Resistant hypertension

The disease burden attributable to arterial hypertension is substantial, accounting for or contributing to 62% of all strokes and 49% of all cases of heart disease, culminating in an estimated 7.1 million deaths a year; equivalent to 13% of total worldwide deaths. 1 Although most cases of hypertension can be effectively treated with lifestyle changes or drugs, or both, hidden within this population lies a cohort at the extreme end of the cardiovascular risk spectrum—those with hypertension that is resistant to treatment.

The aim of this review is to assist non-specialist practitioners in the overall management of patients with resistant hypertension by presenting a comprehensive exploration of the evidence on the recognition, evaluation, and treatment of the condition.

What is resistant hypertension?

International guidelines have defined resistant hypertension as a raised blood pressure (that is, seated clinic blood pressure >140/90 mm Hg) despite treatment with at least three antihypertensive agents (one of which is usually a diuretic) at optimal or best tolerated doses. The recent National Institute for Health and Clinical Excellence (NICE) guideline (see box 1) has been the most prescriptive in formally defining resistant hypertension by suggesting that the three agents would usually be an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker plus a calcium channel blocker plus a thiazide-type diuretic (that is, A+C+D) in accordance with the NICE treatment algorithm. The NICE guidance also suggests that resistant hypertension should be diagnosed only after confirming inadequate blood pressure control despite treatment, by use of ambulatory blood pressure monitoring (that is, mean daytime blood pressure >135/85 mm Hg), thereby excluding so-called white coat hypertension. The optimal target blood pressure in patients treated for resistant hypertension is widely accepted to be <140/90 mm Hg, as it is for all hypertensive patients in general, although lower targets may be appropriate for those with diabetes or chronic kidney disease.

Who gets resistant hypertension?

Data derived from retrospective, cross-sectional population studies of hypertension control in Spain and the United States indicate a resistant hypertension prevalence of between 7.6% and 8.9%. 2 3 In the recent Health Survey for England, 20% of hypertensive patients had uncontrolled blood pressure despite the administration of at least three drugs, making it reasonable to assume the population with resistant hypertension is around 0.5–1 million individuals in England alone. 4 Post hoc analysis of data from large clinical trials of antihypertensive therapy (such as ALLHAT, ASCOT, ACCOMPLISH, LIFE, INVEST, and CONVINCE 5–10) suggests that the prevalence of resistant hypertension could be as high as 35%. However, these highly selected populations tend to be older and contain higher risk individuals with greater cardiovascular comorbidity than the general hypertensive population. 5–10 Amalgamation of the earlier clinical trial data with the more contemporaneous observational findings suggests a resistant hypertension prevalence of 10–20% of the hypertensive population. 11

A US study found that, within a median of 1.5 years after initiation of antihypertensive therapy, about 1 in 50 of the patients developed resistant hypertension (either uncontrolled hypertension with ≥3 antihypertensive drugs or controlled hypertension with ≥4 antihypertensives). 12 This represents an incidence of 1.9% of resistant hypertension in the 205 750 hypertensive patients who began drug therapy. Among those taking three or more medications for at least one month (n=24 499), the prevalence of resistant hypertension was 16.2%. The results were further strengthened by exclusion of patients with pseudo-resistant hypertension and inclusion of a large and ethnically diverse population. 12 The analysis also revealed that patients with resistant hypertension were almost 50% more likely to experience an adverse cardiovascular event over a median follow-up of 3.8 years compared with patients with blood pressure controlled by means of three or fewer antihypertensive drugs. 12 This increased risk was largely caused by the development of

SUMMARY POINTS

Resistant hypertension is defined as high blood pressure that remains uncontrolled despite treatment with at least three antihypertensive agents (one of which is usually a diuretic) at best tolerated doses. A diagnosis of true resistant hypertension should be made only after a thorough assessment to exclude apparent or pseudo-resistant hypertension.

Post hoc analyses of large scale trials of antihypertensive drugs plus retrospective cross sectional observational studies point to a prevalence of resistant hypertension of 10–20% of the general hypertensive population.

Patients with resistant hypertension are almost 50% more likely to experience an adverse cardiovascular event compared with patients with blood pressure controlled by three or fewer antihypertensive agents.

Studies indicate that 5–10% of resistant hypertension patients have an underlying secondary cause for their elevated blood pressure—a prevalence significantly greater than that of the general hypertensive population.

No clinical trials have compared the effectiveness of specific drug regimens for the treatment of resistant hypertension.

The best available evidence supports the use of low dose spironolactone as the preferred fourth drug if the patient’s blood potassium level is ≤4.5 mmol/L. With higher blood potassium levels, intensification of thiazide-like diuretic therapy should be considered.

Renal sympathetic denervation therapy, as a device based intervention, could potentially stimulate a paradigm shift in the management of resistant hypertension.

RESOURCES AND SELECTION CRITERIA

Using the term “resistant hypertension”, we searched the PubMed, Embase, and Cochrane databases for articles from a publication date of January 2000 to June 2012. Further articles were then identified from the reference lists of the articles found in the database search. We restricted our search to those written in the English language, studies on humans, and published work only. Priority was given to systematic reviews, meta-analyses, and clinical guidelines.

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chronic kidney disease. However, the precise long term prognosis of patients with resistant hypertension is still to be determined.

Certain patient characteristics have been associated with an increased likelihood of developing treatment resistant hypertension (see box 2). Many of these characteristics are associated with adverse cardiovascular outcomes and underscore the need for effective treatment of resistant hypertension.

How is resistant hypertension diagnosed?

Apparent or pseudo-resistant hypertension

Before a patient can be labelled as having treatment resistant hypertension, apparent or pseudo-resistant hypertension must be excluded. This is inadequate blood pressure control in a patient receiving appropriate treatment who does not actually have resistant hypertension.

Box 2 | Typical characteristics of patients with resistant hypertension

- Older age; especially >75 years
- High baseline blood pressure and chronicity of uncontrolled hypertension
- Target organ damage (left ventricular hypertrophy, chronic kidney disease)
- Diabetes
- Obesity
- Atherosclerotic vascular disease
- Aortic stiffening
- Sex (women)
- Ethnicity (black)
- Excessive dietary sodium

Most often, pseudo-resistant hypertension arises from (a) poor office blood pressure measurement technique (see supplementary boxes on bmj.com), (b) the “white coat” effect, (c) poor patient concordance with prescribed therapy, or (d) a suboptimal antihypertensive regimen (see box 3).

Medical professionals must also recognise and accept that “clinical inertia” has an important role to play in the suboptimal management of hypertension, particularly when patients require multiple drugs. The term clinical inertia can encompass a poor knowledge of clinical guidelines, a misguided acceptance of elevated blood pressure, or an underestimation of cardiovascular disease risk, all of which can lead to suboptimal blood pressure treatment. It is of prime importance to consider patient and physician factors and eliminate them, before establishing a definitive diagnosis of resistant hypertension.

What is the best method for assessing blood pressure?

In a retrospective analysis of records in a Spanish registry, up to 40% of the patients defined as having resistant hypertension according to office blood pressure readings were later found to manifest a white coat effect when evaluated by ambulatory blood pressure monitoring. This highlights how common the white coat effect (that is, a persistently elevated office blood pressure but a normal home blood pressure—see supplementary boxes on bmj.com) can be. It also emphasises the importance of using ambulatory blood pressure monitoring to confirm resistant hypertension as recommended by the recent NICE guidance. A white coat effect should be suspected in any individual with persistently elevated office blood pressure readings but no signs of target organ damage or signs or symptoms of overtreatment such as postural hypotension, dizziness, or syncope.
What lifestyle factors contribute to resistant hypertension?

Once a diagnosis of true resistant hypertension has been established, the next step is to evaluate the patient for potentially modifiable contributing factors (see box 4).

Obesity is a common feature of patients with resistant hypertension, partly due to an association with sodium retention, enhanced sympathetic nervous system activity, and activation of the renin-angiotensin-aldosterone system (RAAS). There is also an increased likelihood of pseudo-resistant hypertension in obese patients if too small a cuff is applied to a large arm. The HYDRA study of 45,125 primary care patients in Germany found that obese individuals (body mass index >40) had a 5.3-fold greater probability of requiring three antihypertensive drugs and a 3.2-fold greater probability of requiring four antihypertensive drugs to achieve blood pressure control compared with individuals with a normal body mass index (<25).18

The relationship between the prevalence of hypertension, alcohol consumption, and blood pressure is linear.19

Moderate alcohol consumption does not generally elevate blood pressure levels, but heavy alcohol consumption (>21 units/week for men, >14 units/week for women where 1 unit = 8 g or 10 ml of alcohol or a half pint of beer, glass of wine, or shot of spirits), including binge drinking, is associated with raised blood pressure, an increased risk of stroke, and an overall poorer prognosis. Trials of structured interventions to reduce alcohol intake have resulted in significant falls in both systolic and diastolic blood pressures.20

Patients must be asked about the potential use of prescribed and recreational exogenous substances (see box 4) and, where possible, the offending agents stopped, minimised, or substituted appropriately. The effects of these agents can be highly variable and unpredictable, with most patients showing minimal effects whereas others experience substantial elevations in blood pressure. Where there is doubt with regard to which agents should be modified, a specialist opinion may be warranted.

Excessive dietary salt intake is a well recognised risk factor for resistant hypertension. Indeed most patients with resistant hypertension tend to consume more salt than the general population, often exceeding 10 g/day.21 Excess salt directly increases blood pressure and also blunts the action of all antihypertensive agents in general. The effect is magnified in individuals who are particularly salt sensitive (elderly patients, black patients, and those with chronic kidney disease—see box 2). It is therefore important to review an individual’s salt intake, provide dietary advice, and recommend a salt intake <6 g/day (refer to section 11.1.8 page 185 of NICE Clinical Guideline 127 on hypertension—see box 1).

What are the secondary causes of resistant hypertension?

Potentially remediable secondary causes of resistant hypertension are listed in box 4. The prevalence of secondary hypertension is greater in people with resistant hypertension compared with the general hypertensive population, with studies indicating that 5–10% of patients with resistant hypertension have an underlying secondary cause22 23—the most common being hyperaldosteronism, chronic kidney disease (which may either be the cause or adverse sequel of chronic, poorly controlled hypertension), renal artery stenosis, and obstructive sleep apnoea. It is important for the non-specialist to be able to recognise the signs and symptoms that may suggest an underlying disease process. This should include a focused history, thorough physical examination, biochemical evaluation, non-invasive imaging (such as renal ultrasound), and subsequent onward referral to a specialist hypertension clinic if necessary (see boxes 4 and 5).

What target organ damage is seen in resistant hypertension?

Target organ damage refers to left ventricular hypertrophy, hypertensive retinopathy, and renal disease (that is, persistently elevated urinary albumin excretion rate, haematuria, or renal impairment). Electrocardiography and ideally echocardiography should be performed, along
How is concordance with treatment assessed?
An important consideration in patients with resistant hypertension is their concordance with treatment. This is especially important in view of the fact that hypertension is largely asymptomatic and is treated with multiple drugs. Increasingly, “directly observed therapy” clinics are used in specialist centres, where patients are asked to consume their drugs at the clinic and blood pressure is then monitored either by ambulatory blood pressure monitoring or home blood pressure monitoring over the following 6–24 hours to confirm whether there is a response to a witnessed consumption of medication. Urine testing of drug metabolites is also being introduced in specialist clinics to confirm concordance before considering further evaluation and treatment.

What treatments are available for resistant hypertension?
Non-pharmacologic intervention
The aetiology of true resistant hypertension is almost always multifactorial, and a comprehensive management strategy should therefore include recognition and reversal of contributory lifestyle factors. Thus, weight loss; regular exercise; a high fibre, low fat, low salt diet; and moderation of alcohol and caffeine intake should be encouraged, alongside the cessation or down-titration of interfering exogenous substances. Screening for secondary causes should be dictated by the initial clinical and biochemical evaluation, with appropriate investigations, treatments, and specialist referral made when needed (see box 6). A concerted effort should be made to maximise patient concordance with therapy, and, to assist this, interventions should range from promoting patient education, motivation, and “ownership” of their management programme to increasing the frequency of clinic visits, using a multidisciplinary team approach, advocating home blood pressure monitoring as a means of monitoring therapeutic response, and setting realistic goals in achieving blood pressure targets.

Drug intervention
Patients defined as having resistant hypertension will already be receiving or have received at least three antihypertensive drugs. NICE has recommended that this combination should ideally include drugs with potentially synergistic actions—that is, an ACE inhibitor or angiotensin receptor blocker plus a calcium channel blocker plus a thiazide-type diuretic (A+C+D). There is implied consensus with this recommendation in other guidelines (see box 1), but this has not always been explicitly stated in this stepwise fashion. The next question is what to add as the fourth agent to treat resistant hypertension.

To date, there have been no clinical trials that have specifically compared the various treatment options available. Moreover, it is unlikely that any one class of drug (in addition to A+C+D) will be ideal for every case of resistant hypertension. What is clear is that dual RAAS blockade—that is, the combination of an ACE inhibitor and an angiotensin receptor blocker—is not recommended because of a lack of evidence in resistant hypertension, and in light of the “no added value” and increased risk of adverse events seen in high risk patients enrolled in the ONTARGET trial. The best available, albeit weak, evidence (as reviewed in the recent NICE Clinical Guideline 127) is observational and supports the use of low dose spironolactone (that is, 25 mg once daily, increasing to 50 mg once daily) as the preferred fourth agent if the blood potassium concentration is ≤4.5 mmol/L. Spironolactone blocks the action of aldosterone at the mineralocorticoid receptor, thereby stimulating natriuresis and alleviating fluid overload. It can also overcome the phenomenon of “aldosterone rebound” seen with chronic RAAS antagonism, where aldosterone escapes blockade and levels return to baseline. In resistant hypertension patients, spironolactone has also been shown to induce the reduction of left ventricular hypertrophy irrespective of aldosterone status and reduce intra-cardiac volumes in those patients with hyperaldosteronism.

The main adverse effect associated with spironolactone use is breast tenderness and gynaecomastia. This...
is related to both dose and duration of therapy and can take many months or even years to develop. It is usually reversible when the drug is stopped. If the blood pressure response to spironolactone has been effective but the drug is stopped because of gynaecomasia, amiloride or eplerenone can be considered as a substitute. Both these drugs, however, are not as potent as spironolactone and so may require doses above the usual range prescribed. Hyperkalaemia is a risk when using any of these potassium sparing diuretics, especially in those patients with resistant hypertension who are already taking an ACE inhibitor or angiotensin receptor blocker (which is usually the case in these patients) and in individuals with chronic kidney disease or diabetes. Potassium levels should be monitored within two weeks of drug initiation. Subsequent monitoring will largely depend on the index result and whether dose adjustment has been necessary. Furthermore, hyponatraemia may also develop with long term use, especially in elderly patients and when potassium sparing diuretics are combined with pre-existing diuretic therapy.

Alternatively, if the blood potassium level is >4.5 mmol/L, intensification of thiazide-like diuretic therapy (that is, doubling of the dose of the existing thiazide-like diuretic) should be considered. If blood pressure remains poorly controlled despite further diuretic therapy, there is the option of adding an α or β blocker, but this guidance remains empirical in nature in the absence of robust clinical trial evidence.

Centrally acting agonists (methyl dopa and clonidine) or direct vasodilators (hydralazine and minoxidil) are further options. The potential roles of other agents such as endothelin receptor antagonists have yet to be clearly defined. Whatever the final combination of treatments, a patient with resistant hypertension is likely to be receiving at least four antihypertensive drugs daily, and some guidelines have recommended use of fixed combination therapies to reduce the number of tablets—there is some evidence that this may also improve adherence to treatment.

**FUTURE PERSPECTIVES**

A prospective epidemiological study is required to delineate the true prevalence, incidence, and prognostic implications of resistant hypertension, and consensus between national and international professional bodies is required on a universal definition of resistant hypertension to allow robust comparisons between future studies.

**Unanswered questions**

- Is there one class of drug that is commonly the most effective in resistant hypertension?
- What patient characteristics, if any, define which drug is likely to be the most effective?
- What are the ideal constituents of multitarget regimes in resistant hypertension? A prospective randomised controlled trial of different drug combinations is required
- Is there a role for routine plasma renin measurements to stratify drug treatment for resistant hypertension, and would this be cost effective? Is there a role for renin profiling in the management of resistant hypertension?
- Is there clinical benefit from chronotherapy (when one antihypertensive agent is taken at night rather than all being taken together in the morning)?
- What is the future role of device therapies in resistant hypertension management? Do they have an additive effect to antihypertensive drugs?
- What strategies are most effective in supporting adherence to drug regimens and lifestyle factors?
- Are there system based or team based strategies that can organise the health system to better identify, monitor, and treat resistant hypertension?

**Ongoing research**

- Studies of the effect of continuous positive airways pressure in patients with resistant hypertension second to obstructive sleep apnoea (ClinicalTrials.gov identifiers: NCT01508754 and NCT00929175)
- The BHS PATHWAY studies supported by the British Heart Foundation and the National Institute of Health Research Clinical Research Network. PATHWAY 2 focuses on resistant hypertension and is evaluating whether low dose spironolactone is usually the most effective step 4 treatment for resistant hypertension, in comparison with doxazosin or bisoprolol. The participants with resistant hypertension are well characterised and already treated according to NICE guidance with A+C+D. This study will also formally evaluate the value of plasma renin profiling in determining treatment responses in resistant hypertension (refer to www.bhsoc.org/cclinical Research.stm).
- The Resistant Arterial Hypertension Cohort Study (RAHyCo) (ClinicalTrials.gov Identifier NCT01083017) is investigating the epidemiology of resistant hypertension and evaluating the efficacy and feasibility of a standardised treatment regimen (including randomisation of two doses of chlortalidone). It is also studying two interventions in a group of non-compliant patients, and will study environmental and genetic variables of individuals with resistant hypertension within a family design. It plans to enrol 200 patients and is due to complete in April 2018.

**Device therapy**

Interest is growing in device therapy for resistant hypertension, with the objective of improving blood pressure control without resorting to further medication. Two techniques have recently been evaluated: percutaneous transluminal radiofrequency sympathetic denervation of the renal arteries and carotid baroreflex activation.
The former has generated the most interest, with several devices in development. Briefly, the Symplicity HTN-1 and HTN-2 trials have shown substantial blood pressure reductions in response to renal denervation, in the order of 30/15 mm Hg, maintained beyond two years on extended follow-up of the original study cohorts.12,13 It should be noted, however, that, although renal denervation resulted in improved blood pressure control, the patients continued to take antihypertensive drugs, albeit at a reduced number or dose in some patients. A key point is that renal denervation is not a “cure” for resistant hypertension. Further renal denervation therapy trials are ongoing, with devices at various stages of development.14

To date, there have been no safety concerns with renal denervation, in particular no evidence of significant renal artery stenosis or thrombosis in up to two years of follow-up.15,16 There is consensus that renal denervation procedures should be undertaken only in specialist centres with multidisciplinary specialist expertise in the assessment and treatment of complex hypertension (see box 7). The place of such therapies in the more routine treatment of resistant hypertension will ultimately be determined by longer term efficacy and safety data and cost effectiveness analyses.

What is the future of resistant hypertension treatment? The BHS Collaborative Research Working Party has initiated the Prevention And Treatment of resistant Hypertension With Algorithm guided therapY (PATHWAY) studies (see “Future perspectives” box), that will specifically address the most effective way to treat resistant hypertension. These, along with other studies, should answer some of the fundamental questions still outstanding. The results are eagerly awaited and will directly inform future treatment. 

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