

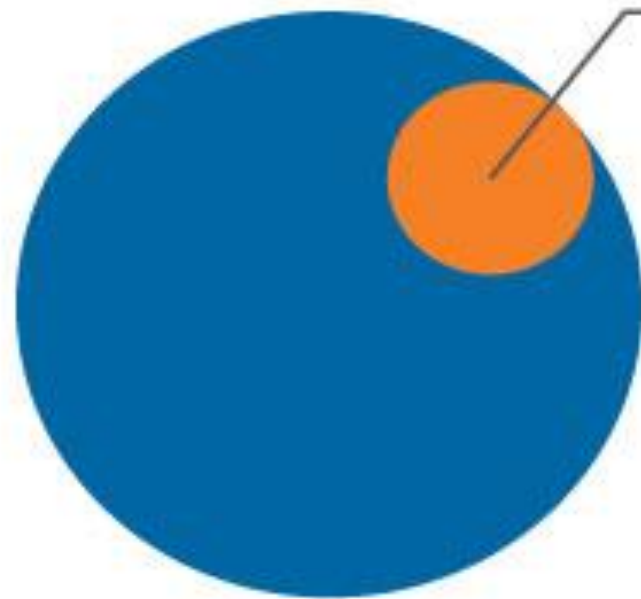
RESISTANT HYPERTENSION AND MANAGEMENT



Definition of Resistant Hypertension

Uncontrolled Hypertension

- Includes all patients who lack BP control on treatment, including those on inadequate treatment regimens, those with poor adherence, those with undetected secondary hypertension, as well as those with true treatment resistance¹



Resistant Hypertension

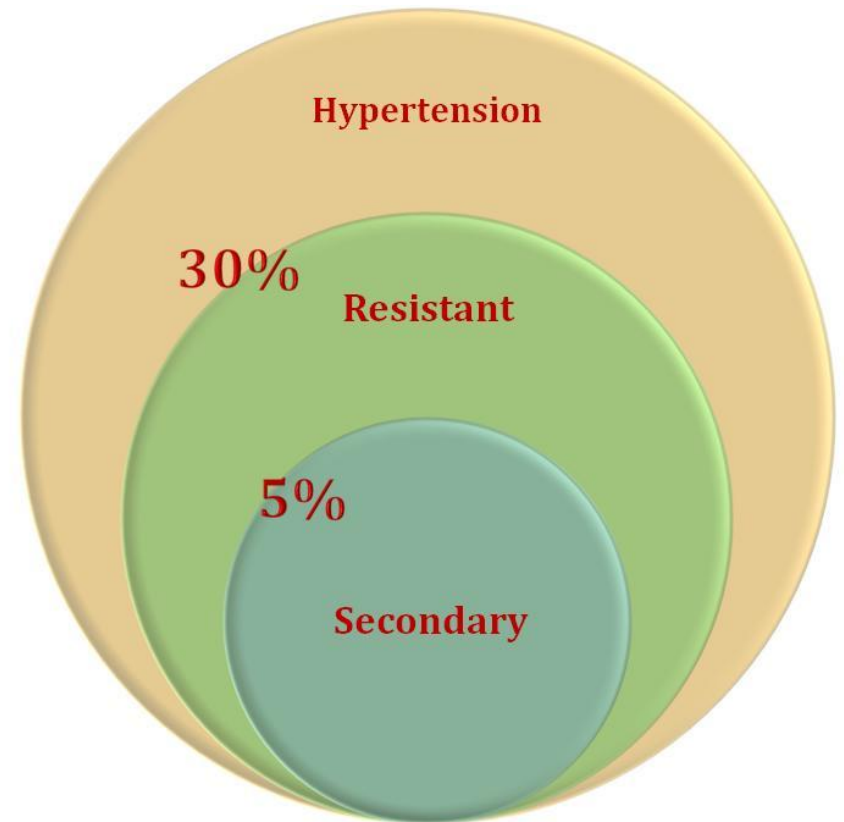
- BP that remains above goal in spite of compliance with full doses of ≥ 3 antihypertensive medications of different classes; ideally, 1 of the 3 agents should be a diuretic¹
 - The treatment plan must include attention to lifestyle measures²
- Includes those patients who achieve BP control but require ≥ 4 antihypertensive agents to do so¹

1. Calhoun DA, et al. *Circulation*. 2008;117:e510-e526.

2. Mancia G, et al. *Eur Heart J*. 2007;28:1462-1536.

Prevalence

- The exact prevalence of resistant hypertension is unknown.
- 20% to 30% reported in various studies.
- NHANES --- 12.8%



Prevalence

- 5- 10% of resistant hypertension patients have an underlying secondary cause for their elevated blood pressure
- Patients with resistant hypertension are almost 50% more likely to experience an adverse cardiovascular event.
- Doctors in primary care can expect to encounter resistant hypertension **one in every 20** hypertensive patients.

Factors That May Influence Prevalence of Resistant Hypertension in Clinical Practice

- Patient-related
 - Age
 - Sex
 - Ethnicity
 - Body size
- Measurement-related
 - Act of taking measurements
 - Time of day
 - Reliance on home blood pressure measurements

Etiology



The Etiology of Resistant Hypertension can be classified as :

1. Primary causes
2. Secondary causes
3. Factors contributing to resistant hypertension

Pathophysiology of resistant or difficult-to-treat hypertension

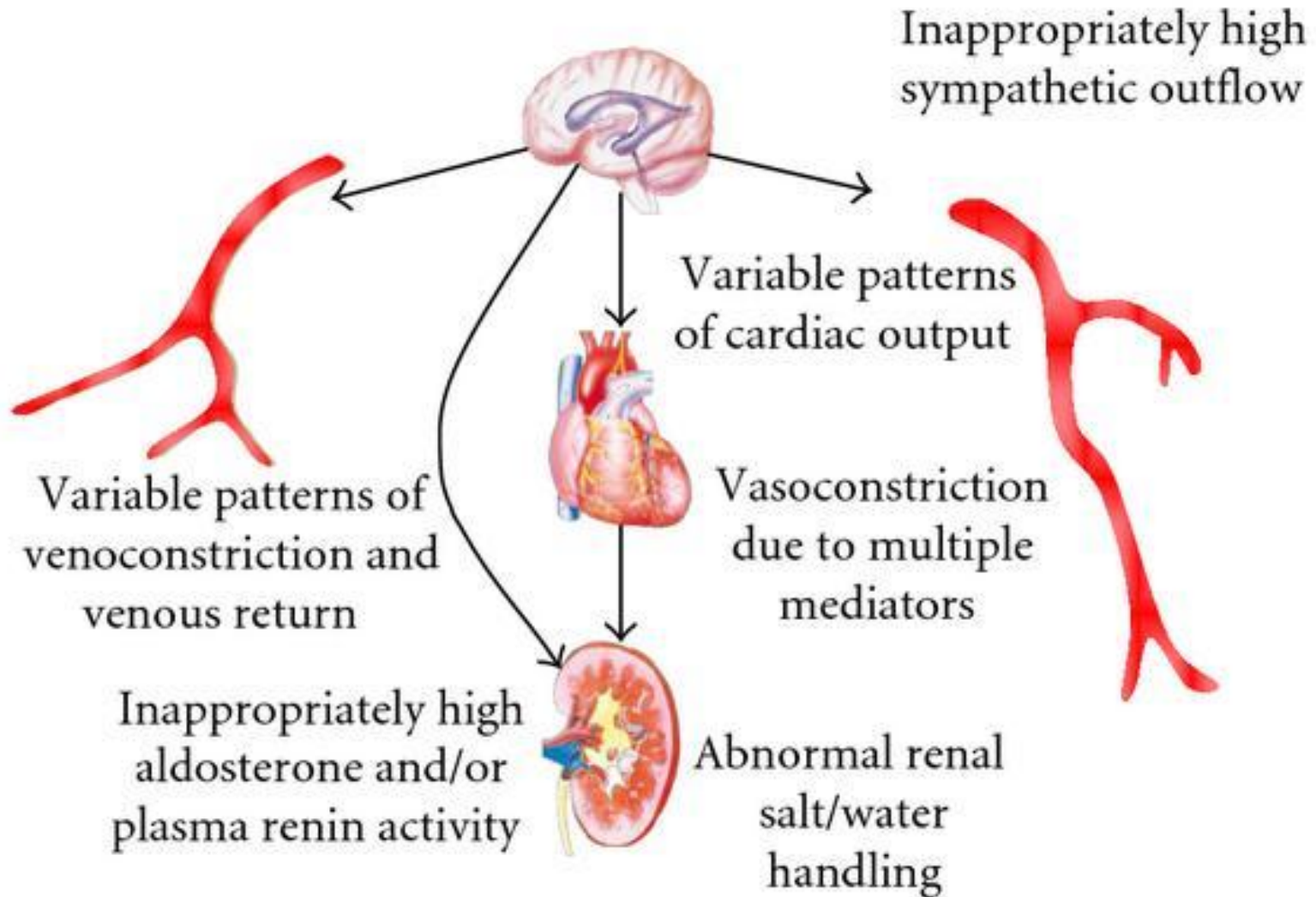


Figure : Demonstrates pathophysiology of resistant hypertension. Increased sympathetic outflow is a fundamental abnormality in most patients.

Risk factors and secondary causes

	Common	Less common
Clinical risk factors	• Pseudo-resistance (poor measurement technique, poor adherence, white-coat effect) • Older age • High baseline BP • Obesity • Excessive dietary salt ingestion • Chronic kidney disease • Diabetes	• Left ventricular hypertrophy • Female sex
Medications interfering with BP control	• Non-narcotic analgesics (NSAIDs, aspirin, COX-2 inhibitors) • Sympathomimetic agents • stimulants • Alcohol	• Oral contraceptives • Cyclosporine • Erythropoietin • Herbal compounds and stimulants
Secondary causes of resistant hypertension	• Obstructive sleep apnea • Renal parenchymal disease • Primary aldosteronism • Renal artery stenosis	• Pheochromocytoma • Cushing's disease • Hyperparathyroidism • Aortic coarctation • Takayasu's disease • Intracranial tumor

Pseudo-resistance

- Blood pressure can be overestimated as a consequence of inaccurate measurement technique.
- The most common causes of overestimated blood pressure are :
 - ▣ using a cuff that is too small.
 - ▣ measuring blood pressure before the patient is sitting quietly.
 - ▣ nonadherence to prescribed antihypertensive therapy.



Management

Diagnosis



- The diagnosis of resistant hypertension requires exclusion of both pseudo-resistance and reversible or organic causes

Investigations

- Urea and electrolytes
- Estimated glomerular filtration rate
- Plasma glucose
- Plasma renin or aldosterone levels
- 24 hour urinary metanephrines or normetanephrines (for phaeochromocytoma)
- Urine analysis—microalbuminuria and macroalbuminuria, haematuria).
- Electrocardiography
- Echocardiography should be performed, along with fundoscopy
- Renal imaging.

Initial investigations for suspected causes of secondary hypertension

Disorder	Suggested Investigation
Primary hyperaldosteronism	Plasma aldosterone: Renin ratio
Thyroid disease	Thyroid function tests
Pheochromocytoma	24-hour urinary catecholamine level Plasma metanephrines
Cushing's syndrome	Urinary Cortisol
Obstructive sleep apnoea	Polysomnography
Renovascular disease	Renal artery duplex scan
Renal Parenchymal disease	Renal ultrasound scan
Coarctation of the aorta	Cardiac ultrasound scan

Indications for specialist referral in hypertensive patients

Suspected secondary hypertension

Hypertension with target-organ damage

eGFR $<30\text{ml/min/1.73m}^2$

eGFR decline of 15% within 3 months

Proteinuria $>1\text{g/day}$

Requiring >4 medications for pressure control

Target organ damage in resistant hypertension

- left ventricular hypertrophy
- Hypertensive retinopathy
- Renal disease (that is, persistently elevated urinary albumin excretion rate, haematuria, or renal impairment)

Treatments available for resistant hypertension

- **Non-pharmacologic intervention**
- **Drug intervention**
- **Device therapy**

Non-pharmacologic Intervention

Modification	Recommendation
Weight reduction	Maintain normal body weight(BMI : 18.5 - 24.9 kg/m ²)
Adopt DASH (Dietary Approach to Stop Hypertension) eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol/d (2.4 gm sodium or 6 gm sodium chloride)
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min/d, most days of the week)
Moderation of alcohol consumption	Limit consumption to no more than two drinks (1 oz or 30 ml ethanol; 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day for most men, and to no more than one drink per day for women and lighter weight persons
Tobacco	Total abstinence

Salt Restriction

- In India, salt intake is very high: 9 and 12 grams daily.
- This is extremely high compared to the WHO recommended intake level of 5 grams daily.
- Attributed to intake of processed foods with salt such as *soft drinks, cornflakes, salted biscuits, butter milk, lassi, salad with salt sprinkled over it, pickles, papads, chinese foods, pakoras, patties, samosas etc.*

- Salt is present in every natural food we eat which is enough to meet the needs of the body under normal circumstances.

< 25 mg (low)		25 - 50 mg (moderate)	50 - 100 mg (moderately high)	> 100 mg (high)
Amla	Horse gram	Raisins	Cauliflower	Amaranth
Bitter gourd	Ragi	Broad beans	Fenugreek	Bacon
Bottle gourd	Vermicelli	Carrots	Lettuce	Egg
Brinjal	Semolina	Raddish	white Field beans	Lobster
Cabbage	Wheat	Black gram dal	Beetroot	
Lady finger	Maida	Green gram dal	Water melon	
Colocasia	Milk	Red gram dal	Bengal gram dal	
Cucumber	Grapes	Lentil	whole Red gram tender	
French beans	Sweetlime	Bengal gram	whole Liver	
Peas	Papaya	Banana	Prawns	
Onion	Orange	Pineapple	Chicken	
Potato	Sapota	Apple		
Tomato (ripe)	Mutton			

Sodium content of food per 100 grams

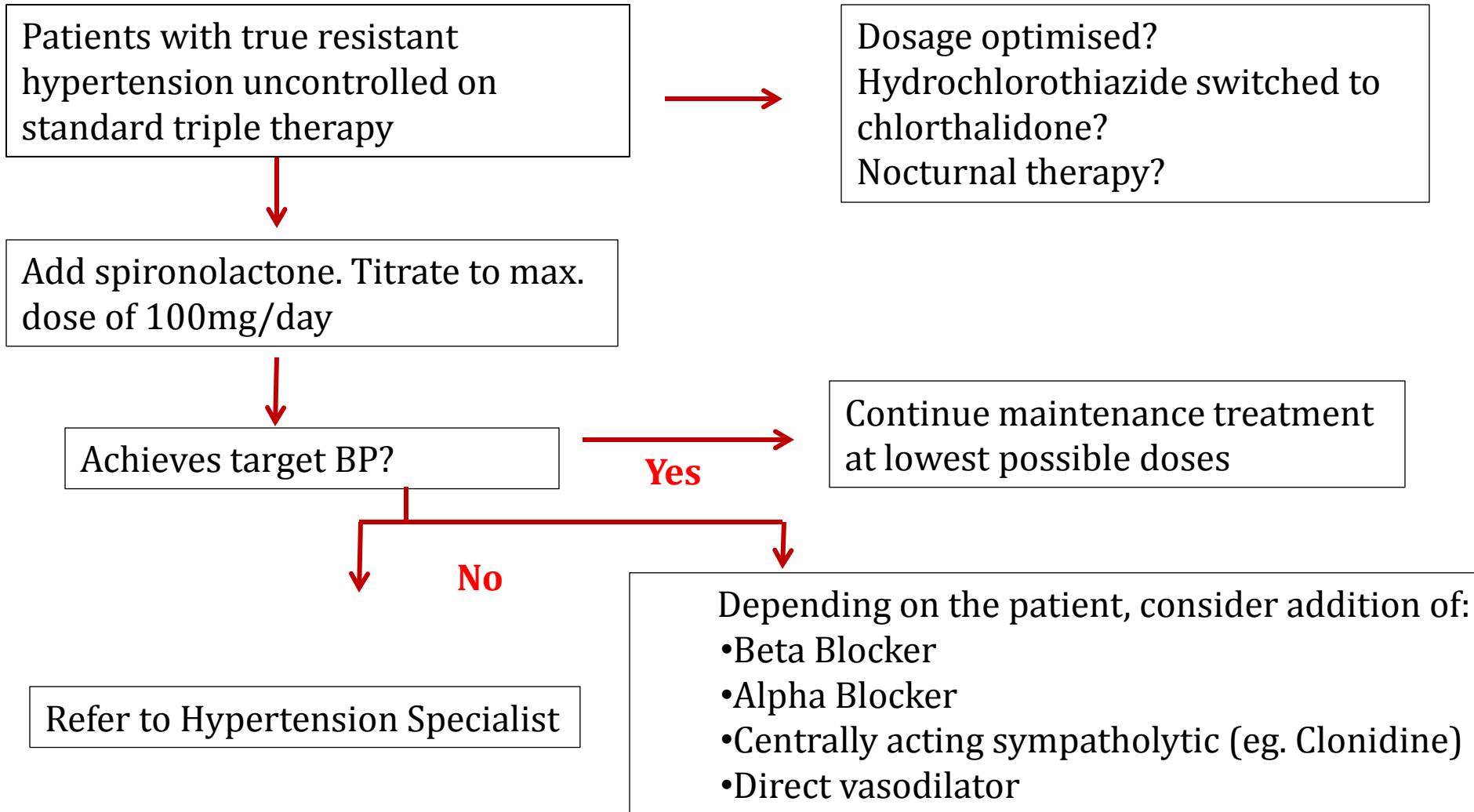
Strategies to reduce excessive salt use in dietary practice

- ❑ Avoid excessive intake of salt in cooking
- ❑ Increase intake of foods low in salt (e.g., fruits and vegetables)
- ❑ Avoid foods high in salt (pre-prepared/processed foods)
- ❑ Refrain from adding salt at the table
- ❑ Increase their awareness of the salt content of food choices in restaurants
- ❑ Promote use of traditional food rather than Western or fast food and junk foods which are high not only in salt but also in calories, sugar, and fat content.

Pharmacotherapy

- Patients defined as having resistant hypertension will already be receiving or have received at least three antihypertensive drugs that is, an ACE inhibitor or angiotensin receptor blocker plus a calcium channel blocker plus a thiazide-type diuretic **(A+C+D)**.
- What to add as the fourth agent to treat resistant hypertension?

Pharmacologic management of resistant hypertension



Options for resistant hypertension

Drug Class	Examples	Recommended Dose	Notes
Alpha Blockers	Prazocin	0.5mg daily; initially nocte, increasing to maintenance dose of 1-10 mg twice daily	Useful option in men with benign prostatic hyperplasia and UTI. Can cause postural hypotension.
Centrally acting sympatholytic	Clonidine	50 mcg twice daily, upto 300 mcg twice daily	Adverse effects : dry mouth and sedation. Abrupt cessation of clonidine: severe rebound HTN
Direct Vasodilators	Minoxidil	5 mg daily, upto 30 mg twice daily	Minoxidil requires co-admin. of beta blocker and loop diuretic to offset tachycardia and fluid retention
	Hydralazine	12.5 mg daily, upto 200 mg daily in divided doses	Fewer adverse effects. Most clinicians with their use elect hydralazine in women and minoxidil in men

Prevention And Treatment of Hypertension With Algorithm-based therapy (PATHWAY) number 2: protocol for a randomised crossover trial to determine optimal treatment for drug-resistant hypertension

- 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 favour of spironolactone–
 - ▣ Spironolactone is the most effective treatment for resistant hypertension,

PATHWAY- 2:

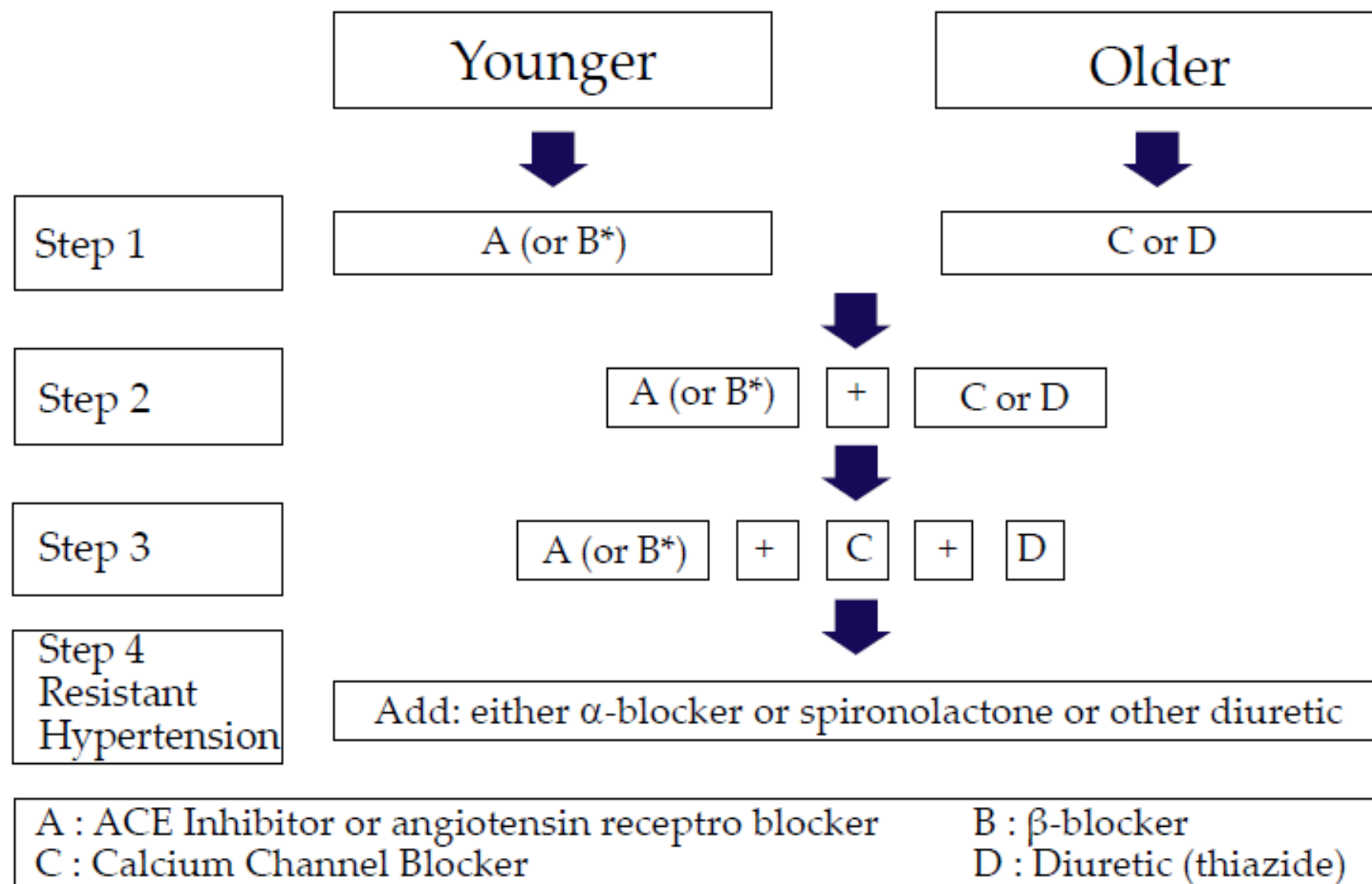
Summary

- Spironolactone was well tolerated with no significant excess adverse effects with the caveat that serum potassium levels and renal function should be monitored on treatment and treatment duration was too short to assess incident gynecomastia (~6% in longer-term studies)

- Spironolactone is the most effective add-on drug.
- The superiority of spironolactone supports a primary role of sodium retention in this condition.



Guidelines



*Combination therapy involving B and D may induce more new onset diabetes compared with other combination therapies. Use β blockers only in special situations. B = Newer β blockers. Younger age: <55 years, Older: >55 years

Device therapy

Two techniques have recently been evaluated:

1. Percutaneous transluminal radiofrequency sympathetic denervation of the renal arteries (RDN).
2. Carotid baroreflex activation.

Renal sympathetic denervation (RDN)

- Considered in patients with severe resistant hypertension, defined as office (SBP) ≥ 160 mmHg (≥ 150 mmHg in patients with type 2 diabetes)
- Focally applied heat (maximum 70°C) destroys the sympathetic nerve fibers located in the adventitia.
- Clinical trials have demonstrated that RDN significantly reduces blood pressure in patients with resistant hypertension.

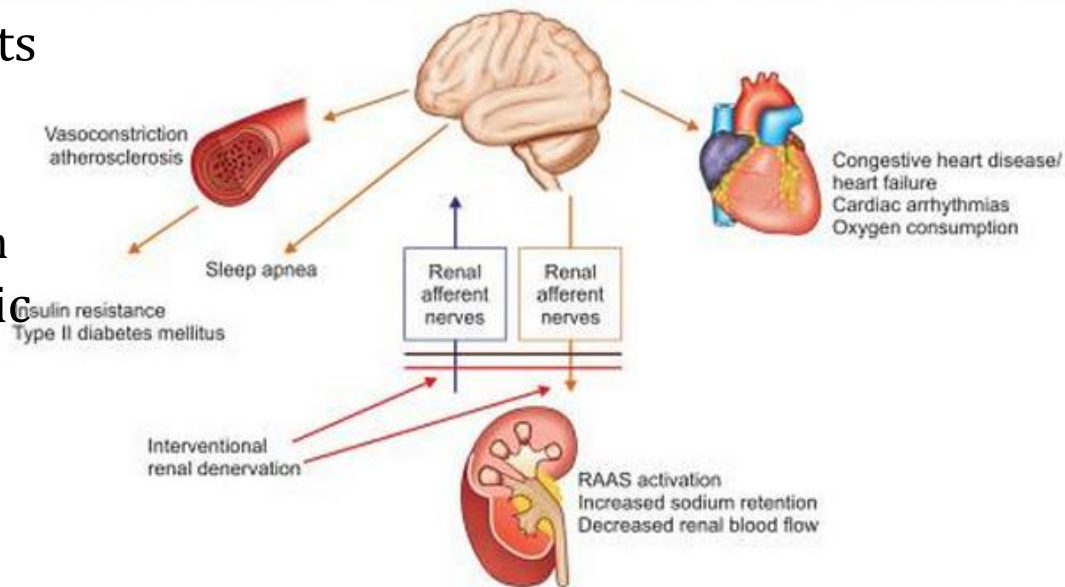


Fig. 1: Effects of renal artery and afferent nerves as a target for renal artery denervation

Systematic approach to Resistant Hypertension

Confirming Resistance to Antihypertensive Therapy

In accordance with the defining criteria of hypertension and of drug resistance



Ruling out Possibilities of Pseudoresistance

Ensure patient adherence to prescribed regimen. Rule out White coat effect by Home BP monitoring



Identification and Correction of Influencing Lifestyle Factors

Ensure implementation of interventions to address obesity, lack of exercise, smoking, alcohol, salt intake



Contd...

Control of Influencing Medication Use

Discontinue or Minimise NSAIDs, sympathomimetics, OCPs, steroids



Workup to Identify Secondary cause of Hypertension

Consider CKD, Sleep apnea, Renal artery stenosis, pheochromocytoma, cushing's syndrome, primary aldosteronism



Drug Therapy

Optimise diuresis (maximize diuretic therapy, consider addition of aldosterone agonist; loop diuretic in advanced CKD, as appropriate);

Evaluate prescribed drug combination; consider inclusion of drugs from different classes with possible synergistic efficacy and acceptable safety;

Optimize dosing to maximize efficacy and ensure smooth 24-hour control



THANK YOU