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Diagnosis and management of resistant hypertension

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Learning objectives

- To understand the definition, prevalence and prognosis of resistant hypertension
- To describe the methods for effective diagnosis of resistant hypertension
- To review the treatment options for resistant hypertension, including lifestyle advice, pharmacological treatment and surgical intervention

Introduction

High blood pressure (hypertension) is one of the most important risk factors for cardiovascular disease,[1 2] which is a significant cause of morbidity and mortality worldwide.[3] Recent surveys from developed countries suggest that the prevalence of hypertension ranges from 20-30%, with 51-80% receiving treatment but only 27-66% with adequate blood pressure control.[4] One subset of uncontrolled hypertensives who do not respond to treatment are known as resistant hypertensives. This article will describe how resistant hypertension is defined, its prevalence and prognosis, methods to diagnose it effectively in routine practice and strategies to effectively manage patients diagnosed with the condition.

Definition of resistant hypertension

Resistant hypertension is generally defined as uncontrolled clinic blood pressure (>140/90 mmHg) after treatment with three or more antihypertensives.[5] In the UK, NICE guidelines specify that these three should include optimal doses of an ACE inhibitor (or an angiotensin receptor blocker), a calcium channel blocker and a diuretic.[6] However, there are some circumstances which preclude resistant hypertension, which must be ruled out before a formal diagnosis can be made. So called 'pseudo-resistant' hypertension can be caused by poor clinic blood pressure measurement technique, patient non-adherence to prescribed medication, patient intolerance to certain anti-hypertensive medications and white coat hypertension (where blood pressure appears high in the clinic but is controlled out-of-the-office on home or ambulatory measurements).[5]

Prevalence and prognosis

Most prevalence studies have been conducted in the United States using routine medical records and in that setting resistant hypertension is thought to be relatively common, affecting anywhere between 9-18% of patients with diagnosed hypertension (table 1).[7-13] However, most of these studies defined resistant hypertension by clinic blood pressure readings alone, so these estimates do not account for those with pseudo-resistant hypertension due to the white coat effect. Indeed, one study by de la Sierra *et al.,*[11] identified a prevalence of 12.2% on clinic readings alone, but 37.5% of these patients were found to have white coat hypertension after undergoing ambulatory blood pressure monitoring, reducing the true prevalence to 7.6%. Even this estimate did not account for those who are non-adherent to therapy. Thus, the true prevalence of resistant hypertension is likely to be lower than previously reported, but due to the complex nature of diagnosis, accurate estimates are difficult to establish.

Because of the difficulty in accurately diagnosing true resistant hypertension, few studies have examined its true prognosis: Daugherty *et al.,*[14] examined the prognosis of resistant hypertension whilst excluding patients deemed non-adherent to medication due to failure to collect medication prescription refills. In a population of 18,036 patients, those with resistant hypertension were found to have a 47% increased rate of death and cardiovascular disease (defined as all-cause mortality and incident cardiovascular events (nonfatal MI, congestive heart failure, stroke, or chronic kidney disease)) compared to non-resistant hypertensive patients. Another study by Pierdomenico *et al.,*[15] examined the prognosis of resistant hypertension in 742 patients, excluding those with white coat resistant hypertension. They demonstrated an increased rate of cardiovascular disease events of 2.9 times (compared to controlled hypertensive individuals) but this study was unable to account for patients who were pseudo-resistant due to non-adherence. Were such a study able to identify and follow-up patients with true resistant hypertension, it is likely that the associated cardiovascular risk would be higher than previously observed, since white coat hypertension in particular is likely to bias estimates towards lower associated risk.[16]

Examinations and diagnosis

Careful clinical examination of patients presenting with apparent resistant hypertension is required to avoid misdiagnosis due to pseudo-resistant hypertension (figure 1). In the first instance, clinic blood pressure should be measured carefully in a relaxed, temperate environment, with the patient sitting quietly, their arm outstretched and supported.[6] Where blood pressure is raised under these conditions, a second reading (and third if the latter reading is substantially different) should be taken and the lowest measurement recorded as the clinic blood pressure level.[6] Where clinic blood pressure remains raised in the clinic, patients should be referred for 24-hour ambulatory blood pressure monitoring to rule out the presence of white-coat resistant hypertension.[17] Patients with a daytime ambulatory blood pressure of >135/85mmHg or 24-hour average of >130/80mmHg should be considered uncontrolled on ambulatory monitoring (*i.e.* they do not display a white coat effect).

The final stage in diagnosis of true resistant hypertension is to confirm whether or not the patient is adhering to their prescribed medication. Non-adherence to medication is common amongst hypertensive patients, with estimates ranging from 7-48%.[18 19] Total or partial non-adherence is thought to account for between 12-66% of patients presenting with apparent resistant hypertension.[14 20-22] Detecting non-adherence can be challenging and traditional methods such as direct questioning and pill counts are known to provide unreliable estimates of true medication adherence.[23] The most commonly used approach in routine clinical practice is directly observed

dosing:[24] Blood pressure is measured before and after medication is directly observed being taken by a member of the clinical care team in a clinic setting, ideally using ambulatory blood pressure monitoring. Where a patient's blood pressure falls below 140/90mmHg (clinic) following directly observed dosing, non-adherence to medication can be assumed. Where blood pressure does not fall under observed dosing, a definitive diagnosis of resistant hypertension is likely but cannot be guaranteed. For example, some determined patients may hide the pills they have taken in their mouth and discard them once they have left the clinic.[24]

The 'gold-standard' measure of medication adherence is to take a urine sample after the patient has taken their medications and examine the sample for relevant drug metabolites using high-performance liquid chromatography-mass spectrometry.[20 22] This technique has been recently developed in the UK[20] and Germany[22] and has been shown to be effective at accurately detecting non-adherence to specific drugs types. It is increasingly being used in clinical practice in the UK although its availability is not yet widespread.

Treatment

Before deciding on the appropriate treatment for resistant hypertension, it is important to examine the possible causes of resistant hypertension. Evidence for the contribution of lifestyle factors such as excessive alcohol consumption, obesity and high salt intake towards manifestation of resistant hypertension is conflicting,[25-27] but most clinical guidelines recommend that patients are encouraged to eat a diet rich in fruit and vegetables and low in saturated fat, exercise regularly and lose weight, reduce their alcohol and sodium consumption and stop smoking.[28] Consumption of any exogenous substances which may contribute to resistant hypertension such as liquorice, non-steroidal anti-inflammatory drugs (NSAIDs) or recreational drugs (e.g. steroids, cocaine, yohimbine) should also be stopped.[29] Other secondary causes of apparent resistant hypertension may include chronic kidney disease, hyperaldosteronism, obstructive sleep apnoea, renal artery stenosis and target organ damage and these should be excluded.[29]

Pharmacological intervention

Treatment of resistant hypertension is focused on the addition of fourth-line therapy where blood pressure is not controlled by treatment with three drugs, described by NICE as A+C+D: *i.e.* an angiotensin-converting-enzyme (ACE) inhibitor or an angiotensin II receptor blocker (A), a calcium channel antagonist (C) and a thiazide or thiazide-like diuretic (D) (figure 2).[6] Until the recent publication of the PATHWAY-2 study,[30] the choice of the fourth-line agent was empirical, reflecting

the absence of randomised controlled trials comparing different options. Although the causes of resistant hypertension are poorly understood, one hypothesis is that it is caused by inappropriate sodium retention in the kidneys.[31] For this reason, NICE guidelines in the UK recommend spironolactone therapy as a fourth-line agent in patients with potassium of <4.5mmol/l who are likely to respond to a mineralocorticoid receptor blocker (figure 2).[6] For patients with potassium of >4.5mmol/l it is recommended that the existing diuretic (thiazide or thiazide-like) is doubled. Switching to a loop diuretic such as furosemide or bumetanide may be helpful if control is not achieved (figure 2).[6]

The PATHWAY-2 study[30] was conducted to establish whether Spironolactone was the most effective add on agent for resistant hypertension, determine whether plasma renin would predict the most effective treatment for individual patients and whether Spironolactone would be most effective in patients with low renin as a marker of sodium retention. This double-blind, placebo-controlled, crossover trial compared Spironolactone with two alternative fourth-line treatments targeting different pathogenic mechanisms: Doxazosin, an α1-adrenoceptor blocker which reduces peripheral resistance and the β1-adrenoceptor blocker Bisoprolol, which inhibits renin release and reduces cardiac output. A particular strength of the trial was the use of home monitoring to exclude white coat hypertension and directly observed therapy to exclude patients who were not taking their background medication.

Patients aged 18-79 years with seated systolic BP ≥140mmHg (≥135mmHg for diabetes) backed up with home readings of ≥135mmHg despite treatment for at least 3 months with maximally tolerated doses of three drugs were rotated through 12 weeks of once daily treatment with each of Spironolactone (25-50mg, 285 patients), Bisoprolol (5-10mg, 285 patients), Doxazosin modified release (4-8mg, 282 patients) and placebo (274 patients) in a randomised order. The dose was doubled after six weeks of each cycle and the primary outcome was the reduction in home blood pressure with spironolactone compared with placebo and then followed by comparisons with the other two agents. The average reduction in home systolic BP by spironolactone was superior to placebo (-8.70 mmHg [95% CI-9.72 to -7.69], p<0.0001), superior to the mean of the other two active treatments (doxazosin and bisoprolol; -4.26 [-5.13 to -3.38]; p<0.001) and superior when compared with the individual treatments; versus doxazosin (-4.03[-5.04 to -3.02];p<0.001 and versus bisoprolol (-4.48 [5.50 to -3.46];p<0001). Spironolactone was the most effective blood pressure-lowering agent throughout the distribution of baseline plasma renin but it was particularly effective in patients with lower renin levels. Reductions in eGFR were recorded with all of the treatments most likely

reflecting a reduction in renal perfusion pressure with blood pressure lowering. It is therefore important to monitor electrolytes and renal function in the weeks after initiation of spironolactone treatment, after drug escalation and periodically afterwards. Patients with eGFR <45 ml/min were excluded from PATHWAY-2 so there are no data regarding whether it is safe to use spironolactone in patients with resistant hypertension and CKD 3b or worse. Similarly, the study included predominantly white Caucasians so it not clear whether the results are transferable to other ethnic groups.

PATHWAY-2 has therefore established a clear hierarchy for drug treatment of resistant hypertension in which spironolactone is the most effective fourth-line agent in addition to A+C+D, provided that the potassium level is not >4.5mmol/l in which case intensification of existing diuretic therapy is recommended.[6] Bisoprolol and doxazosin are less effective alternatives for those intolerant of spironolactone. Spironolactone substantially increased the chances of achieving blood pressure control relative to the other two agents with almost 60% achieving BP control within 3 months of starting treatment. A significant dose response was observed with spironolactone suggesting that higher doses than 50mg might be even more effective.[30]

For those patients who are intolerant to Spironolactone, evidence-based treatment options are more limited but other potassium-sparing diuretics can be tried (provided the potassium is <4.5mmol/l) including Amiloride or Eplerenone; the latter acts in a similar way to Spironolactone but has less metabolic side effects. The impact of Amiloride on blood pressure in patients with uncontrolled blood pressure and an indication for diuretic treatment was examined in the recent PATHWAY-3 trial.[32] The study enrolled 440 patients to either Amiloride (10-20mg) alone, Hydrochlorothiazide (25-50mg) alone, or the combination Amiloride (5-10mg) + Hydrochlorothiazide (12.5-25mg) and followed patients up for 24 weeks. The trial observed significant reductions in home systolic blood pressure in all treatment groups, with the greatest reductions observed in the combination therapy arm of the trial (3.4 mmHg lower blood pressure reduction than Hydrochlorothiazide alone, p=0.007). The findings of PATHWAY-3 are yet to be published in full, but it is anticipated that the findings of this trial will become more widely adopted into routine clinical practice in the coming years. If a patient develops hyperkalaemia or deterioration in renal function on potassium-sparing diuretics, they must be stopped and alternative treatments include the use of beta-blockers, alpha-blockers or centrally acting agents such as Moxonidine.

When drug intolerance is an issue, a recent study by Antoniou *et al.,*[33] demonstrated significantly lower blood pressure at 12 month follow-up (by 17±5/9±3 mmHg) in patients with multiple antihypertensive drug intolerances through the use of sequentially initiated monotherapies, combinations of maximally tolerated doses or fractional tablet doses, liquid formulations, transdermal preparations and off-label tablet medications (figure 2). This was a small (55 patients), non-randomised trial and whilst promising, should not be considered definitive evidence. Indeed, most alternative treatment approaches in resistant hypertension have a much weaker evidence base to support their use in clinical practice, and should therefore be used with caution, only being attempted after all other options have been exhausted.

Due to availability of resources, it is anticipated that these alternative approaches to treatment would be best delivered in the context of specialist hypertensive clinics, rather than routine Primary Care. Medical treatment of resistant hypertension is often complex, involving several changes to drug therapy and doses, careful monitoring of renal function and electrolytes, assessment of adverse effects and intolerances and frequent visits to the clinic. Achieving improved blood pressure control in these patients is challenging and is best achieved with a close relationship between medical and nursing specialists in hypertension, pharmacists and individual patients with resistant hypertension.

Interventional therapies

Renal Denervation

Renal sympathetic activation increases renal vascular resistance, reduces renal blood flow causes renin release and increases sodium reabsorption, all of which will potentially increase blood pressure. Increased sympathetic outflow has been implicated in resistant hypertension and renal denervation has been proposed as an effective method of interrupting sympathetic supply to the kidney resulting in reduced blood pressure.[34] Renal denervation involves disruption of renal sympathetic nerves along the renal artery by radio-ablation catheters inserted through the femoral artery.[34]

Early results from studies using denervation to treat patients with resistant hypertension were encouraging (table 2). In the Symplicity HTN-1 trial,[35] 45 patients receiving a mean number of 4.7 antihypertensive drugs with uncontrolled hypertension underwent catheter-based renal denervation. A significant reduction of systolic and diastolic blood pressures of 14 and 10 mmHg, respectively ($p<0.026$) were reported at 4 weeks. Even greater reductions were noted at 12 months (27/17 mmHg ($p<0.026$)) and 36 months (33/19 mmHg ($P<0.01$)) but long term data were only

available for 24 patients.[36] This was followed by the Symplicity HTN-2 trial,[37] were 106 patients were randomised to have renal denervation or usual care (control). After 6 months of treatment, office systolic and diastolic blood pressure was reduced by 32/12 mmHg (P<0.0001), home blood pressure by 20/12 mmHg (P<0.001) and ambulatory blood pressure by 11/7 mmHg (P<0.007) in the renal denervation group, but only for 20 patients.

These promising results were followed by the first trial in which patients were blinded to the treatment allocation (undergoing a sham procedure): the Symplicity HTN-3 trial (table 2).[38] A total of 535 patients with severe resistant hypertension were randomly assigned in a 2:1 ratio to undergo renal denervation or a sham procedure. The study failed to achieve its primary and secondary efficacy end points. The mean reduction in office blood pressure was 14.1 mmHg with denervation and 11.7 mmHg with placebo at 6 months and was highly significant for both groups compared with baseline (P<0.001) but not between-groups (2.4 mmHg, p=0.26). Similarly, the mean systolic blood pressure difference in 24-hour ambulatory blood pressure at 6 months was only 2.0 mmHg and again not significant (P=0.98). The safety of the procedure was confirmed with minimal procedural complications and preservation of renal function but many centres suspended use when the results were released.

The lead author on Symplicity HTN-2 has subsequently argued that the degree of denervation in Symplicity HTN-3 may have been unsatisfactory in some patients, contributing the negative outcome.[39] Factors causing variation in effectiveness may have included operator inexperience (many had no prior experience of the technique) and failure to ablate both the distal renal artery and the full circumference of both renal arteries.[40] In keeping with this, the number of ablations per patient was significantly related to the degree of blood pressure reduction.[40]

A further criticism of SYMPLICITY HTN-3 was the assessment of adherence to antihypertensive treatment prior to enrolment and during the course of the study.[41] Although patients were asked to keep a medication diary, adherence to medication was never formally tested by directly observed dosing[24] or by urine antihypertensive drug assay,[20 22] as is common in routine clinical practice.[42] Although a *post hoc* analysis eliminating those with medication changes did not affect the primary outcome or pre-specified secondary outcomes, a substantial decrease in blood pressure in the sham group might suggest a change in patient behaviour despite self-reported documentation of medication adherence or changes in prescribed antihypertensive medication during the course of trial participation.[40]

If renal denervation is to be adopted as a routine clinical procedure, the ability to identify and target those patients who are more likely to respond to denervation would be a major advantage. Results from SYMPLICITY HTN-3 have indicated certain patient-related characteristics which may predict a favourable response to the procedure, such as high baseline systolic blood pressure (≥180 mmHg), age <65 years, and eGFR ≥60 ml/min/1.73 m^2. However, until further robust, randomised prospective studies are conducted taking these factors into account, and demonstrating clear benefit, such a procedure cannot be recommended for routine clinical practice.[41]

Carotid baroreceptor stimulation

Compensatory changes in sympathetic nervous system function are an important component of primary hypertension. Decreased parasympathetic and increased sympathetic tone increase peripheral vascular resistance, reduce renal blood flow and increase sodium retention. A surgically implantable device for the treatment of resistant hypertension (the Rheos System) has been developed to administer baroreceptor activation therapy (BAT) via electrical stimulation of the carotid baroreceptors.[43] The theory is that stimulation of the carotid baroreceptors will modulate sympathovagal balance that is commonly deranged in patients with resistant hypertension.[43]

The Rheos Pivotal Trial was a randomised double blind controlled trial that evaluated the effects of BAT over 12 months in 322 patients with resistant hypertension.[44] All eligible subjects were implanted with the Rheos System which consists of a pulse generator and leads that are tunnelled subcutaneously to each carotid sinus. Once the device was activated a month later, 265 patients were randomised in a 2:1 ratio to receive BAT immediately (Group A) or after a six month deferral (Group B). The trial was designed to demonstrate the efficacy and safety of the Rheos device via five pre-specified co-primary end points for efficacy and safety (acute efficacy, sustained efficacy, procedural safety, BAT safety and device safety). The trial did not meet the procedural safety and the short term efficacy end points. The responder analysis at six months yielded 54% responders in Group A (device on) and 46% responders in Group B (device off) which did not represent a significant difference. The procedural safety related to the placement of the carotid lead and involved transient (4.4%) or permanent (4.8%) nerve injury that occurred at the time of implant. On the other hand, mean reductions in systolic blood pressure of up to 35 mmHg were observed at 12 months in all patients participating in the trial. Additionally, over 50% of patients were able to achieve a systolic blood pressure of ≤140 mmHg.

These reductions are comparable to the results of the DEBuT (Device Based Therapy) feasibility study in which systolic blood pressure was reduced from 180 mmHg by 30 mmHg after 12 months of BAT in 26 subjects.[45] In addition, long term open label, non-randomised follow up of the Rheos Pivotal Trial suggested that up to 76% of the initial 322 patients implanted qualified as clinically significant responders with a mean blood pressure reduction of 35/16 mmHg.[46] Medication use was reduced by the end of the randomised phase and remained lower during the follow up period of between 22 to 53 months; 55% achieved target blood pressure.[46] These longer-term observations have involved limited number of patients and further data on larger numbers of patients are needed to confirm the efficacy and safety of the carotid baroreceptor stimulation. Even if the procedure is proven to be effective, it is not without limitations, including the need for surgery (with general anaesthetic) and procedural complications.

Central arteriovenous anastomosis

A novel way of treating resistant hypertension is to add a low-resistance compartment to the arterial tree by creating a central arteriovenous anastomosis between the distal iliac vein and artery with an arteriovenous coupler device-the ROX coupler.[47] The ROX CONTROL HTN study[48] was one of the first randomised trials of this procedure, enrolling 83 patients with resistant hypertension to either continued pharmacological treatment plus placement of the arteriovenous coupler (n=44) or usual care (n=39). After 6 months of follow up, significant reductions in office systolic blood pressure were seen in patients in the arteriovenous coupler group (mean reduction 26.9 mmHg (SD 23.9) $p<0.0001$) mmHg but not in the control group. Similarly, mean 24-hour ambulatory systolic readings were reduced in the intervention group (13.5 mmHg (SD 18.8) $p<0.0001$) but not in controls. Reductions in diastolic pressure were also more pronounced in the arteriovenous coupler group than in the control group. Complication rates were high, however, with 12 of the 42 developing late ipsilateral venous stenosis requiring intervention with venoplasty or stenting in all affected patients. These preliminary results are of interest but limited due to the absence of a sham-control group and formal assessment of adherence. The complication rate is also of concern.[49] Further studies will clarify whether the ROX coupler is a realistic option for patients with resistant hypertension

Conclusions

Resistant hypertension is thought to affect up to 1 in 6 patients with treated hypertension. Diagnosis is complex and requires carefully measured clinic blood pressure and investigations to exclude white coat hypertension and patient non-adherence to therapy. New evidence supports the use of

Spironolactone as the first choice treatment in patients with resistant hypertension who already on three agents (including a diuretic).[30] In patients who remain uncontrolled on optimal treatment, there are a number of alternative treatment options and surgical procedures which can be considered, including prescription of loop diuretics or centrally acting agents, alternative drug formulations (liquid form or transdermal preparations) which allow lower than normal doses to be prescribed, renal denervation, carotid baroreceptor stimulation and central arteriovenous anastomosis. However, the evidence supporting each of these is limited and in some cases, conflicting and therefore more prospective randomised controlled trials are required before any can be adopted into routine clinical practice.

Key points

- Patients with uncontrolled blood pressure on three or more medications should be suspected as having resistant hypertension.
- In patients with suspected resistant hypertension, it is important to exclude white coat hypertension and patients who are non-adherent to treatment.
- Spironolactone is the most effective treatment at lowering blood pressure in patients with resistant hypertension who already on three agents (including a diuretic).
- The benefits of renal denervation, carotid baroreceptor stimulation and central arteriovenous anastomosis remain inconclusive and these procedures should not be adopted in routine clinical practice.

Competing interests

JS holds a Medical Research Council Strategic Skills Post-doctoral Fellowship. RJMcM holds an NIHR Professorship and leads the self-management theme of the NIHR Oxford CLAHRC. The views and opinions expressed are those of the authors and do not necessarily reflect those of the MRC, NHS, NIHR, or the Department of Health. The authors declare no other competing interests.

Contributions

JPS and UM wrote the first draft. All authors subsequently refined the manuscript and approved the final version. RJM is the guarantor.

MCQs

1. **What is the definition of resistant hypertension?**
   - **A. A patient with uncontrolled blood pressure on 3 or more medications**
   - B. A patient who is non-adherent to medication
   - C. A patient with blood pressure >170/100 mmHg
   - D. A patient who refuses to have their blood pressure measured
   - E. A patient with clinic blood pressure >140/90 mmHg but a home blood pressure or <135/85 mmHg

The correct answer is A. An individual with resistant hypertension may have a blood pressure of >170/100 mmHg but is not classed as 'resistant' unless they are taking three or more medications. Non-adherence to medication (answer B) and white coat hypertension (answer E) are exclusions for resistant hypertension.

2. **What should be excluded before making a formal diagnosis of resistant hypertension?**
   - A. The white coat effect
   - B. Non-adherence to medication
   - C. Normal clinic blood pressure measured under controlled conditions
   - **D. All of the above**
   - E. None of the above

The correct answer is D. The presence of white coat hypertension, patient non-adherence to treatment (or intolerance to certain anti-hypertensive medications) and poor clinic blood pressure measurement technique can all result in 'pseudo-resistant' hypertension.

3. **What is the best way to test patients for non-adherence to therapy?**
   - A. Ask patients to be honest
   - B. Pill counts
   - C. Observed dosing
   - **D. Analysis of urine samples for drug metabolites**
   - E. Analysis of blood samples for drug metabolites

The correct answer is D. Pill counts and observed dosing are both recognised methods of examining non-adherence to therapy but have been shown to be unreliable estimates of true medication adherence. They may be used where high-performance liquid chromatography-mass spectrometry is not available for analysis of drug metabolites in the urine. Even if this approach is available, it should not be considered to be perfect, since patients may be adherent most of the time but appear non-adherent if they fail to take their medications before giving the urine sample.

4. **What is the best fourth-line treatment in patients with resistant hypertension on three drugs (including a diuretic)?**
    A. Bisoprolol
    B. Doxazosin
    C. Spironolactone
    D. Nifedipine
    E. Ramipril

The correct answer is C. Bisoprolol or Doxazosin may be considered if the patient does not tolerate Spironolactone, or if they have high levels of serum potassium (>4.5mmol/l). Ramipril is an ACE inhibitor and should be considered as a first line therapy for hypertension (unless the patient of black ethnicity or aged 55 years or over). Nifedipine is a calcium channel blocker and should be consider as a second line therapy before resistant hypertension is considered.

5. **What does renal denervation involve?**
    A. Disruption of carotid plexus by radio-ablation catheters inserted through the femoral artery.
    B. Disruption of renal sympathetic nerves along the renal artery by radio-ablation catheters inserted through the femoral artery.
    C. Disruption of renal blood supply using catheters inserted through the femoral artery.
    D. Disruption of renal sympathetic nerves using an arteriovenous coupler device.
    E. Implant a pulse generator with leads that are tunnelled subcutaneously into the carotid sinus.

The correct answer is B. Disruption of carotid plexus (answer A), or the renal blood supply (answer C) will not denervate the renal sympathetic nerves. The use of an arteriovenous coupler device (answer

D) or an implantable pulse generator in the carotid sinus (answer E) are other interventional therapies which have been proposed as potential treatments for patients with resistant hypertension, but do not involve renal denervation.

6. **Which surgical procedure is recommended for patients who remain uncontrolled on optimal treatment?**
    A. Renal denervation
    B. Carotid baroreceptor stimulation
    C. Central arteriovenous anastomosis
    D. Any of the above – all procedures have been found to be equally effective
    E. None of the above – the evidence supporting any one procedure remains inconclusive

The correct answer is E. All of the answers (A-C) have been proposed as potential therapies for patients with resistant hypertension, but as yet, none have been shown to be effective over and above pharmacological treatment in properly conducted, blinded, randomised controlled trials. Therefore, they should not be recommended for use in routine clinical practice.

Figures and tables

Figure 1. Stages of diagnosis of resistant hypertension

BP=blood pressure

Figure 2. Options for pharmacological treatment of resistant hypertension

This algorithm is empirical and represents possible treatment options to consider, rather than definitive evidence-based recommendations. Changes to drug therapy and doses should be done with careful monitoring of renal function and electrolytes, assessment of adverse effects and intolerances via frequent visits to the clinic.

A+C+D refers to the NICE treatment algorithm of step-wise up-titration of drug therapy: step 1 – angiotensin-converting-enzyme (ACE) inhibitor or an angiotensin II receptor blocker (A); step 2 – a calcium channel antagonist (C); step 3 – a thiazide or thiazide-like diuretic (D).

All suggested therapies are given with starting doses which can be up-titrated prior to changing drug type.

Table 1. Studies examining the prevalence of resistant hypertension

Study	Country	Study type	Population	Total population	Definition of resistant hypertension	Prevalence
Chia & Ching (2014)[13]	Malaysia	Routine medical records	All patient with hypertension	1,217	BP ≥140/90mmHg on ≥3 drugs (including a thiazide diuretic)	8.8% (95% CI 7.3-10.5)
Persell (2011)[7]	United States	Routine medical records	Non pregnant adults with hypertension	5,230	BP >140/90mmHg on 3 drugs or any level of BP ≥4 drugs	8.9% (95% CI 7.7-10.1)
McAdam-Marx *et al.,* (2009)[8]	United States	Routine medical records	Adults with hypertension	29,474	BP ≥140/90mmHg (≥130/80 mmHg for those with diabetes & CKD) and on ≥3 drugs (including a thiazide)	9.1% (95% CI 8.7-9.4)
Egan *et al.,* (2011)[9]	United States	Routine medical records	Adults with hypertension	3,555	BP >140/90mmHg on ≥3 drugs or any level of BP on ≥4 drugs	11.8% (95% CI 10.7-12.9)
Sim *et al.,* (2013)[10]	United States	Routine medical records	Adults with hypertension	470,386	BP >140/90mmHg on ≥3 drugs or any level of BP on ≥4 drugs	12.8% (95% CI 12.7-12.9)
De la Sierra *et al.,*[11]	Spain	ABPM registry	Treated adults with hypertension	68,045	BP ≥140/90mmHg on ≥3 drugs (including a thiazide diuretic)	12.2% (95% CI 11.9-12.4)
Egan *et al.,* (2013)[12]	United States	Routine medical records	Adults with hypertension with ≥2 clinical visits and ≥1 medication prescribed	468,877	BP >140/90mmHg on ≥3 drugs or any level of BP on ≥4 drugs	18.0% (95% CI 17.8-18.1)

BP=Blood pressure; ABPM=Ambulatory blood pressure monitoring; CI=Confidence interval

Table 2. Trials examining the efficacy of renal denervation in resistant hypertension

Study	Year	Total population	Mean age (years)	Sex (% female)	Intervention group	Control group	Follow-up	Primary outcome	BP change in intervention group	BP change in control group	Difference
SYMPLICITY HTN-1	2009	45	58±9	20 (44%)	Catheter-based renal denervation (n=45)	None (non-randomised)	12 months	Assessment of periprocedural and long-term safety	-16/11 mmHg	n/a	n/a
SYMPLICITY HTN-2	2010	106	58±12	45 (42%)	Catheter-based renal denervation (n=52)	Usual care (n=54)	6 months	Clinic systolic BP at 6 months	-32/12 mmHg	1/0 mmHg	33/11 mmHg (p<0·0001)*
SYMPLICITY HTN-3	2014	535	57	210 (39%)	Catheter-based renal denervation (n=364)	Sham surgery control (n=171)	6 months	Clinic systolic BP at 6 months	-14/7 mmHg	-12/5 mmHg	2/2 mmHg (p=0.26)*

BP=Blood pressure;

*Systolic blood pressure comparison

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