Resistant hypertension

An approach to management

SAYEH HEIDARI NEJAD MD, MPH
OMAR AZZAM MB ChB, MRCP (UK), FRACP
MARKUS P. SCHLAICH MD, FESC, FAHA, ISHF

Resistant hypertension (RH) is a prevalent and significant cause of morbidity and mortality. Adverse health outcomes, including cardiovascular disease, hypertension-mediated organ damage and chronic kidney disease, can be significant. This article describes the means for GPs to identify predisposing and contributing factors to RH and recommends an evidence-based approach to diagnosis and management.

Hypertension affects nearly one billion individuals worldwide and is a common presentation in general practice. It is one of the most significant modifiable risk factors for disability and death worldwide.[1] The global prevalence of resistant hypertension (RH) is 5 to 30%; this wide range is due to variability in the definition and the analysed population among different studies. The prevalence is estimated to be about 10 to 15% in the treated population based on the latest RH definitions (excluding apparent causes).[2]

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KEY POINTS

- Resistant hypertension (RH) affects about 10 to 15% of treated patients diagnosed with hypertension and is associated with an increased risk of adverse cardiovascular outcomes and hypertension-mediated organ damage (HMOD).
- True RH must be confirmed by adequate in-office and out-of-office blood pressure (BP) measurements (home or ambulatory). Common causes of apparent RH include white-coat hypertension, nonadherence with prescribed antihypertensive therapy, inadequate antihypertensive combination therapy and the use of interfering concomitant medications.
- Obesity, obstructive sleep apnoea and renal parenchymal disease are among the most common contributing features of RH; affected patients should be screened for secondary causes of hypertension (especially primary aldosteronism) regardless of their age.
- Management of RH relies on lifestyle measures (maintaining a healthy weight through regular physical activity and a healthy diet, salt restriction, limiting alcohol intake and smoking cessation), pharmacotherapy and interventional approaches, where required.
- Pharmacotherapy includes a combination of a renin-angiotensin-system blocker, a long-acting calcium channel blocker and a diuretic at maximally tolerated doses, ideally as a single pill combination.
- Spironolactone is currently recommended as the preferred fourth-line therapy, with alpha blockers, beta blockers, centrally acting sympatholytic agents, or vasodilators as alternatives.
- If BP control cannot be achieved with the above strategies, interventional approaches such as renal denervation and novel therapeutic agents (once available) should be considered.

MedicineToday 2023; 24(8 Suppl): 23-28

Dr Heidari Nejad is a Medical Registrar at the Dobney Hypertension Centre, Royal Perth Hospital, Perth. Dr Azzam is a Consultant Nephrologist and General Medicine Physician at the Dobney Hypertension Centre, Royal Perth Hospital, Perth. Professor Schlaich is the Chair in Clinical Research at the Dobney Hypertension Centre, Royal Perth Hospital; Professor at the Medical School at the University of Western Australia; and a Consultant Nephrologist and Hypertension Specialist at the Royal Perth Hospital, Perth, WA.

Defining resistant hypertension

The European Society of Cardiology/European Society of Hypertension (ESC/ESH) 2018 guidelines defined RH as a diagnosis given to patients who are above the target blood pressure (BP) despite being on maximally tolerated doses of three antihypertensive drug classes, including a diuretic, and preferably a long-acting calcium channel blocker and a renin-angiotensin system blocker (i.e. ACE inhibitor or angiotensin receptor blocker

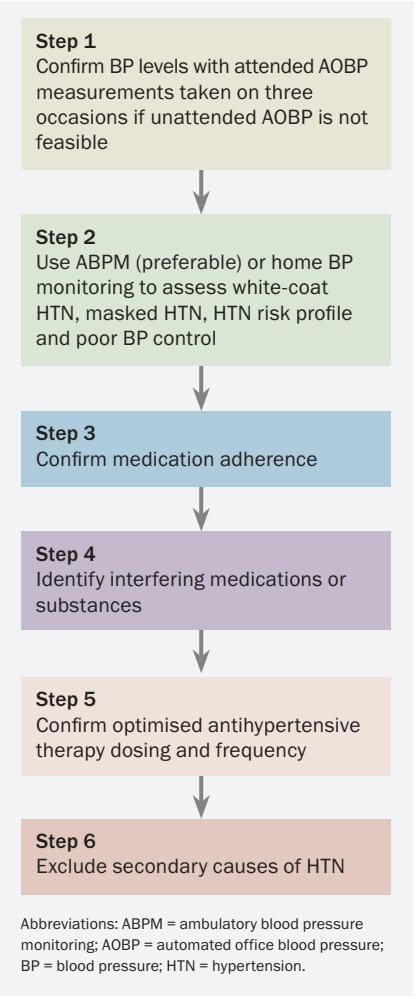

Figure 1. Steps for diagnosis of true resistant hypertension.

[ARB]).[3] Patients who require treatment with four or more classes of antihypertensive medication are also considered to have RH, regardless of their BP.[4]

The American College of Cardiology/American Heart Association 2018 hypertension guidelines adopt a lower office BP threshold of 130/80 mmHg or higher for the definition of hypertension, compared with most other guidelines (including those for Australia), which propose an office BP threshold of 140/90 mmHg or higher.[4]

RH is associated with a higher incidence of adverse cardiovascular outcomes, including myocardial infarction, cerebrovascular events and congestive heart failure.[5] It is also associated with a higher incidence of hypertension-mediated organ damage (HMOD), chronic kidney disease (CKD) and all-cause mortality.[6] Hence, it is crucial to identify and treat RH aggressively to improve outcomes.

Risk factors and pathophysiology

Predictive risk factors for difficult-to-control hypertension include:[7]

- higher baseline BP (especially systolic)
- older age
- obesity
- African-American heritage
- male sex
- presence of left ventricular hypertrophy
- CKD
- diabetes.

The underlying pathophysiology of RH is a combination of volume and sodium retention, aldosterone excess and sustained increased activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system.[8-11] The endothelin-1 pathway is another important contributor to the pathophysiology of RH; blockade of this pathway has recently demonstrated promising outcomes in the management of RH.[12]

Clinical assessment

The patient should be asked about potential contributing lifestyle and dietary factors, including their salt and alcohol intake, weight and height, level of physical activity and sleep patterns. Details of personal and family history of hypertension and presence of cardiovascular risk factors should be obtained.

On physical examination, the signs of secondary hypertension as well as evidence of HMOD, including hypertensive retinopathy, left ventricular hypertrophy, microalbuminuria and CKD, should be sought. The basic and extended screening tests for HMOD are detailed in Box 1.

Diagnosis

RH can be true or apparent. Diagnosis of true RH requires the exclusion of undetected secondary causes of hypertension and pseudoresistant hypertension, which is defined as seemingly treatment-resistant hypertension that is primarily due to interfering factors in BP measurement or treatment.[3]

The ESC/ESH 2018 guidelines list five of the most common causes of pseudoresistant hypertension to be excluded in confirming the diagnosis of true RH. These include poor adherence to antihypertensive therapy, poor office BP measurement techniques, suboptimal antihypertensive therapy, white-coat phenomenon, and severe brachial artery calcification.[3] Figure 1 summarises the proposed steps in diagnosing true RH.

Diagnostic steps

Step 1. Measure BP accurately

Office BP measurement remains the basis of diagnosing and managing hypertension. Automated office BP (AOBP), with the attending clinician absent from the room, is the most reliable method of office BP measurement, and was used in The Systolic BP Intervention Trial (SPRINT) and other studies.[13,14] However, the triplicate standardised attended AOBP is the most feasible method in primary care. If attended AOBP is performed on three or more occasions under standardised conditions, the result is comparable in reliability to unattended AOBP.[15] Figure 2 displays the international consensus on standardised AOBP.[16]

Step 2. Exclude white-coat hypertension, masked hypertension and poor BP control

White-coat hypertension is defined as elevated office BP, but normal out-of-office BP. It is estimated that white-coat hypertension might be present in 28 to 39% of individuals with apparent RH.[2] The white-coat phenomenon can be significantly reduced or eliminated by AOBP that is unattended.[17] However, relying solely on office BP measurements can result in missed diagnoses of

RH in patients with masked hypertension; such patients may have BP exceeding the recommended targets during ambulatory blood pressure monitoring (ABPM), but not during office BP measurement. Additionally, the initial reason for a patient's clinic visit, such as pain or other medical issues, could influence the office BP readings.[18]

Patients whose RH was confirmed by ABPM have a higher prevalence of HMOD and cardiovascular disease.[19] ABPM recordings provide additional relevant indices, such as 24-hour BP variability, morning BP surge, and ambulatory arterial stiffness index, which have some predictive value. Overall, there is clear evidence that office BP measurements alone are inadequate in identifying RH. ABPM with or without home BP monitoring must be used to confirm the diagnosis.[3]

Step 3. Confirm adherence to medication

Partial medication adherence and complete nonadherence occurs in 17 to 46% and 9 to 35% of patients with RH, respectively.[19] The high prevalence of nonadherence in this patient group is in part attributable to polypharmacy, complex medication regimens, high incidence of medication intolerance and adverse effects and poor patient–clinician relationship.[13] Some of the practical methods to assess medication adherence include direct questioning about adherence in a nonjudgemental manner, medication adherence questionnaires, pill counts, and electronic pill boxes. The less feasible (but more reliable) methods of assessing adherence include biochemical assay of medications or their metabolites in blood or urine, as well as observed pill intake when patients' medication is administered in the clinic with their BP measured before and several hours after medication consumption.[19]

Step 4. Identify interfering substances or medications

Concurrent use of a variety of medications (e.g. over-the-counter medications, substances and homeopathic medications) can raise BP or interfere with the effects of antihypertensives by increasing sympathetic activity, increasing intravascular volume or decreasing sodium excretion.[2] NSAIDs are possibly the most common drugs to raise BP or interfere with effects of antihypertensives.[3] Some of the other common agents that affect BP include homeopathic medications, decongestants, stimulants used for weight loss (e.g. phentermine), oral contraceptives, recreational drugs (e.g. cocaine, anabolic steroids), ciclosporin and corticosteroids, through volume retention.[2]

Step 5. Confirm optimised antihypertensive therapy dosing and frequency

Failure of treatment intensification is a common cause of high BP.[20,21] It is crucial to optimise the dose of all three recommended antihypertensive medications in RH to the maximum tolerated dose.

Step 6. Exclude secondary causes of hypertension

The prevalence of secondary causes of hypertension is approximately 10% in adult populations.[22] Obstructive sleep apnoea, primary aldosteronism and renovascular and renal parenchymal diseases are among the most prevalent secondary causes of hypertension. It is important to remember that secondary causes of hypertension can also occur in the elderly.[22,23]

RH is a common indication for secondary hypertension screening, in addition to grade 3 hypertension, grade 2 hypertension in adults younger than 40 years of age, acute worsening in previously well-controlled cases of hypertension, evidence of extensive HMOD, clinical or biochemical signs of secondary causes and hypertension in children and adolescents.[3] A list of secondary causes of hypertension and the initial screening is outlined in the Table.

Interpreting some initial screening tests for RH (e.g. aldosterone-renin ratio to exclude primary hyperaldosteronism) may pose challenges if patients are taking antihypertensive medications that could interfere with the accuracy of these tests.[24] GPs should seek the opinion of relevant specialists, particularly if the initial screening tests yield results that are inconclusive or suggestive of secondary causes.

1. WORKUP FOR HYPERTENSION-MEDIATED ORGAN DAMAGE

Basic screening

- ECG to screen for LVH and ischaemia; document cardiac rhythm and heart rate
- eGFR and electrolytes to screen for renal disease
- Urine ACR to screen for renal disease
- Fundoscopic examination[3] to detect retinopathy

Extended screening, if indicated

- Transthoracic echocardiography
- Carotid ultrasonography
- Abdominal and doppler studies, CT angiography or MR angiography
- Pulse wave velocity
- Brain imaging
- Cognitive function testing

Risk factors for further prognostication

- HbA_{1c}, fasting BGL or OGTT to screen for diabetes
- Fasting lipid profile to screen for dyslipidaemia
- 24-hour urinary sodium, creatinine and protein levels to assess salt intake

Abbreviations: ACR = albumin: creatinine ratio; BGL = blood glucose level; CT = computed tomography; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated haemoglobin; LVH = left ventricular hypertrophy; MR = magnetic resonance; OGTT = oral glucose tolerance test.

Management

The general principles of treatment for RH are the same as those for milder forms of hypertension, including:

- the modification of contributory lifestyle factors
- the cessation of interfering substances/medications, where possible

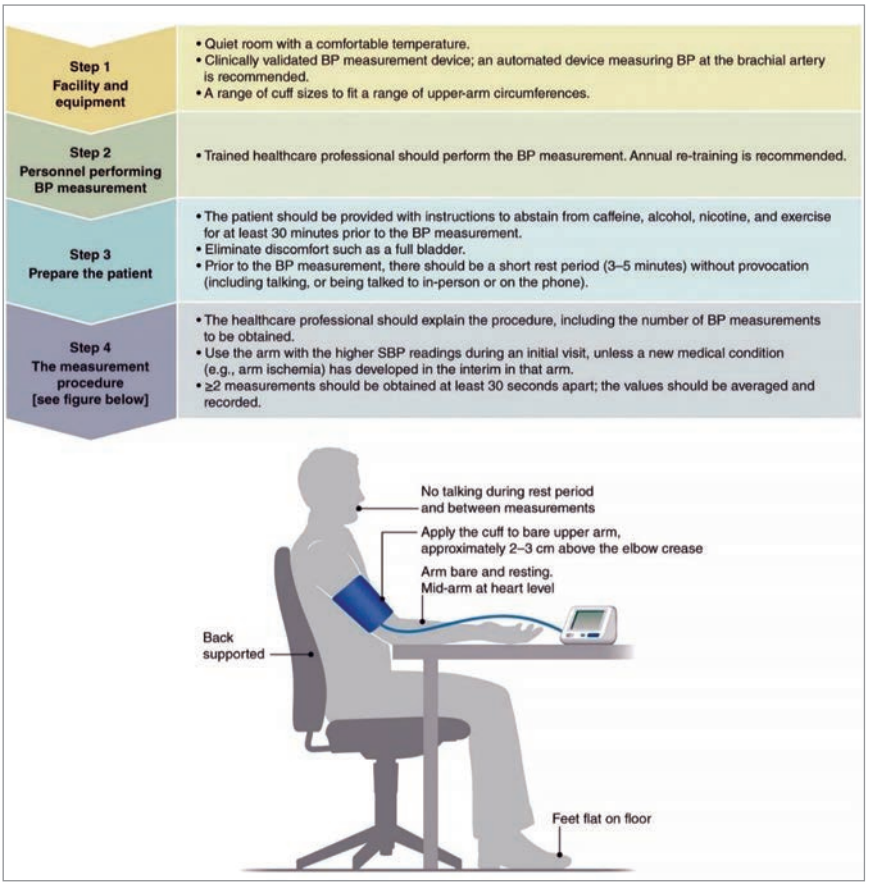

Figure 2. Steps for implementing standardised office blood pressure measurement.[16]
Abbreviation: SBP = systolic blood pressure.

- the sequential addition of guideline-recommended antihypertensive agents with different modes of action, ideally in the form of single pill combinations to improve adherence
- using the full armamentarium of antihypertensive drugs, where required.

Promising novel drugs for RH, such as the dual endothelin antagonist, aprocitentan, and the aldosterone synthase inhibitor, baxdrostat, are in the advanced stages of clinical development and may facilitate improved BP control in RH when they become available.[12,25] Interventional approaches, such as renal denervation, should be considered a safe and effective means of achieving sustained BP reduction at various stages of the patient's management.[26]

Lifestyle modification

Patients with RH are more likely to be non-adherent to lifestyle and dietary measures, such as limiting alcohol intake, reducing sodium intake, maintaining a healthy weight and performing regular physical activity.[3]

Regular light to moderate physical activity (including long-term aerobic exercise and heated pool exercise) showed favourable outcomes as a successful BP lowering intervention.[27,28]

Smoking cessation and minimal alcohol intake should be recommended in individuals with RH, as with all other patients diagnosed with hypertension.[29]

Overweight and obese individuals with RH should aim for a 6 to 8% decrease in body weight to achieve a 5 and 4 mmHg reduction in systolic and diastolic BP, respectively.[29]

High dietary sodium intake significantly contributes to RH and is a well-known factor in antihypertensive medication resistance. A reduced sodium intake of less than 1500 mg daily decreases office systolic and diastolic BP readings by 22.7 and 9.1 mmHg, respectively.[30] The BP-lowering effect of sodium restriction is similarly profound in patients with CKD and RH.[31] Diets, such as the DASH and Mediterranean diets, can help with BP control, but have not been well studied in the management of RH (Box 2).

Pharmacotherapy

The antihypertensive regimen for the management of RH is usually based on comorbidities, underlying secondary causes, previous medication intolerances and financial constraints.

A common and effective combination includes an ACE inhibitor or ARB, a long-acting calcium channel blocker and a thiazide or thiazide-like diuretic. This combination should be prescribed at maximally tolerated doses at an appropriate frequency, with reference to the half-life of the medications involved.

Maximised diuretic therapy is essential for the treatment of RH, as volume retention and sodium excess are common causes of RH, even though obvious signs of hypervolaemia (such as lower limb oedema) may be absent.[30-32] An important consideration for the management of ongoing residual hypertension is the switching of thiazide therapy to a more potent diuretic (e.g. indapamide or chlorthalidone) if the estimated glomerular filtration rate (eGFR) is 30 mL/min/1.73 m^2 or greater. Chlorthalidone is frequently used in the USA, but rarely prescribed in Australia, despite being a more potent diuretic with a longer half-life than hydrochlorothiazide.[35]

The recently published results from the Diuretic Comparison Project suggested no significant difference in cardiovascular outcomes and noncancer-related deaths between chlorthalidone and hydrochlorothiazide, but found more frequent hypokalaemia with the use of

TABLE. INVESTIGATING SECONDARY CAUSES OF HYPERTENSION

Secondary cause	Suggestive symptoms and signs	Screening investigations
Obstructive sleep apnoea	Snoring; obesity (but can be present in nonobese); morning headache; daytime somnolence	Epworth score and home-based ambulatory polygraphy
Renal parenchymal disease	Mostly asymptomatic; diabetes; haematuria, proteinuria, nocturia; anaemia, renal mass in adult polycystic CKD	Plasma creatinine and electrolyte levels, eGFR; urine dipstick for blood and protein, urinary albumin: creatinine ratio; renal ultrasound
Atherosclerotic renovascular disease	Older patients; widespread atherosclerosis (especially PAD); diabetes; smoking; recurrent flash pulmonary oedema; abdominal bruit	Duplex renal artery Doppler ultrasound, CT angiography or MR angiography
Fibromuscular dysplasia	Younger patients; more common in women; abdominal bruit	
Primary aldosteronism	Mostly asymptomatic; muscle weakness (rare)	Baseline plasma aldosterone, renin and potassium levels; aldosterone: renin ratio
Phaeochromocytoma	Episodic symptoms (the 5 'Ps'): paroxysmal hypertension, pounding headache, perspiration, palpitations and pallor; labile BP; BP surges precipitated by use of medications (e.g. beta blockers, metoclopramide, sympathomimetics, opioids and TCA)	Plasma or 24-hour urinary fractionated metanephrines
Cushing's syndrome	Moon face, central obesity, skin atrophy, striae and bruising; diabetes; chronic steroid use	24-hour urinary free cortisol (two measurements) or midnight salivary cortisol (two measurements) or 1 mg dexamethasone suppression test
Thyroid disease (hyperthyroidism or hypothyroidism)	Changes in weight, heart rate, skin, eyes, thoughts, emotions or energy	Thyroid function tests
Hyperparathyroidism	Hypercalcaemia, hypophosphataemia	Parathyroid hormone, serum calcium
Coarctation of the aorta	Usually detected in children or adolescents; different BP (≥20/10 mmHg) between upper and lower extremities or between right and left arm and delayed radial to femoral artery pulsation; low ABI; interscapular ejection murmur; rib notching on chest x-ray	Echocardiography

Abbreviations: ABI = ankle brachial index; BP = blood pressure; CKD = chronic kidney disease; CT = computed tomography; eGFR = estimated glomerular filtration rate; MR = magnetic resonance; PAD = peripheral arterial disease; TCA = tricyclic antidepressants.

Adapted with permission from Cheung AK, et al. Am J Med 2023; 136: 438-445.[16]

chlorthalidone.[36] Given that single pill combinations are associated with improved adherence, hydrochlorothiazide and indapamide are likely to remain the preferred choices, as, unlike chlorthalidone, they are both available in combination with renin-angiotensin system blockers as single pill combinations. If a patient's eGFR is 30 mL/min/1.73 m^2 or lower, the benefit of thiazide-like therapy is less, and loop diuretics (e.g. frusemide or bumetanide) can be added to the regimen or used as a substitute.[3]

The mineralocorticoid receptor antagonist (MRA) spironolactone is currently considered the preferred fourth-line agent, to be used in addition to previously maximised combination therapy.[8,37] If spironolactone is not tolerated, eplerenone can be used as an alternative.[38] The potassium-sparing diuretic amiloride is no longer available in Australia. Common adverse effects of MRAs include hyperkalaemia and reduction in eGFR, which require close monitoring. With particular reference to spironolactone, high doses of MRAs can cause gynaecomastia and erectile dysfunction and preferably should not be prescribed at doses greater than 50 mg daily in people with primary RH. Such adverse effects are minimal with eplerenone, which is less potent and requires twice daily dosing due to its shorter half-life.

There are limited data to guide the choice of a fifth-line antihypertensive agent, if uncontrolled hypertension persists despite the recommended regimens. A reasonable approach is to add further agents based on comorbidities and the patient's preference.

Patients with a baseline heart rate above 70 beats per minute and those with a diagnosis of coronary artery disease or heart failure would benefit from the addition of beta blockers. Labetalol, carvedilol and

2. DIETS TO HELP WITH BLOOD PRESSURE CONTROL[32-34]

The Dietary Approaches to Stop Hypertension (DASH) diet

- High consumption of whole nutrient-dense foods, such as fruits, vegetables, whole grains, lean protein sources and low fat dairy products
- Limited consumption of high-calorie, high-fat and high-sugar foods, with a reduction in sodium intake to typically less than 2300 mg per day (lower targets for people with high blood pressure)

The Mediterranean diet

- High consumption of fruits, vegetables, whole grains, legumes, nuts, fish and olive oil
- Limited consumption of red and processed meat, sweets and refined grains

nebivolol have vasodilatory effects and are more effective in lowering BP compared with other commonly used beta blockers.[39]

Centrally acting agents (e.g. methyldopa or clonidine) can be used to suppress sympathetic nervous activity, which is usually elevated in RH. In the Resistant Hypertension Optimal Treatment (ReHOT) trial, clonidine was shown to have similar efficacy to spironolactone in lowering BP; however, common adverse effects of clonidine include somnolence, dry mouth sensation and rebound phenomena.[40] More advanced and better tolerated centrally acting sympatholytic agents, such as the selective imidazoline receptor agonist moxonidine, are a useful alternative.

Other available medications for RH management include alpha blockers (e.g. prazosin) or direct vasodilators (e.g. hydralazine or minoxidil). The latter group should generally be used with a loop diuretic to address the common adverse effect of hypervolaemia and lower limb oedema.[3]

Promising novel drugs

New classes of medications with substantial BP-lowering efficacy are under investigation. Baxdrostat, an aldosterone synthase inhibitor, resulted in reduced office systolic BP readings over 12 weeks of 20.3, 17.5 and 12.1 mmHg at 2 mg, 1 mg and 0.5 mg doses, respectively, confirming the significant dose-related BP-lowering effect when added to stable doses of three antihypertensive medications in the management of RH.[25] Aprocitentan, a dual endothelin antagonist, was recently shown to have a significant dose-dependent reduction in office and 24-hour ABPM after four weeks of therapy in individuals with RH on three background antihypertensive medications. The greatest BP-lowering effect was evident in elderly patients and those with macroalbuminuria and stage 3 to 4 CKD.[12]

Interventional therapies

Interventional approaches (e.g. renal denervation) have been shown in multiple sham-controlled trials to exert substantial BP-lowering effects in various forms of hypertension, including RH. The catheter-based procedure has a favourable safety profile with long-term BP-lowering efficacy demonstrated to nine years postprocedure.[41,42] This method aims to inhibit renal sympathetic efferent nerve activity, which contributes to reduced renal blood flow, decreased urinary salt, reduced water excretion and high renin release in the kidneys.[43] The ESH recently issued a position paper on renal denervation, summarising the available evidence and providing recommendations for its use in routine clinical practice (Box 3).[44] A position paper on the use of renal denervation in an Australian context is in preparation.

3. RECOMMENDATIONS REGARDING RENAL DENERVATION[44]

The European Society for Hypertension 2018 guidelines include a consensus on the following:

- Renal denervation can be used to treat hypertension, in addition to lifestyle changes and blood pressure-lowering drugs, based on consistent results of several sham-controlled clinical trials
- Renal denervation therefore expands therapeutic options to address the first objective of hypertension treatment, which is to effectively reduce elevated blood pressure and achieve blood pressure targets
- Renal denervation is considered a safe endovascular procedure without significant short-term or long-term adverse effects based on data available for up to three years
- Renal denervation is an alternative or additive, not a competitive treatment strategy
- A structured pathway for the clinical use of renal denervation in daily practice is recommended
- Patients' perspective and preference, as well as patients' stage of hypertensive disease, including comorbidities, should lead to an individualised treatment strategy in a shared decision-making process, which carefully includes the various options of treatment, including renal denervation

Conclusion

RH remains challenging to manage and is a modifiable risk factor for adverse health outcomes. Recommended management of RH includes: excluding pseudoresistant hypertension; identifying relevant contributing factors, focusing on lifestyle modification; using simple medication regimens (ideally, in the form of single pill combinations of guideline-recommended drugs with different modes of action), adding further drug classes as required (based on comorbidities); and considering renal denervation as an evidence-based option to safely and effectively lower BP. Appropriate management of RH results in improved cardiovascular outcomes for this high-risk patient cohort. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: Professor Schlaich has received consulting fees, and travel and research support from Medtronic, Abbott, Novartis, Servier, Pfizer, and Boehringer-Ingelheim. Dr Nejad and Dr Azzam: None.

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