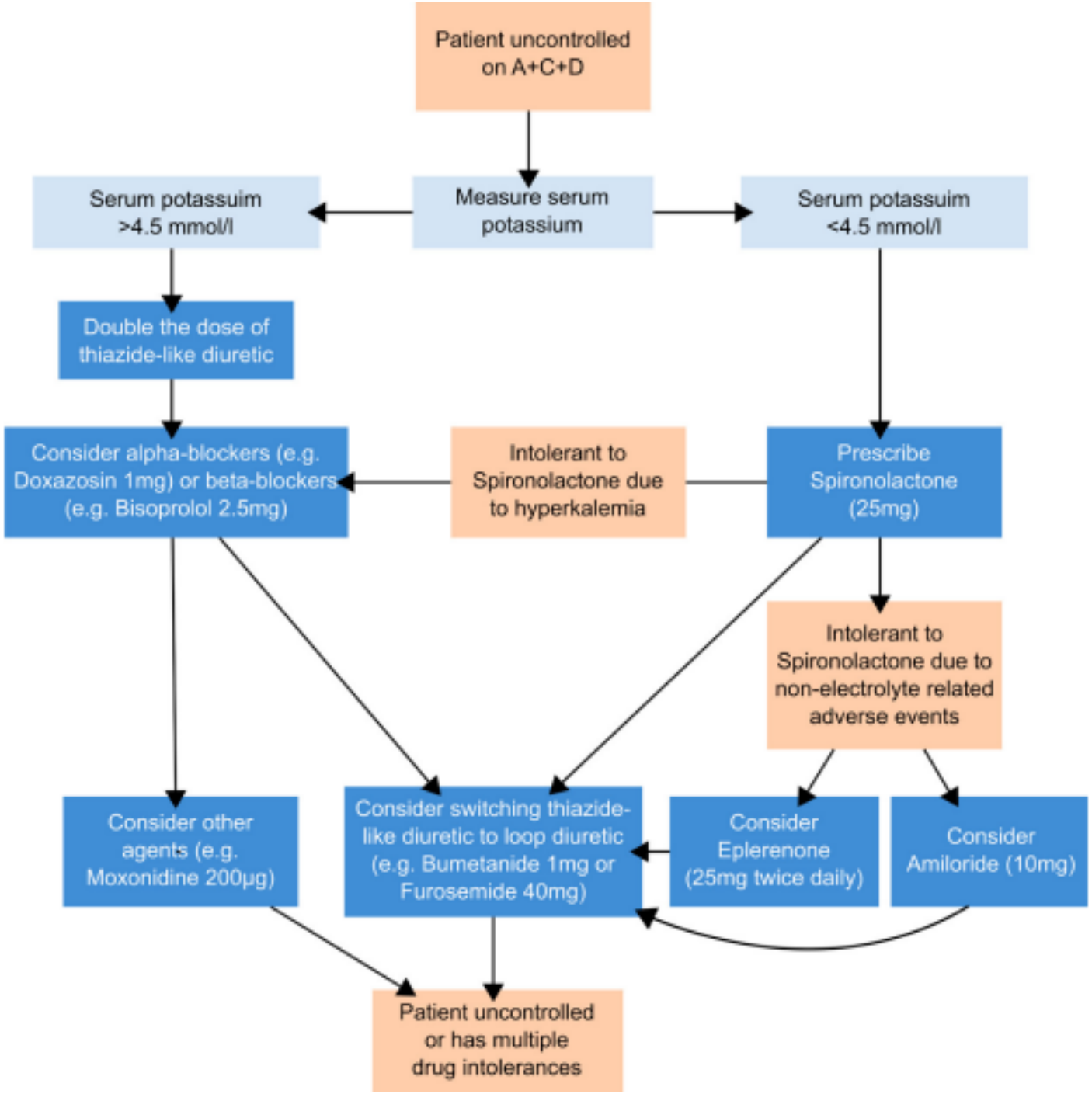
Amphetamines

Antidepressants

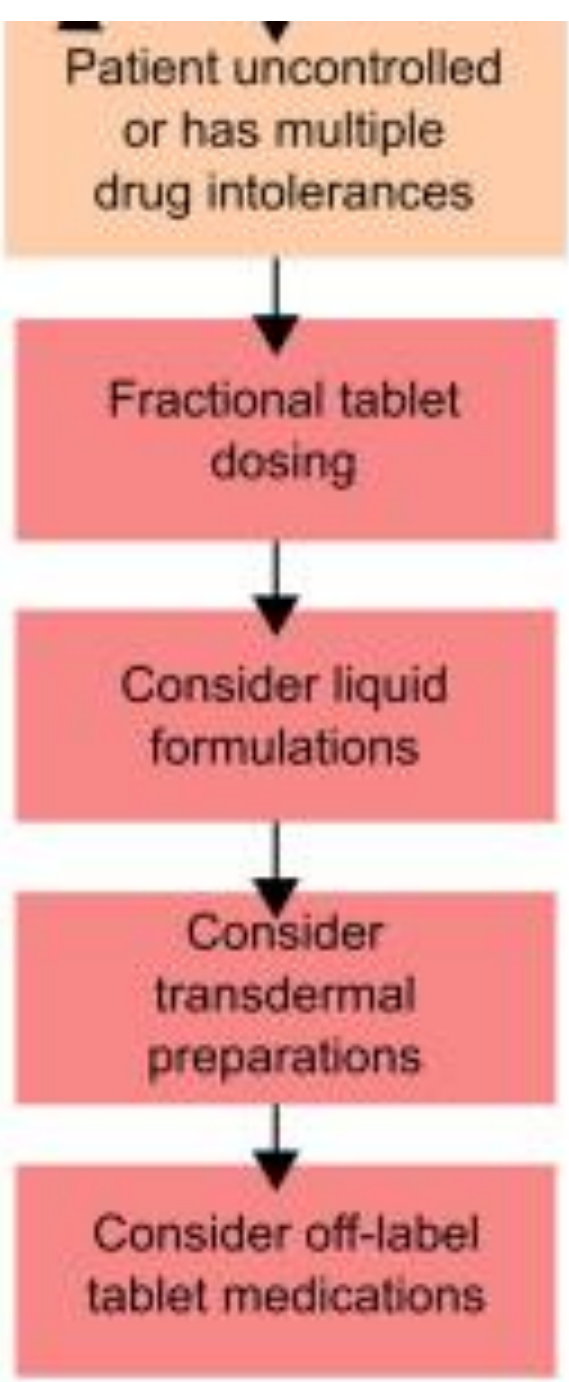
Stages of diagnosis of resistant hypertension



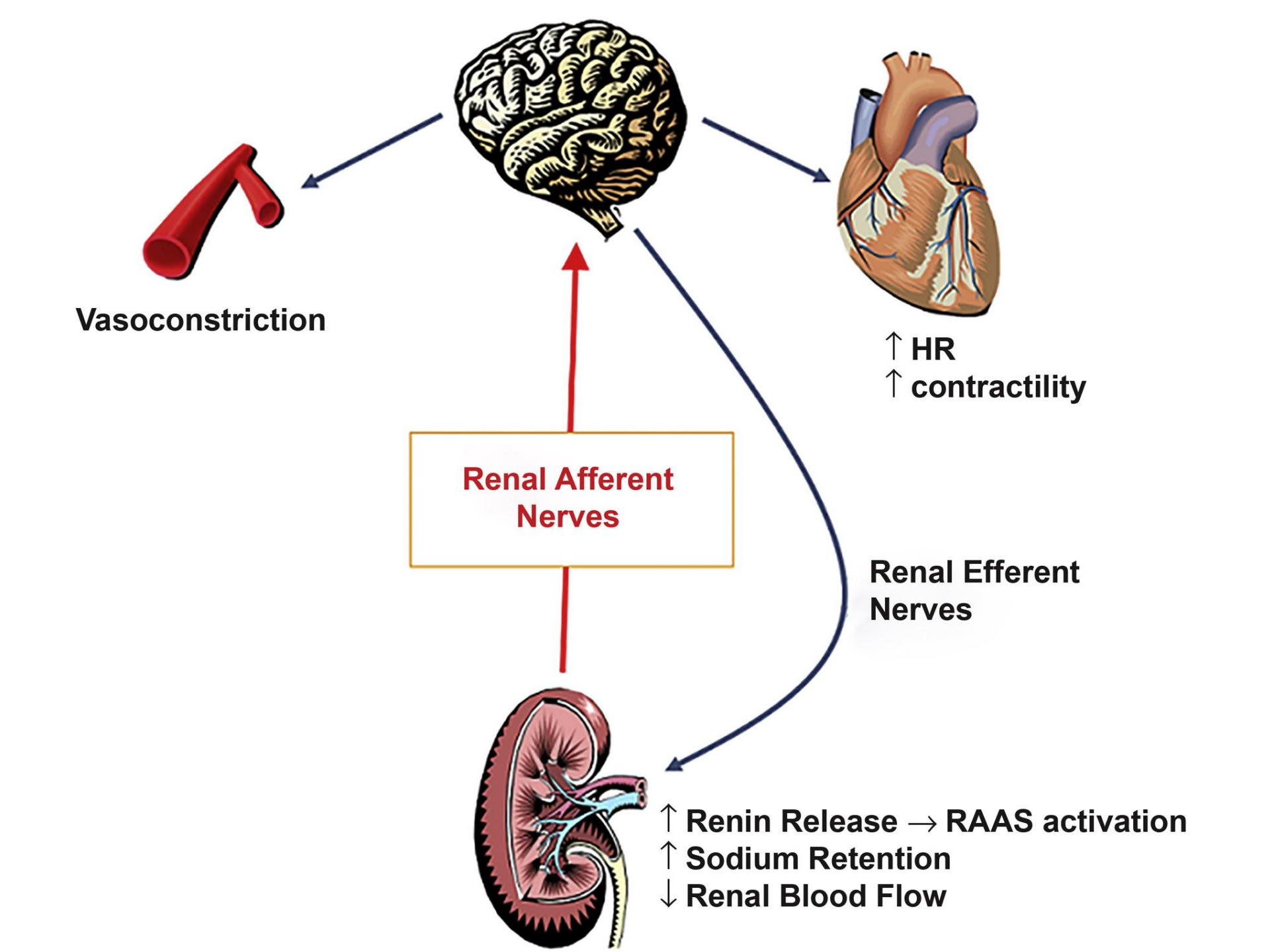

2. Rule out white coat hypertension
If BP is uncontrolled, refer for ambulatory blood pressure monitoring
3. Rule out non-adherence to medication
If BP is uncontrolled (daytime >135/85mmHg; 24-hour >130/80mmHg) on ambulatory blood pressure monitoring, consider:
- Directly observed dosing
- Toxicological urine analysis
Diagnosis
If BP is uncontrolled a formal diagnosis of resistant hypertension can be made



Options for pharmacological treatment of resistant hypertension


Patient uncontrolled or has multiple drug intolerances
Fractional tablet dosing
Consider liquid formulations
Consider transdermal preparations
Consider off-label tablet medications

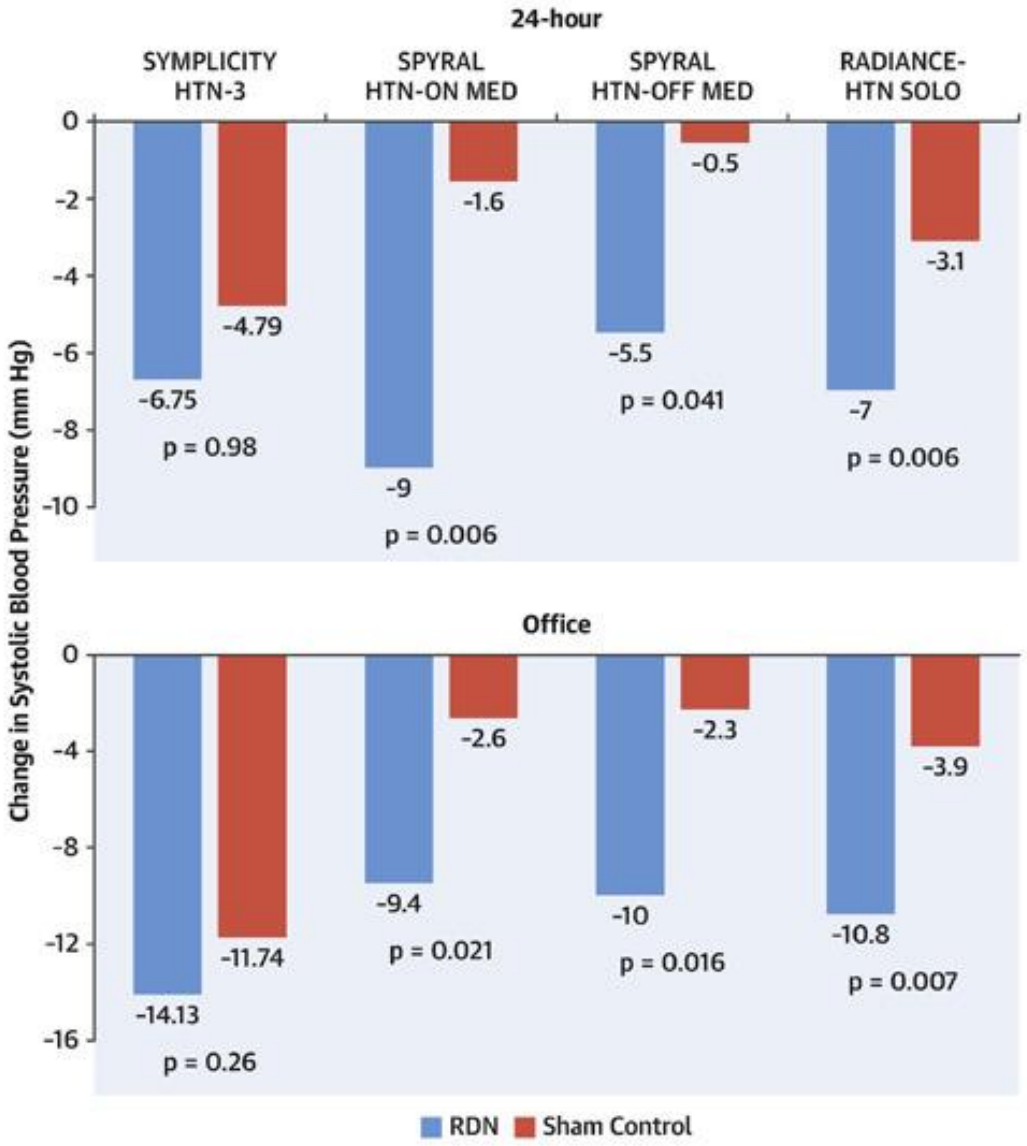
RENAL DENERVATION


Vasoconstriction
↑ HR
↑ contractility
Renal Afferent Nerves
Renal Efferent Nerves
↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow

The Symplicity Flex Ablation Catheter

Radiofrequency energy is delivered for 2 min at each site

CENTRAL ILLUSTRATION: Mean Changes in Systolic Blood Pressure From Baseline for 24-H Ambulatory and Office Blood Pressure in 4 Prospective, Randomized, Sham-Controlled Trials of Renal Denervation



Weber, M.A. et al. J Am Coll Cardiol Intv. 2019;12(12):1095-105.

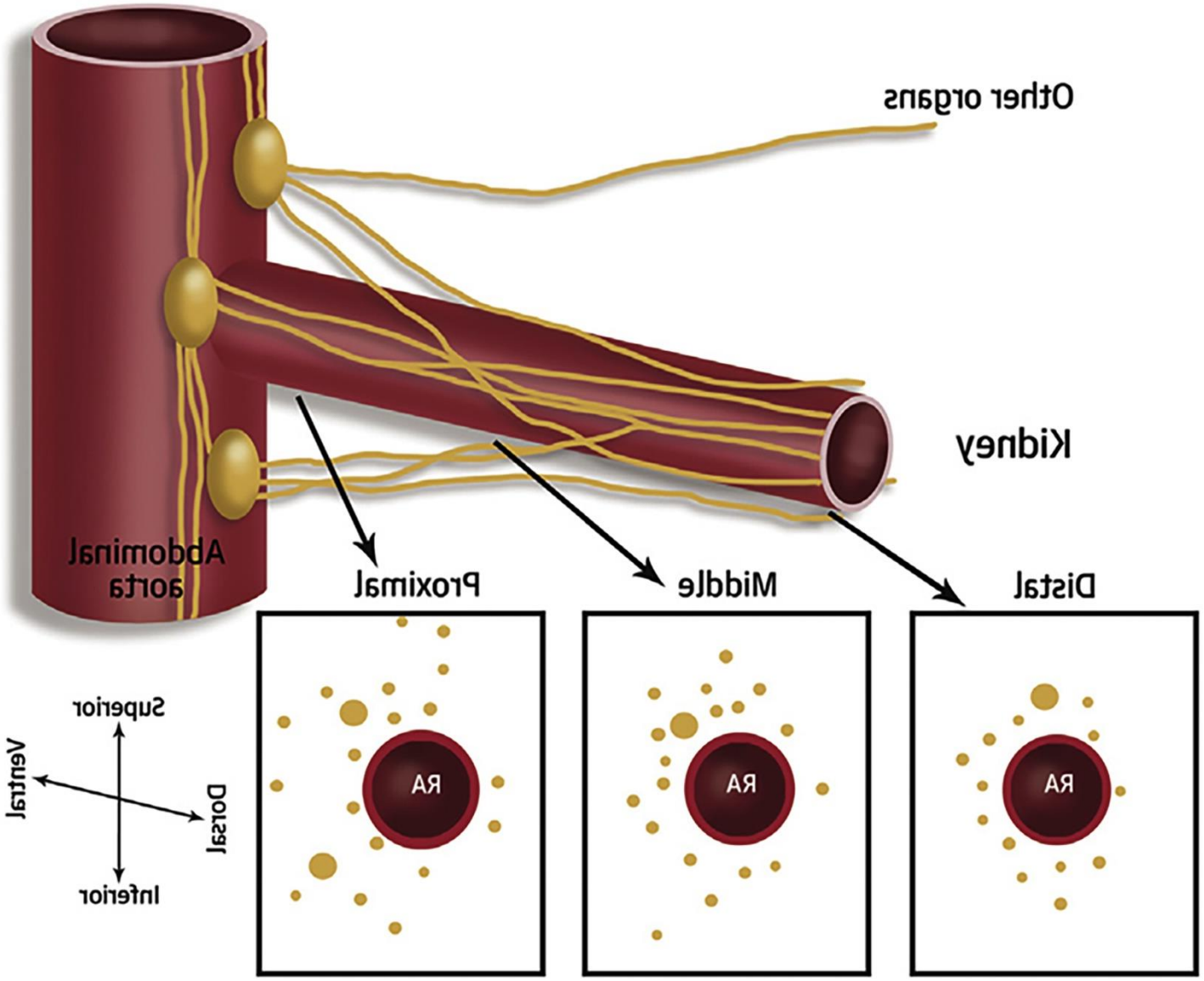
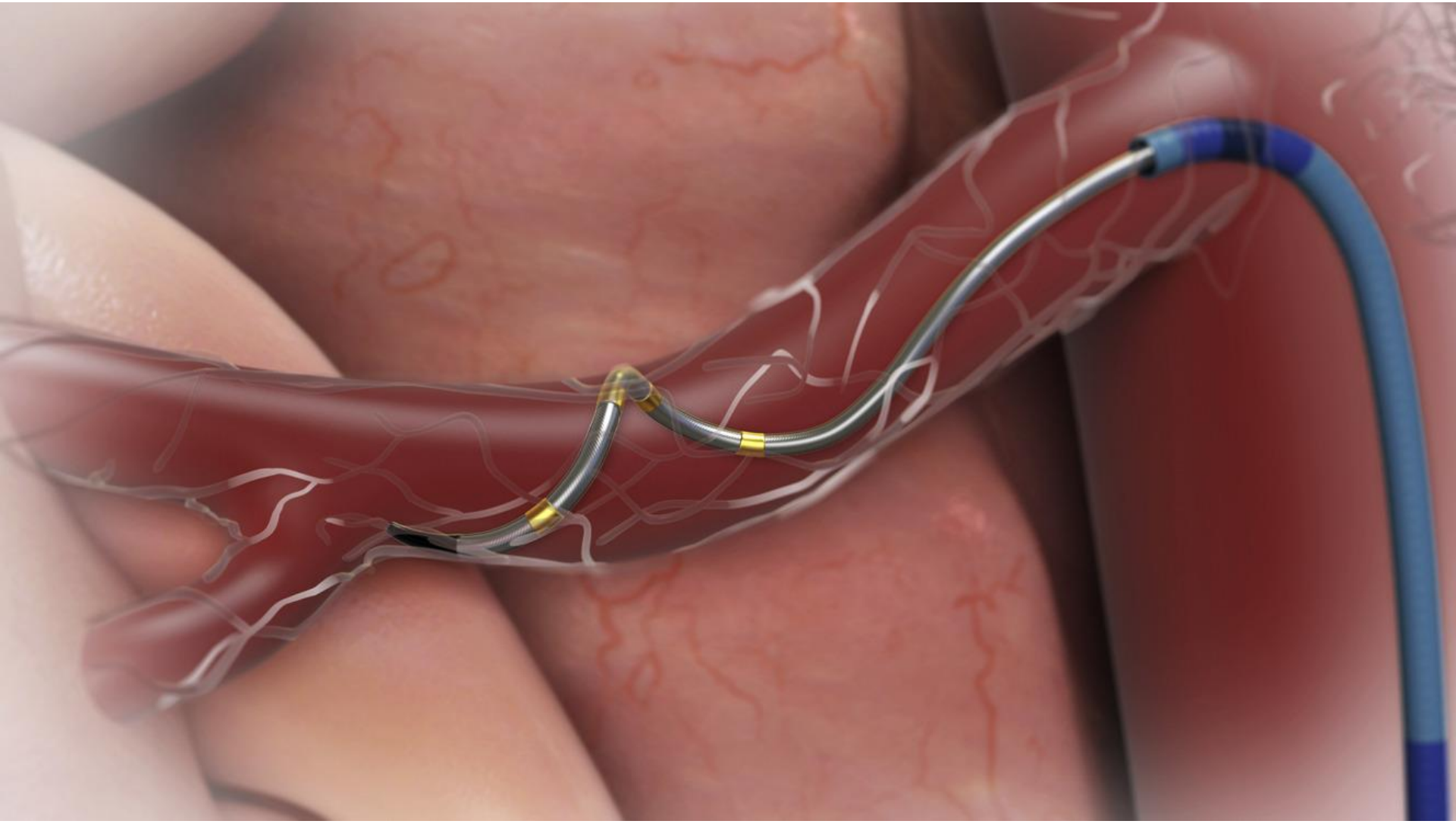


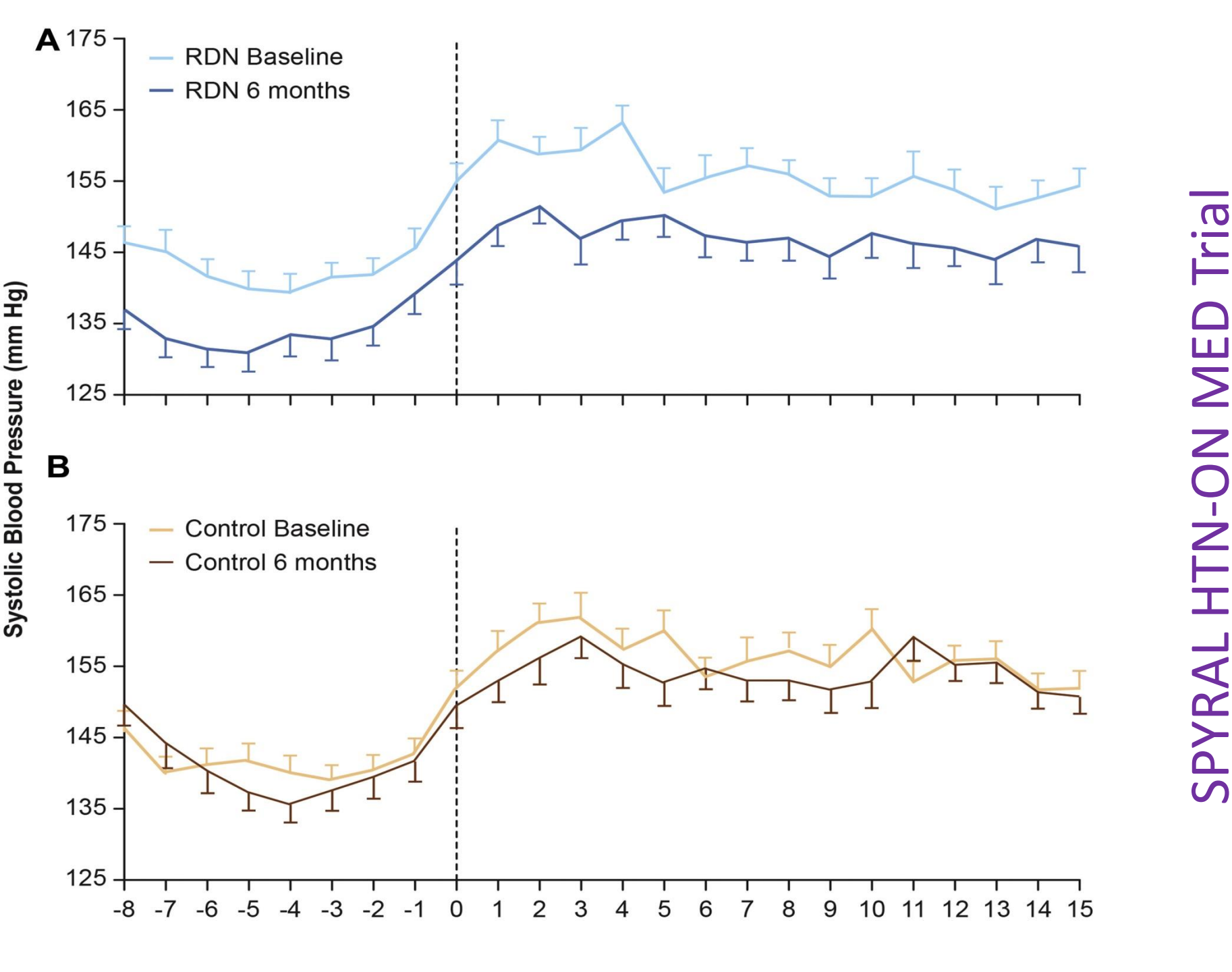
Diagram of RA Nerve Density in Different Segments of the RAs

Although there were fewer nerves surrounding the RA in the distal segment compared with the proximal and middle segments, and the mean distance from the RA lumen to nerve location was least in the distal segment

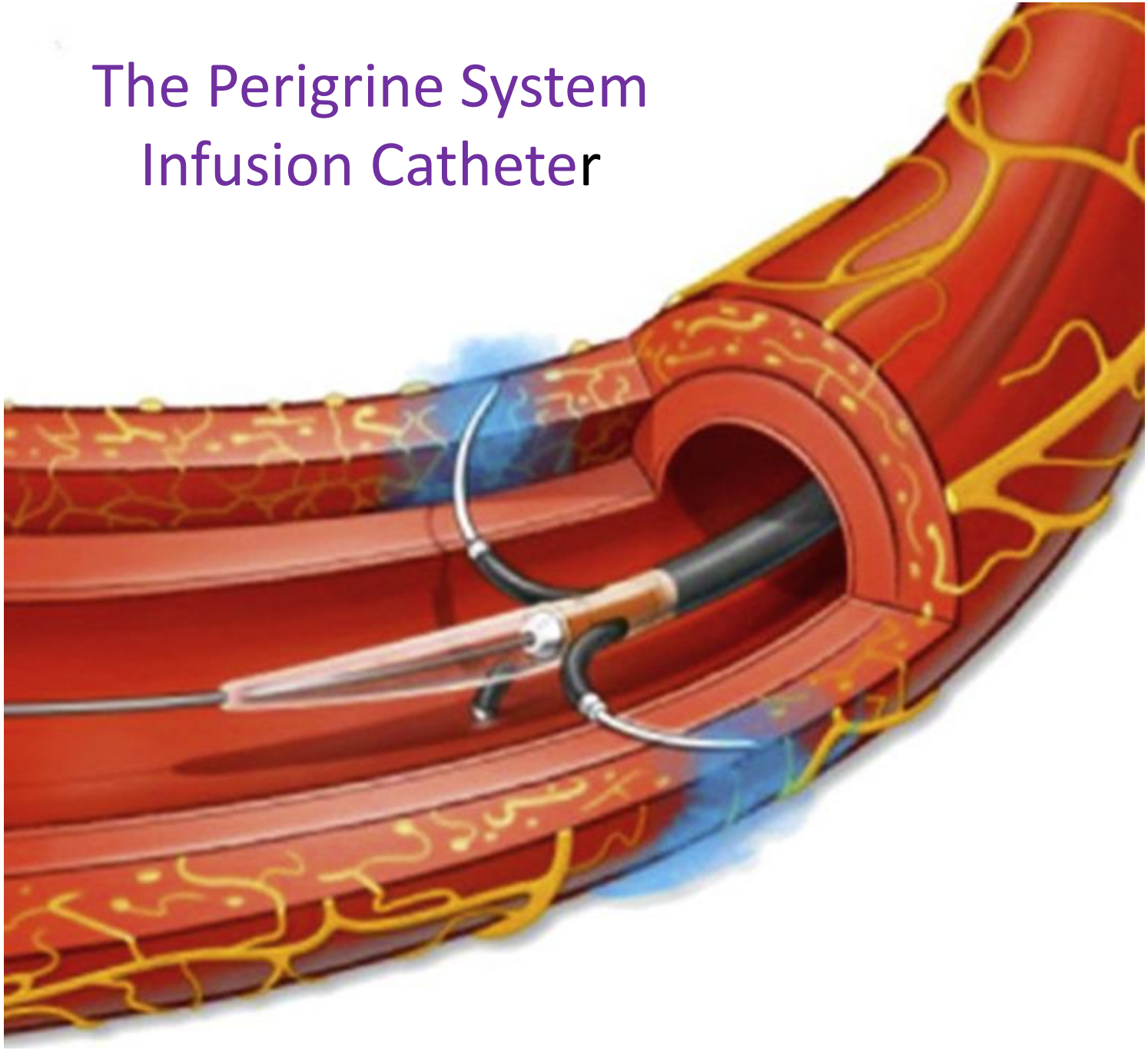


The Symplicity Spyral Catheter

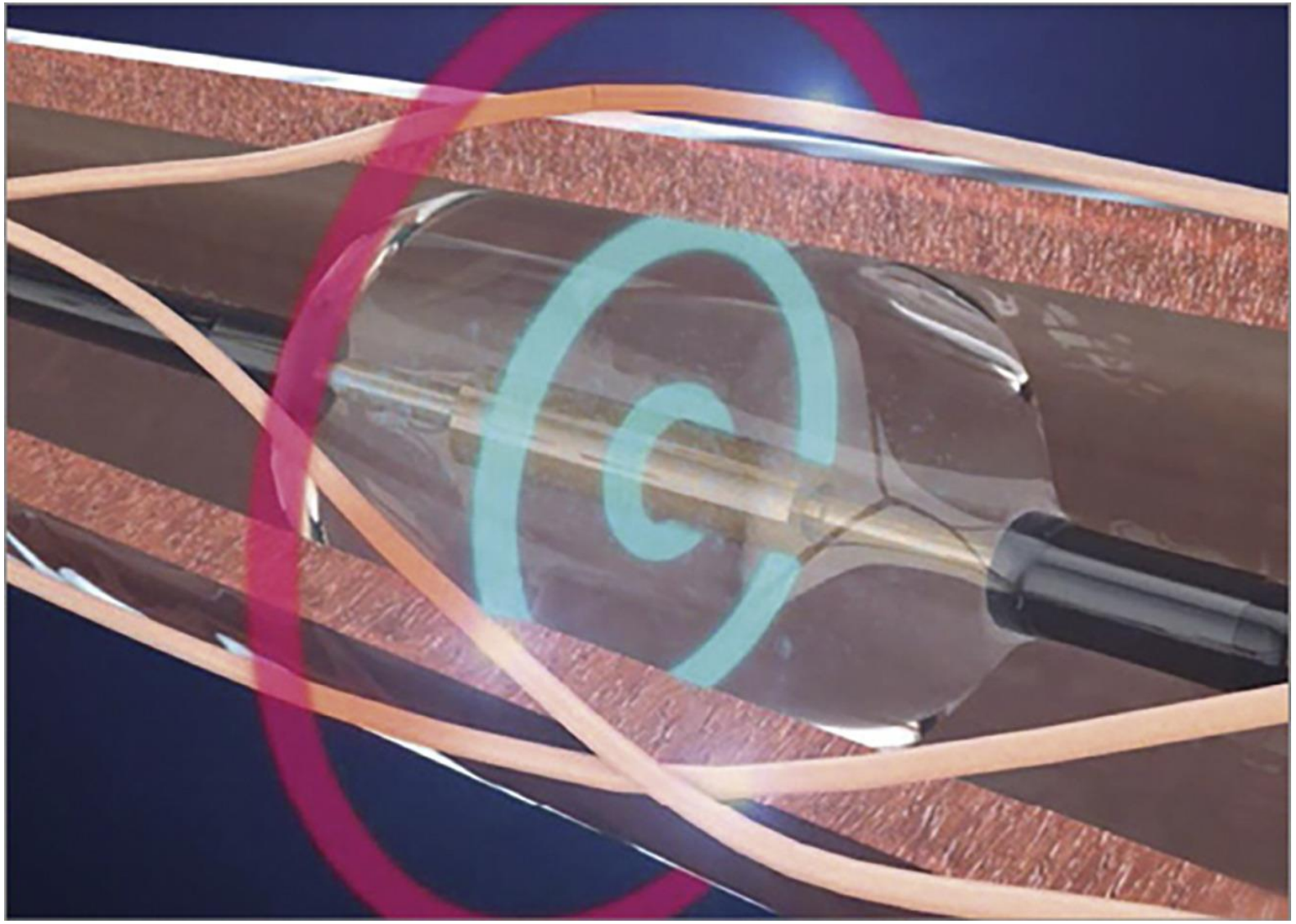
Radiofrequency energy is delivered simultaneously at 4 sites for 60 s


A
RDN Baseline
RDN 6 months
B
Control Baseline
Control 6 months
Systolic Blood Pressure (mm Hg)
175
165
155
145
135
125
-8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
SPYRAL HTN-ON MED Trial

The Perigrine System Infusion Catheter



The tips of 3 injection needles are inserted through the renal artery in a circumferential pattern and penetrate the adventitia to a depth of about 3.5 mm relative to the intimal surface. The blue color represents the circumferential spread of alcohol within the adventitial layer



The red circle indicates the heat generated from the ultrasound energy in the tissue delivering energy within the artery. The blue circle indicates active cooling from circulating water within the artery to protect the artery from heat.

Table 2 Trials examining the efficacy of renal denervation in resistant hypertension

Study	Year	Total population	Mean age (years)	Sex (% female)	Intervention group	Control group	Follow-up	Primary outcome	BP change in intervention group	BP change in control group	Difference
Symplicity HTN-1	2009	45	58±9	20 (44%)	Catheter-based renal denervation (n=45)	None (non-randomised)	12 months	Assessment of periprocedural and long-term safety	−16/11 mm Hg	n/a	n/a
Symplicity HTN-2	2010	106	58±12	45 (42%)	Catheter-based renal denervation (n=52)	Usual care (n=54)	6 months	Clinic systolic BP at 6 months	−32/12 mm Hg	1/0 mm Hg	33/11 mm Hg (p<0.0001)*
Symplicity HTN-3	2014	535	57	210 (39%)	Catheter-based renal denervation (n=364)	Sham surgery control (n=171)	6 months	Clinic systolic BP at 6 months	−14/7 mm Hg	−12/5 mm Hg	2/2 mm Hg (p=0.26)*

*Systolic blood pressure comparison.
BP, blood pressure.

- Transcatheter renal denervation for treating hypertension is an emerging clinical procedure.

- Improved catheter design, procedure technique, and medication use have confirmed its feasibility.

- With safety and efficacy established, we must now define how denervation will fit into clinical practice.

Key points

- Patients with uncontrolled blood pressure on three or more medications should be suspected as having resistant hypertension.
- In patients with suspected resistant hypertension, it is important to exclude white coat hypertension and patients who are non-adherent to treatment.
- Spironolactone is the most effective treatment at lowering blood pressure in patients with resistant hypertension who already on three agents (including a diuretic).
- The benefits of renal denervation, carotid baroreceptor stimulation and central arteriovenous anastomosis remain inconclusive and these procedures should not be adopted in routine clinical practice.