
بسم الله الرحمن الرحيم

Resistant HTN

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Resistant HTN

Hypertension was defined as resistant to treatment when appropriate lifestyle measures and treatment with optimal or best tolerated doses of three or more drugs

(a Thiazide/Thiazide-like diuretic, an RAS-blocker and a CCB) fail to lower office BP to <140/90mmHg.

The inadequate BP control should be confirmed by out-of-office BP measurement showing an uncontrolled 24 h BP (130mmHg SBP or 80mmHg DBP) values.

Patients with resistant hypertension are at higher risk of HMOD, CKD, and premature CV events

Pseudo-resistant hypertension

Several possible causes of pseudo-resistant hypertension should be evaluated and ruled out before concluding that the patient has resistant hypertension:

1) Poor adherence to prescribed medicines is a frequent cause of pseudo-resistant hypertension, occurring in <_50% of patients assessed by therapeutic drug monitoring, and is directly related to the number of tablets prescribed.

Confirmation of adherence to antihypertensive medications may be provided by drug screening of urine or blood whenever available or by pharmacodynamic markers of exposure to medications [bradycardia on BBs, increase blood levels of uric acid on diuretics, increase in plasma renin concentration on diuretics or RAS blockers, increases in urine N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) concentration on ACEi and specific drug-related side effects]

History should include accurate information on use of drugs or substances potentially interfering with BP control either by impairing the efficacy of antihypertensive drugs or by increasing BP.

Careful evaluation of the drugs taken by patients is made easier by use of standardized questionnaires or drug–drug interaction-checking applications or web-tools.

TABLE 20. Medications and other substances that may increase BP

Medication/substance	Proposed mechanism	Comments
NSAIDs	Inhibition of COX-1 and 2 decreasing PG I2 and E2 synthesis with subsequent reduction in urinary Na excretion and an increased systemic vascular resistance.	Mild, dose-dependent increase in BP. Increased risk with age, preexisting hypertension, salt-sensitive patients, patients with renovascular hypertension.
Paracetamol (acetaminophen)	Presumably via inhibition of cyclooxygenases and reduced production of prostaglandins.	Increased relative risk of 1.34 of hypertension with almost daily paracetamol use.
Estrogens and progestins	Increased renin synthesis (by estrogens) leading to RAS activation and subsequent Na and water retention.	Mild, sustained increase in BP (6/3 mmHg increase with high doses of estrogen (>50 µg of estrogen and 1–4 µg progestin) but can be severe, common in premenopausal women, cause hypertension in 5% of women.
Glucocorticoids	Enhanced Na reabsorption and fluid retention via stimulation of mineralocorticoid receptors. Increased systemic vascular resistance due to upregulation of AT1 receptors on vascular smooth muscle cells.	Dose-dependent, low doses have less effect on BP, more common in older patients, or with a family history of primary hypertension.
Calcineurin inhibitors	Reduced NO production, ET-1 overproduction, systemic and renal vasoconstriction, renal Na retention.	Dose-dependent, mild-to-moderate increase in BP. Severe hypertension has been reported. Increased risk with preexisting hypertension, elevated creatinine levels and maintenance therapy with corticosteroids. See Section 20.8.2
Antidepressants SNRIs	Increased noradrenaline release causing adrenergic activation and increased SNS activity.	Dose-dependent, mild (2/1 mmHg) increase in BP.
Nasal decongestants	Vasoconstriction due to stimulation of alpha-1 receptors on vascular smooth muscles.	Dose-dependent, sustained increase in BP.
Erythropoietin-stimulating agents	Increased thromboxane, reduced prostacyclin levels and activation of the local RAS.	Dose-dependent, mild increase in BP, increased risk with preexisting hypertension, or when the initial hematocrit

Stimulants - Modafinil - Amphetamines - Methylphenidate	 Block noradrenaline or dopamine reuptake. Promote release of catecholamines	Caffeine may cause persistent BP effects with regular consumption. Genetic polymorphisms may affect BP response.
VEGF inhibitors	Decreased NO production via VEGFR-2 antagonism and stimulation of ET-1 receptors promoting vasoconstriction.	A class effect. The incidence of hypertension is dose-related, risk is increased by preexisting hypertension, old age and overweight. See Section 20.8.2.
Substances of abuse - MDMA - PCP - Methamphetamine - Cocaine - Alcohol	Increased release and inhibited reuptake of monoamine neurotransmitters with subsequent SNS activation. Increased CNS catecholamine release with decreased neuronal uptake. Cocaine induces an increase in arterial wall stiffness and atherosclerosis. Alcohol increases SNS and RAS activity.	Cocaine induces acute but not chronic increase in BP. Alcohol causes a dose-dependent, sustained increase in BP independent from obesity or salt intake.
Herbal products - Licorice - Ephedra - St. John's wort - Yohimbine - Ginseng (high doses) - Ma huang	Chronic excessive liquorice use mimics hyperaldosteronism by stimulating the mineralocorticoid receptor and inhibiting cortisol metabolism. Ephedra activates the alpha-1 receptor increasing SNS activity.	Licorice: Dose-dependent, sustained increase in BP characterized by hypokalemia, metabolic alkalosis and suppressed plasma renin activity and aldosterone levels Yohimbine causes acute, dose-dependent increase in BP.
Diet pills - Sibutramine - Phenylpropanolamine	Increased levels of norepinephrine with subsequent activation of noradrenergic transmission	Mild increase in BP.

Pseudo-resistant hypertension

(2) White-coat phenomenon (in which office BP is elevated but BP is controlled at ABPM or HBPM) is not uncommon in these patients, hence the recommendation to confirm office hypertension with ABPM or HBPM before confirming the diagnosis of resistant hypertension

Pseudo-resistant hypertension

3) Poor office BP measurement technique, including the use of cuffs that are too small relative to the arm circumference, can result in a spurious elevation of BP.

(4) Marked brachial artery calcification, especially in older patients with heavily calcified arteries

(5) Clinician inertia, resulting in inadequate doses or irrational combinations of BP-lowering drug therapies

Recommendations	Class[a]	Level[b]
It is recommended that hypertension be defined as resistant to treatment (i.e. resistant hypertension) when: • Optimal doses (or best-tolerated doses) of an appropriate therapeutic strategy, which should include a diuretic (typically an ACE inhibitor or an ARB with a CCB and a thiazide/thiazide-type diuretic), fails to lower clinic SBP and DBP values to <140 mmHg and/or <90 mmHg, respectively; and • The inadequate control of BP has been confirmed by ABPM or HBPM; and • After exclusion of various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension.	I	C

Contributing demographic and clinical factors are obesity (or large weight gains), excessive alcohol consumption, high sodium intake, advanced HMOD and atherosclerotic disease as well as older age, male sex, Black African origin, low income, depression, high BP values at hypertension diagnosis and a 10-year CV risk score >20% .

The pathophysiology of true-resistant hypertension involves an interplay between multiple neurohumoral factors such as increased levels of aldosterone , endothelin-1, vasopressin and increased sympathetic activity .

These factors contribute to volume and sodium overload, increase in peripheral vascular resistance, arterial stiffness and more advanced HMOD, including cardio renal damage .

Other causes of resistant hypertension

(1) Lifestyle factors, such as obesity or large gains in weight, excessive

alcohol consumption, and high sodium intake.

(2) Intake of vasopressor or sodium-retaining substances, drugs prescribed

for conditions other than hypertension, or some herbal remedies and recreational drug use (cocaine, anabolic steroids, etc.).

Other causes of resistant hypertension

(3) Obstructive sleep apnoea (usually, but not invariably, associated with obesity).

(4) Undetected secondary forms of hypertension.

(5) Advanced HMOD, particularly CKD or large-artery stiffening.

Diagnostic approach to resistant hypertension

Diagnosis of resistant hypertension requires detailed information about:

(1) The patient's history, including lifestyle characteristics, alcohol and dietary sodium intake, interfering drugs or substances, and sleep history.

(2) The nature and dosing of the antihypertensive treatment.
3) A physical examination, with a particular focus on determining the presence of HMOD and signs of secondary hypertension.

Diagnostic work-up

Exclusion of pseudoresistant hypertension requires :

(i) the demonstration of an elevated ABPM;

(ii) the exclusion of an origin of the BP elevation from inaccurate BP measurement, e.g. the spurious BP increase associated with marked brachial artery calcification, especially in older patients or in patients with advanced CKD;

(iii) the exclusion of a secondary cause of hypertension or

(iv) the exclusion of poor adherence to the prescribed treatment regimen.

The prevalence of secondary hypertension, especially primary aldosteronism and atherosclerotic renal artery stenosis (particularly in older patients or patients with CKD) can be as high as 10–20% of patients with resistant hypertension .

Search for OSA (by sleep history and specific tests) should not be omitted because of the frequent involvement of this condition in resistant hypertension, including night-time hypertension .

Optimizing lifestyle changes and ongoing drug therapy

Effective treatment of resistant hypertension should combine

(i) lifestyle changes (particularly reduction of sodium and alcohol intake, implementation of regular physical activity and weight loss in overweight or obese patients)

(ii)discontinuation of interfering substances,

(iii) rationalization of current treatment and

(iv) the sequential addition of antihypertensive drugs to the existing triple therapy.

Replacing current drugs with a more rational and possibly simpler treatment regimen is based on use of combination

therapies that are appropriate to a patient‘s age, ethnicity, compelling indications for certain drug classes, comorbidities and

risk of drug–drug interactions.

Drugs should be used at the maximal tolerated doses and SPCs should be preferred when available to reduce pill burden and improve adherence to treatment.

Because volume retention of multifactorial origin is frequent, reducing sodium intake (<2 g/day) or NaCl intake (<5 g/day) and increasing the intensity of diuretic therapy, particularly in older patients, patients of Black African origin or CKD patients, should be implemented.

If eGFR is 30 ml/min, BP control may be improved by increasing the dose of the existing Thiazide diuretic or by switching to a possibly more potent and longer acting Thiazide-like diuretic (indapamide or chlorthalidone).

If eGFR is <30 ml/min, a loop diuretic (furosemide, bumetanide and torsemide) should replace Thiazide/Thiazide-like diuretics, although even under this circumstance, Thiazides may retain their natriuretic and antihypertensive effects.

In the CLICK trial, patients with stage 4CKD

(eGFR 15–29 ml/min/1.73m2) and poorly controlled hypertension, showed an about roughly 10mmHg 24-h SBP reduction with chlortalidone versus placebo, and the BP-lowering effect was particularly evident in patients already on loop diuretics .

Furosemide and bumetanide should be administered twice daily, because of their short duration of action, whereas longer acting agents, such as torsemide, can be administered once daily .

The dose or intake frequency of the loop diuretic may be increased in patients with severe CKD and/or albuminuria .

Careful monitoring of kidney function,

serum electrolyte levels and fluid status is required to detect dehydration, hypokalemia, hyponatremia, hypovolemia or worsening of kidney function.

After optimizing the ongoing therapy, a stepwise addition of other antihypertensive drugs

should be considered if BP is still not at goal.

Fourth and subsequent lines of antihypertensive therapy

In patients with resistant hypertension, the fourth line treatment should include the MRA spironolactone, including those in patients with HFrEF.

A secondary analysis of the TOPCAT trial has shown beneficial effects of spironolactone also in patients with HFpEF, a condition in which difficult-to-control hypertension is frequent.

In it was recommended that spironolactone (25–50 mg/day) should be used with caution in patients with an eGFR <45 ml/min and a plasma potassium concentration >4.5 mmol/l.

Thus, the efficacy and safety of spironolactone in patients with more advanced CKD or higher potassium levels at baseline have not yet been established.

The spironolactone-associated risk of hyperkalemia is greater in patients with CKD, particularly if the drug is added to a treatment regimen that usually already includes an RAS blocker, making it necessary to closely monitor plasma potassium and eGFR after treatment initiation and, depending on individual risk and the CKD stage, at least annually or at three to 6 month intervals thereafter.

newer potassium binders (can reduce the risk of hyperkalemia, without increasing sodium) overload such as:

patiromer

sodium zirconium

cyclosilicate

The other steroidal MRA, eplerenone, has lesser potential to interfere with progesterone or androgen receptors and can, thus, be used alternatively to lower BP, but it is less potent than spironolactone .

Alternative drugs can be amiloride, to be used at high dosages (10–20mg per day), which was as effective as spironolactone25–50mg per day) in reducing Bp.

(However, this can lead to an increased pill burden as the marketed dose of amiloride is only 5 mg, and the drug is not available as a single agent but only in combinations (usually 5 mg) in many countries.

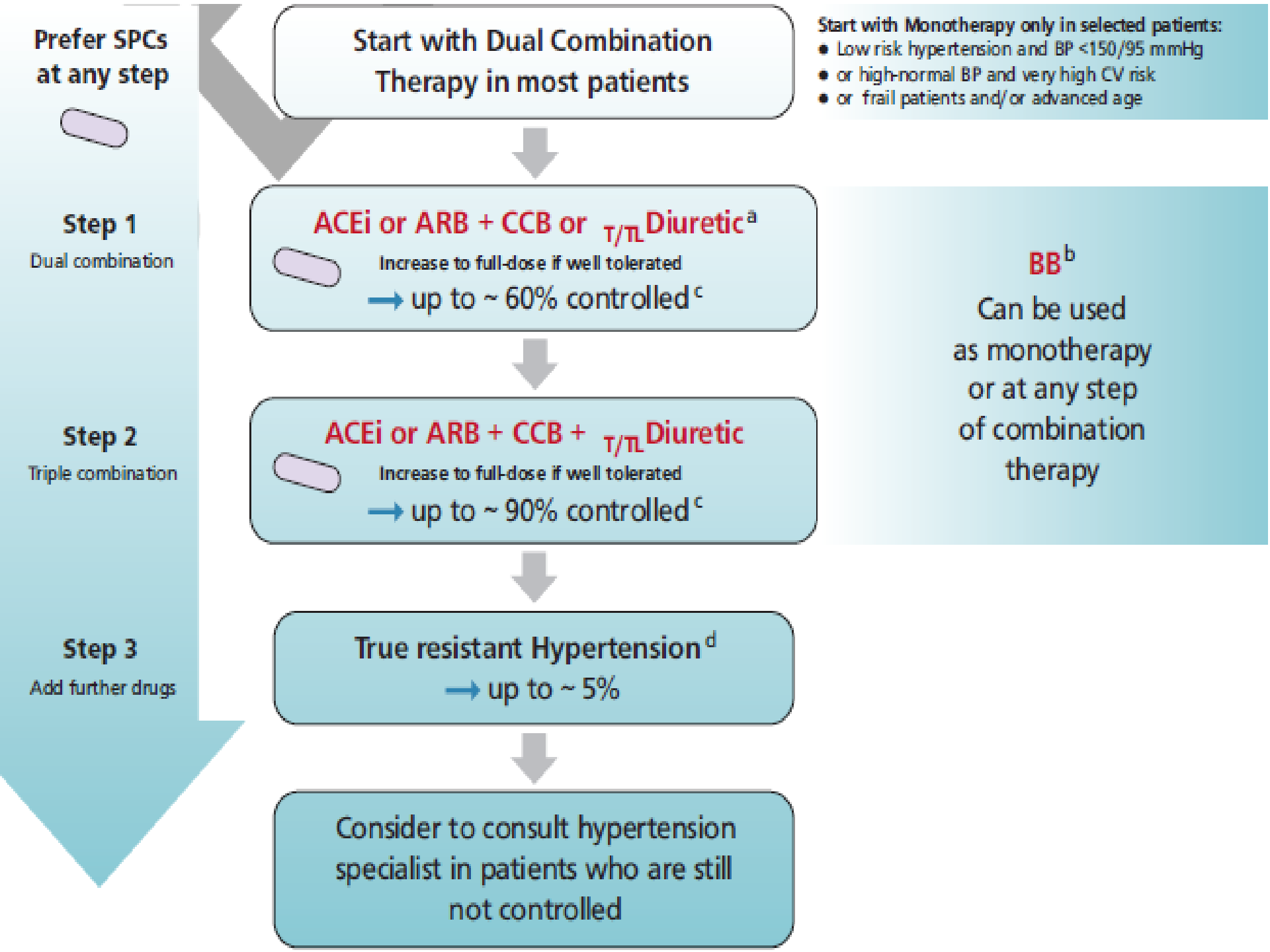
Finally, new more selective non steroidal MRAs such as finerenone (approved for the treatment in diabetic kidney disease), esaxerenone (approved for the treatment of hypertension in Japan), and ocedurenone , in development for resistant hypertension in CKD) might provide future alternatives to spironolactone for patients with resistant hypertension .

Ocedurenone (0.25–0.50 mg/day) reduced BP in patients with resistant hypertension and stage 3b/4 CKD with a higher incidence of hyperkalemia at the highest dose .

Finally, the use of selective aldosterone synthase inhibitors such as baxdrostat has been shown to effectively lower BP in patients with resistant hypertension in a phase 2 trial and may, thus, develop into an additional treatment.

This approach will avoid the noxious overall effects of aldosterone by reducing its synthesis instead of blocking its effects on mineralocorticoid receptors.

Spironolactone as well as all above discussed alternatives should be used with caution in patients with reduced eGFR and baseline potassium levels >4.5 mmol/l.


Prefer SPCs at any step
Start with Dual Combination Therapy in most patients
Start with Monotherapy only in selected patients:
• Low risk hypertension and BP <150/95 mmHg
• or high-normal BP and very high CV risk
• or frail patients and/or advanced age
Step 1
Dual combination
ACEi or ARB + CCB or T/TL Diuretic[a]
Increase to full-dose if well tolerated
→ up to ~ 60% controlled[c]
BB[b]
Can be used as monotherapy or at any step of combination therapy
Step 2
Triple combination
ACEi or ARB + CCB + T/TL Diuretic
Increase to full-dose if well tolerated
→ up to ~ 90% controlled[c]
Step 3
Add further drugs
True resistant Hypertension[d]
→ up to ~ 5%
Consider to consult hypertension specialist in patients who are still not controlled

If confirmation of true resistant hypertension by ABPM is not feasible, HBPM may be used.		
It is recommended to manage resistant hypertension as a high-risk condition, because it is frequently associated with HMOD and increased CV risk.	I	B
In patients with resistant hypertension, BP should be reduced below 140/90 mmHg and below 130/80 mmHg, if well tolerated.	I	B
In resistant hypertension, it is recommended to reinforce lifestyle measures.	I	B

Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or BB or Alpha-1 blockers or Centrally acting agents (clonidine), or amiloride (if available).	II	B
Thiazide/Thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥ 30 ml/min/1.73 m^2.	I	B
Loop diuretics may be considered in patients with an estimated eGFR < 45 ml/min/1.73 m^2 and should be used if eGFR falls below 30 ml/min/1.73 m^2.	I	B
Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 ml/min/1.73 m^2.	II	B

RDN can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 ml/min/1.73m^2	II	B
Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ABPM and assessment of HMOD, particularly kidney function and serum potassium levels. Regular use of HBPM and monitoring of drug adherence are desirable.	I	C

Recommended treatment of resistant hypertension is: • Reinforcement of lifestyle measures, especially sodium restriction.[395] • Addition of low-dose spironolactone[c] to existing treatment;[310,392,394] • Or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone,[c] amiloride,[c] a higher-dose thiazide/thiazide-like diuretic, or a loop diuretic;[d 357] • Or the addition of bisoprolol or doxazosin.[310]	I	B

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

comorbidity

OSA: CPAP

Obesity:GLP1 receptor agonist ,bariatric surgery

SGLT2 :moderate BP lowering effect

Sacubitril-valsartan

DEVICE-BASED TREATMENT OF HYPERTENSION

Increased activity of the SNS is one of the important factors in the pathophysiology of hypertension, especially in obesity, OSA and CKD .

Efferent sympathetic nerves to the kidneys increase renin release via beta1-adrenergic receptor activation at the level of the juxta-glomerular cells, decrease renal perfusion and GFR, increase tubular reabsorption of sodium and induce a rightward shift of the BP-natriuresis curve.

Conversely, increased afferent sensory nerve signaling to the central nervous system in response to kidney ischemia, injury or inflammatory, fibrotic processes and other alterations of the tissue environment leads to reflex sympathetic activation, with peripheral vasoconstriction, increased BP and aggravation of HMOD.

The rationale of RDN is to modulate the overactive signaling between the kidneys and the central SNS, which may be at least partly responsible for the sympathetic hyperactivity of resistant hypertension.

The introduction of endovascular catheter-based RDN devices has allowed to obtain RDN in a minimally invasive fashion.

RDN has been shown to reduce whole-body and renal sympathetic activity in humans , although not in all studies . However, a recent meta-analysis of available studies has reported a limited relationship between the RDN-dependent reduction of sympathetic activity as measured by microneurography and the BP reduction.

This is compatible with the possibility that more than just a neural factor is responsible for the RDN-dependent therapeutic effects

Recommendations and statements	CoR	LoE
RDN can be considered as a treatment option in patients an eGFR >40 ml/min/1.73m^2 who have uncontrolled BP despite the use of antihypertensive drug combination therapy, or if drug treatment elicits serious side effects and poor quality of life.	II	B
RDN can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 ml/min/1.73m^2.	II	B
Selection of patients to whom RDN is offered should be done in a shared decision-making process after objective and complete patient's information.	I	C
Renal denervation should only be performed in experienced specialized centers to guarantee appropriate selection of eligible patients and completeness of the denervation procedure.	I	C

Carotid baroreceptor stimulation

Other device-based treatments