Diagnosis and management of resistant hypertension: state of the art

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Abstract | Resistant hypertension is defined as a lack of ambulatory blood pressure response to optimized medical treatment after exclusion of secondary hypertension in patients who are fully adherent to antihypertensive therapy. Patients with resistant hypertension are at high risk of complications, particularly cardiovascular events, and optimization of medical treatment remains the cornerstone of their management. Such optimization should be based on simple algorithms and include the use of aldosterone antagonists. The available data from clinical trials do not support the use of device-based approaches such as renal denervation, baroreflex activation therapy or arteriovenous anastomosis for the treatment of resistant hypertension in the majority of patients. Therefore, device treatment remains a last-resort for patients with truly resistant hypertension in the context of clinical research in highly skilled tertiary referral centres. Future research should focus on improving understanding of the intrinsic (physiological and psychological factors) and extrinsic (environmental stressors) mechanisms that contribute to a lack of response to blood-pressure-lowering drugs in adherent patients. The use of biomarkers to identify patients with early target organ damage and new technologies, such as renal nerve stimulation, to predict blood pressure responses to renal denervation could aid the selection of patients who might benefit from device therapies.

Secondary hypertension
Elevated blood pressure that results from an underlying, identifiable and often correctable cause.

White-coat effect
An increase in blood pressure due to arousal of the patient in response to a medical environment or the observer measuring the blood pressure.

Hypertension is the predominant driver of cardiovascular disease — the leading cause of morbidity and mortality worldwide[1] — and patients with resistant hypertension are at particularly high risk of cardiovascular complications[2,3]. True resistant hypertension refers to a diagnosis of essential hypertension with exclusion of all other potential causes of uncontrolled blood pressure, including secondary hypertension, pseudo-resistance due to poor adherence to antihypertensive therapy or the white-coat effect[4,5].

The risk of resistant hypertension is increased in patients with high sympathetic drive owing to obesity, diabetes mellitus, renal dysfunction or obstructive sleep apnoea[6–9]. Treatment options include lifestyle interventions, intensive pharmacological therapy, renal denervation, stimulation of the carotid sinus and arteriovenous anastomosis. To date, the efficacy of device-based therapies for resistant hypertension has not been proved; however, these approaches provide opportunities for further research.

In this Review, we discuss the epidemiology, associated risks, diagnosis and management of resistant hypertension. We highlight the limitations of clinical trials of device-based therapies conducted to date and propose directions for future research.

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Epidemiology

Most epidemiological studies lack key elements for ascertaining the presence of resistant hypertension, such as assessment of medication adherence and measurement of ambulatory blood pressure. The ideal design to estimate the prevalence of true resistant hypertension would be a large prospective cohort study of hypertensive patients with blood pressure control ascertained by ambulatory monitoring after forced titration up to the maximally tolerated doses of three different classes of hypertensive medications, including a diuretic. To date, such a prospective study has not been published, and the prevalence of resistant hypertension has been estimated using data from observational studies and outcome-based clinical trials.

Prevalence

The reported prevalence of resistant hypertension among patients who are receiving antihypertensive therapy is highly variable, ranging from 9% to 18%[10], owing to divergent diagnostic approaches and the non-exclusion of patients with pseudo-resistant hypertension. A meta-analysis that included 961,035 individuals reported a mean prevalence of resistant hypertension in 20 observational studies of 13.7% (95% CI 11.2–16.2) and

Key points

- Resistant hypertension is an elevated ambulatory blood pressure after exclusion of secondary hypertension in patients who are fully adherent to treatment with antihypertensive drugs.
- Resistant hypertension is associated with increased risks of adverse health outcomes, including cardiovascular and renal events and all-cause mortality.
- Ambulatory blood pressure monitoring is the gold standard for diagnosis of resistant hypertension; this method enables the identification of patients with isolated nocturnal hypertension, sustained hypertension or white-coat hypertension.
- Optimization of medical treatment using simple, easy-to-understand algorithms is the cornerstone of management of resistant hypertension.
- The available data from clinical trials do not support the use of renal denervation, baroreflex activation therapy or arteriovenous anastomosis for the treatment of resistant hypertension in routine clinical practice.
- The use of biomarkers of early target organ damage and new technologies such as renal nerve stimulation could aid the selection of patients with resistant hypertension who might benefit from device therapies.

White-coat hypertension
A raised in-office blood pressure in the presence of a normal 24 h or daytime ambulatory blood pressure.

a mean prevalence in four randomized trials of 16.3% (95% CI 10.7–21.9); however, pseudo-resistance caused by suboptimal drug dosing, poor medication adherence and the white-coat effect could not be ruled out[10].

Among 68,045 patients with hypertension enrolled in the Spanish Ambulatory Blood Pressure Monitoring Registry, 8,295 (12.2%) had resistant hypertension defined as an increased office blood pressure while on treatment with three or more antihypertensive drugs, including a diuretic, but the prevalence decreased to 5,184 (7.6%) after exclusion of those with white-coat hypertension[11]. In the MINISAL-SIIA study, which included 1,284 patients with hypertension recruited from 47 Italian centres and excluded those with secondary or white-coat hypertension, the prevalence of resistant hypertension among patients on stable drug therapy was 8.2% and increased 1.5-fold per 1 s.d. increase in age and body mass index[12]. However, among those who adhered to lifestyle interventions to reduce blood pressure (as indicated by urinary sodium excretion <100 mmol per 24 h and a body mass index of 18–25 kg/m^2) the prevalence of resistant hypertension was only 0.8%.

Associated risks

Resistant hypertension is associated with adverse health outcomes. In a retrospective analysis that included 205,750 US patients with incident hypertension, the incidence of resistant hypertension within a median of 1.5 years from initiation of antihypertensive treatment was 1.9% with a rate of 0.7 cases per 100 patient-years of follow-up[3]. Patients with resistant hypertension had higher rates of diabetes mellitus at baseline (17.7%) than those with treatment-responsive hypertension (9.6%). In addition, multivariable-adjusted analyses showed that resistant hypertension was significantly associated with an increased risk of cardiovascular events (myocardial infarction, congestive heart failure or stroke) during a median follow-up of 3.8 years (HR 1.47, 95% CI 1.33–1.62; P<0.001)[3].

The results of four subsequent studies strengthened the evidence for an association between resistant hypertension and cardiovascular events[8,13–15]. However, only one of these studies[8] applied ambulatory blood pressure monitoring (ABPM) to exclude patients with pseudo-resistance, and none of the studies assessed treatment adherence. The study that used ABPM assessed the associations between resistant hypertension and cardiovascular and renal events in 436 patients with chronic kidney disease (CKD) and a diagnosis of office hypertension[8]. In this study, resistant hypertension was associated with a higher risk of cardiovascular events (HR 1.98, 95% CI 1.14–3.43) and renal events (HR 2.66, 95% CI 1.62–4.37) than was pseudo-resistance (cardiovascular HR 1.24, 95% CI 0.55–2.78; renal HR 1.18, 95% CI 0.45–3.13) or sustained hypertension (cardiovascular HR 1.11, 95% CI 0.67–1.84; renal HR 2.14, 95% CI 1.35–3.40).

Among 14,684 patients enrolled in ALLHAT, apparent resistant hypertension was associated with increased risk of all-cause mortality (HR 1.30, 95% CI 1.11–1.52), coronary heart disease (HR 1.44, 95% CI 1.18–1.76), heart failure (HR 1.88, 95% CI 1.52–2.34), stroke (HR 1.57, 95% CI 1.18–2.08) and end-stage renal disease (ESRD; HR 1.95, 95% CI 1.11–3.41)[14]. Similarly, a longitudinal cohort study of 470,386 individuals with hypertension enrolled in the Kaiser Permanente Southern California health-care programme reported significant associations between resistant hypertension and all-cause mortality (HR 1.06, 95% CI 1.03–1.08), ischaemic heart events (HR 1.24, 95% CI 1.20–1.28), congestive heart failure (HR 1.46, 95% 1.40–1.52), cerebrovascular accident (HR 1.14, 95% CI 1.10–1.19) and ESRD (HR 1.32, 95% CI 1.27–1.37)[15]. In a prospective study that included 1,911 patients with treated hypertension, resistant hypertension was associated with an increased risk of cardiovascular events compared with no history of resistant hypertension (HR 2.22, 95% CI 1.21–4.05)[13].

The high rates of complications that are associated with resistant hypertension[8,13–15] underscore the need for intensive medical treatment in these high-risk patients. In addition, a need exists to free the health-care resources that are required to facilitate the optimization of this treatment, in particular by providing unrestricted access to ABPM[16].

Diagnosis

Resistant hypertension is defined as a seated office blood pressure of at least 140 mmHg systolic or 90 mmHg diastolic despite treatment with the maximally tolerated dose of three or more antihypertensive agents, one of which must be a diuretic[4,5] (BOX 1). In addition, some guidelines recommend that the daytime ambulatory blood pressure

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Box 1 | **Diagnosis of resistant hypertension**

- Exclude secondary hypertension, for example, as a result of primary aldosteronism, Cushing syndrome, renal artery stenosis, aortic coarctation, obstructive sleep apnoea, consumption of glycyrrhizin-rich foods or use of illicit drugs that increase blood pressure[17].
- In-office blood pressure ≥140/≥90 mmHg on optimized treatment with three or more drugs, including a diuretic.
- Ambulatory blood pressure ≥135/≥85 mmHg during the daytime or ≥130/≥80 mmHg over 24 h.
- Confirm adherence by an objective method, for example, witnessed drug intake or measurement of drugs levels in blood or urine.

should be at least 135 mmHg systolic or 85 mmHg diastolic on the same regimen[4,5,17] to exclude white-coat hypertension. The first step in diagnosis is exclusion of secondary hypertension using the procedures that are outlined in current clinical practice guidelines[17].

Blood pressure measurement

ABPM is the current gold standard in blood pressure measurement[18–21]. The US Preventive Services Task Force[18], the UK National Institute for Health and Clinical Excellence[19], the European Society of Hypertension[20] and Hypertension Canada[21] all recommend ABPM as the method of choice for the diagnosis of hypertension[18–21]. Therefore, the time has come to revise the diagnosis of resistant hypertension to make ABPM a *condicio sine qua non*.

Although the accuracy of ABPM can be limited by artefacts related to cuff size, movement, body position, short-term blood pressure variability and interference with sleep[22], the increased number of readings, the absence of terminal digit preference and observer bias, and minimization of the white-coat effect all contribute to the prognostic superiority of ambulatory blood pressure compared with office blood pressure[23,24]. The major contribution of ABPM to risk stratification is the cross-classification between office and ambulatory blood pressure that enables true hypertension to be differentiated from white-coat hypertension in untreated[25] and treated patients[26]. The results of event-driven studies convincingly demonstrate that the risk of cardiovascular disease is lower in patients with white-coat hypertension than in those with raised ambulatory blood pressure, even after controlling for concomitant risk factors[27].

Self-measured home blood pressure shares some of the advantages of ABPM compared with office blood pressure measurement, such as the greater number of readings and identification of the white-coat effect[16]. However, home blood pressure measurement cannot replace 24 h ABPM as the gold standard to exclude pseudo-resistant hypertension for several reasons. First, home blood pressure measurement does not enable easy recording of blood pressure during the night, which is the period during which blood pressure is most predictive of adverse cardiovascular outcomes[28]. Second, diagnosis of isolated nocturnal hypertension, which confers a cardiovascular risk equal to that of an elevated daytime or 24 h ambulatory blood pressure[29], is feasible only using 24 h ABPM. This is an important limitation of home blood pressure measurement given that the prevalence of isolated nocturnal hypertension is 7% among white individuals[29,30] and 10–11% among black individuals[29] and Asians[29,30]. Finally, and most importantly, use of home blood pressure measurement instead of ABPM leads to a missed diagnosis of masked or sustained hypertension, which is associated with high cardiovascular risk, in over 25% of patients[31]. Thus, 24 h ABPM is the cornerstone of the diagnosis and management of resistant hypertension, although self-measurement of blood pressure might be used, in addition to ABPM, to aid optimization of drug treatment[16]. For example, self-measurement of blood pressure might be considered in patients who resent ABPM because the blood pressure measurements disturb their sleep quality or interfere with strenuous physical labour at work.

Drug adherence

Pharmacological treatment cannot be effective if patients do not take their medication, and poor drug adherence is a major problem in those with resistant hypertension[32–34]. As non-adherence is a major cause of pseudo-resistance, drug adherence should always be assessed in these patients.

Indirect methods to evaluate drug adherence, such as pill counts, patient interviews, self-reported drug use, heart rate on β-blockers or activation of the renin–angiotensin–aldosterone system in response to treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor blockers, are vulnerable to bias or misclassification. The patient-interview-based eight-item Morisky Medication Adherence Scale can be used to assess adherence, with scores of 8, 6–7 and <6 indicating high, medium and low adherence, respectively[35]. However, the scores obtained using the Morisky questionnaire have been shown to correlate poorly with drug levels in urine samples[36].

Rates of prescription refills provide objective data but require a closed pharmacy system and do not enable evaluation of whether the prescribed drugs were actually taken by the patient[37]. The same limitation applies to electronic medication monitors that produce quantifiable results and track patterns of medication use[34] but require return visits, drug repackaging and expensive technology. The gold-standard objective methods of assessing drug adherence are witnessing drug intake[38] and measuring the levels of drugs or their metabolites in body fluids[39].

Gupta and colleagues used high-performance liquid chromatography coupled with tandem mass spectrometry of blood and urine samples to assess adherence in 676 British and 672 Czech patients with hypertension (mean age 55.1 years)[40]. In both populations, women were 55–65% less adherent to antihypertensive treatment than were men ($P \leq 0.014$). Each 10-year increment in age was associated with a >30% reduction in non-adherence ($P < 0.001$), and the risk of non-adherence increased by ≥75% per unit increase in the number of prescribed antihypertensive

Terminal digit preference
A tendency to round measurements to a particular end digit, resulting in the occurrence of this digit at a higher frequency than would be expected by chance alone. When blood pressure is measured by the auscultatory approach, the last digits of the systolic and diastolic readings should always be even and should not be rounded to 0 or 5. The terminal digits 0, 2, 4, 6 and 8 should each have a frequency of approximately 20%.

medications ($P<0.001$)[40]. The risk of non-adherence in both populations was consistently 63–76% higher for diuretics ($P\leq0.005$) than for ACE inhibitors, with little difference in adherence between ACE inhibitors and other drug classes[40].

Poor adherence is an indicator of poor prognosis in patients with pseudo-resistant hypertension[41,42]. An analysis of data from the Italian Health Search/Thales database reported that among 18,806 newly diagnosed patients with hypertension who were aged ≥35 years and initially free of cardiovascular disease, 8.1% were classified as having high adherence (at least 80% of days covered by filled prescriptions), 40.5% had intermediate adherence (40–79% of days covered by filled prescriptions) and 51.4% low adherence (<40% of days covered by filled prescriptions) 6 months after the index diagnosis[41]. During a mean follow-up of 4.6 years, the crude incidence of the composite cardiovascular end point (first-ever acute coronary syndrome, angina pectoris and cerebrovascular events such as transient ischaemic attack) was 7.4, 8.4, and 7.5 per 1,000 patient-years, in low, intermediate and high adherers, respectively. Following statistical modelling and cumulative adjustments for confounders, high adherence was associated with a significantly reduced risk of acute cardiovascular events (HR 0.62, 95% CI 0.40–0.96; $P=0.032$) compared with low adherence.

Educational measures and behavioural interventions, such as providing incentives and reminders, can improve treatment adherence in patients with resistant hypertension[4,43]. However, a systematic review of such interventions reported that those that increased long-term adherence to antihypertensive medications involved a combination of convenient care, counselling, self-monitoring, reinforcement, familial therapy and additional supervision[44]. Such interventions are complex and difficult to sustain; therefore, they are not consistently effective.

A meta-analysis of data from 16 randomized clinical trials that included 2,742 patients with chronic diseases (median age 39 years, 50.3% women) found that mobile telephone text messaging interventions (personalized messages, two-way communication or a daily text message) significantly improved medication adherence (OR 2.11, 95% CI 1.52–2.93; $P<0.001$) even after adjustment for publication bias (OR 1.68, 95% CI 1.18–2.39; $P=0.005$)[45]. Furthermore, repeated biochemical screening for non-adherence (liquid chromatography–tandem mass spectrometry of urine samples) at intervals of 4.5–8.9 months was associated with a reduction in blood pressure and an improvement in adherence in two European cohorts of patients with hypertension who were initially non-adherent[46]. However, data from clinical trials of renal denervation (discussed below) suggest that more than 50% of patients with refractory hypertension remained non-compliant with medications when blood and urine samples were analysed to assess adherence[36,47–49]. These data provide further evidence that drug adherence is a dynamic phenomenon that is influenced by complex psychosocial determinants and cannot be captured by any single assessment, and that changes in adherence are a major potential confounder in trials of new treatment modalities for resistant hypertension.

Management

Blood pressure regulation depends on afferent and efferent nervous traffic between the central nervous system, the kidney, the heart and the aortic and carotid baroreceptors (FIG. 1). In particular, renal sympathetic nerves have an important role in the pathogenesis of hypertension. The efferent sympathetic nervous outflow to the kidney stimulates renin release, angiotensin II generation and hyperaldosteronism, promotes sodium and water retention and reduces renal blood flow[50]. Sympathetic nervous drive to the kidney is increased in patients with hypertension, particularly in those with resistant hypertension[51]. Other causes of resistant hypertension include CKD, hyperaldosteronism and obstructive sleep apnoea[52].

The approach to the management of resistant hypertension, once confirmed by ABPM and assessment of adherence, should be comprehensive and include lifestyle measures (such as reducing body weight in overweight patients, dietary salt intake and excessive alcohol intake and increasing physical activity[4,43]) and management of risk factors[4,43] (such as dyslipidaemia, insulin resistance, poor glycaemic control in patients with diabetes mellitus and smoking) in addition to pharmacological treatment.

Medical treatment

Optimization of pharmacological treatment of confirmed resistant hypertension is based on a few simple principles (BOX 2). First, use combinations of antihypertensive drugs with different modes of action in line with the AB/CD algorithm[53] (FIG. 2), which, in contrast to voluminous multipage guidelines, is easy to understand for physicians who are not hypertension specialists[53]. Second, use antihypertensive agents with a long duration of action based on their molecular structure, so-called forgiving drugs, rather than extended-release dosage formulations[54]. Third, titrate each drug to the highest dose that does not produce adverse effects. Fourth, include a diuretic in the drug combination. Fifth, once the right combination has been found by rotating through and combining drug classes, stimulate adherence by reducing the pill load by prescription of single-pill combination tablets comprising two or three antihypertensive agents in adjustable doses[34]. Sixth, use aldosterone receptor antagonists or β_1-blockers if not contraindicated.

Spironolactone. Consistent with the notion that resistant hypertension is common among patients with primary hyperaldosteronism, mineralocorticoid receptor antagonists provide significant benefit in lowering blood pressure when added to existing multidrug regimens[55–57]. To date, the strongest evidence to support the use of mineralocorticoid receptor antagonists originates from the PATHWAY-2 trial of the aldosterone receptor blocker spironolactone[58]. In this double-blind, placebo-controlled crossover study, 335 patients were randomly assigned to sequential treatment with

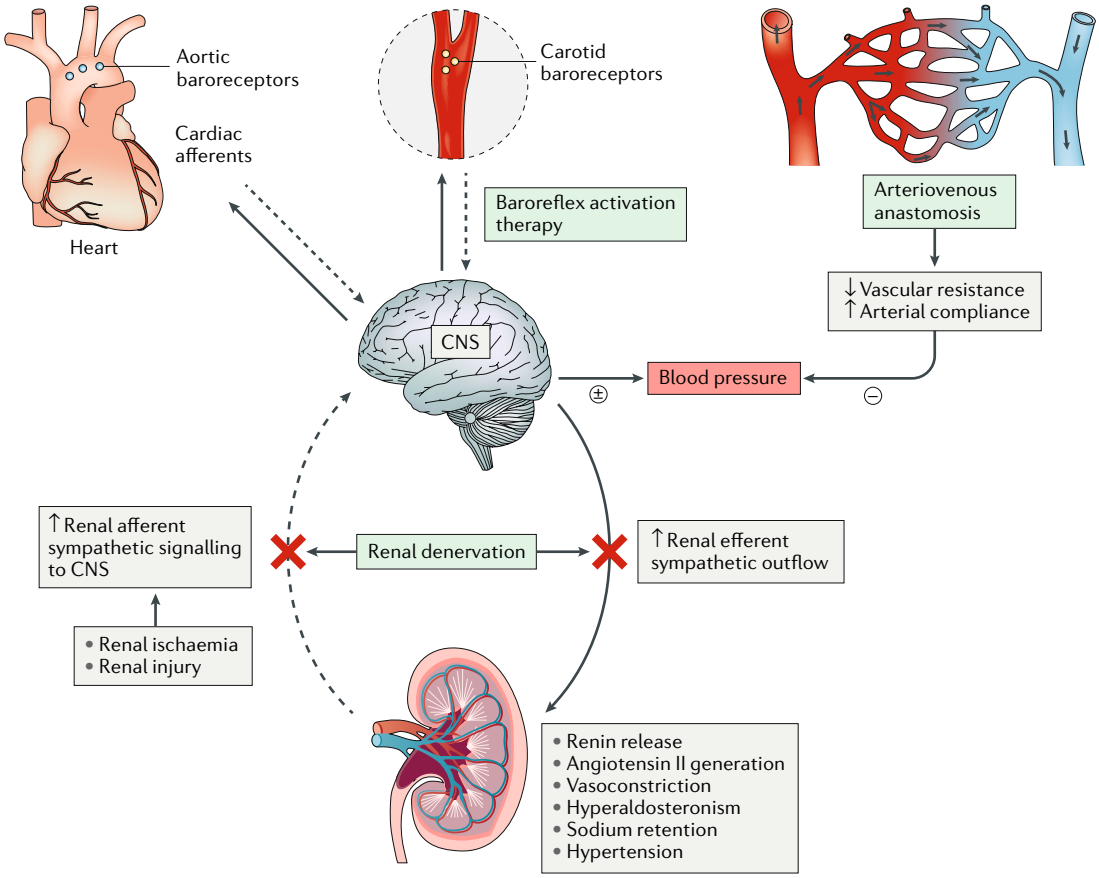

Fig. 1 | **Rationale for use of device therapy in resistant hypertension.** Efferent signalling from the brain to the kidney (solid arrow) stimulates renin release, angiotensin II generation, vasoconstriction, hyperaldosteronism and sodium retention, thereby increasing blood pressure. Afferent autonomous nervous signalling to the central nervous system (CNS) originates from the kidney, the heart and the aortic and carotid baroreceptors (dashed arrows) and can increase or decrease blood pressure. An imbalance between afferent and efferent signalling to and from the brain increases stroke volume, heart rate and peripheral vascular resistance and further contributes to the pathogenesis of hypertension. The aim of renal denervation and stimulation of the carotid baroreceptors is to rectify this imbalance in the sympathetic modulation of blood pressure. Arteriovenous anastomosis decreases arterial resistance and augments arterial compliance, potentially resulting in a reduction in blood pressure.

spironolactone, doxazosin, bisoprolol and placebo[58]. Eligibility criteria included age 18–79 years, seated clinic systolic pressure ≥140 mmHg (≥135 mmHg in diabetic patients), home systolic blood pressure (mean of 18 readings over 4 days) ≥130 mmHg and treatment for at least 3 months with the maximally tolerated doses of three antihypertensive agents. The mean reduction in home systolic blood pressure with spironolactone was 8.7 mmHg (95% CI 7.7–9.7 mmHg) greater than with placebo, 4.0 mmHg (95% CI 3.0–5.0 mmHg) greater than with doxazosin, 4.5 mmHg (95% CI 3.5–5.5 mmHg) greater than with bisoprolol and 4.3 mmHg (95% CI 3.4–5.1 mmHg) greater than the mean reduction with doxazosin and bisoprolol. Spironolactone was also the most effective blood-pressure-lowering treatment throughout the distribution of baseline plasma renin levels, but its margin of superiority and likelihood of being the best drug for the individual patient were greater at the lower end of the plasma renin distribution. In only six of 285 patients who received spironolactone, serum potassium exceeded 6.0 mmol/l on a single occasion[58]. This observation demonstrates that spironolactone can be administered without excessive risk of hyperkalaemia.

The follow-up period in the PATHWAY-2 trial was only 3 months. However, observational studies with longer duration of spironolactone treatment for resistant hypertension suggest that the magnitude of the initial blood pressure response is durable and that among the reported adverse effects of the drug, only gynaecomastia is exposure-dependent[59,60]. The PATHWAY-2 results cannot be extrapolated to patients with treatment-resistant hypertension and an estimated glomerular filtration rate <45 ml/min/1.73 m^2, because such patients were excluded from the trial[58].

Amiloride. The most common adverse effect of spironolactone is breast tenderness with or without breast enlargement, particularly in men. In patients who experience this adverse effect, amiloride can be used as an alternative therapy. Amiloride antagonizes the epithelial sodium channel in the distal collecting duct of the kidney and functions as an indirect aldosterone antagonist. In a blinded comparison, 10 mg of amiloride daily, 25 mg

Box 2 | **Pharmacological treatment of resistant hypertension**

- Combine first-line drugs with different modes of action such as thiazides or thiazide-like diuretics, selective β_1-blockers, long-acting dihydropyridine calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARBs) according to the AB/CD rule[53] (FIG. 2).
- Maximize diuretic treatment.
- Add a mineralocorticoid receptor antagonist (MRA) such as spironolactone.
- Loop diuretics should be used only in patients with an estimated glomerular filtration rate of <30 ml/min/1.73 m^2; MRAs should not be used in these patients because of the risk of severe hyperkalaemia.
- Second-line agents include centrally acting antihypertensive drugs, α_1-blockers, non-dihydropyridine calcium-channel blockers, the vasodilator hydralazine and the direct renin inhibitor aliskiren.
- Dual inhibition of the renin angiotensin system by combining ACE inhibitors, ARBs and/or aliskiren should be avoided.
- Aliskiren should be used with restraint in patients with diabetes or chronic kidney disease owing to the high likelihood of adverse effects.
- Use of potent vasodilators, such as minoxidil, should be attempted only as a last resort.

of spironolactone daily or a combination of both were used as add-on therapy in African-American patients whose blood pressure was not controlled on a regimen consisting of a diuretic (a thiazide diuretic in 92% of patients and a loop diuretic in the remaining 8%) and a calcium-channel blocker[57]. After 9 weeks of treatment, the mean decreases in systolic/diastolic blood pressure with these interventions compared with placebo were 12.2/4.8 mmHg with amiloride, 7.3/3.3 mmHg with spironolactone and 14.1/5.1 mmHg with both agents[57].

Arterial vasodilators. Treatment with arterial vasodilators, such as the potassium-channel opener minoxidil[61] or the selective endothelin type A antagonist darusantan[62], can also be considered for patients with resistant hypertension in the countries in which these drugs are registered. However, adverse effects, including fluid retention, oedema (which occurs in >25% of patients)[62], focal necrosis of the papillary heart muscle[61] and subendocardial areas of the left ventricle[62], arrhythmia[61,62], pericardial effusion[61] and heart failure[61,62], limit their clinical application to patients in whom other medical treatment options have failed.

Follow-up. Clinical practice guidelines fall short in describing how blood pressure must be followed up in patients with resistant hypertension. However, the same principles apply for follow-up as for the use of ABPM for the diagnosis of resistant hypertension. After each optimization step of the drug regimen, ABPM should be repeated within 2–3 weeks to determine whether adequate blood pressure reduction has been achieved. If further adjustments in therapy are required, as is often the case, repeating ABPM at 2–3-week intervals until control is achieved is justified. Once daytime and night-time blood pressures are controlled, ABPM must be repeated at 3–6-month intervals. Self-measurement of blood pressure at home can be used to obtain confirmatory evidence that awake blood pressure control is maintained[63]. To obtain a self-measured blood pressure equivalent to the daytime ABPM, 6 days of measurement are required with two readings in the morning and two in the evening. After the measurements from the first day are excluded, the average of the 24 remaining readings should be <135 mmHg systolic and <85 mmHg diastolic[23,24] to indicate a therapeutic response.

Device-based treatment

Potential options for the device-based management of resistant hypertension include renal denervation, baroreflex activation therapy and arteriovenous anastomosis (FIG. 1).

Renal denervation. The use of renal denervation to lower blood pressure in patients with hypertension is based on sound evidence of the role of the sympathetic nervous system[64,65] and the kidneys[66] in the pathogenesis of the disorder. Minimally invasive catheter-based ablation of renal sympathetic nerves represents a major leap forward compared with the unselective sympatholytic surgery that was used as a therapy for essential hypertension from the 1930s until the 1980s[67].

In 2009, the nonrandomized SYMPLICITY HTN-1 trial reported that percutaneous radiofrequency catheter-based renal sympathetic denervation was a feasible, effective and safe intervention for the treatment of resistant hypertension[68]. This first-in-human study included 45 patients with a mean systolic/diastolic blood pressure at enrolment of 177/101 mmHg who were receiving treatment with a mean of 4.5 antihypertensive drugs. At 12 months after renal denervation, the mean systolic/diastolic blood pressure of these patients had decreased by 27/17 mmHg (REF.[68]). Following this proof-of-concept study, the open SIMPLICITY HTN-2 trial randomly assigned 106 patients with resistant hypertension (mean blood pressure on treatment with a mean of 5.2 drugs of 178/98 mmHg) to undergo renal denervation and continue with current treatment or to continue current treatment alone[69]. At 6-month follow-up, office blood pressure had decreased by a mean of 32/12 mmHg in the denervation group but had not changed from baseline in the control group.

In contrast to the SYMPLICITY HTN-1 and HTN-2 trials, the single-blind SYMPLICITY HTN-3 trial included a sham control group[70]. The primary and secondary efficacy end points in this trial were the changes in systolic blood pressure at 6 months as assessed using office blood pressure and 24 h ABPM, respectively[70]. The decreases in systolic pressure in the denervation group (n = 364) versus the control group (n = 171) were 14.1 versus 11.7 mmHg on office blood pressure and 6.8 versus 4.8 mmHg on ABPM, resulting in baseline-adjusted between-group differences of 2.4 mmHg (95% CI 2.1–6.9 mmHg; P = 0.26) and 2.0 mmHg (95% CI −1.0 to 5.0 mmHg; P = 0.98), respectively[70].

The findings of SYMPLICITY HTN-3 (REF.[70]) together with similarly disappointing results from other renal denervation trials that confirmed the safety but not the efficacy of the procedure[47,71–77] (TABLE 1) have led to considerable doubt regarding the potential clinical application of the intervention in patients with

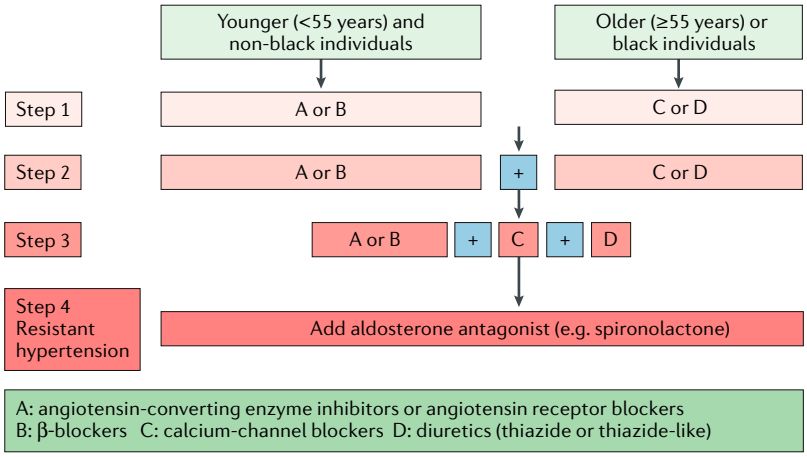

Fig. 2 | **Recommendation for combining blood-pressure-lowering drugs.** First-line drugs with different modes of action should be combined according to the AB/CD rule. Figure adapted with permission from REF.[53], BMJ Publishing Group Ltd.

treatment-resistant hypertension. Notable exceptions to these disappointing results were the findings of the DENERHTN study[78] and the INSPiRED pilot trial[36]. The DENERHTN trial reported that in patients with resistant hypertension, renal denervation together with a standardized step-care antihypertensive treatment regimen resulted in an approximately 6 mmHg greater mean reduction in 24 h, daytime and nighttime systolic blood pressure levels at 6 months than did standardized step-care antihypertensive treatment alone[78]. Design characteristics that differentiated the DENERHTN trial from other studies of renal denervation included blinded assessment of daytime systolic blood pressure, the primary end point of mean change in daytime systolic blood pressure from baseline to 6 months as assessed by ABPM, the recruitment and monthly follow-up of patients at highly specialized tertiary referral centres, assessment of drug adherence at every clinic visit and the standardized drug treatment regimen[78].

The INSPiRED pilot trial[36] received ethical clearance after publication of SYMPLICITY HTN-3 (REF.[70]). Following optimization of therapy with three or more antihypertensive drugs, patients with resistant hypertension were randomly assigned to continued medical treatment ($n = 9$) or to medical treatment combined with renal denervation using the EnligHTN multielectrode system ($n = 6$). At 6 months, the baseline-adjusted between-group differences in systolic/diastolic blood pressure were 19.5/10.4 mmHg for office blood pressure (7.6/2.2 mmHg in the control group versus −11.9/−8.2 mmHg in the renal denervation group; $P = 0.088$) and 22.4/13.1 mmHg for 24 h blood pressure (0.7/0.3 mmHg in the control group versus −21.7/−12.8 mmHg in the renal denervation group; $P \leq 0.049$) (TABLE 1). Electrocardiogram voltages, indicative of left ventricular mass, and the number of prescribed drugs were also lower in the renal denervation group than in the control group, but quality of life and medication adherence (assessed by measuring drug levels in urine) were similar in both groups[36]. The results of the INSPiRED trial, which used a stringent protocol in highly selected patients, suggest that the efficacy of renal denervation in patients with truly resistant hypertension in whom all other treatment options have failed should be investigated in future trials with a larger sample size.

In view of the disappointing results of trials of renal denervation in patients with resistant hypertension, subsequent trials have enrolled patients with untreated hypertension[48] or treated mild hypertension[79,80] and evaluated treatment responses at 3 months rather than 6 months. For example, the SPYRAL HTN-OFF MED study evaluated the effect of renal denervation on blood pressure in the absence of antihypertensive medications[48]. This proof-of-concept trial was designed in collaboration with, and approved by, the US Food and Drug Administration (FDA)[81] and set up in accordance with consensus documents on the design of renal denervation trials[82–84]. It differed substantially from previous renal denervation trials (TABLE 1) in terms of the hypertensive population enrolled, the renal denervation technique used and the absence of concomitant treatment with antihypertensive medications[48]. Eligible patients were drug naive (90%) or discontinued their antihypertensive medications for 3–4 weeks before enrolment (10%) and had an office systolic blood pressure of 150–180 mmHg, a mean 24 h ambulatory systolic blood pressure of 140–170 mmHg and an office diastolic blood pressure of ≥90 mmHg. In contrast to previous studies of renal denervation in which only the main renal artery was treated and a small number of ablations were delivered in a non-circumferential pattern, the renal denervation procedure in the SPYRAL HTN-OFF MED study involved the delivery of a larger number of ablations in a circumferential pattern within the main artery, renal artery branches and accessible accessory arteries. From baseline to 3-month follow-up, office and 24 h ambulatory systolic and diastolic blood pressure decreased significantly ($P \leq 0.003$) by 10.0/5.3 mmHg in the renal denervation group ($n = 38$) and by 5.5/4.8 mmHg in the control group ($n = 42$), resulting in mean baseline-adjusted differences of 7.7/4.9 mmHg (95% CI 1.5 to 14.0/−1.4 to 8.5 mmHg; $P \leq 0.016$) on office measurement and 5.0/4.4 mmHg (95% CI 0.2–9.9/1.6–7.2 mmHg; $P \leq 0.041$) on ambulatory monitoring[48]. These data provide biological proof of principle that renal denervation as done in this trial lowers blood pressure in untreated patients with hypertension[48].

Our interpretation of the SPYRAL HTN-OFF MED results is that the effect of renal denervation on office blood pressure was of similar magnitude to that reported in response to monotherapy in placebo-controlled trials of antihypertensive drugs[85]. In view of the invasiveness of the procedure, the short follow-up period (3 months) and the current state of knowledge regarding renal denervation, the investigators conclude that one could not confidently claim therapeutic efficacy or endorse use of catheter-based renal denervation beyond an investigational technology[48]. The SPYRAL HTN-ON MED trial, which is due to report in 2018 (REF.[79]), has a design similar to that of

Table 1 | **Change in 24 h SBP in randomized controlled trials of renal denervation**

Trial	Year	Control group		Renal denervation group		Mean ΔSBP (95% CI)	Refs
		n	Δ (s.d.)	*n*	Δ (s.d.)		
Intra-arterial radiofrequency ablation							
SYMPLICITY HTN-2	2010	25	−3.0 (19)	20	−11.0 (15)	−8.0 (−17.9 to 1.9)	69
OsloRDN	2014	10	−21 (13)	9	−10.0 (11)	11.0 (0.20 to 21.8)	71
PRAGUE	2014	54	−8.1 (17)	52	−8.6 (12)	−0.5 (−6.1 to 5.1)	72
SYMPLICITY HTN-3	2014	162	−4.8 (17)	329	−6.8 (15)	−2.0 (−5.0 to 1.1)	70
SYMPLICITY HTN-J	2015	19	−1.4 (10)	22	−7.5 (12)	−6.1 (−12.8 to 0.64)	73
DENERHTN	2015	53	−9.5 (13)	48	−15.4 (13)	−5.9 (−11.0 to −0.8)	78
SYMPLICITY-FLEX	2015	35	−3.5 (10)	32	−7.0 (11)	−3.5 (−8.5 to 1.5)	75
ReSet	2016	33	−2.6 (13)	35	−3.7 (16)	−1.1 (−8.0 to 5.8)	76
DENERVHTA	2016	13	−23.6 (14)	11	−5.7 (14)	17.9 (6.7 to 29.1)	74
SYMPATHY	2017	41	−6.6 (21)	83	−5.6 (21)	1.0 (−7.1 to 9.1)	47
INSPiRED	2017	9	0.7 (20)	6	−21.7 (15)	−22.4 (−40.1 to −4.7)	36
SPYRAL HTN-OFF MED	2017	36	−0.5 (10)	35	−5.5 (11)	−5 (−9.9 to −0.11)	48
Externally delivered ultrasound energy							
WAVE IV	2017	21	−5.9 (15)	28	−7.1 (13)	−1.2 (−9.2 to 6.8)	77

Δ indicates the difference of 24 h systolic blood pressure (SBP) from baseline to follow-up in mmHg. ΔSBP indicates the difference of the change in the 24 h SBP between the renal denervation and control groups.

SPYRAL HTN-OFF MED but requires patients to be treated with a consistent triple-drug antihypertensive regimen before enrolment.

The randomized sham-controlled WAVE IV trial of renal denervation was unique in that externally delivered ultrasound energy rather than invasive intra-arterial radiofrequency ablation was used to sever the renal nerves[77]. This trial reported no significant differences in change in office blood pressure at 12 and 24 weeks and in 24 h ambulatory blood pressure at 24 weeks of follow-up in the control ($n = 39$) and renal denervation groups ($n = 42$)[77]. The ongoing RADIANCE-HTN randomized trial of renal denervation using intravascular delivery of ultrasound energy is expected to report in 2018 (REF.[86]).

Chemical renal denervation using the infusion of very low doses of dehydrated ethanol directly into the adventitial space might be a promising alternative approach to catheter-based renal denervation. The feasibility and safety of this endovascular approach was shown in a clinical study that included 18 patients with resistant hypertension[87]. The procedure was successful in all participants, led to minimal or no injury to the normal renal arterial wall and resulted in a mean decrease in office systolic blood pressure from 175 ± 17 mmHg at baseline to 151 ± 26 mmHg (decrease of 24 mmHg) at 6-month follow-up. However, the efficacy of chemical renal denervation has not yet been assessed in a randomized clinical trial.

To our knowledge, only four trials of renal denervation in patients with resistant hypertension[36,38,47,88] and none of the trials of other devices discussed in this Review applied a stringent approach to assess drug adherence. In the OsloRDN trial, 19 of 65 screened patients (29.2%) were excluded because ambulatory blood pressure normalized after witnessed drug intake just before the qualifying visit[38]. In DENERHTN[88], drug adherence was assessed at the 6-month visit in 85 of 106 patients (80.2%) by determining the urinary *N*-acetyl-seryl-aspartyl-lysyl-proline:creatinine ratio[81] and by using ultra-high-performance liquid chromatography–tandem mass spectrometry to detect the drugs in urine or plasma[39]. The prevalence of non-adherence in this trial was approximately 50% in the renal denervation and control groups. SYMPATHY[47] and INSPiRED[36] are the only trials of renal denervation in which drug adherence was assessed by measuring urinary drug concentrations at baseline and follow-up. In 78 of 139 (56.1%) patients in the SYMPATHY trial, blood samples were drawn synchronously with blood pressure measurements and neither patients nor physicians knew that adherence was being monitored. In 80% of patients, fewer medications were detected than prescribed and adherence changed during follow-up in 31% of patients[47]. In the INSPiRED pilot trial[36], non-adherence was observed in four of nine (44%) patients randomly assigned to the control group and in three of six (50%) patients allocated to renal denervation. Non-adherence at any time from baseline to the 6-month visit occurred in eight (88.9%) patients in the control group and four (66.7%) patients in the renal denervation group. In the SPYRAL HTN-OFF MED trial ($n = 80$)[48], overall compliance with the requirement to be off antihypertensive medications from baseline until the 3-month visit was 85.5%. Although largely neglected to date, these data indicate that patient adherence to medical treatment is an important potential confounder that must be considered when designing future trials of renal denervation and other therapies for resistant hypertension.

Baroreflex activation therapy. The activation of baroreceptors results in enhanced parasympathetic and reduced sympathetic nervous activity, which generates a reduction in blood pressure[89,90] (FIG. 1). Studies in dogs demonstrated that prolonged baroreflex activation leads to a substantial reduction in mean arterial pressure by restraining the sympathetic nervous system[89]. A subsequent study in 12 patients with resistant hypertension demonstrated that electrical stimulation of the carotid baroreceptors inhibited sympathetic nerve activity and acutely decreased arterial blood pressure[90].

The nonrandomized US Rheos Feasibility trial evaluated the response of ten patients with multidrug-resistant hypertension to baroreflex activation therapy using the implantable Rheos Baroreflex Hypertension Therapy System[91]. Dose–response testing before hospital discharge showed a mean reduction in systolic blood pressure of 41 mmHg (from 180 mmHg to 139 mmHg), with a peak response at 4.8 V (P<0.001) and no clinically significant bradycardia. In addition, no adverse effects of device implantation were reported.

Subsequently, the DEBuT-HT (Device-Based Therapy in Hypertension Trial) nonrandomized feasibility study assessed the safety and efficacy of carotid baroreflex activation therapy using the Rheos device in 45 patients with a blood pressure of ≥160/90 mmHg while on treatment with at least two antihypertensive agents[92]. The device therapy had a favourable safety profile and resulted in mean reductions in office systolic/diastolic blood pressure of 21/12 mmHg after 3 months and 33/22 mmHg after 2 years.

The double-blind, randomized Rheos Pivotal Trial[93] assessed the safety and efficacy of carotid baroreflex activation therapy in 265 patients with resistant hypertension. Following implantation of the Rheos device, the participants were randomly assigned to undergo immediate stimulation (n = 181) or delayed stimulation 6 months after implantation (n = 84)[93]. The primary end point was the change in office blood pressure at 6 months as measured by an automated oscillometric device and a treatment response was defined as a decrease in systolic blood pressure of ≥10 mmHg compared with levels before implantation. At 6 months, 54% of patients in the immediate-stimulation group and 46% of those in the delayed-stimulation group (who at this point had not received stimulation) were classed as responders; this difference was not statistically significant given the 20% superiority margin (P = 0.97). The mean decrease in systolic blood pressure from baseline at 6 months was 16 mmHg in the stimulated group versus 9 mmHg in the control group (P = 0.08). At 12 months, the decrease in systolic blood pressure from baseline was similar in the stimulated and delayed-stimulation groups (mean of 25 mmHg). Thus, the study failed to meet its efficacy end point. The criteria for baroreflex activation therapy safety and device safety were met, but those for procedural safety were not met owing to the occurrence of surgical complications, wound complications or nerve injury in 25.5% of patients[93].

A combined long-term follow-up study of the US Rheos Feasibility trial[91], DEBuT-HT[92] and the Rheos Pivotal Trial[93] included 143 participants who had completed 5 years of follow-up and 48 participants who had completed 6 years of follow-up[94]. Mean office blood pressure decreased significantly during the 6-year follow-up period from 179 to 144 mmHg systolic (P<0.0001) and from 103 to 85 mmHg diastolic[94]. In 27% of patients, the median number of medications also decreased from six to three, in 34% medication use remained stable at a median of five and in 39% it increased from a median of five to a median of seven (REF.[94]). However, this observational study does not provide proof of the clinical effectiveness of baroreceptor activation therapy for resistant hypertension because the DEBuT-HT study[92] and the US Rheos Feasibility trial[91] were nonrandomized, the randomized Rheos Pivotal Trial[93] did not reach its primary efficacy end point and a large number of the participants in the three studies were lost to follow-up (62.7% at 5 years and 87.5% at 6 years)[91–93].

The single-arm, open-label Barostim *neo* trial assessed the efficacy of a second-generation carotid baroreceptor-stimulating device in 30 patients with resistant hypertension[95]. This device was designed to work with a single electrode implanted unilaterally, making the surgical procedure much simpler than that required for previous devices. Baroreflex activation therapy with this device resulted in a mean reduction in office systolic/diastolic blood pressure of 26/12 mmHg at 6 months. A subsequent single-arm study of the same device in 51 patients with resistant hypertension reported significant decreases in mean 24 h ambulatory systolic blood pressure (from 148 to 140 mmHg; P<0.01) and diastolic blood pressure (from 82 to 77 mmHg; P<0.01) at 6 months after device implantation[96].

A study that investigated acute responses to carotid baroreceptor stimulation using the second-generation device in 18 patients with resistant hypertension reported that stimulation with intensities that produced tolerable adverse effects in the short term resulted in a mean decrease in systolic blood pressure of 16.9 mmHg (P = 0.002)[97]. However, stimulation intensities had to be lowered in 12 patients (66.7%) to avoid adverse effects with chronic treatment. This reduced stimulation intensity resulted in a significant reduction in efficacy with a mean decrease in systolic blood pressure of only 6.3 mmHg (P = 0.028).

An alternative approach to baroreceptor activation therapy is to use an endovascular implant (inserted via an arterial catheter) to increase circumferential and longitudinal wall stretch at the level of the carotid baroreceptors, potentially resulting in activation of the baroreflex and lowering of blood pressure[98]. An uncontrolled open-label study explored whether carotid baroreceptor stimulation could be achieved using this approach (that is, insertion of an internal carotid artery stent)[99]. In this prospective first-in-human study, which included 30 patients with resistant hypertension, the primary and secondary efficacy end points were the incidence of serious adverse events at 6 months and the changes in office and 24 h ambulatory blood pressure, respectively. During 6 months of follow-up, four patients (13%) developed serious adverse events, including hypotension (n = 2), worsening hypertension (n = 1),

Nocebo effect
Adverse events occurring as a result of negative expectations (the opposite of the placebo effect). A nocebo response occurs when a patient's symptoms are worsened by the administration of an inert, sham or placebo treatment.

intermittent claudication ($n = 1$) and wound infection ($n = 1$)[99]. At baseline, the mean systolic/diastolic blood pressures were 184/109 mmHg on office measurement and 166/100 mmHg on 24 h ABPM; at 6 months, these blood pressures had decreased by 24/12 mmHg and 21/12 mmHg, respectively ($P < 0.001$)[99]. However, in view of the absence of a control group and the open-label design, interpretation of the efficacy of this intravascular approach remains difficult.

Overall, the evidence supporting carotid baroreceptor stimulation as a treatment modality in resistant hypertension remains weak. The most important limitations are the single-arm unblinded design of most studies published to date[91,92,95,96,100] (with the exception of the first 6 months of follow-up in the Rheos Pivotal Trial[93]), the failure to meet the primary efficacy end point in the Rheos Pivotal Trial[93], the variable follow-up duration, the use of office rather than 24 h ABPM[91–95,100], the lack of reliable data on adherence and the possible influence of the nocebo effect[101].

Arteriovenous anastomosis. The novel arteriovenous ROX Coupler (ROX Medical, San Clemente, CA, USA) reduces blood pressure by adding a low-resistance, high-compliance venous segment to the central arterial tree[102] (FIG. 1). This self-expanding, stent-like device is preloaded within a delivery catheter[103] and is placed under fluoroscopic guidance to create a 4 mm anastomosis between the iliac artery and vein, which delivers a calibrated amount of arterial blood into the venous system (≈800 ml/min)[104].

An open-label, randomized trial assessed the efficacy of this device in 83 patients with uncontrolled hypertension (defined as baseline office systolic blood pressure ≥140 mmHg and mean daytime ambulatory blood pressure ≥135 mmHg systolic and ≥85 mmHg diastolic despite antihypertensive treatment)[105]. The primary end point was the mean change from baseline in office and 24 h ambulatory systolic blood pressure at 6 months[105]. In the arteriovenous coupler group ($n = 39$), mean office systolic blood pressure decreased by 26.9 mmHg from 175 mmHg and mean 24 h systolic blood pressure decreased by 13.5 mmHg from 157 mmHg, whereas in the control group ($n = 44$) mean office systolic blood pressure decreased by 3.7 mmHg from 171 mmHg and mean 24 h systolic blood pressure decreased by 0.5 mmHg from 156 mmHg (REF.[105]). The baseline-adjusted between-group differences were significant ($P < 0.001$). At 12 months, mean office and 24 h systolic/diastolic blood pressure in the arteriovenous coupler group remained significantly lower than at baseline (reductions of 25.1/20.8 mmHg and 12.6/17.4 mmHg, respectively; $P < 0.001$)[106]. However, the control group was not available for analysis, rendering the 12-month findings of this open-label study far from convincing. Therefore, replication of the trial is necessary. Another major concern is that after coupler therapy, 14 patients (33%) developed ipsilateral venous stenosis[106]. Although this complication can be managed with conventional strategies, the acute and long-term safety of the approach (for example, the haemodynamic effects of arteriovenous fistula formation) remain to be proved.

Carotid body resection

Carotid bodies are primary peripheral chemoreceptors that orchestrate a systemic response to hypoxia. Data from animal[107] and human studies[108] demonstrate that pathological afferent signalling emanating from the carotid body drives a sympathetically mediated elevation in blood pressure. A proof-of-principle study investigated the safety and feasibility of unilateral carotid body resection as a blood-pressure-lowering therapy in 15 patients with resistant hypertension[108]. Although the procedure was shown to be safe and feasible, it did not result in statistically significant differences in office or ambulatory systolic blood pressure at 1, 3, 6 and 12 months of follow-up compared with baseline levels. The study was limited by the absence of a control group and the low number of patients.

Carotid body resection might be further investigated as an approach to decrease sympathetic activity in patients with heart failure. A first-in-human study included ten men with systolic heart failure, of whom four underwent unilateral right-sided carotid body resection and six underwent bilateral carotid body resection[109]. At 1-month follow-up, carotid body resection was associated with a significant decrease in muscle sympathetic nerve activity from 86.6 bursts per 100 heart beats to 6.9 bursts per 100 heart beats ($P = 0.03$)[109].

Future perspectives

Clinical trial design

Poor insight into the pathophysiological mechanisms that increase blood pressure and weak features of study design explains why most trials of devices to treat resistant hypertension failed to reach their efficacy end points. In particular, assuming that renal denervation would be efficacious in a large number of patients with a variety of conditions was overly optimistic. In rats, transplantation of a kidney from a hypertensive to a normotensive animal induces hypertension, although by definition the transplanted kidney is not innervated[66]. Moreover, essential hypertension is characterized by membrane abnormalities that could affect the function of the vasculature and organs in various ways[110], and in elderly patients, isolated systolic hypertension is caused by stiffening of the large arteries rather than by increased sympathetic tone[111]. In 2012, we proposed that renal denervation would not work in patients with isolated systolic hypertension[112]. This view has now been confirmed by experts in the field[113]. Therefore, selection of patients with essential hypertension for enrolment in future trials requires not only the exclusion of those with pseudo-resistance using ABPM and checking adherence to an optimized drug regimen but also an assessment of the extent to which hypertension is dependent on volume overload and sodium retention as opposed to increased peripheral arterial resistance, which is the hallmark of increased sympathetic tone. Measurement of the cardiac index and mean arterial pressure is required for non-invasive estimation of systemic arterial resistance. Furthermore, one cannot expect treatment-resistant patients with

severe target organ damage to respond to renal denervation or other device therapies. The European Network Coordinating Research on Renal Denervation (ENCOReD) study demonstrated that worse renal function at baseline was associated with a lower probability of improvement in 24 h blood pressure (OR for 20 μmol/l increase in serum creatinine 0.60; $P = 0.05$) and a higher probability of experiencing no blood pressure decrease (OR 1.66; $P = 0.01$) in response to the intervention[114].

Incomplete renal denervation due to a lack of adequate depth of nerve injury and predictive circumferential nerve ablation has been suggested to contribute to the variable blood-pressure-lowering effect[115]. Acute blood pressure and heart rate responses to renal nerve stimulation might provide a procedural end point indicating effective renal denervation and might identify the anatomical localization within the renal arterial system to be preferentially denervated[116]. Renal nerve stimulation might also address the large variability in the local anatomy of the renal sympathetic nerves[117]. Patients with accessory arteries that cannot be engaged for renal denervation should not be enrolled in clinical trials of this intervention[118], although they might benefit from the procedure. We hope that rolling renal denervation out to untreated patients or treated patients with mild hypertension will not stop manufacturers from supporting clinical trials in highly selected adherent patients with truly resistant hypertension in whom all other treatment options have failed but who represent a much smaller number of clients and therefore a less profitable market.

Biomarkers

The introduction in clinical practice of circulating or urinary metabolic or proteomic biomarkers is a promising development that could potentially lead to improvements in the management of resistant hypertension. These biomarkers can provide insights into the pathophysiology of hypertension and enable the identification of early target organ damage at a stage when prevention of organ failure is still possible and/or predict responses to therapy.

Circulating dephospho-uncarboxylated matrix Gla protein (dp-ucMGP)[119], urinary mucin 1 (REF.[120]) and CKD273 (REF.[121]) could potentially be used for the early detection of patients with treatment-resistant hypertension who are at the greatest risk of irreversible kidney damage. dp-ucMGP is a marker of vitamin K status, whereas active MGP is a strong local inhibitor of vascular calcification[122] that helps to maintain the integrity of the renal microcirculation[119,123]. Mucin 1 is a high-molecular-mass (400 kDa), heavily *O*-glycosylated, type I membrane-tethered glycoprotein that is a key component of the luminal epithelial mucobarrier[124]. In normal kidneys, mucin 1 is expressed in the thick segment of the loop of Henle and in the distal tubules and collecting ducts; the amino-terminal α-subunit of mucin 1 is shed into the urine when renal function starts to decline. CKD273 is a multidimensional urinary classifier consisting of 273 peptide fragments[121] that has been shown to predict deterioration of renal function[125] before the development of microalbuminuria[121] and to predict cardiovascular complications in the general population[125]. The FDA has encouraged further studies of CKD273 as a diagnostic tool and risk predictor in patients with CKD[126].

Other biomarkers of cardiovascular complications include the urinary proteomic classifiers HF1 and HF2, which consist of 85 and 671 peptides, respectively, and have been shown to predict imminent diastolic left ventricular dysfunction and cardiovascular complications in the general population[127,128]. In addition, urinary markers of citric acid metabolism have been reported to predict the treatment response to spironolactone in patients with treatment-resistant hypertension[129]. Use of omics technologies, after proper validation of biomarkers in randomized clinical trials[130], will likely revolutionize the selection of patients with resistant hypertension for current and future therapies and enable a personalized approach to their management.

Conclusions

Once a diagnosis of resistant hypertension is confirmed, optimization of drug treatment remains the cornerstone of its management. For now, device treatment should remain the last resort in adherent and truly resistant patients with severe hypertension in whom all other efforts to reduce blood pressure have failed[112] and should be offered to patients only within the context of clinical research in highly skilled tertiary referral centres. Severely hypertensive patients who are intolerant to multiple antihypertensive drugs or patients who are confirmed to be non-adherent might also be candidates for device-based approaches once their safety and efficacy are proved in randomized controlled clinical trials[131]. However, in non-adherent patients, educational measures, behavioural interventions and eHealth interventions[4,43,45] would probably be a better strategy. Future research should focus on a better understanding of the intrinsic (for example, physiological and psychological factors) and extrinsic (for example, environmental stressors) mechanisms that contribute to an adherent patient's lack of responsiveness to blood-pressure-lowering drugs. Biomarkers predictive of target organ damage and new technologies, such as renal nerve stimulation, might help to select patients who might benefit from device therapies.

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