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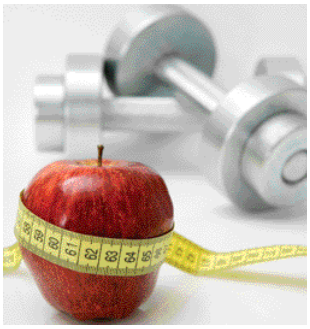

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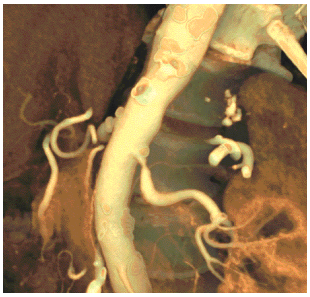

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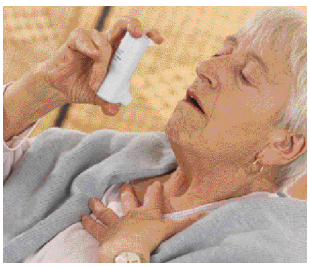

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Clinical Investigations from the RACP

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Investigation of the patient with hypertension

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors and written by members of the Royal Australasian College of Physicians.

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The diagnosis of hypertension should be made over several visits of the patient to the GP surgery. Use of a mercury sphygmomanometer remains the most accurate method of measuring a patient's blood pressure level. However, mercury devices are being phased out of the clinical environment, and automated blood pressure devices are now frequently used. Such devices require validation initially and every six months to ensure accuracy.

If available, 24-hour ambulatory blood pressure monitoring is useful to confirm the diagnosis of hypertension, particularly when the presence of white-coat (or office) hypertension is likely. White-coat hypertension should be suspected in a patient with:

- significant variations in blood pressure measurements between visits to the GP or between practitioner measurements
- elevated blood pressure measurements, who is otherwise fit and healthy
- resistant hypertension
- symptoms suggestive of both hypotension and hypertension.

Twenty-four-hour ambulatory blood pressure monitoring (Table 1)[1] is also useful to evaluate a patient for 'reverse white-coat hypertension', now known as masked hypertension. Masked hypertension occurs when a patient's blood pressure is higher when measured outside the doctor's office than when measured inside the office – that is, the patient has a controlled office blood pressure level but an elevated home or 24-hour blood pressure level. This condition is not yet fully understood, but is thought to represent an increased risk for cardiovascular disease.

Patients with elevated home blood pressure but controlled office blood pressure should undergo 24-hour ambulatory blood pressure monitoring. Current evidence strongly suggests that 24-hour blood pressure readings are more accurately associated with target organ damage than office blood pressure measurements.[2] This supports the use of out of office blood pressure monitoring in patients with suspected hypertension.

IN SUMMARY

- **The diagnosis of hypertension should be made over several visits of the patient to the GP surgery.**
- **Twenty-four-hour ambulatory blood pressure monitoring is useful to evaluate a patient for white-coat hypertension or masked hypertension.**
- **Home blood pressure monitoring is now frequently used by patients in the management of their condition.**
- **All patients with hypertension should be screened for diseases of the kidney, which are probably the most common secondary cause of hypertension.**
- **Other secondary causes of hypertension to consider include primary aldosteronism and phaeochromocytoma.**

Home blood pressure monitoring is now frequently used by patients in the management of their condition. Patients should be instructed on the correct method of using a home device.[3] Generally, two or three measurements should be made with the patient sitting down, and the average measurement recorded. Note that the upper limit of normal home blood pressure level is lower than that of the office levels (mean of multiple readings) at below 135/85 mmHg (Table 1). Some authors advocate ignoring the first reading. There are many blood pressure monitoring devices that have been validated as being acceptable for clinical use.[3]

End-organ damage caused by hypertension and associated clinical conditions

The presence of end-organ damage places the patient with hypertension in a higher risk category and correspondingly lowers his or her blood pressure target. It is therefore imperative to evaluate the patient for end-organ damage to stratify the patient's risk and to monitor the status of the end organs. The commonly affected organs – the heart, kidneys, vasculature and cerebrovascular system – can generally be easily assessed.

History and physical examination will identify the majority of clinical conditions associated with hypertension (Table 2). These are diseases that should be considered in any patient with hypertension with each disease managed on its merits. Generally, antihypertensive therapy should be used when one or more of these associated conditions is present, regardless of blood pressure.

All patients diagnosed with hypertension should have initial screening tests undertaken, as listed in Table 3.

Investigations for secondary hypertension

Chronic kidney disease

All patients with hypertension should be screened for diseases of the kidney, which are probably the most common secondary cause of hypertension. If a urinalysis and estimated glomerular filtration rate (eGFR) measurement are both normal, significant kidney disease can be excluded in most cases. If these measurements are abnormal, then an ultrasound or a computed tomography scan of the kidneys will give further information about renal anatomy and exclude other reversible problems. If chronic kidney disease is diagnosed, referral should be considered, according to the Kidney Health Australia guidelines.[4]

Primary aldosteronism

Primary aldosteronism is a syndrome of hypertension accompanied by salt and water retention secondary to excess levels of aldosterone. Hypokalaemia is commonly described in patients with primary aldosteronism; however, in about 50% of patients with primary aldosteronism, the serum potassium levels are normal. Potassium levels in the

Investigation of the patient with hypertension

An elevated blood pressure measured during a patient's routine physical examination must be carefully considered before a diagnosis of hypertension can be made. White-coat hypertension can be a possible cause of the increase, but hypertension can be a symptom of other serious conditions.

continued

Table 1. Normal values for office, 24-hour and home blood pressure in nonpregnant adults*[1]

Blood pressure reading	Normal value (mmHg)
Office (seated, resting)	<140/90
24-hour	
• Daytime (awake)	<135/85
• Night-time (asleep)	<120/70
• 24-hour average	<130/80
Home (awake, mean of multiple measurements)	<135/85

* 24-hour blood pressure ranges reproduced with permission from *Guide to management of hypertension 2008. Updated September 2010* (in production). © National Heart Foundation of Australia.[1]

lower normal range and bicarbonate levels in the upper normal range in the absence of diuretic therapy are suggestive of an excessive secretion of mineralocorticoid (aldosterone).

Primary aldosteronism should be considered in patients with:

- proven resistant hypertension
- low or low-normal serum potassium
- a family history of primary aldosteronism.

The aldosterone to renin ratio is generally the most simple and sensitive test available to screen patients for primary aldosteronism. An elevated ratio is suggestive, but not diagnostic, of aldosteronism.

The aldosterone to renin ratio is influenced by some medications:

- beta blockers suppress renin production and therefore increase the aldosterone to renin ratio
- diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers stimulate renin release and therefore lower the aldosterone to renin ratio.

Measurement of the aldosterone to renin ratio should be performed after a washout period of at least one week while the patient is not taking any medications (if safe). If this is not possible or unsafe, the use of prazosin (1 to 5 mg three times a day) and/or verapamil (180 to 240 mg daily) instead of the usual agents will have minimal effect on the ratio during the seven- to 10-day period prior to the blood test.

To confirm the diagnosis of primary aldosteronism, patients with an elevated aldosterone to renin ratio should have suppression testing and, possibly, adrenal vein sampling, best undertaken in specialist units. If a patient has a family history of aldosteronism, a diagnosis of familial hyperaldosteronism type 1 (dexamethasone-suppressible aldosteronism) should be considered.

In patients for whom the series of investigations to determine primary aldosteronism is too difficult or in whom treatment with adrenalectomy surgery would not be an option, it is quite reasonable to use a therapeutic trial of a mineralocorticoid blockade, such as spironolactone 12.5 to 25 mg daily or amiloride 5 to 10 mg twice daily. Extreme caution should be exercised when using a mineralocorticoid blockade, especially in patients with a reduced eGFR or those also taking ACE inhibitors, angiotensin receptor blockers, other diuretics or NSAIDs, because of the risk of hyperkalaemia and/or a further reduction in eGFR.

Phaeochromocytoma

Although phaeochromocytoma is a rare disease, it should be considered in patients with hypertension:

- who are younger in age (<30 years)
- who have a family history of phaeochromocytoma
- that is resistant or
- who have flushing symptoms.

The 24-hour urinary catecholamine excretion test is often used to screen patients for phaeochromocytoma. However, the fasting plasma metanephrine and normetanephrine measurement is now available. It is a simpler test, which avoids the need for urine collection, and is highly sensitive for phaeochromocytoma. A low positive result (i.e. less than three to four times the upper limit of normal) may well be a false-positive result because the test lacks specificity, but a strongly positive result (i.e. more than four times the upper limit of normal) is generally diagnostic of phaeochromocytoma.

False-positive results can be reduced by the patient fasting before the test, repeating the test (if a low positive result is given) and withdrawing drugs that lead to false-positive tests. Such agents include alpha and beta blockers, sympathomimetics and tricyclic antidepressant agents. Furthermore, 24-hour urine metanephrine excretion testing is helpful in positive cases because this test is more specific for a tumour and will exclude false positives.

Renovascular disease

In view of the possibility of fibromuscular hyperplasia of the renal artery, it is reasonable to screen for renal artery stenosis in younger (<30 years) patients with hypertension, particularly young women. Patients with fibromuscular hyperplasia generally respond well to endovascular revascularisation, with approximately 80% of patients having their hypertension significantly improved or completely resolved after the procedure.[5] The gold standard test for renovascular disease is the digital subtraction angiogram and should be performed when there is a high index of suspicion for the condition. Other useful screening tests include the computed tomography renal angiogram and MRI of the kidneys. The Doppler ultrasound is a less useful screening test.

Table 2. Clinical conditions and end-organ disease associated with hypertension*†[1]

Associated clinical conditions

Diabetes

- In either of the following:
  - adults with diabetes aged >60 years
  - adults with diabetes and microalbuminuria

Cerebrovascular disease

- Ischaemic stroke
- Transient ischaemic attack
- Cerebral haemorrhage

Coronary heart disease

- Myocardial infarction
- Angina
- Coronary revascularisation

Chronic heart failure

Chronic kidney disease

- Diabetic nephropathy
- Glomerulonephritis
- Hypertensive kidney disease

Aortic disease

- Dissecting aneurysm
- Fusiform aortic aneurysm

Peripheral arterial disease

(clinical diagnosis or ankle brachial index <0.9)

Hypercholesterolaemia

- Total cholesterol >7.5 mmol/L

Family history or previous diagnosis of:

- premature cardiovascular disease or
- familial hypercholesterolaemia

End-organ disease

Left ventricular hypertrophy

- Diagnosed by electrocardiogram or echocardiogram

Microalbuminuria

- Defined as either of the following:
  - albumin/creatinine ratio ⩾2.0 mg/mmol (males) or ⩾2.5 mg/mmol (females) on a spot urine screening test‡
  - 24-hour urinary albumin excretion rate ⩾20 µg/min

Chronic kidney disease

- Presence of either of the following:
  - proteinuria defined as protein/creatinine ratio ⩾30 mg/mmol‡ on a spot urine test or urine protein >300 mg/day on a timed urine sample
  - estimated glomerular filtration rate§ <60 mL/min/1.73 m^2

Vascular disease

- Atherosclerotic plaque (aorta, carotid, coronary, femoral and iliac arteries) evident on ultrasound or radiology
- Hypertensive retinopathy (grade II or greater)

*Adapted with permission from *Guide to management of hypertension 2008. Updated September 2010* (in production). © National Heart Foundation of Australia.[1]

† Conditions that warrant immediate treatment with antihypertensive drugs, regardless of blood pressure or overall cardiovascular risk profile.

‡ Value for ratio where albumin or total protein is measured in milligrams per litre and creatinine is measured in millimoles per litre. Reference range will differ where laboratories report creatinine level expressed in micromoles per litre.

§ Estimated glomerular filtration rate obtained using the Modification of Diet in Renal Disease (MDRD) study GFR equation (used by most pathology laboratories and routinely reported with serum creatinine in adults). This method is generally accurate for GFR below 60 mL/min/1.73 m^2. Studies are underway to validate this in Aboriginal and Torres Strait Islander populations.

Table 3. Initial investigations in patients with hypertension*[1]

- Dipstick test for haematuria (plus urine microscopy if positive)
- Dipstick test for proteinuria (plus 24-hour urinary protein excretion measurement if positive)
- Assessment for microalbuminuria – preferably using albumin/creatinine ratio on a spot urine (plus 24-hour urine collection if positive)
- Blood analysis for levels of sodium, potassium, chloride, bicarbonate, urea, creatinine, uric acid, haemoglobin, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, liver enzymes, fasting glucose and total cholesterol
- Electrocardiogram for conduction disturbances, arrhythmia, strain pattern, coronary artery disease or left ventricular hypertrophy

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Atherosclerotic renal artery stenosis is now managed less aggressively. A series of studies has been published and presented that does not demonstrate convincing evidence of benefit of treatment for either progression of chronic kidney disease or control of hypertension. Therefore, it is reasonable in older patients (i.e. those with risk factors for atherosclerosis) not to screen for renal artery stenosis or revascularise if blood pressure is controlled and kidney function is stable. (See cari.org.au for the 2009 Caring for Australasians with Renal Impairment Guidelines on Renovascular Disease).[6]

Other causes of hypertension

Other causes of hypertension are rare. Generally, patients who have been fully investigated and still have uncontrolled hypertension should be referred to a specialist.

Current targets for hypertension control

In the *Guide to management of hypertension 2008* (updated September 2010; in production), blood pressure targets have been simplified (Table 4).[1] Note that 'lower if tolerated' is emphasised, reflecting the growing body of evidence that lowering blood pressure beyond the target is beneficial, rather than harmful.

Achieving blood pressure targets is difficult. Even in clinical trials or trials of different drugs in patients with hypertension, blood pressure targets are only met

continued

Table 4. Blood pressure treatment targets in adults*[1]

Patient group	Target (mmHg)
People with proteinuria >1 g/day (with or without diabetes)	<125/75
People with the following associated clinical condition(s) or end-organ damage:[†] • coronary heart disease • diabetes • chronic kidney disease • proteinuria (>300 mg/day) • stroke/transient ischaemic attack	<130/80
People with none of the above conditions	<140/90 or lower if tolerated

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† Specific lower blood pressure targets have not been established for other high-risk groups (e.g. those with peripheral arterial disease, those with familial hypercholesterolaemia or those at high absolute risk of cardiovascular disease) due to the current lack of evidence from clinical trials. Targets will be set when evidence becomes available.

in 50 to 80% of such patients. Although there are medical reasons for this suboptimal rate, one of the major causes is a reluctance of the doctor to change medication at patient visits, even if the target has not been met. It is important that this is recognised as a barrier to effective treatment in the absence of other causes of treatment failure, such as nonadherence with therapy, symptoms or other patient-related factors.

Management of hypertension uncontrolled by medications

Resistant or nonresponsive hypertension is diagnosed when a patient has not responded to the maximum dose of at least two agents prescribed to control hypertension. Twenty-four-hour ambulatory blood pressure monitoring is useful in this circumstance as the gold standard noninvasive measurement of blood pressure in a patient undergoing either nonpharmacological or pharmacological treatment of hypertension. About 30% of patients with resistant office hypertension despite therapy may have controlled hypertension when assessed by 24-hour ambulatory blood pressure monitoring.[7] If ambulatory blood pressure monitoring is not available, home blood pressure monitoring can be used.

Nonadherence or poor compliance with medication and white-coat hypertension can generally be assessed by 24-hour blood pressure monitoring. Asking the patient to document physical activity and timing of medication administration will usually allow an assessment of adherence to be made.

Sleep apnoea should be considered in the patient who is overweight or snores heavily. The patient should be asked what other drugs he or she is taking because of the possibility that other drugs may raise blood pressure levels. Finally, a high salt intake is increasingly recognised as contributing to resistant hypertension, particularly in patients receiving ACE inhibitor-based treatment, who are not taking a diuretic or are fluid overloaded.

Investigation or referral is appropriate in the patient with nonresponsive hypertension proven by 24-hour ambulatory blood pressure monitoring. It is reasonable to use a combination of an ACE inhibitor or angiotensin receptor blocker, with a calcium channel blocker and/or a diuretic in such patients. Other useful agents to trial include prazosin, spironolactone, beta blockers and frusemide (especially when there is fluid retention); however, care must be taken because of interactions and side effects when multiple agents are used.

Conclusion

The investigation of patients with hypertension is now directed towards assessment of end-organ damage, associated clinical conditions and secondary causes. The importance of correct blood pressure measurement both in the GP surgery and outside it is now better understood and forms a major part of the assessment and ongoing management of the patient with hypertension. MT

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COMPETING INTERESTS: None

Hypertension
treating to target

The choice of antihypertensive agent is determined by its effectiveness, and its indications and contraindications for the individual patient. Whichever agent is used, it is important to treat to goal.

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Hypertension is the most frequently managed problem in Australian general practice.[1] The prevalence rate in the adult population is 29%.[2] The benefits of blood pressure lowering have been detailed in numerous randomised, placebo-controlled trials and meta-analyses.[3] However, hypertension is still described as the most important health problem that is suboptimally managed.

In the Australian Diabetes, Obesity and Lifestyle (AusDiab) study, treatment for hypertension was justified in 54% of patients not treated.[2] Of those taking antihypertensive medication, only 40% had reached target blood pressure readings (defined as <140/90 mmHg). Blood pressure control rates can therefore be substantially improved.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) study achieved target blood pressure levels in 66% and 70% of patients, respectively.[4,5] Hence higher rates of blood pressure control are achievable.

Failure to reach blood pressure targets may be due to the patient, the GP or systems issues. This article discusses some of the reasons why blood pressure targets set by the National Heart

IN SUMMARY

- **The decision to treat elevated blood pressure with drugs should be determined by an individual's high absolute risk of having an adverse cardiovascular event.**
- **Not treating to target therefore means that such individuals are at high residual risk.**
- **Failure to reach blood pressure targets may be due to the patient, the GP or systems issues.**
- **The choice of antihypertensive agent is determined by its effectiveness, and its indications and contraindications for the individual patient.**
- **Most patients will require two or more drugs to reach their target blood pressure.**
- **Drug therapy should always be accompanied by appropriate advice on behavioural modifications.**

continued

Table 1. Blood pressure treatment targets in adults*[6]

Patient group	Target (mmHg)
Patients with proteinuria >1 g/day (with or without diabetes)	<125/75
Patients with associated condition(s) or end organ damage:† • coronary heart disease • diabetes • chronic kidney disease • proteinuria (>300 mg/day) • stroke/transient ischaemic attack	<130/80
Patients with none of the above	<140/90 or lower if tolerated

* Adapted with permission from *Guide to management of hypertension 2008. Updated September 2010* (in production). © National Heart Foundation of Australia.[6]

† Specific lower blood pressure targets have not been established for other high-risk groups (e.g. those with peripheral arterial disease, those with familial hypercholesterolaemia or those at high absolute risk of cardiovascular disease) due to the current lack of evidence from clinical trials. Targets will be set when evidence becomes available.

Foundation's guidelines are not reached, what the target blood pressure readings are and ways in which these targets may be achieved.[6]

Why are we not reaching blood pressure targets?

A qualitative study has investigated the barriers to initiating medication and treating elevated blood pressure to target levels in general practice.[7] In this study, the main barrier preventing or delaying diagnosis reported by GPs was a lack of confidence in the accuracy and representativeness of blood pressures recorded in their clinic. The other main barriers were the time-poor nature of general practice and perceived patient attitude. The fact that multiple readings are needed over several visits imposed some difficulties – for example, in patients who were infrequent attendees or were not interested in their blood pressure or saw a different doctor each time they attended. Initiation of treatment was often hampered by patient unwillingness to take medications.

The study also found that the decision to treat to target was clouded by doctors' fear of adverse events (particularly in the elderly) clinical inertia and perceived patient attitude. Adopting a patient-centred care approach and distrust of the evidence underlying the management of hypertension had a pervasive impact.

In this study, difficulties associated with initiating and treating to target were often discussed together, but overall treating to target was viewed as being more difficult. Looking at the study results from a treating to target perspective only, the barriers that prevented optimal management of hypertension were perceived patient attitude, GP attitude and systems issues.

Perceived patient attitude

GPs believe that patients often fail to take responsibility for their own health and resist making necessary lifestyle changes. Cost, access and adherence are also issues.

GP attitude

GPs undertook an informal risk–benefit analysis whereby they weighed up what they were trying to achieve against what the patient wanted. The witnessing of drug attributed side effects, particularly in the elderly, made GPs more risk averse.

Systems issues

GPs felt that there needed to be greater access to specialist care and home and ambulatory blood pressure monitoring, and improved Medicare support for the management of complex hypertension.

How can we reach blood pressure targets?

Patients with high absolute cardiovascular risk and elevated blood pressure need to be treated to recommended target blood pressures (Table 1), otherwise they will have a significant residual adverse risk.

Multiple large studies have shown that all antihypertensive medications have similar efficacy.[8] Therefore, medication choice after initiation is driven by the individual patient's response, comorbidity (Table 2) and the possible combinations of antihypertensive agents (Table 3).[9,10]

To facilitate a successful and sustainable treatment regimen, the lowest recommended dose of the selected drug should be started and then reviewed after six weeks. At this stage, if the patient is unable to tolerate the medication or if it is deemed to be ineffective, the patient should be switched to an antihypertensive drug from a different class. If there has been a partial response but target blood pressure has not been reached, rather than increasing the dose of the first agent, a second agent from a different pharmacological class should be added at a low dose. This approach minimises adverse events and maximises efficacy. The effective tolerated medications should be titrated up until target blood pressure is reached; however, additional medications may need to be added to achieve this.

Lifelong medication is usually required because age is the most important determinant of adverse risk. Once blood pressure has been stabilised, the interval between visits can be lengthened – for example, patients should be reviewed every three months for the next 12 months, and then six monthly thereafter while their blood pressure remains stable.

Behavioural modification is an important component of treatment and, if significant lifestyle changes are made and maintained, patients may be able to stop or reduce drug therapy.[11] Lifestyle interventions remain the cornerstone of hypertension management.

Combination therapy

About 60% of patients with elevated blood pressure will not achieve blood pressure

Table 2. Choice of antihypertensive agent in patients with comorbid and associated conditions*[6]

Condition	Potentially beneficial	Potentially harmful	
		Caution	Contraindicated
Angina	Beta blockers (except oxprenolol, pindolol), CCBs, ACE inhibitors		
Atrial fibrillation	Remodelling: ACE inhibitors, angiotensin II receptor antagonists† Rate control: verapamil, diltiazem, beta blockers		
Asthma/COPD		Cardioselective beta blockers (e.g. atenolol, metoprolol): use cautiously in mild/moderate asthma/COPD only	Beta blockers (except cardioselective agents)
Bradycardia, second- or third-degree atrioventricular block			Beta blockers, verapamil, diltiazem
Depression		Beta blockers, clonidine, methyldopa, moxonidine	
Gout	Losartan	Thiazide diuretics	
Heart failure	ACE inhibitors, angiotensin II receptor antagonists,† thiazide diuretics, beta blockers‡ (bisoprolol, carvedilol, metoprolol controlled release), spironolactone	CCBs (especially verapamil, diltiazem)	Alpha blockers in aortic stenosis Beta blockers in uncontrolled heart failure
Post myocardial infarction	Beta blockers (except oxprenolol, pindolol), ACE inhibitors, eplerenone		
Pregnancy	This section is currently under review§		
Chronic kidney disease	ACE inhibitors, angiotensin II receptor antagonists†		
Tight bilateral renal artery stenosis (unilateral in a patient with solitary kidney)		ACE inhibitors, angiotensin II receptor antagonists	
Post stroke	ACE inhibitors, angiotensin II receptor antagonists, low-dose thiazide-like diuretics		
Type 1 or type 2 diabetes with proteinuria or microalbuminuria	ACE inhibitor, angiotensin II receptor antagonists†	Beta blockers, thiazide diuretics¶	

Abbreviations: ACE = angiotensin-converting enzyme; CCB = calcium channel blocker.

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† Careful monitoring of kidney function is required if a combination of ACE inhibitors and angiotensin II receptor antagonists are used.

‡ Particular beta blockers are now indicated for the treatment of heart failure. See the Heart Foundation's *Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006* (available at www.heartfoundation.org.au).

§ This information is currently being reviewed by the Heart Foundation. Please visit www.heartfoundation.org.au/Professional_Information/Clinical_Practice/Hypertension for updated information.

¶ When used in combination with an ACE inhibitor, may be beneficial in type 2 diabetes.

continued

Table 3. Recommended and discouraged combination therapy for the management of elevated blood pressure*[6,9,10]

First drug	Additional drug	Recommendation
The most effective combination (based on the best available evidence)		
ACE inhibitor or angiotensin II receptor antagonist†	CCB	Particular role in patients with diabetes or lipid abnormalities
Other effective combinations		
ACE inhibitor or angiotensin II receptor antagonist†	Thiazide diuretic	Particular role in patients with heart failure or post stroke
	Beta blocker	Recommended post myocardial infarction or in patients with heart failure
Beta blocker	Dihydropyridine CCB	Particular role in patients with coronary heart disease
Thiazide diuretic	CCB	
	Beta blocker	Not recommended in patients with glucose intolerance, metabolic syndrome or established diabetes
Combinations to avoid		
ACE inhibitor or angiotensin II receptor antagonist	Potassium-sparing diuretic	Avoid combination due to risk of hyperkalaemia
Verapamil	Beta blocker	Avoid combination due to risk of heart block
ACE inhibitor	Angiotensin II receptor antagonist	In a large trial,[9] combination therapy did not reduce cardiovascular death or morbidity in patients with vascular disease or diabetes, but increased the risk of hypotensive symptoms, syncope and renal dysfunction‡

ABBREVIATIONS: ACE = angiotensin-converting enzyme; CCB = calcium channel blocker.

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† ACE inhibitors and angiotensin II receptor antagonists have been shown to be equally efficacious in the prevention of combined end points of cardiovascular disease death, myocardial infarction, stroke and heart failure admissions in patients at high risk due to past cardiovascular events.

‡ Combination therapy reduces proteinuria. Trials to determine the effect of combination therapy on progression of renal disease in subjects with proteinuria are under way.[10]

targets with one medication alone.[6] Therefore, most patients will require a combination of two or more medications to achieve adequate blood pressure control.

Effective drug combinations for hypertension are shown in Table 3. The angiotensin converting enzyme (ACE) inhibitor and calcium channel blocker combination has been given precedence due to the results of the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial.[12] If required, other useful agents include, for example, alpha blockers and centrally-acting agents. Each change in treatment needs to be trialled for at least six weeks.

Still not at target?

If target blood pressure is not reached despite maximal doses of at least two appropriate agents after a reasonable period, then the following factors outlined below should be considered.

Medication adherence

- Has the patient ceased medication due to side effects or cost?
- Could the patient change to a long-acting preparation with once-daily administration?
- Could the patient change to a combination preparation to enhance adherence?
- Would the patient benefit from the use of adherence aids (e.g. dosette boxes, Webster packs, written instructions or patient education materials)?

Other substances that may increase blood pressure

- Is the patient taking a prescribed medication (e.g. NSAIDs or prednisolone)?
- Is the patient taking an over the counter (e.g. NSAIDs) or a complementary medication (e.g. ginseng, St. John's Wort)?
- Is alcohol, recreational drugs or other drug use (including caffeine, licorice) an issue?
- Does the patient have a high salt intake (particularly in those taking ACE inhibitors or angiotensin II receptor antagonists)?

Adverse lifestyle factors

- Can the patient be motivated to take greater responsibility for his or her health and become a partner in management decisions?
- Can the patient increase physical activity or reduce kilojoule intake (if appropriate)?

Systems issues

- Are there any other social or economic barriers that are impacting negatively on the patient's health?
- Would the patient benefit from a Home Medicines Review?

- Is a practice recall or reminder system appropriate to assist in management?

Therapeutic inertia

- Do you need to increase a current agent or add another agent?

Measurement issues

- Could there be a white coat effect? Home blood pressure monitoring should be encouraged, if appropriate, or ambulatory blood pressure monitoring considered.
- Is there a blood pressure measurement artifact (e.g. inappropriate cuff size)?

Secondary hypertension

- Does the patient have chronic kidney disease, primary aldosteronism, phaeochromocytoma or renovascular disease?
- Could the patient have obstructive sleep apnoea?
- Is the patient volume overloaded (in particular, chronic kidney disease should be ruled out)?
- Would the patient benefit from referral to a specialist?

Can we achieve blood pressure targets in the elderly?

It is recognised that achieving recommended blood pressure target levels in the very elderly may be difficult because of their altered physiological responses, comorbidity and polypharmacy, with the potential for side effects and medication interactions. The elderly are the most at risk of adverse cardiovascular events.

Randomised, controlled trials have demonstrated that drug therapy is just as effective in advanced age. The most recent study to show this was the Hypertension in the Very Elderly Trial (HYVET).[13] This placebo-controlled trial (mean age 83.6 years) showed a 39% reduction in the rate of death from a stroke, a 21% reduction in the rate of death from any cause, a 23% reduction in the rate of death from cardiovascular causes, and a 64% reduction in the rate of heart failure in patients taking active treatment versus placebo.

Most importantly, the HYVET study reported fewer serious adverse events in the active treatment group, and preliminary analyses revealed no increase in postural hypotension. If symptoms suggest postural hypotension, but it is not demonstrable in the clinic, it should be confirmed with ambulatory blood pressure monitoring. If confirmed, treatment should be based on the standing blood pressure. In the elderly, isolated elevated systolic blood pressure is more prevalent due to large vessel stiffness associated with ageing. In these circumstances, a calcium channel blocker or diuretic-based treatment regimen is recommended.

Conclusion

Drug therapy is warranted in patients with a high risk of adverse cardiovascular events together with appropriate behavioural modification. All groups of blood pressure lowering drugs have similar efficacy but specific agent recommendations are made based on the patient's characteristics. It is important to treat to goal whichever agent is used. Most often, this requires more than one drug to reduce fatal and nonfatal cardiovascular events. MT

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MedicineToday PEER REVIEWED ARTICLE

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Management of hypertension

Addressing the impediments to effective management of hypertension will have major implications in the prevention of cardiovascular and renal adverse events.

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Although hypertension is the most common reason for GP consultations, there remains a large treatment gap, with fewer than 25% of patients with hypertension attaining target blood pressure. In addition, the prevalence of hypertension in Australia appears to be increasing. In 2001, the Australian Diabetes, Obesity and Lifestyle (AusDiab) study showed a prevalence of hypertension of 28.6% in adults in Australia, while some later, but significantly smaller, studies have suggested that the prevalence of hypertension may be much higher.[1,2]

Improved management of hypertension has major implications for the prevention of major cardiovascular and renal adverse events. Effective blood pressure management reduces the incidence of stroke, coronary heart disease (CHD), congestive heart failure (CHF) and peripheral arterial disease (PAD), and prevents the progression of renal disease to end stage when renal replacement therapy (dialysis and/or transplantation) is required.

This review summarises the impediments to the effective management of hypertension and discusses current Australian antihypertensive treatment recommendations. Further information can be obtained from the National Heart Foundation of Australia's publication *Guide to management of hypertension 2008* (updated September 2010; in production; see: www.heartfoundation.org.au).[3]

Impediments to effective management of hypertension

Several factors act to impede the effective management of high blood pressure. These are summarised in Table 1 and discussed below.

Accuracy of blood pressure measurement

The issues affecting the accuracy of blood pressure measurement relate to machine accuracy, observer error and measurement technique.

Due to environmental concerns, there has been a movement away from the use of mercury sphygmomanometers without the simultaneous development of an equally robust and accurate replacement instrument. Electronic and aneroid sphygmomanometers need regular validation and, if inaccurate, require service and calibration. These instruments can be simply validated against a mercury sphygmomanometer using a 'Y' connector.

IN SUMMARY

- **The prevalence of hypertension appears to be increasing; however, the therapeutic gap remains unchanged, with most patients with hypertension not attaining target blood pressure.**
- **Therapeutic inertia appears to be one of the main contributors to the low rates of attainment of target blood pressure.**
- **Strategies such as mentoring programs that have been demonstrated to address therapeutic inertia need to be more widely implemented.**
- **Improved management of hypertension has major implications for the prevention of major cardiovascular and renal adverse events.**

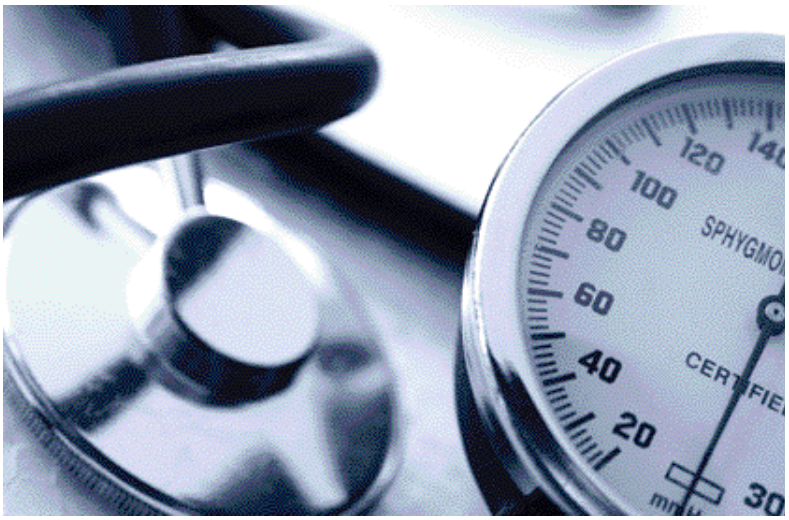
The well-known observer error of rounding to five or zero has been the subject of education and audit programs with some effect. Less well recognised is the tendency in a busy practice to question the patient while measuring blood pressure. The act of speaking raises blood pressure by 10 to 15 mmHg and may lead to inappropriately elevated readings. The use of incorrectly sized cuffs may also affect measurement accuracy: too small a cuff causes spurious elevations, whereas the use of an excessively large cuff may inappropriately decrease blood pressure readings.

The presence of a white coat effect or of a reverse white coat effect may also influence the accuracy of clinic blood pressure readings. To diagnose these and assess their magnitude, multiple blood pressure readings outside the clinic setting are needed. This may be achieved by home blood pressure monitoring by the patient using a validated home blood pressure monitor or by ambulatory blood pressure monitoring; however, different normal ranges apply (Table 2).

Unrecognised secondary hypertension

Patients who appear unresponsive to therapy may have an underlying secondary cause for their hypertension. Not all patients with phaeochromocytoma display the classical symptoms of tachycardia and episodes of pallor and sweating ('flushes'). Indeed, many may be totally asymptomatic as epitomised by the finding of phaeochromocytomas at postmortems performed for traumatic death.[4] In cases of genuine therapeutic resistance, 24-hour urinary catechol, metanephrine and normetanephrine levels (with a urinary creatinine level) should be measured to confirm phaeochromocytoma.

Similarly, the incidence of hyperaldosteronism (Conn's syndrome) is much higher than usually taught, being closer to 10% than 1% of patients with hypertension.[5] Further, more than 95% of patients with hyperaldosteronism are normokalaemic, negating the measurement of plasma potassium concentration as a screening test. If hyperaldosteronism is suspected or therapeutic resistance is being investigated, an aldosterone-to-renin ratio needs to be measured. However, this ratio may be affected by various antihypertensive agents, which may alter either the renin or the aldosterone levels. Beta blockers decrease renin levels, resulting in a spuriously elevated ratio. Other drugs that may affect renin and/or aldosterone levels, and thus the aldosterone-to-renin ratio, include angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics and the oral contraceptive pill.



Obstructive sleep apnoea is another frequently unrecognised cause of therapeutic resistance. Treatment of the sleep apnoea often restores therapeutic responsiveness in patients with hypertension. Thus it is appropriate to investigate sleep apnoea in patients who appear resistant to antihypertensive therapy if they snore and are overweight or obese.

Unrecognised use of prohypertensive substance

Agents such as NSAIDs, including COX-2 inhibitors, are in common use and cause therapeutic resistance in patients with hypertension. Recreational drugs such as amphetamines and cocaine, alternative medicines such as St John's wort and ginseng, and even foods such as liquorice may also be responsible for therapeutic resistance (for more complete lists see *Guide to management of hypertension 2008* [updated September 2010; in production] pp. 9,10).[3]

Additionally, the efficacy of ACE inhibitors and ARBs may be ameliorated or entirely abrogated by a high dietary salt intake. Measurement of the 24-hour urinary sodium excretion quickly elucidates whether this may be the cause. In assessing sources of unrecognised salt intake, one should be aware of cultural variations that may mask this on

Table 1. Impediments to effective management of hypertension

- Accuracy of blood pressure measurement
- Unrecognised secondary hypertension
- Unrecognised use of prohypertensive substances
- Failure to diagnose the need for pharmacological therapy
- Therapeutic inertia
- Compliance issues

Table 2. Upper limits of normal for home and ambulatory blood pressures*[3]

	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Ambulatory		
24-h average	130	80
Awake average	135	85
Asleep average	120	70
Home measurement		
Daytime	135	85

* Adapted with permission from *Guide to management of hypertension 2008. Updated September 2010* (in production). © National Heart Foundation of Australia.[3]

routine questioning. For example, various sauces used in Asian foods – soy, oyster, fish, teriyaki – are very high in salt, and kosher meat preparation is a significant contributor to salt intake.

Failure to recognise the need for pharmacological therapy

In patients with hypertension the presence of an associated condition such as diabetes or evidence of end-organ damage such as albuminuria (in the patient who doesn't have diabetes), left ventricular hypertrophy or vascular disease indicate the need for pharmacological therapy in addition to lifestyle measures. In the absence of these comorbidities, some patients with mild-to-moderate hypertension who are at high risk for cardiovascular events may not receive pharmacological therapy unless they are assessed appropriately. To differentiate those patients who require pharmacological therapy in addition to lifestyle measures, a cardiovascular risk assessment should be undertaken.

Therapeutic inertia

Therapeutic inertia is probably best defined as therapy not being increased despite patients having repeatedly elevated blood pressure readings. It is not unique to blood pressure management; it has also been reported in lipid management. Therapeutic inertia appears to be the main cause for the failure of patients to attain blood pressure targets as indicated by studies in both primary care (general practice) and specialist clinics.[6-9] Confronted with repeatedly elevated blood pressure readings, 80% of doctors do nothing, 3% change treatment to an equally inefficacious dose of another agent, and the remainder are equally split between increasing the dose of the existing agent or adding a second agent.

Compliance issues

Generally, compliance issues are of lesser importance in contributing to the failure to attain blood pressure targets than usually thought. Side effects of medication do affect compliance, with patients ceasing or reducing doses without informing their doctor, but the issue of once- or twice-daily dosing appears to have little impact. However, the issue of multiple medications is of importance. Many patients with hypertension, particularly those in older age groups, have several other conditions (e.g. diabetes and hyperlipidaemia) for which they also require medication, and often more than one drug for each condition. This requirement for multiple drugs may affect compliance in two ways:

- there may be confusion as to whether an individual dose of a particular medication has been taken, leading to its omission
- issues of cost may occur, with patients omitting to take one or more drugs until they can afford to purchase them again.

Improving blood pressure management

Blood pressure guidelines should in general provide a succinct, up-to-date (at the time of publication) summary of the evidence for who to treat and blood pressure targets and an integrated summary of the various clinical trials to provide therapeutic recommendations. Although guidelines are necessary to provide the framework for treatment, research has shown that of themselves they do little to improve practice and increase the number of patients attaining their appropriate blood pressure target.[10] Overlaying traditional education programs, such as lectures or seminars, do little to change practice.[10] Mentoring programs, whether undertaken by physicians, nurses or pharmacists, that provide stepwise guidance for increasing therapy do appear to improve outcomes.[11]

It has been suggested that the paucity of experience during both undergraduate and postgraduate training in the ongoing

management of chronic disease forms the basis of clinical inertia and for therapeutic gaps such as occur in hypertension management.[8] This inexperience results in a lack of confidence in how to increase therapy and to determine what are maximum acceptable doses and the preferred therapeutic combinations. Mentoring programs provide a milieu in which to acquire this experience and confidence and thus overcome therapeutic inertia.

Current Australian recommendations

The most recent *Guide to the management of hypertension 2008* (updated September 2010; in production) provides new blood pressure targets and therapeutic recommendations.[3]

Table 3. Identification of patients who need immediate initiation of antihypertensive treatment*[3]

- Patients with a systolic blood pressure of 180 mmHg or greater, and/or diastolic blood pressure of 110 mmHg or greater (i.e. grade 3 [severe] hypertension)
- Patients with isolated systolic hypertension plus a widened pulse pressure (i.e. a systolic blood pressure of 160 mmHg or greater and a diastolic blood pressure of 70 mmHg or less)
- Patients with evidence of end-organ damage or one or more associated conditions (such as diabetes, cerebrovascular disease, chronic kidney disease, peripheral arterial disease), irrespective of blood pressure
- Patients at high absolute risk of cardiovascular disease
- Early treatment should also be considered in Aboriginal and Torres Strait Islander adults with hypertension after careful assessment of cardiovascular risk, and in patients at a 10 to 15% risk of a cardiovascular event in the next five years as estimated using a risk calculator.

* Adapted with permission from *Guide to management of hypertension 2008. Updated September 2010* (in production). © National Heart Foundation of Australia.[3]

Blood pressure targets

As the risk for cardiovascular events as a function of blood pressure is a continuum, the general advice is to reduce blood pressure as far as is tolerated. For patients with end-organ damage or with conditions such as diabetes or previous cardiovascular events, a target of less than 130/80 mmHg has been set, and for patients with proteinuria greater than 1 g/day, a target of less than 125/75 mmHg has been set.

Therapeutic recommendations

Initiating therapy in uncomplicated hypertension

Regardless of the antihypertensive treatment chosen, all patients with hypertension should be advised on lifestyle modification, including the need for regular physical activity, smoking cessation, maintenance of an ideal weight, salt restriction and limiting alcohol intake. Recommendations for immediate initiation of antihypertensive treatment in patients are listed in Table 3.

As a consequence of accumulating evidence, thiazide diuretics are no longer recommended as first-line therapy for hypertension in patients under 65 years of age. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated an excess incidence of new onset diabetes of approximately 2% per annum in patients treated with thiazides compared with those treated with ACE inhibitors.[12] This confirmed the incidence of new onset diabetes shown in the Medical Research Council (MRC) trials.[13,14] However, in patients aged over 65 years, in whom systolic hypertension becomes more prominent, thiazides have a demonstrated benefit.[15]

Beta blockers are no longer recommended as first-line therapy for uncomplicated hypertension in any age group. The Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA) highlighted the propensity of combined thiazide and beta blocker therapy to cause new onset diabetes with an incidence approaching 5% per annum.[16] This trial sparked a number of meta-analyses focusing on the association between treatment with beta blockers and new onset diabetes, and all recommended that beta blockers no longer be used as first-line therapy in uncomplicated hypertension.[17]

ACE inhibitors and ARBs are now considered interchangeable. A large number of clinical trials have demonstrated equivalent outcomes for ACE inhibitor and ARB therapy. Unfortunately, all these trials have been powered to demonstrate noninferiority and, apart from the incidence of side effects in which ARBs have shown a definite advantage, the question of whether ARBs are the superior therapy has yet to be answered.

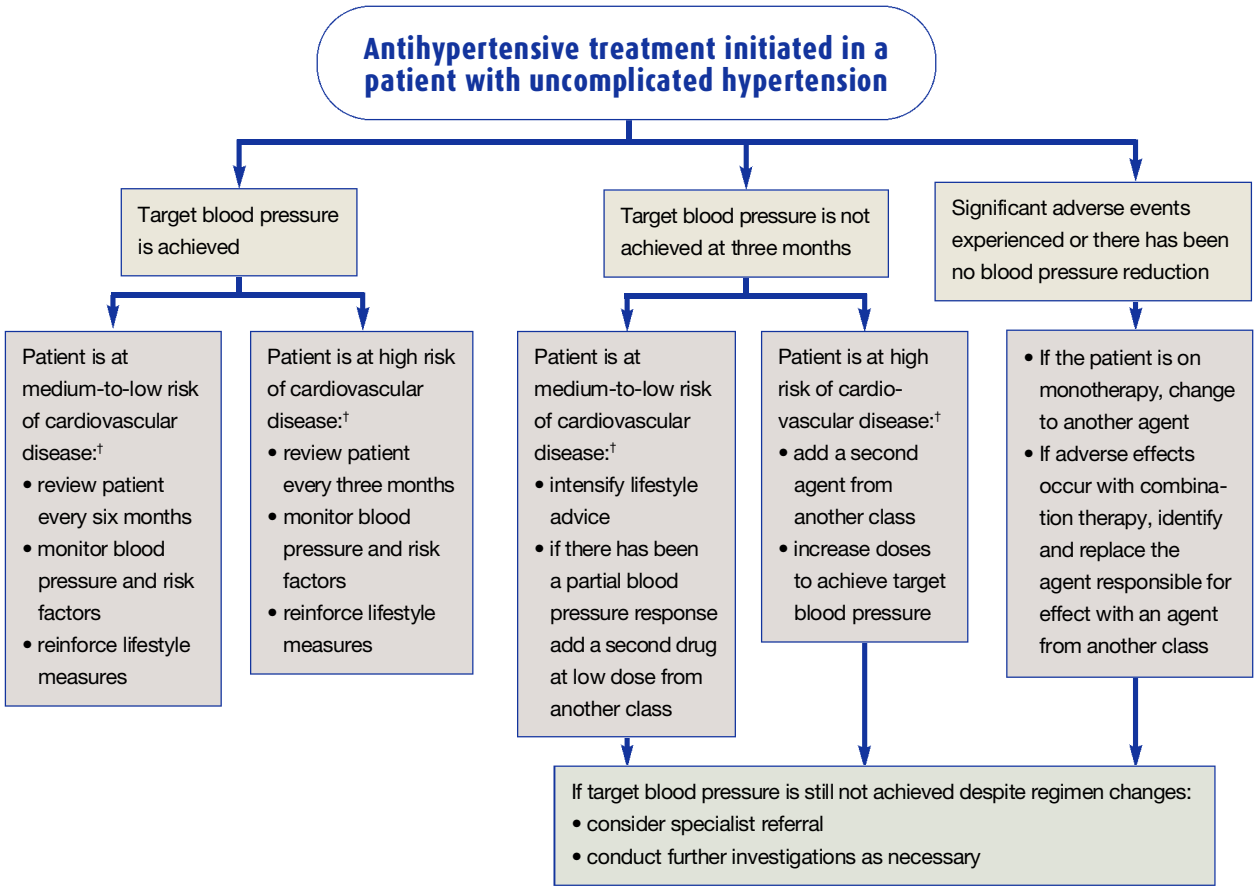
For patients with uncomplicated hypertension, an antihypertensive agent from one of the following classes is recommended for initial and maintenance therapy: ACE inhibitors, ARBs, dihydropyridine calcium channel blockers (CCBs) or low dose thiazide diuretics (for patients aged 65 years or over).

Combination therapy in uncomplicated hypertension

Combination therapy is necessary for patients with hypertension in whom blood pressure targets are not met on monotherapy. A preferred combination of an ACE inhibitor (or ARB) and a calcium channel blocker (CCB) has been recommended based on the findings of the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living

continued

Maintenance and follow up of patients being treated for uncomplicated hypertension*



* Adapted with permission *Guide to management of hypertension 2008. Updated September 2010* (in production). © National Heart Foundation of Australia.[3]
† Cardiovascular risk assessed clinically and/or using a risk calculator.

With Systolic Hypertension (ACCOMPLISH) trial.[18] Most trials of combination therapy have compared ACE inhibitor or CCB based therapy with beta blocker based therapy; few have directly addressed the question of a preferred second agent in ACE inhibitor (or ARB) therapy. ACCOMPLISH compared treatment with amlodipine or hydrochlorothiazide added to treatment with the ACE inhibitor benazepril (not currently available in Australia). This trial was stopped early due to a 19.6% reduction in cardiovascular events (including cardiac death) in the CCB group compared with the thiazide group. For those with side effects from CCBs, the combination of a thiazide and ACE inhibitor (or ARB) still provides adequate blood pressure control.

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) showed poorer outcomes with combined ACE inhibitor and ARB therapy than with either agent alone,[19] suggesting that the combination should be avoided. The findings of ONTARGET contrast with those of the Candesartan And Lisinopril Microalbuminuria (CALM II) study, in which no difference in adverse events between single and dual agent therapy was observed.[20] CALM II compared lisinopril 40 mg/day with candesartan 16 mg/day plus lisinopril 20 mg/day, whereas ONTARGET compared ramipril 10 mg/day, telmisartan 80 mg/day and the combination ramipril 10 mg/day plus telmisartan 80 mg/day. The different reported adverse outcomes may reflect the overall level of renin angiotensin system (RAS) blockade. In CALM II the levels of RAS blockade in single and dual agent therapy were equivalent. In contrast, in ONTARGET the level of RAS blockade in the dual therapy group was significantly

greater than that in either of the single therapy groups. As a consequence adverse events such as hyperkalaemia, which are dose related, would be predicted to be increased in the dual therapy group.

Thus, although combined therapy with an ACE inhibitor and an ARB may have benefit in selected groups (e.g. by reducing proteinuria while managing hypertension in patients with renal disease), its general use cannot be recommended until the adverse outcome question has been addressed with an appropriately designed and powered trial.

The flowchart on page 18 summarises the steps in the stabilisation, maintenance and follow up of patients after the initiation of antihypertensive treatment.

Conclusion

Hypertension remains the most common reason for GP consultations; however, despite guidelines and numerous education programs and audit programs, the significant therapeutic gap has remained unchanged. Recognition of the factors (such as therapeutic inertia) that are the main contributors to this and the widespread implementation of strategies (such as mentoring programs) that have been shown to work may in the longer term reduce this therapeutic gap. MT

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Hypertension

Dietary and lifestyle measures in a nutshell

Elevated blood pressure is affected by diet and activity and is the most important contributor to cardiovascular and cerebrovascular events. Elevated blood pressure and hypertension are preventable and, if present, can be reduced by lifestyle alterations.

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Cardiovascular and cerebrovascular diseases are the most common causes of death in the Western world and are becoming increasingly common in developing countries. It is an enormous expense for individuals, government and society in general. The most important overall contributor to cardiovascular death is increased blood pressure. It is a more important contributor than diabetes, smoking, obesity or elevated cholesterol.

Hypertension, defined as a blood pressure level higher than 140/90 mmHg, contributes to about 50% of the increased risk of cardiovascular disease due to blood pressure. The other half is contributed by blood pressure above the optimal level of less than 120/80 mmHg but below the International Society of Hypertension and European Society of Hypertension guidelines level of 140/90 mmHg for initiation of drug therapy.

Aetiology of hypertension

If the exact cause of essential hypertension was known, treatment paths could be clearly defined; however, hypertension is not caused by one factor alone. It is probably due to abnormalities in a variety of factors that contribute to the resulting increase in blood pressure.

There are specific inherited genetic defects that increase blood pressure. Most of these defects involve abnormalities in the handling of sodium by the body, either because of a defect in the kidney or because of an abnormality in the hormonal systems that control sodium excretion. An exception to this is phaeochromocytoma, which causes blood pressure elevation because of high levels

IN SUMMARY

- **Half of all heart attacks and strokes occur in people who do not meet the guidelines for drug treatment.**
- **A low plasma potassium level and/or a low potassium dietary intake is associated with a threefold or greater increase in strokes and sudden death.**
- **Successful implementation of sodium restriction lowers blood pressure to a similar extent as drug monotherapy.**
- **Dietary advice should be holistic, recommending a reduction in sodium, saturated fats and alcohol consumption, and an increase in potassium and complex carbohydrate consumption. This can be achieved by eating less processed foods and animal fat and more fresh fruit and vegetables and fish.**
- **No randomised trial has proven at what level lifestyle intervention should start. Common sense suggests that it is safe and worthwhile in all people.**

of catecholamines, which in turn causes a loss of sodium. Monogenetic diseases are relatively uncommon but it has been postulated that minor deficiencies in the various inherited processes determine if a person is unable to cope with extremes of lifestyle and environment.

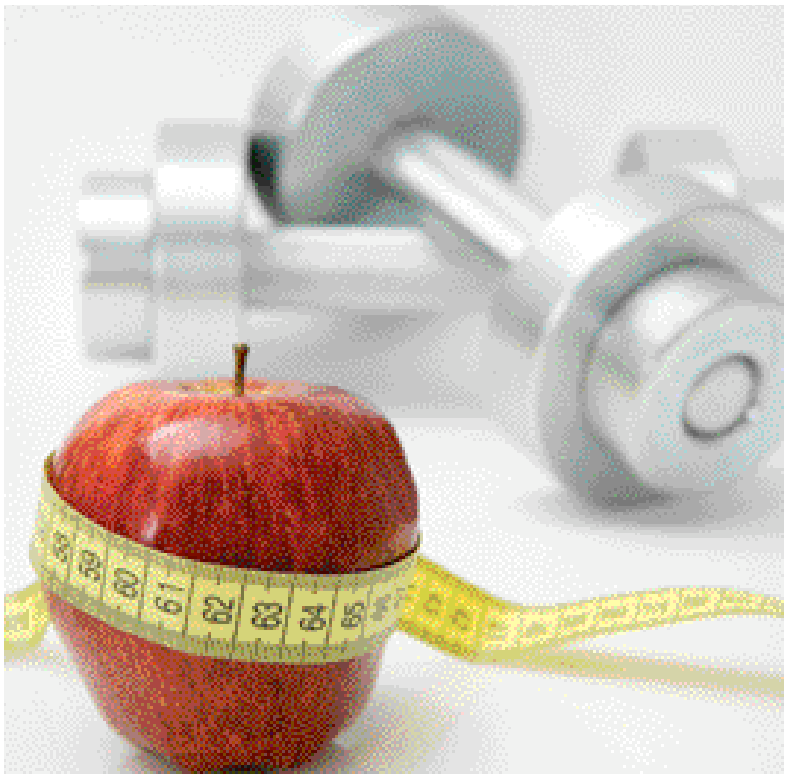
When populations moved from a 'hunter-gatherer' existence into our current form of society, cardiovascular disease and elevated blood pressure, which were almost nonexistent in the initial society, became more common. There is a genetic component involved but this is only expressed under appropriate conditions. When populations moved away from a hunter-gatherer existence the following lifestyle changes occurred:

- food intake changed with an increase in sodium chloride, refined carbohydrates and saturated fat and a decrease in potassium and fibre
- activity was usually reduced
- smoking was likely to increase.

The result was that people gained weight, developed diabetes and had increased blood pressure and cholesterol levels, which all contributed to the cardiovascular epidemic. There is a question of whether obesity, diabetes or high blood pressure is the most important problem but this does not need to be answered. The strategies to reduce all of them are based on similar principles.

Interventions for hypertension

There are three approaches for the prevention of hypertension. The first and ideal is to prevent blood pressure reaching a level at which it causes end-organ damage. This is primary prevention. It is debated whether this approach should be applied to everyone or just groups and individuals at risk. A second approach is to wait until blood pressure is elevated and a diagnosis of hypertension is made. Then treatment with lifestyle interventions can be used to reduce blood pressure. The third important approach is to concentrate not only on interventions that reduce blood pressure but also on lifestyle changes that reduce total cardiovascular risk. The approach needs to be holistic, reducing all risk factors. All the major modifiable risk factors (raised blood pressure, high cholesterol, high blood sugar, obesity) are continuous variables and values inside the normal range contribute to cardiovascular risk (see the flowchart on page 22).



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Reducing blood pressure

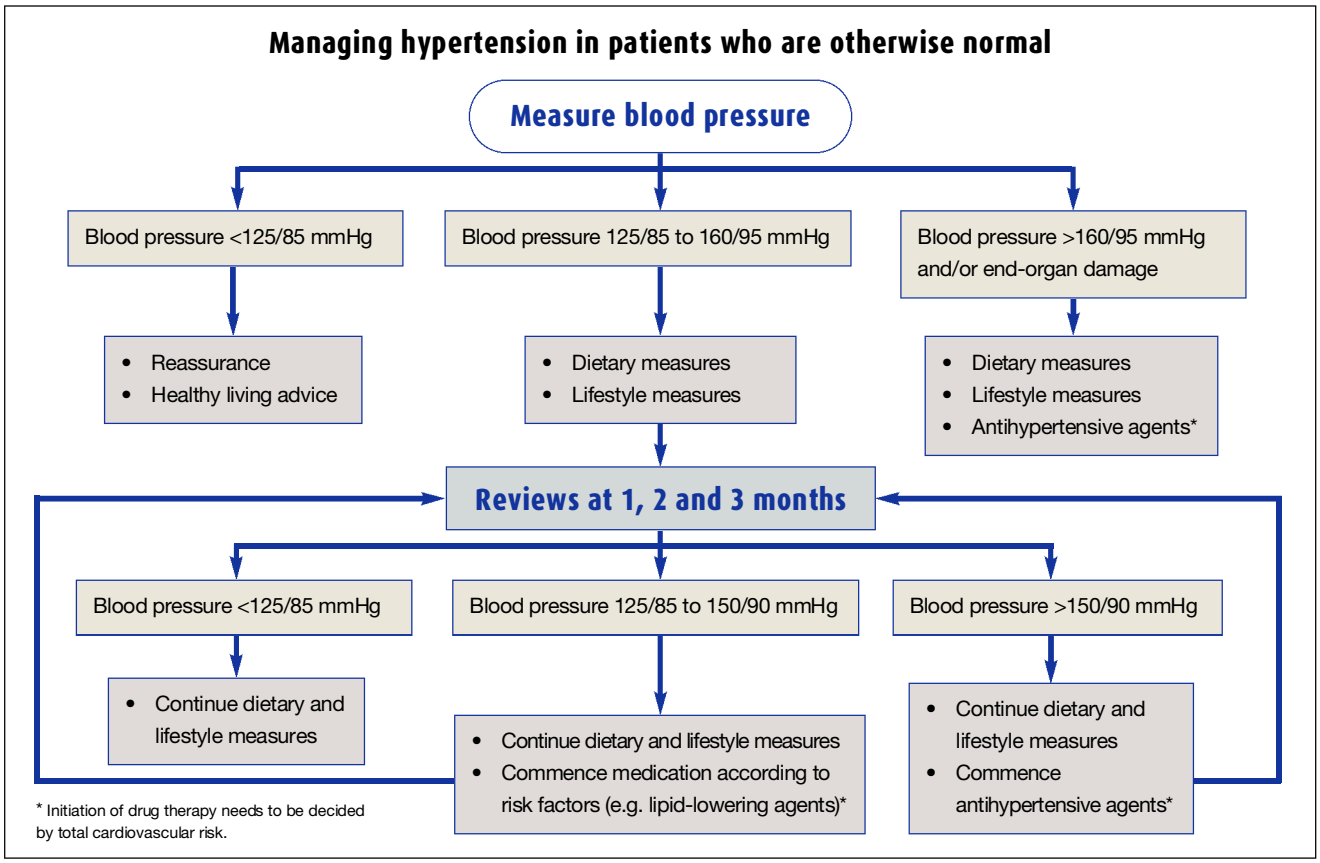
High sodium intake and low potassium, calcium and magnesium intakes all have epidemiological associations with elevated blood pressure and cardiovascular deaths. The significance of the association (p value) may be high but the correlation coefficient (r value) may be low. Therefore, low calcium and/or low magnesium intakes only account for a very small number of people with elevated blood pressure.

Calcium and magnesium

Studies have shown that calcium and magnesium supplementation have little or no effect on blood pressure. However, a diet with an adequate intake of calcium and magnesium is justifiable to prevent bone disease and possible arrhythmias.

Sodium and potassium

Modestly restricting sodium intake to about 70 mmol/day reduces blood pressure by 6/3 mmHg, similar to the decrease of 8/5 mmHg achieved by placebo-controlled monotherapy. All guidelines advocate sodium restriction and most doctors advise patients to reduce sodium intake; however, in most cases this is lip service, because few doctors measure patients' 24-hour excretion of sodium. Unless this is measured there is little information about what has been achieved. Dietary recall is notoriously inaccurate for sodium



intake, unless performed in a research centre. Sodium is so universally present in processed and fast foods that individuals find it difficult to reduce their salt intake. In Australia, the addition of salt in cooking and at the table probably accounts for about 10 to 15% of daily salt intake.

Potassium supplementation has been shown to reduce blood pressure in humans, as well as in rats but it is not commonly practiced. Increased potassium intake reduces the incidence of strokes. Low plasma potassium levels in the Systolic Hypertension in the Elderly Program (SHEP) were associated with a three- to fourfold increase in stroke and sudden death. The epidemiological factor that has the strongest correlation with the prevalence of high blood pressure is the sodium to potassium ratio, either in the diet or the urine. If this ratio is less than one, hypertension is uncommon.

The effects of sodium reduction and potassium increase are usually assessed by short-term studies measuring blood pressure. However, the benefits are probably much greater because there is epidemiological and experimental evidence of an association between a high sodium intake and cardiac hypertrophy, vessel stiffness osteoporosis and other conditions, all of which have adverse contributions to health.

Reducing weight

There is a clear association of obesity with hypertension. Obesity causes activation of the sympathetic nervous system and a variety of hormones that can alter blood pressure. These almost certainly contribute to increased blood pressure but it is likely that the sodium content of the diet makes a further contribution. Blood pressure falls during weight loss.

Morbidly obese people frequently have high blood pressure, diabetes and elevated cholesterol levels. Hyperbariatric surgery may cause major weight loss and resolution of these factors. It is tempting to assume that this benefit is because of the weight loss but as the dietary intake is markedly restricted, the effect may be due to the altered food intake.

Moderating alcohol intake

One or two standard units (10 g) of alcohol each day appear to have a beneficial effect on cardiovascular outcomes, although this is likely to be confounded. Higher alcohol intake is associated with an increase in blood pressure and adverse events. Blood pressure rises by 1 mmHg for each standard drink. Some people who drink six or more drinks a day have an elevated blood pressure that is unresponsive to drugs or they have poor compliance, and the only way to achieve control is by reducing or stopping alcohol ingestion.

Increasing physical activity

Increased physical activity has the beneficial effect of reducing blood pressure. Exercise only needs to be of modest intensity for 30 minutes five times a week to see a reduction in blood pressure. This exercise can also be completed in 10-minute sessions. Increased activity reduces cardiovascular events and should be encouraged, especially in the sedentary. Exercise associated with a dietary program

may also help weight loss. However, the absence of the need for weight loss is not a reason to cease exercise. It has beneficial effects on glucose metabolism independent of weight loss due to its beneficial effects on lean body mass.

Importance of sleep

Sleep blood pressure is an important predictor of outcome and there is evidence that poor sleep patterns may be associated with adverse outcomes. The presence of sleep apnoea is an important cause of difficult to treat hypertension and should be considered in overweight people and, if present, treated. There is also evidence that poor sleep patterns, independent of sleep apnoea syndrome may be associated with hypertension and increased morbidity. There may also be an association with depression. However, although there is this association there is at present no evidence regarding treatment outcomes.

Reducing complications

Smoking cessation

There is little direct association between smoking and elevated blood pressure. When smoking is ceased there may be a modest weight gain. However, the benefits of stopping smoking on cardiovascular outcomes exceed any harmful effect of the gain in weight, although this should be limited as much as possible.

Cholesterol and lipid management

Management of cholesterol and lipids should be routine in all patients with hypertension. In obese people, reduction of fat and oil intake assists in weight loss. In nonobese people, substitution of saturated fat with mono- or polyunsaturated fats will lower cholesterol. Reduction of saturated fat intake is far more important than reduction of cholesterol intake. Intake of omega-3 unsaturated fatty acids (fish oils) lowers plasma cholesterol and has some blood pressure-lowering effect. Use of mono- or polyunsaturated margarine is recommended over butter and the use of margarines with naturally occurring sterols may be helpful, although the cost may be greater than using pharmacological therapy for the effect achieved.

Patient selection

Most people with hypertension will eventually need drug therapy to attain the ideal blood pressure goal (less than 130/80 mmHg). Initiation of drug therapy is based on an individual's absolute risk score rather than a single risk factor measurement such as blood pressure. Nonpharmacological therapy should be initially used in most people and this consists of reducing sodium chloride intake, increasing potassium intake, reducing weight if overweight and initiating an exercise program if sedentary.

If a patient's initial blood pressure is less than 160/90 mmHg it is probable that nonpharmacological therapy should be continued for up to three months. It should be instituted at the first visit because three or four visits will be required before it is known if blood pressure needs to be pharmacologically treated. To determine whether your advice or that of the dietitian is being followed, a 24-hour urine sample should be collected to determine the sodium and potassium excretion and, therefore, intake. Patients with hypertension should have their renal function, fasting cholesterol and fractions, triglycerides and glucose measured. All patients should be given advice to reduce their intake of saturated fat, although how strongly this advice is stressed will depend on the patients' plasma levels.

If drug therapy is required, the reduction in sodium intake makes patients more responsive to most drug therapies, particularly ACE inhibitors (e.g. perindopril and ramipril) and angiotensin receptor blocking drugs (e.g. irbesartan, telmisartan and candesartan). The response to dihydropyridine calcium blocking drugs (such as amlodipine, felodipine, lercanidipine and nifedipine) is independent to sodium intake, and if a person continues with a high salt intake or has a disorder that retains sodium, these may be the drug of choice.

Lifestyle changes and dietary restriction in many people with established hypertension will frequently not be adequate to control blood pressure because of either end-organ damage or failure to implement drug therapy to the required degree. More than one antihypertensive drug is usually required to achieve the blood pressure target and the use of combined tablets (amlodipine and valsartan, enalapril and lercanidipine, felodipine and ramipril, indapamide and perindopril, perindopril and amlodipine and trandolapril and verapamil) can improve compliance and reduces the cost to the patient. Diuretics have usually been part of such combinations, particularly with ACE inhibitors and angiotensin receptor blockers as this improves their effectiveness.

The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial showed that treatment with an ACE inhibitor and amlodipine resulted in improved outcomes. Many patients with elevated blood pressure also have elevated cholesterol and combination tablets across the therapeutic classes, such as amlodipine and atorvastatin, are indicated in such cases.

Nonoptimal blood pressure or patients with prehypertension

The role of lifestyle interventions is probably most important in patients who do not meet the guidelines' indication for drug therapy or have nonoptimal blood pressure. Half of all strokes and heart attacks occur in people who do not qualify for drug treatment according to the guidelines. Blood pressure levels track so a person with a blood pressure of 130/85 mmHg is more likely to become hypertensive than a person

Table. Factors that emphasise need for early lifestyle intervention*

Family history
Hypertension
Heart attack
Stroke
Diabetes
Personal history
Obesity
Diabetes
Elevated lipid concentration
Metabolic syndrome
End-organ damage
Elevated absolute risk score
At-risk populations
Aboriginies
Torres Strait Islanders
Polynesians
South Asians

* Intervention independent of blood pressure level but essential if blood pressure is more than 130/85 mmHg.

with a blood pressure of 120/80 mmHg.

A large segment of the population has nonoptimal blood pressure and treatment needs to be based on community education, individual advice (including communication of absolute risk) and government action. The government should act on issues such as food labelling, reducing the sodium content of foods either by introducing voluntary standards or by legislated levels, and providing incentives for people to eat 'healthy cardiovascular foods'. Similar issues are relevant for measures to reduce obesity and diabetes in our society.

Specific groups at risk

A population-based approach to managing hypertension would probably achieve the best outcome at a lower cost. However, there are certain groups in whom lifestyle advice should be given earlier (Table). If there is a family history of stroke, heart attack or hypertension, nonpharmacological and lifestyle changes should be implemented as early as possible. Patients with diabetes have salt-sensitive hypertension and patients with renal disease are salt sensitive. Older patients develop renal impairment and are unable to handle a sodium load. In these groups, salt restriction should be started early together with an increase in potassium intake, except in the case of people with renal failure.

Advice to patients

Alterations to food intake should be multifaceted, as well shown in the Dietary Approaches to Stop Hypertension (DASH) study. The advice from this study to be given to patients is to eat more fresh and less processed foods. Most processing involves the removal of potassium and the addition of sodium chloride. Processed meats and many cereals have salt added, which is unnecessary and converts a potentially healthy food into one with negative health values. Unprocessed muesli meets the requirements of being a healthy food but most people eat toasted muesli that has had sodium chloride and/or sugar added to it and has been toasted in oil, again converting a healthy food into one with negative health values. A fruit muesli bar may be a less healthy option than a chocolate bar.

The advice is to eat more fruit and vegetables, avoid animal fat and refined carbohydrates. Patients should also be advised to eat fish one or two times a week and exercise at least three times a week for a minimum of 30 minutes.

Patients should learn to read food labels and avoid foods with a high saturated fat and sodium content. If the sodium content is greater than 300 to 400 mg per 100 g the food is salty and should be eaten in small quantities or avoided. It is difficult to find many staple foods that do not contain this much sodium.

The problem for patients is to understand what the food label means and to obtain staple foods that meet their requirements. Most breads contain more salt than is recommended and a low-sodium high-potassium bread is needed. Unfortunately, food labelling does not include the potassium content; if it was present the advice would be to choose foods with more potassium than sodium.

Achieving lifestyle alterations for an individual is difficult due to the demands of life in our society and the 'convenience' of processed foods. A program based on education coupled with alterations in the foods consumed is required to reduce blood pressure (prevent hypertension), diabetes and obesity, and thereby restore cardiovascular health.

Conclusion

Cardiovascular disease is the most common cause of death in Australia and hypertension is the most important modifiable risk factor for cardiovascular disease on a population level. Hypertension is a lifestyle disease and can be treated and ideally prevented by lifestyle management. Hypertension, diabetes, abnormal lipids and obesity all interact and lifestyle management should be directed at all of these rather than one in isolation.

Half of all cardiovascular deaths and strokes occur in people who do not meet the blood pressure level for drug treatment set out in the guidelines but have nonoptimal blood pressure. Hence, the importance of ascertaining an individual's absolute risk score.

A dietary reduction of sodium and increase in potassium can reduce blood pressure and cardiovascular mortality. Lifestyle advice should be given to all individuals at risk of cardiovascular disease and backed up with education programs to alert the patient to the dangers of hypertension. Foodstuffs to enable patients to follow dietary advice need to be more readily available. MT

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Renal artery stenosis and hypertension

Whom and how to screen and treat

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Associate Professor Mangos is Convenor and Dr MacGinley a member of the Caring for Australasians with Renal Impairment (CARI) Renovascular Working Group. The group's evidence-based guidelines on the management of renovascular disease was published in April 2010 and is available on the CARI website (www.CARI.org.au).

Patients with renal artery stenosis are at high risk of cardiovascular events. Aggressive medical therapy to lower cardiovascular risk is the first priority in these patients; endovascular treatment is required in only a few carefully selected cases.

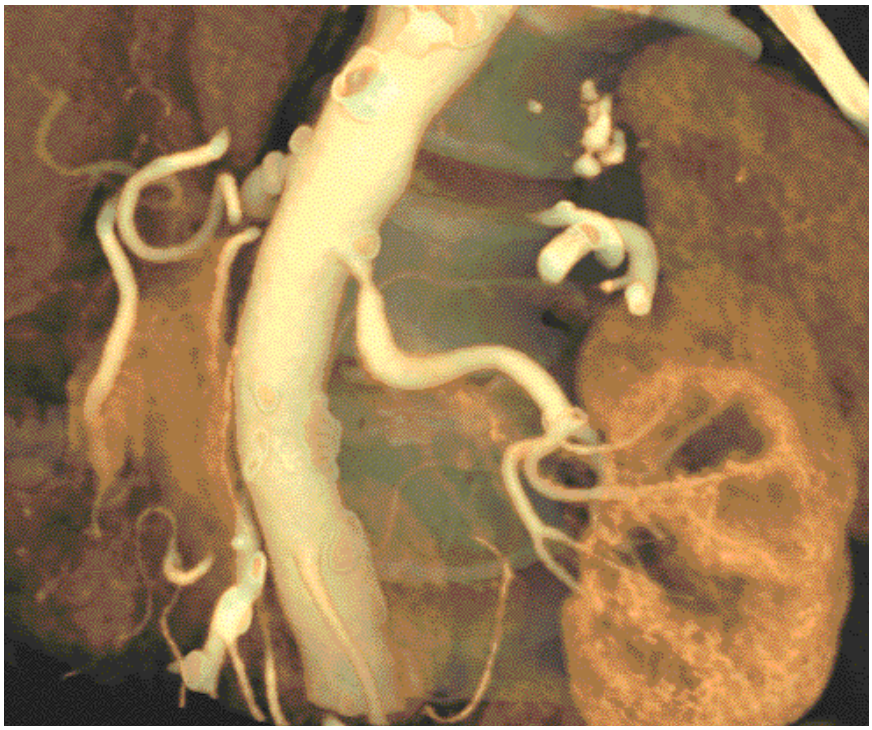
Renovascular disease, often presenting in the patient with vascular disease and no other symptoms, has been considered a common and potentially treatable cause of secondary hypertension. However, whether medical therapy or endovascular treatment is the optimal strategy for patients with renovascular disease has been an area of contention. Recent evidence now suggests that the benefit of angioplasty of the renal arteries may be limited to selected patients.

The scope of this review is to direct clinicians to the groups of patients who may require screening, to discuss the appropriate modalities of screening and to consider the selection of patients for intervention in addition to the successful medical management that currently occurs.

IN SUMMARY

- **Renovascular disease is common and is an underlying cause in a significant proportion of patients who have refractory hypertension.**
- **The appropriate selection of patients for investigation and subsequent interventional treatment is the key. Interventional treatment for severe renal artery stenosis (RAS) is reasonable in patients with poorly controlled hypertension despite taking more than four antihypertensive agents, pulmonary oedema with normal left ventricular systolic function, a progressive decline in renal function or recent end-stage kidney disease.**
- **Although magnetic resonance angiography and spiral computed tomography angiography are more accurate than other imaging techniques in detecting RAS, the benefits of these modalities must be weighed against their potential side effects.**
- **Appropriate medical therapy with multiple medications, including antihypertensive agents, antiplatelet agents and statins, is probably as effective in the nonselected population as interventional therapies.**
- **Cardiovascular mortality is high in patients with RAS: the key aim of therapy is to target cardiovascular risk factors to prevent mortality and morbidity.**

continued



PHOTOLIBRARY

Figure 1. Spiral computed tomography angiogram showing severe stenosis of the left renal artery.

Who develops renal artery stenosis?

The following case is typical of a patient who may present in general practice and in whom a diagnosis of renal artery stenosis (RAS; Figure 1) should be considered. Comments on the appropriate assessment and treatment of this patient are discussed later in the article.

Case study

A 75-year-old man comes to your practice with a blood pressure of 160/70 mmHg. He has been a smoker, had high lipid levels and had poorly controlled hypertension for the past 10 years despite taking four antihypertensive agents.

Clinical examination demonstrates carotid bruits, no renal bruits and a fourth heart sound. His serum creatinine level is 150 µmol/L (estimated glomerular filtration rate [eGFR] 45 mL/min) and urinalysis shows 1+ protein.

The ultrasound of his renal tract shows a discrepancy in renal size (right 10 cm; left 7.8 cm) and a suggestion of increased velocity in the renal artery of the smaller kidney; however, there is too much interference to make any significant conclusion about the presence of RAS.

How should this patient be further evaluated and treated?

Aetiology of renal artery stenosis

With the increasing incidence of hypertension, chronic kidney disease (CKD) and/or diabetes in our population, the finding of atherosclerotic disease of the cerebral and coronary vessels in patients with these conditions is expected. However, we now know that there is a high likelihood that such patients will also have renal artery atherosclerotic disease.

Studies from the 1960s and 1970s showed that 27% of patients over 50 years of age had more than 50% stenosis of their renal artery (autopsy data) and up to 6% of cohorts with hypertension undergoing arteriography had RAS. In patients with refractory hypertension, between 20 and 40% of unselected subjects have been shown to have RAS.[1]

There is evidence that RAS is progressive, with studies conducted prior to interventions or medical treatments (such as statins) estimating a 14 to 39% progression of lesions over one to six years.[2] A clearer understanding of accurate progression rates is difficult to obtain because this atherosclerotic population has a high mortality rate. In the recent Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) study, 26% of patients with atherosclerotic renovascular disease died from a cardiovascular event during the five-year study duration.[3]

Classification of renovascular disease

Renovascular hypertension is systemic hypertension due to narrowing of the renal arteries. Although large and small (that is, intrarenal) vessel disease can exist, from a haemodynamic point of view, a proximal stenosis is significant when there is a pressure gradient across the stenosis. This pressure gradient triggers intrarenal adaptive mechanisms distally, leading to renal ischaemia and hypertension. The presence of coexistent small vessel disease will render the kidney nonresponsive to revascularisation.

RAS has two main aetiologies: atherosclerosis and fibromuscular dysplasia. Atherosclerosis accounts for 70 to 90% of cases of RAS and usually involves the ostium and proximal third of the main renal artery.[4] Fibromuscular dysplasia is a collection of vascular diseases that affects the intima, media and adventitia and is responsible for 10 to 30% of cases of RAS.[5]

Despite the many studies in the literature, there is no unifying classification of the degrees of stenosis versus severity and outcome. At least a 50% narrowing is necessary to produce a pressure gradient as mentioned above, as shown by a study

combining three-dimensional magnetic resonance angiography (MRA) and direct measurements across a stenotic lesion.[6] Despite a lack of consensus, most authors use a reduction in luminal diameter of 50% as a cut-off point to define the presence of haemodynamically significant RAS.[6] In the Caring for Australasians with Renovascular Disease (CARI) guidelines, the following classification has been devised based on the likelihood of progression:[1]

- less than 50% stenosis: insignificant
- 50 to 70% stenosis: moderate
- more than 70% stenosis: severe.

Diagnosis and assessment

Although all the imaging modalities used to investigate RAS have improved over the past decade, they do have potential side effects, which must be considered when selecting the most appropriate investigation for each patient. Additionally, in groups in whom significant harm is possible from undergoing screening diagnostic tests, there is the principal that any tests should be performed only in those who have a high pretest probability of having the disease. In the context of RAS, such patients may have impaired renal function, hypertension requiring more than four antihypertensive agents, diabetes or vasculopathy, or a renal bruit.

Case study continued

The patient has had refractory hypertension for many years, and investigations have revealed that the renal vascular bed is affected with a shrunken kidney (likely from ischaemia) and proteinuria of a level consistent with vascular disease. Although it is possible that this patient might experience side effects from imaging, he has a high pretest probability of having RAS and should therefore be further investigated.

Which imaging test to use?

The reported diagnostic accuracies of the different imaging tests used to investigate the renal arteries overlap, and the sensitivities and specificities of these tests vary according to methodological issues, specific patient groups and gold standard comparisons. The selection of the diagnostic test will depend on local resources available, cost and local expertise and experience, in addition to patient factors.

Duplex ultrasonography

The least invasive test is duplex ultrasonography, which, in the hands of teams with technical expertise, is a useful screening tool. Unfortunately, subsequent tests are often required because of the high rate of false-positive and false-negative results. Of note, the sensitivity and specificity of ultrasonography vary depending on the skill of the laboratory, and generally this investigation is of limited use in obese individuals. The calculation of the renal resistive index (RI) may predict the response to revascularisation – for example, a low RI indicates a healthy kidney distal to a stenosis.

Intra-arterial digital subtraction angiography

Intra-arterial digital subtraction angiography (IA-DSA) is regarded as the definitive tool to diagnose the presence of RAS. It is the only investigation that directly measures the lumen size of the renal artery and can measure a pressure gradient across most lesions. However, it is invasive, does not establish the functional nature of the stenotic lesion, and the degree of stenoses may be subject to substantial interobserver variations. In patients with large atherosclerotic burden, the significant complication of cholesterol embolic syndrome can result.

Renal scintigraphy

Renal scintigraphy is no longer recommended for the diagnosis of RAS based on its poor accuracy and the promised functional benefits in trials have not resulted in better outcomes in either treatment or diagnosis.

Table. Selection of patients for revascularisation of high-grade renal artery stenoses*

- Patients with refractory hypertension (blood pressure >160/100 mmHg and resistant to more than four antihypertensive agents)
- Patients who experience a greater than 30% rise in serum creatinine level after the commencement of ACE inhibitor or ARB therapy
- Patients with a progressive and rapid decline in kidney function with other causes excluded
- Patients with proven episodes of pulmonary oedema and normal baseline left ventricular function (often associated with severe hypertension)
- Patients with a high-grade stenosis (>70%) recently commenced on dialysis who have viable kidney tissue diagnosed by nuclear scanning (to attempt to recover dialysis-independent kidney function)

* Based on evidence reviewed in references 1 and 4. Includes evidence from both case studies and randomised controlled trials.

ABBREVIATIONS: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker.

Spiral computed tomography angiography

It is reasonable to recommend spiral computed tomography angiography (spiral CTA) as an accurate, minimally invasive screening test, especially suited to the diagnosis of RAS due to fibromuscular dysplasia. However, in patients who have moderate CKD (eGFR <60 mL/min) or more severe CKD, prehydration with intravenous saline (with or without n-acetyl cysteine or sodium bicarbonate) should be used to reduce the incidence of contrast nephropathy. If contrast nephropathy develops, management is expectant, and dialysis is rarely required. Usually renal function recovers

fully, although it is not uncommon to observe some loss of GFR in patients with underlying CKD secondary to the contrast insult.

Gadolinium-enhanced MRA

Gadolinium-enhanced MRA is highly sensitive in detecting atherosclerotic RAS and has significantly higher accuracy than any other modality in excluding the disease. The use of gadolinium in patients with eGFR less than 30 mL/min should be avoided in view of the risk of the relatively recently described nephrogenic systemic fibrosis, which is most likely to occur with repeated doses of gadolinium in patients with end-stage kidney disease. Nephrogenic systemic fibrosis is an illness causing fibrosis of skin and other tissues (not unlike scleroderma) and may not be reversible.

Case study continued

If the resources were available, the specialist would most likely consider spiral CTA for this patient or move directly to IA-DSA because he has poorly controlled hypertension.

What to do when renal artery stenosis is diagnosed?

Patients with renovascular disease have a markedly increased risk of coronary events, stroke, heart failure and death. Indeed, the risk of these events is significantly greater than the risk of progression to end-stage kidney disease. Although the immediate concern in patients with RAS is the control of blood pressure, overall cardiovascular mortality needs to be reduced. Aggressive medical therapy to reduce this risk is the first priority and supported by the evidence.[1,3] Referral to a renal specialist (or a similar hypertension specialist) for consideration of the involvement of interventional vascular clinicians is required in only a few selected cases (see the Table). There is no indication for recurrent imaging to follow renal size or the degree of stenosis. Knowledge of any progression of a stenosis does not dictate the required intervention. However, vascular physicians may organise follow-up imaging for patients with stented arteries at six months then yearly.

Diet and lifestyle

As in patients with other vascular diseases, salt restriction, weight loss, physical activity and cigarette cessation are likely to benefit patients with RAS by reducing their overall cardiovascular risk. In the recent ASTRAL study, patients with any degree of RAS (vascular burden) had a high mortality, probably secondary to uncontrolled hypertension or the existence of vascular disease in other beds.[3]

Medical therapy

In patients with unilateral RAS, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are useful for their ability to improve blood pressure and their overall cardiovascular benefit. A small initial rise in serum creatinine (less than 30%) is usually transient (i.e. occurring for less than three months) and acceptable.[5]

Bilateral RAS is considered a contraindication to the use of ACE inhibitors and ARBs. Acute renal failure occurs in about 30% of patients with bilateral RAS but is usually reversible. Initiation of ACE inhibitor or ARB therapy in such patients would usually be undertaken in hospital and in patients in whom the benefit would be very high (for example, in those with congestive heart failure).[7] It is essential that renal function is monitored if ACE inhibitors or ARBs are used in patients with bilateral RAS (greater than 60%) or in patients with RAS (greater than 60%) to a solitary functioning kidney. This includes initial testing at five and seven days and then two weeks after the initiation of a low dose of the medication.

Generally, ACE inhibitors should be used before ARBs in view of the large body of evidence for ACE inhibitors in many vascular disease states, and their lower cost. However, evidence for the use of ARBs in reducing mortality from cardiovascular disease is accumulating.

No other agents have been shown specifically to be as beneficial as ACE inhibitors or ARBs in this vascular population, but beta blockers, calcium channel blockers, diuretics and centrally acting agents are often used in combination due to the refractory hypertension that occurs in these patients.[5]

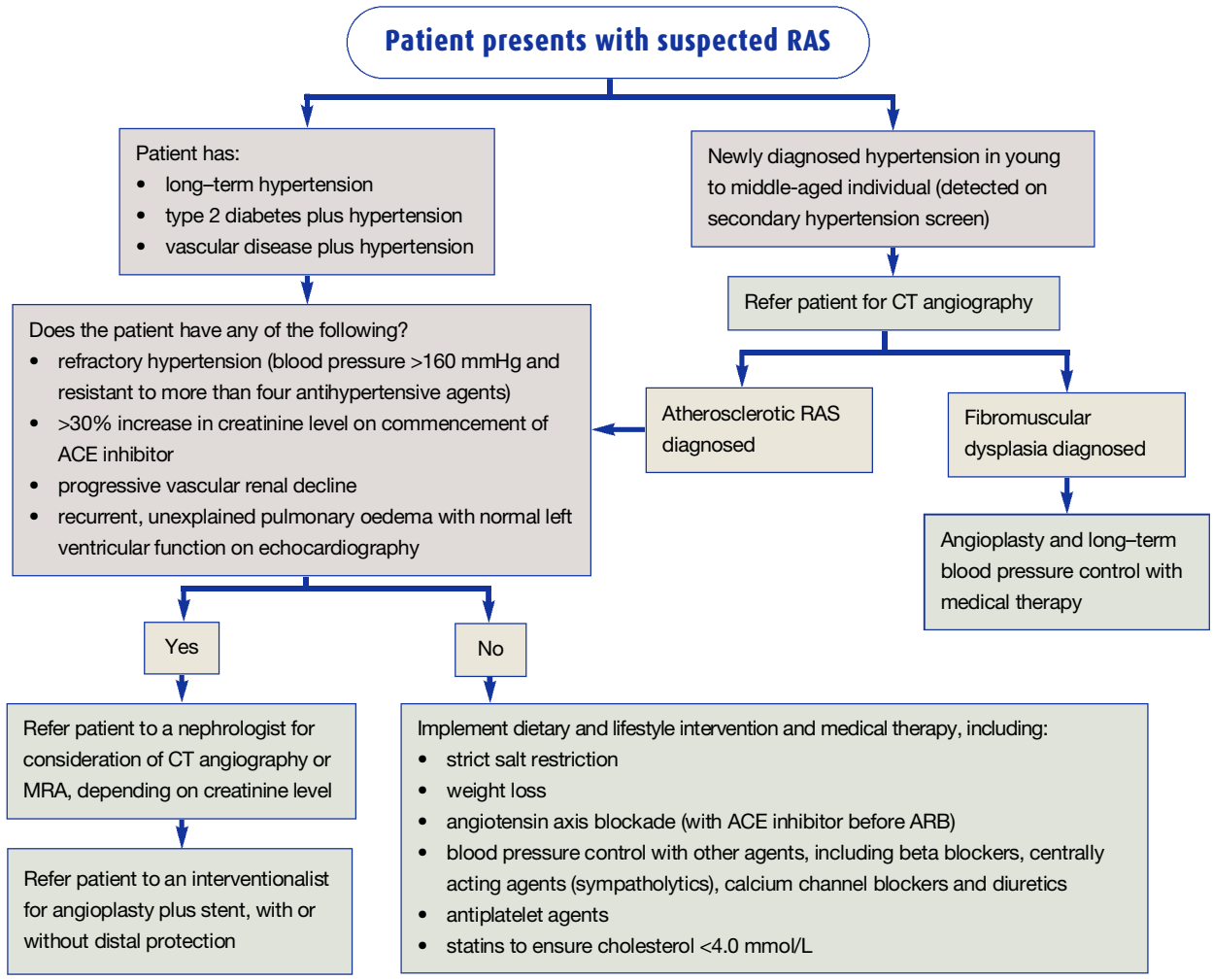
Although not formally studied in any comparative studies versus placebo, it would be standard practice for all patients with renovascular disease to be taking aspirin and/or another antiplatelet agent and a statin, both to delay renal disease progression and to reduce their high risk of cardiovascular mortality.

Endovascular treatment – definitely not for all

The effect of endovascular treatment of RAS on blood pressure reduction has been studied in more than 60 uncontrolled studies. Controlled studies have now involved more than 1000 unselected patients with renovascular disease randomised to medical treatment or renal angioplasty, with or without stenting (the largest of these studies being the ASTRAL study).[3] There has been no difference in either blood pressure reduction or renal decline after 12 months when medical therapy has been compared with revascularisation overall. Disappointingly, the adverse event rate in those undergoing angioplasty has ranged from 10 to 25% in the controlled studies, indicating that angioplasty is not without serious complications.

Since there is no level 1 evidence (that is, evidence from systematic review of randomised controlled trials) supporting the use of revascularisation for unselected patients, it seems reasonable to restrict revascularisation to those patients with high-grade lesions (that is, greater than 70% stenosis) associated with specific clinical problems (see the Table) in specialised centres

Diagnosing and managing renal artery stenosis (RAS)[1,4]



ABBREVIATIONS: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CT = computed tomography; MRA = magnetic resonance angiography.

(demonstrating low complication rates). In making a decision regarding endovascular intervention in renovascular disease, clinicians must also consider the age of the patient and relative prognosis regarding other comorbidities – for example, a conservative approach is probably appropriate for older patients.

When the clinical decision to revascularise has been reached, the procedure of choice in patients with atherosclerotic RAS is renal artery stenting (Figure 2), with or without a distal protection device (a device that prevents intraluminal cholesterol from seeding and damaging the kidney downstream from the angioplasty). This is because angioplasty alone has been associated with significant rates of restenosis, and surgical revascularisation is very expensive and has no proven benefit over medical or endoluminal therapy.[4]

There have been no studies of revascularisation in patients with mild or moderate renal stenosis. It seems prudent to offer medical therapy early in these individuals, given the natural history of progressive stenosis in atherosclerotic renal disease.

Fibromuscular dysplasia should be treated by balloon angioplasty alone, based on currently available uncontrolled data.[4]

The flowchart on this page summarises the steps in the diagnosis and management of RAS based on the evidence reviewed in both the CARI guidelines and a recent *New England Journal of Medicine* review.[1,4]

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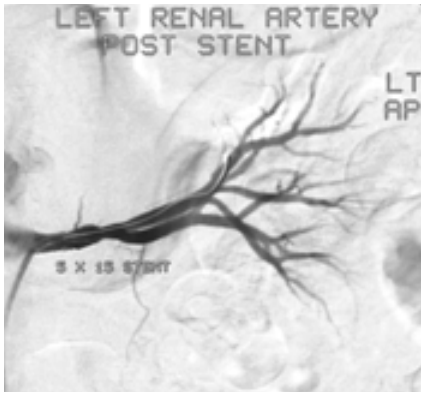

Figure 2. Stent placed in the left renal artery of an elderly woman with atherosclerotic renal artery stenosis.

Case study continued

Based on this patient's poorly controlled hypertension and the evidence of renal damage with a shrunken kidney, proteinuria, reduced eGFR and probable high RI (not clear due to a poorly performed ultrasound), a renal specialist became involved.

Angiography, with the use of very little contrast and prior nephroprotective strategies, was undertaken and demonstrated a near occluded RAS on the side of the shrunken kidney but only a 50% stenosis on the 10 cm kidney side. Because of this patient's age and these findings, angioplasty was not carried out. The renal specialist became involved in the aggressive medical control of this man's refractory hypertension and his high, long-term cardiovascular risk.

Conclusion

The number of patients diagnosed with renovascular disease is likely to increase with the rising incidence of hypertension and diabetes in our population. Although the imaging modalities for renal artery disease have improved, their side effects need to be balanced against their improved sensitivity when considering their use.

Medical therapy with multiple medications is probably as effective in the nonselected population of patients with renovascular disease as interventional therapies. Only in carefully selected patients and under specific circumstances should angioplasty, with or without stenting (depending on the RAS aetiology), be considered and its benefits carefully balanced against its risks. MT

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Hypertension and obstructive airways disease in the elderly

Achieving target blood pressure levels while maintaining good control of respiratory disease requires careful treatment choices but, given the range of agents available, can almost always be achieved.

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Systemic hypertension and obstructive airways disease – usually chronic obstructive pulmonary disease (COPD) or asthma – are very common in the elderly, and frequently coexist. Tobacco smoking is known to increase the impact of hypertension as a risk factor for cardiovascular disease, and airflow obstruction itself is an independent risk factor for future cardiovascular events.[1]

Lung function impairment is associated with a higher risk of comorbid disease, particularly hypertension and cardiovascular disease, and an increased risk of hospitalisation and mortality.[2,3] Conversely, heat failure is an independent predictor of all-cause mortality in patients with COPD.[4]

Treating a patient with both hypertension and respiratory disease can be complex because some antihypertensive medications can affect the airways. Achieving target blood pressure levels while maintaining good control of respiratory disease requires careful choice of treatment. This article focuses on potential effects of treatments for hypertension on airflow obstruction, and the possible effects of treatments for airflow obstruction on blood pressure. COPD is briefly described in the box on page 33.[5-8]

IN SUMMARY

- **Think of obstructive airways disease in elderly patients when commencing treatment for hypertension.**
- **COPD should be sought in patients with other smoking related diseases. COPD, hypertension and heart failure frequently coexist, and contribute to poorer outcomes; all should be treated as optimally as possible.**
- **Smoking cessation and treatment of modifiable risk factors, including obstructive sleep apnoea, are vital for managing COPD and hypertension and for reducing cardiovascular risk.**
- **Thiazide diuretics, calcium channel blockers and angiotensin II receptor antagonists appear to be relatively safe in patients with airflow obstruction.**
- **ACE inhibitor side effects of cough and bronchospasm do not appear to be more frequent in patients with airflow obstruction, but may be more troublesome if they occur.**
- **Beta blockers are generally contraindicated in patients who have significant reversible airflow obstruction.**
- **Beta blockers as treatment for hypertension (in comparison with treatment of heart failure in which the risk–benefit considerations are different) are best avoided in patients with COPD. Cardioselective beta blockers may be considered for cautious use in COPD if there is a compelling indication.**

Lung changes with ageing

Even in the healthy elderly population, lung function declines with age. Airway size becomes smaller, mainly as a result of alterations in the supporting connective tissue. The diameter of the alveolar ducts increases and the alveolar surface declines, changes that are thought to be due to alterations in the relative proportions of elastin and collagen that affect lung compliance and airway support. Chest wall compliance may decrease, due to a combination of kyphosis and arthritis, and respiratory muscle strength declines. These changes result in a progressive decline in forced expiratory flow in one second (FEV_1) and vital capacity with age that is independent of tobacco smoke or environmental exposures. The effects mimic those observed in emphysema (Figure 2), and can put an elderly patient in a compromised respiratory position, even without the added burden of asthma or COPD.

Lifestyle modification

Many of the lifestyle changes that improve quality of life and breathlessness in patients with airways disease are also effective in lowering blood pressure and reducing cardiovascular risk. Smoking cessation is essential. Good nutrition and weight management should be strongly encouraged – overweight and obesity are associated with an increased risk of hypertension, and excess weight is also associated with increased breathlessness in patients with airflow obstruction. Exercise training, in the form of either a formal pulmonary rehabilitation program or a home or community based program, is a vital component of managing patients with COPD and can also improve blood pressure control.

Pharmacotherapy for hypertension

Initial therapy for systemic hypertension will depend on the individual patient's characteristics, including the presence of other cardiovascular risk factors (such as tobacco smoking) and associated medical conditions (such as diabetes mellitus). The aims of treatment are to restore blood pressure to a prespecified target blood pressure level and reduce overall cardiovascular risk; the target will depend on an individual's combination of cardiovascular risks. Thiazide diuretics, calcium channel blockers, angiotensin II receptor antagonists and possibly angiotensin converting enzyme (ACE) inhibitors may be suitable first line therapy (see Table).[9]

Thiazide diuretics

Thiazide diuretics remain first line therapy for the majority of patients with uncomplicated systemic hypertension;[9] no direct studies of the use of these agents have been performed in hypertensive patients with COPD or asthma. There is a theoretical risk that thiazides – as potassium losing drugs – may indirectly worsen carbon dioxide retention in hypercapnic COPD.[10] This is very rarely a clinical issue in patients with stable COPD, but it is sometimes observed in hospital patients with unstable COPD using high dose diuretics. Hence, caution is recommended when prescribing diuretics to treat patients with unstable, hypercapnic COPD.

Corticosteroids and beta agonists may also increase potassium loss, so regular monitoring of electrolyte levels or use of a potassium sparing diuretic should be considered in patients taking any of these treatments, and particularly if they are taking a combination of treatments. Results from one study have suggested that thiazides interfere with mucus production,[11] but this does not seem to be a clinical problem. There are also potential benefits of diuretics in patients with lung disease, as peripheral oedema due to right heart failure, malnutrition or other causes is common in this group.

ACE inhibitors

Many ACE inhibitors are available, and these are particularly useful for treating patients with systolic, and probably diastolic, cardiac dysfunction and heart failure.[9] ACE inhibitors have been shown to reduce cardiovascular risk in patients

with multiple risk factors, especially hypertension and diabetes. The benefits and side effects of treatment are likely to be class effects, and it is advisable to monitor electrolytes.

Cough is the most common side effect, being reported by 10 to 20% of patients.[12] Bronchoconstriction has been reported but appears to be much less frequent. Cough and bronchoconstriction are both probably due to suppression of kininase II: angiotensin converting enzyme catalyses the conversion of angiotensin I to angiotensin II but also inhibits kininase II, which may lead to an increase in bradykinin and substance P in the lung. Bradykinin induces cough and bronchoconstriction in susceptible patients by stimulating sensory C-fibres and phospholipase A2. Substance P is a neurotransmitter for C-fibres and can induce bronchoconstriction.[13]

COPD: an underdiagnosed disease of the elderly

COPD is mainly a disease of the elderly, with a prevalence that increases steeply with age. It is the third leading cause of the total burden of disease and injury in the Australian population, outranked only by ischaemic heart disease and stroke.[5]

Tobacco smoking remains the most important cause of COPD: about half of all smokers develop some airflow obstruction, and between 15 and 20% have clinically significant disease (Figure 1).[6] Other causes include:

- exposure to occupational dust and fumes, including organic dust
- outdoor and indoor air pollution (including environmental tobacco smoke)
- bronchial hyperresponsiveness
- α_1-antitrypsin deficiency
- recurrent respiratory infections in childhood.

Even in patients with severe disease, COPD is significantly underdiagnosed. Symptoms often develop gradually, and shortness of breath may be attributed to normal ageing or deconditioning or erroneously attributed to coexisting heart failure. COPD should be suspected in all smokers, particularly those with other smoking related diseases.

Clinical examination has poor sensitivity for detecting mild to moderate COPD and for assessing its severity; spirometry remains the most useful method of diagnosing, assessing and monitoring patients with the disease. Severity can be rated according to the COPDX plan as mild, moderate or severe.[3] Patients who are most likely to run into trouble with drugs that worsen airways disease are those with moderate or severe disease.

There is overlap between COPD and asthma. Many patients with COPD have some reversibility of airflow obstruction with bronchodilators; conversely, some nonsmokers with chronic asthma develop irreversible airflow obstruction. Both new-onset asthma and persistent asthma are more common in the elderly than is often appreciated, and rates of hospitalisation for asthma are highest in people who are 65 years of age and older.[7]

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is common, conservatively estimated to affect 4% of middle aged men. OSA may coexist with COPD, and may complicate management of COPD.[8] Recognition and treatment are important for reducing overall cardiovascular risk, improving overnight oxygen levels (which may be already compromised by airways disease) and potentially improving blood pressure control. Risk factors for obstructive sleep apnoea overlap those for hypertension (e.g. increasing age, tobacco smoking and obesity); obstructive sleep apnoea is also an independent risk factor for hypertension.

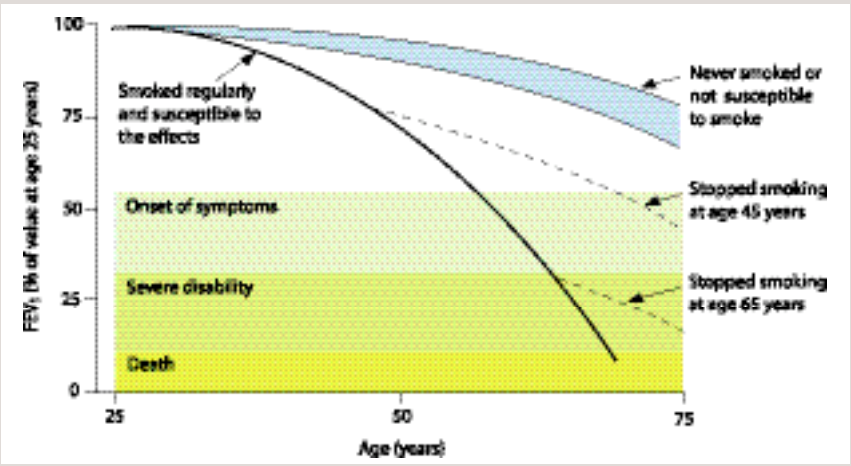

Figure 1. Time course of COPD. The decline in FEV_1 for a hypothetical susceptible smoker and the effect of stopping smoking early or late in the course of COPD is shown, along with the decline for a hypothetical nonsmoker and nonsusceptible smoker.

FROM REFERENCE 6 (AND ADAPTED FROM FLETCHER C, PETO R. THE NATURAL HISTORY OF CHRONIC AIRFLOW OBSTRUCTION. BMJ 1977; 1: 1645-1648).

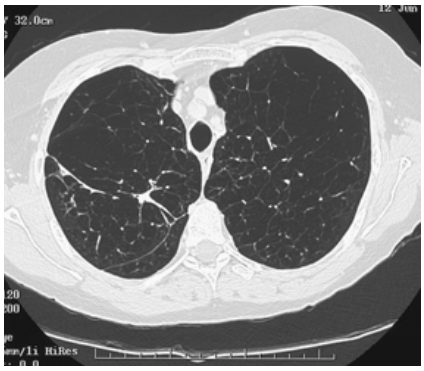

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Figure 2. High resolution chest CT scan of a 70-year-old woman with emphysema. Extensive emphysematous changes with bullae are visible in both lungs.

ACE inhibitors are safe in the large majority of patients with obstructive airways disease. Only a limited number of studies of cough and bronchial reactivity in patients with COPD or asthma have been performed, and most have not shown an increase in cough or bronchospasm induced by ACE inhibitors in patients with underlying airways disease, compared with those without underlying airways disease.[13] However, patients have usually been continued on their maintenance bronchodilator treatment in these studies.

Asthma and bronchospasm are rare as side effects of treatment with ACE inhibitors, but need to be recognised if they occur because the effects are likely to be more disabling in patients with underlying airways disease. Replacing the ACE inhibitor with another should not be tried because patients who experience cough or bronchospasm when using one agent in this class generally have the same problem with others. The cough will usually settle within a month after drug withdrawal.[13]

Angiotensin II receptor antagonists

Angiotensin II receptor antagonists appear to have similar effects to ACE inhibitors in heart failure or renal disease, or after myocardial infarction. However, angiotensin II receptor antagonists do not inhibit kininase II and thus do not lead to accumulation of bradykinin and substance P. Cough is an uncommon side effect, and most studies suggest that its incidence is similar in patients receiving treatment or a placebo. There are, however, case reports of bronchoconstriction with angiotensin II receptor antagonists,[14] which is possibly related to inhibition of endogenous nitric oxide release in the airways. Clinical experience with use of these drugs in patients with use of airways disease is limited, and they may not be entirely free of the side effects of ACE inhibitors.[10] Overall, angiotensin II receptor antagonists are a reasonable choice in patients with airways disease who, because of cough or bronchospasm, are intolerant of ACE inhibitors.

Calcium channel blockers

Long acting calcium channel blockers are useful for treating hypertension, particularly in elderly patients with angina or isolated systolic hypertension.[9] There have been no studies on their use in hypertensive patients with airways disease. Calcium channel blockers may modestly decrease bronchial reactivity,[13] and thus may have beneficial but probably neutral airway effects in patients with airways disease.

Beta blockers

Beta blockers may be useful in patients with both hypertension and coronary heart disease and are increasingly used in treating heart failure. In patients with airways disease, however, this is the class of antihypertensive agents most likely to cause side effects. Beta blockers increase airway resistance and generally should not be used in patients with asthma or other reversible airways disease – the severity of the bronchoconstrictor response is unpredictable, and occurs mainly in this group.[10,15] There is usually little to no effect in healthy people, but severe bronchoconstriction can be seen even in those with mild asthma with beta blocker use.

Table. Antihypertensives for patients with obstructive airways disease[10]

Optimal	
None established	
Possible	
Thiazide diuretics	
Calcium channel blockers	
Angiotensin II receptor antagonists	
Contraindicated or to be used with caution	
Beta blockers	
Beta blockers with alpha blocking activity	
ACE inhibitors (monitor for side effects of cough or bronchoconstriction)	

Most of the airway side effects that are caused by beta blockers are related to interference with beta-2 mediated bronchodilatation. Beta-2 receptors are the main adrenoreceptors on airway smooth muscle; beta-1 receptors account for 10 to 30% of receptors on submucosal glands and alveolar walls. The cardioselective beta-1 blockers (atenolol, metoprolol, bisoprolol) have less effect than nonselective drugs (e.g. propranolol) on lung function, although their cardioselectivity may be lost at higher doses. The cardioselectivity is also relative, and airflow obstruction can certainly worsen at therapeutic doses of a cardioselective drug. Decline in lung function with non-cardioselective drugs can be seen in mild and moderate COPD, as well as in severe COPD.[16]

Nonselective beta blockers with intrinsic sympathomimetic activity (pindolol, oxprenolol) may cause less bronchoconstriction than beta blockers without this activity. However, they remain contraindicated in asthmatic patients, and in those with airflow obstruction.[10]

If a patient with severe hypertension and COPD is unable to tolerate other

classes of antihypertensive medications, a cardioselective beta blocker could be trialled while maintaining optimal bronchodilator treatment.[13] The potential benefits must be weighed against the potential risks. For treatment of hypertension alone, in general it is likely that other suitable agents can be found. The benefit–risk ratio will also need to be considered in a patient with additional indications for beta blockade, such as heart failure or angina, and underlying airways disease. Spirometry is recommended at baseline for assessing the severity of the airways disease and degree of reversibility, and over time to monitor for any decline. Referral to a respiratory physician for review of airways disease should be considered if significant airways disease is present and/or to a cardiologist for review of treatment if a beta blocker is needed.

Carvedilol, a nonselective beta blocker that has alpha blocking activity, is generally used in the treatment of heart failure, not of hypertension alone. It appears to be well tolerated in patients with COPD, but asthma is a contraindication.

A recent randomised crossover trial of beta-1 selective blockers (bisoprolol and metoprolol) and carvedilol in patients with chronic heart failure and COPD showed that all were well tolerated, with no change in New York Heart Association functional class or six minute walk distance. However, there were demonstrable changes in airway function, most marked in those on carvedilol.[17]

In patients with heart failure, combined alpha and beta blockers should be used with great caution in patients with any airways disease because the alpha blockade may fail to prevent bronchoconstriction caused by the beta blockade.[10]

Combination and alternative therapies

Patients who have severe hypertension or hypertension that is not controlled by a single agent may require combination therapy.[9] The recommendations for use of single medications in patients with coexisting airways disease also apply to their use in combinations.

A recent postmarketing surveillance study of the combination drug telmisartan and amlodipine reported no significant respiratory issues, but the incidence of COPD was very small, at 0.5% of cases.[18]

Some patients are either resistant to or intolerant of the usual initial therapies. In such individuals, alternatives include prazosin, which is an alpha blocker, and also methyldopa or clonidine, which are centrally acting antiadrenergic agents. There is little information on their effects in airways disease, but clonidine may variably increase airway responsiveness in patients with asthma.[10] Given the lack of guidelines for using these drugs in this situation, use in patients with airways disease should be cautious.

The direct acting vasodilator hydralazine is not reported to cause airway side effects, but studies are lacking. It is often used in combination with a beta blocker, and its use in patients with airways disease is likely to be limited for that reason.

Pharmacotherapy for asthma or COPD

Inhaled treatments

Bronchodilator treatments do not usually worsen hypertension, but cardiovascular side effects can occur with some medications. The inhaled short-acting beta-2 agonists salbutamol and terbutaline remain recommended for relief of intermittent wheeze and dyspnoea in asthma and COPD. Palpitations and, less commonly, tachycardia are known side effects, particularly in the elderly.

Although some observational studies report an association between use of beta-2 agonists and the risk of acute myocardial infarction, it is likely that any increased risk is related to latent cardiovascular disease rather than to the direct effects of beta-2 agonists.[19]

Short-acting anticholinergics (ipratropium bromide) are also useful in COPD.[6] There is no evidence of worsening of hypertension with either of these medication groups.

The inhaled long-acting beta-2 agonists, salmeterol and eformoterol are useful in asthma control in combination with an inhaled corticosteroid. Inhaled corticosteroids alone have not been recognised to worsen hypertension. Combined preparations of salmeterol and fluticasone and of eformoterol and budesonide are commercially available. Long-acting beta-2 agonists are not currently listed as single agents on the PBS for treating COPD, although they have been shown to have benefits.[6] A combination of salmeterol and fluticasone is listed on the PBS for treatment of COPD. Palpitations and tachycardia can occur with any beta-2 agonist (short or long acting), particularly in the elderly, and can be troublesome. Aggravation of hypertension, however, does not appear to be a problem.

Tiotropium bromide, a long-acting anticholinergic, is a useful maintenance treatment for patients with COPD. Cardiovascular side effects, including hypertension, do not appear to be a clinical problem.

Theophylline is rarely used these days for COPD or asthma because of its narrow therapeutic index and significant side effects.[6] Some COPD patients with disabling breathlessness may find it helpful, but it is not advised in patients with severe hypertension. Cardiac arrhythmias are a known side effect – this is of particular concern in patients with COPD, who often have other risk factors for coronary artery disease.

In patients with COPD who have a documented response or severe COPD with frequent exacerbations, it is possible to use an inhaled corticosteroid, beclomethasone, budesonide or fluticasone.[6] The role of these agents in managing patients with persistent asthma is well established. Inhaled corticosteroids, as

single agents, are not currently listed on the PBS for use in COPD, but may have benefits in these situations. Some systemic absorption occurs, with potential for easy bruising, cataract formation and osteoporosis, but worsening of hypertension is not seen to be a clinical problem. Results from a recent study suggest that a very low dosage of inhaled corticosteroid (50 to 200 μg/day) may reduce the risk of myocardial infarction.[20]

Systemic treatments

Use of short term high dose oral corticosteroids for exacerbations of asthma or COPD is often associated with retention of fluid and development or worsening of pre-existing hypertension. Blood pressure should be monitored in patients on this treatment. The effect is dose related, improves as the dose is reduced and is not associated with long term blood pressure change. Some patients may require adjustment of antihypertensive medication, but generally observation is all that is needed. Long term oral corticosteroids are rarely required in asthma or COPD; if used, the dose should be reduced to the minimum possible.

Conclusion

Obstructive airways disease should always be considered in an elderly patient before antihypertensive treatment is commenced, especially if there is a history of smoking or suggestive clinical features. Spirometry is a valuable tool for diagnosing and monitoring airflow obstruction. Aggressive control of risk factors is important for cardiovascular risk reduction, as well as improving disease control and symptoms in both hypertension and COPD. The presence of airflow obstruction may modify pharmacotherapy for hypertension but, given the range of drugs available, good control of blood pressure without worsening of airways disease can almost always be achieved. MT

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Management of chronic hypertension in pregnancy

Almost all pregnant women who present with hypertension during the first 20 weeks of gestation are likely to have chronic hypertension. However, the normal physiological fall in blood pressure during the first and second trimesters can make it difficult to diagnose chronic hypertension in women whose blood pressure before the pregnancy was unknown.

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Up to 20% of the adult population are affected by hypertension, defined as a resting blood pressure of 140/90 mmHg or above. The prevalence of hypertension increases with age.[1] An estimated 2% of Australian women of childbearing age are hypertensive and, of the 10 to 12% of pregnancies affected by elevated blood pressure, one in five (20%) is related to chronic hypertension.

Virtually all pregnant women who present with hypertension during the first 20 weeks of gestation are likely to have chronic hypertension. However, because of the physiological fall in blood pressure during the first and second trimesters, it can be difficult to diagnose chronic hypertension in women whose blood pressure before pregnancy is unknown. Of those women diagnosed with chronic hypertension, at least 80% will have essential hypertension (Figure 1). However, an

IN SUMMARY

- **About 10 to 12% of pregnancies are complicated by hypertension; 20% of these are due to chronic hypertension.**
- **Pre-eclampsia is the most likely event to complicate the pregnancy of a woman with chronic hypertension.**
- **Tests are indicated in all women with known chronic hypertension to assess the severity of the hypertension and to investigate possible secondary causes.**
- **Antihypertensive treatment is recommended when the systolic or diastolic blood pressure consistently reaches or exceeds 160 mmHg and 100 mmHg, respectively. Admission to hospital or an antenatal day-assessment unit may be required for pregnant women with such blood pressure levels.**
- **The decision to treat intermediate blood pressures of 140 to160 mmHg (systolic) or 90 to 100 mmHg (diastolic) is based on clinical opinion. Admission to hospital or an antenatal day-assessment unit is recommended for pregnant women with these blood pressures if new-onset proteinuria develops.**
- **Methyldopa and labetalol are currently the agents of choice in hypertensive pregnant women due to their efficacy and safety profile.**

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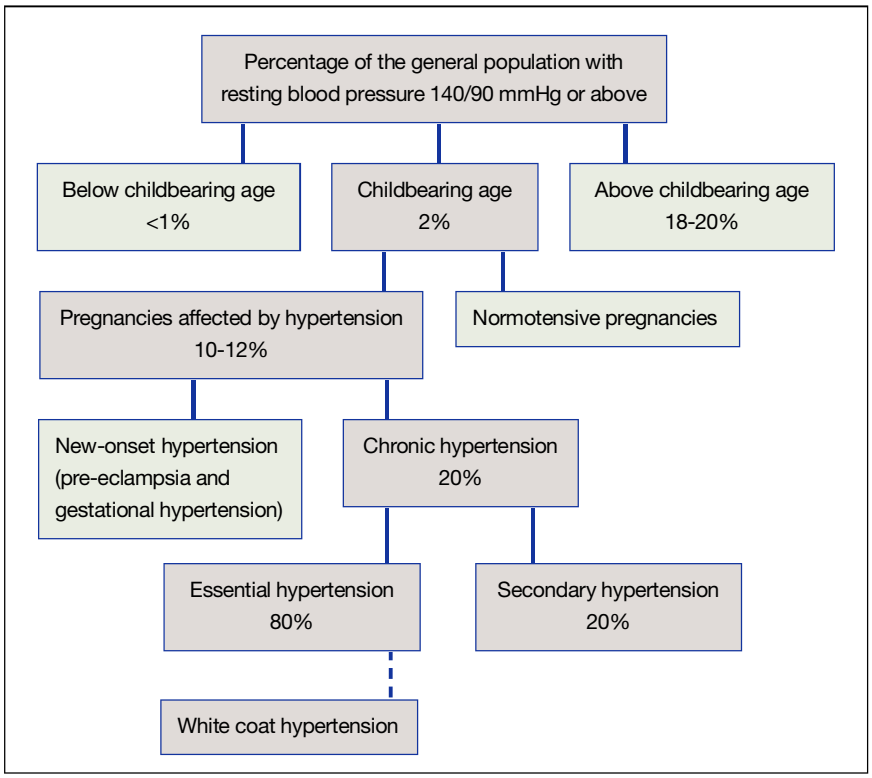

Figure 1. Causes of hypertension in pregnancy.

underlying cause should be investigated in all cases, as essential hypertension remains a diagnosis of exclusion.

Common secondary causes of chronic hypertension are listed in Table 1.[2-5] Absence of these conditions suggests a diagnosis of essential hypertension; however, it is important to remember that complete appraisal of possible secondary causes may have to be deferred until after delivery.

An additional cause of apparent hypertension in pregnancy is 'white coat hypertension'. The frequency and significance of this condition in pregnancy has not been defined; however, one study suggests that it is present in over 30% of women diagnosed with essential hypertension. It may also be associated with an increased incidence of pre-eclampsia compared with normotensive women.[6] Similarly, an elevated 24-hour mean pulse pressure – even in women who have normal measured systolic and diastolic pressures – has also been found to predict complications in pregnancy, including gestational hypertension and pre-eclampsia.[7]

Significance of chronic hypertension in pregnancy

It is important to distinguish between mild and severe hypertension. There is no consensus on the diagnosis of the former; however, most authors agree that systolic and diastolic pressures above 170 mmHg and 110 mmHg, respectively, represent severe hypertension.[8,9] Studies in pregnant and nonpregnant women have demonstrated a reduction in stroke and other cardiovascular complications when antihypertensive treatment is initiated at or above these levels. Many clinicians will now treat systolic and diastolic levels of 160 mmHg and 100 mmHg, respectively, particularly in an outpatient

PHOTOLIBRARY

setting.[10,11] Although the gestational risks associated with chronic hypertension (e.g. superimposed pre-eclampsia, intrauterine fetal growth restriction and stillbirth, placental abruption and premature delivery) are increased, outcomes correlate more closely with elevated uric acid levels and proteinuria than with blood pressure levels.[12-19] The exception appears to be cases of severe and uncontrolled hypertension during the first trimester, when fetal and maternal morbidity and mortality are markedly increased.[20]

Other indicators of poor prognosis include:

- previous severe pre-eclampsia in women with chronic hypertension
- failure of blood pressure to fall during the second trimester
- the presence of secondary hypertension
- a history of longstanding severe hypertension
- pre-existing chronic kidney disease.

Clinical features

A detailed history and physical examination are essential in seeking a possible

cause for the chronic hypertension or, equally importantly, ascertaining new-onset hypertension. Known pre-existing hypertension, treated or untreated, can be most helpful, particularly if an elevated blood pressure is evident before 30 weeks' gestation.

It is imperative to determine if there is a family history of hypertension or renal disease. A history of urinary infection, renal colic, haematuria and/or proteinuria should be sought, and women questioned about their drug ingestion (including hormonal preparations) prior to the pregnancy. A history of rash, arthritis or diabetes may point to a systemic disease, while episodic palpitations, headache or flushing may suggest a phaeochromocytoma.

Physical examination should include blood pressure measurements (Korotkoff sounds I and V) while the woman is seated. Blood pressure should be measured in both arms using an appropriately sized cuff, and the femoral pulses should be palpated. Auscultation in the epigastrium and over the renal angles posteriorly may be of value for diagnosing renal artery stenosis (Figure 2). Evidence of any systemic disease should be recorded. Examination should also ascertain evidence of end-organ damage due to hypertension. This requires examination of the precordium for left ventricular hypertrophy, urinalysis and optic fundoscopy.

Recent studies have suggested that 24-hour ambulatory blood pressure appraisal may have application in the diagnosis and management of women with chronic hypertension in pregnancy. This option can be considered, particularly if the diagnosis of hypertension is in doubt.[6,7]

Preconception counselling

Ideally, women who have hypertension and/or renal disease should be seen and investigated, a diagnosis established, and the underlying condition stabilised prior to a planned pregnancy. The potential risks of pregnancy can be discussed at this time and an assessment made of the likely prognosis. Also at this time, the risks of perinatal morbidity and mortality and the potential for deterioration of any underlying kidney disease should be fully explained to those women with significant prenatal renal dysfunction (a serum creatinine of 130 μmol/L or greater).[21]

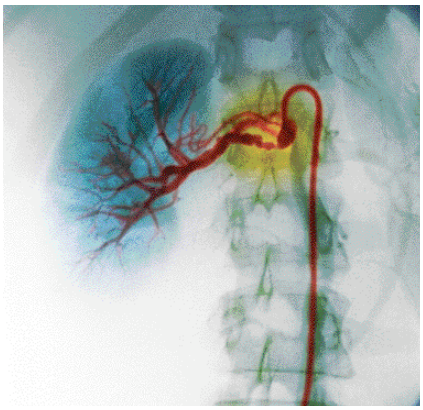

Figure 2. Renal artery stenosis, a cause of secondary hypertension in pregnancy.

Clinical and laboratory monitoring

Tests should be performed in all women with known chronic hypertension to assess the severity of the hypertension, ascertain if there is any end-organ damage and investigate possible causes of the hypertension. Appropriate tests are outlined in Table 2.

Pregnant women with chronic hypertension, whether essential or secondary, should be observed frequently during their pregnancy by an obstetrician and a physician who are familiar with the management of pre-eclampsia and hypertension during pregnancy.

Statistically pre-eclampsia, which is often causatively associated with intrauterine growth restriction, is the most likely event to complicate the pregnancy of a woman with chronic hypertension. Early detection and appropriate management of this complication assumes the highest priority after 20 weeks' gestation. Table 3 summarises the monitoring of hypertension in pregnant women.

Admission to hospital or an antenatal day-assessment unit is recommended for

Table 1. Causes of secondary hypertension in pregnancy

Chronic kidney disease

The most important renal disorders to consider are glomerulonephritis, reflux nephropathy and adult polycystic kidney disease. It is important to assess the degree of renal impairment and the prognosis of the underlying renal disease when determining the risk in relation to pregnancy. The risk associated with kidney disease may be substantially greater than that associated with the hypertension.[2,3]

Renal artery stenosis

Renal artery stenosis is usually due to fibromuscular dysplasia in young women.[4]

Systemic disease with renal manifestations

Diabetes mellitus and systemic lupus erythematosus are the most common conditions. The extent of other organ involvement also determines the degree of risk associated with pregnancy.

Endocrine disorders

Endocrine causes of hypertension include phaeochromocytoma, Cushing's syndrome and primary hyperaldosteronism. Although rare, phaeochromocytoma has grave prognostic implications for both maternal and fetal welfare.[5] Measurement of fasting plasma free metanephrines or 24-hour urinary catecholamines should be considered in women with very labile or severe hypertension. Measurement of renin and aldosterone concentrations during pregnancy is problematic.

Aortic coarctation

Rare, but more likely in younger women.

Table 2. Recommended investigations for pregnant women with hypertension

- **Urinalysis for protein, blood and glucose.** If proteinuria is evident on dipstick analysis, a spot urine collection for measurement of the urinary protein:creatinine ratio or a 24-hour urinary protein collection should be obtained.
- **Direct urinary microscopy.** Performed to detect the presence of casts, and white and red blood cells (including red cell morphology).
- **Midstream urine culture**
- **Blood tests.** These include measurement of electrolytes, creatinine, uric acid and blood glucose; full blood examination; and other tests (measurement of antinuclear antibodies, C3 or C4 complement fractions, or HbA_{1C}) as clinically indicated.
- **ECG**
- **Renal ultrasound and Doppler studies.** These should be considered, particularly if the hypertension is severe, proteinuria is identified or a renal bruit is evident.
- **Twenty-four-hour urine collection.** For estimation of catecholamine excretion if there is a concern regarding a possible phaeochromocytoma. At least two consecutive collections are advised. Where available, plasma free metanephrines are a suitable alternative.

women with a confirmed systolic blood pressure over 160 mmHg or a diastolic blood pressure over 100 mmHg. This approach is also recommended for women who have less severe hypertension (a systolic blood pressure between 140 and 160 mmHg and/or a diastolic blood pressure between 90 and 100 mmHg) if the hypertension is accompanied by newly developed proteinuria at any stage of the pregnancy. This enables assessment of maternal and fetal welfare and facilitates discussion among all parties involved so that pharmacological treatment can be commenced under close supervision. Before labour and delivery, review by an obstetric anaesthetist is also recommended, particularly if the woman is obese.

Drug treatment

The continued administration or initiation of antihypertensive therapy in women with chronic hypertension in pregnancy (except for the acute treatment of severe hypertension) remains controversial. The physiological fall in blood pressure that manifests during the first half of pregnancy in most women may allow antihypertensive medication to be reduced or withdrawn. Although treatment is associated with a significant reduction in severe hypertension-related morbidity, it has not been shown to alter the risk of superimposed pre-eclampsia, preterm delivery, placental abruption or perinatal death.[22-24]

To initiate or increase drug therapy at too low a blood pressure level may result in a large number of women being unnecessarily exposed to medication and, depending on the drug used, result in compromised fetal growth and development. It should be recognised that over 20% of unselected normal pregnancies, usually late in the third trimester, can record a maximum prenatal blood pressure of at least 140/90 mmHg.[9] Thus, the clinician needs to be aware that a single reading in a consultation room may not be representative of future readings. Pregnant women with borderline hypertension (according to gestational age) may therefore benefit from increased vigilance, either at a day-assessment unit or by instigating 24-hour ambulatory blood pressure monitoring. The latter can help determine the blood pressure pattern before treatment is initiated.

The decision to initiate drug treatment in a pregnant woman with chronic hypertension depends on several factors in addition to the blood pressure level itself. These factors include:

- whether the patient has renal or cardiovascular disease, or is at risk of target organ damage
- whether the patient has a past history of stroke
- the stage of gestation.

Most authors would agree that treatment should be started when, on careful and reproducible appraisal, the blood pressure reaches or exceeds a systolic pressure of 160 mmHg or a diastolic pressure of 100 mmHg. For systolic pressures between 140 and 160 mmHg, or diastolic pressures between 90 and 100 mmHg, direct evidence of a benefit from treatment is lacking, although appropriate studies are limited. The decision to treat patients who have these intermediate blood pressure levels will therefore be opinion-based, after consideration of such factors as the consistency and trend of the hypertension, the presence of systemic disease and the gestational age of the fetus. In the third trimester, an increase in the requirement for antihypertensive therapy should be anticipated.

As is evident from the above discussion, the appropriate target blood pressure for pregnant women with hypertension has not been and perhaps, given the multiple variables involved, cannot be strictly defined. Logically, for a given patient, a commonsense approach will be to maintain levels safely below those which prompted the initiation of treatment.

Choice of antihypertensive medication

Drugs that have been used for many years in pregnant women with some measure of safety are noted in Table 4. Labetalol and methyldopa have been used most often, followed by other beta blockers, hydralazine and, more recently, calcium

channel blockers, prazosin and clonidine.

Methyldopa and clonidine

Methyldopa is the drug that has been most studied in pregnancy and has the best safety and efficacy profile.[25-27] It has been shown to maintain uteroplacental blood flow and fetal haemodynamics[28] and is considered first-line therapy for chronic hypertension in pregnancy. However, it should not be used in women who have a history of depression or are currently depressed.

Clonidine is a centrally active vasodilator like methyldopa; few studies have evaluated its efficacy or safety in pregnancy.

Labetalol

Labetalol, a beta blocker with some alpha-adrenoreceptor-blocking activity, is now widely used because of its efficacy and safety profile. It has been shown to be as effective as methyldopa. Although studies have not documented adverse fetal effects with labetalol, there are as yet no follow-up safety trials (as exist for methyldopa) in children whose mothers received labetalol while pregnant to justify its use ahead of methyldopa.[29-31]

Hydralazine

Hydralazine is often used parenterally in hypertensive emergencies but can also be administered orally. It can result in headache, palpitations and dizziness when used alone and hence it is often administered with methyldopa or a beta blocker. It appears safe and efficacious for chronic treatment, although long-term studies are lacking. High doses and protracted use can be associated with a lupus-like syndrome.

Other beta blockers

There is evidence of differential effects among the beta blockers when used in pregnancy. Maternal therapy with atenolol (a cardioselective drug with no intrinsic sympathomimetic activity) was associated with impaired fetal growth in two studies, especially when used before the third trimester. Distinct from this is the beneficial effect on fetal growth found with oxprenolol, a nonselective agent possessing intrinsic sympathomimetic activity.[32-35] Thus, drugs within a pharmacological class may not always have identical effects and the findings for one drug cannot always be extrapolated to others within the class. In general, it would appear that beta blockers are best reserved for treatment during the third trimester.

Table 3. Monitoring hypertensive women during pregnancy

- Record any symptoms and enquire about fetal movements at each visit.
- Perform a physical examination at each visit, including measurement of blood pressure (with an appropriately sized cuff) and assessment of uterine size.
- Refer the patient for an obstetric ultrasound early in the pregnancy to confirm the gestational age of the fetus. Additional scans can be obtained as clinically indicated.
- Order biochemical and haematological tests (as outlined in Table 2) at the initial visit. Some tests will need repeating according to clinical demands. In particular, women with underlying chronic kidney disease should have renal function assessed regularly. In other women, repeat testing for proteinuria may be of value for the detection of superimposed pre-eclampsia (particularly later in the second and third trimesters).
- Collect a urine sample for urinalysis to detect protein in the urine at each visit. If the test is positive at any visit, an accurate 24-hour urine protein estimation (ideally) or measurement of a spot urinary protein:creatinine ratio should be performed.

Calcium channel blockers

Of the calcium channel blockers, nifedipine has been used extensively for the acute lowering of blood pressure in late pregnancy, but in large doses it may inhibit uterine contractions.[36,37] It can also produce a marked drop in blood pressure when given in combination with magnesium sulphate in an emergency situation and should be used with care in this context.

Although nifedipine is not recommended for use during early pregnancy, recent data have shown no evidence of a major teratogenic risk with calcium channel blockers taken in early pregnancy.[38] Nifedipine has been used successfully for chronic hypertension in pregnancy without adverse effects, although no difference has been observed in maternal or fetal outcomes in these studies.[39,40]

ACE inhibitors

ACE inhibitors (and, by association through mode of action, angiotensin-receptor blockers) are contraindicated in pregnancy. They have been associated with an increased risk of fetal, particularly cardiovascular, malformations in early pregnancy, and other adverse sequelae late in pregnancy.[41]

Delivery

Decisions regarding the delivery of a baby when a woman has hypertension are complex. Careful consideration is required in each case, with consultation between the obstetric, medical, paediatric, midwifery and anaesthetic members of the team caring for the woman. Such decisions are determined by fetal and/or maternal factors.

Timing

The general principle is that the pregnancy should be allowed to proceed as far as possible provided that both maternal and fetal wellbeing is maintained. In many women with chronic hypertension, blood

continued

Table 4. Summary of antihypertensive drugs commonly used in pregnancy*

Drug	Dose	Action	Contraindications*	Practice points*
Methyldopa	250–750 mg tds	Central	Depression	Slow onset of action over 24 hours. Dry mouth, fatigue and blurred vision may occur, which usually settle with time
Labetalol	100–400 mg tds	Beta blocker with mild vasodilator (alpha blocker) effect	Asthma, chronic airflow obstruction and heart block	Headache, nausea and scalp tingling may occur, which usually resolve within 24 to 48 hours. Not available for IV use in Australia
Oxprenolol	40–160 mg tds	Beta blocker		Bradycardia and bronchospasm may occur
Hydralazine	25 mg (po); 5–10 mg (IV bolus)	Peripheral vasodilator	Concurrent systemic lupus erythematosus or past rash	May aggravate hyper-reflexia and tachycardia. Often used peripartum
Nifedipine	20 mg bd; 60 mg daily (slow release)	Calcium channel antagonist	Aortic stenosis	Headache, flushing, tachycardia, peripheral oedema and red shins may occur
Prazosin	0.5–5 mg tds	Alpha-1 blocker		First dose effect: orthostatic hypotension

* Refer to full prescribing information for each drug for complete listings of contraindications and precautions. It should be remembered that evidence-based data are limited for most agents and their use is sometimes indicated despite the stated risk. Nonetheless, the clinician should carefully address the relevant issues for each patient before commencing treatment with any agent (see text).

pressure remains well controlled and no fetal or maternal problems mandating premature delivery arise. In such cases it is usual for the pregnancy to be allowed to continue, under close supervision, with the aim of vaginal delivery at term. In other cases, and almost always in the setting of superimposed pre-eclampsia, early delivery is necessitated by the occurrence of one or more of a number of 'endpoints' representing fetal or maternal compromise.

Occasionally, the patient's blood pressure becomes impossible to control despite maximal doses of medications. This can occur in the absence of proteinuria, fetal abnormalities or other features of pre-eclampsia. In these cases, delivery may be necessary to prevent likely maternal cerebral haemorrhage, the indication being 'failed blood pressure control'.

Mode of delivery

The mode of delivery should be determined by obstetric considerations. If there is evidence of fetal compromise the obstetrician will usually favour caesarean section. The vaginal route of delivery is favoured unless delivery is required urgently, such as in cases of fetal distress, antepartum haemorrhage or severe pre-eclampsia.

Regional anaesthesia is extremely helpful in most cases, and caesarean section should be performed under regional block unless there is maternal coagulopathy (most often thrombocytopenia) or other unusual factors. Despite the undoubted utility of an epidural block, it does not provide complete blood pressure control and so usual monitoring and hypertension therapy should be continued.

Location

Delivery should be conducted in a centre with adequate facilities to care for the mother with severe hypertension or other features of severe pre-eclampsia, and for preterm infants.

Postpartum management

For many women with chronic hypertension, a period of instability follows delivery for seven to 14 days, during which time it may be extremely difficult to achieve adequate blood pressure control. This instability is more pronounced in women who have sustained superimposed pre-eclampsia, but is also seen in those who do not have this complication.

Typically, the blood pressure will be exaggerated on the second or third day after delivery and will remain sustained for several days thereafter. It is often necessary to increase medication or commence new antihypertensive therapy at this time. The use of methyldopa postpartum should be avoided because of the risk of aggravating postnatal depression. An elevated risk of eclampsia remains for up to about five days postpartum, after which time it is much less common.

Conclusion

Chronic hypertension in pregnancy is not uncommon; its incidence is likely to be increasing as women defer pregnancy until they are older. The clinician needs to distinguish between new-onset and chronic hypertension and be aware of possible secondary causes – chronic kidney disease in particular. Specific treatment targets remain unclear, but avoidance of severe hypertension, familiarity with appropriate antihypertensive agents, early awareness of superimposed pre-eclampsia, and recognition of the need for a team approach to management are crucial to the long-term wellbeing of mother and child. Postpartum, the blood pressure is often labile, and it can be several weeks before it stabilises. MT

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