The articles in this series are independently researched and compiled by PSA commissioned authors and peer reviewed.

Hypertension

By Ian Heslop

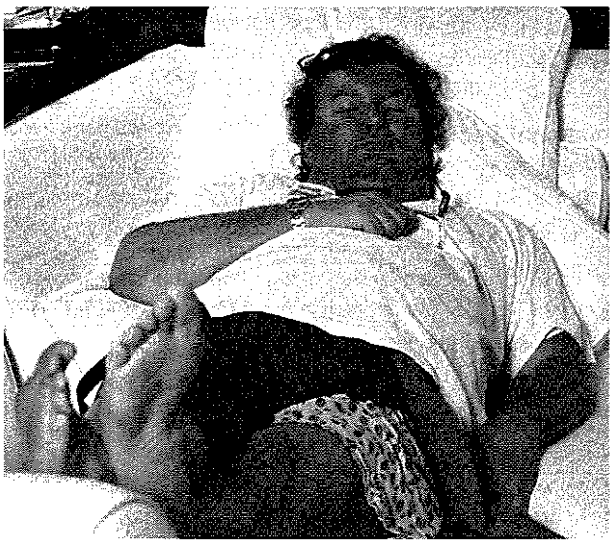
Learning objectives

After reading this article you should:

- Have an understanding of the classification and definitions of hypertension.
- Understand the importance of combining absolute cardiovascular risk with blood pressure measurements in the diagnosis and assessment of hypertension.
- Be aware of how appropriate first line antihypertensive agents are selected for individual patients and how the patient should be managed with those agents.
- Have an understanding of the new National Heart Foundation of Australia guidelines for the management of hypertension and the recent reappraisal of the current role of beta blockers in the management of hypertension.

Introduction

Hypertension is known to be a major risk factor for coronary artery disease, heart failure, renal disease and stroke and studies have demonstrated that approximately 20% of the world's population may be affected.[1,2] In Australia, like other westernised countries, the prevalence of hypertension is higher, with estimates suggesting that 29% of the Australian population is affected and 15% being untreated.[4] In future years, the worldwide incidence of hypertension is expected to increase, due mainly to the effects of an increasingly ageing population and also the westernisation of lifestyles in developing countries.[5] It is assumed that this adopted 'westernised lifestyle' will encourage associated increases in obesity, reduced physical exercise and increased dietary salt intake in those countries.[5] For many years the diagnosis and management of hypertension has been an important issue for primary healthcare providers[1,2] as it is a known modifiable risk factor for cardiovascular disease and the associated morbidity, mortality and economic burden of those diseases.[1] It is also recognised that hypertension is often poorly or under treated,[5,6] and that compliance and persistence with antihypertensive medication is often poor.[6] Over the past two decades there have been regular reviews and revisions of the management guidelines for this condition with most recent



there are clear associations with hypertension and obesity, salt and alcohol intake.[1,11]

discussions centring around a reappraisal of the role of beta blockers. New National Heart Foundation of Australia (NHF) guidelines for the management of hypertension have recently been released, as have National Institute for Health and Clinical Excellence (NICE) guidelines in the UK.[3,7-10] This article is a brief review of the current management guidelines for hypertension with a discussion of the reasoning behind the recent changes.

Classification

Hypertension is generally classified into either essential (or primary) hypertension or secondary hypertension. Only 5% of cases have easily identifiable causes such as renal disease, Cushing's disease, phaechromocytoma, pregnancy or medications such as corticosteroids, oestrogens, NSAIDs and alcohol and can therefore be classified as secondary hypertension. The vast majority (95%) of cases have no clear identifiable cause and are therefore classified as essential hypertension.[1,11,12]

Epidemiology and pathophysiology

Key epidemiological factors are age, gender and ethnic background. The prevalence of hypertension increases with age, and men are more likely to develop hypertension at an early age than women.[1] It is recognised that hypertension is more prevalent in black than white populations, with the prevalence of hypertension being reported as being 50% greater in African-American than Caucasian populations in

the USA.[1] African-American and Afro-Caribbean populations also have lower renin activity and a poorer response to angiotensin-converting enzyme inhibitors (ACEIs).[1,13] An in-depth discussion of the causes and pathophysiology of hypertension is outside the scope of this article as they are both multifactorial and complex. But the development of hypertension is believed to be due to a combination of both genetic and environmental factors, and there are clear associations with hypertension and obesity, salt and alcohol intake.[1,11] Arterial blood pressure is the product of cardiac output and peripheral vascular resistance and therefore blood pressure (and hypertension) is affected by factors which have an impact on these paramenters.[1,13] These include factors such as stimulation of the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS) and parasympathetic nervous system as well as an interplay between the vasoactive substances produced by the vascular endothelium and a variety of other vasoactive mediators such as bradykinin, endothelin, endothelial derived relaxing factor (EDRF) and atrial natriuretic peptide (ANP).[1,13]

Clinical features

Most cases of essential hypertension are asymptomatic, symptoms such as headache being more commonly experienced in secondary or malignant hypertension.[1] The lack of symptoms is often a cause for non-compliance and poor persistence with antihypertensive medication, as patients (and sometimes supporters) have poor insight into the long-term health risks associated with untreated hypertension and discontinue therapy if side effects start to impact onto their lifestyle. If hypertension remains untreated, key organs within the body are chronically exposed to persistently high blood pressure resulting in end organ or target organ damage. Most organs are protected from this effect and maintain normal tissue blood flow, but key organs such as the kidney, heart, brain and eye may be affected resulting in hypertensive nephrosis, left ventricular hypertrophy, increased risk of haemorrhagic strokes, dementia and hypertensive encephalopathy.[1,14] Hypertension has several effects on the eye and may cause hypertensive retinopathy, occlusion of the retinal vein and artery and ischaemic optic neuropathy.[14]

Table 1: Definitions and classification of blood pressure levels (mmHg)[3]

Category	Systolic (mmHg)	Diastolic (mmHg)	Follow up
Normal	< 120	<80	Recheck in 2 years*
High-normal	120-139	80-89	Recheck in 1 year*
Grade 1 (mild) hypertension	140-159	90-99	Confirm within 2 months**
Grade 2 (moderate) hypertension	160-179	100-109	Reassess or refer within 1 month**
Grade 3 (severe) hypertension	≥180	≥110	Reassess or refer within 1-7 days as necessary**
Isolated systolic hypertension	≥140	≤90	As for category corresponding to systolic BP
Isolated systolic hypertension with widened pulse pressure	≥160	≤70	As for grade 3 hypertension

N.B. If a patient's systolic and diastolic blood pressures fall into different categories, the higher category is applied

* or earlier depending on patient's absolute cardiovascular risk

**or see when to intervene

Diagnosis and assessment

A 'normal range' for blood pressure and a diagnostic level for hypertension is difficult to define as blood pressure is a continuous variable with a wide distribution in the general population.[1] The International Society of Hypertension and World Health Organisation definition of hypertension, which is a sustained blood pressure of equal to or greater than 140/90mmHg, is commonly quoted.[1,12,13] But as patients often exhibit hypertension-related health problems at lower blood pressures it is important not to just consider blood pressure readings in isolation but also to consider absolute cardiovascular risk, both in the diagnosis and treatment of the condition.[1] The measurement of blood pressure is fraught with inaccuracy due to a variety of patient-related or observer-related factors. It is therefore important that diagnostic and therapeutic decisions are based on the presence of sustained elevated blood pressure measurements recorded on multiple occasions.[3] Therapeutic decisions should not be made on isolated single results.[3,7,9,13] Blood pressure measurements should be made using an appropriate recommended and accurate technique and repeated several times if necessary.[3] A regularly serviced mercury sphygmomanometer should be used or the instrument should be regularly validated against a mercury sphygmomanometer.[3] The patient's blood pressure should be measured on both arms at the first assessment and then subsequent measurements should be made on the arm with the higher reading.[3] The use of ambulatory or home blood pressure monitoring may help to identify patients with 'white coat hypertension' and prevent unnecessary treatment.[3,13,15] White coat hypertension occurs in about 20% of patients with elevated blood pressure and although patients tend to have a lower cardiovascular risk than patients with sustained hypertension it may be a precursor of sustained hypertension and must be monitored.[3,13] As the division between normotension and hypertension is arbitrary, it is important that the patient has a thorough clinical assessment with the aim of excluding and treating any possible secondary or drug-induced causes of the hypertension and to assess the patient's

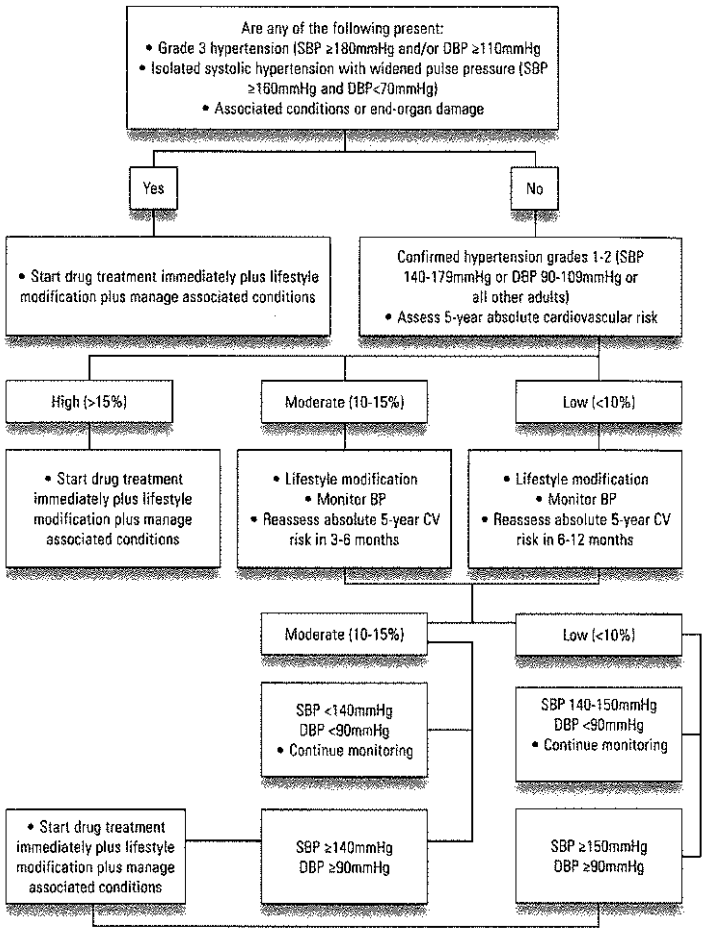
The articles in this series are independently researched and compiled by PSA commissioned authors and peer reviewed.

absolute cardiovascular risk.[3,7,9,13] International definitions of hypertension vary but the NHF Guidelines use the diagnostic levels and follow up recommendations listed in Table 1 with the recognition that individual cardiovascular risk assessment be used to determine the appropriate management for each patient.[3]

Absolute cardiovascular risk

Absolute cardiovascular risk is the risk of a patient experiencing a cardiovascular event over a pre-defined period (usually five or 10 years).[3] Elevated blood pressure is a major determinant of the risk of cardiovascular events such as myocardial infarction or stroke and other key risk factors include diabetes, cigarette smoking, male gender, and dyslipidaemia. Also, in Australia we must be aware of key ethnic risk groups such as Aboriginal and Torres Strait Islanders.[3] All patients with confirmed hypertension should be assessed to identify all cardiovascular risk factors, detect end-organ damage and associated clinical conditions (Table 2) and identify possible causes of secondary hypertension.[3] The new NHF guidelines recommend that high cardiovascular risk should be assumed for patients aged 75 years and over, patients with pre-existing cardiovascular disease and patients with associated clinical conditions and end-organ disease.[3] All other patients should have their cardiovascular risk estimated using the modified New Zealand cardiovascular risk calculator.[3] But it must be recognised that CV risk calculators may significantly underestimate the cardiovascular risk in Aboriginal, Torres Strait Islander, Maori or Pacific Islander peoples.[3] Patients with high absolute cardiovascular risk (greater than 15% risk of a cardiovascular event within the next five years) need immediate antihypertensive therapy.[3]

Figure 1: When to initiate blood pressure-lowering drug treatment[3]



Management of hypertension

When to initiate therapy

All patients with confirmed hypertension should have a therapeutic plan aimed at reducing both blood pressure and absolute cardiovascular risk and the management strategies used will be related to the patient's absolute cardiovascular risk.[3,9,13] Figure 1, taken from the new NHF guidelines, summarises their current recommendations with regard to the stratification of therapy based on blood pressure measurements and absolute cardiovascular risk. The diagram shows that high risk patients should be treated immediately with lifestyle modification and drug treatment whereas moderate and mild risk patients are initially treated with lifestyle modification and undergo an appropriate period of monitoring before drug treatment is commenced.[3]

Treatment goals

Treatment goals for hypertension have gradually lowered in recent years as the relationship between blood pressure and outcome became better understood and it became evident that lower blood pressures are associated with better outcomes.[3,16] Table 3 summarises the treatment targets for adults from the current NHF guidelines.[3] In most management guidelines it is recognised that targets such as these will be difficult to obtain in many patients, but it is accepted that any improvement in blood pressure and/or cardiovascular risk is beneficial.[3,9]

Lifestyle modification

Lifestyle modification is an important intervention and should form an integral part of the management of all patients, as it may abolish the need for medication in some patients and reduce the need in others.[3,17,18] NHF recommendations centre around the 'SNAP' risk factors (Smoking cessation, Nutrition, Alcohol and Physical activity).[3]

Smoking cessation

Although smoking cessation has little effect on blood pressure reduction, it is the most important lifestyle modification for reducing absolute cardiovascular risk.[1,3,17]

Table 2: Associated clinical conditions and end-organ disease[3]

Associated clinical conditions (ACC)	End-organ disease
• Diabetes • Cerebrovascular disease o Ischaemic stroke o Cerebral haemorrhage o Transient ischaemic attack • Coronary heart disease o Myocardial infarction o Angina o Coronary revascularisation • Chronic heart failure • Chronic kidney disease o Diabetic nephropathy o Glomerulonephritis o Hypertensive kidney disease • Aortic disease o Dissecting aneurysm o Fusiform aortic aneurysm • Peripheral arterial disease • Hypercholesterolaemia • Family history of: o Premature cardiovascular disease o Familial hypercholesterolaemia	• Left ventricular hypertrophy • Microalbuminuria • Chronic kidney disease • Vascular disease o Atherosclerotic plaque evident on ultrasound or radiology o Hypertensive retinopathy

Table 3: NHF treatment targets for adults[3]

Patient group	Blood pressure target (mmHg)
Adults with proteinuria >1g/day (in people with/without diabetes)	<125/75
People with associated condition/s or end-organ damage: • Coronary heart disease • Diabetes • Renal insufficiency • Proteinuria 0.25-1.0g/day • Stroke/TIA	<130/80
People with none of the following: • Coronary heart disease • Diabetes • Renal insufficiency • Proteinuria (≥0.25g/day • Stroke/TIA	<140/90 or lower if tolerated

Weight reduction

Obesity is associated with the development of hypertension and weight loss has been proven to reduce blood pressure by an average of 2mmHg per kg of body weight lost.[1,3,19] Body mass index (BMI) is often used to define obesity but visceral adiposity appears to be more important in defining the relationship between obesity and blood pressure[19] and patients' BMI and waist circumference should be assessed and monitored.[3] The NHF recommends management goals of BMI of less than 25kg/m^2 and a waist circumference of 94cm for males and 80cm for females or less.[3] Patients should be advised that to reach and maintain a healthy weight they must make lifestyle changes that they can enjoy and maintain for a lifetime, which requires both increased physical activity and reduced energy intake.[3]

Diet

Studies have shown reductions in blood pressure of 5-7mmHg when sodium intake is reduced to 90-100mmol/day.[1,3] This may be further reduced if low salt intake is combined with a thiazide diuretic.[1] Patients should be encouraged to reduce their salt intake (less than 65mmol/day[3]) and avoid processed foods with a high salt content.[1,3] Potassium chloride may be sometimes used to substitute salt in the diet with no adverse effects[1] but care may be required in patients taking ACE inhibitors. Patients must also follow a diet low in saturated fat and high in plant-based foods.[1]

Alcohol

The causal relationship has not been confirmed but there is a clear association between alcohol intake and blood pressure in both sexes, with binge drinking being associated with the greatest risk.[1,17] Abstinence from alcohol in hypertensive patients can reduce systolic blood pressure by 5-8mmHg.[1] Patients should be encouraged to reduce alcohol intake to safe drinking levels[1,3,17] (two standard drinks per day for men and one standard drink per day for women[3]) and to abstain where possible.

Physical exercise

Physical inactivity is a well recognised risk factor for cardiovascular disease and regular aerobic exercise can reduce blood pressure. All patients should be advised to become more active and have at least 30 minutes of moderate intensity physical activity on most if not all days of the week. Regular aerobic exercise can reduce blood pressure and patients should be advised to do at least 30 minutes of moderate intensity exercise on five or more days per week.[3,17]

Pharmacological management

Choice of first-line therapy

The pharmacological management of hypertension has changed and evolved over the last 10-20 years. Until recently a traditional stepped care approach was recommended

The articles in this series are independently researched and compiled by PSA commissioned authors and peer reviewed.

involving a fairly dogmatic approach of using either beta blockers or low-dose thiazide diuretics as first line agents, followed by the addition of other antihypertensive agents if blood pressure control was not achieved. This was further developed into a more individualised stepped care approach, whereby an appropriate first line agent was chosen based on the patient's individual characteristics and factors such as:[3,13]

- The patient's cardiovascular risk profile
- The presence of target organ disease, clinical cardiovascular diseases, renal disease or diabetes
- Contraindications with concomitant diseases or potential interactions with concomitant therapies
- Evidence for a reduction in cardiovascular events with the antihypertensive agent
- Social and lifestyle effects such as side effects and improved quality of life
- Economic factors such as the cost of therapy to both the patient and the health care system.

Five common drug groups were recommended for the initial management of hypertension: the low-dose thiazide diuretics, the beta blockers, the angiotensin converting enzyme inhibitors (ACEIs), the angiotensin II receptor antagonists (A2RAs) and the calcium channel blockers (CCBs). As all were shown to reduce blood pressure to a similar extent but differed in their adverse effect profiles and cost,[3,8,19,20] the selection of first line agent was based on their potential for favourable or unfavourable effects on any concomitant diseases.

For many years beta blockers were widely used for first line treatment in hypertension and are still recommended as first line agents in some treatment guidelines.[21-23] One explanation for their popularity was that studies confirmed the value of beta blockers after myocardial infarction (MI), in angina and in heart failure and clinicians made assumptions based on their effectiveness in the secondary prevention of coronary heart disease that they should also be effective for primary prevention in hypertension.[21-23] But the use of beta blockers for primary treatment of hypertension has been recently challenged[21] as comparisons with other antihypertensive agents showed them to be less effective in preventing major cardiovascular events such as stroke.[2,21-23] It was unclear whether these conclusions applied to all beta blockers or only to the drugs commonly used in hypertension trials (mainly atenolol), but researchers recommended that beta blockers should not remain the first choice agents for the treatment of primary hypertension.[2,22,23] Beta blockers were also found to be less effective than ACEIs and CCBs at reducing the risk of diabetes, especially when used in combination with thiazide diuretics.[2,7,9]

These findings were incorporated firstly into the 2006 update of the National Institute for Health and Clinical Excellence (NICE) and the British Hypertension Society recommendations for the pharmacological management of hypertension. The main recommendations were that beta blockers were no longer recommended for first line management of any patient group and that CCBs and thiazides are recommended as first line agents in elderly and black people as they are the most clinically effective agents for lowering blood pressure in these patient groups.[2,7,9] The updated NICE treatment recommendations are summarised in Figure 2. The current recommendation is that unless there are contraindications,

Figure 2: Current NICE guidelines for the treatment of hypertension[7-9]

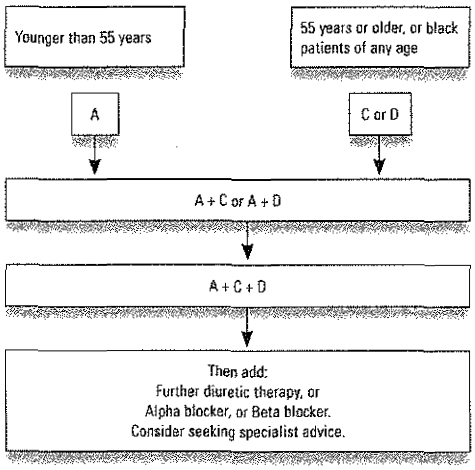
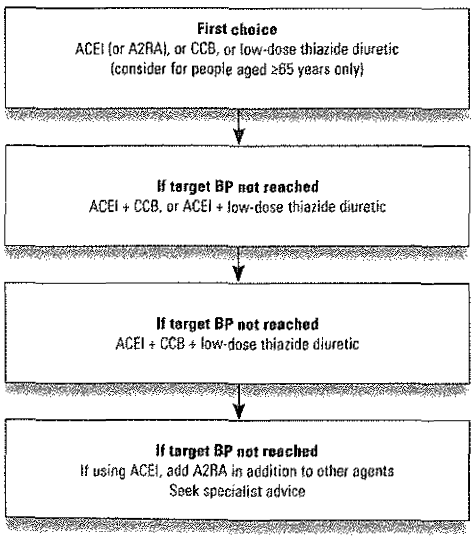


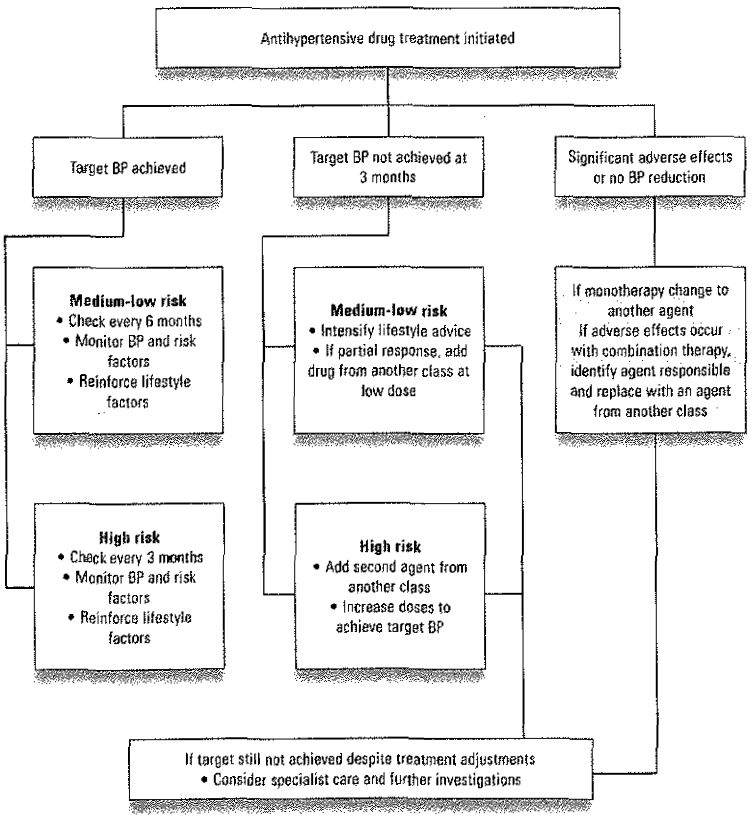
Figure 3: NHF recommendations for initiating drug treatment for newly diagnosed uncomplicated hypertension[3]



ACEIs should be used for initial therapy in patients under the age of 55 years, whereas patients 55 years or older (or black patients) requiring drug treatment should be commenced on either a CCB or thiazide diuretic.[7,9] But the NICE guidelines do suggest that beta blockers may still be considered for younger patients, particularly women of childbearing potential, patients with evidence of increased sympathetic drive or patients intolerant of or who have contraindications to ACEIs or A2RAs.[7] They also recommend that beta blockers should not be withdrawn if there is a compelling reason for beta blocker use such as in angina or a previous MI.[7]

In light of the recent findings regarding beta blockers, the NHF has now also reviewed its guidelines for the management of hypertension; these are summarised in Figure 3. The new NHF guidelines discuss that ACEIs (or A2RAs if the patient suffers from ACEI cough), dihydropyridine CCBs and low-dose thiazide diouretics are equally effective for first line use for initial or maintenance therapy and the initial drug choice should be based on:[3]

Figure 4: NHF recommendations for stabilisation, maintenance and follow-up after initiation of antihypertensive therapy[3]



- The patient's age
- The presence of associated clinical conditions and end-organ damage
- The presence of co-morbidities (and the favourable and unfavourable effects of the antihypertensive agent on these conditions)
- Potential drug interactions
- Implications for adherence
- Cost.

Thiazide diuretics have been associated with increased risk of diabetes, therefore NHF recommends that the first-line use of thiazide diuretics should be limited to elderly patients (≥65 years of age) in whom the benefits of managing hypertension and reducing the risk of stroke outweigh the risk of diabetes.[3] Again for the reasons stated above, beta blockers are no longer recommended as first-line agents in uncomplicated hypertension although the guidelines state that it is reasonable to continue beta blocker therapy in patients with well-controlled hypertension already taking a beta blocker.[3]

Achieving target blood pressure[3]

The aim of therapy should be to achieve target blood pressure (Table 3) and combination therapy may be required to reach target levels.[3] The lowest recommended dose of the first-line agent should be prescribed and the effect monitored. If the patient is unable to tolerate this agent it should be replaced with a drug from a different class. The patient should be monitored (Figure 4) and if target blood pressure is not reached, instead of increasing the dose of the first agent, a second agent (from a different class) should be introduced at a low dose.[3] This approach is aimed at maximising the antihypertensive effect of the agents whilst minimising side effects.[3] Again the patient is monitored: if the blood pressure continues to be above target, the dose of one agent (but not the thiazide diuretic if being used) is increased to the maximum recommended dose of the agent before increasing the dose of the second agent.[3] A stable response to a dose may take 3-4 weeks. Therefore dose increments should be made at six weekly intervals.[3] Once the regime is stable, combined preparations or the use of long-acting agents that may be administered once daily may help adherence and compliance.[3] Combination therapy is required to reach target levels in 50-75% of patients and occasionally patients may require a combination of 3-4 agents. Table 4 summarises commonly used combinations recommended in the NHF guidelines.[3] If the patient fails to respond to initial therapy with at least two agents the patient should be assessed for possible reasons. These may include non-compliance, undiagnosed secondary hypertension, 'white coat' hypertension as well as other factors, but in some patients *recommended target levels may not be achievable.*[3]

The articles in this series are independently researched and compiled by PSA commissioned authors and peer reviewed.

Conclusions

Hypertension is a major risk factor for cardiovascular disease and it is believed that the worldwide prevalence will increase in the future. Recent Australian and international guidelines for the management of hypertension recommend the assessment and treatment of patients with the aim of reducing both blood pressure and absolute cardiovascular risk to target levels. When appropriate, drug therapy should be utilised with lifestyle modification, and initial drug therapy will consist of ACE inhibitors, calcium channel blockers or low-dose thiazide diuretics with the choice of agent based on the presence of concomitant disorders and potential adverse effects.[3,7,9,20]

Ian Heslop (BSc(Hons) MSc GradCertBT MRPharmS AACPA MSHP) is currently a Senior Lecturer at the School of Pharmacy & Molecular Sciences at James Cook University, Queensland teaching in the areas of clinical therapeutics and pharmacy practice. Before moving into academia, he was a clinical pharmacist for more than 16 years in a range of clinical specialties in both Australian and UK hospitals.

References

1. Thomas M. Hypertension – clinical features and investigations. Hosp Pharm. 2007;14(Apr):111-6.
2. Williams B. Evolution of hypertensive disease: a revolution in guidelines. Lancet. 2006;368(Jul 1):6-8.
3. National Heart Foundation of Australia (National Blood Pressure and Vascular Disease Advisory Committee). Guide to management of hypertension 2008. Quick reference guide for health professionals. Deakin: National Heart Foundation of Australia; 2008.
4. Briganti EM, Shaw JE, Chadban SJ, Zimmet PZ, Welborn TA, McNeil JJ, et al. Untreated hypertension among Australian adults: the 1999-2000 Australian Diabetes, Obesity and Lifestyle Study (AusDiab). MJA. 2003;179(Aug 4):135-9.
5. Editorial. Don't forget hypertension. Lancet. 2007;369(May 26):1764.
6. Simons LA, Ortiz M, Calcino G. Persistence with antihypertensive medication: Australia-wide experience, 2004-2006. MJA. 2008;188(Feb 18):224-7.
7. National Collaborating Centre for Chronic Conditions. Hypertension: management in adults in primary care: pharmacological update. London: Royal College of Physicians; 2006.
8. Gormer B. Hypertension - pharmacological management. Hosp Pharm. 2007;14(Apr):119-25.
9. National Institute for Health and Clinical Excellence. Hypertension: management of hypertension in adults in primary care (NICE guideline 34). London: NICE; 2006.
10. National Prescribing Service. NPS News 52: Managing hypertension as a cardiovascular risk factor. Surry Hills: National Prescribing Service Ltd; 2007.
11. Beevers G, Lip GYH, O'Brien E. The pathophysiology of hypertension. BMJ. 2001;322(Apr 14):912-6.
12. Hughes J. Hypertension. Aust Pharm. 1999;18(10):603-13.
13. August P. Initial Treatment of Hypertension. NEJM. 2003;348(Feb 13):610-7.
14. Wong T, Mitchell P. The eye in hypertension. Lancet. 2007;369(Feb 3):425-35.
15. Pickering TG, Shimbo D, Haas D. Ambulatory Blood-Pressure Monitoring. NEJM. 2006;354(Jun 1):2368-74.
16. Kannel WB, Vasan RS. Aggressive lowering of blood pressure. Lancet. 2006;368(Aug 19):627-8.
17. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, et al. British Hypertension Society Guidelines: Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. J of Hum Hypertension. 2004;18:139-85.
18. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, et al. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. BMJ. 2004;328(Mar 13):634-40.
19. Messerli FH, Williams B, Ritz E. Essential Hypertension. Lancet. 2007;370(Aug 18):591-603.
20. National Prescribing Service. NPS News 52: Managing hypertension as a cardiovascular risk factor. Surry Hills: NPS Ltd; 2007.
21. Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? Lancet. 2004;364(Nov 6):1684-9.
22. Lindholm LH, Carlberg B, Samuelsson O. Should ß blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet. 2005;366(Oct 29):1545-53.
23. Beevers DG. The end of β blockers for uncomplicated hypertension? Lancet. 2005;366(Oct 18):1510-2.

CPD questions on pages 586

Table 4: Recommended and non-recommended antihypertensive combinations from NHF Guidelines[3]

Effective combinations	
Combination	**Notes**
ACEI (or A2RA) + CCB	Most effective combination - useful in the presence of diabetes or lipid abnormalities
Thiazide diuretic + ACEI (or A2RA)	Useful in the presence of heart failure or post stroke
ACEI + A2RA	Useful in people with both diabetes and chronic kidney disease
ACEI + beta blocker	Recommended post-MI or in people with heart failure
Beta blocker + dihydropyridine CCB	Useful in the presence of coronary heart disease
Thiazide diuretic + CCB	
Beta blocker + alpha blocker	Not recommended in people with glucose intolerance, metabolic syndrome or diabetes
Avoid the following combinations	
Combination	**Notes**
ACEI (or A2RA) + potassium sparing diuretic	Risk of hyperkalaemia
Beta blocker + verapamil or diltiazem	Avoid combination with verapamil and caution with diltiazem due to risk of bradycardia and heart block