Resistant Hypertension: Definition, Prevalence and Clinical Implications

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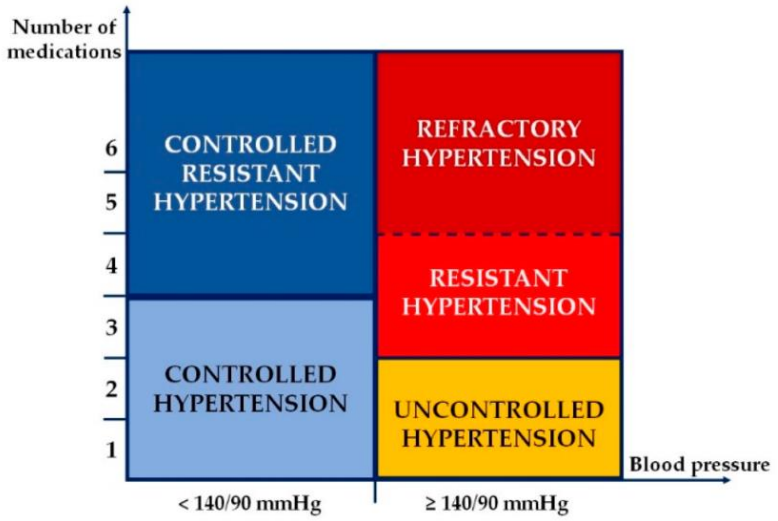
Definitions

- Resistant Hypertension
  - Failure to achieve goal BP despite **adherence** to 3 antihypertensive drug regimen.
    - ➢ One of the agents is a diuretic.
    - ➢ Drugs are optimally dosed.
  - Controlled BP with 4 or more antihypertensive drugs.



2018 ESH/ESC Guidelines:

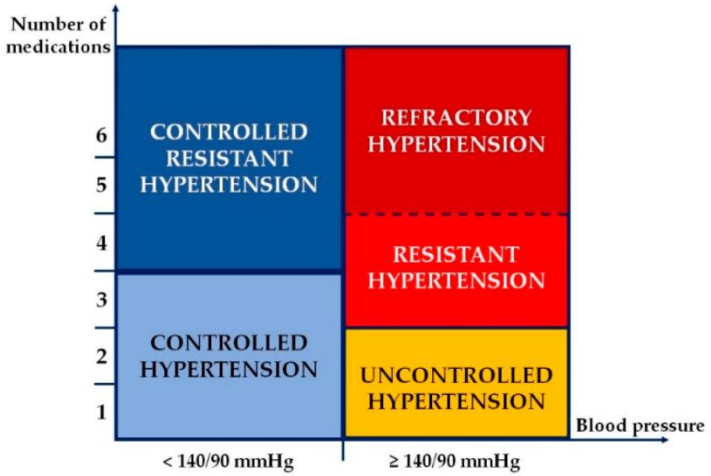
treatment strategy fails to lower office SBP and DBP values to <140 mmHg and/or <90 mmHg, and is

confirmed by ABPM or HBPM

in patients whose adherence to therapy has been confirmed

Definitions

- Uncontrolled Hypertension
  - Blood pressures not at goal
    - General goal < 140/<90
      - Specific populations < 130/<80
        - » CKD, ASCVD, DM and CHF
  - Causes
    - Previously undiagnosed Hypertension
    - Medication Non-adherence
    - Resistant Hypertension



Resistant Hypertension-Associated Phenotypes

2017 ACC/AHA guideline introduced two new concepts:

- **1- Controlled R-HTN ➔** at least four antihypertensive medications and achieving an adequate office BP control.

- **2- Refractory R-HTN (rfR-HTN)➔** elevated office BP values while on treatment with five or more antihypertensive drugs

(including a long-acting thiazide-type diuretic, such as indapamide or chlorthalidone, or a mineralocorticoid receptor antagonist (MRA), such as spironolactone .)

The prevalence of rfR-HTN:

- Spanish Registry in 2004 (70,997 treated patients) ➔ R-HTN (16.9%) and rfR-HTN (7.9% of R-HTN and 1.4% of the entire treated group)

- in the REGARD Study ➔ rfR-HTN = 0.5%

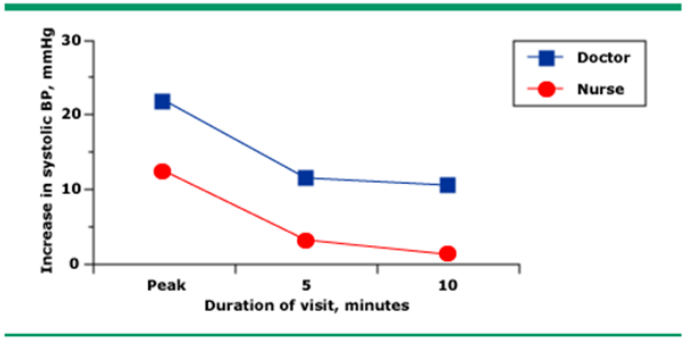
Compared with R-HTN, patients with rfR-HTN were younger, had a longer duration of HTN, a higher prevalence of obesity, diabetes mellitus, dyslipidemia, chronic kidney disease and target organ damage and previous history of CV events

- **3- masked uncontrolled HTN**➔ receiving four or more antihypertensive medications and achieving an adequate office BP control, but with elevated out-of-office BP

- screening of masked uncontrolled HTN should be performed in all patients with controlledR-HTN, due to higher CV risk and thus needing a more aggressive therapeutic strategy

- **Pseudo-Resistant Hypertension**
  - Inaccurate Measurement
    - patient has been seated quietly in a chair with back supported for five minutes.
    - cuffs are too small relative to the arm circumference
  - White coat effect.
  - Marked brachial artery calcification
  - Inadequate treatment regimen.
  - Poor adherence to antihypertensive th
    - Multiple medications.
    - Frequent changes.
    - Side effects.
    - Cost !!!

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



- confirmed inadequate control of BP (by ABPM or HBPM)

Pathophysiology of Resistant Hypertension

R-HTN is broadly attributed to two underlying processes:

- **renin-angiotensin-aldosterone system**

endothelial dysfunction, sympathetic activation and oxidative stress ➔ inflammation, calcification and fibrosis

in R-HTN due to several non-genomic pro-inflammatory effects that can maintain a pharmacologically resistant state

- **Sympathetic nervous system activation**

- impaired parasympathetic tone and increased sympathetic activation ➔ early stages of HTN + development of target organ damage.
- mechanisms of sympathetic activation ➔cardiopulmonary reflex dysfunction, chemoreceptor stimulation, baroreflex dysfunction, central factors, insulin and leptin➔ vascular remodeling + endothelial dysfunction + arterial stiffness in hypertensive state
- in patients with R-HTN➔ significant activation of renal sympathetic system
- sympathetic activation is more pronounced in patients with R-HTN

- **Role of Genetics: ?**

- it is probably caused by both common and rare gene variants.

Incidence and Prognosis of Resistant Hypertension

- the true prevalence (After applying a strict definition (see above) and having excluded causes of pseudoresistant Hypertension) = is likely to be <10% of treated patients.

Clinical Implications of Resistant Hypertension

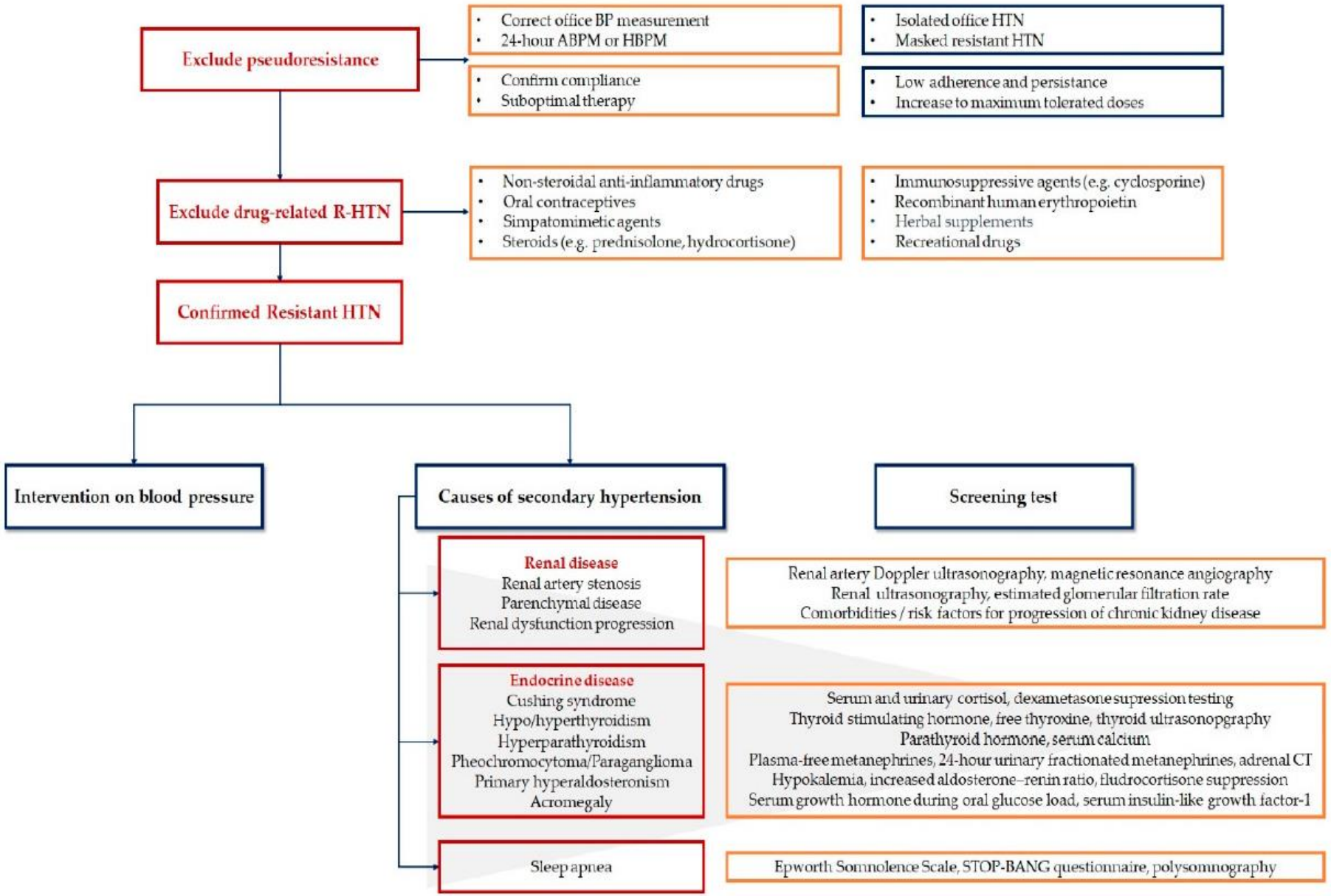
- Higher incidence
  - Cardiovascular events, particularly stroke
    - More LVH, carotid intimal thickening
  - Progressive kidney disease
  - CHF
  - Death

Cardiovascular Risk in Resistant HTN

- 4.98 + 2.9 years follow-up
- Events: fatal/nonfatal MI, revascularization (CAD or PVD), CHF, stroke and ESRD
- Event-rate per 100 patient-yrs
  - **True Responders,** n = 340**, rate= 0.87**
  - **Masked HTN,** n = 126**, rate= 2.42**
  - **False Resistant**, n = 146**, rate= 1.2**
  - **True Resistant ,** n = 130**, rate= 4.1**

Diagnostic approach of resistant hypertension

Diagnostic approach of resistant hypertension



The Road to Better Management in Resistant Hypertension—Diagnostic and Therapeutic Insights. Pharmaceutics **2021**

Diagnostic approach to resistant hypertension

(1) The history:

- lifestyle characteristics,
- alcohol and dietary sodium intake,
- interfering drugs or substances,
- sleep history.

(2) A physical examination,

- presence of HMOD (hypertension mediated organ damage)
- signs of secondary hypertension.

(3) The nature and dosing of the antihypertensive treatment.

(4) **Confirmation of treatment resistance** by out-of-office BP measurement (ABPM or HBPM).

(5) **Laboratory tests :**

- electrolyte abnormalities (hypokalaemia),
- associated risk factors (diabetes),
- organ damage (advance renal dysfunction),
- secondary hypertension: primary aldosteronism , atherosclerotic renal artery stenosis (in older patients or with CKD)

(6) Confirmation of adherence to BP-lowering therapy.

Confirm Treatment Resistance: ABPM and, if not available, HBPM

- **White-coat uncontrolled HTN**
- **Masked uncontrolled HTN**
- **Sustained uncontrolled HTN**

- **Exclude Pseudo-resistance**
- **Exclude Drug-Related Resistant Hypertension**
- **Exclude Secondary Causes of Hypertension**

Secondary causes of Resistant Hypertension

- **primary aldosteronism**
- **renal artery stenosis (in older patients or with CKD)**
- Obstructive Sleep Apnea (OSA) is prevalent!!
- Obesity
- CKD
- Pheocromocytoma
- Cushing's syndrome

Lifestyle factors.

- Dietary salt consumption:

  Assessment of 24 hrs UNa excretion (**goal <100 meq/24 hrs**).

- Alcohol consumption:

  Alcohol should be limited to 1 ounce/day in RH patients.

- Obesity or large gains in weight
- Intake of vasopressor or sodium-retaining substances , OCP
- Sleep

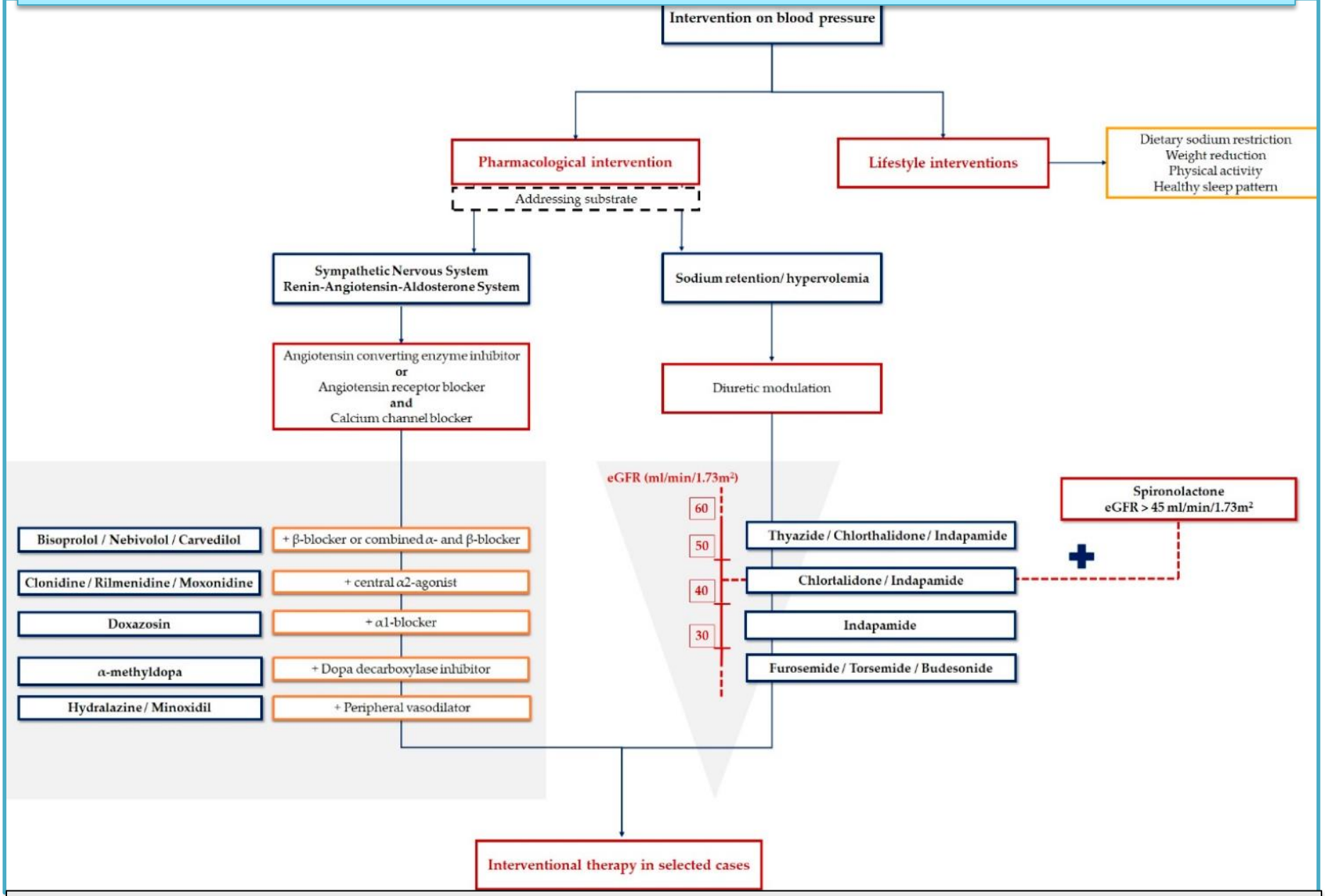
Drug-related causes of Resistant Hypertension

- NSAIDs
- Steroids
- Sympathomimetics
  - Decongestants
  - Weight Loss Meds
  - Cocaine
- Oral Contraceptives
- Erythropoeitin
- Licorice

- Stimulants
  - Methylphenidate
  - Amphetamine
  - Modanifil
- Calcineurin Inhibitors
- Herbal Meds
  - Ephedra
  - Ma huang
- Tricyclic antidepressants

Therapeutic Approach of Resistant Hypertension

Therapeutic approach of resistant hypertension.



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Nonpharmacological Strategies:

Lifestyle changes

- Weight Reduction
- Dietary Sodium Restriction
- The DASH Diet
- Physical Activity
- Other Risk Factors
- Psychological Counseling
- Discontinuation of interfering substances,

Pharmacological Strategies

The optimal drug treatment of resistant hypertension has been poorly studied.

- Optimizing the Three-Drug Regimen
- Optimizing the Diuretic Treatment
- Adding a Mineralocorticoid Receptor Antagonist
- Adding Beta-Blocker or Alfa+beta-Blocker
- Adding alfa1-Blocker or a Peripheral Vasodilator

Treatment of resistant hypertension

Diuretic:

- The most effective strategy seems to be additional diuretic treatment to decrease volume overload +
- with the restriction of salt intake, particularly in patients with CKD.

- ➢ increasing the dose of the existing diuretic
- ➢ or by switching to a more potent thiazide-like diuretic (chlorthalidone or indapamide).
- ➢ A loop diuretic should replace thiazides/thiazide-like diuretics if the eGFR is **<30** mL/min.

- Although resistant hypertension may show a BP reduction if the existing diuretic dose is further increased ➔ most patients require the administration of additional drugs.

fourth-line treatment ?

- should involve a blockade of aldosterone = MRAs

Spironolactone: up to 50 mg/day.

- Antiandrogenic side effects ➔ breast tenderness or gynaecomastia (in 6%), impotence in men, and menstrual irregularities in women.
- Patients with an eGFR >_45 mL/min and a plasma potassium <4.5 mmol/L.

eplerenone (50 - 100 mg/day). ➔ (due to androgen-like side effects of spironolactone)

Amiloride (10 - 20 mg/day) ➔ effective as spironolactone 25–50 mg daily) in reducing BP (PATHWAY-2 Study)

as alternatives to spironolactone.

Bisoprolol : (5 - 10 mg/day)

Doxazosin : (4 - 8 mg/day)

- Neither was as effective as spironolactone, but they did reduce BP significantly vs. placebo

- Thus, bisoprolol and doxazosin have an evidence base for the treatment of resistant hypertension when spironolactone is contraindicated or not tolerated.

Direct vasodilators: such as **hydralazine** or **minoxidil**:

- are infrequently used because they may cause severe fluid retention and tachycardia.

New BP-lowering drugs: (nitric oxide donors, vasopressin antagonists, aldosterone synthase inhibitors, neutral endopeptidase inhibitors, and endothelin antagonists) are all under investigation.

Device-based hypertension treatment

Renal denervation

- Sympathetic nervous system → renal vascular resistance + renin release, + sodium reabsorption
- Catheter-based radiofrequency, ultrasound, or perivascular injection of neurotoxic agents such as alcohol has been introduced as a minimally invasive treatment option
- clinical evidence → is conflicting.

- Symplicity HTN-1 and HTN-2 trials ➔
- two RCTs with a sham procedure ➔ failed to document the superiority of renal denervation compared with the sham procedure in reducing BP, but did confirm the safety of the procedure.
- Another RCT (DENERHTN) ➔ superiority of renal denervation in combination with optimized pharmacotherapy compared with pharmacotherapy alone.
- The PRAGUE-15 study ➔ similar effects between renal denervation and optimized pharmacotherapy (mainly by adding spironolactone) + the latter was associated with more side effects and high discontinuation rates.
- Beyond resistant hypertension, interim data in the first 80 patients treated with renal denervation but with no background antihypertensive therapy showed a modest effect of renal denervation vs. sham control on 24 h ambulatory BP after 3

complicated by

- (i) the complex pathophysiology of hypertension,
- (ii) the lack of clinically applicable measures of sympathetic activity,
- (iii) the absence of predictors of the long-term BP response following renal denervation,
- (iv) the absence of reliable markers of procedural success to immediately

- establish whether denervation has been achieved.

- The evidence➔ isolated systolic HTN (increased aortic stiffness) ➔ limited response to renal denervation and baroreceptor stimulation

Major uncertainties remain

- The purpose → ablate the sympathetic nerves (by radiofrequency or ultrasound)

in patients with R-HTN taking 4–5 antihypertensive drugs by three

- studies called **SYMPLICITY** (Catheter-based renal sympathetic denervation for resistant hypertension: a multicenter safety and proof-of-principle cohort study).
- It was first used in
- **SYMPLICITY HTN-1** (a human feasibility trial)
- **SYMPLICITY HTN-2** study (larger randomized prospective) →a reduction in office BP and a good safety profile when using this device.

- **SYMPLICITY HTN-3** (The first sham-controlled randomized clinical trial) ➔ little to no effect on BP in patients with severe R-HTN
- Possible explanations are incomplete nerve ablation due to poorly designed catheter electrodes
- inexperienced operators,
- non-adherence to the multidrug pharmacological regimen
- not including ABPM in the efficacy analysis.

- Since then, the Renal Denervation for Hypertension (DENER-HTN) ➔ a statistically significant reduction in daytime ambulatory systolic BP (–5.9 mmHg) in hypertensive patients on a three-drug regimen randomized to renal sympathetic denervation, when compared to patients taking four antihypertensive medications without
- renal denervation.

- Recently, **SPYRAL-OFF MED Pivotal trial** (catheters have been re-designed to allow complete circumferential renal nerve ablation.)

- sham-controlled, randomized trial that uses this type of catheter and evaluates renal sympathetic denervation independently of antihypertensive drugs.

- ➔ significant BP reduction (–4.7 mmHg in 24-h ambulatory BP and –6.6 mmHg in office BP) after 3 months of followup

- Radiofrequency from renal sympathetic denervation can be replaced with ultrasound, as new research demonstrated—Paradise Renal Denervation System, ReCor Medical. This technique also showed a reduction of BP in its own proof-of-concept trial

Carotid baroreceptor stimulation:

1- pacemaker = (Rheos and BAROSTIM NEO systems)

2- stent: (MobiusHD).

- leads to a reduction of sympathetic signals to the vessels, heart an kidneys ➔ reduction of BP.

implantable pulse generator

- RCT with the first generation of an implantable pulse generator showed sustained BP-lowering efficacy (and sympathetic nervous system inhibition), but with some concerns about procedural and longer term safety.
- A second-generation unilateral device has been developed to improve safety and sustained efficacy. BP at 12 months post-implantation was similar, with a better safety profile for the second-generation device.

- **Rheos Pivotal Trial** → no superiority of baroreceptor activation therapy for reducing BP compared to medical therapy after a six-months follow-up,
- more than half achieved a systolic BP less than 140 mmHg

stent: (MobiusHD).

A dedicated stent-like device designed to stretch the carotid bulb and increase baroreflex sensitivity.

- lowere coste and simple intervention.
- Shown evidence of BP-lowering efficacy of this new approach,
- but data from ongoing RCTs are needed to definitively understand its
- longer-termefficacy and safety.

Creation of an arterio-venous fistula

- The central iliac arterio-venous anastomosis (4 mm) ➔ unloading the arterial vascular bed into the venous system.
- the ROX CONTROL HTN trial (a stent-like nitinol device) ➔ resistant HTN ➔ RCT= At 6 months, office and ambulatory BP were significantly reduced in the coupler group compared with the control group.
- safety aspects ➔ Ipsilateral venous stenosis = occurred in 29% of patients.
- no reports of RV- failure or high-output cardiac failure after device implantation over the short-term, but longer follow-up is clearly needed.

Other devices

Surgical resection of the carotid body / endovascular carotid body modification by ultrasound-guided ablation

The carotid body is innervated by nerve fibres from the vagus nerve through the cervical ganglion and the carotid sinus nerve.

Stimulation of the carotid body drives sympathetic tone, resulting in an increase in BP and minute ventilation.

- reductions in BP and sympathetic overactivity in patients with heart failure.

In summary,

- device-based therapy for hypertension is a fast moving field.
- Further sham-controlled studies are needed before device-based therapies can be recommended for the routine treatment of hypertension outside of the framework of clinical trials.

Looking into the Future

New therapeutic agents:

- neutral endopeptidase inhibitors: leading to a decrease of angiotensin-II

=> **Omapatrilat** vs. Enalapril (OCTAVE) trial ➔ antihypertensive effect was superior, more angioedema (2.17% versus 0.68%)

- **sacubitril/valsartan** (ARB-blockers and neprilysin inhibitors) ➔promotes vasodilation, increases sodium excretion and displays antihypertrophic and antifibrotic properties ➔ reducing office and ambulatory central aortic and brachial pressures in elderly patients with systolic HTN and arterial stiffness

- drugs prevents the degradation of natriuretic peptides into metabolites and promotes vasodilation, increases sodium excretion and displays antihypertrophic and antifibrotic properties

- **finerenone** (BAY94-8662)=nonsteroidal mineralocorticoid receptor antagonists➔ Anti-fibrotic ,LVH , Pro- BNP , proteinuria, BUT not significantly influence BP (lower vHyperkalemia).

- **Aminopeptidase:** a membrane-bound zinc metalloprotease ➔
- **Firibastat** ➔

TAKE HOME MASSAGE

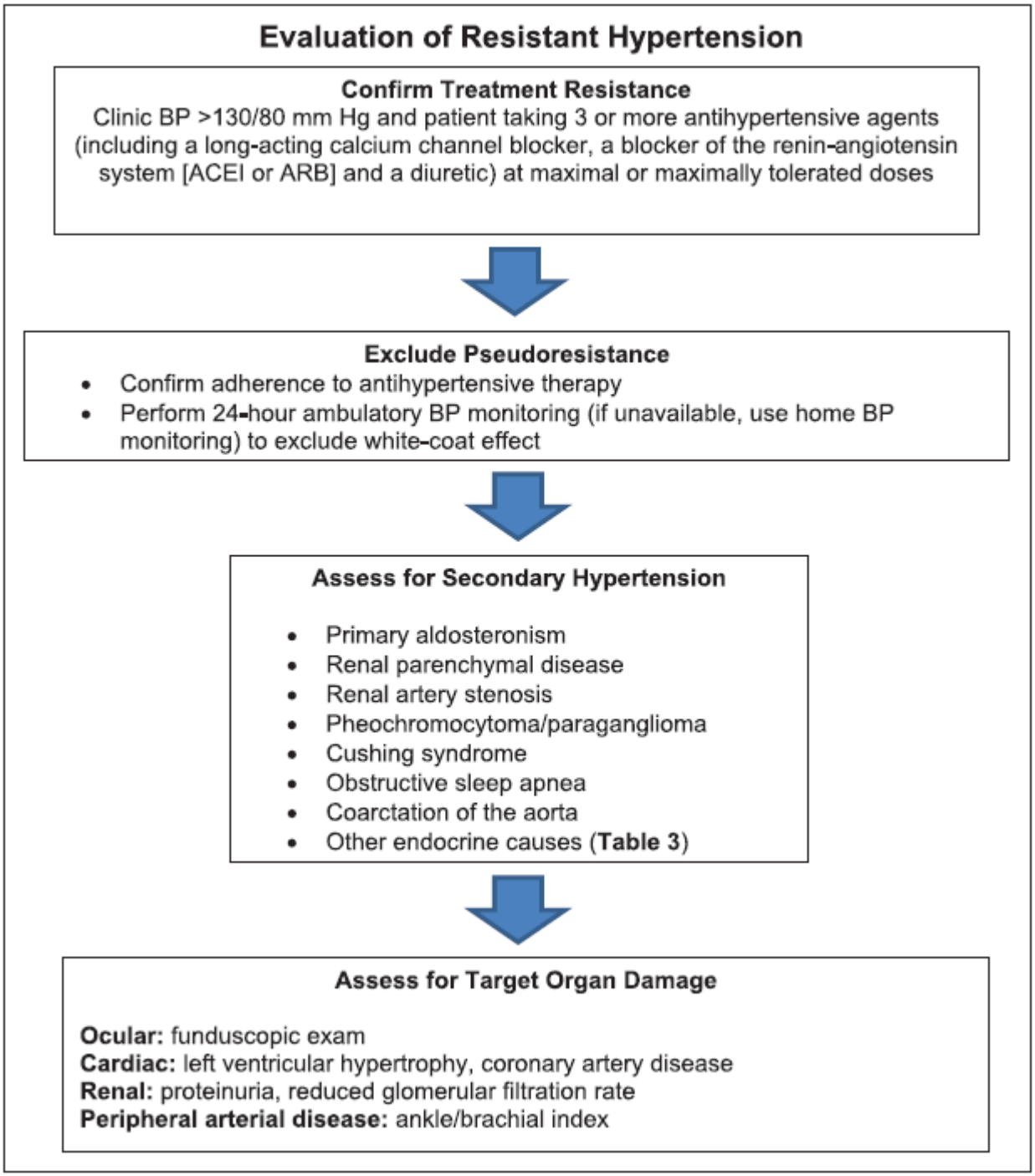
- The importance of RH is underscored by the associated risk of adverse outcomes compared with non-RH.

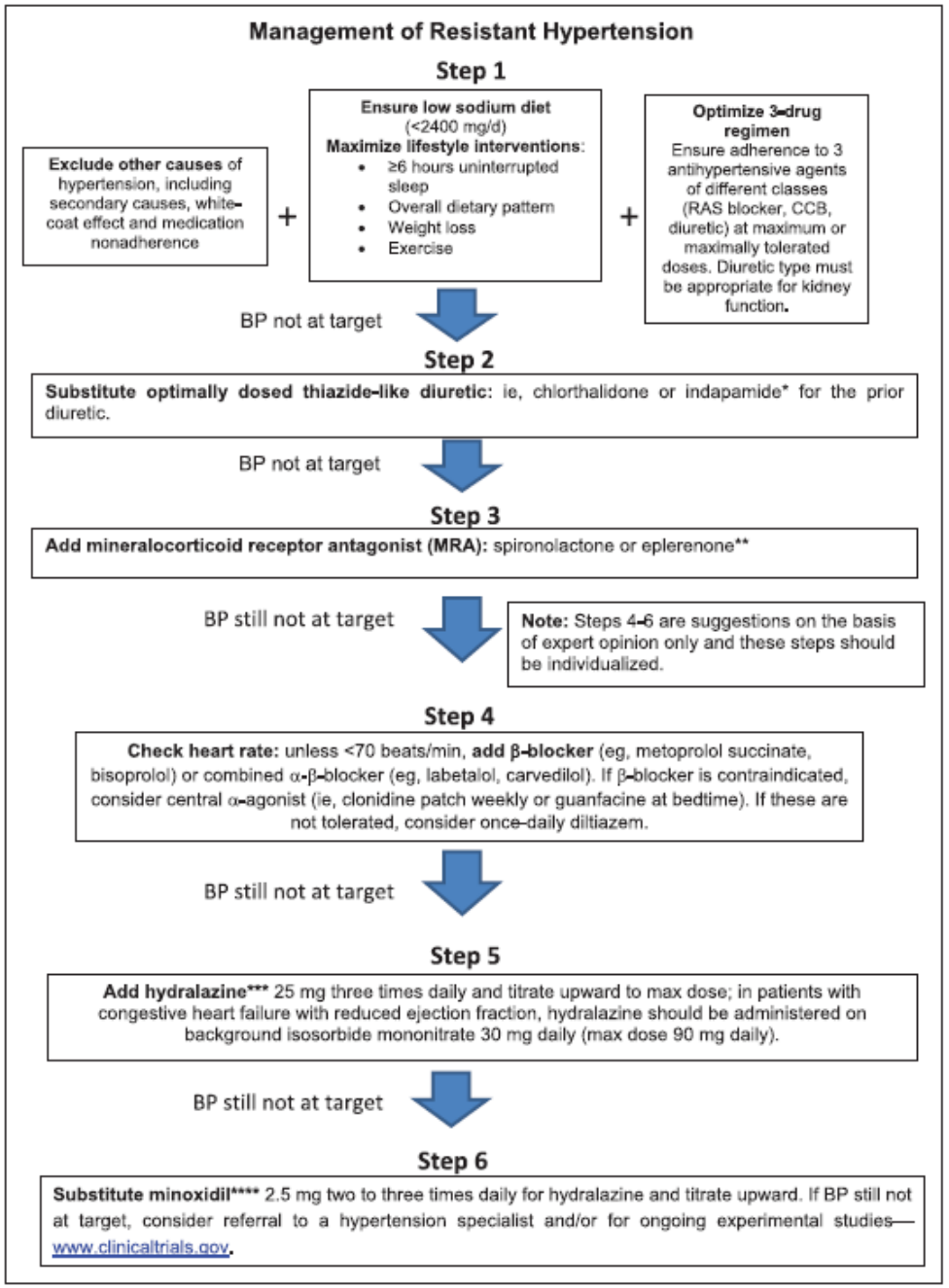
- antihypertensive medication adherence is confirmed
- out-of-office BP recordings exclude a white-coat effect,

- contributing lifestyle issues,
- detection of drugs interfering with antihypertensive medication effectiveness,
- screening for secondary hypertension,
- assessment of target organ damage. پ

- Management of RH includes maximization of lifestyle interventions,
- use of long-acting thiazide-like diuretics (chlorthalidone or indapamide),
- addition of a mineralocorticoid receptor antagonist (spironolactone or eplerenone),

- and, if BP remains elevated, stepwise addition of antihypertensive drugs with complementary mechanisms of action to lower BP.


Evaluation of Resistant Hypertension
Confirm Treatment Resistance
Clinic BP >130/80 mm Hg and patient taking 3 or more antihypertensive agents (including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system [ACEI or ARB] and a diuretic) at maximal or maximally tolerated doses
Exclude Pseudoresistance
Confirm adherence to antihypertensive therapy
Perform 24-hour ambulatory BP monitoring (if unavailable, use home BP monitoring) to exclude white-coat effect
Assess for Secondary Hypertension
Primary aldosteronism
Renal parenchymal disease
Renal artery stenosis
Pheochromocytoma/paraganglioma
Cushing syndrome
Obstructive sleep apnea
Coarctation of the aorta
Other endocrine causes (Table 3)
Assess for Target Organ Damage
Ocular: funduscopic exam
Cardiac: left ventricular hypertrophy, coronary artery disease
Renal: proteinuria, reduced glomerular filtration rate
Peripheral arterial disease: ankle/brachial index


Management of Resistant Hypertension
Step 1
Exclude other causes of hypertension, including secondary causes, white-coat effect and medication nonadherence
+
Ensure low sodium diet (<2400 mg/d)
Maximize lifestyle interventions:
≥6 hours uninterrupted sleep
Overall dietary pattern
Weight loss
Exercise
+
Optimize 3-drug regimen
Ensure adherence to 3 antihypertensive agents of different classes (RAS blocker, CCB, diuretic) at maximum or maximally tolerated doses. Diuretic type must be appropriate for kidney function.
BP not at target
Step 2
Substitute optimally dosed thiazide-like diuretic: ie, chlorthalidone or indapamide* for the prior diuretic.
BP not at target
Step 3
Add mineralocorticoid receptor antagonist (MRA): spironolactone or eplerenone**
BP still not at target
Note: Steps 4-6 are suggestions on the basis of expert opinion only and these steps should be individualized.
Step 4
Check heart rate: unless <70 beats/min, add β-blocker (eg, metoprolol succinate, bisoprolol) or combined α-β-blocker (eg, labetalol, carvedilol). If β-blocker is contraindicated, consider central α-agonist (ie, clonidine patch weekly or guanfacine at bedtime). If these are not tolerated, consider once-daily diltiazem.
BP still not at target
Step 5
Add hydralazine*** 25 mg three times daily and titrate upward to max dose; in patients with congestive heart failure with reduced ejection fraction, hydralazine should be administered on background isosorbide mononitrate 30 mg daily (max dose 90 mg daily).
BP still not at target
Step 6
Substitute minoxidil**** 2.5 mg two to three times daily for hydralazine and titrate upward. If BP still not at target, consider referral to a hypertension specialist and/or for ongoing experimental studies—www.clinicaltrials.gov.

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

Conclusions

- Resistant Hypertension is defined as uncontrolled HTN with BP > 140/90 on ≥ 3 meds or controlled on ≥ 4 meds
  - Exclude non-adherent patients
  - Prevalence ranges from 1.9 – 8.9% of HTN patients
- Check for OSA in all patients and consider meds and other secondary causes
  - Note from a nephrologist
    - CONTROL VOLUME with DIURETICS
- Increased CV event rates occur compared to controlled hypertension


با تشکر از حسن توجه شما

Table 24 Resistant hypertension characteristics, secondary causes, and contributing factors (adapted from reference[385])

Characteristics of patients with resistant hypertension	Causes of secondary resistant hypertension	Drugs and substances that may cause raised BP
Demographics • Older age (especially >75 years) • Obesity • More common in black people • Excess dietary sodium intake • High baseline BP and chronicity of uncontrolled hypertension	**More common causes** • Primary hyperaldosteronism • Atherosclerotic renovascular disease • Sleep apnoea • CKD	**Prescribed drugs** • Oral contraceptives • Sympathomimetic agents (e.g. decongestants in proprietary cold remedies) • Non-steroidal anti-inflammatory drugs • Cyclosporin • Erythropoietin • Steroids (e.g. prednisolone and hydrocortisone) • Some cancer therapies
Concomitant disease • HMOD: LVH and/or CKD • Diabetes • Atherosclerotic vascular disease • Aortic stiffening and isolated systolic hypertension	**Uncommon causes** • Phaeochromocytoma • Fibromuscular dysplasia • Aortic coarctation • Cushing's disease • Hyperparathyroidism	**Non-prescription drugs** • Recreational drugs (e.g. cocaine, amphetamines, and anabolic steroids) • Excessive liquorice ingestion • Herbal remedies (e.g. ephedra and ma huang)

BP = blood pressure; CKD = chronic kidney disease; HMOD = hypertension-mediated organ damage; LVH = left ventricular hypertrophy.

Treating hypertension with selected comorbidities drug class.

Comorbidity	Favor	Avoid	Comment
Atrial fibrillation (AF)	ARB		ARBs may reduce AF recurrence
Aortic disease	Beta blockers		Patients with thoracic aorta disease
Chronic kidney disease (CKD)	ACEI or ARB		ARB if ACEI not tolerated
Diabetes	ACEI or ARB if albuminuria present		Consider usual first line drugs if no albuminuria
Heart failure (preserved EF)	Diuretics for volume overload		Add ACEI or ARB and beta blocker for incremental BP control; also consider angiotensin receptor – neprilysin inhibitor and mineralocorticoid receptor antagonists
Heart failure (reduced EF)	GDMT beta blockers	Non-DHP calcium antagonists	
Peripheral arterial disease			Consider usual first line drugs
Post-kidney transplant	Calcium antagonist	Use ACEI with caution	Calcium antagonist can improve kidney graft survival and GFR; 1st month post-transplant BP target (<160/90) to avoid hypotension – induced graft thrombosis
Secondary stroke prevention	Thiazide, ACEI, ARB or thiazide + ACEI combination		If previously treated, restart drugs a few days post-event; if not previously treated, start drug treatment a few days post-event if BP ≥140/90.
Stable ischemic heart disease	GDMT beta blockers ACEI or ARB		
• Angina	GDMT beta blockers		Add DHP calcium antagonists for additional BP control
• Post-MI or ACS	GDMT beta blockers		
Valvular heart disease			
• Aortic stenosis (asymptomatic)			Initiate treatment with low medication doses and up-titrate slowly
• Aortic insufficiency	Avoid beta blockers, non-DHP calcium antagonists		Avoid drugs that slow heart rate