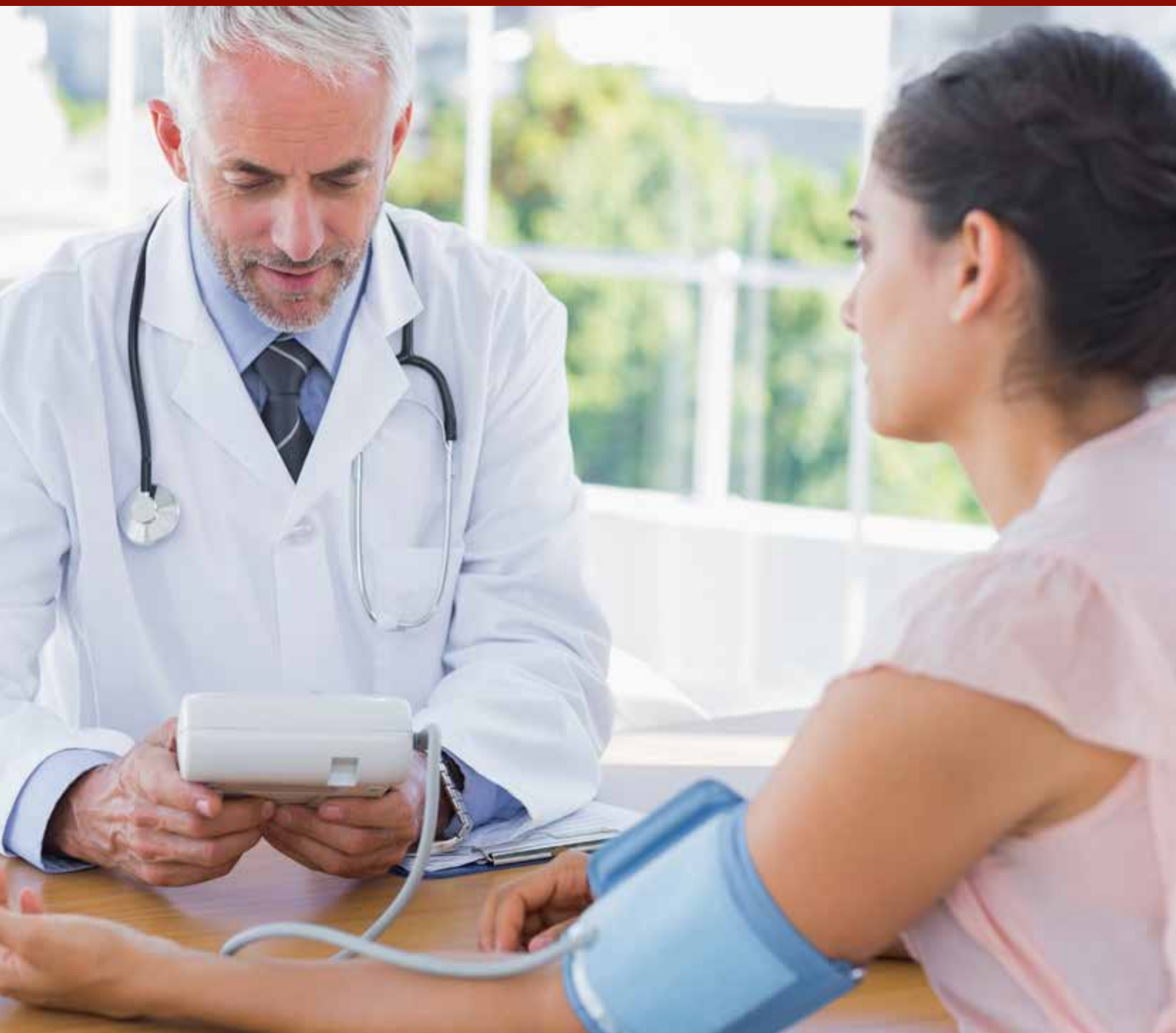
Heart Foundation®

Guideline for the diagnosis and management of hypertension in adults

2016



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Abbreviations and acronyms

ABI	Ankle brachial index
ABPM	Ambulatory blood pressure monitoring
ACCESS	Acute Candesartan Cilexetil Evaluation in Stroke Survivors
ACCOMPLISH	Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin converting enzyme
ACR	Albumin/creatinine ratio
ALTITUDE	Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints
AMSTAR	A Measurement Tool to Assess Systematic Reviews
ARB	Angiotensin receptor blocker
BMI	Body mass index
BPLTTC	Blood Pressure Lowering Treatment Trialists' Collaboration
CHHIPS	Controlling Hypertension and Hypotension Immediately Post-Stroke
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CR	Controlled release
CT	Computerised tomography
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
ECG	Electrocardiograph
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GFR	Glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAPPy	Hypertension Adherence Program in Pharmacy
HBPM	Home blood pressure monitoring
HDL	High-density lipoprotein
HOPE	Heart Outcomes Prevention Evaluation
HYVET	Hypertension in the Very Elderly Trial
JNC	Joint National Committee (on Prevention Detection Evaluation and Treatment of High Blood Pressure)
KDIGO	Kidney Disease Improving Global Outcomes
LDL	Low-density lipoprotein
mmHg	Millimetres of mercury
NBPVDAC	National Blood Pressure and Vascular Disease Advisory Committee
NHMRC	National Health and Medical Research Council
NICE	National Institute of Clinical Excellence
NSAID	Non-steroidal anti-inflammatory drugs
NVDPA	National Vascular Disease Prevention Alliance
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
PCR	Protein/creatinine ratio
PICO	Patient, Intervention, Comparison, Outcome
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
RACGP	Royal Australian College of General Practitioners
SCAST	Scandinavian Candesartan Acute Stroke Trial
SNAP	Smoking, Nutrition, Alcohol, Physical activity
SNRIs	Serotonin and norepinephrine reuptake inhibitors
SOMANZ	The Society of Obstetric Medicine of Australia and New Zealand
SPRINT	Systolic Blood Pressure Intervention Trial
SPS3	Secondary Prevention of Small Subcortical Strokes
TGA	Therapeutic Goods Administration
TIA	Transient ischaemic attack
VA NEPHRON-D	Veteran Affairs – Nephropathy in Diabetes, Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy
WHO	World Health Organization

Contents

Tables, figures and boxes

I. Summary of recommendations

Recommendations on methods of blood pressure measurement

Methods of measuring blood pressure	Grade of recommendation	Level of evidence
a. If clinic blood pressure is ≥140/90 mmHg, or hypertension is suspected, ambulatory and/or home monitoring should be offered to confirm the blood pressure level.	Strong	I
b. Clinic blood pressure measures are recommended for use in absolute CVD risk calculators. If home or ambulatory blood pressure measures are used in absolute CVD risk calculators, risk may be inappropriately underestimated.	Strong	–
c. Procedures for ambulatory blood pressure monitoring should be adequately explained to patients. Those undertaking home measurements require appropriate training under qualified supervision.	Strong	I
d. Finger and/or wrist blood pressure measuring devices are not recommended.	Strong	–

Recommendations for treatment strategies and treatment targets for patients with hypertension

Recommendations for treatment strategies and treatment targets for patients with hypertension	Grade of recommendation	Level of evidence
a. Lifestyle advice is recommended for all patients.	Strong	
b. For patients at low absolute CVD risk (<10% 5-year risk) with persistent blood pressure ≥160/100 mmHg, antihypertensive therapy should be started.	Strong	I
c. For patients at moderate absolute CVD risk (10–15% 5-year risk) with persistent blood pressure ≥140 mmHg systolic and/or ≥90 mmHg diastolic, antihypertensive therapy should be started.	Strong	I
d. Once decided to treat, patients with uncomplicated hypertension should be treated to a target of <140/90 mmHg or lower if tolerated.	Strong	I
e. In selected high cardiovascular risk populations where a more intense treatment can be considered, aiming to a target of <120 mmHg systolic blood pressure can improve cardiovascular outcomes.	Strong	II
f. In selected high cardiovascular risk populations where a treatment is being targeted to <120 mmHg systolic, close follow-up of patients is recommended to identify treatment related adverse effects including hypotension, syncope, electrolyte abnormalities and acute kidney injury.	Strong	II
g. In patients with uncomplicated hypertension ACE inhibitors or ARBs, calcium channel blockers, and thiazide diuretics are all suitable first-line antihypertensive drugs, either as monotherapy or in some combinations unless contraindicated.	Strong	I
h. The balance between efficacy and safety is less favourable for beta-blockers than other first-line antihypertensive drugs. Thus beta-blockers should not be offered as a first-line drug therapy for patients with hypertension not complicated by other conditions.	Strong	I
i. ACE inhibitors and ARBs are not recommended in combination due to the increased risk of adverse effects.	Strong	I

Recommendation for starting drug treatment with more than one drug

Combination versus monotherapy	Grade of recommendation	Level of evidence
a. For patients with very high baseline blood pressure (>20 mmHg systolic and >10 mmHg diastolic above target), starting treatment with more than one drug may be considered.	Weak	–

Recommendations for patients with hypertension and prior stroke and/or TIA

Patients with hypertension and prior stroke or transient ischaemic attack	Grade of recommendation	Level of evidence
a. For patients with a history of TIA or stroke, antihypertensive therapy is recommended to reduce overall cardiovascular risk.	Strong	I
b. For patients with a history of TIA or stroke, any of the first-line antihypertensive drugs that effectively reduce blood pressure are recommended.	Strong	I
c. For patients with hypertension and a history of TIA or stroke, a blood pressure target of <140/90 mmHg is recommended.	Strong	I

Recommendations for patients with hypertension and chronic kidney disease

Patients with hypertension and chronic kidney disease	Grade of recommendation	Level of evidence
a. In patients with hypertension and chronic kidney disease, any of the first-line antihypertensive drugs that effectively reduce blood pressure are recommended.	Strong	I
b. When treating hypertension in patients with chronic kidney disease in the presence of micro or macro albuminuria,* an ARB or ACE inhibitor should be considered as first-line therapy.	Strong	I
c. In patients with chronic kidney disease, antihypertensive therapy should be started in those with systolic blood pressures consistently >140/90 mmHg and treated to a target of <140/90 mmHg.	Strong	I
d. Dual renin-angiotensin system blockade is not recommended in patients with chronic kidney disease.	Strong	I
e. For patients with chronic kidney disease, aiming towards a systolic blood pressure of <120 mmHg has shown benefit, where well tolerated.	Strong	II
f. In people with chronic kidney disease where treatment is being targeted to <120 mmHg systolic, close follow-up of patients is recommended to identify treatment related adverse effects including hypotension, syncope, electrolyte abnormalities and acute kidney injury	Strong	I
g. In patients with chronic kidney disease, aldosterone antagonists should be used with caution in view of the uncertain balance of risks versus benefits.	Weak	–

*Table of equivalents for measures of micro and macro albuminuria can be found in Table 4.10.

Recommendations for patients with hypertension and diabetes

Patients with hypertension and diabetes	Grade of recommendation	Level of evidence
a. Antihypertensive therapy is strongly recommended in patients with diabetes and systolic blood pressure ≥140 mmHg.	Strong	I
b. In patients with diabetes and hypertension, any of the first-line antihypertensive drugs that effectively lower blood pressure are recommended.	Strong	I
c. In patients with diabetes and hypertension, a blood pressure target of <140/90 mmHg is recommended.	Strong	I
d. A systolic blood pressure target of <120 mmHg may be considered for patients with diabetes in whom prevention of stroke prioritised.	Weak	–
e. In patients with diabetes where treatment is being targeted to <120 mmHg systolic, close follow-up of patients is recommended to identify treatment related adverse effects including hypotension, syncope, electrolyte abnormalities and acute kidney injury.	Strong	–

Recommendations for patients with hypertension and prior myocardial infarction

Patients with hypertension and previous myocardial infarction	Grade of recommendation	Level of evidence
a. For patients with a history of myocardial infarction, ACE inhibitors and beta-blockers are recommended for the treatment of hypertension and secondary prevention.	Strong	II
b. Beta-blockers or calcium channel blockers are recommended for symptomatic patients with angina.	Strong	II

Recommendations for patients with hypertension and chronic heart failure

Patients with hypertension and chronic heart failure	Grade of recommendation	Level of evidence
a. In patients with chronic heart failure, ACE inhibitors and selected beta-blockers* are recommended.	Strong	II
b. ARBs are recommended in patients who do not tolerate ACE inhibitors.	Strong	I

*Carvedilol; bisoprolol (beta-1 selective antagonist); metoprolol extended release (beta-1 selective antagonist); nebivolol

Recommendations for patients with hypertension and peripheral arterial disease

Patients with hypertension and peripheral arterial disease	Grade of recommendation	Level of evidence
a. In patients with peripheral arterial disease, treating hypertension is recommended to reduce CVD risk.	Strong	–
b. In patients with hypertension and peripheral arterial disease, any of the first-line antihypertensive drugs that effectively reduce blood pressure are recommended.	Weak	
c. In patients with hypertension and peripheral arterial disease, reducing blood pressure to a target of <140/90 mmHg should be considered and treatment guided by effective management of other symptoms and contraindications.	Strong	–

Recommendations for treatment of hypertension in older persons

Older persons with hypertension	Grade of recommendation	Level of evidence
a. Any of the first-line antihypertensive drugs can be used in older patients with hypertension.	Strong	I
b. When starting treatment in older patients, drugs should be commenced at the lowest dose and titrated slowly as adverse effects increase with age.	Strong	–
c. For patients >75 years of age, aiming towards a systolic blood pressure of <120 mmHg has shown benefit, where well tolerated, unless there is concomitant diabetes.	Strong	II
d. In older persons where treatment is being targeted to <120 mmHg systolic, close follow-up of patients is recommended to identify treatment-related adverse effects including hypotension, syncope, electrolyte abnormalities and acute kidney injury.	Strong	II
e. Clinical judgement should be used to assess the benefit of treatment against the risk of adverse effects in all older patients with lower grades of hypertension.	Strong	–

Recommendations for patients with hypertension and suspected blood pressure variability

Patients with hypertension and suspected blood pressure variability	Grade of recommendation	Level of evidence
a. For high-risk patients with suspected high variability in systolic blood pressure between visits, a focus on lifestyle advice and consistent adherence to medications is recommended.	Strong	I
b. Drug therapy should not be selected based on reducing blood pressure variability per se but in accordance with current recommendations, which already prioritise the most effective medications.	Strong	

Recommendations for the use of renal denervation in treatment resistant hypertension

Patients with treatment resistant hypertension	Grade of recommendation	Level of evidence
a. Optimal medical management with a focus on treatment adherence and excluding secondary causes is recommended.	Strong	II
b. Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery is currently not recommended for the clinical management of resistant hypertension or lower grades of hypertension.	Weak	II

Recommendation for patients with hypertension requiring antiplatelet therapy

Antiplatelet therapy for patients with hypertension	Grade of recommendation	Level of evidence
a. Antiplatelet therapy, in particular low-dose aspirin, is recommended in patients with hypertension and previous CVD events unless bleeding risk is increased.	Strong	I

II. What's new in this edition?

The National Heart Foundation of Australia's *Guideline for the diagnosis and management of hypertension in adults – 2016* provides updated recommendations on the management of hypertension at a time when knowledge in this area is rapidly changing.

In contrast to the previous edition, *Guide to management of hypertension 2008 (updated 2010)*, this guideline provides a description of recent evidence rated according to the National Health and Medical Research Council (NHMRC) standards and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) levels of evidence. The former guideline predominantly focused on primary prevention. However, this edition includes both a primary and secondary prevention focus on the contemporary management of hypertension in the context of an ageing population with increasing complexities.

For primary prevention, the emphasis in this guideline is on targeting absolute risk, preferably assessed using the methodology of the National Vascular Disease Prevention Alliance's (NVDPA's) *Guidelines for the management of absolute cardiovascular risk.* However this approach is limited to particular age groups (>35 in Aboriginal and Torres Strait Islander peoples, >45 in non-Indigenous Australians) and does not always account for important comorbidities or target organ damage in hypertension that are known to increase risk. It has therefore been necessary to make recommendations based on recent evidence outside the patient groups covered by the absolute cardiovascular risk guidelines. Furthermore, a number of important recent trials have addressed blood pressure targets as a single risk factor in people with moderate or high risk assessed by other methods.

This edition of the guideline offers advice on new areas including out-of-clinic blood pressure measurement using ambulatory or home procedures, white-coat hypertension and blood pressure variability. There has been considerable development of treatment strategies and targets according to selected co-morbidities, which often occur in combination. These include stroke and transient ischaemic attack (TIA), chronic kidney disease, diabetes, myocardial infarction, chronic heart failure, peripheral artery disease and obstructive sleep apnoea.

An additional key difference is the new evidence for a target blood pressure of <120 mmHg in particular patient groups. In selected high cardiovascular risk populations, there is a recommendation to aim for this lower target with close follow-up to identify adverse effects including hypotension, syncope, electrolyte abnormalities and acute kidney injury.

Hypertension is a major risk factor and antecedent of cardiovascular and end organ damage (myocardial infarction, chronic kidney disease, ischaemic and haemorrhagic stroke, heart failure and premature death). It should not be treated alone, but include assessment of all cardiovascular risk factors in a holistic approach, incorporating patient-centred lifestyle modification.

1 Introduction

Statement of purpose: This guideline aims to arm health professionals working across the Australian healthcare system, in particular those working within primary care and community services, with the latest evidence for controlling blood pressure, including methods for diagnosis and monitoring, and effective treatment strategies for patients with hypertension with and without co-morbidities.

This guideline builds on the previous Guide to management of hypertension (updated 2010).

The guideline emphasises the role of absolute cardiovascular disease (CVD) risk assessments where appropriate, and the importance of allied health professionals in assisting with adherence to medications and lifestyle advice.

This guideline adheres to the fundamental principles applied to previous guidelines including:

- to base recommendations on high-quality studies identified from an extensive literature review
- to prioritise data from large systematic reviews and randomised controlled trials, adding observational and other studies where appropriate.

While not provided in previous versions, this edition includes the level of evidence and grade of the recommendations on major diagnostic and treatment issues in accordance with NHMRC standards and GRADE definitions as outlined in Table 1.1 and Table 1.2. Where there is no direct evidence for a recommendation that guideline developers agreed clearly outweighed any harm, the level of evidence is noted with a dash. Only English-language titles were reviewed and this edition will only be published in English.

Due to changing evidence on several diagnostic and therapeutic aspects of hypertension and its influence on CVD risk, there are many updated practice considerations and recommendations throughout the document.

Table 1.1 Grading of Recommendations Assessment, Development and Evaluation (GRADE)[1]

Grade of recommendation	Description
Strong	Benefits clearly outweigh drawbacks/harms
Weak	It is less clear that the benefits outweigh the drawbacks/harms

Table 1.2 National Health and Medical Research Council levels of evidence[2]

Level of evidence	Intervention	Diagnostic accuracy	Prognosis
I	Systematic review of Level II studies	Systematic review of Level II studies	Systematic review of Level II studies
II	A randomised controlled trial	Test accuracy independent blinded with relevant reference standard	A prospective cohort study
III-1	Pseudo-randomised controlled trial	Test accuracy independent blinded with relevant reference standard	All or none of the persons experience the outcome
III-2	Comparative study with concurrent controls; non-randomised trial, cohort study, case-control study, interrupted time series with control group	Comparison with reference standard that does not meet the criterial required for Level II and III-1 evidence	Analysis of prognostic factors in persons from single arm of randomised controlled trial
III-3	Comparative study without concurrent controls; historical control study; two or more single arm studies, interrupted time series without a parallel control group	Diagnostic case control study	A retrospective cohort study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no standard reference)	Case series or cohort study of persons at different stages of disease

Evidence classification definitions

The studies that supported the development of recommendations in this guideline can be defined as:

- **Systematic reviews** – Comprehensive search of literature following a structured plan with the goal of reducing bias by identifying, appraising and synthesising all relevant studies on a particular topic.
- **Meta-analysis** – Use of statistical techniques to synthesise the data from several studies into a single quantitative estimate or summary effect size. Systematic reviews often include a meta-analysis.
- **Randomised controlled trial** – A study in which similar people are randomly assigned to experimental or control groups to test the efficiency of a drug or treatment.
- **Cochrane review** – The Cochrane Collaboration is an international not-for-profit organisation that promotes, supports and disseminates systematic reviews and meta-analyses on the efficacy of interventions in the healthcare field.
- **Observational studies** – These studies draw inferences from a sample to a population where the independent variable is not controlled by the investigator. One common observational study is the possible effect of a treatment, where the assignment of subjects into a treated or control groups is not controlled by the investigator.

1.1 Scope of the guideline

This guideline details evidence primarily on essential hypertension for use by qualified healthcare professionals. Current evidence-based guidelines in other areas are listed in Section 1.2. Areas not included are aligned to associated guidelines and include:

- assessment and management of hypertension in people <18 years of age
- accelerated hypertension in emergency care settings
- specialist management of secondary hypertension
- diagnosis and treatment of hypotension
- hypertension in pregnancy.

1.2 Related guidelines

While every effort has been made to ensure these guidelines are comprehensive, they should be considered in the context of other affiliated clinical guidelines.

- American Heart Association. Management of patients with peripheral artery disease (lower extremity, renal, mesenteric and abdominal aortic). www.heart.org
- Australian Government Department of Health. Australia's Physical Activity and Sedentary Behaviour Guidelines. www.health.gov.au
- Central Australian Rural Practitioners Association Standard Treatment Manual. www.carpa.org.au
- Diabetes Australia and the Royal Australian College of General Practitioners (RACGP). General practice management of type 2 diabetes. www.diabetesaustralia.com.au
- European Society of Hypertension and European Society of Cardiology. Guidelines for the management of arterial hypertension. www.eshonline.org
- Joint National Committee (JNC8) on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. www.nih.gov
- Kidney Health Australia. Chronic Kidney Disease (CKD) management in general practice. www.kidney.org.au
- Kidney Disease Improving Global Outcomes (KDIGO). Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. www.kidgo.org
- National Health and Medical Research Council. National evidence based guidelines for the management of chronic kidney disease in type 2 diabetes. www.nhmrc.gov.au
- National Health and Medical Research Council. Australian guidelines to reduce health risks from drinking alcohol. www.nhmrc.gov.au
- National Health and Medical Research Council. Smoking cessation guidelines for Australian general practice. www.nhmrc.gov.au
- National Health and Medical Research Council. Australian dietary guidelines. www.nhmrc.gov.au
- National Health and Medical Research Council. Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia. www.nhmrc.gov.au
- National Heart Foundation of Australia. Guidelines for the management of Acute Coronary Syndromes. www.heartfoundation.org.au
- National Heart Foundation of Australia. Reducing risk of heart disease: An expert guide to clinical practice for secondary prevention of coronary heart disease. www.heartfoundation.org.au
- National Heart Foundation of Australia. Guidelines for the prevention, detection and management of chronic heart failure. www.heartfoundation.org.au
- National Institute of Clinical Excellence (NICE). Clinical management of primary hypertension in adults. www.nice.org.uk
- National Stroke Foundation. Clinical guidelines for stroke management. www.strokefoundation.com.au
- National Vascular Disease Prevention Alliance. Guidelines for the management of absolute CVD risk. www.cvdcheck.org.au
- Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. www.racgp.org.au
- Royal Australian College of General Practitioners. Smoking, nutrition, alcohol, physical activity (SNAP): A population health guide to behavioural risk factors in general practice. www.racgp.org.au
- Royal Australian College of General Practitioners. Supporting smoking cessation: A guide for health professionals. www.racgp.org.au
- The Society of Obstetric Medicine of Australia and New Zealand (SOMANZ). Guideline for the management of hypertensive disorders of pregnancy. www.somanz.org

1.3 Methodology

The members of the National Blood Pressure and Vascular Disease Advisory Committee (NBPVDAC) were selected based on their recognised expertise, and nominated to represent their endorsing organisation. Conflict of interest disclosures of the NBPVDAC have been recorded. The literature review clinical questions were developed using the Patient, Intervention, Comparison, Outcome (PICO) framework. The clinical questions were oriented to outcomes (CVD events, morbidity and mortality). A complete list of the clinical questions is available in Appendix 1. Clinical questions were assigned to NBPVDAC members to lead the review of evidence and draft recommendations.

Systematic literature searches were conducted on MEDLINE, Embase, Cinahl and The Cochrane Library from 2010 to 2014. Key literature relevant to PICOs identified up to December 2015 was also reviewed and included. Publications in languages other than English were not included. Current international guidelines for the management of hypertension, including those published by the US Joint National Committee (JNC) on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, the UK National Institute of Clinical Excellence (NICE), the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) were reviewed for key literature. Two committee members confirmed the key literature to be reviewed for each clinical question, a third party (external to NBPVDAC) assessed them for bias using A Measurement Tool to Assess Systematic Reviews (AMSTAR) and the NBPVDAC then approved them. Committee members produced evidence summaries that were approved by the committee and used to draft recommendations. The committee met regularly to review the literature and reach consensus recommendations. The committee agreed that the SPRINT trial,[3] published shortly after the public consultation process, had the potential to alter recommendations. The SPRINT study was evaluated by the committee alone and was not sent out for external review.

In keeping with NHMRC stipulations for guideline development, a period of open public consultation was undertaken offering access to the draft guideline via the Heart Foundation website (www.heartfoundation.org.au). Before publication, the guideline was reviewed by endorsing organisations. This guideline was developed with significant contributions of experts, who acted in an honorary capacity, and resourced by the National Heart Foundation of Australia.

1.3.1 Disclaimer

This guideline is designed to provide information to assist clinical decision-making and is based on the best available evidence at the time of development. The information and recommendations in this guideline may not be appropriate for use in all situations and the decision to apply recommendations cited here must consider the individual patient circumstances, the wishes of patients, clinical expertise and resources. The National Heart Foundation takes no responsibility for damages arising out of the use or non-use of the information or recommendations contained herein.

1.4 Epidemiology of blood pressure

Elevated blood pressure, known as hypertension, is an important and treatable cause of CVD morbidity and mortality. Hypertension is an independent risk factor for myocardial infarction, chronic kidney disease, ischaemic and haemorrhagic stroke, heart failure and premature death. Left untreated and/or uncontrolled, hypertension is associated with continuous increases in CVD risk, and the onset of vascular and renal damage.

In 2012–13, 6 million Australians (34%) aged 18 years and over were hypertensive, as defined by blood pressure ≥140/90 mmHg, or were taking antihypertensive medication. Of these, more than 4.1 million (68%) had uncontrolled or untreated hypertension.[4] The proportion of Australians with untreated or uncontrolled hypertension was greater in men than women (24.4% versus 21.7%), and was shown to increase with age peaking at 47% in individuals over 75 years of age. The incidence of untreated or uncontrolled hypertension was lowest in the Northern Territory (19.6%) and highest in Tasmania (28.6%).[4] The prevalence of hypertension has also been associated with lower household income and residing within regional areas of Australia.[5] While approximately one-third of the Australian population have been told by a doctor that they have high blood pressure, only half are reported to be taking their prescribed medication.

Aboriginal and Torres Strait Islander peoples have a greater prevalence of risk factors for CVD and have a higher risk of premature cardiovascular events (by absolute CVD risk assessment). In 2012–2013, at least 25% of Aboriginal and Torres Strait Islander adults were estimated to have untreated or uncontrolled hypertension.[6] Aboriginal and Torres Strait Islander adults were 50% more likely to die from circulatory diseases compared with non-Indigenous Australians.[7]

Vascular events associated with hypertension are a significant burden to the Australian healthcare system. CVD has the highest level of healthcare expenditure of any disease group, with direct costs at $7.7 billion in 2008–2009, an increase of 48% from 2000–2001.[8] Patients admitted to hospital are the most expensive component of healthcare expenditure accounting for $4.52 billion, followed by prescriptions at $1.68 billion. Thus, it is imperative that health professionals work to identify and manage hypertension to improve blood pressure control and reduce the CVD burden within Australia.

Despite strong evidence regarding the benefits of controlling hypertension and the large number of available therapies, controlling raised blood pressure and CVD risk in individual patients and at a population level remains a large national challenge. Findings suggest that controlled blood pressure is associated with lower risk of stroke, coronary heart disease, chronic kidney disease, heart failure and death. Hypertension is a significant determinant of an individual's overall cardiovascular risk. Lowering blood pressure by only 1–2 mmHg within a population is known to markedly reduce cardiovascular morbidity and mortality.[9–10] Modifying lifestyle factors can effectively delay or prevent the onset of hypertension, contribute to the reduction of blood pressure in treated patients with hypertension and, in some cases, may reduce or abolish the need for antihypertensive therapy.

2 Definition and classification of hypertension

Elevated blood pressure is an established risk factor for CVD and an important determinant of CVD risk. As blood pressure has a continuous relationship with CVD risk, a scientific distinction between normotension and hypertension is arbitrary.

As a result, cut-off values for categories can vary among international guidelines. In practice, however, cut-off values are used to aid diagnosis and management decisions. The blood pressure categories and grades of hypertension are described in Table 2.1.

2.1 Hypertensive urgencies and emergencies

Conditions identified as hypertensive urgencies and emergencies require immediate thorough clinical assessment and a decision regarding the urgency for blood pressure lowering. Confirmed follow-up is essential to ensure effective blood pressure control. Markedly elevated blood pressure by itself, in the absence of symptoms of target organ damage, does not automatically require emergency therapy. Treatment with oral agents and follow up care within a few days are recommended.

Hypertensive urgencies are severe blood pressure elevations (>180/110 mmHg) that are not immediately life threatening but are associated with either symptoms (e.g. severe headache) or moderate target organ damage. Treatment with oral drugs and follow-up within 24–72 hours are recommended.

Hypertensive emergencies exist when blood pressure is very high (often >220/140 mmHg) and acute target organ damage or dysfunction is present (e.g. heart failure, acute pulmonary oedema, acute myocardial infarction, aortic aneurysm, acute renal failure, major neurological changes, hypertensive encephalopathy, papilloedema, cerebral infarction, haemorrhagic stroke). Hospitalisation (usually in an intensive care unit), close blood pressure monitoring and parenteral antihypertensive drug therapy are indicated.

Accelerated hypertension (severe hypertension accompanied by the presence of retinal haemorrhages and exudates) and malignant hypertension (severe hypertension with retinal haemorrhages and exudates plus papilloedema) have a similar and very poor prognosis without treatment. The presence of these features indicates the need for urgent treatment by experienced practitioners. Accelerated hypertension may occur more frequently than appreciated and carries a poor prognosis despite treatment.

Table 2.1 Classification of clinic blood pressure levels in adults

Diagnostic category*	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High-normal	130–139	and/or	85–89
Grade 1 (mild) hypertension	140–159	and/or	90–99
Grade 2 (moderate) hypertension	160–179	and/or	100–109
Grade 3 (severe) hypertension	≥180	and/or	≥110
Isolated systolic hypertension	>140	and	<90

*When a patient's systolic and diastolic blood pressure levels fall into different categories, the higher diagnostic category and recommended actions apply.

3 Hypertension and absolute CVD risk assessments

For many years, hypertension guidelines have used blood pressure thresholds to determine the need to treat and the type of treatment. It is, however, now well accepted that the management of patients with hypertension should also consider the individual's absolute CVD risk.

There are several tools to estimate absolute CVD risk. The NVDPA developed a calculator for the Australian population, which is available at www.cvdcheck.org.au.

Expressed as a percentage, this calculator estimates an individual's risk of a cardiovascular event over a defined period (5 years). The concept of absolute CVD risk is based on the following:

- Individuals with hypertension often present with additional risk factors that are modifiable (e.g. blood lipids, diabetes, smoking) and non-modifiable (e.g. age, sex, ethnicity).
- The combined effect of multiple risk factors results in a CVD risk that is greater than the sum of its individual components. As a result, moderate reductions in several risk factors may be more effective in reducing overall risk than a major reduction in one risk factor.
- Treatment strategies for individuals at high absolute risk of a cardiovascular event may differ from those at low absolute CVD risk despite presenting with similar blood pressure readings.

3.1 When and who to assess for absolute CVD risk

An absolute CVD risk assessment is a systematic approach that occurs within clinical practice and includes a detailed medical history, cholesterol and diabetes status. Absolute CVD risk assessments are not appropriate for all patients with hypertension. The absolute CVD risk assessment is primarily designed for primary prevention in Australian adults >45 years of age or for Aboriginal and Torres Strait Islander peoples >35 years of age with no known CVD.

Those with persistently elevated blood pressure ≥180/110 mmHg (Grade 3) or those with target organ damage already have a high absolute CVD risk, and therefore calculation is not necessary. The risk assessment algorithm and treatment options are not appropriate for people with known CVD (e.g. those with established vascular disease, including prior myocardial infarction, prior stroke and/or transient ischaemic attacks (TIAs), peripheral arterial disease, end-stage kidney disease, heart failure, atrial fibrillation or aortic disease). The calculator at www.cvdcheck.org.au only applies to adults >45 years of age and Aboriginal and Torres Strait Islander peoples >35 years. Using the calculator for younger adults may over or underestimate absolute CVD risk. In people not eligible for absolute CVD risk assessment, other factors can be considered to assist in the evaluation of risk, such as those listed below, and the presence of evidence of target organ damage such as renal impairment, albuminuria, cardiac hypertrophy or vascular disease (refer below).

Clinical judgement should be applied to patients with additional risk factors not included within the calculator. Risk may be underestimated in patients who:

- are sedentary and overweight or obese
- are socially deprived or from ethnic minority groups
- have poor mental health
- have increased triglycerides, fibrinogen, apolipoprotein B, or high-sensitivity C-reactive protein
- have elevated fasting glucose but do not meet the requirements for diabetes diagnosis
- have a family history of premature CVD (immediate relative before 55 years of age for men and before 65 years of age for women).

When conducting an absolute CVD risk assessment, clinic blood pressure measures should be used. The calculator was developed using clinic blood pressures, and has not been validated for ambulatory, automated or home blood pressure measures.

A medical history and physical examination to assess for target organ damage and investigate secondary causes of hypertension may alter treatment strategies. For patients with additional co-morbidities, treatment strategies according to absolute CVD risk are not always appropriate. For those patients with hypertension eligible for absolute CVD risk assessment, the goal is to reduce the level of absolute CVD risk by managing multiple risk factors concurrently, not blood pressure in isolation. A search for organ damage should be considered and particular effort should be made to ensure adherence to blood pressure lowering medications and lifestyle factors.

Box 3.1 Treatment decision aid

In aiding your decision to treat, you should:

1. Determine if the patient is eligible for absolute CVD risk assessment.

Eligible: Adults ≥45 years of age (>35 years of age for Aboriginal and Torres Strait Islander peoples) without a known history of CVD or other co-morbidities.

Ineligible: Adults <45 years of age (<35 years of age for Aboriginal and Torres Strait Islander peoples) without known CVD defined as prior myocardial infarction, prior stroke and/or TIA, peripheral arterial disease, heart failure, atrial fibrillation or aortic disease, and those with end-stage kidney disease undergoing dialysis.

2. Establish if the patient is considered high risk (>15% chance of cardiovascular event in the next 5 years).

Adults with any of the following do not require an absolute CVD risk assessment as they are already considered high risk:

- diabetes and >60 years of age
- diabetes with microalbuminuria (urinary albumin creatinine ratio 2.5–25 mg/mmol for males, 3.5–35 mg/mmol for females)
- moderate or severe chronic kidney disease defined by macroalbuminuria (urinary albumin creatinine ratio >25 mg/mmol for males and >35 mg/mmol for females) or estimated glomerular filtration rate (GFR) <45 mL/min/1.73 m^2
- familial hypercholesterolaemia
- systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg
- serum total cholesterol >7.5 mmol/L
- Aboriginal or Torres Strait Islander adult >74 years of age

3. Calculate and manage absolute CVD risk.

Currently, www.cvdcheck.org.au underestimates risk in Aboriginal and Torres Strait Islander patients. In accordance with the Central Australian Rural Practitioners Association Standard Treatment Manual, it is recommended to add 5% to the calculated risk score.

Further information can be found within the 2012 Guidelines for the management of absolute CVD risk.[13]

4 Evaluation and diagnosis of hypertension

The evaluation of blood pressure and the diagnosis of hypertension should include blood pressure measurements, medical history, physical examination, assessment of absolute CVD risk (where appropriate), laboratory investigations and further diagnostic tests when required.

The full diagnostic process aims to:

- identify all cardiovascular risk factors
- detect end organ damage and related clinical conditions
- investigate any causes of secondary hypertension
- establish if, what and when treatment should be initiated.

4.1 Blood pressure measurement

A comprehensive assessment of blood pressure should be based on multiple measurements taken on several separate occasions, at least twice, one or more weeks apart, or sooner if hypertension is severe. Blood pressure can be measured in a number of ways, each providing different, but complementary, information. Clinic blood pressure can be measured using a mercury sphygmomanometer or an automated digital device with or without the health professional present. Home blood pressure monitoring (HBPM) and 24-hour ambulatory blood pressure monitoring (ABPM) offer different information and aid in the diagnosis of other blood pressure–related conditions. In many instances, clinic measures may not be sufficient, thus HBPM and/or ABPM may be required to establish an accurate blood pressure reading on which to inform treatment decisions.

4.1.1 Blood pressure measuring devices

The hypertension societies of Britain and Canada provide guidance on the range of appropriate devices for measuring blood pressure.[14–15] In addition, the High Blood Pressure Research Council of Australia has a short video comparing mercury, aneroid and electronic machines available at www.hbprca.com.au/hcp/off-the-cuff-dvds/.[16]

Testing and verifying the accuracy of all devices should be performed regularly, according to manufacturer's instructions.

Mercury sphygmomanometer

The mercury sphygmomanometer has traditionally been used in the measurement of clinic blood pressure, as it is reliable and provides accurate non-invasive readings. However, due to occupational health and safety together with environmental reasons, mercury is being phased out of clinical use. Thus, non-mercury devices, including aneroid sphygmomanometers, are recommended for routine clinical use.

Electronic devices

Electronic devices are increasingly being used in hospitals and primary care. Electronic devices can be used to perform automated office blood pressure measurement. This measurement technique avoids auscultation-induced errors and minimises white-coat hypertension effects, as measures can be taken without a health professional present.[17]Automated office blood pressure measurement has been shown to have a good correlation with other out-of-clinic measures[17] and the patient does not have to be alone to obtain an accurate reading.[18] A list of blood pressure monitors validated by the British Hypertension Society, including clinic, ambulatory and home blood pressure monitors is available at www.bhsoc.org.[14] All automated devices require regular maintenance to ensure accurate readings as any leak in the rubber tubing can make cuff deflation hard to control and lead to underestimation of systolic blood pressure and overestimation of diastolic blood pressure.

4.2 Blood pressure measurement in the clinic

Most of the clinical studies demonstrating the effectiveness and benefits of treating hypertension have been based on clinic blood pressure measures. Clinic blood pressure can be measured using a mercury sphygmomanometer or an automated digital device. For the measurement and evaluation of clinic blood pressure, this guideline strongly recommends adherence with the procedure outlined in Table 4.1.

Table 4.1 Measurement and evaluation of clinic blood pressure

Measurement of clinic blood pressure	
Devices	• Auscultation methods using an accurately validated mercury sphygmomanometer. Use of electronic sphygmomanometer, calibrated according to manufacturer's instructions. • A cuff with bladder length of ≥80% and width ≥40% of mid-upper arm circumference. Using standard-sized cuffs on large arms can artificially overestimate blood pressure. Where the arm is too large for oversized cuffs, consider using an appropriate cuff on the forearm and auscultating the radial artery. • Some digital/automated devices may not measure blood pressure accurately if there is pulse irregularity (e.g. atrial fibrillation).[19–20] Thus palpate the radial or brachial pulse before measuring with an automated device. If pulse irregularity is suspected, measure blood pressure manually using direct auscultation over the brachial artery.
Measurement conditions	• A quiet, appropriate environment at room temperature. • Patient should be seated (with legs not crossed) and relaxed for several minutes before measurement. • Patients should refrain from caffeine and smoking for at least 2 hours before measurement.
Measurement methods	**All clinic measurements** • Selected arm should be free of constricting clothing to avoid impediment of the cuff. • Wrap cuff snugly around upper arm with the centre of the cuff bladder positioned over the brachial artery and the lower border of the cuff approximately 2 cm above the elbow bend. • Place cuff at heart level by supporting the arm. **Non-automated blood pressure measurement** • Palpate the radial pulse while inflating the cuff and note the pressure at which it ceases to be palpable. Inflate the cuff a further 30 mmHg above this pressure. • Deflate cuff at rate of 2–3 mmHg/beat or less and note the pressure at which radial pulse appears. • Fully deflate the cuff, wait approximately 30 seconds, and then inflate the cuff to at least 30 mmHg above that at which the radial pulse reappeared. • While deflating, auscultate over the brachial artery in the antecubital fossa (elbow pit). • Record systolic and diastolic blood pressure to the nearest 2 mmHg. For the systolic reading, record the level at which two consecutive beats are heard (phase I Korotkoff), even if they then disappear transiently with progressive deflation (known as the auscultatory gap). For the diastolic reading use disappearance of sound (phase V Korotkoff). Use muffling of sound (phase IV Korotkoff) only where the sound continues to 0 mmHg. • Wait 30 seconds before repeating on the same arm. **Automated office blood pressure measurement** • Health professionals should ensure correct cuff size and positioning. • Health professionals should set the automated device to start the first measurement after 5 minutes of rest and to take a total of three blood pressure readings at 1–2 minute intervals. • Patients should be seated in a quiet room alone for measurement. • Health professionals should push the start button before leaving room.
For first blood pressure measurements	• Measure both arms, particularly if there is evidence of peripheral arterial disease. • Where there is variation >5 mmHg between arms, use the arm with the higher reading for all subsequent measures. • Where there is suspected postural hypotension (e.g. older patients and/or those with diabetes), measure both sitting and standing blood pressure. Repeat measurement after patient has been standing for at least 2 minutes.

Measurement of clinic blood pressure	
Evaluation of measurement	• Take three measurements and average the last two. If readings vary more than 10 mmHg systolic or 6 mmHg diastolic, have the patient rest quietly for 5 minutes then re-measure. • Hypertension diagnosis should be based on multiple measurements taken on several separate occasions. That is at least twice, one or more weeks apart, or sooner if hypertension is severe.
Common errors that can cause inaccurate measures	• Cuff placed over thick clothing • Inappropriate cuff size • Worn cuff • Non-validated and/or serviced sphygmomanometer • Arm elevated above heart • Failure to identify variance between arms • Patient not rested or talking during measurement • Failure to palpate radial pulse before auscultatory measurements • Deflation of cuff too quickly • Re-inflation to repeat measure before cuff has fully deflated • Rounding off reading by >2 mmHg • Taking a single measure

In summary, a comprehensive assessment of blood pressure measurement in the clinic includes:

- patients seated and relaxed
- multiple measurements taken on at least two separate occasions, one or more weeks apart, or sooner if hypertension is severe
- use of a calibrated device with appropriate cuff size
- measurement on both arms during the initial assessment
- evaluation for errors that may lead to inaccurate measures.

4.3 Blood pressure measurement outside of the clinic

Clinic blood pressure, while a modest predictor of CVD,[21] is subject to considerable error and variation. Blood pressure measured in the clinic may be affected by stress, drugs, pain and/or the presence of medical staff (white-coat hypertension). Blood pressure may also vary throughout the day and between days in the same individual. Theoretically, the more sources of variation accounted for (within visit, within day and between days) the more reliable the blood pressure prediction. APBM and HBPM are both methods for measuring blood pressure outside of the clinic that assist in building an accurate blood pressure profile on which to base therapeutic decisions. However, clinic blood pressure remains the only blood pressure measure to be validated when estimating absolute CVD risk using available risk assessment calculators.

24-hour ABPM provides measures at intervals of 15–30 minutes and requires the patient to wear a portable measuring device, usually on the non-dominant arm, while they go about their normal day and while they are sleeping. The patient is asked to record information on symptoms and events that can affect blood pressure readings. Upon inflation of the cuff the patient is instructed to remain quiet and still while the reading takes place. The measurements are downloaded and numerous analyses can be performed including blood pressure variability, morning surge, blood pressure load and the ambulatory arterial stiffness index. The resulting profile is particularly useful for the diagnosis of hypertension, especially when white-coat or masked hypertension is suspected. Detailed resources can be found within The European Society of Hypertension consensus paper about which patients should have ambulatory monitoring, how to interpret the data and how to introduce the service in routine clinical practice[22] and the National Heart Foundation and High Blood Pressure Research Council consensus statement and practical guide.[23]

HBPM is performed using fully automated machines that record blood pressure from the patient's brachial artery. Many are available for purchase and are in widespread use.

A standardised, protocol containing resources for Australian patients and doctors on how to assess home blood pressure has been developed.[24]

A list of validated devices is available online at www.bhsoc.org. HBPM provides additional prognostic information on mortality over and above clinic measures, and is particularly useful during long-term follow-up, and it assists in patients' understanding of hypertension, promotes involvement in self-management and improves adherence to treatment strategies. HBPM can also be used to investigate relationships between episodic symptoms and variations in blood pressure (e.g. light-headedness due to medication-induced hypotension), and in the diagnosis of masked or white-coat hypertension.

HBPM and APBM provide different information about blood pressure and should be regarded as complementary, rather than competitive or alternative. The choice between methods depends on indication, availability, ease, cost of use and patient preference. Clinical indications for conducting out-of-clinic measurements and criteria for diagnosing hypertension using different blood pressure measurement methods are detailed in the tables below. For example, a blood pressure measure ≥140 mmHg in the clinic or ≥130 mmHg on 24-hour ABPM are both criteria for a diagnosis of hypertension. Out-of-clinic measures are necessary for the diagnosis of white-coat and masked hypertension.

Table 4.2 Clinical indications for out-of-clinic blood pressure measurements

Clinical indications for out-of-clinic blood pressure measurements
Suspicion of white-coat hypertension
Suspicion of masked hypertension
Identified white-coat hypertension
Marked variability of clinic or clinic and home blood pressure measurements
Autonomic, postural, post-prandial and drug-induced hypotension
Identification of true resistant hypertension
Suspicion of nocturnal hypertension or absence of nocturnal dipping, for example in patients with sleep apnoea, chronic kidney disease or diabetes

Table adapted with permission from European Society of Hypertension guidelines[25] and Ambulatory blood pressure monitoring in Australia: 2011 consensus position statement.[23]

Table 4.3 Criteria for diagnosis of hypertension using different methods of blood pressure measurement

Method of measurement	Systolic (mmHg)		Diastolic (mmHg)
Clinic blood pressure	≥140	and/ or	≥90
ABPM daytime (awake)	≥135	and/ or	≥85
ABPM night-time (asleep)	≥120	and/ or	≥70
ABPM over 24 hours	≥130	and/ or	≥80
HBPM	≥135	and/ or	≥85

ABPM, ambulatory blood pressure monitoring; HBPM, home blood pressure monitoring

Out-of-clinic measures, in particular ABPM, are now of considerable scientific interest and there is a large body of evidence supporting the benefits of using them to confirm diagnosis of hypertension.[26–30] As a result, international guidelines, including the US Preventive Services Task Force and the United Kingdom 2011 NICE clinical guidelines[31] recommend ABPM as a cost-effective diagnostic technique for all patients with suspected hypertension.

This guideline reviewed three key systematic reviews from 2012–2013[26–28] comparing home and clinic blood pressure, and one primary study[29] comparing the prognostic value of office, home and ambulatory blood pressure measures. The first systematic review included eight studies and 17,698 participants (both untreated hypertensives and normotensives) and compared the predictive value of HBPM versus clinic blood pressure on cardiovascular and all-cause mortality.[26] The number of blood pressure measures ranged from 1–28 at home and 2–6 in the clinic. After a follow-up of 3.5–10.9 years, both home and clinic measures significantly predicted cardiovascular events, however home blood pressure was also a significant predictor of all-cause and cardiovascular mortality, where clinic blood pressure was not. In support, a second systematic review involving 19,698 participants also found HBPM a significant predictor of cardiovascular mortality and events after adjusting for clinic blood pressure.[28] Additionally, a review of 2,485 patients reported HBPM to be as good as ABPM and superior to clinic measurement in predicting preclinical organ damage.[27]

The primary study including 502 participants (264 normotensives, 238 newly diagnosed hypertensives)[29] reported the prognostic value of clinic versus HBPM versus ABPM measurements with a follow-up time of 16.1±3.9 years. Blood pressure measures were determined by the mean of four clinic measures within 3 weeks, 14 duplicate home measures, and 24-hour ambulatory recordings. This study found all three methods predictive of cardiovascular events however ambulatory blood pressure provided prognostic information on risk above and beyond clinic and home blood pressure measures.[29]

In summary, clinic, home and ambulatory blood pressures measures all predict the risk of a cardiovascular event, however home and ambulatory measures are stronger predictors of outcomes, with hazard ratios roughly double that of clinic blood pressure per 10 mmHg increase. Treatment decisions should therefore be based on ABPM or HBPM where available. However, clinic blood pressure remains the only blood pressure measure to be used when estimating absolute CVD risk using available risk assessment calculators.

Table 4.4 Recommendations on methods of blood pressure measurement

Methods of measuring blood pressure	Grade of recommendation	Level of evidence
a. If clinic blood pressure is ≥140/90 mmHg, or hypertension is suspected, ambulatory and/or home monitoring should be offered to confirm the blood pressure level.	Strong	I
b. Clinic blood pressure measures are recommended for use in absolute CVD risk calculators. If home or ambulatory blood pressure measures are used in absolute CVD risk calculators, risk may be inappropriately underestimated.	Strong	–
c. Procedures for ambulatory blood pressure monitoring should be adequately explained to patients. Those undertaking home measurements require appropriate training under qualified supervision.	Strong	I
d. Finger and/or wrist blood pressure measuring devices are not recommended.	Strong	–

Table 4.5 Reviewing ambulatory blood pressure monitoring data

Considerations in reviewing ABPM data
• Ensure that ABPM consists of at least two measurements per hour during waking hours and that the average consists of at least 14 daytime measurements,[31] and 70% of readings obtained over the 24-hour period.
• Compare the recorded profile with standard values.
• The normal range for ambulatory blood pressure differs from clinic blood pressure.
• Consider patient diary and physical activity information, and time of drug treatment, where relevant.
• Hypertension diagnosis is supported if patient's average ABPM reading exceeds standard values for daytime or night-time, or if ambulatory blood pressure load (area under the blood pressure-time curve) is reported and exceeds the reference range by more than 20%.[23]
• Mean night-time systolic ambulatory blood pressure should be at least 10% lower than the daytime level. Patients who do not show night-time lowering of blood pressure ('non-dippers') are at increased CVD risk.[30]

ABPM, ambulatory blood pressure monitoring

Table 4.6 Guidance for home blood pressure measurement[24]

Guidance for home blood pressure measurement	
Devices	• Use of a validated device. • Based on cuff-oscillometric method using upper arm cuff.
Measurement conditions	• Morning measurements before breakfast, morning medications and after 5 minutes in sitting position. • Evening measurements before retiring, after medications and after 5 minutes in sitting position.
Frequency of measurement and recording	• Two consecutive measures, 1 minute apart. • All values should be recorded with notes to explain obvious variations (e.g. consuming coffee before measurement).

4.4 Medical history

Patients with hypertension are most often asymptomatic; however specific symptoms can suggest secondary hypertension or hypertensive complications requiring further investigation. Thus a full medical and family history with particular attention to blood pressure management, risk factors, end organ damage and causes of secondary hypertension is recommended.

Table 4.7 Medical history to assist with diagnosis and evaluation of hypertension

Personal family and medical history relevant to hypertension
Blood pressure
• New onset hypertension
• Duration of raised blood pressure and previous levels
• ABPM or HBPM measures (if known)
• Current antihypertensive medications
• Previous antihypertensive therapy, efficacy and adverse effects
• Medications that influence blood pressure (including complementary medicines, and those containing high salt)[32]
Risk factors
• Family and personal history of chronic kidney disease, hypertension, diabetes, dyslipidaemia, stroke, early onset coronary heart disease (before 55 years of age for men and before 65 years of age for women), low birth weight
• Modifiable lifestyle factors including smoking, diet, weight control, obesity, exercise, recreational drug use, alcohol intake
• Personal, psychosocial and environmental factors that could influence the effectiveness of antihypertensive care including education, family situation, work environment, financial concerns, or associated psychological stress
• Depression, social isolation and quality of social support
History and symptoms of end organ damage and CVD
• Past or current symptoms of ischaemic heart disease, heart failure, cerebrovascular disease or peripheral arterial disease
• Past or current symptoms that suggest chronic kidney disease (e.g. nocturia, haematuria)
Symptoms related to causes of secondary hypertension
• Phaeochromocytoma: frequent headaches, sweating, palpitations
• Sleep apnoea: obesity, snoring, daytime sleepiness
• Complementary and/or recreational drug intake
• Hypokalaemia: muscle weakness, hypotonia, muscle tetany, cramps, cardiac arrhythmias
• Symptoms suggestive of thyroid disease

ABPM, ambulatory blood pressure monitoring; HBPM, home blood pressure monitoring

Table adapted with permission from the 2013 ESH/ESC Guidelines for the Management of Arterial Hypertension.[33]

4.4.1 Complementary medicines

Patients frequently use complementary medicines in combination with conventional medicines. For this reason, it is important to consider the potential for pharmacodynamic and pharmacokinetic interactions between them. There are several medications and complementary therapies that influence blood pressure and can interfere with blood pressure lowering drugs. Some of these are listed in Table 4.8 and should be reviewed as a part of taking a full history. Additional resources are available from NPS Medicinewise www.nps.org.au and the Therapeutic Goods Administration (TGA) www.tga.gov.au.

Table 4.8 Substances and medications that may influence blood pressure[34–38]

Drugs and medications that may influence blood pressure
Non-steroidal anti-inflammatory drugs (NSAIDS; conventional and cyclooxygenase-2 selective)*
Sympathomimetics (decongestants, diet pills, cocaine)
Stimulants (methylphenidate, dexmethylphenidate, dexamphetamine, amphetamine, methamphetamine, modafinil)
Excessive alcohol consumption
Oral oestrogen contraceptives
Hormone replacement therapy
Corticosteroids
Clozapine
Serotonin-norepinephrine reuptake inhibitor (SNRI, e.g. venlafaxine)
Monoamine oxidase inhibitors: reversible (moclobemide), irreversible (phenelzine, tranylcypromine)†
Haemopoietic drugs (darbepoetin, epoetin alpha, epoetin beta, methoxy pegepoetin beta)
Rebound hypertension due to abrupt withdrawal of bromocriptine, clonidine
Bupropion[34]
Over-the-counter medications that may influence blood pressure
Herbal supplements: bitter orange, Ginseng, guarana
Caffeine pills and caffeine-containing products including black tea, green tea and cola nut‡
Natural liquorice
St John's wort may reduce efficacy of prescribed cardiovascular drugs
Energy drinks[35, 36]

*NSAIDs vary with respect to cardiovascular risk.[38]

†The use of monoamine oxidase inhibitors in combination with tyramine-rich foods (e.g. matured or out of date cheese, fermented or matured meats, yeast and soy bean extracts, and others) can lead to a hypertensive crisis.

‡Caffeine consumption is associated with dose-related increases of 5–15 mmHg and 5–10 mmHg in systolic and diastolic blood pressure for several hours. However due to small samples sizes in existing trials the long-term effects of regular caffeine consumption on hypertension and cardiovascular outcome are uncertain.[31]

4.5 Physical examination and laboratory investigations

Physical examination and laboratory investigations assist with the diagnosis of hypertension and the assessment of a patient's CVD risk. A range of initial laboratory investigations are recommended in all patients with suspected hypertension and, where secondary hypertension or target organ damage is suspected (e.g. sudden onset of hypertension or abrupt alterations in blood pressure control), a range of additional investigations can be performed to confirm diagnosis.

Table 4.9 Physical examination and initial laboratory investigations to support diagnosis, and identify secondary causes of hypertension

Physical examination
Signs of secondary hypertension and/or organ damage
• Pulse rate, rhythm and character
• Jugular venous pulse and pressure
• Evidence of cardiac enlargement (displaced apex, extra heart sounds)
• Evidence of cardiac failure (basal crackles on lung auscultation, peripheral oedema, abdominal signs (e.g. pulsatile liver)
• Evidence of arterial disease (e.g. carotid, renal, abdominal or femoral bruits, abdominal aortic aneurysm, absent femoral pulses, radio-femoral delay)
• Palpation of enlarged kidneys (polycystic kidneys)
• Abnormalities of the optic fundi (e.g. retinal haemorrhages, papilloedema, tortuosity, thickening or arteriovenous nipping of retinal arteries, exudates or diabetic retinopathy)
• Evidence of abnormalities of the endocrine system (e.g. Cushing's syndrome, thyroid disease)
Evidence of obesity
• Waist circumference (cm) measured in standing position midway between the lower border of the costal margin and uppermost border the iliac crest
• Calculate BMI: body weight without shoes divided by height^2 (kg/m^2)

BMI, body mass index

Table 4.10 Laboratory investigations for all patients

Initial laboratory investigations for all patients

Urine dip stick for blood

- If abnormal, send urine for microscopy.

Albuminuria and proteinuria status

- Highly recommended for all patients and mandatory for those with diabetes.
- Albuminuria and proteinuria can be measured using the ratio of concentrations to creatinine in urine, reagent strips in spot urine samples and timed urine collections. The relationships between methods of measures are not exact. Approximate equivalents are shown in the table* below.
- To assess albuminuria status, urinary albumin/creatinine ratio in first-void spot urine specimens is recommended.[39] Where first-void is not possible, spot urine is acceptable.
- If spot urine is in the macroalbuminuria range, a 24-hour protein level is recommended.
- Proteinuria is defined as >500 mg/day protein excretion rate. Urine PCR can be used for quantification and monitoring of proteinuria where albuminuria measures are not available.

	ACR (mg/mmol)	Albumin excretion (mg/day)	PCR (mg/mmol)	Protein excretion mg/day	Protein reagent strip
Microalbuminuria	Male 2.5–25 Female 3.5–35	30–300	Male 4–40 Female 6-60	50–500	Trace to +1
Macroalbuminuria	Male >25 Female >35	>300	Male >40 Female >60	>500*	≥ +1

Blood tests

- Fasting glucose
- Fasting serum total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and triglycerides
- Serum urea, electrolytes and creatinine (with estimation of GFR)
- Haemoglobin and/or haematocrit

12-lead ECG

- Detection of atrial fibrillation, left ventricular hypertrophy and evidence of previous ischaemic heart disease

ECG, electrocardiograph; ACR, albumin/creatinine ratio; PCR, protein/creatinine ratio; GFR, glomerular filtration rate

*Albuminuria and proteinuria equivalents table developed in consultation with Kidney Health Australia.[40]

4.6 Additional diagnostic tests for selected patients

Additional investigations can be undertaken as indicated by clinical suspicion for organ damage, CVD and chronic kidney disease following a full medical history and physical examination.

Table 4.11 Additional diagnostic tests that can be considered to determine asymptomatic organ damage, CVD and chronic kidney disease

Additional diagnostics for selected patients
CVD • Echocardiography – Can be used in patients with hypertension to diagnose left ventricular hypertrophy, or where left atrial dilatation or concomitant heart disease is suspected. • Carotid ultrasound – Ultrasound scanning of carotid arteries can be considered to rule out asymptomatic atherosclerosis, particularly in older adults.
Chronic kidney disease • Renal artery imaging • Renal artery duplex ultrasound, renal nuclear medicine and/or CT angiography For investigation of renovascular causes of hypertension (e.g. fibromuscular dysplasia in young females with hypertension, older patients who may have atherosclerotic renal artery disease and patients with a renal and/or femoral bruit).
Peripheral arterial disease Ankle-brachial index (ABI) – In those with risk factors for peripheral arterial disease including hypertensive patients with diabetes, vascular bruit, older age and/or smokers ABI is recommended. An index <0.9 is diagnostic for peripheral arterial disease.[41]
Other • Plasma aldosterone/renin ratio – Primary aldosteronism occurs in 5–10% of patients with hypertension and is not excluded by normal serum potassium. It should be considered in patients with hypertension, especially those with moderate-to-severe or treatment-resistant hypertension, and those with hypokalaemia. Referral to a specialist for investigation is recommended when primary aldosteronism is suspected. Interpretation is difficult in treated patients. Refer to the clinical practice guideline: Case detection, diagnosis and treatment of patients with primary aldosteronism.[42] • Metanephrine and normetanephrine excretion (with creatinine) and/or plasma catecholamine, metanephrine and normetanephrine concentration, 24-hour urinary catecholamine – These tests are indicated when there are symptoms of episodic catecholamine excess and/or episodic hypertension (suggestive of phaeochromocytoma).

CT, computerised tomography; ABI, ankle brachial index

5 Lifestyle advice for confirmed hypertension

It is well established that in patients with elevated blood pressure that lowering blood pressure reduces cardiovascular events and reduces premature mortality.[3, 43, 44] The timing and intensity of interventions is determined by numerous factors including the severity of hypertension, the patient's absolute CVD risk and the presence of associated clinical conditions or end organ damage.

Lifestyle advice is recommended for all patients with or without hypertension and regardless of drug therapy. A national survey of adult patients attending general practice showed that 62.7% were overweight, 13.5% were daily smokers, 23% drank high-risk levels of alcohol and only 43% of adults did at least 30 minutes of moderate intensity physical activity daily.[45] Trials using lifestyle interventions in patients with hypertension have shown reductions in blood pressure and a reduction in combined cardiovascular events and total mortality.[46–48] The following recommendations align with the national guidelines for physical activity, obesity, nutrition and alcohol. A detailed guide on how to work with patients on the lifestyle risk factors of smoking, nutrition, alcohol and physical activity is available from the Royal Australian College of General Practitioners (RACGP).[49]

Lifestyle advice can be structured and tailored to individual need using the 5As approach (ask, assess, advise, assist, arrange), and motivational interviewing can be used to encourage behaviour change.[49] Improving lifestyle assists with reducing blood pressure and contributes to the control of other CVD risk factors and general health. Importantly, long-term adherence to lifestyle improvement may delay or prevent the onset of hypertension, contribute to the reduction of blood pressure in patients with hypertension already on therapy and, in some cases, may reduce or abolish the need for antihypertensive therapy.

Table 5.1 Recommendations and resources for lifestyle advice

Assess and manage lifestyle risk factors in all patients. Assess patient's readiness to change lifestyle behaviours.				
Factor	**Assess**	**Targets**		**Assistance/resources**
Physical activity	Patient's ability to safely exercise	Accumulate 150–300 minutes of moderate intensity activity or 75–150 minutes of vigorous activity each week. Muscle strengthening activities on at least 2 days each week.		Australia's physical activity and sedentary behaviour guidelines 2014[50] www.essa.org.au
Weight control	– Waist circumference – BMI	Waist circumference <94 cm males <90 cm Asian males <80 cm females	BMI <25 kg/m^2	NHMRC Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia 2013[51] SNAP 2015[49]
Diet	Diet (fruit and vegetables, fat and salt)	Total fat account for 20–35% of energy intake Salt to ≤6 g/day for primary prevention and 4 g/day for secondary prevention Five serves of vegetables and two serves of fruit daily		NHMRC Australian dietary guidelines 2013[52] SNAP 2015[49]
Smoking cessation	Amount smoked, dependence, readiness to change	Cessation of smoking		Quitline (13QUIT) Smoking cessation guidelines for Australian general practice 2014[53] SNAP 2015[49]
Alcohol intake	Frequency and volume of alcohol	For healthy men and women, drinking no more than two standard drinks on any day and no more than four on any one occasion.		NHMRC Guidelines to Reduce Health Risks from Drinking Alcohol 2009 SNAP 2015[49]

NHMRC, National Health and Medical Research Council; SNAP, Smoking, nutrition, alcohol and physical activity; BMI, body mass index

5.1 Physical activity

There is strong epidemiological evidence that regular physical activity and moderate to high levels of cardiorespiratory fitness provide protection against hypertension and all-cause mortality in both normotensive and hypertensive individuals.[54–56] Regular aerobic exercise has been shown to lower daytime systolic and diastolic blood pressure by up to 3.2 mmHg and 2.7 mmHg, respectively, without affecting night-time blood pressure.[57] Australia's physical activity and sedentary behaviour guidelines provide age-specific recommendations relevant to all patients.[50] For patients with hypertension, it is also recommended that training be postponed if resting blood pressure is poorly controlled (≥ Grade 3).[58]

It is important to judge a patients' level of activity against these recommendations. For patients who do not engage in any regular physical activity, the important message is that any activity is better than none. These patients can be encouraged to start small and build up to the recommended amount[49] as sudden vigorous physical activity in sedentary individuals has been associated with an increased risk of cardiovascular events.[60]

Patients with chronic conditions and complex needs can be referred to an accredited exercise physiologist or physiotherapist or cardiac rehabilitation. Patients with stable blood pressure can be referred to physical activity programs run by accredited exercise professionals. Conduct a review of changes to physical activity at 3–6 month intervals.[49]

Box 5.1 Physical activity for patients with hypertension[50, 58, 59]

For adults 18–64 years, aim for

- Accumulation of 150–300 minutes (2.5–5 hours) of moderate-intensity activity or 75–150 minutes (1.25–2.5 hours) of vigorous intensity activity, or an equivalent combination of both each week.
- Muscle strengthening activities on at least 2 days each week.

For adults >65 years, aim for

- Some form of physical activity, no matter what their age, weight, health problems or abilities.
- Accumulate at least 30 minutes of moderate-intensity physical activity on most, preferably all, days.
- Older adults who currently engage in vigorous physical activity should carry on doing so, providing recommended safety procedures and guidelines are adhered too.

Box 5.2 Physical activity for patients with chronic conditions

Individuals with any of the following require medical review and supervised physical activity:

- unstable angina
- blood pressure ≥180 mmHg systolic or ≥110 mmHg diastolic
- uncontrolled heart failure or cardiomyopathy
- myocardial infarction within the last 3 months
- severe aortic stenosis
- resting tachycardia or arrhythmias
- chest discomfort or shortness of breath at rest or low activity
- diabetes with poor glycaemic control.

5.2 Weight control

In 2014–15, 63.4% of Australians were overweight or obese.[4] While the biological mechanisms through which obesity may directly cause hypertension are yet to be fully understood, there is evidence that weight loss is associated with a reduction in blood pressure and improved glycaemic control,[51] improvements in markers of chronic kidney disease[51] and reduced CVD risk and all-cause mortality.[61–64]

In adults with a BMI greater than 35 kg/m^2, a weight reduction of 2 kilograms can result in a clinically meaningful reduction in systolic blood pressure.[51] In two separate studies, a weight reduction of 1 kilogram was associated with lowering systolic and diastolic blood pressure by an average of 1 mmHg,[65] and a weight reduction of 5–10 kilograms was associated with systolic and diastolic blood pressure reductions of 7/3 mmHg and 13/7 mmHg, respectively.[66, 67] The NHMRC Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia[51] details the different thresholds at which waist circumference increases the risk of chronic disease and lists targets of <94 cm for males (<90 cm for Asian males) and <80 cm for females. It is recommended that all patients with hypertension aim for a healthy BMI and waist circumference.

Table 5.2 Body mass index classifications

Classification	BMI (kg/m2)
Healthy weight	18.5–24.9
Overweight	25–29.9
Obesity I	30–34.9
Obesity II	35–39.9
Obesity III	40 or more

BMI, body mass index

Box 5.3 Practical recommendations for weight control[51]

- Set achievable intermediate goals in consultation with patients and assess progress regularly.
- Convey the message that a small amount of weight loss can improve blood pressure and sustained greater weight loss has the potential to reduce the need for antihypertensive medications.[68]
- Advise that a combination of lifestyle modifications works better than a single intervention.[69]
- Clinical judgement should be used when using BMI for targets in adults that are highly muscular and in some populations, such as Asian and older populations, and/or those with additional co-morbidities, and/or risk factors that may be of concern at different BMIs.[70]
- Emphasise that there is no quick solution; lifestyle changes must be practical and able to be maintained for a lifetime.

5.3 Dietary modification

The intake of food high in saturated fat, added salt, added sugars and/or excessive alcohol consumption, are all associated with increased risk of obesity and/or chronic diseases, including CVD. The link between saturated fat intake, serum cholesterol and CVD is well established. There is a link between higher salt, excessive alcohol intake and elevated blood pressure. Conversely, a reduction in blood pressure is seen in both normotensive and hypertensive patients with a decrease in sodium intake and lowering alcohol consumption.

Consumption of a diet that emphasises the intake of vegetables, fruits and whole grains, including low-fat dairy products such as in the Dietary Approaches to Stop Hypertension (DASH) diet may be combined with exercise and weight loss to maximise blood pressure reduction.[71]

5.4 Salt restriction

There is evidence for a relationship between sodium intake and blood pressure.[72] Sodium restriction has been shown to lower systolic and diastolic blood pressure, particularly in patients with hypertension,[73] and lowering blood pressure is associated with better cardiovascular outcomes.[74, 75] Despite this, direct evidence for a benefit in cardiovascular outcome via individual salt restriction continues to be debated.[76, 77]

A 2012 Cochrane review estimated the effects of low-sodium versus high-sodium intake on blood pressure from 167 trials. In a review of 167 studies, a low sodium intake was found to be associated with an average reduction in systolic blood pressure of 5.48 mmHg and 10.21 mmHg in patients with hypertension from Caucasian and Asian populations, respectively.[73] Current literature remains inconclusive around the benefit of very low sodium intake (<3 g/day),[76] and the efficacy of long-term individual dietary salt restriction advice[77] on cardiovascular outcome.

In supporting the benefits of salt restriction on blood pressure and cardiovascular health, it is recommended to:

- advise patients to reduce salt intake to <6 g/day for primary prevention and <4 g/day for secondary prevention
- advise patients to limit salt by choosing foods processed without salt, foods labelled 'no added salt' or 'low salt' and not to add salt to meals
- counsel patients that salt is listed as sodium on food labels and to choose food with <400 mg/100g of salt. Low-salt foods are those with less than 120 mg/100 g of salt.

For patients with normal renal function increasing dietary potassium can reduce systolic blood pressure by 4–8 mmHg in patients with hypertension.[78] This can be achieved by eating a wide variety of fruits and vegetables, plain unsalted nuts and legumes. Patients taking potassium-sparing diuretics must limit potassium intake to avoid severe hyperkalaemia.

5.5 Dietary fat

There is no evidence that consumption of fat is directly associated with the development of hypertension, however an intake of unhealthy dietary fat is associated with increased risk of CVD. It is currently recommended that total fat intake account for 20–35% of total energy intake and total saturated and trans fats comprise no more than 10% of energy intake.[79]

5.6 Smoking cessation

Despite the smoking rate in Australia decreasing over the past two decades, 14% of Australians aged 15 and over are still daily smokers.[4] This percentage is significantly higher in the Aboriginal and Torres Strait Islander population where in 2012–13, 40% of those aged 15 and over were smokers.[6] On average, a smoker's life expectancy is up to 10 years less than non-smokers, and 60% of long-term smokers will die prematurely from a smoking-related disease. Smoking cessation has been shown to reduce blood pressure and overall CVD risk.[81] In fact, the risk of a coronary event declines rapidly after quitting and within 2–6 years can be similar to that of a non-smoker.[80] Structured advice from a general practitioner has been shown to increase cessation rates by two-thirds, compared with no-advice, and is highly cost effective.[82] One such structured framework is the 5As approach (ask, assesss, advise, assist, arrange).[49, 83] Further information can be found in the Smoking cessation guidelines for Australian general practice 2014.[51]

5.7 Moderate alcohol consumption

The epidemiological link between alcohol consumption and CVD has been extensively studied. Consumption of ≤2 standard drinks a day for healthy men and women can cause an immediate increase in blood pressure, however this has not been associated with elevated CVD risk.[84] In contrast, consumption of ≥2 standard drinks a day for men and ≥1 standard drinks a day for women has been found to increase the risk of developing hypertension.[85–87] Further resources and recommendations can be found in the NHMRC Guidelines to Reduce Health Risks from Drinking Alcohol[88] and the Smoking, nutrition, alcohol, physical activity guide.[49]

5.8 Relaxation therapies

Overall relaxation interventional studies have considerable heterogeneity and do not provide convincing evidence of blood pressure reduction.[31, 89, 90]

Box 5.4 Practical recommendations to support long-term lifestyle changes

- Tailor advice to patients' needs and set realistic goals.
- Give regular encouragement.
- Respond positively to any incremental success.
- Provide specific written instructions.
- Review progress regularly.
- Refer to other health professionals for ongoing support and follow-up where appropriate.

6 Antihypertensive therapy for confirmed hypertension

6.1 Treatment thresholds for antihypertensive drug therapy

As blood pressure increases, it is more difficult to control with lifestyle modification alone and antihypertensive medication becomes necessary. The benefits for blood pressure lowering in patients with significantly elevated blood pressures are well established.[91–93] The benefit for initiating drug therapy in patients with lower blood pressures with or without comorbidities has been less certain. Here we review a meta-analysis that supports the initiation of drug therapy in patients with mild hypertension with and without co-morbidities, respectively.

The first meta-analysis assessed individual data from 15,226 patients with mild hypertension (140–159 mmHg) with no history of cardiovascular events derived from two separate datasets. One dataset from the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) included 6,361 individuals of whom 96% had diabetes and 61% had previous antihypertensive treatment, the other dataset included 8,905 individuals who had no prior treatment and did not have diabetes. The study reported findings for both cohorts and collectively found that blood pressure lowering therapy led to beneficial cardiovascular effects for uncomplicated patients with mild hypertension, with statistically significant reductions observed for stroke, cardiovascular death and all-cause mortality.[74] Corresponding relative reductions in 5-year CVD risk were similar for all levels of baseline blood pressure.[94]

This evidence showing benefit of blood pressure lowering on cardiovascular outcomes for patients with lower blood pressure suggests that the decision to initiate drug treatment should consider a patient's absolute CVD risk together with accurate blood pressure readings.

6.2 Treatment targets using antihypertensive drug therapy

While the blood pressure is an independent predictor of cardiovascular risk, and lowering blood pressure reduces cardiovascular events and all-cause mortality, effective treatment targets have been ever changing and debated.

Earlier evidence suggested there is no benefit on cardiovascular outcome or all-cause mortality by treating to lower (<130/80 mmHg) compared to standard (<140/90 mmHg) targets in patients with hypertension, across a range of co-morbidities.[95, 96] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial also found no significant overall difference in cardiovascular events between patients with type 2 diabetes assigned to a systolic blood pressure target of <120 mmHg and those assigned to a target of <140 mmHg.[97] These studies have used blood pressure level to define the target for antihypertensive drug therapy rather than participants absolute CVD risk. This evidence was largely used to support a treatment target of <140/90 mmHg in many international guidelines.[37, 98–103] Differences exist in the recommendations for the treatment for older persons, which can be reviewed in Section 10.2.

There is, however, consistent emerging evidence demonstrating benefit of treating to optimal blood pressure for certain patient populations, particularly those at high CVD risk.[3, 44, 94] A systematic review of 10 trials and 51,971 participants examining the effect of blood pressure lowering treatment in patients stratified by absolute CVD risk reported that patients at high absolute CVD risk (>15%) receive a greater benefit from blood pressure lowering treatment than patients at lower absolute CVD risk.[94] This trial included participants with prior cardiovascular events and patients already being treated for hypertension.

The Systolic Blood Pressure Intervention Trial (SPRINT) randomly assigned 9,361 persons >50 years of age at high CVD risk with a systolic blood pressure >130 mmHg to a systolic blood pressure target of <140 mmHg or <120 mmHg. Patients with diabetes, congestive heart failure, proteinuria or an eGFR <20 mL/min/1.73 m^2, those with adherence concerns and those with polycystic kidney disease or previous stroke were excluded from the study. Included patients had an estimated absolute CVD 10-year risk of at least 20%, with many having prior cardiovascular events, evidence of vascular disease or mild to moderate renal impairment. The group treated to a target of <120 mmHg achieved a mean of systolic blood pressure of 121.4 mmHg and had significantly fewer cardiovascular events (myocardial infarction, acute coronary syndrome, stroke, heart failure or cardiovascular death) and lower all-cause mortality compared to those in the standard treatment group (achieved mean systolic blood pressure 136.2 mmHg).[3] The number needed to treat to reduce one cardiovascular event over a 3-year period was 61. Patients >75 years of age benefited equally from being treated to a target of <120 mmHg systolic. Treatment related adverse events were significantly increased in the intensively treated patients with more frequent hypotension, syncopal episodes, acute kidney injury and electrolyte abnormalities compared with standard treatment (4.7% v 2.5%).

Collectively, these data suggest that clear cut-offs for defining hypertension may not represent all those whom benefit from blood pressure lowering, and emphasises the importance of absolute CVD risk with evidence of benefit from blood pressure lowering therapy for patients with mild hypertension (140–159 mmHg systolic) stratified as moderate to high absolute CVD risk.

There are genuine concerns about treating to optimal systolic blood pressure in all patient groups. The SPRINT trial[3] was ceased early, thus the already significant increase in adverse events associated with treating to optimal blood pressure targets was only reported over a 3-year period. It should also be noted that SPRINT applied the principles of automated office blood pressure measurement (i.e. patient alone in a room while three measurements are taken after 5 minutes of rest), a blood pressure measurement technique that generally yields lower blood pressure readings than those obtained by conventional clinic blood pressure (i.e. in presence of health professionals).

Accordingly, this guideline recommends that all those requiring antihypertensive drugs should be treated to a target of <140/90 mmHg. In those at high risk in whom it is deemed safe on clinical grounds and in whom drug therapy is well tolerated, aiming for a systolic blood pressure of target <120 mmHg is reasonable. This recommendation is subject to review as more information around treatment targets in particular patients becomes available.

Box 6.1 When to consider more intense treatment targets

While it is becoming increasingly apparent that certain patients may benefit from being treated to optimal blood pressures targets, it is currently difficult to broaden this recommendation to all patients due to the limited populations studied and the lack of long-term adverse effects data. The best clinical trial evidence is the SPRINT study,[3] but a number of considerations related to the study population and methods do not yet provide confidence that a target systolic blood pressure of 120 mmHg can be applied to everyone with hypertension.

The selection of a blood pressure target should be based on an informed, shared decision-making process between patient and doctor (or healthcare provider) considering the benefits and harms, and reviewed on an ongoing basis. The following issues should be considered.

- Much of the evidence supporting the treatment to optimal blood pressure (120 mmHg systolic) is derived from patients with existing co-morbidities or already receiving antihypertensive therapy.
- Aiming for a systolic blood pressure target of 120 mmHg may be inherently difficult in patients with high baseline pressures and where attaining 140 mmHg is already presenting a challenge.
- Much of the evidence for lower treatment targets is based on systolic blood pressure. There is general support for diastolic blood pressure to be <90 mmHg.
- For patients that have a long history of hypertension, achieving a systolic blood pressure of 120 mmHg may be inherently difficult.
- The mean reduction in systolic blood pressure in SPRINT was 18 mmHg, thus the benefit over harms for achieving a systolic blood pressure of 120 mmHg in patients with more severe grades of hypertension remains uncertain.
- The effect of intensive treatment in patients <50 years of age has not been directly tested.
- SPRINT used automated office blood pressure measurement (i.e. patient was alone in a room while three measurements are taken with an automated device). This blood pressure measurement technique generally yields lower blood pressure readings than those obtained by conventional clinic blood pressure and is more akin to out of office measurements.
- The SPRINT trial did not include patients with diabetes and, while ACCORD found intensive treatment reduced the risk of stroke, there was no improvement in all-cause mortality.[97]
- SPRINT included patients assessed as high cardiovascular risk using an algorithm that slightly differs from the Australian absolute CVD risk algorithm at www.cvdcheck.org.au.

6.3 Choice of antihypertensive drugs

Most classes of antihypertensive drugs used as monotherapy lower blood pressure by similar amounts, however the individual response can be unpredictable. An estimated 50–70% of patients will not achieve blood pressure targets with a single drug and, in these circumstances, at least two antihypertensive drugs from different classes are required to control blood pressure.

The initial drug choice should consider the patient's age, presence of associated clinical conditions or end organ damage, potential interaction with other drugs and implications for adherence, cost and patient choice. The recommendations in this guideline are based on evidence for drug classes, rather than individual drugs. Product information sheets should always be checked.

A large number of randomised controlled trials and subsequent systematic reviews demonstrate that the beneficial effects of antihypertensive drugs are due to blood pressure lowering per se and are largely independent of drug class and mechanism of action.[104] With the exception of alpha and beta-blockers, the remaining classes of antihypertensive drugs are similar in their ability to reduce blood pressure and effect on cardiovascular and all-cause mortality, with some differences seen in outcomes such as the development of heart failure and diabetes, and prevention of stroke.[75, 105–111]

While angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are the most widely used antihypertensive drugs, their mechanism of action differs. ACE inhibitors reduce the synthesis of angiotensin-2 by inhibiting the action of ACE. ARBs bind directly to the angiotensin-1 receptor, preventing its activation by angiotensin-2. In head-to-head trials, they are equally effective in blood pressure reduction and prevention of cardiovascular events overall,[112] however may have important differences in their efficacy in some clinical conditions, such that they are not necessarily interchangeable. For example, ACE inhibitors have been clearly demonstrated to prevent the onset of nephropathy and to reduce mortality in early diabetes[113] and are more effective in preventing coronary heart disease in patients with hypertension,[114] whereas ARBs have been demonstrated to better prevent kidney failure in people with advanced diabetic nephropathy[115–117] but inferior in the prevention of coronary heart disease in patients with hypertension.[114]

Despite mechanistic differences, single drug therapy using first-line therapy classes of thiazide diuretics, calcium channel blockers, ACE inhibitors or ARBs are similar in their efficacy to reduce blood pressure. However when combination therapy is initiated, the combination of ACE and calcium channel blockers is superior to the combination of ACE inhibitors and diuretics, and beta-blockers and diuretics, in their effects on various cardiovascular events and mortality.[118, 119] The effects of other combinations are less well studied. The only combination not recommended is that of more than one ACE inhibitor, ARBs and renin inhibitors. Findings from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET),[120, 121] the Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy (VA NEPHRON-D),[122] and the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) trial[123] found that the combinations of two or more of these agents was associated with increased incidence of adverse outcomes and no reduction in incidence of any important clinical outcomes.

A 2015 meta-analysis involving 55 blood pressure lowering randomised controlled trials and 195,267 patients comparing drug classes with placebo, showed that blood pressure lowering is accompanied by significant reductions in the relative and absolute risk of stroke and major cardiovascular events, independent of the antihypertensive drug class.[104] In a separate meta-analysis of 58 head-to-head randomised controlled trials (247,006 patients with hypertension) drug class did not significantly affect outcomes when the blood pressure effect was equivalent.[114] However, when compared, authors reported differences in outcomes supporting the suggestion that in preventing specific conditions some drug classes are preferable. This analysis, together with a meta-analysis of 123 blood pressure lowering trials[44] show diuretics as superior in preventing heart failure,[44] and calcium channel blockers superior in prevention of stroke[44] and all-cause mortality.[114]

In patients with hypertension without co-morbidities, two key systematic reviews support the findings that all drug classes are equally effective in the reduction of blood pressure, but differ in their efficacy in preventing certain outcomes. The largest network analysis included 88 trials and 214,729 individuals with hypertension, without diabetes and with no history of acute stroke, myocardial infarction or heart failure.[105] The five main drug classes were analysed for their effect on cardiovascular morbidity and mortality. There was no significant difference in the effect of any of the 10 drug pair-wise comparisons on cardiovascular mortality. Calcium channel blockers were shown to reduce all-cause mortality and the incidence of stroke when compared to beta-blockers. ACE inhibitors were reported to reduce the incidence of myocardial infarction when compared to beta-blockers.[105]

The second, a network meta-analysis of 25 trials involving patients with hypertension but without prior stroke or cardiovascular event assessed the effectiveness of drug classes (thiazide diuretics, calcium channel blockers, ACE inhibitors, ARBs, alpha-blockers and beta-blockers) across 15 pair-wise comparisons. There were few class differences, and no drug class stood out as superior across multiple outcomes.[107]

This guideline recommends that thiazide diuretics, calcium channel blockers, ACE inhibitors or ARBs are suitable first-line drugs for the treatment of hypertension, either as monotherapy or in some combinations, noting any possible contra-indications or co-morbidities. For combination therapy, ACE inhibitors and calcium channel blockers are superior to diuretics combined with either an ACE inhibitor or a beta-blocker.

Table 6.1 Recommendations for treatment strategies and treatment targets for patients with hypertension

Treatment strategies and treatment targets for patients with hypertension	Grade of recommendation	Level of evidence
a. Lifestyle advice is recommended for all patients.	Strong	
b. For patients at low absolute CVD risk (<10% 5-year risk) with persistent blood pressure ≥160/100 mmHg, antihypertensive therapy should be started.	Strong	I
c. For patients at moderate absolute CVD risk (10–15% 5-year risk) with persistent blood pressure ≥140 mmHg systolic and/or ≥90 mmHg diastolic, antihypertensive therapy should be started.	Strong	I
d. Once decided to treat, patients with uncomplicated hypertension should be treated to a target of <140/90 mmHg or lower if tolerated.	Strong	I
e. In selected high cardiovascular risk populations where a more intense treatment can be considered, aiming to a target of <120 mmHg systolic blood pressure can improve cardiovascular outcomes.	Strong	II
f. In selected high cardiovascular risk populations where a treatment is being targeted to <120 mmHg systolic, close follow-up of patients is recommended to identify treatment related adverse effects including hypotension, syncope, electrolyte abnormalities and acute kidney injury.	Strong	II
g. In patients with uncomplicated hypertension ACE inhibitors or ARBs, calcium channel blockers, and thiazide diuretics are all suitable first-line antihypertensive drugs, either as monotherapy or in some combinations unless contraindicated.	Strong	I
h. The balance between efficacy and safety is less favourable for beta-blockers than other first-line antihypertensive drugs. Thus beta-blockers should not be offered as a first-line drug therapy for patients with hypertension not complicated by other conditions.	Strong	I
i. ACE inhibitors and ARBs are not recommended in combination due to the increased risk of adverse effects.	Strong	I

Figure 6.1 Treatment strategy for patients with newly diagnosed hypertension

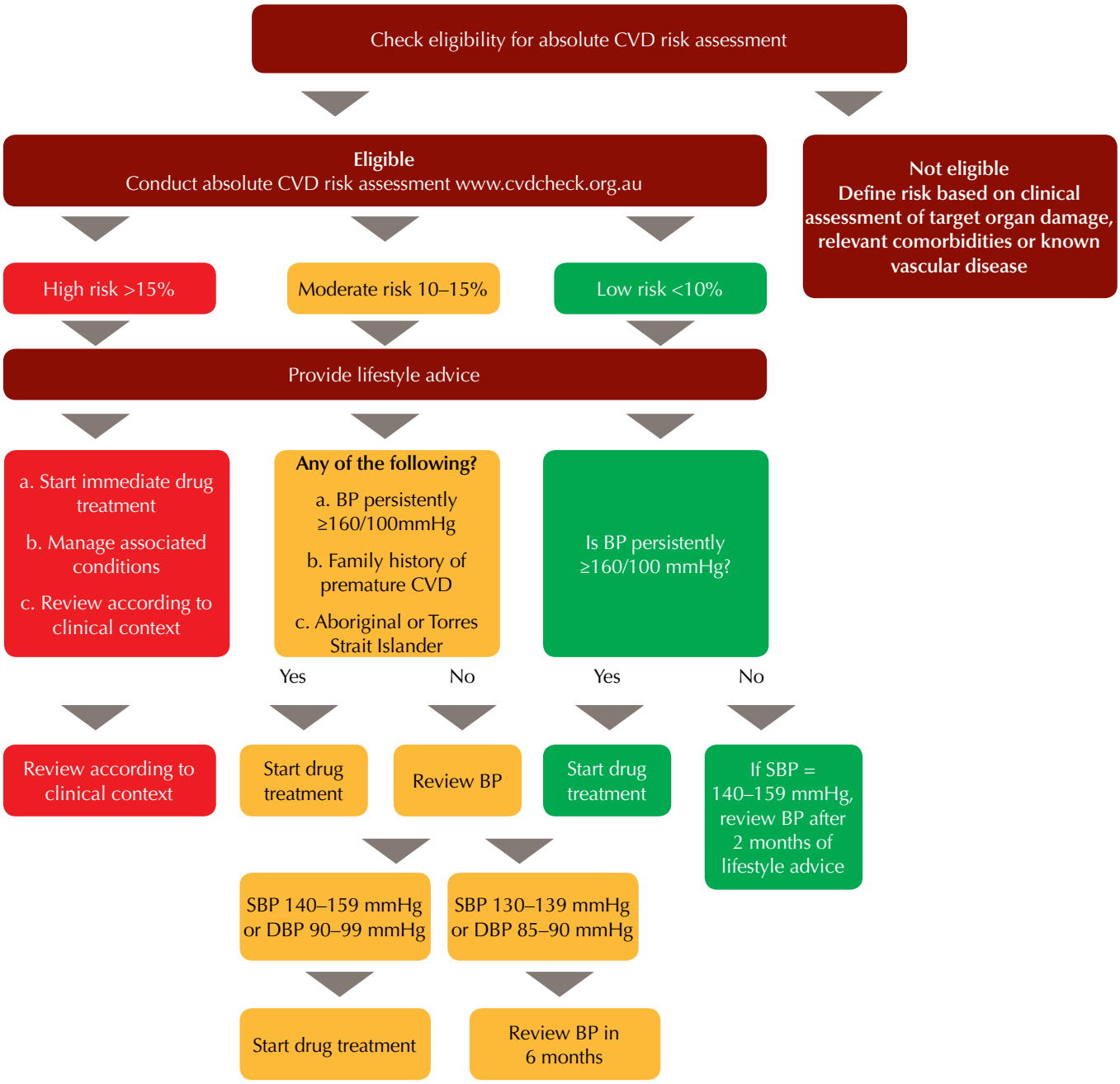
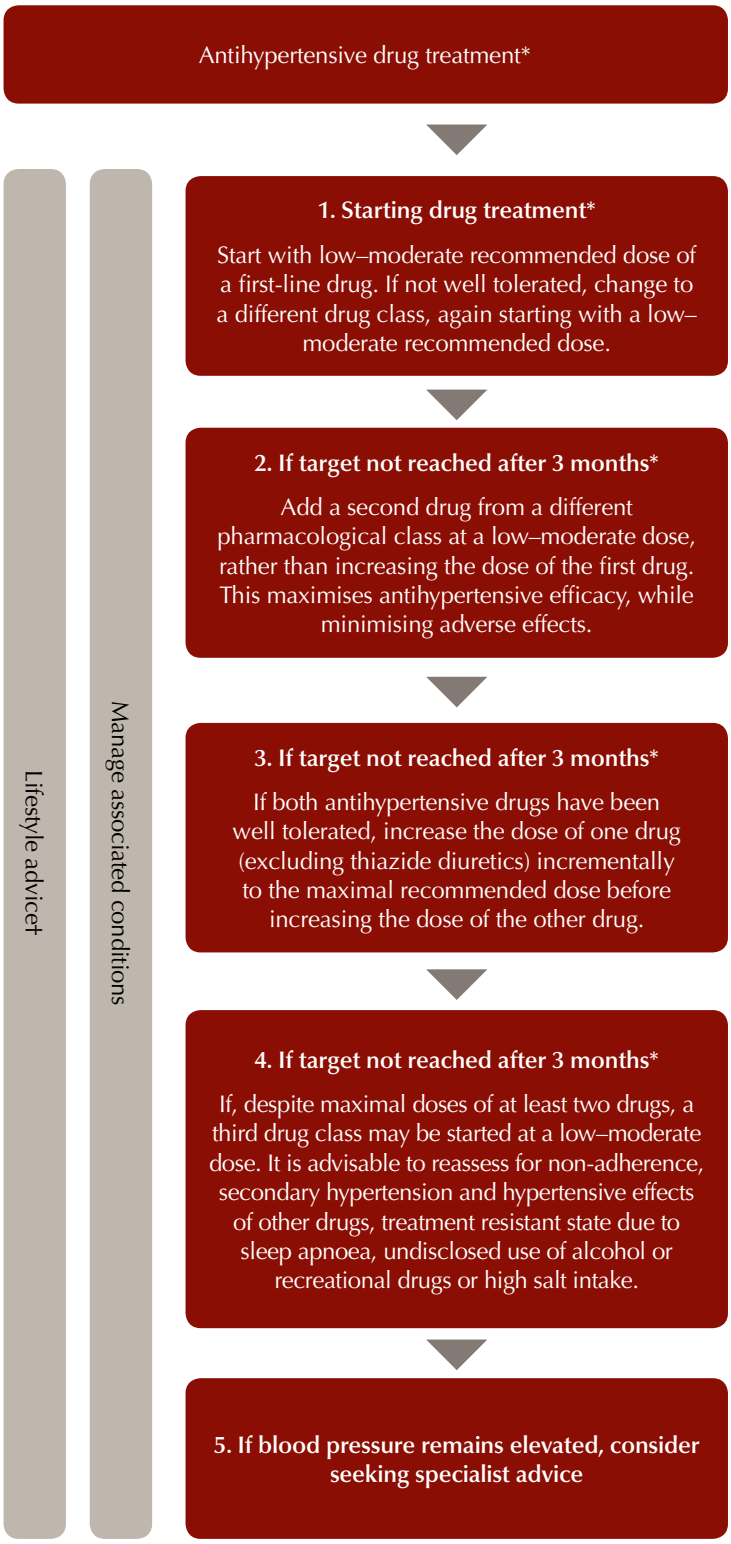


Figure 6.2 Drug treatment strategy to reach blood pressure target



*Maximum effect of drug likely to be seen in 4–6 weeks. If baseline blood pressure is severely elevated earlier reviews may be considered. For steps 1–4, review every 4–6 weeks for tolerance, efficacy and adverse effects. †All patients should receive lifestyle advice with follow-up based on clinical context.

Table 6.2 Effective drug combinations

First drug		Second drug	Comment
Effective combination			
ACE inhibitor or ARB*	plus	Calcium channel blocker	Particularly useful in presence of diabetes and/or lipid abnormalities[124]
ACE inhibitor or ARB*	plus	Thiazide diuretic	Useful in presence of heart failure or post stroke
ACE inhibitor or ARB*	plus	Beta-blocker	Recommended post myocardial infarction or in patients with heart failure†
Beta-blocker	plus	Dihydropyridine calcium channel blocker	Useful in presence of symptomatic coronary heart disease
Thiazide diuretic	plus	Calcium channel blocker	
Thiazide diuretic	plus	Beta-blocker	Not recommended in presence of glucose intolerance, metabolic syndrome or established diabetes
Combinations to use with care			
Diltiazem	plus	Beta-blocker	Due to risk of heart block, but risk is less than with verapamil
ACE inhibitor or ARB	plus	Potassium-sparing diuretic	Due to risk of hyperkalaemia
Combinations to avoid			
ACE inhibitor	plus	ARB	Increased risk of renal dysfunction[120]
Verapamil	plus	Beta-blocker	Due to risk of heart block

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker

*In head-to-head trials ACE inhibitors and ARB's are equally effective in blood pressure reduction and prevention of cardiovascular events overall, however may have important differences in their efficacy, so that they are not interchangeable, in some clinical conditions.

†Carvedilol; bisoprolol (beta-1 selective antagonist); metoprolol extended release (beta-1 selective antagonist); nebivolol.[125]

Table 6.3 Antihypertensive drugs and their contraindications

Drug class	Contraindications	
	Compelling	Possible
ACE inhibitors	Pregnancy	Women with child bearing potential
or	Angioedema	
ARBs	Hyperkalaemia	
	Bilateral renal artery stenosis	
Calcium channel blockers (dihydropyridines)		Heart failure
Diuretics (low-dose thiazide)	Gout	Glucose intolerance
	Age*	Metabolic syndrome
		Hypercalcaemia
		Hypokalaemia
Beta-blockers	Asthma	Type 1 or 2 diabetes
Not first-line therapy†	Bradycardia	Metabolic syndrome
	A-V block (grade 2 or 3)	Glucose intolerance
	Uncontrolled heart failure	Athletes and active patients
		Chronic obstructive pulmonary disease (except for vasodilator beta-blockers)
		Depression

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker

*Thiazide diuretics have been associated with increased risk of diabetes[126] onset and should be used as a first-line therapy only in older patients where the benefit of managing hypertension outweighs the risk of diabetes onset.

†Beta-blockers are no longer recommended as a first-line therapy in uncomplicated hypertension due to an increased risk of developing diabetes and the trend towards worse outcomes compared to those treated with other classes of antihypertensive drugs.[122] For patients with well-controlled hypertension already taking a beta-blocker, it is reasonable to continue use.

7 Doses and safety of antihypertensive drugs

Treatment of hypertension is long term, therefore the tolerability and safety of drugs is particularly important. To minimise adverse effects and maximise tolerability of antihypertensive drugs, start with low to moderate doses and gradually increase where required.

All effective drugs have adverse effects and it is not possible to predict which patients will experience them. Listening carefully to patients and confirming temporal relationships between drug treatment changes and clinical effects can enhance recognition of adverse effects and improve management. Most patients want to know something about potential adverse effects before starting a new drug. Table 7.1 lists common adverse effects and selected rare, but serious, effects. If more information is required, refer to the approved Product Information and Consumer Medicines Information available from the National Prescribing Service at www.nps.org.au, the TGA at www.tga.gov.au or the **Australian Medicines Handbook.**[128] The TGA encourages reporting of all suspected adverse reactions to prescription drugs. Reporting seemingly insignificant or common adverse reaction is useful and may highlight a widespread problem.

Table 7.1 Usual dose ranges and adverse effects for antihypertensive drugs for adults

Antihypertensive	Usual dose range	Comments
ACE inhibitors		
Captopril	12.5–50 mg twice daily	**Note:** Lower initiating doses are clinically appropriate in some settings to maximise tolerability. **Selected adverse effects:** Cough Hyperkalaemia (risk increased by renal impairment) Renal impairment (risk increased by hypovolaemia or NSAIDs) Angioedema (infrequent; may occur after years of treatment)
Enalapril	5–40 mg daily in one or two doses	
Fosinopril	10–40 mg once daily	
Lisinopril	5–40 mg once daily	
Perindopril arginine	5–10 mg once daily	
Perindopril erbumine	4–8 mg once daily	
Quinapril	5–40 mg daily in one or two doses	
Ramipril	2.5–10 mg daily in one or two doses	
Trandolapril	1–4 mg once daily	
ARBs/Sartans		
Candesartan	8–32 mg once daily	**Note:** Lower initiating doses are clinically appropriate in some settings to maximise tolerability. Use cautiously if history of angioedema with ACE inhibitors. **Selected adverse effects:** Hyperkalaemia (risk increased by renal impairment) Renal impairment (risk increased by hypovolaemia or NSAIDs) Cough and angioedema are rare
Eprosartan	400–600 mg once daily	
Irbesartan	150–300 mg once daily	
Losartan	50–100 mg once daily*	
Olmesartan	20–40 mg once daily	
Telmisartan	40–80 mg once daily	
Valsartan	80–320 mg once daily	

Table 7.1 Usual dose ranges and adverse effects for antihypertensive drugs for adults (continued)

Antihypertensive	Usual dose range	Comments
Calcium channel blockers		
Note: Effects vary according to relative effects on vascular, myocardial and conducting tissue.		
Dihydropyridine calcium channel blockers		
Amlodipine	2.5–10 mg once daily	**Note:** Lower initiating doses are clinically appropriate in some settings to maximise tolerability. Long-acting (once daily) products are preferred. Minimal effect on myocardial contractility and cardiac conduction. Do not treat calcium channel blocker induced peripheral oedema with diuretics. **Selected adverse effects:** Peripheral vasodilation (peripheral oedema, flushing, headache, dizziness), postural hypotension, tachycardia, palpitations, chest pain, gingival hyperplasia
Felodipine	CR, 5–20 mg once daily	
Lercanidipine	10–20 mg once daily	
Nifedipine	10–40 mg twice daily CR, 20–120 mg once daily	
Other (non-dihydropyridine) calcium channel blockers		
Diltiazem	CR, 180–360 mg once daily	**Note:** Lower initiating doses are clinically appropriate in some settings to maximise tolerability. Less peripheral vasodilation than dihydropyridines. Reduce heart rate and depress cardiac contractility (verapamil more than diltiazem). **Selected adverse effects:** Bradycardia, constipation (particularly verapamil, may be severe), atrioventricular block, heart failure.
Verapamil	80–160 mg two or three times daily CR, tablet 180–480 mg daily. If >240 mg give in two doses CR capsule 160–480mg daily	
Thiazide-like diuretics*		
Note: loop diuretics not recommended as an antihypertensive unless volume overload is present.		
Chlorthalidone**	12.5–25 mg once daily. A starting dose of 12.5 mg on alternate days may be appropriate in some patients	**Note:** Lower initiating doses are clinically appropriate in some settings to maximise tolerability. Effects on electrolytes, lipids and blood glucose are dose dependent, start with a low dose and increase slowly. Chlorthalidone has a longer duration of action (45–60 hours) and is 1.5–2.0 times more potent than hydrochlorothiazide on a per-milligram basis.[129] If plasma potassium is low during therapy, potassium supplements may be used. **Selected adverse effects:** Postural hypotension, dizziness, hypokalaemia, hyponatraemia, hyperuricaemia, hyperglycaemia
Hydrochlorothiazide	25 mg once daily	
Indapamide	1.5 mg once daily. CR, 1.5 mg has similar antihypertensive effect to 2.5 mg tablet but lower risk of hypokalaemia	

Antihypertensive	Usual dose range	Comments
Beta-blockers		
Note: Beta-blockers vary in pharmacological/physicochemical properties which can affect tolerability.		
Atenolol	25–100 mg daily in one or two doses	**Note:** Lower initiating doses are clinically appropriate in some settings to maximise tolerability. Stop beta-blockers slowly over >2 weeks to avoid problems, e.g. rebound hypertension, myocardial infarction. Atenolol: not recommended monotherapy (poor outcomes in meta-analysis); consider changing if current monotherapy. **Selected adverse effects:** Bradycardia, postural hypotension, worsening of heart failure (transient), bronchospasm, cold extremities
Carvedilol	12.5–50 mg daily in one or two doses	
Labetalol	100–400 mg twice daily	
Metoprolol	50–100 mg once or twice daily CR 23.75–190 mg once daily	
Nebivolol	5 mg once daily	
Oxprenolol	40–160 mg twice daily	
Pindolol	10–30 mg daily in two or three doses	
Propranolol	40–320 mg daily in two or three doses	
Other antihypertensive drugs		
Amiloride (potassium sparing diuretic)	Diuretic-induced hypokalaemia: 2.5–5 mg daily	**Note:** Generally, not used for its antihypertensive effects. Can be used in patients with hyperaldosteronism who do not tolerate spironolactone **Selected adverse effects:** Hyperkalaemia (risk increased by renal impairment and other drugs that increase potassium concentrations)
Clonidine (centrally acting alpha2 and imidazoline agonist)	Initially 50–100 mcg twice daily, increase every 2–3 days. Maintenance 150–300 mcg twice daily	**Note:** When stopping, avoid severe rebound hypertension by reducing dose over >7 days. **Selected adverse effects:** Postural hypotension, constipation, bradycardia, dry mouth, CNS effects (e.g. sedation, dizziness)
Hydralazine (peripheral, mostly arteriolar, vasodilator)	50–100 mg daily in two doses	**Note:** Used for refractory hypertension usually with a beta-blocker and diuretic. **Selected adverse effects:** Palpitations, flushing, headache, oedema Tachycardia, may exacerbate angina (prevent reflex tachycardia by using with a beta-blocker or verapamil) Lupus-like syndrome (risk increased by doses >100 mg daily for >6 months)
Methyldopa (centrally acting alpha2 agonist)	250–2000 mg daily in two to four doses	**Note:** Predominately used for hypertension in pregnancy. Limit use in other patients. adverse effects limit use (except in pregnancy). **Selected adverse effects:** CNS effects (e.g. sedation, dizziness), hepatitis, hepatic necrosis, positive Coombs test, haemolytic anaemia

Table 7.1 Usual dose ranges and adverse effects for antihypertensive drugs for adults (continued)

Antihypertensive	Usual dose range	Comments
Moxonidine (centrally acting imidazoline agonist with minor alpha2 agonist activity)	200–600 mcg daily in one or two doses. Maximum single dose is 400 mcg	**Note:** When stopping, withdraw over a few days. Maximum single dose is 400 mcg. Only 400 mcg and 200 mcg tablets are available in Australia. Effect on cardiovascular outcome and mortality has not been tested. **Selected adverse effects:** Dry mouth, CNS effects (e.g. somnolence, dizziness), bradycardia, vasodilation
Prazosin (selective alpha blocker, peripheral vasodilator)	Initially 0.5 mg twice daily for 3–7 days. Maintenance, 3–20 mg daily in two or three doses	**Note:** Reduce risk of first-dose hypotension by starting at night in low dose. Before starting consider withholding diuretics and reducing dose of beta-blockers or calcium channel blockers. **Selected adverse effects:** Hypotension (first-dose and postural), may be profound; high risk: dose increase, advanced age, diuretic or volume depletion, adding antihypertensives
Spironolactone (aldosterone antagonist)	Blood pressure control‡ 12.5–50 mg Primary hyperaldosteronism 50–200 mg daily in one or two doses Heart failure 25–50 mg once daily	**Notes:** Reduces potassium excretion. Effective as add-on therapy in patients with resistant hypertension.[130] **Selected adverse effects:** Hyperkalaemia (risk increased by renal impairment), hyponatraemia Anti-androgenic effects (eg. mastalgia, gynaecomastia, sexual dysfunction)

CR, controlled release; mcg, microgram; NSAID, nonsteroidal anti-inflammatory drug; CNS, central nervous system

*Usually unnecessary to exceed the dose shown as drug has a flat dose response curve.

†Some evidence to suggest chlorthalidone like diuretics reduce cardiovascular risk compared to other thiazide diuretics.[131]

‡Not currently approved by TGA for blood pressure lowering.

This table was adapted with permission from Australian Medicines Handbook, July 2015.[124]

8 Initiating treatment with combination therapy

Combination therapy, defined by the use of at least two antihypertensive drugs, is required in up to 50–70% of patients to reach blood pressure targets. It is widely accepted that combining two classes of antihypertensive drug lowers blood pressure more than doubling the dose of one drug. If baseline blood pressure is very high and starting treatment using two drugs (combination) compared to one (monotherapy) is being considered, the benefits and limitations of this approach should be carefully evaluated.

Starting treatment with two drugs

Potential benefits include:

- a more rapid reduction in blood pressure
- less drug and dosage changes, which has been suggested to have a positive effect on drug adherence[132]
- reducing risk of clinical inertia.

Potential limitations include:

- assessment of efficacy of individual drug
- attribution of adverse effects to individual drug
- single pill combination drugs (two antihypertensive drugs combined into a single pill), may not be subsidised by the Pharmaceutical Benefits Scheme (PBS) for initiation of antihypertensive therapy.

Starting treatment with one drug and gradually progressing to combination therapy

This approach allows for:

- accurate assessment of specific drug efficacy.
- clear attribution of adverse effects
- possible avoidance of over-treating patients who respond favourably to monotherapy.

While combination therapy is more effective in lowering blood pressure than monotherapy,[133–135] direct evidence of its effect on cardiovascular outcomes is less clear.

Table 8.1 Recommendation for starting drug treatment with more than one drug

Combination versus monotherapy	Grade of recommendation	Level of evidence
a. For patients with very high baseline blood pressure (>20 mmHg systolic and >10 mmHg diastolic above target), starting treatment with more than one drug may be considered.	Weak	–

9 Treatment strategies and treatment targets for selected co-morbidities

It is generally understood that elevated blood pressure is associated with an increased risk of cardiovascular events although direct evidence for patients with specific conditions remain to be confirmed. For many conditions, the decision of when to start blood pressure lowering therapy and the targets to maximise benefits and minimise harms remain a focus of research and debate.

With the exception of alpha-blockers and beta-blockers, the remaining pharmacological classes of antihypertensive drugs are similar in their ability to lower blood pressure and in their effect on cardiovascular morbidity and mortality in patients across a range of co-morbidities. There are some differences between drug classes in outcomes such as the development of heart failure and onset of diabetes, stroke and all-cause mortality.[44, 75, 105–111, 114]

Earlier evidence suggested no benefit on cardiovascular outcome or all-cause mortality by treating to more intense (<130/80 mmHg) compared to standard (<140/90 mmHg) targets in patients with hypertension, across a range of co-morbidities[95, 96] and are associated with increases in adverse effects. Therefore, treatment targets in other international guidelines have been relaxed to reflect this.[33, 136]

Here, we review the literature associated with drug choices and treatment targets for patients with hypertension and the co-morbid conditions of diabetes, chronic kidney disease, chronic heart failure and peripheral arterial disease, as well as those post stroke and post myocardial infarction. Further information on the management of stroke and TIA is available in the Clinical guidelines for stroke management.

9.1 Stroke and TIA

Cerebrovascular disease due to stroke or TIA is a leading cause of death and disability, with primary prevention being the most effective strategy to reduce global burden of this condition. Hypertension is the major risk factor for both first and recurrent stroke. Thus optimal management of elevated blood pressure in patients with a history of stroke or TIA is important to prevent recurrent strokes together with other major cardiovascular events.

9.1.1 Drug choice

Several systematic reviews demonstrate that blood pressure lowering is more important than the antihypertensive drug used.[94, 104, 114] The Perindopril Protection Against Recurrent Stroke Study (PROGRESS), in particular, demonstrated for the first time the benefits of blood pressure lowering in preventing recurrent stroke and other cardiovascular events in patients with and without hypertension (defined by systolic blood pressure >160 mmHg).[137] Although PROGRESS suggested greater benefits in patients receiving combination therapy of an ACE inhibitor and a diuretic, the comparison with monotherapy was not randomised, leaving some doubt around the optimal level of blood pressure for prevention of recurrent stroke. There is also some uncertainty regarding the ideal drug, or combination of drugs, for optimal protection from recurrent stroke. In attempt to answer this, a 2015 meta-analysis used a random effect model involving 251,838 participants from 17 randomised controlled trials to identify the most effective class in reducing the long-term risk of stroke.[138] Comparing ACE inhibitors, ARBs, ACE inhibitor/ARBs, beta-blockers, calcium channel blockers and thiazide-like diuretics, the ratio risk for stroke occurrence was only significant lower with calcium channel blockers and higher with beta-blockers.[138] The support for calcium channel blockers in preventing stroke has been further strengthened in a meta-analysis of 123 blood pressure lowering trials.[44] A post-hoc analysis of the PROGRESS trial demonstrated significant benefits of blood pressure lowering, including 120–139 mmHg systolic for both ischaemic stroke and intracenrebral haemorrhage.[139]

This guideline recommends that all first-line drugs that effectively lower blood pressure are recommended for treating hypertension in patients who have had a prior stroke or TIA.

9.1.2 Treatment targets

There is no direct randomised evidence in patients with hypertension with a history of stroke or TIA that indicates that intensive blood pressure lowering to a target of <130 mmHg is beneficial in preventing recurrent stroke or improving survival. In 2013, the Secondary Prevention of Small Subcortical Strokes (SPS3) trial, confirmed the results of PROGRESS by showing a trend towards benefits of 'more' (<130 mmHg systolic blood pressure target) compared to 'less' (130–149 mmHg systolic blood pressure target) blood pressure lowering in 3,020 patients with a history of small vessel 'lacunar' type ischaemic stroke.[140] However, the results were not significant for a reduction in the rates of recurrent stroke or other major cardiovascular outcomes including myocardial infarction and vascular death after a follow-up of 3.7 years. The findings were consistent for a sub-group of 2,706 patients considered hypertensive at baseline.[140]

In summary, treatment, even in patients with mild hypertension without prior disease, has been associated with significant reduction in stroke, cardiovascular death and all-cause mortality.[74] Post stroke or TIA, the use of any drug class effective in lowering blood pressure is appropriate.

9.1.3 Acute stroke

The management of high blood pressure in the setting of acute stroke has been a controversial and complex area. International guidelines recommend against starting blood pressure lowering therapy within seven days of a stroke[33] due to evidence showing no effect and no harm of early intervention. The Candesartan for Treatment of Acute Stroke (SCAST) trial found no significant difference in cardiovascular events between those treated early with ARB or placebo.[141] A trial involving 4,071 Chinese patients also found no difference in death or major disability at 14 days between patients treated to lower blood pressure targets.[142] Moreover, a meta-analysis including 17,011 participants randomised to treatment within 48 hours of acute stroke found insufficient evidence that lowering blood pressure during the acute phase of stroke improves functional outcome.[143] Some small trials, such as Controlling Hypertension and Hypertension Immediately Post-Stroke (CHHIPS)[144] and the Acute Candesartan Cilexetil Therapy in Stroke Survival (ACCESS)[145] have, however, suggested a benefit for early intervention.

Finally, for patients with acute intracerebral haemorrhage early control of elevated blood pressure is not associated with improved mortality, but there is some evidence to indicate improved functional recovery among survivors.[146]

While these studies provide no evidence of benefit for early blood pressure lowering in acute ischaemic stroke, they show no excess harms. As long-term adherence to secondary prevention medication (blood pressure lowering) is associated with treatment initiation in hospital, commencement of antihypertensive therapy when the patient is deemed clinically stable is appropriate.[147] Further trials are needed to identify which people are most likely to benefit from early treatment and how soon after stroke is treatment most effective.

Table 9.1 Recommendations for patients with hypertension and prior stroke and/or TIA

Patients with hypertension and prior stroke or transient ischaemic attack	Grade of recommendation	Level of evidence
a. For patients with a history of TIA or stroke, antihypertensive therapy is recommended to reduce overall cardiovascular risk.	Strong	I
b. For patients with a history of TIA or stroke, any of the first-line antihypertensive drugs that effectively reduce blood pressure are recommended.	Strong	I
c. For patients with hypertension and a history of TIA or stroke, a blood pressure target of <140/90 mmHg is recommended.	Strong	I

9.2 Chronic kidney disease

Chronic kidney disease is commonly defined by a reduction in GFR and/or proteinuria (including albuminuria). Hypertension is a major risk factor and a consequence of chronic kidney disease. Blood pressure control is fundamental to the care of patients with chronic kidney disease at all stages regardless of the underlying cause. Individuals with early chronic kidney disease with or without hypertension are at an increased risk of a cardiovascular event. Thus, blood pressure lowering is an effective strategy in preventing cardiovascular events in patients with moderately reduced GFRs[108] and those with end-stage kidney disease undergoing dialysis.[148, 149]

9.2.1 Drug choice

A systematic review in 2013 of individual patient data from 23 trials compared the effect of different classes of blood pressure lowering drugs in 152,920 participants with and without reduced estimated GFRs.[108] The analysis included patients with or without hypertension and those with and without established CVD. Compared with placebo, blood pressure lowering regimens were associated with a reduction in total mortality, cardiovascular mortality, cardiovascular events, incidence of stroke and incidence of coronary heart disease. This association remained consistent in those with and without reduced estimated GFRs and, importantly, irrespective of treating with ACE inhibitor, calcium channel blocker or diuretic based regimens. There were, however, fewer cases of heart failure in patients with estimated GFR >60 mL/min/1.73 m^2 when taking ACE inhibitor regimens compared to calcium channel blockers.[108]

A study evaluating the efficacy of drug combinations in participants with hypertension and/or at 'high risk',[150] thus not all diagnosed with chronic kidney disease, found that a combination treatment with an ACE inhibitor and a calcium channel blocker reduced the incidence of strokes, cardiovascular events and all-cause mortality compared to combination treatment with a beta-blocker and a diuretic.[150] A sub-analysis of the ACCOMPLISH trial has also reported ACE inhibitor and calcium channel blocker as more effective in preventing doubling serum creatinine and end-stage kidney disease, although less effective in preventing proteinuria, when compared to a thiazide diuretic.[151]

In summary, direct evidence suggests that most classes of blood pressure lowering drugs have a similar effect in reducing cardiovascular events and all-cause mortality in patients with chronic kidney disease. When treating with diuretics the choice should be dependent upon the stage of chronic kidney disease and the extracellular fluid volume overload in the patient. Generally, thiazides are effective only in those with normal renal function or mild impairment. More detailed information on the use of diuretics in patients with chronic kidney disease can be found in international KDIGO guidelines.[152] Indirect evidence from analysis including patients without chronic kidney disease suggests that combination therapy of ACE inhibitors and calcium channel blockers may be superior to a beta-blocker and diuretic combination therapy.

9.2.2 Treatment targets

For patients with hypertension and chronic kidney disease, four key systematic reviews and a large randomised controlled trial have investigated the effect of treating to standard versus lower blood pressure targets. Firstly, the BPLTTC prospective meta-analysis in 2013 found that intensive blood pressure targets had no additional effect on major cardiovascular events and did not vary according to calculated eGFR.[108] Secondly, a systematic review in 2013 assessing 'more' versus 'less' intensive treatment in 9,287 participants found no reduction in overall mortality, cardiovascular mortality, cardiovascular events or serious adverse events with intensive treatment. Intensive treatment was associated with a reduced risk of kidney failure for those with proteinuria, but not those without proteinuria.[153] Thirdly, a systematic review from 2011 involving 2,272 participants found that lower blood pressure targets defined by systolic blood pressure <125–130 mmHg had no benefit on cardiovascular mortality, cardiovascular events or all-cause mortality.[154] In addition both a systematic review including 4,975 participants[155] and a separate post hoc analysis involving 23,422 participants[154] found no benefit of more intensive therapy (combination therapy) over monotherapy on mortality and cardiovascular outcomes in patients with chronic kidney disease. These results were similar in subgroups at high renal risk by low GFR and/or elevated albuminuria.[155]

However the SPRINT trial[3] and subsequent meta-analysis show that some patients with chronic kidney disease indeed benefit from intensive blood pressure lowering (refer to Box 6.1) and consideration for more intense treatment may significantly improve cardiovascular outcomes in some patients.

Table 9.2 Recommendations for patients with hypertension and chronic kidney disease

Patients with hypertension and chronic kidney disease	Grade of recommendation	Level of evidence
a. In patients with hypertension and chronic kidney disease, any of the first-line antihypertensive drugs that effectively reduce blood pressure are recommended.	Strong	I
b. When treating hypertension in patients with chronic kidney disease in the presence of micro or macro albuminuria,* an ARB or ACE inhibitor should be considered as first-line therapy.	Strong	I
c. In patients with chronic kidney disease, antihypertensive therapy should be started in those with systolic blood pressures consistently >140/90 mmHg and treated to a target of <140/90 mmHg.	Strong	I
d. Dual renin-angiotensin system blockade is not recommended in patients with chronic kidney disease.	Strong	I
e. For patients with chronic kidney disease, aiming towards a systolic blood pressure of <120 mmHg has shown benefit, where well tolerated.	Strong	II
f. In people with chronic kidney disease where treatment is being targeted to <120 mmHg systolic, close follow-up of patients is recommended to identify treatment related adverse effects including hypotension, syncope, electrolyte abnormalities and acute kidney injury	Strong	I
g. In patients with chronic kidney disease, aldosterone antagonists should be used with caution in view of the uncertain balance of risks versus benefits.	Weak	–

*Table of equivalents for measures of micro and macro albuminuria can be found in Table 4.10: Laboratory investigations for all patients.

Further information on how to manage patients with chronic kidney disease and those on haemodialysis are available from Kidney Health Australia[40] and the International KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease.[152]

9.3 Diabetes

Elevated blood pressure is common among patients with diabetes. The combination of diabetes and hypertension places individuals at significantly increased risk of CVD.

9.3.1 Drug choice

Blood pressure lowering is clearly effective in reducing cardiovascular events in patients with diabetes. Four large separate systematic reviews have investigated efficacy differences between drug classes to lower blood pressure and found that drug class had no significant difference on all-cause mortality.[111, 113, 134, 156]

A 2013 systematic review with network meta-analysis of 63 trials and 36,917 participants with diabetes and all levels of albuminuria, examined single drug or combinations of all blood pressure lowering classes on all-cause mortality.[134] Unfortunately, blood pressure status was not reported. After a 12-month follow-up, there was no significant difference between drug classes with the exception of beta-blockers which increased the risk of all-cause mortality compared to calcium channel blockers, ACE inhibitors or ARBs.[134] A second review of 27 trials compared ACE inhibitors or ARB and calcium channel blockers with beta-blocker–based regimens in patients with and without diabetes that may or may not have been hypertensive or have had established CVD.[110] Again there was no difference in total mortality, cardiovascular mortality or number of major cardiovascular events between drug classes in those with and without diabetes. ARB regimens were, however, reported to provide less protection against stroke but greater protection against heart failure, in patients with diabetes compared to individuals without diabetes.[110]

A Cochrane systematic review including seven trials that compared ACE inhibitors versus ARB and ACE inhibitors versus calcium channel blockers in 5,587 diabetic participants also found no effect of drug classes on all-cause mortality.[153] Additionally, a fourth paper conducted a subgroup analysis on 5,173 patients with diabetes from a larger trial investigating the reduction of cardiovascular morbidity and mortality seen with using combinations therapies containing an ACE inhibitors and calcium channel blockers versus other combinations. Here, ACE inhibitors and calcium channel blocker combinations did not differ compared to other combinations in their effect on cardiovascular mortality or risk of myocardial infarctions, but did reduce the incidence of fatal and non-fatal strokes and peripheral arterial disease.[150] Finally, the largest systematic review and meta-analysis published in 2015 assessed the association between blood pressure lowering treatment regimens in 100,354 patients with diabetes.[156] Consistent with the earlier data, drug class did not affect all-cause mortality or cardiovascular events. The key exception was that diuretics were associated with a significantly lower risk of developing heart failure.[156]

9.3.2 Treatment targets

In patients with hypertension and diabetes there has been no large body of evidence to support treating systolic blood pressures to <140 mmHg, with the exception of those also presenting with proteinuria or albuminuria, to systolic blood pressure targets of <130 mmHg. A systematic review including 7,314 patients with diabetes were allocated to lower blood pressure targets (<130/85 mmHg) versus standard targets (<140–160/90–100 mmHg) and followed up for outcomes after 3.9–5 years.[157] Authors found that lowwer blood pressure targets increased the number of serious adverse events but had no effect on total mortality, cardiovascular mortality, myocardial infarction, chronic heart failure or end-stage kidney failure. There was an association with a reduction in stroke risk with reduced systolic blood pressures.[157] In addition, results of the ACCORD study indicate that there was some reduction in the risk of stroke in patients with type 2 diabetes when targeting systolic blood pressure of <120 compared with <140.[97]

A second systematic review of five trials including 7,321 participants also found that intensive blood pressure targets (<130/80 mmHg) had no effect on mortality or myocardial infarction after 1.9–5.3 years follow up.[158] The intensive blood pressure targets were associated with a significant decreased risk of stroke but also with an increase in rates of serious adverse events.[158] The largest meta-analysis of 40 trials, published in 2015[151] was also unable to demonstrate that blood pressure lowering in those with systolic blood pressure <140 mmHg has any effect on lowering the risk of CVD or reduced mortality among patients. Blood pressure lowering was, however, associated with a reduced risk of stroke, retinopathy and progression of albuminuria in patients with diabetes who had systolic blood pressures both less than and greater than 140 mmHg. A systematic review with network meta-analysis involving 36,917 participants investigated the benefit of intensive blood pressure lowering with combination therapy on clinical outcome. Here the effectiveness of six different antihypertensive combinations was not associated with improved mortality or renal outcomes when compared to monotherapy in patients with diabetes.[134] The more intensive treatment with combination therapy did not improve outcomes compared to less intensive treatment with monotherapy for all combinations reviewed. The SPRINT trial did not include patients with diabetes.

Two retrospective reviews of trials in which participants achieved a specific target rather than randomising to lower targets[159, 160] have reported beneficial cardiovascular outcomes for patients with hypertension that achieved a specific blood pressure target. It should be noted that such reviews likely select for a cohort of participants associated with a lower risk of having a cardiovascular event. For example, participants who had the lowest baseline blood pressure were also more compliant with treatment and thus blood pressure lowering was most effectively achieved.

9.4 Myocardial infarction

Elevated blood pressure, particularly systolic blood pressure, is a significant factor contributing to a myocardial infarction. However, for hypertensive patients post myocardial infarction there is no clear evidence to alter current drug treatment strategies, but also no clear evidence to suggest that lower treatment targets provide additional clinical benefit.

9.4.1 Drug choice

In the early phase post myocardial infarction, beta-blockers have been shown to reduce re-infarctions in the first two weeks.[161–163] A 2014 meta-analysis of 60 trials and 102,003 participants found that beta-blockers reduced recurrent infarction and mortality in the short term (up to 30 days post perfusion), but not in the long term.[164] This meta-analysis is dominated by large studies that used beta-blockade in the short term, and further complicated by the fact that reperfusion was not standard therapy when most of the studies included were conducted. An earlier meta-analysis assessed the benefit of short-term and long-term beta-blockade in 5,477 patients post myocardial infarction and concluded that long-term treatment prevented recurrent infarction and improved overall mortality.[165] Current guidelines for the treatment of myocardial infarction recommend the use of ACE inhibitors and beta-blockers in all patients who can tolerate these medications without regard to the presence of hypertension.[166]

9.4.2 Treatment targets

Systematic reviews or large randomised controlled trials evaluating blood pressure targets in patients post myocardial infarction are lacking.

Table 9.3 Recommendations for patients with hypertension and diabetes

Patients with hypertension and diabetes	Grade of recommendation	Level of evidence
a. Antihypertensive therapy is strongly recommended in patients with diabetes and systolic blood pressure ≥140 mmHg.	Strong	I
b. In patients with diabetes and hypertension, any of the first-line antihypertensive drugs that effectively lower blood pressure are recommended.	Strong	I
c. In patients with diabetes and hypertension, a blood pressure target of <140/90 mmHg is recommended.	Strong	I
d. A systolic blood pressure target of <120 mmHg may be considered for patients with diabetes in whom prevention of stroke prioritised.	Weak	–
e. In patients with diabetes where treatment is being targeted to <120 mmHg systolic, close follow-up of patients is recommended to identify treatment related adverse effects including hypotension, syncope, electrolyte abnormalities and acute kidney injury.	Strong	–

Table 9.4 Recommendations for patients with hypertension and prior myocardial infarction

Patients with hypertension and previous myocardial infarction	Grade of recommendation	Level of evidence
a. For patients with a history of myocardial infarction, ACE inhibitors and beta-blockers are recommended for the treatment of hypertension and secondary prevention.	Strong	II
b. Beta-blockers or calcium channel blockers are recommended for symptomatic patients with angina.	Strong	II

9.5 Chronic heart failure

Chronic heart failure represents the final common pathway for various cardiac diseases and is a major healthcare burden across the globe. Hypertension is the leading risk factor for developing heart failure, and preventing heart failure is a large benefit associated with blood pressure lowering drugs. Hypertension is more common in patients with established heart failure with preserved left ventricular ejection fraction.

9.5.1 Drug choice

In patients with heart failure and systolic dysfunction or in patients with asymptomatic systolic dysfunction, ACE inhibitors are recommended for all patients.[125,167] Beta-blockers are also recommended for all patients with heart failure and systolic dysfunction, who remain mildly or moderately symptomatic, despite appropriate doses of ACE inhibitors.[125,168] In the trials that support the above recommendations, not all patients had hypertension therefore the benefits cannot solely be attributed to blood pressure lowering. ARBs are recommended only in patients who are intolerant of ACE inhibitor treatment.[125,167] This recommendation is further supported by a meta-analysis that reported ARBs as less effective in reducing total morbidity and mortality in comparison to ACE inhibitors.[169]

In a meta-analysis of differences between antihypertensive treatments heart failure was more likely to occur in those given calcium channel blockers compared to those given diuretics, ACE inhibitors or beta-blockers.[110] A network meta-analysis involving 223,313 patients published in 2011 also reported diuretics as the most effective class of drugs in preventing heart failure.[170]

There are no preferred drugs for the treatment of heart failure with preserved ejection fraction. Three randomised controlled trials evaluating the efficacy of angiotensin receptor blockade found no effect on all-cause mortality.[171–173]

9.5.2 Treatment targets

Systematic reviews or large trials evaluating blood pressure targets in patients with chronic heart failure are lacking. Studies of 'more versus less' intense treatment in patients with heart failure have compared combination therapy versus monotherapy against cardiovascular and all-cause mortality,[169, 173, 174] however it should be noted that participants may not have been hypertensive at baseline.

It should also be noted that many of the trials examining drug efficacy with heart failure include patients without hypertension. Intensive blood pressure lowering therapies are not associated with a reduction in all-cause mortality in this population. The largest benefit associated with blood pressure lowering is in prevention and delaying the onset of this debilitating and costly condition.

Table 9.5 Recommendations for patients with hypertension and chronic heart failure

Patients with hypertension and chronic heart failure	Grade of recommendation	Level of evidence
a. In patients with chronic heart failure, ACE inhibitors and selected beta-blockers* are recommended.	Strong	II
b. ARBs are recommended in patients who do not tolerate ACE inhibitors.	Strong	I

*Carvedilol; bisoprolol (beta-1 selective antagonist); metoprolol extended release (beta-1 selective antagonist); nebivolol

9.6 Peripheral arterial disease

Peripheral arterial disease describes narrowing and weakening affecting central and peripheral arteries (inclusive of the aorta and its peripheral branches). Peripheral arterial disease commonly affects the legs when exercising as less oxygen-rich blood reaches the legs and causes pain (intermittent claudication). Intermittent claudication is the most common symptom of peripheral arterial disease, although not present in all patients. In addition to leg pain, other symptoms may include foot wounds that will not heal and gangrene. Peripheral arterial disease results in a large number of hospital admissions and is associated with significant morbidity and mortality. Patients with peripheral arterial disease have almost three times the risk of a cardiovascular event and death.[175]

Hypertension is a common and important risk factor for peripheral arterial disease. It is reported that 2–5% of patients with hypertension have intermittent claudication and 25–55% of patients with peripheral arterial disease present with hypertension.[176] Given the co-existence of peripheral arterial disease and hypertension and the many overlapping risk factors and outcomes, reducing patients' overall cardiovascular risk in addition to targeting risk factors is important.

9.6.1 Drug choice and treatment targets

A 2013 systematic review of antihypertensive treatment in peripheral arterial disease assessed eight randomised trials with over 3,610 patients and reported that the evidence for various antihypertensive drugs is poor and it is unknown whether significant benefits outweigh the risk of treatment.[177] The Heart Outcomes Prevention Evaluation (HOPE) study included 1,715 patients with symptomatic peripheral artery disease (3,099 had an ABI <0.9) within a randomised controlled trial comparing ACE inhibitor and placebo.[177] Here the ACE inhibitor was associated with reduced incidence of cardiovascular death, myocardial infarction and stroke.

Despite the absence of data on blood pressure drug choice and treatment targets for patients with peripheral arterial disease, the overwhelming evidence on the benefit of lowering blood pressure suggests that lowering blood pressure in these patients is recommended. The inclusion criteria for the SPRINT trial included patients who had peripheral artery disease using a wide definition (revascularisation for peripheral artery disease or large abdominal aortic aneurysm or stenosis of the carotid or lower limb arteries). The proportion of included patients that met these inclusion criteria and their outcomes were unclear at the time of preparing these guidelines.

For a more detailed assessment and management of peripheral arterial disease, refer to the 2011 American College of Cardiology guidelines. [41]

Table 9.6 Recommendations for patients with hypertension and peripheral arterial disease

Patients with hypertension and peripheral arterial disease	Grade of recommendation	Level of evidence
a. In patients with peripheral arterial disease, treating hypertension is recommended to reduce CVD risk.	Strong	–
b. In patients with hypertension and peripheral arterial disease, any of the first-line antihypertensive drugs that effectively reduce blood pressure are recommended.	Weak	
c. In patients with hypertension and peripheral arterial disease, reducing blood pressure to a target of <140/90 mmHg should be considered and treatment guided by effective management of other symptoms and contraindications.	Strong	–

10 Treatment strategies for associated conditions

10.1 White-coat and masked hypertension

White-coat hypertension applies to untreated individuals and is a condition in which blood pressure measured in a clinical setting is usually at hypertensive levels but measured in non-medical setting is usually normal. Thus, ABPM or HBPM is necessary for the diagnosis of white-coat hypertension. When considering the management of patients with white-coat hypertension, more frequent follow-ups are recommended as these patients can progress to sustained hypertension[178] and have a higher CVD risk.[179] Furthermore, patients with white-coat hypertension have been shown to have a comparable risk of stroke to patients with sustained hypertension.[180]

Masked hypertension differs from white-coat hypertension in that blood pressure measured in a clinical setting is usually normal but measured in non-medical settings is usually hypertensive. It is termed 'masked' hypertension, as it is undetectable in the clinic. Individuals in whom the level of suspicion might be heightened would include clinically normotensive patients with evidence of end organ disease, regular heavy drinkers, smokers and patients with diabetes.[181] Increasing evidence supports the position that masked hypertension is associated with increased risk of cardiovascular events and mortality compared to true normotensives.[182–185] Thus, when suspected, patients should be carefully screened and considered for ABPM. As for white-coat hypertension, masked hypertension is reserved to define untreated individuals.

People with established white-coat and masked hypertension are at greater risk of developing sustained hypertension[178] and increased cardiovascular risk[179] however evidence for drug treatment improving outcomes is limited. A sub-group analysis from the Systolic Hypertension in Europe (Syst-Eur) trial found that drug treatment has less of an effect on blood pressure and cardiovascular outcomes in white-coat versus sustained hypertension,[186] however this finding was based on a small number of events.

Box 10.1 Practical recommendations for diagnosis and treatment of white-coat and masked hypertension

- Establish a diagnosis using ambulatory and/or home blood pressure monitoring
- In those with white-coat hypertension without additional risk factors lifestyle advice with frequent review is recommended.
- For those at high CVD risk, drug treatment may be considered in addition to lifestyle advice.
- In those with identified masked hypertension, drug therapy and lifestyle advice is recommended. These patients are reported to have increased CVD risk.[179, 182, 184, 187]

10.2 Older persons

Hypertension remains a risk factor for cardiovascular morbidity and mortality in older patients, however the balance of benefits and harms when considering antihypertensive drugs in this group are often reported as unclear. Many trials demonstrating the benefit of blood pressure lowering therapy do not involve older patients and, while these patients will benefit from reducing their risk of a cardiovascular event, intense treatment has the possibility of increasing adverse effects such as syncope and falls, that may counteract any benefit from blood pressure reduction. Here, two important trials investigating the efficacy of drug choice and treatment targets on age have been reviewed. These trials examined two different age groups, those over 65 years of age[75] and those over 80 years of age.[92]

10.2.1 Drug choice

There are many trials showing the beneficial effects of treatment in older patients using thiazide diuretics, beta-blockers, calcium channel blockers, ACE inhibitors or ARBs.[92, 93, 188–191] A prospective analysis from the BPLTTC compared the benefits of different antihypertensive therapies in those under and over 65 years of age and found no evidence that different classes are more or less effective in the younger versus older patients.[75]

10.2.2 Treatment targets

The Hypertension in the Very Elderly Trial (HYVET) compared the active treatment with placebo in 3,845 healthy patients ≥80 years of age with systolic blood pressures of ≥160/110 mmHg, and found evidence of benefit from active treatment. After a follow-up of 1.8 years, treating to a target blood pressure of <150/80 mmHg was associated with a 21% reduction in total mortality, a 34% reduction in any cardiovascular events and a 30% reduction in stroke.[92] Extending treatment by another year showed further benefit in cardiovascular and all-cause mortality compared to placebo.[192] A separate analysis of kidney function in this population suggested that low and high eGFR, (defined by >45 and ≥75 ml/min/1.73 m^2), may be associated with increased cardiovascular risk in this older population.[193] The SRRINT trial (refer to Box 6.1) has been the first large randomised trial to show clear benefit on cardiovascular and all-cause mortality by treating to a target of <120 mmHg, where tolerated.[3] The SPRINT authors reported a significant increase in adverse effects in patients treated to 120 mmHg systolic and thus should be used with caution.[3]

In summary, patients >75 years of age benefit from blood pressure lowering treatment independent of the drug class used and continue to benefit from blood pressure lowering therapy with systolic blood pressures targeting <120 mmHg associated with improved cardiovascular and all-cause mortality where tolerated.

Table 10.1 Recommendations for treatment of hypertension in older persons

Older persons with hypertension	Grade of recommendation	Level of evidence
a. Any of the first-line antihypertensive drugs can be used in older patients with hypertension.	Strong	I
b. When starting treatment in older patients, drugs should be commenced at the lowest dose and titrated slowly as adverse effects increase with age.	Strong	–
c. For patients >75 years of age, aiming towards a systolic blood pressure of <120 mmHg has shown benefit, where well tolerated, unless there is concomitant diabetes.	Strong	II
d. In older persons where treatment is being targeted to <120 mmHg systolic, close follow-up of patients is recommended to identify treatment-related adverse effects including hypotension, syncope, electrolyte abnormalities and acute kidney injury.	Strong	II
e. Clinical judgement should be used to assess the benefit of treatment against the risk of adverse effects in all older patients with lower grades of hypertension.	Strong	–

10.3 Pregnancy

Hypertension in pregnancy is defined as for those outside of pregnancy (≥140/90 mmHg). The Society of Obstetric Medicine of Australia and New Zealand reviewed hypertensive disorders in pregnancy and their 2014 guideline provides further information.[194]

10.4 Blood pressure variability

There is accumulating evidence to show visit-to-visit blood pressure variability and, to a lesser extent other variability parameters, are independent risk factors for adverse cardiovascular outcomes in high-risk patients.[195–197] In these reviews, the prognostic value of blood pressure variability was obtained from different sources including ABPM,[197] day-to-day variability assessed by home monitoring[196] and clinic visit-to-visit variability[195] and with-in visit variability.[198] Findings that blood pressure variability was associated with an increased risk of cardiovascular events were consistent across reviews.

This strengthening association between visit-to-visit blood pressure variability and increased risk of cardiovascular events leads one to question whether there is direct evidence for improved outcomes if variability is reduced. There is increasing literature that evaluates the effect of different antihypertensive drugs on blood pressure variability, however two systematic reviews that report the drug class effect and within class effects on variability of blood pressure on cardiovascular outcome are key.[199, 200] Webb et al demonstrated the effect of treatment on systolic blood pressure variation was correlated with the risk of stroke independently of differences in mean systolic blood pressure[199] and that nonselective beta-blockers increased the risk of stroke compared to B1-selective beta-blockers and other antihypertensive drugs.[200]

There are several interpretative and practical hurdles to overcome before assessment and treatment of variability can be incorporated into routine care. Firstly, randomised controlled trials demonstrating a direct reduction in cardiovascular events by reducing blood pressure variability, independent of other risk factors are lacking. Secondly, visit-to-visit variability is difficult to assess accurately in the clinic. Therefore, the clinical applicability of reducing variability to improve patient outcomes remains a research issue. Further work is required to identify what level of variability warrants attention, how variability can be incorporated accurately into absolute CVD risk and development of accurate ways in which blood pressure variability can be assessed within the clinical setting.

Table 10.2 Recommendations for patients with hypertension and suspected blood pressure variability

Patients with hypertension and suspected blood pressure variability	Grade of recommendation	Level of evidence
a. For high-risk patients with suspected high variability in systolic blood pressure between visits, a focus on lifestyle advice and consistent adherence to medications is recommended.	Strong	I
b. Drug therapy should not be selected based on reducing blood pressure variability per se but in accordance with current recommendations, which already prioritise the most effective medications.	Strong	

10.5 Treatment-resistant hypertension

Treatment-resistant hypertension is defined as systolic blood pressure of >140 mmHg in a patient taking three or more antihypertensive drugs, including a diuretic, at optimal tolerated doses. Poor compliance with therapy and white-coat hypertension should be ruled out. Secondary causes for hypertension should also be considered and specialist review may be required to address some of these issues.

It is estimated that 20–30% of patients treated for hypertension have uncontrolled blood pressure, however the true prevalence of resistant hypertension is estimated at 8–18%.[179, 201] Treatment-resistant hypertension increases the risk of developing left ventricular hypertrophy, microalbuminuria, kidney failure and coronary artery disease. Treatment-resistant hypertension further amplifies its effect in those patients with co-morbidities. For example, a trial of more than 10,000 participants with coronary artery disease found that treatment resistant hypertension was associated with up to a 73% increase in myocardial infarction and a 45% increase in mortality compared to patients with coronary artery disease and controlled hypertension.[202, 203]

Specialist referral is recommended if blood pressure remains elevated despite maximal tolerated doses of three antihypertensive drugs and patients have been reassessed for non-adherence, secondary hypertension, hypertensive effects of other drugs, sleep apnoea, undisclosed use of alcohol or recreational drugs and high salt intake.

Few drugs are specifically targeted at resistant hypertension, however, under specialist advice with careful consideration to blood potassium levels, spironolactone can be used as an add-on drug.[31] Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery, or renal denervation, is an invasive catheter-based technique, carried out using local anaesthesia, whereby the neurogenic reflexes involved in blood pressure control are disrupted (ablation). Renal denervation (as it is commonly known) is currently being investigated as a treatment option for some patients with treatment-resistant hypertension.

The current evidence for the efficacy of renal denervation for treatment-resistant hypertension is variable and derived from a limited number of patients and studies. Three key publications provide the main evidence. Symplicity HTN-2 was an open-labelled randomised control trial of 106 patients with resistant hypertension that found a blood pressure reduction of 33/11 mmHg (SD 17/11) with renal denervation after 6 months compared to controls.[204] While the larger trial, Symplicity HTN-3, involving 535 patients found no additional reduction in blood pressure after renal denervation compared to sham procedure,[205] a secondary analysis suggests that patient and procedural factors, together with varying numbers of ablations, may explain the findings.[206] The impact of careful medical management has been suggested to be superior to renal denervation in one small randomised trial.[207] To date, the most rigorously conducted study found renal denervation was not effective in patients with treatment-resistant hypertension or lower grades of hypertension.[206]

Table 10.3 Recommendations for the use of renal denervation in treatment resistant hypertension

Patients with treatment resistant hypertension	Grade of recommendation	Level of evidence
a. Optimal medical management with a focus on treatment adherence and excluding secondary causes is recommended.	Strong	II
b. Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery is currently not recommended for the clinical management of resistant hypertension or lower grades of hypertension.	Weak	II

10.6 Obstructive sleep apnoea

There is a well-documented association between obstructive sleep apnoea and hypertension. Obstructive sleep apnoea appears to be responsible for a large proportion of blood pressure increase or absence of reduction at night-time, and is now acknowledged as a frequent and modifiable cause of resistant hypertension. While such an association may be mediated by coexisting risk factors, such as obesity, a large body of evidence supports an independent role of obstructive sleep apnoea in the pathogenesis of daytime hypertension.[208]

Prevalence of hypertension in obstructive sleep apnoea patients ranges from 35% to 80% and appears to be influenced by obstructive sleep apnoea severity. Approximately 40% of patients with hypertension and up to 80% of patients with resistant hypertension are diagnosed with obstructive sleep apnoea.[209] The diagnosis of obstructive sleep apnoea is based on the composite of symptoms, clinical findings and an overnight recording of sleep and breathing parameters. More detail can been found in the 2014 Obstructive Sleep Apnoea in Adults: a clinical practice guideline from the American College of Physicians[210] and from the Australasian Sleep Association (www.sleep.org.au). The impact of suspected or confirmed obstructive sleep apnoea on blood pressure is best assessed by an ABPM showing abnormalities during the night.

A few prospective studies have linked severe obstructive sleep apnoea to fatal and nonfatal cardiovascular events and all-cause mortality. The association appears to be closer for stroke than heart disease and to be weak with obstructive sleep apnoea of mild-to-moderate severity.[208]

There is currently no good evidence to recommend a specific antihypertensive drug class that may demonstrate superior antihypertensive efficacy in patients with obstructive sleep apnoea. Management includes lifestyle changes and continuous positive air pressure therapy (CPAP).

A 2014 study has shown that weight loss achieves similar blood pressure reduction to CPAP therapy and additive effects when treatments are combined.[211] Reduction of alcohol intake and exercise may also help to reduce apnoea severity and its blood pressure effects.

CPAP therapy has clearly been shown to reduce symptoms and severity of obstructive sleep apnoea. The impact of CPAP therapy for obstructive sleep apnoea on blood pressure levels has been investigated in patients with and without hypertension. Four meta-analyses of studies of CPAP therapy in obstructive sleep apnoea have been published in recent years.[212–215] Collectively, these trials included 1,876 participants and have associated CPAP therapy with reductions in systolic and diastolic blood pressure. A 2014 systematic review and meta-analysis[215] included 31 randomised controlled trials that compared CPAP with either passive or active treatment. In a random-effects meta-analysis vs passive treatment (29 trials and 1,820 subjects) they observed a significant difference of 2.6±0.6 mmHg and 2.0±0.4 mmHg in systolic and diastolic blood pressure, in favour of treatment with CPAP.[215]

Despite the varying methodologies in the above studies, the overall findings are consistent in that CPAP therapy results in a significant, but small, reduction of blood pressure, which is most pronounced in patients with severe obstructive sleep apnoea that regularly use CPAP and who have pre-existing hypertension.

Table 10.4 Summary of effective antihypertensive drugs for clinical conditions

Clinical condition	Inclusive of	Effective antihypertensive drugs
Stroke and TIA	Ischaemic stroke Cerebral haemorrhage TIA	Any of the first-line drugs that effectively reduce blood pressure: ACE inhibitors, ARBs*, calcium channel blockers or thiazide diuretics
Chronic kidney disease	Diabetic nephropathy Glomerulonephritis Hypertensive kidney disease	Any of the first-line drugs that effectively reduce blood pressure: ACE inhibitors or ARBs*, calcium channel blockers and thiazide diuretics
	Presence of proteinuria defined as PCR 3500 mg/g†	ACE inhibitor or ARB*
Diabetes	Diabetes and >60 years of age Diabetes and microalbuminuria urinary albumin/creatinine ratio 32.0 mg/mmol (males) 32.5 mg/mmol (females)	Any of the first-line drugs that effectively reduce blood pressure: ACE inhibitors, ARBs*, calcium channel blockers or thiazide diuretics
Ischaemic heart disease	Myocardial infarction Angina	Remodelling: ACE inhibitor or ARB* and calcium channel blockers Rate control: beta-blocker (except oxprenolol, pindolol)
Chronic heart failure	Preserved ejection fraction	Beta-blocker, ACE inhibitor or ARB* (for those that do not tolerate ACE inhibitors)
Peripheral arterial disease	ABI <0.9	Any of the first-line drugs that effectively reduce blood pressure: ACE inhibitors, ARBs*, calcium channel blockers or thiazide diuretics
Treatment resistant hypertension		Any drug combination that effectively reduces blood pressure
Older patients		Any of the first-line drugs that effectively reduce blood pressure: ACE inhibitors, ARBs*, calcium channel blockers or thiazide diuretics
Pregnancy		Refer to Society of Obstetric Medicine of Australia and New Zealand.[194]

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ABI, ankle brachial index

*In head-to-head trials, ACE inhibitors and ARBs are equally effective in blood pressure reduction and prevention of cardiovascular events overall, however may have important differences in their efficacy, so that they are not interchangeable, in some clinical conditions. †Value for ratio where albumin or total protein is measured in mg/L and creatinine is measured in mmol/L. Reference range will differ where laboratories report creatinine level expressed in µmol/L.

11 Strategies to maximise adherence

Patients who adhere to treatment regimens are three times more likely to achieve blood pressure targets and have reduced cardiovascular events compared to patients who are less adherent.[216]

There is no single intervention to improve adherence. A 2015, retrospective analysis of observational studies involving 9,725 patients found that the answer to "Do you recall not having taken your medicines over the last four weeks?" was an independent predictor of blood pressure control.[217] This question can be integrated into routine clinical practice and used to quickly evaluate a patient's adherence. An Australian-based trial, Hypertension Adherence Program in Pharmacy (HAPPy), found increased adherence and greater reduction in systolic blood pressure with a guided intervention package that included blood pressure monitoring, training on self-measurement, motivational interviewing, a review of medication efficiency and prescription refill reminders.[218]

Table 11.1 Strategies to maximise adherence to treatment plan

Communication	
• Express empathy. • Treat patient as a partner in management decisions. • Assess patient's expectations of treatment.	• At each visit, ask the patient, "Do you recall not having taken your medicines over the last four weeks?" • Discuss consequences of non-adherence (i.e. stroke, accelerated hypertension).
Tailoring advice	
• Discuss treatment options and agree on an initial plan. • Provide specific, written instructions and education materials. • Involve the patient's family or carer in the management plan.	• Use self-measurement of blood pressure for monitoring, where appropriate. • Consider referral for a Home Medicines Review. • Evaluate the social and economic barriers that may affect medication supply and storage. • Ensure the patient accepts the possibility of their specific therapy's side effects.
Maintaining motivation	
• Explain the risks and benefits of treatment, and risks of not treating. • Clearly explain that drug treatment may be lifelong. • Reassure the patient about their prognosis and the ability to lead a normal life.	• Address quality of life issues including any new symptoms or side effects of treatment. • Address psychosocial factors that may limit adherence (i.e. manage depression if present*). • Reinforce lifestyle advice at follow-up visits. • Establish a long-term relationship between the patient and practitioner.

*The National Heart Foundation has developed a depression screening tool for patients with coronary artery disease which is available at www.heartfoundation.org.au.

12 Managing other cardiovascular risk factors

12.1 Lipid-lowering drugs

In primary prevention, combining a lipid-lowering drug with blood pressure lowering drugs has been shown to provide greater protection from cardiovascular events.[219, 220] The lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial[219] found the addition of a statin to antihypertensive therapy reduced the incidence of the primary cardiovascular outcomes and this effect was more marked in patients on amlodipine-based therapy compared to atenolol-based therapy. Collectively, the data suggest that statins provided added benefit to patients with hypertension stratified at high absolute CVD risk. In Australia, lipid-lowering therapy is recommended in patients without prior cardiovascular events stratified at moderate to high absolute CVD risk, treating to an LDL cholesterol target of <2.0 mmol/L.[13]

In secondary prevention, stains are beneficial in patients with:

- coronary heart disease where statins therapy is recommended to achieve LDL cholesterol levels <1.8 mmol/L[221]
- post-stroke where statin therapy is recommended for all patients post ischaemic stroke or TIA (not used routinely for haemorrhagic stroke)[222]
- heart failure patients where statin therapy is also recommended to reduce risk of ischaemic events and subsequent chronic heart failure in those not contraindicated[165]
- diabetes, where statin therapy is recommended to achieve LDL cholesterol target of <1.8 mmol/L.[223]

12.2 Antiplatelet therapy

While the beneficial role of antiplatelet therapy is well established for secondary prevention,[224] a benefit in outcome compared to the risk of bleeds is less established for primary prevention. This guideline therefore confirms previous recommendations that aspirin should be considered for secondary prevention of cardiovascular events and for those at high risk of an event with well-controlled blood pressure.[225] Aspirin is not recommended for CVD prevention in patients with hypertension at low-moderate risk, where harms may outweigh benefits.

Table 12.1 Recommendation for patients with hypertension requiring antiplatelet therapy

Antiplatelet therapy for patients with hypertension	Grade of recommendation	Level of evidence
a. Antiplatelet therapy, in particular low-dose aspirin, is recommended in patients with hypertension and previous CVD events unless bleeding risk is increased.	Strong	I

13 Monitoring responses to drug treatment

13.1 Follow-up of patients with hypertension

After starting therapy, patients should be reviewed at 4–6 week intervals to evaluate adherence, adverse effects, tolerability and efficacy. For patients with significantly elevated baseline blood pressure, shorter reviews times may be considered.

Electrolytes and creatinine should be measured at baseline and then 2 weeks after commencing therapy in people at high risk of changes in kidney function. This is to ensure detection of hyperkalaemia or dramatic changes in kidney function.

Once blood pressure has stabilised, the interval between visits can be lengthened to 3–6 months.[226] Once blood pressure is stable, there is no evidence that true blood pressure changes within a 12-month period,[227, 228] however reviews every 6 months allow for reinforcement of lifestyle changes, assessment of new risk factors, a review of medication adherence and repeat prescriptions. For patients who remain on treatment, an annual investigation for additional risk factors or end organ damage should be considered.

13.2 Withdrawing drug therapy

Antihypertensive therapy is usually considered lifelong unless the diagnosis is in doubt or the patient requests a trial cessation of treatment due to significant lifestyle modifications. Withdrawal should not be considered in patients at high CVD risk and/or those with associated clinical conditions such as stroke, diabetes or chronic kidney disease. Withdrawal can be considered in some patients. If long-term effective antihypertensive therapy is withdrawn, patients need ongoing regular blood pressure monitoring and recommencement of drug therapy if blood pressure increases. The timing of a rise in blood pressure following withdrawal of effective antihypertensive therapy is unpredictable and may be delayed for weeks to months.

Successfully maintaining desired targets after stopping therapy is more likely in those of a younger age, previously on a single antihypertensive drug, with lower pre-treatment blood pressure and willingness to accept and maintain lifestyle modifications. Furthermore, there is evidence to suggest that team-based care involving practice nurses and allied health professionals can reduce blood pressure more effectively than standard clinic care alone.[229]

14 Patients' perspectives

Poor daily adherence to antihypertensive drugs is a key contributor to the inability to achieve target blood pressure. About half of all Australian patients taking antihypertensive drugs discontinue treatment by 24 months and approximately 19% do not collect a second prescription.[230] Understanding a patient's perspective on living with hypertension and their experience with medications can aid adherence.

There are several established factors related to the patient's health condition that may negatively impact adherence, including:

- the severity of the diagnosed hypertension
- co-morbidities
- lack of physical symptoms
- duration of the treatment
- frequent changes in treatment
- complexity of the regimen
- stress
- time
- the financial burden of buying prescriptions.

For a more in-depth review, refer to the National Heart Foundation's 'Improving adherence in cardiovascular care toolkit'.[231]

In 2012, a systematic review involving 53 studies from 16 countries assessed patients' understanding of the cause of their hypertension and their perspectives on taking antihypertensive drugs.[232] The authors found that non-adherence to treatment was often a result of a patient's misunderstanding of the causes of hypertension; there was a common belief that stress or symptoms are the key markers of raised blood pressure. Patients intentionally adjusted their dose or skipped their medication without consulting their doctor for a range of reasons including disliking taking drugs, a fear of addiction or tolerance and adverse effects. Interestingly, the beliefs were similar across ethnic and geographical groups suggesting that ethnic-specific interventions around adherence may not be beneficial.[232] The authors suggested that to improve adherence, clinicians should determine a patients' understanding of the causes of hypertension, explain the lack of symptoms (silent disease) and address any concerns about adverse effects. The 2011 UK hypertension guidelines developed recommendations based on patients' perspectives by reviewing transcripts from 40–50 peoples' experience of being diagnosed, treated and educated about hypertension.[31] The recommendations include:

- Provide appropriate guidance and materials about the benefits of drugs and adverse effects to help people make informed choices.
- People vary in their attitudes to their hypertension and the experience of treatment. It may be helpful to provide details of organisations that provide useful information and opportunities to share patient experiences.
- Provide appropriate review of care to monitor blood pressure, symptoms and medication, and provide lifestyle advice.[31]

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Appendix 1

Summary of clinical questions (with search terms)

1. What is the best method to measure blood pressure (BP) (traditional technique/automated) in adults (home vs ambulatory vs office) to predict the development of cardiovascular disease (CVD)* events and mortality resulting from elevated BP?
2. In adults with treated primary hypertension, what is the impact of different frequencies of BP monitoring (within clinic; ambulatory blood pressure monitoring; self-measurement at home) to assess response to treatment and to predict CVD* events and mortality?
3. What is the evidence that BP lowering therapy (as opposed to no BP lowering therapy) prevents CVD events among adults, with BP <140/90 mmHg and no prior CVD events, who are stratified high absolute CVD risk†?
4. What is the evidence that BP lowering therapy prevents CVD events among adults with mild hypertension (Grade1) and no prior CVD events who are stratified at high/moderate (>10%) absolute CVD risk†?

a. Does increased BP variability add to CVD risk prediction over and above BP pressure alone?

b. Does a reduction of BP variability in adults prevents CVD* events and mortality?

5. In adults with hypertension does a class[es] of BP lowering therapy (fixed dose or combination therapy) compared to another class[es] of BP lowering therapy (fixed dose or combination therapy) result in a) clinically different BP control and b) prevention of CVD* events and mortality?
6. In adults with hypertension and existing co-morbidities (stroke, chronic kidney disease, diabetes, peripheral artery disease, myocardial infarction and chronic heart failure) does aclass[es] of BP lowering therapy (fixed dose or combination therapy) compared to another class[es] of BP lowering therapy (fixed dose or combination therapy) result in a) clinically different BP control and b) prevention of CVD* events and mortality?
7. What is the evidence that lower BP targets compared to standard BP targets prevents CVD* events and mortality with acceptable tolerability among adults with hypertension and co-morbidities (post stroke, chronic kidney disease, diabetes, peripheral artery disease, myocardial infarction and chronic heart failure)?
8. In adults with resistant hypertension, does renal denervation in addition to standard medical therapy compared to medical therapy alone improve BP control?

*CVD – A term used to describe a variety of heart diseases, illnesses, and events that impact the heart and circulatory system, including high blood pressure and coronary artery disease.

†Absolute CVD risk – The likelihood of a person experiencing a cardiovascular event within the next five years. Risk is calculated as a percentage, using the Framingham Risk Equation and is stratified into low (<10%), moderate (10–15%) and high risk (>15%).

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