Hypertension is one of the most commonly encountered conditions in general practice. While most patients respond to one or more of the common antihypertensive agents, a significant number continue to have blood pressure measurements above targets despite our best efforts. Such ‘difficult-to-control’ hypertension represents a significant clinical challenge. In this article we discuss possible approaches to tackling difficult-to-control hypertension.

How common is the problem?
Up to a third of patients with known hypertension are not controlled to target. While the introduction of QOF targets improved the rates of detection and treatment of hypertension, more still needs to be done. Current joint British Hypertension Society (BHS) and National Institute for Health and Clinical Excellence (NICE) guidelines suggest blood pressure treatment targets of <140/85mmHg for most patients, with tighter targets of <130/80mmHg for patients with diabetes.

Other groups of patients, such as those with chronic renal disease, may also benefit from tighter blood pressure treatment targets to reduce progression of their disease.

Treatment targets are to some extent arbitrary as there is benefit in reducing blood pressure further in many patients.

The UK blood pressure treatment guidelines are currently under review and it is possible that lower treatment targets may be suggested in the revised version.

When should we describe hypertension as difficult to control?
Hypertension could be described as difficult to control for many reasons. The standard definition of resistant hypertension is blood pressure that remains above target despite treatment with optimum doses of three antihypertensive agents, usually ACE inhibitor/angiotensin-II receptor blocker (ARB) + calcium-channel blocker (CCB) + thiazide diuretic (see Figure 1).

However, in addition to resistant hypertension, there are many other scenarios in which hypertension...
becomes difficult to control. These include nonadherence with medication, patients intolerant of several antihypertensive medications due to side-effects, those with periods of hypotension alternating with hypertension, and those with white-coat hypertension, where assessment of treatment efficacy in the normal clinic setting becomes difficult.

What are the possible causes?

Some causes of difficult-to-control hypertension are listed in Table 1. Nonadherence with antihypertensive medications is probably common and should be explored in any patient with difficult-to-control hypertension. Witnessed medication administration sometimes sheds light on this but is time-consuming. Accurate blood pressure measurement using a validated measurement device is important, as is the use of the correct size of arm cuff (see Figure 3). White-coat effect can be detected using ambulatory or home blood pressure monitoring.

The effects of concomitant medications on blood pressure control should also be considered, eg combined oral contraceptives. Further thought should also be given to whether there is an underlying secondary cause for the hypertension (see Table 2). Around 5 per cent of patients have a secondary cause, which is more likely to be found in younger patients and those with severe hypertension. For example, persistent hypokalaemia may prompt a search for aldosteronism, while sweating, headaches and palpitations may suggest a phaeochromocytoma. In these cases, preliminary investigations may include plasma renin and aldosterone levels, or urinary catecholamines or metanephrines, respectively.

However, if there is suspicion of a secondary cause of hypertension, referral to a hypertension clinic for specialist investigation is appropriate.

Intolerances to single antihypertensive medications are common. However, a significant number of patients have problems with almost every different class of antihypertensive that is tried. In such cases, psychological assessment of their illness behaviour may be helpful.

In general, ARBs are the best-tolerated antihypertensive agents, with a similar side-effect profile to placebo in most patients, and may be the best choice of therapy in these patients.

Adding in vs increasing the dose

As a general rule it is always more effective to add in another antihypertensive than to increase the dose of a single agent. A recent meta-analysis suggested that while adding a second class of antihypertensive agent has an additive effect on decreasing blood pressure, doubling the dose of a single antihypertensive only resulted in one-fifth of the equivalent effect. Increasing the dose of ACE inhibitor or ARB does not result in an increased incidence of side-effects, unlike other antihyperten-
sive agents such as beta-blockers, CCBs and thiazide diuretics. Combining different antihypertensive classes may be the most effective approach, but it is also true that an adequate dose of drugs inhibiting the renin-angiotensin system can be achieved without necessarily increasing side-effects.

Management of difficult-to-control hypertension

True resistant hypertension is common and is thought to be mainly due to a relative excess of sodium.

In a recent study, dietary salt restriction was very effective in lowering blood pressure in patients with resistant hypertension. A salt-restricted diet resulted in decreases in office systolic and diastolic blood pressures of 22.7 and 9.1mmHg respectively, compared with a high-salt diet. Significant differences were also seen in 24-hour ambulatory blood pressures (see Figure 1). Therefore, nonpharmacological approaches are important in the management of difficult-to-control hypertension.

Current treatment guidelines suggest that patients who remain uncontrolled despite treatment with adequate doses of three different antihypertensive agents (usually A+C+D, see Figure 2) should receive further therapy with more diuretic, such as a potassium-sparing diuretic or loop diuretic, an alpha-blocker or a beta-blocker. However, there is limited evidence to guide choice of drug therapy at this stage.1

Additional diuretic therapy is probably the favoured approach in most cases due to the relative sodium excess in these patients. Low-dose spironolactone (12.5-50mg daily) appears to be effective in resistant hypertension.7 Newer agents such as endothelin antagonists also hold promise.8

The BHS has recently embarked upon a large British Heart Foundation (BHF)-funded research study to find the best next treatment in patients with resistant hypertension (PATHWAY-2 study). Patients entering the study are rotated through add-on treatment with bisoprolol, spironolactone, doxazosin and placebo in a randomised, double-blinded design, and factors determining drug response including renin and haemodynamic measures are assessed at baseline and on each therapy.

In general, a similar blood pressure reduction is achieved with the addition of each new antihypertensive agent. Our current first-line approach in most patients with resistant hypertension is to add further diuretic – often a potassium-sparing diuretic such as spironolactone or amiloride. If the patient has reduced glomerular filtration rate (GFR, <50-60ml per minute), loop diuretic therapy may be preferable to thiazide as the latter becomes ineffective at lower GFRs, although metolazone (Metenix) may retain efficacy (with careful monitoring). Other options include the addition of alpha blockade, beta blockade or the direct renin inhibitor aliskiren (Rasilez). Centrally acting drugs such as the imidazoline receptor agonist moxonidine or methyldopa may be useful in selected cases, although the side-effect of depression is limiting in the use of methyldopa.

Very difficult-to-control hypertension may respond to the vasodilator minoxidil (Loniten); however, this would usually be introduced under specialist supervision and

Table 1. Possible causes of difficult-to-control hypertension

- nonadherence with antihypertensive medications
- underlying secondary cause, eg renal artery stenosis, pheochromocytoma (see Table 2)
- multiple drug intolerances
- unresponsive to chosen antihypertensive agents
- alternating hypertension and hypotension
- concomitant medications affecting blood pressure, eg NSAIDs, COCs
- excessive salt intake – dietary, drug formulations, eg effervescent painkillers
- white-coat effect
- use of undersized arm cuff for blood pressure measurement

Figure 3. Blood pressure cuffs. The correct size of arm cuff should be used: a cuff that is too small will result in overestimation of a patient’s blood pressure.
needs to be combined with a loop diuretic and beta blockade to counteract the fluid retention and tachycardia. Minoxidil is unacceptable to many women as it causes marked hirsutism.

As stated above, the principal reason for true resistant hypertension is usually sodium retention. Under specialist supervision, combined diuretic therapy (thiazide plus loop diuretic, spironolactone, amiloride or metolazone) can be very effective at blood pressure control but careful monitoring of electrolytes and volume status is required to use such regimens safely.

Which patients should be referred to secondary care?

Effective blood pressure reduction has repeatedly been shown to reduce the risk of vascular events. A reasonable approach would be to refer any patients in whom blood pressure remains uncontrolled despite treatment with at least three antihypertensive agents, patients in whom a secondary underlying cause is suspected, and those in whom multiple drug intolerances or white-coat hypertension are making treatment choices and assessment difficult. Lifestyle factors and adherence should be addressed in all patients.

Conclusions

Hypertension management remains a major challenge despite the range of antihypertensive agents available to us. Current treatment guidelines suggest approaches to the management of difficult-to-control hypertension, but much of this lacks an evidence base at present. The ongoing PATHWAY-2 study of resistant hypertension treatment in the UK will help to address this issue.

Meanwhile, salt restriction and further diuretic therapy appear to be the most helpful approaches to managing patients with difficult-to-control hypertension.

References


Dr Mackenzie is honorary consultant physician and Thomas MacDonald is professor of clinical pharmacology in the Hypertension Research Centre, University of Dundee

Table 2. Causes of secondary hypertension

- renal parenchymal disease
- renovascular disease
  atherosclerotic renal artery stenosis
  fibromuscular dysplasia
- hyperaldosteronism
  Conn’s adenoma
  bilateral adrenal hyperplasia
- phaeochromocytoma
- Cushing’s disease
- hyperparathyroidism
- coarctation of aorta
- medications, eg COCs, sympathomimetics, NSAIDs, ciclosporin
- excessive liquorice ingestion
- sleep apnoea

Table 3. Doses of commonly used antihypertensive medications above which the authors may prefer to add another agent rather than further increase dose

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CPD: Learning into Practice

Identify patients on your list or in the practice with hypertension not controlled to target BPs. Then identify those that are on 3 or more antihypertensive drugs.

Decide how many you can reasonably look at in more detail.

For each patient, work out a plan for the actions that might be taken at their next review to identify why they have uncontrolled hypertension and what might be done to improve control.

- Can you identify why they are not controlled to target?
- Do they have resistant hypertension?
  - Have they had an ambulatory BP measurement?
  - Do you need a larger cuff size to measure their BP accurately?
  - Are they collecting their prescriptions regularly (adherence)?
- Could they have a secondary cause of their hypertension?
  - What blood tests have they had? What tests might you do?
  - Have they been referred?

Consider reviewing the records of this set of patients in (say) 6 months’ time to see if any improvements have been made to hypertension control.

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