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# How to diagnose and manage resistant hypertension

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**Abstract**
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FEATURE

# How to diagnose and manage resistant hypertension

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*The number of truly drug-resistant hypertensive patients is small if careful attention is paid to blood pressure measurement, lifestyle measures are instituted and treatment is adjusted as required. An effective drug combination for the treatment of resistant hypertension is an ACE inhibitor (or angiotensin II receptor blocker), a calcium channel blocker and a thiazide-like diuretic, with possibly the addition of a fourth drug.*

## Key points

- **Around half of patients on antihypertensive treatment have blood pressures above target. However, only about one in three of these patients are truly treatment resistant.**
- **Apparent treatment resistance can be avoided by careful attention to blood pressure measurement, avoiding therapeutic inertia, careful choice of an effective and well-tolerated regimen, and by working together with the patient to implement lifestyle measures and maximise compliance with an antihypertensive regimen.**
- **Some old drugs retain their usefulness in the setting of resistant hypertension, and newer innovations have not shown unequivocal benefit.**

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Resistant hypertension is generally defined as the situation that exists when blood pressure remains above target (usually 140/90 mmHg, or 130/80 mmHg in individuals with diabetes) despite the use of at least three antihypertensive drugs in maximum tolerated doses. Resistant hypertension is but one of many reasons for treatment failure in hypertension.

Hypertension is common and has serious consequences, and blood pressure is often above desired levels in patients treated for the condition. However, most of these inadequately treated patients will not be truly resistant to antihypertensive drug treatment.

The World Health Organization estimates that around one in three deaths globally (about 17 million in 2008) are from cardiovascular disease, with the majority of these (9.4 million) being attributable to hypertension.[1] Hypertension is held responsible for around 45% of deaths due to heart disease and about 51% of deaths due to stroke. Worldwide, about 40% of adults over 25 years of age are hypertensive, with the highest prevalence in low-income countries.

In Australia, about 30% of those aged 25 years and older are hypertensive, a prevalence that is similar to that reported in the USA.[2,3] A recent study of people aged over 60 years in Melbourne and rural Victoria showed that 52% of those on antihypertensive treatment had blood pressures of more than 140/90 mmHg.[4] The most recent National Health and Nutrition Examination Survey (NHANES) in the USA found that 48% of hypertensive patients had blood pressure greater than 140/90 mmHg on treatment.[3] Thus only half of treated patients are adequately controlled. Observational

data in the general population indicate that control of blood pressure is the key factor in reducing the excess mortality risk in this group, confirming results from numerous prior randomised trials that were more selective in their inclusion criteria.[5]

This article discusses the criteria for hypertension being considered treatment resistant, the reasons this occurs and how patients can be treated. The flowchart on this page summarises the diagnosis and treatment of resistant hypertension.

## Criteria for determining treatment resistance

Criteria for determining whether hypertension is resistant to treatment are relative, decided by consensus and have changed over time. Key elements contributing to the decision are the level of blood pressure that should be attained and the minimum treatment that should be prescribed (and taken) before hypertension is declared to be treatment resistant.

Initial suggestions were that blood pressure should be clearly above target, and a level of 150/100 mmHg was chosen arbitrarily.[6] Recent consensus is that any blood pressure above target is sufficient to indicate resistance. Broad agreement exists for the use of at least three drugs, one of which should be a diuretic, before hypertension can be considered to be treatment resistant.[6,7]

The most detailed recommendation comes from the UK National Institute for Health and Care Excellence (NICE) guidelines for the clinical management of primary hypertension in adults.[8] These guidelines offer explicit directions for initiation and escalation of treatment, with the recommendation that a three-drug regimen includes an ACE inhibitor or angiotensin II receptor blocker, a calcium channel blocker and a thiazide-like diuretic.

## Reasons for apparent antihypertensive drug resistance

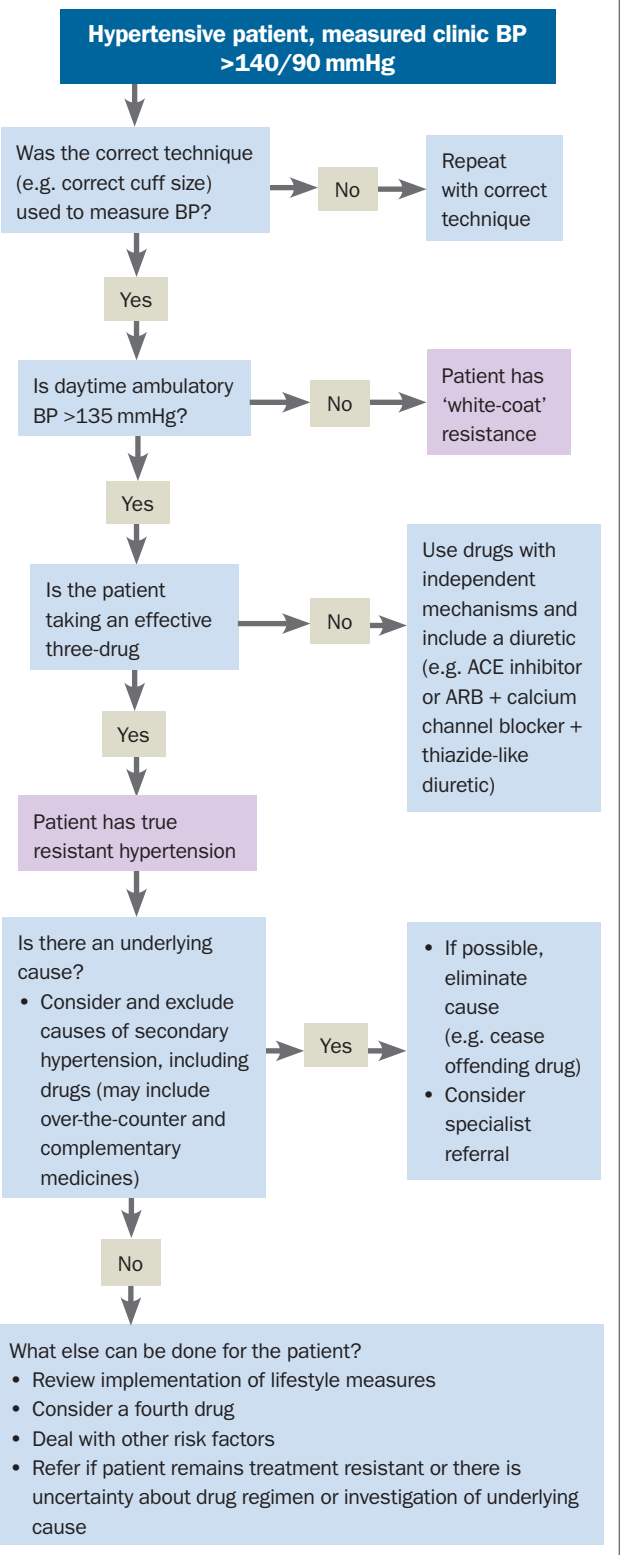
### Incorrect blood pressure measurement

The technique and method of measuring blood pressure is important to ensure that blood pressure is truly above target.

Measuring blood pressure in obese subjects can be quite a challenge.[9] The use of a cuff that is too small in obese patients results in overestimation of blood pressure.[10] Occasionally, it may not be physically possible to have an appropriately wide cuff in a short, obese arm; in such a situation, the use of a cuff around the forearm can provide a solution.[10]

Typically, office blood pressure has been utilised to define treatment resistance. The recognition of 'white-coat' hypertension in other contexts prompted the use of ambulatory blood pressure to evaluate resistant hypertension. One study found that patients with elevated blood pressure in the office but not on ambulatory measurements (i.e. white-coat hypertension) had similar rates of cardiovascular events to those whose blood pressure had fallen to acceptable levels on treatment.[11] Those who had elevated blood pressure on ambulatory measurements as well as office measurements (true resistant hypertension) had more cardiovascular events than those with acceptable blood pressure on treatment, whereas those with elevated ambulatory but adequate office pressure (masked

**Resistant hypertension: diagnosis and management**




Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; BP = blood pressure.

**1. Causes of secondary hypertension**

- Obstructive sleep apnoea (especially common in resistant hypertension)
- Primary aldosteronism
- Cushing's syndrome
- Renal parenchymal disease
- Renal artery stenosis
- Phaeochromocytoma
- Drugs or chemicals (see Box 2)

hypertension) had an intermediate rate of cardiovascular events.[11] Other studies have reported similar findings.[12,13] Thus a strong case can be made for measuring ambulatory pressure when resistant hypertension is suspected.

If ambulatory blood pressure is unavailable, home blood pressure measurement is a reasonable substitute. It should be noted that the ambulatory equivalent of a clinic blood pressure of above 140/90 mmHg is a daytime ambulatory blood pressure of above 135/85 mmHg.[14] Using a cut-off level of 140/90 mmHg on ambulatory measurements will misclassify patients as being adequately treated when they are not.

### Treatment inertia

Agreement about the minimum treatment requirement before hypertension is declared resistant discloses a large group of patients who are neither controlled nor on a three-drug regimen. For the most part, these circumstances indicate treatment inertia, a problem to which both patients and doctors contribute. A recent study conducted in Melbourne and rural Victoria found that just over half of treated hypertensive subjects had blood pressures of 140/90 mmHg or higher and nearly 80% of these were on one or two antihypertensive drugs.[4] Of even greater concern, only 20% of patients whose blood pressure on treatment was 160/100 mmHg or higher were on three drugs. Uncontrolled hypertension often has more to do with treatment inertia than with treatment resistance.

### Drug side effects and noncompliance

At times patients complain of intolerable drug side effects, making it difficult to find a regimen that is both effective and well tolerated. If many medications elicit symptoms suggestive of hypotension it would be important to consider and exclude 'white-coat resistance'.

Occasionally, it may have to be accepted that, at least from the patient's perspective, the cost in side effects is not worth the gain. The patient might decide that daily symptoms incurred in the treatment of an asymptomatic condition are unacceptable when there is no certain benefit, only a reduction in the risk of a possible future cardiovascular event.

Another reason for apparent drug resistance is nonadherence to prescribed treatment. Failure to take medications as prescribed is common across a wide range of illnesses.[15] Compliance may peak around the time of an outpatient appointment, making it more difficult to detect noncompliance.[16] Dosing frequency and regimen complexity contribute to limited persistence with prescribed treatment.[17]

A range of solutions make good sense: for example, better communication between doctor and patient, patient education and involving the patient in their own management (such as home blood pressure measurement).[15,18] However, empirical evidence of efficacy of these approaches is limited. A recent systematic review recommends the simplification of dosing regimens to improve compliance and suggests that education alone is not particularly effective.[19]

## What characterises the treatment-resistant patient?

Excluding hypertensive patients with 'white-coat resistance', therapeutic inertia and noncompliance leaves a core of patients whose blood pressure is genuinely resistant to drug treatment. The size of the problem is difficult to estimate.

One study determined the incidence of resistance in 205,750 patients with incident hypertension and found that 1.9% developed resistant hypertension within a median of 1.5 years from initial treatment (0.7 cases per 100 person-years of follow up).[20] Prevalence has been estimated from population studies where treatment details are difficult to ascertain and from large clinical trials where participants may not be representative of the wider population. A recent review pooled data from several studies (including epidemiological studies and controlled trials) to report a prevalence of resistant hypertension of 14.8% in treated hypertensive patients.[21]

Those with resistant hypertension are more likely to smoke and drink alcohol to excess; more likely to be older, male and obese; and more likely to have diabetes, target organ damage and cardiovascular disease or a high predicted cardiovascular risk.[22-25] Adverse cardiovascular outcomes and mortality are increased in patients with resistant hypertension, providing a strong imperative to gain control of blood pressure.[20,21,26,27]

## Secondary hypertension, including drug-induced hypertension

Secondary hypertension is more common in patients with resistant hypertension than in unselected patients.[7] The causes of secondary hypertension that should be considered are listed in Box 1.[7,28]

Resistant hypertension has a strong association with sleep apnoea, but the response to treatment is variable and meta-analyses report a modest average fall in blood pressure with CPAP.[7,28,29] Hyperaldosteronism and renal parenchymal disease are also common in patients with resistant hypertension.[7]

Other important causes of secondary hypertension are the drugs that raise blood pressure or interfere with the efficacy of antihypertensive drugs (Box 2). Common examples are NSAIDs, sympathomimetics (nasal decongestants, appetite suppressants), steroids (oral contraceptives, glucocorticoids) and related agents (e.g. liquorice, which inhibits 11beta-hydroxysteroid dehydrogenase allowing cortisol to activate mineralocorticoid receptors). Several of the new anticancer

drugs (and especially the antivascular endothelial growth factor therapies) can affect blood pressure.[30]

## What can be done for treatment-resistant patients?

### Lifestyle adjustment

Obesity, moderate alcohol consumption and excessive intake of salt all increase blood pressure. Strategies to lose weight and reduce the intakes of alcohol and salt help lower blood pressure. The challenge for the patient and the treating physician has been the implementation and maintenance of lifestyle change. Salt reduction appears to be particularly effective in the setting of treatment resistance.[31]

### Pharmacological treatment

Optimising the antihypertensive regimen is important for patients with resistant hypertension. The use of certain drugs in combination is more effective than combinations of other drugs.[32,33] An ACE inhibitor (or angiotensin II receptor blocker), a calcium channel blocker and a diuretic, as recommended by NICE, is an effective combination.[8] Combinations of an ACE inhibitor and an angiotensin II receptor blocker (dual renin–angiotensin–aldosterone blockade) or an ACE inhibitor and a beta blocker are less than additive in lowering blood pressure.

The addition of a fourth drug is reasonable once the best three-drug combination has been established for the individual patient. There is a paucity of evidence for effective add-on medications in this setting. After early promising results, the endothelin antagonist darusentan has been shown to be relatively ineffective at lowering ambulatory blood pressure.[34] The only drugs for which there is evidence for efficacy from randomised controlled trials in the setting of resistant hypertension are spironolactone and minoxidil.[35-37] Minoxidil is effective but difficult to use: its use is regularly accompanied by fluid retention and tachycardia that may need to be combated by other drugs (diuretics and beta blockade), and it can cause hirsutism.[37]

Another approach that has been shown to be useful in a randomised trial is sequential nephron blockade (the concurrent use of diuretics that act at different sites of the renal tubule).[38] The obvious hazard with this approach is volume depletion and renal impairment.

Several other drugs can be used to lower blood pressure but have not been trialled in the setting of resistant hypertension. These include vasodilators such as hydralazine, alpha adrenergic receptor antagonists and centrally acting antihypertensive drugs.

### Device-based procedures

Two device-based procedures have been used in recent years to treat patients with resistant hypertension: renal denervation and carotid-baroreceptor nerve stimulation. At present, neither procedure can be unequivocally recommended. Deployment should be performed in specialised units, preferably in clinical trials that will help define the place of these new treatments.

#### *Renal denervation*

Renal denervation had been rapidly adopted after unrandomised proof-of-principle and randomised but unblinded studies showed very substantial efficacy: a fall of 27/17 mmHg at 12 months in the former study and 32/12 mmHg at six months in the latter.[39,40] Unfortunately, the keenly awaited double-blind, sham-controlled study (Symplicity-3) has recently reported disappointing results: a 2.39 mmHg between group difference for office blood pressure and a 1.96 mmHg between group difference in 24-hour ambulatory systolic blood pressure.[41] Whether the apparent difference in efficacy in these three studies is a result of more rigorous evaluation of efficacy in Symplicity-3, differences in the patient population enrolled in the three studies or the experience of the operators is hotly debated.

**2. Hypertension induced by drugs or chemicals**

- Sympathomimetic agents (weight-loss pills, decongestants, amphetamine and amphetamine-like substances, cocaine, herbal agents such as ephedra [ma huang])
- Steroids and related substances
  - oral contraceptive pills and exogenous oestrogen
  - exogenous glucocorticoids and mineralocorticoids
  - liquorice (allows cortisol to activate mineralocorticoid receptors)
- Antidepressants
- Alcohol
- Immunosuppressants (especially cyclosporin)
- Erythropoietin
- Anticancer drugs (especially anti-VEGF drugs)

Abbreviation: VEGF = vascular endothelial growth factor.

#### *Carotid-baroreflex activation*

Baroreflex activation is more difficult to deploy than renal denervation and is not yet generally available. Initial promising results in a non-randomised study[42] were followed by less impressive results in a randomised blinded study (the device was implanted but not switched on in the control group). In this study, baroreflex activation resulted in no significant difference between treated subjects and controls (16 ± 29 mmHg and 9 ± 29 mmHg, respectively).[43]

## Summary

If careful attention is paid to measuring blood pressure, instituting lifestyle measures and adjusting treatment as required, the number of truly drug-resistant hypertensive patients is small. A second look for underlying causes of hypertension is warranted in this group, including in particular the possibility that concurrent treatment is contributing to elevated blood pressure. Some old drugs retain their usefulness in the setting of resistant hypertension, and newer innovations have not shown unequivocal benefit. **CT**

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

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