ABC of Hypertension

SIXTH EDITION

D. Gareth Beevers, Gregory Y. H. Lip and Eoin O`Brien

WILEY Blackwell

www.abcbookseries.com

BMJ|Books

ABC of

Hypertension

Sixth Edition

ABC series

An outstanding collection of resources for everyone in primary care

The *ABC* series contains a wealth of indispensable resources for GPs, GP registrars, junior doctors, doctors in training and all those in primary care

- **Highly illustrated, informative and a practical source of knowledge**
- **An easy-to-use resource, covering the symptoms, investigations, treatment and management of conditions presenting in day-to-day practice and patient support**
- **Full colour photographs and illustrations aid diagnosis and patient understanding of a condition**

For more information on all books in the *ABC* series, including links to further information, references and links to the latest official guidelines, please visit:

www.abcbookseries.com

WILEY Blackwell

BMJ | Books

ABC of

Hypertension

Sixth Edition

D. Gareth Beevers
Emeritus Professor of Medicine,
University Department of Medicine,
City Hospital,
Birmingham,
UK

Gregory Y. H. Lip
Professor of Cardiovascular Medicine
University of Birmingham Centre for Cardiovascular Sciences,
City Hospital,
Birmingham
UK

Eoin O'Brien
Professor of Molecular Pharmacology,
The Conway Institute,
University College Dublin,
Ireland

WILEY Blackwell

BMJ Books

This edition first published 2015, © 1981, 1987, 1995, 2001, 2007 by John Wiley & Sons Ltd.

BMJ Books is an imprint of BMJ Publishing Group Limited, used under licence by John Wiley & Sons.

Registered Office
John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Offices
9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com/wiley-blackwell

Library of Congress Cataloging-in-Publication Data is applied for.

ISBN 978-0-470-65962-5

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Set in 9.25/12pt Minion by SPi Publisher Services, Pondicherry, India

1 2015

Contents

Preface

The first edition of the *ABC of Hypertension* was published in 1981. It arose out of a series of review articles published in the *British Medical Journal*. The first, starting in 1979, was a set of reviews called the *ABC of Blood Pressure Measurement* from Dublin. This was followed by the *ABC of Blood Pressure Reduction* from Birmingham. Since that time, there have been many advances in our understanding of high blood pressure, its causes and consequences as well as its treatment. One of the major advances in hypertension research and treatment has been a greater understanding of the epidemiology of high blood pressure. Whilst there is no doubting the importance of genetic influences in the causes of hypertension, it is clear that environmental and lifestyle factors are of prime importance, if only because of their potential reversibility. It is now generally accepted that the health of the nation can be advanced by an improvement of the nation's diet with less salt, fat and sugar. That understanding was not part of our thinking in 1981.

The drug treatment of hypertension has been one of the greatest advances in cardiovascular medicine since the Second World War. There have been a great many excellent long-term randomised controlled trials that have shown clearly that lowering blood pressure saves lives. The Hypertension in the Very Elderly Trial (HYVET) published in 2008 is a landmark as it will probably be the last placebo-controlled trial in hypertension. We now know who to treat; the next generation of trials will, one hopes, give us more information on how to treat.

In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) has provided well-researched guidelines on the optimum management of hypertension. Whilst we have been influenced by the NICE guidelines, as well as the American and European guidelines, we have sometimes deviated from their views.

The prime importance of the accurate measurement of blood pressure, and in particular the primacy of 24-h ambulatory blood pressure monitoring (ABPM) in assessing cardiovascular risk, has been a feature of hypertension research and treatment over the last 32 years. The NICE guideline published in 2011 acknowledged that there was sufficient evidence to recommend ABPM for all patients suspected of having hypertension on the grounds that its use in clinical practice would save patients being prescribed antihypertensive drugs unnecessarily for the treatment of transient elevation of blood pressure in patients with white coat hypertension. As a result, ABPM needs to be provided for a large number of patients in clinical practice and the measurement section of this edition reflects this recommendation.

The *ABC of Hypertension* is written to aid the management of hypertension everywhere and not just in the United Kingdom. We have been delighted that there have been Turkish, Polish and Spanish translations of our previous editions.

Predictions in medicine are often proved misleading, so we have opted to avoid making them. It will be interesting to see what our seventh edition will emphasise in a few years time.

D. Gareth Beevers
Gregory Y. H. Lip
Eoin O'Brien

CHAPTER 1

The prevalence and causes of hypertension

OVERVIEW

- The distribution of blood pressure in the general population is as a continuous variable forming a roughly normal of 'Gaussian' curve, with no clear dividing lines between low, normal or high readings.
- The dividing lines above which an individual is considered to have hypertension are pragmatic, based on the results of the many placebo-controlled trials of antihypertensive drug therapy.
- From a practical point of view, blood pressures of 140/90 mm Hg or more are considered to be raised and some individuals whose pressures are persistently in this range would be considered to require drug treatment.
- The prevalence of 'clinical' hypertension increases with advancing age. Five to ten percent of teenagers have a blood pressure of 140/90 mm Hg or more at first screening. At the age of 80 years, this figure rises to a 70–75%.
- Average blood pressures and the prevalence of hypertension are higher in people of African origin in Western countries. Hypertension is rapidly becoming commoner in all developing countries.
- In about 5% of all hypertensives, underlying renal or adrenal diseases are identifiable (secondary hypertension). In the remaining 95%, no underlying cause can be found (essential or primary hypertension).
- Essential hypertension runs in families and part of this tendency is related to genetic factors. No single gene is related to essential hypertension; to date, around 27 candidate genes have been investigated, but they only explain a 1–2 mm Hg variation in blood pressure.
- Several lifestyle factors are implicated in the causation of hypertension. These include obesity, heavy alcohol consumption, a low intake of fruit and vegetables and lack of exercise.
- The most important lifestyle factor causing hypertension is a diet with a high salt content as is common in almost all developing countries.

Blood pressure in populations

In the population, blood pressure is a continuous, normally distributed variable. No separate subgroups of people with and without hypertension exist. A consistent continuous gradient exists between usual levels of blood pressure and the risk of coronary heart disease and stroke, and this gradient continues down to blood pressures that are well below the average for the population (Figure 1.1). Above blood pressures of 115/70 mmHg, the risk of developing cardiovascular events doubles for every 20/10mmHg rise in blood pressure. This means that much of the burden of renal disease and cardiovascular disease (CVD) related to blood pressure can be attributed to blood pressures within the so-called 'normotensive' or average range for Western populations. Most cardiovascular events are therefore blood pressure-related rather than hypertension-related.

The main concern for clinicians is what level of blood pressure needs drug treatment. The pragmatic definition of hypertension is the level of blood pressure at which treatment is worthwhile. This

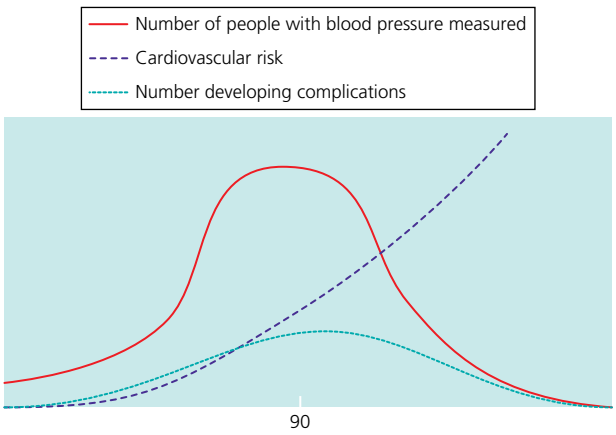


Figure 1.1 The distribution of diastolic blood pressure in the general population, the risk of cardiovascular disease (CVD) and the number of people who develop CVD.

ABC of Hypertension, Sixth Edition. D. Gareth Beevers, Gregory Y. H. Lip and Eoin O'Brien.

level varies from patient to patient and balances the risks of untreated hypertension in different types of patients and the known benefits of reducing blood pressure, while taking into account the disadvantages of taking drugs and the likelihood of side effects.

Hypertension: a disease of quantity not quality

'In an operational sense, hypertension should be defined in terms of a blood pressure level above which investigation and treatment do more good than harm.' Grimley Evans J, Rose G. Hypertension. Br Med Bull1971;27:37–42

Systolic blood pressure continues to rise with advancing age, so the prevalence of hypertension (and its complications) also increases with age. By contrast, diastolic pressures tend to level off at the age of about 50 years and tend to decline thereafter (Figure 1.2).

Hypertension thus is as much a disorder of populations as of individual people. Globally, high blood pressure and its vascular consequences, heart attack and stroke, account for more deaths than any other common medical condition and is a major burden of disease (Figure 1.3).

As hypertension is the most important risk factor for CVD, achievement of a universal target systolic blood pressure of 140 mm Hg or less should produce a reduction of 28–44% in the incidence of stroke and 20–35% of coronary heart disease. This could prevent about 21 400 deaths from stroke and 41 400 deaths from coronary heart disease in the United Kingdom each year. It would also mean about 42 800 fewer fatal and nonfatal strokes and 82 800 fewer coronary heart disease events per year in the United Kingdom alone. Globally, as hypertension is becoming more common, coronary heart disease and stroke correspondingly are becoming common, particularly in developing countries.

A recently published analysis of pooled data from different regions of the world estimated the overall prevalence and absolute burden of hypertension in 2000 and the global burden in 2025. Overall, 26.4% of the adult population in 2000 had hypertension and 29.2% were projected to have this condition by 2025. The estimated total number of adults with hypertension in 2000 was 972 million: 333 million in economically developed countries and 639 million in economically developing countries. The number of adults with hypertension in 2025 is thus predicted to increase by about 60% to a total of 156 billion.

The development of hypertension reflects a complex and dynamic interaction between genetic and environmental factors. In some primitive communities in which obesity is rare and salt intake is low, hypertension is virtually unknown, and blood pressure does not increase with advancing age.

Studies have investigated Japanese people migrating from Japan to the west coast of America. In Japan, high blood pressure is common and the incidence of stroke is high, but coronary heart disease is rare. When Japanese people migrated across the Pacific Ocean to California, a reduction in the prevalence of hypertension and stroke was seen, but the prevalence of coronary heart disease (CHD) increased. These studies strongly suggest that, although racial differences exist in the predisposition to hypertension, environmental factors still play a significant role.

The United Kingdom also has a pronounced north–south gradient in blood pressure, with pressures higher in the north of the country. Studies that compare urban and rural populations in African populations also show clear differences in blood pressure between urban and rural societies with the same genetic composition.

In the United Kingdom, hypertension accounts for approximately 12% of Primary Care consultation episodes and approximately £1 billion in drug costs in 2006. The diagnosis, treatment and follow-up of patients with hypertension is one of the most common interventions in primary care, particularly since the National Service Frameworks for CVD prevention includes routine screening for hypertension.

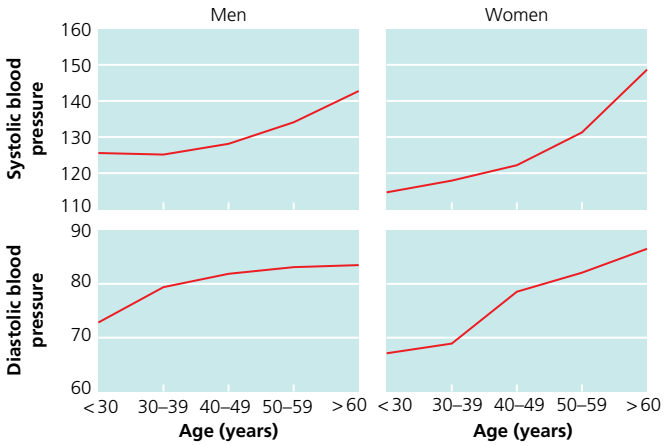


Figure 1.2 Average systolic and diastolic blood pressures in men and women in the Birmingham Factory Screening Project. This figure excludes 165 patients who were receiving antihypertensive drugs. Source: Reproduced with permission from Lane, D.A., *et al*. (2002) *Journal of Human Hypertension*, 16, 267–273.© Nature Publishing.

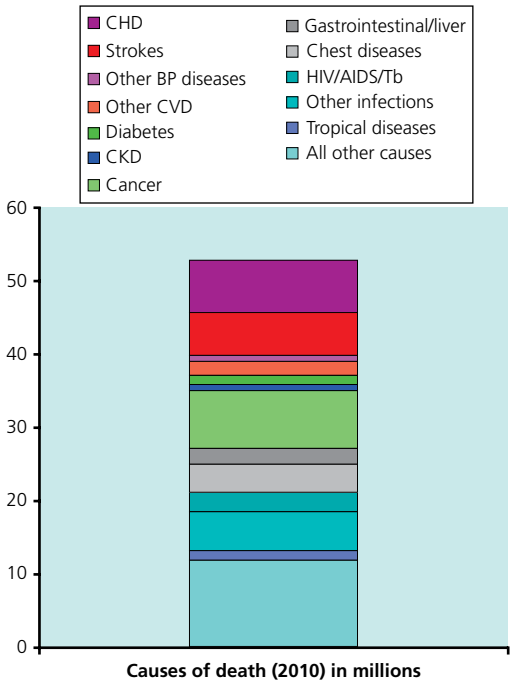


Figure 1.3 Worldwide causes of death in 2002 in millions. CKD: chronic kidney disease. Source: Adapted from Mackay, J., & Mensah, G.A. (2004) *The Atlas of Heart Disease and Stroke*. World Health Organisation, Geneva.

Prevalence

Depending on age, in up to 5% of people with hypertension in the general population depends on the arbitrary criteria used for its definition, as well as the population studied. In 2853 participants in the Birmingham Factory Screening Project, the odds ratios for being hypertensive after adjustment for age were 1.56 and 2.40 for African-Caribbean men and women, respectively, and 1.31 for South Asian men compared with Europeans (Table 1.1).

The Third National Health and Nutrition Examination Survey 1988–91 (NHANES III) showed that 24% of the adult population in the United States, which represents more than 43 million people, have hypertension (>140/90 mm Hg or receiving treatment for hypertension). The prevalence of hypertension varied from 4% in people aged 18–29 years to 65% in people older than 80 years. Prevalence is higher among men than women, and the prevalence in African-Americans is higher than in Caucasians and Mexican-Americans (32.4, 23.3 and 22.6%, respectively). Most cases of hypertension in young adults result from increases in diastolic blood pressure, whereas in elderly people, isolated increases in systolic blood pressure are more common and account for 60% of cases of hypertension in men and 70% in women (Figure 1.4). Hypertension generally affects ≤10% of the population up to the age of 34 years. By the age of 65, however, more than half of the population has hypertension.

Table 1.1 The prevalence of hypertension (≥160/95) in three ethnic groups in the Birmingham Factory Screening Project. Insufficient numbers of South Asian women were examined to provide meaningful prevalence rates

Population	Men (%)	Women (%)
African-Caribbean	30.8	34.4
European	19.4	12.9
South Asian	16.0	—

Source: Data from Lane, D.A., *et al*. (2002) *Journal of Human Hypertension*, 16, 267–273.

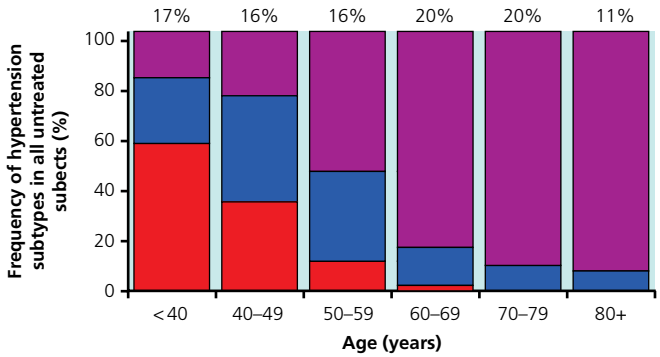


Figure 1.4 Frequency distribution of untreated hypertensive individuals by age and hypertension subtype. Numbers at the top of bars represent the overall percentage distribution of all subtypes of untreated hypertension in that age group. Purple boxes, isolated systolic hypertension (ISH, SBP ≥140 mm Hg and DBP <90 mm Hg); Blue boxes, systo-diastolic hypertension (SDH, SBP ≥140 mm Hg and DBP ≥90 mm Hg), Red boxes, isolated diastolic hypertension (IDH, SBP <140 mm Hg and DBP ≥90 mm Hg). Source: Reproduced with permission from Franklin, S.S., *et al*. (2001) *Hypertension*, 37, 869–874. © Lippincott Williams & Wilkins.

In the Health Survey for England, hypertension (systolic BP ≥ 140 mm Hg and/or Diastolic BP ≥ 90 mm Hg) was found to be prevalent in roughly 20% of 30–32-year olds, 30% of 30–40 year olds, 40% of 40–50 year olds and so on (Figure 1.5).

Incidence

Few data are available on the incidence of new onset hypertension. The incidence of hypertension does increase sharply with age, with higher rates in men.

Follow up of people in the Framingham Heart Study after 30 years found that the 2-year incidence of new onset hypertension increases from 3.3% in men and 1.5% in women aged 30–39 years to 6.2% in men and 8.6% in women aged 70–79 years. People with 'high-normal' blood pressure at first examination were at greater risk of developing sustained hypertension over the ensuing years (Figure 1.6). Some authorities argue controversially that people

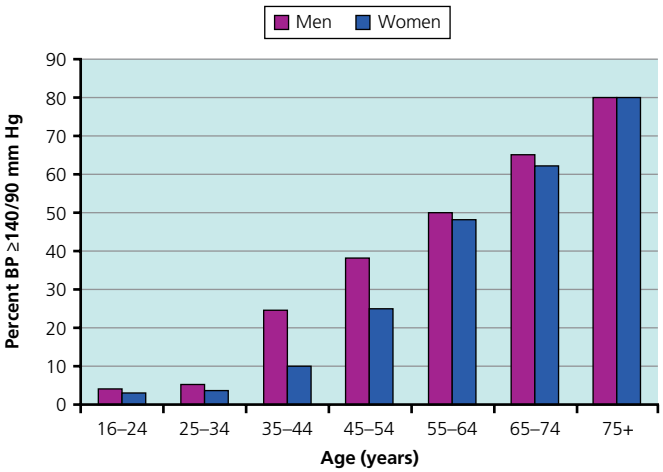


Figure 1.5 The prevalence of hypertension in England 2010. Health Survey for England. Source: Adapted from McCormack, T., *et al*. (2013) *British Journal of Cardiology*, 20 (Suppl 1), S3–S15. © Health and Social Care Information Centre.

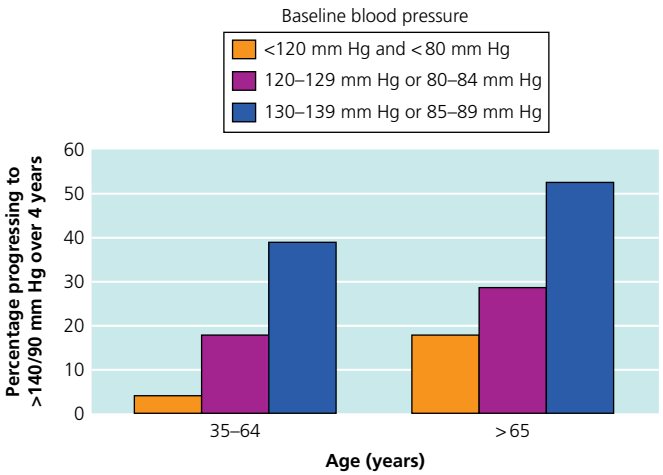


Figure 1.6 Progression to develop new-onset hypertension in the Framingham Heart Study. Source: Reproduced with permission from Vasan, R.S., *et al*. (2001) *Lancet*, 358, 1682–1686. © Elsevier.

with high-normal blood pressure should be classified or labelled as 'pre-hypertensive'.

'High-normal' blood pressure is one of the strongest predictors for the later development of hypertension. At the individual level, however, blood pressure in childhood is poorly predictive of later levels of blood pressure or the risk of hypertension.

Factors affecting population blood pressure

Age

In western societies, blood pressure increases with increasing age, and people with high baseline blood pressures have a faster increase than those with normal or below average pressures. In rural non-Westernised societies, however, hypertension is rare, and the increase in pressure with age is much smaller. The level of blood pressure accurately predicts coronary heart disease and stroke at all ages, although in very elderly people, the relation is less clear. This may be because many people with increased blood pressures have died and those with lower pressure may have subclinical or overt heart disease that causes their blood pressure to decrease.

Ethnic origin

People of African origin have been studied well in North America, but whether these data can be fully applicable to the African-Caribbean populations in the United Kingdom or similar populations in Africa or the West Indies is uncertain. Almost all studies of people of African origin from urban communities, however, show a higher prevalence than in Caucasian people (Tables 1.1 and 1.2). Yet, hypertension is rare in black people who live in rural Africa. Whether any particular level of blood pressure carries a worse prognosis in people of African origin or whether survival is much the same as in people of European origin but with more strokes and fewer heart attacks is uncertain.

Even when correction is made for obesity, socioeconomic and dietary factors, ethnic factors remain in the predisposition to hypertension. These differences are probably related to ethnic differences in salt sensitivity and handling. There is little evidence to show that people of African origin in the United Kingdom and United States consume more salt than people of European origin. There is evidence that salt loading raises blood pressure more in people of African origin and that salt restriction is more beneficial (Figure 1.7). These differences in salt sensitivity may also be related to the finding that plasma levels of renin and angiotensin in African-American people are about half those in Americans of European origin. As discussed later, differences in renin may explain ethnic differences in responses to antihypertensive drugs.

Gender

Before the age of about 50 years, hypertension is less common in women than men (Figure 1.2). After this age, blood pressure in women gradually increases to about the same level as in men. Consequently, the complications of hypertension are less common in younger women. This protection may be related to beneficial effects of oestrogens or harmful effects of androgens on vascular risk.

Increasing evidence shows that women with a past history of preeclampsia and pregnancy-induced or gestational hypertension have an increased risk of hypertension and CVD in later life. Such women should be considered to be at higher risk and need regular monitoring.

Table 1.2 Blood pressure in populations of African origin in the United Kingdom: review of 14 adult cross-sectional studies in 1978

Blood pressure	Men	Women
Systolic higher than Europeans	10 of 14 studies	10 of 12 studies
Diastolic higher than Europeans	11 of 14 studies	10 of 12 studies
Hypertension more common	8 of 10 studies	8 of 9 studies

Source: Data from Agyemang, C. (2003) *Journal of Human Hypertension*, 17, 523–534.

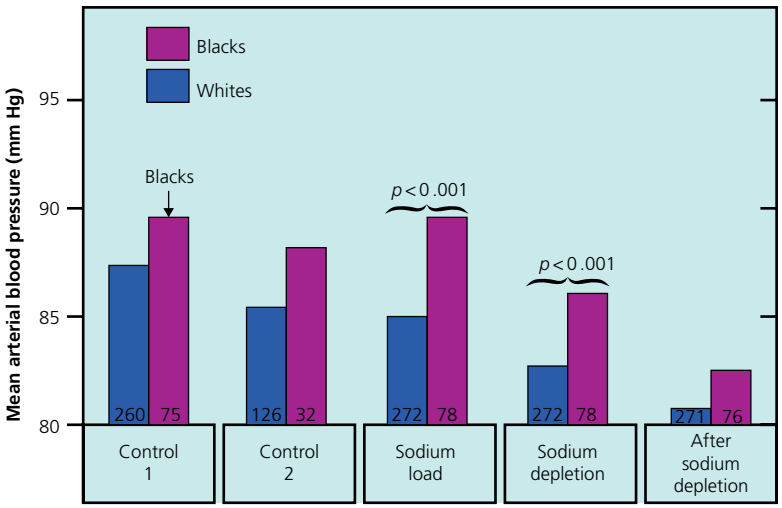


Figure 1.7 The effects of salt loading and salt restriction on blood pressure in US black and white normotensives individuals. Source: Reproduced with permission from Luft, F.C., *et al*. (1979) *Circulation*, 59, 643–650. © Lippincott Williams & Wilkins.

Table 1.3 The prevalence of secondary hypertension. The prevalence of primary aldosteronism would be greater if more up-to-date biochemical & radiological criteria were used

A total of 686 men from a random sample of Swedish population			
Renal artery stenosis	4	Glomeruloneghritis	15
Aortic coarctation	1	Haematuria due to stone	3
Primary aldosteronism	1	Renal tuberculosis	4
Phaeochromocytoma	0	Gouty nephropathy	3
Parathyroid	2	Renal dysplasia	2
Hydronephrosis	7	Phenacetin nephropathy	1

Source: Data from Berglund, G., *et al*. (1976) *British Medical Journal*, 2, 554–556.

Underlying diseases affecting blood pressure

In around 5% of people with hypertension, the high blood pressure is explained by underlying renal or adrenal diseases (Table 1.3). In the remaining 95%, no clear cause can be identified. Such cases of hypertension are described as 'essential' or 'primary' hypertension. Essential hypertension is related to the interplay of genetic and environmental factors, but the precise role of these is uncertain. Unsurprisingly, secondary hypertension is less common in primary care than in hospital practice.

Environmental and lifestyle causes of hypertension

Salt

Salt intake has a consistent and direct effect on blood pressure. As stated earlier, migration studies in African and Japanese people have shown changes in blood pressure when moving from one environmental background to another. The factor most likely to be involved is a change in salt intake.

Many potential mechanisms for how salt causes hypertension have been suggested (Table 1.4). Evidence from observational epidemiological studies, animal models and randomised-controlled trials in patients with hypertension and normal blood pressure all point to a causal relation between salt and blood pressure. The potential clinical and public health impact of relatively modest salt restriction is thus substantial.

The INTERSALT project, which involved more than 10 000 men and women aged 20–59 years in 52 different populations in 32 countries, quite clearly showed that the increase in blood pressure with advancing age in urban societies was related to the amount of salt in the diet. Positive associations between urinary excretion of sodium (a marker of salt intake) and blood pressure were observed within (Table 1.5) and between populations. In men and women of all ages, an increase in sodium intake of 100 mmol/day was estimated to be associated with an average increase in systolic blood pressure of up to 6 mm Hg. The association was larger for older people (Figure 1.8).

This finding was supported by a meta-analysis of the many individual population surveys of blood pressure in relation to salt intake. In 1991, Law *et al.* performed a meta-analysis of 78 observational studies on the effect of sodium intake on blood pressure and reported that a reduction in daily salt intake of about 3 g (attainable by moderate reductions in dietary intake of salt) in people aged 50–59 years should lower systolic blood pressure by an average of 5 mm Hg. An average reduction in blood pressure of this magnitude in the general population of most Western

Table 1.4 Possible mechanisms for the association between a high salt intake and hypertension

- Increased circulating fluid volume
- Inappropriate sodium:renin ratio, with failure of renin to suppress
- Increased intracellular sodium
- Waterlogged, swollen endothelial cells that reduce the interior diameter of arterioles
- Permissive rise in intracellular calcium, which leads to contraction of vascular smooth muscle cells and vasoconstriction
- Association between a high salt intake and high calorie intake with obesity

Table 1.5 The number of centers where positive relationships were found between salt excretion, as a marker for salt intake, and the height of the systolic blood pressure in the INTERSALT study of 52 centers in 32 countries. It is unusual to find positive correlations between salt and blood pressure within populations

Variable	Adjusted for	
	Age and sex	Age, sex, body mass index (kg/m²), alcohol and potassium intake
Centres with positive correlations	39	33
Centres with significant positive correlations	15	3

*P < 0.001.
Source: Reproduced with permission from Intersalt Cooperative Research Group. (1988) *British Medical Journal*, 297, 319–328. © BMJ Publishing Group Ltd.

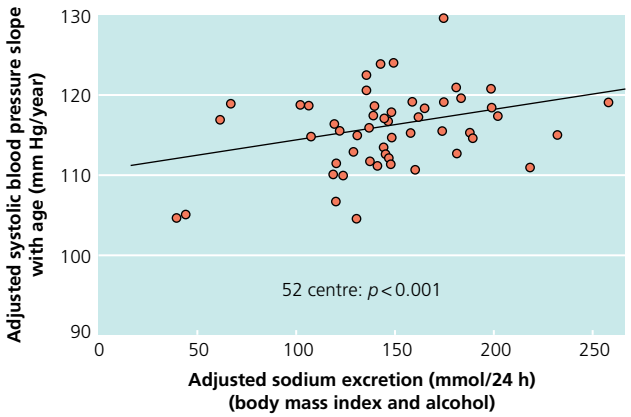


Figure 1.8 The relationship between 24-h urinary sodium excretion and the rise in blood pressure with advancing age; 52 centers in 32 countries.
Source: Reproduced with permission from Intersalt Cooperative Research Group. (1988) *British Medical Journal*, 298, 319–328. © BMJ Publishing Group Ltd.

countries would reduce the incidence of stroke by 25% and the incidence of ischaemic heart disease by 15%.

A systematic review and meta-analysis of prospective studies published 1966–2008 concluded that high salt intake is associated with significantly increased risk of stroke (pooled relative risk 1.23, 95% CI 1.06–1.43; $p = 0.007$) and total cardiovascular disease (1.14, 0.99–1.32; $p = 0.07$), supporting the role of a substantial population reduction in salt intake for the prevention of CVD.

A number of clinical trials also show reductions in blood pressure after restriction of salt intake (see Chapter 8). In a recent study by He and MacGregor in the United Kingdom, a reduction in daily salt intake from 10 to 5 g over 1 month in a group of men and women aged 60–78 years with hypertension resulted in an average fall in systolic blood pressure of 7 mm Hg. In a meta-analysis of 31 trials with a minimum duration of 4 weeks, lowering 24-h urinary sodium excretion by 75 mmol was associated with average decreases in blood pressure of 5 mm Hg for systolic and 2.7 mm Hg for diastolic amongst hypertensive patients.

Whilst there is good evidence from observational studies and trials of salt restriction that there is a close relationship between salt intake and blood pressure and that salt restriction leads to a significant reduction in blood pressure in people with hypertension, there is much less evidence on the long-term effects of salt on CVD. The limited number of observational studies does suggest that a high salt intake does cause stroke and all cause cardiovascular mortality and morbidity. Only one of four outcome trials was able to demonstrate a significant reduction in CVD mortality. The pooled results of all four studies showed a 20% reduction, but this effect was not statistically significant. No trial has been specifically designed to examine the long-term effects of salt restriction. Such a study would require a 10- to 20-year follow-up of several thousand patients, half randomised to salt restriction advice and half to continue their usual diet. All participants would need to be seen annually. It is unlikely that such a trial will ever be conducted.

The value of the restriction of salt intake in people without hypertension is more controversial. Data pooled from the limited studies available suggest that reduction of salt intake to about 6 g/day should reduce systolic blood pressure by about 2 mm Hg and diastolic pressure by 1 mm Hg. Although clinically unimportant, this reduction, if genuine and sustained, would be expected to bring about a 17% reduction in the prevalence of hypertension.

Potassium

The relation between intake of sodium, intake of potassium and blood pressure is complex and has not been resolved completely. The effect of dietary intake of potassium on blood pressure is difficult to separate from that of salt.

In hypertensive patients, a 0.6 g/day increase in dietary potassium intake results in a1.0 mm Hg reduction in systolic BP and a 0.52 mm Hg reduction in diastolic BP. The average reduction in BP depends on ethnicity and on the relative intakes of sodium, magnesium and calcium. For example, if the dietary sodium chloride intake is high, there is a greater BP reduction with an increased intake of dietary potassium. Blacks have a greater decrease in BP than Caucasians with an equal potassium intake.

Table 1.6 The relation between 24 hour urinary potassium excretion and blood pressure in 52 populations in the INTERSALT study

Variable	Blood pressure	
	Systolic	Diastolic
Centres with positive correlations	24	29
Centres with significant positive correlations	0	2
Centres with negative correlations	28	23
Centres with significant negative correlations	2	2

Source: Reproduced with permission from Intersalt Cooperative Research Group. (1988) *British Medical Journal*, 297, 319–328. © BMJ Publishing Group Ltd.

The INTERSALT project showed that high intake of potassium was associated with a lower prevalence of hypertension (Table 1.6). Urinary sodium and potassium ratios in the United States showed marked differences between black and white people, despite little difference in their sodium intake or excretion. Dietary intake of potassium has also been related inversely to the risk of stroke. The antihypertensive effects of potassium chloride and other potassium salts are the same, which indicates that it is the potassium that matters. Most of the potassium in the diet is not in the form of potassium chloride but potassium citrate and potassium bicarbonate.

Potassium-induced reduction in BP may lower the incidence of stroke (cerebrovascular accident, CVA), coronary heart disease, myocardial infarction and cardiovascular events. For example, higher consumption of potassium to 4.7 g/day would decrease future CVD, with estimated decreases of 8–15% in stroke and 6–11% in heart attacks. Almost all potassium in the diet is contained in fruit and vegetables. The beneficial effects of fruit and vegetables are complex and may be due to potassium, vegetable flavinoids, vitamin C, vegetable protein and possibly dietary fibre.

Calcium and magnesium

A weak inverse association exists between intake of calcium and blood pressure. Nonetheless, data from clinical trials of calcium supplementation on blood pressure are inconsistent, and the overall effect probably is minimal.

A weak relation also exists between intake of magnesium and blood pressure, but the use of magnesium supplements has been disappointing.

Weight

People who are obese or overweight tend to have higher blood pressures than thin people. In the US National Health Examination Survey (NHANES III), hypertension (>160/90 or on treatment) was seen in 10–25% of men with a body mass index (BMI) of 22.5 and 40–60% in men with a BMI of 37.5 severely obese). Even after taking into account the confounding effects of obese arms and inappropriate cuff sizes on blood pressure measurement, a positive relation still

exists between blood pressure and obesity – whether expressed as BMI (weight (kg)/(height (m)^2)), relative weight, skinfold thickness or waist to hip ratio. An increase in body weight from childhood to young adulthood is a major predictor of adult hypertension.

This association is clearly related to a high energy diet, although other dietary factors may be implicated (e.g., high intake of salt). The risk is greater in patients with truncal obesity, which may be a marker for insulin resistance, activation of the sympathetic nervous system, or other pathophysiological mechanisms that link obesity and hypertension. The close association of obesity with diabetes mellitus, insulin resistance and impaired glucose tolerance and high levels of plasma lipids also partly explains why obesity is such a powerful risk factor for CVD. In general, trials of weight reduction show changes in mean systolic blood pressure and diastolic blood pressure of about 5.2 mm Hg in patients with hypertension and 2.5 mm Hg in people with normal blood pressure. This translates roughly to a reduction in blood pressure of 1 mm Hg for each kilogram of weight loss.

Obstructive sleep apnoea

Obesity is also related to obstructive sleep apnoea (OSA), which is characterised by snoring, sleep disturbance and day time sleepiness. There is a close association between OSA and hypertension; as many as one-third of hypertensive patients and about 80% of those with resistant hypertension have OSA. In addition, severe OSA is associated with excess CVD. It is unclear whether OSA is in itself an independent risk factor for CVD. Recent analyses suggest that the link between OSA and hypertension is abolished after taking into account the degree of obesity. There is, however, evidence that nasal continuous positive airway (CPAP) treatment does have a small blood pressure lowering effect.

Alcohol

Epidemiological studies have shown a positive relation between alcohol consumption and blood pressure, which is independent of age, obesity, cigarette smoking, social class and sodium excretion (Figure 1.9).

In the British Regional Heart Study, about 10% of cases of hypertension (blood pressure ≥160/95 mm Hg) could be attributed to moderate or heavy drinking. Generally, the greater the alcohol consumption, the higher the blood pressure, although teetotallers seem to have slightly higher blood pressures than moderate drinkers.

The reversibility of hypertension related to alcohol has been shown in population surveys and alcohol loading and restriction studies. A reduction in weekly alcohol consumption is associated with clinically significant decreases in blood pressure, independent of weight loss, in people with normal blood pressure and those with hypertension. A reduction in intake of about three drinks per week was estimated to result in an average fall in supine systolic blood pressure of 3.1 mm Hg.

The mechanisms of the relation between alcohol and blood pressure are uncertain, but they are not explained by BMI or salt intake. The effects of alcohol on blood pressure may include

- A direct pressor effect of alcohol
- Sensitisation of resistance vessels to pressor substances

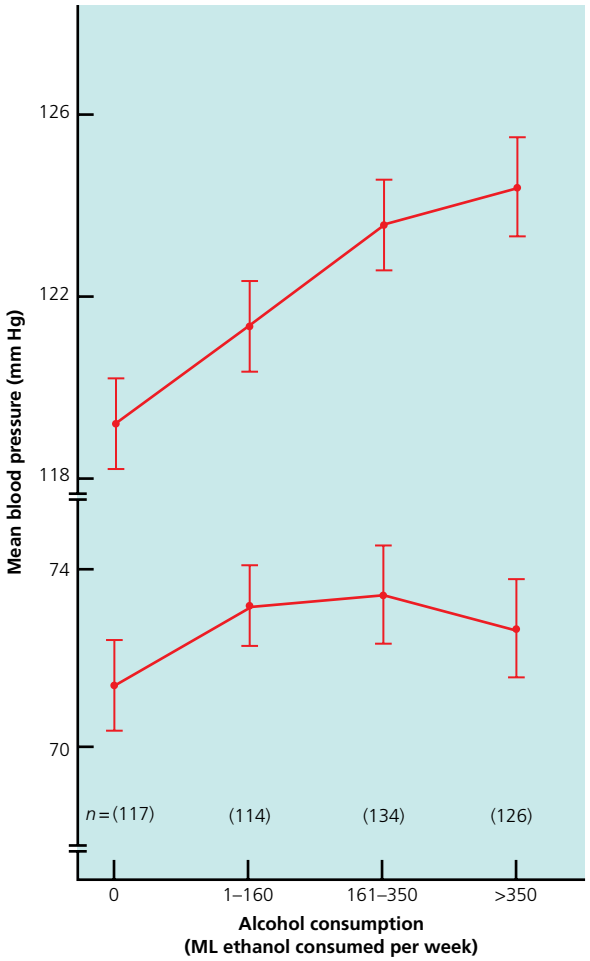


Figure 1.9 The relationship between alcohol intake and systolic and diastolic hypertension in the general population. Source: Reproduced with permission from Arkwright, P.D., *et al*. (1982) *Circulation*, 66, 60–66. © Lippincott Williams & Wilkins.

- Stimulation of the sympathetic nervous system (possibly as a result of fluctuating levels of alcohol in blood)
- Increased production of adrenocorticoid hormones.

A synergistic effect of alcohol and hypertension has been suggested to increase the risk for stroke. Alcohol excess can also lead to atrial fibrillation which can further contribute to the risk of stroke. Also alcohol withdrawal-induced transient peaks in blood pressure may predispose to the risk of stroke. Binge drinking is a significant risk factor for stroke. All hypertensive patients should be cautioned about the hazards of alcohol excess (21 units or more per week in men or 14 units in women). Binge drinking is a significant risk factor for stroke, and hypertensive patients should be cautioned about the risks of alcohol.

Stress

Psychological or environmental stress may play a small part in the aetiology of hypertension, although studies frequently have been confounded by other environmental or lifestyle factors, Although research has focused on possible direct effects of psychosocial 'stress' on blood pressure, 'stressors' such as poverty,

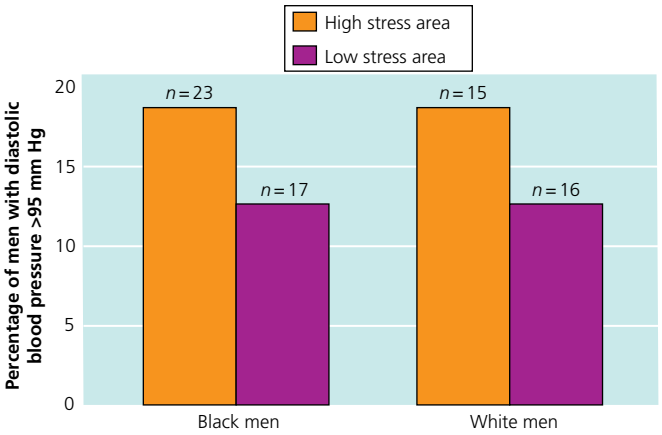


Figure 1.10 Stress, ethnicity, and hypertension in men. Stress was classified by residential area and local crime rates. Source: Data from Harburg, E., *et al*. (1973) *Journal of Chronic Diseases*, 26, 595–611.

unemployment and poor education are involved, as are other aspects of lifestyle that are linked to hypertension (including obesity, a diet high in salt and physical inactivity) (Figure 1.10).

Although stressful stimuli may cause an acute rise in blood pressure, whether this has any significance in the long term is doubtful. A reduction in psychological stress through biofeedback techniques may reduce blood pressure in the clinic, although little effect on ambulatory blood pressure recordings at home is seen.

One systematic review of observational studies concluded that acute stress is probably not a risk factor for hypertension, whilst chronic stress and particularly the nonadaptive response to stress were more likely causes of sustained hypertension.

In a recent meta-analysis of trials that involved stress management techniques such as meditation and biofeedback with at least 6 months of follow-up, only eight trials that met the inclusion criteria were identified and the findings were inconsistent, with very small pooled falls in systolic and diastolic blood pressure (1.0/1.1 mm Hg). There is some evidence that whilst stress management maneuvers may have a small effect on blood pressures measured in the clinic, they have little or no effect on 24-h home-monitored blood pressures.

Exercise

Blood pressure increases sharply during physical activity, but people who undertake regular exercise have lower blood pressures (Table 1.7). Such people, however, also may have a healthier diet and more sensible drinking and smoking habits (Figure 1.11). A recent study has demonstrated that Olympic medalists have a longer life expectancy than the general population of the countries they represented.

Recent studies suggest an independent relation between increased levels of exercise and lower blood pressures; vigorous exercise might be harmful, but all other grades of exercise are increasingly beneficial. Observational epidemiological studies also show that physical activity reduces the risk of heart attack and

Table 1.7 Results of eight studies of the effects of exercise on systolic and diastolic blood pressure

Study number	Fall in systolic blood pressure (mm Hg)	All in diastolic blood pressure (mm Hg)
1	8.0	6.0
2	10.0	9.0
3	10.0	8.0
4	9.7	6.8
5	15.0	11.5
6	4.6	2.4
7	3.0	2.4
8	4.6	2.5

Meta-analysis or pooling of these data is inappropriate because of differences in the trial protocols and duration.

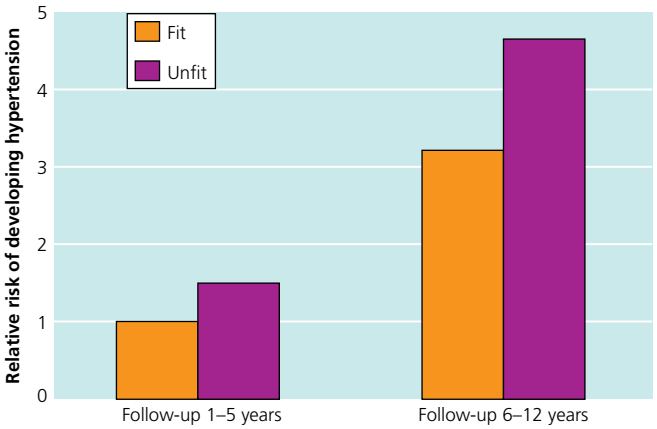


Figure 1.11 Physical fitness and the risk of developing hypertension. Source: Data from Blair, S.N., *et al*. (1984) *JAMA*, 252, 487–490.

stroke, which may be mediated by beneficial effects on blood pressure. In the British Regional Heart Study, an inverse association between physical activity and systolic and diastolic blood pressure was seen in men who did not have evidence of ischaemic heart disease. This association was independent of age, BMI, social class, smoking status, total levels of cholesterol and levels of high-density lipoprotein cholesterol.

For hypertensive subjects, a regular graduated exercise regime, alone or as an adjunct to medical therapy, can improve hypertension control at relatively lower doses of antihypertensive pharmacological agents, and reduce adverse events from blood pressure lowering.

Other dietary factors

Blood pressure in vegetarians is generally lower than in nonvegetarians. Substitution of animal products with vegetable products reduces blood pressure. The mechanisms of this beneficial effect of a vegetarian diet are uncertain (Figure 1.12). It may, in part, be related to a lower intake of dairy products or salt. Alternatively, the lower blood pressures may be related to a higher dietary intake of vegetable proteins.

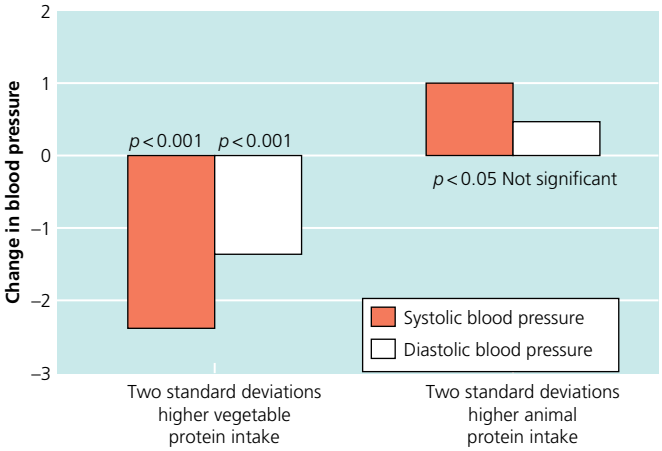


Figure 1.12 Animal and vegetable intake and systolic and diastolic blood pressure in the INTERMAP study of dietary constituents and blood pressure. Source: Data from Elliott, P., *et al*. (2006) *Archives of Internal Medicine*, 166, 79–87.

Large amounts of Omega 3 fatty acids from fish oils may reduce blood pressure in people with hypertension. In observational studies, important inverse associations of blood pressure with intake of fibre and protein have been reported.

Although caffeine acutely increases blood pressure, tolerance to this pressor effect is generally believed to develop rapidly. A recent report suggests an association of raised blood pressure with an excessive intake of cola drinks, with an effect seen with 'diet' and high-energy cola drinks. This may be related to their caffeine content.

Further Reading

Boddins-Domingo, K., Chertow, G.M., Coxon, P.G., *et al.* (2010) Projected effect of dietary salt restrictions on future cardiovascular disease. *New England Journal of Medicine*, 362, 590–599.

Brown, M.J. (2006) Hypertension and ethnic group. *British Medical Journal*, 332, 833–836.

Butt, M., Dwivedi, G., Khair, O. & Lip, G.Y. (2010) Obstructive sleep apnoea and cardiovascular disease. *International Journal of Cardiology*, 139, 7–16.

Clarke, P.M., Walter, S.J., Hayen, A., *et al.* (2012) Survival of the fittest: retrospective cohort study of the longevity of Olympic medalists. *British Medical Journal*, 345, e8308.

He, F.J. & MacGregor, G.A. (2009) A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *Journal of Human Hypertension*, 23, 363–384.

Houston, M.C. (2011) The importance of potassium in managing hypertension. *Current Hypertension Reports*, 13, 309–317.

Law, M.R., Frost, C.D., Wald, N.J., *et al.* (1991) By how much does dietary salt reduction lower blood pressure? Analysis of observational data among populations. *British Medical Journal*, 302, 811–815.

MacMahon, S.W., Alderman, M.H., Lindholm, L.H., *et al.* (2008) Blood-pressure-related disease is a global priority. *Lancet*, 371, 1480–1482.

MacMahon, S.W., Neal, B. & Rodgers, A. (2005) Hypertension – time to move on. *Lancet*, 365, 1108–1109.

Sánchez-de-la-Torre, M., Campos-Rodriguez, F. & Barbé, F. (2013) Obstructive sleep apnoea and cardiovascular disease. *Lancet*, 1, 61–72.

Staessen, J., Wang, J., Bianchi, G. & Birkenhäger, W.H. (2003) Essential hypertension. *Lancet*, 361, 1629–1641.

Strazzullo, P., D'Elia, L., Kandala, N.B. & Cappuccio, F.P. (2009) Salt intake, stroke and cardiovascular disease: meta-analysis of prospective studies. *British Medical Journal*, 339, b4567.

CHAPTER 2

Hypertension and vascular risk

OVERVIEW

- Malignant or accelerated hypertension is a rare form of very severe hypertension usually associated with bilateral retinal haemorrhages, cotton wool spots and hard exudates with or without papilloedema. In the untreated state, around 80% are dead within 2 years.
- There is a continuous relationship between the height of the blood pressure and the chances of developing strokes and heart attacks. This gradient of risk extends down into the so-called normal range so that an individual with a blood pressure that is average for his or her age has a greater risk than a similar individual whose pressure is well below average.
- Cardiovascular risk is directly related to the height of the systolic blood pressure in all ages. By contrast, diastolic blood pressure is a poorer predictor of risk as after the age of about 60, when it ceases to rise with advancing age.
- Isolated systolic hypertension, where the diastolic pressure is not raised, is common in the elderly and carries a high risk of stroke and other cardiovascular events.
- White coat hypertension, where blood pressures are only raised during clinical consultations, is common and associated with a prognosis, which is much the same as in individuals with persistently normal pressures.
- The height of the blood pressure is closely related to strokes, heart attack, left ventricular hypertrophy, heart failure, atrial fibrillation and renal failure. There is also some relationship between blood pressure and the risk of vascular dementia.
- Cardiovascular morbidity and mortality are also closely related to the height of the serum total cholesterol: HDL cholesterol ratio, cigarette smoking and the presence of diabetes mellitus. All these risk factors should be assessed in people with hypertension.

Blood pressure and risk

Very high blood pressure that exceeds 200/120 mm Hg is relatively uncommon and affects only 0.5% of the adult population. Malignant, or malignant phase hypertension with retinal haemorrhages, exudates with or without papilloedema is even rarer, being seen in about 3 per 100 000 population. Malignant hypertension carries a very grave prognosis when untreated, with nearly 90% of patients dying within 2 years (Figure 2.1).

Most patients die of renal failure, stroke or left ventricular failure. With modern treatment, survival is much improved, with >90% of patients surviving 5 years (Figure 2.2). Age, decade of MHT diagnosis, renal function (as reflected by baseline creatinine) and follow-up systolic blood pressure were all independent predictors of survival (all $p < 0.0001$).

Early detection and management of mild grades of hypertension means that malignant hypertension is declining in incidence. Often, no underlying cause of the increased blood pressure is identifiable, but intrinsic renal disease is seen more often in patients with malignant hypertension than in those with non-malignant hypertension.

Malignant hypertension

The pooled data from many of the long-term follow-up studies of well-defined unselected populations now means that accurate data are available on the relation between baseline blood pressure and the subsequent risk of heart attack and stroke (Figure 2.3).

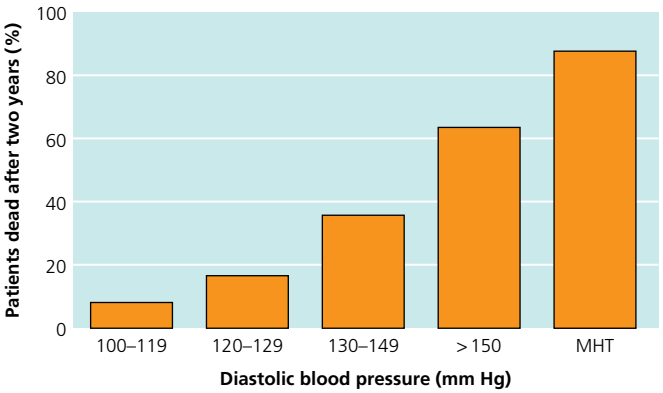


Figure 2.1 The 2-year survival of moderate-to-severe and malignant (MHT) hypertension before the advent of acceptable antihypertensive therapy. Source: Data from Leishman, A.W.D. (1959) *British Medical Journal*, 1, 1361–1368.

ABC of Hypertension, Sixth Edition. D. Gareth Beevers, Gregory Y. H. Lip and Eoin O'Brien.

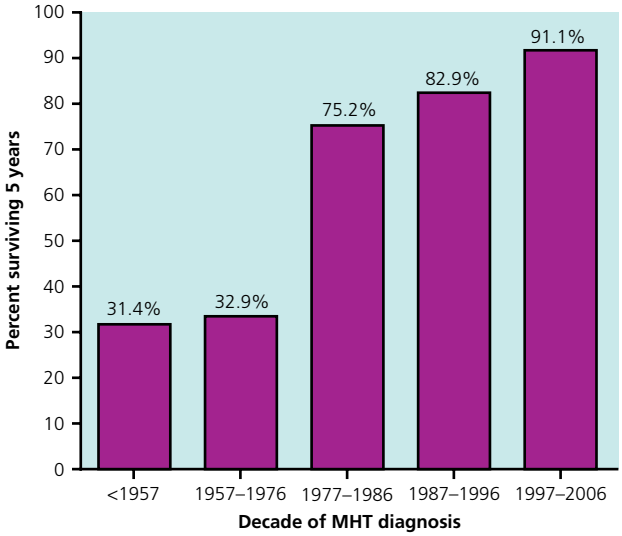


Figure 2.2 The 5-year survival by decade in patients with treated malignant hypertension, at City Hospital, Birmingham. Source: Reproduced with permission from Lane, D.A., *et al*. (2009) *American Journal of Hypertension*, 22, 1199–1204. © Elsevier.

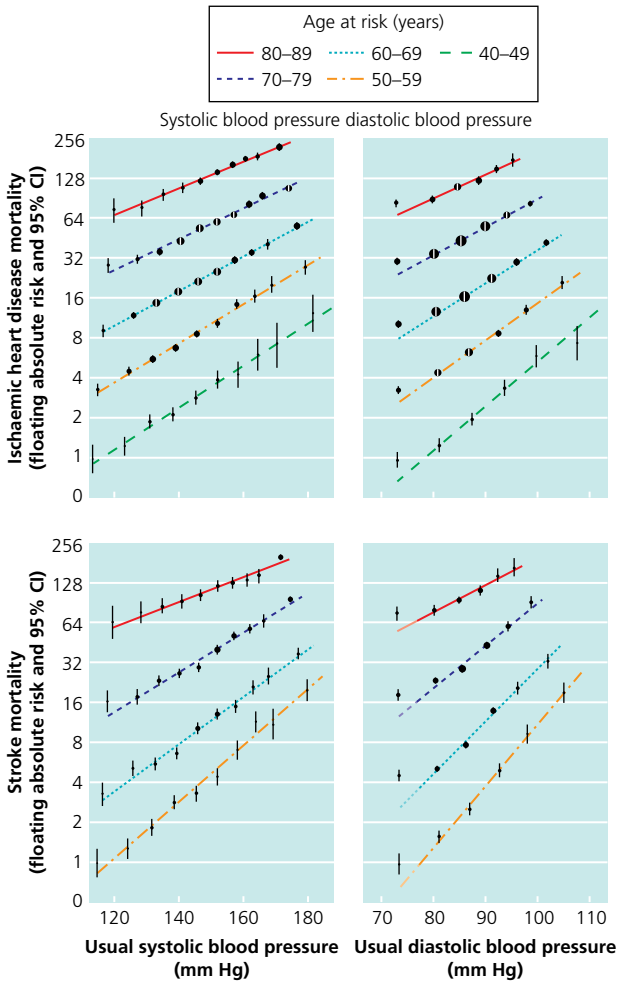


Figure 2.3 Mortality from coronary heart disease (top) and stroke (bottom) in relation to systolic and diastolic blood pressure at screening. Source: Reproduced with permission from Lewington, S., *et al*. (2002) *Lancet*, 360, 1903–1913. © Elsevier.

This close relation between the height of the blood pressure and the risk of heart attack and stroke continues down to pressures that are average or even below the average for the general population. This means that people with systolic blood pressures as low as 130 mm Hg are at greater risk than those with even lower pressures. In the absence of concomitant-unrelated diseases (such as cancer) or pre-existing cardiovascular damage (such as after myocardial infarction), low systolic and diastolic pressures are not associated with increased mortality or morbidity.

As stated in Chapter 1, clinical hypertension begins at that level where clinical intervention is beneficial to the individual patient. In contrast, the view of blood pressure from the public health perspective would imply a need to reduce the average blood pressure of the whole population and not just those individuals with abnormally increased blood pressures.

Systolic and diastolic blood pressures

In people older than 45 years, the risks of stroke and coronary heart disease are related more closely to systolic blood pressure, even after adjustment for underlying diastolic blood pressure. Isolated systolic hypertension thus becomes more common with increasing age and may be the result of thickening of the brachial artery, which would reflect arterial damage. Even in the presence of a normal or low diastolic blood pressure, systolic hypertension is an accurate predictor of cardiovascular risk.

It remains possible that diastolic pressure may be more important than systolic pressure in younger adults, although not much data on this point exist. In addition, diastolic pressure may exert its harmful effects only above a certain threshold of around 110 mm Hg. A blood pressure of 200/100 mm Hg thus may be less harmful than a blood pressure of 180/120 mm Hg in younger patients.

The relative risks of stroke according to categories of baseline blood pressure in 6545 people who participated in the Copenhagen City Heart Study show that the highest risk is present in people with isolated systolic hypertension and systo-diastolic hypertension, while isolated diastolic hypertension seems to carry a lower risk (Figure 2.4).

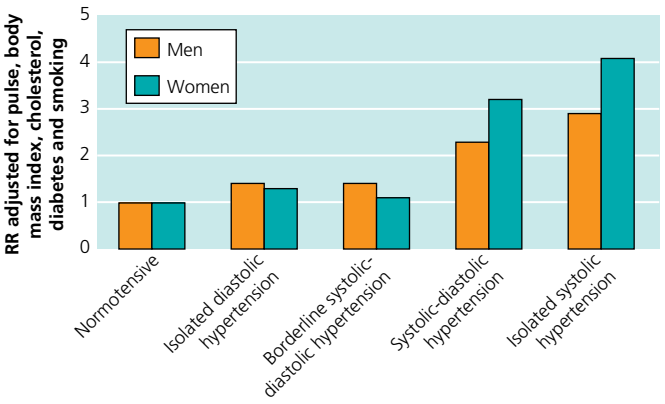


Figure 2.4 The relative risk RR of stroke in relation to normotension, systo-diastolic hypertension, and two grades of isolated systolic hypertension in the Copenhagen City Heart Study. Source: Reproduced with permission from Nielsen, W.B., *et al*. (1997) *American Journal of Hypertension*, 10, 634–639. © Oxford University Press Journals.

Isolated diastolic hypertension is relatively uncommon and is usually seen in younger people, in whom the number of cardiovascular events is small. The significance of isolated diastolic hypertension in the long term remains uncertain. High systolic and diastolic blood pressures are treatable cardiovascular risk factors. Good detection, treatment and control result in a substantial reduction in the numbers of heart attacks and strokes.

White coat hypertension

It has long been known that in many patients with raised blood pressures in the clinic, these pressures settle with repeated measures or when measured automatically in the more familiar home environment. Until recently, the prognostic significance of this so-called 'white coat hypertension' was uncertain. Pooled follow-up data are now available from several prospective studies comparing clinic or office hypertension with 24-h ambulatory blood pressure measured in the home with fully automatic monitors (ABPM). These reveal four distinct patient groups; (1) those who are persistently **normotensive** in the clinic and at home, (2) those whose pressures are persistently **hypertensive**, (3) those whose pressures are only raised in the clinic, labeled as **white-coat hypertension** and (4) those whose pressures are normal in the clinic but whose pressures are persistently raised when they are at home, so-called **revealed or masked hypertension**.

At follow-up, the persistent hypertensives and the revealed hypertensives had a broadly similar poor outlook whilst the persistent normotensives and the white-coat hypertensives both had a lower morbidity and mortality (Figure 2.5).

The prognostic value of home blood pressure monitoring (HBPM) where the patient measures his or her pressure with a semi-automatic desk top monitor is less certain as there have been fewer long-term follow-up studies.

There is, as yet, no consensus on what action should be taken in people with revealed or masked hypertension whose blood pressures are normal in the clinical setting but are raised at home.

For predicting clinical outcomes, the 2011 NICE guidelines focused on comparing 24-h ABPM, home blood pressure monitoring (HPBM) and clinic measurements (CBPM). Their systematic review of the available literature concluded that for the prediction of adverse outcomes in hypertension ABPM should be the 'gold standard' (Table 2.1). This may change when more studies of HBPM become available.

Cardiovascular diseases and blood pressure

Stroke

Stroke is one of the most devastating consequences of hypertension and results in premature death or considerable disability. About 80% of strokes in patients with hypertension are ischaemic, being caused by an intra-arterial thrombosis or embolisation from the heart or carotid arteries. The remaining 20% of cases are the result of various haemorrhagic causes.

In the United Kingdom, about 40% of all strokes are attributable to systolic blood pressures ≥140 mm Hg. After adjustment for age, men aged 40–59 years with systolic blood pressures of 160–180 mm Hg are at about a fourfold higher risk of stroke during the next 8 years than men with systolic blood pressures of 140–159 mm Hg. Amongst treated hypertensive patients, the risk of stroke is closely related to the accuracy of blood pressure control (Figure 2.6).

Atrial fibrillation

Hypertension is also associated with an increased risk of atrial fibrillation. The presence of both conditions is additive to the risk of stroke. The incidence of stroke in patients with both conditions

Table 2.1 The relative importance of clinic blood pressure (CBPM), 24-h ambulatory (ABPM) and home blood pressure mesasurement (HBPM) from the National institute of Health and Clinical Excellence (NICE)

ABPM versus CBPM (nine studies):
- ABPM was superior to CBPM (eight studies).
- There was no difference between ABPM and CBPM (one study).

HBPM versus CBPM (three studies):
- HBPM was superior to CBPM (two studies).
- There was no difference between HBPM and CBPM (one study).

HBPM versus ABPM versus CBPM (two studies):
- HBPM was similar to ABPM and both were superior to CBPM (one study).
- There was no difference between HBPM, ABPM and CBPM (one study).

Source: From Krause, T., *et al*. (2011) *British Medical Journal*, 343, d4891.

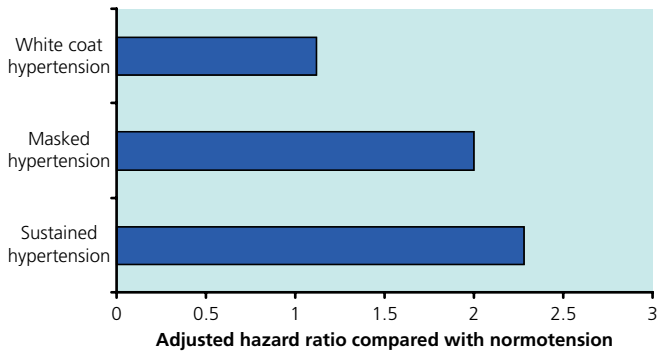


Figure 2.5 Adjusted hazard ratio compared with persistent normotension (HR = 1.0) of persistent hypertension, white-coat hypertension, and revealed or masked hypertension. Meta-analysis of 8-year follow up in seven prospective studies in 11 502 individuals. Source: Data from Fagard, R.H. (2007) *Journal of Hypertension*, 25, 2193–2198.

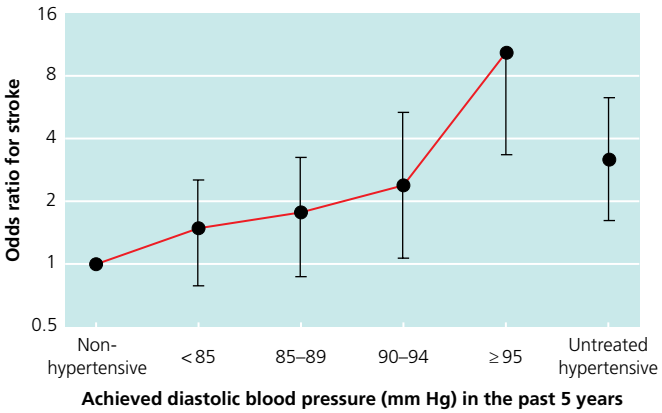


Figure 2.6 Blood pressure control and odds ratio for stroke in a study of 267 cases and 534 controls. Source: Reproduced with permission from Du, X., *et al*. (1997) *British Medical Journal*, 314, 272–276. © BMJ Publishing Group Ltd.

Table 2.2 The CHA_2DS_2VASc scoring system for stroke risk in patients with atrial fibrillation PVD: peripheral vascular disease

		Score
C	Congestive cardiac failure or left ventricular dysfunction	1
H	Hypertension of BP ≥140/90 mm Hg	1
A	Age ≥ 75 years	2
D	Diabetes mellitus	1
S	Stroke or systemic thromboembolismansient or transient ischaemic attack	2
V	Vascular disease (previous myocardial infarction, PVD, or aortic plaque	1
A	Age 65–74 years	1
S	Sex female	1
Maximum possible score		**9**

Source: Adapted from Lip, G.Y.H., *et al*. (2007) *European Heart Journal*, 28, 753–759.

is 8% per year. Hypertension is a featured risk factor in stroke risk assessment scores for atrial fibrillation, such as the CHA_2 DS_2–VASc scores. Uncontrolled blood pressure substantially increases the risk of stroke in atrial fibrillation, even amongst anticoagulated patients (Table 2.2). Hypertensives with hypokalaemia, due to diuretics or to aldosterone excess, are particularly at risk of developing atrial fibrillation and other arrhythmias.

Abundant evidence from clinical trials shows that lowering blood pressure prevents all kinds of stroke. It has been commented that stroke should no longer occur as a result of hypertension and that when it does, it is a marker for poor control of blood pressure and inferior healthcare provision. Recent evidence suggests that the β blockers are less effective at preventing stroke than other antihypertensive agents.

Dementia

Elderly people with hypertension are at risk of all forms of stroke and frequently sustain multiple small, asymptomatic cerebral infarcts that may lead to progressive loss of intellectual or cognitive function and dementia. An association also exists between hypertension and Alzheimer's disease.

A recent meta-analysis of six longitudinal studies concluded that hypertension was significantly associated with increased risk of incident vascular dementia (OR 1.59, CI: 1.29–1.95, $p < 0.0001$), and in five cross-sectional studies, it was associated with the risk of prevalent vascular dementia (OR 4.84, CI: 3.52–6.67, $p < 0.00001$).

The importance of the vascular contribution to cognitive impairment and dementia was recently highlighted in a 2011 consensus statement from American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention and Council on Cardiovascular Surgery and Anesthesia.

Evidence as to whether lowering blood pressure leads to a reduction of dementia or loss of cognitive function is conflicting. A Cochrane systematic review concluded that there was no convincing evidence from the trials that blood pressure lowering in later life prevents the development of dementia or cognitive impairment in hypertensive patients with no apparent prior cerebrovascular disease.

Coronary heart disease

In patients with hypertension, fatal coronary heart disease was more common than fatal stroke, but recent trends suggest a reversal of these frequencies. Adequate treatment of hypertension reduces the risk of heart attack by about 20%, although this figure is based on blood pressure lowering by thiazides and β blockers rather than newer antihypertensive agents. Many drugs used for the acute coronary syndromes and hypertension commonly treat both these conditions simultaneously.

Hypertension may lead to coronary heart disease because of its contribution to the formation of coronary atheroma, with an interaction with other risk factors such as hyperlipidaemia and diabetes mellitus.

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is a common manifestation of hypertensive target organ damage. In a recent semi-systematic review of 30 studies, including 37 700 untreated and treated patients, the prevalence of LVH ranged from 36 to 41%, with no difference between women and men, whilst eccentric LVH was more common than concentric hypertrophy.

LVH occurs as a result of increased after load on the heart, caused by raised peripheral vascular resistance. Subsequently, the increased muscle mass outstrips its blood supply and this, coupled with the decreased coronary vascular reserve, can result in myocardial ischemia – even in patients with normal coronary arteries.

Evidence also shows that a high intake of salt and increased levels of angiotensin II in the plasma increase the chances of developing LVH. The angiotensin blocking drugs reduce LVH more than other classes of drug. The prevalence of LVH is similar in patients with isolated systolic hypertension and systolic–diastolic hypertension.

LVH secondary to hypertension is a major risk factor for myocardial infarction, stroke, sudden death and congestive cardiac failure. This increased risk is in addition to that imposed by hypertension itself. In addition, patients with hypertension and LVH are at increased risk of cardiac arrhythmias (atrial fibrillation and ventricular arrhythmias) and atherosclerotic vascular disease (coronary and peripheral artery disease). When LVH on the ECG is accompanied by repolarisation abnormalities (also called 'strain' pattern), morbidity and mortality are even higher (Figure 2.7).

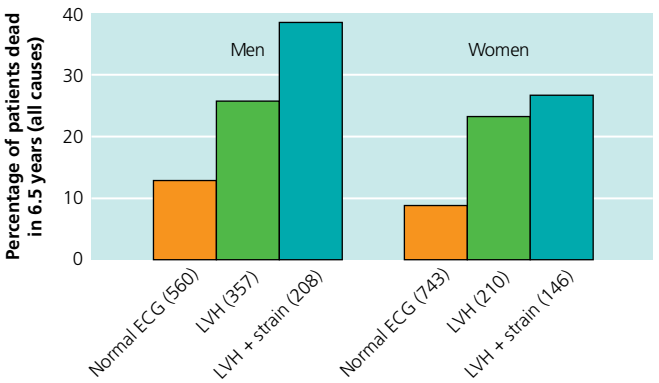


Figure 2.7 Death rates in hypertensive men and women in relation to baseline measures of left ventricular hypertrophy (LVH) with or without repolarization abnormalities (strain) in the Glasgow Blood Pressure Clinic. Source: Data from Dunn, F.G., *et al*. (1990) *Journal of Hypertension*, 8, 775–782.

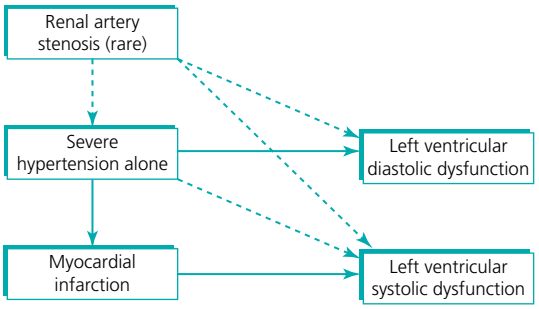


Figure 2.8 Schematic representation of the relation between hypertension and left ventricular failure.

Heart failure

In many epidemiological studies, such as the Framingham Heart Study, hypertension is the principal cause of heart failure. People with blood pressure >160/95 mm Hg have a sixfold higher incidence of heart failure than those with pressures <140/90 mm Hg. Hypertension as a cause of heart failure, however, is confounded by the underlying predisposition to coronary artery disease. Most cases of heart failure are the result of left ventricular systolic dysfunction that results from damage to the ventricle after myocardial infarction (Figure 2.8).

The presence of LVH on an electrocardiogram itself significantly increases the risk of heart failure. The presence of gross LVH can result in impaired ventricular compliance and relaxation, which leads to diastolic heart failure or 'heart failure with normal systolic function'. The latter can result in left atrial dilatation, and the precipitation of atrial fibrillation. The development of atrial fibrillation per se can precipitate pulmonary oedema, especially if LVH and diastolic dysfunction are present.

Finally, hypertension in association with renal artery stenosis but with no intrinsic myocardial disease can cause 'flash' pulmonary oedema that is related to high levels of plasma renin and angiotensin. This can be corrected by treatment of the renal artery stenosis.

Over many years, heart failure in association with untreated hypertension may lead slowly to a decrease in blood pressure as the left ventricular function progressively worsens. Patients whose hypertension mysteriously has normalised may have a bad outlook, as this normalisation is the result of a silent or clinically overt myocardial infarction or the development of left ventricular systolic dysfunction.

Large vessel arterial disease

Hypertension contributes to atheromatous vascular disease in all vascular beds. Peripheral artery disease manifested by intermittent claudication is about three times more common in patients with hypertension (Table 2.3). Such patients also may have renal artery stenosis, which may contribute to their hypertension. Disease in the aorta coupled with hypertension may result in the development of abdominal aortic aneurysms (Table 2.4). High pulsatile wave stress and atheromatous disease can lead to dissection of aortic aneurysms, which carries a high short-term mortality. Extracranial carotid artery disease is also more common in people with hypertension.

Table 2.3 Blood pressure and the risk of intermittent claudication

Risk factor	Relative risk (95% CI) of intermittent claudication
Systolic blood pressure ≥160 mm Hg	3.4 (2.3–6.9)
Diastolic blood pressure ≥90 mm Hg	3.2 (1.9–11.6)
Smoking ≥15 cigarettes per day	8.8 (3.0–25.6)

Source: Adapted with permission from Hughson, W.G., *et al*. (1978) *British Medical Journal*, 1, 1379–1381. © BMJ Publishing Group Ltd.

Table 2.4 Prevalence of abdominal aortic aneurysm in patients with hypertension: an analysis of published papers

Study	Prevalence (%)
Scriffen (1995)	11.9
Vardulaki (2000)	4.8
Spittel (1997)	6.5
Lindholt (1997)	17.8
Williams (1996)	
Men	5.2
Women	0.1
Grimshaw (1994)	7.7

Source: Reproduced with permission from Makin, A.J., *et al*. (2001) *Journal of Human Hypertension*, 15, 447–454. © Nature Publishing.

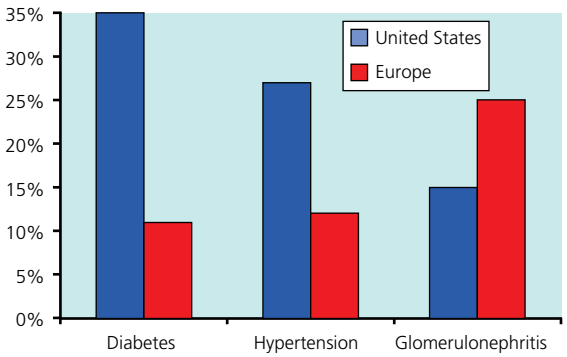


Figure 2.9 The causes of end-stage renal disease in the United States and Europe. The striking disparities are probably due to differences of criteria in the two continents. A large proportion of patients with diabetes or glomerulonephritis will also have hypertension. In many patients, the diagnosis of glomerulonephritis will have been unproven. Source: Data from Valderrábano, F., *et al*. (1995) *Nephrology Dialysis Transplantation*, 10 (Suppl 5), 1–25.

Renal disease

Renal dysfunction commonly is associated with hypertension, diabetes and intrinsic renal disease (Figure 2.9), although some controversy exists as to whether mild-to-moderate essential hypertension alone leads to renal failure. This is because it remains unclear whether people with hypertension who develop progressive renal failure may have had undiagnosed primary renal disease in the first place. Malignant hypertension often leads to progressive renal failure. Almost all primary renal diseases cause an increase in blood pressure, which is mediated by high levels of renin and

Table 2.5 Relative risk of overall and cardiovascular death in relation to microproteinuria

	No proteinuria	Less than 100 mg/l	100 mg/l or more
All cause RR of death	1	1.2	2.0
RR for cardiovascular death	1	1.2	2.2

Source: Adapted from Castiglia, E. (1998) *Journal of Human Hypertension*, 12, 575–581.

Table 2.6 Prevalence and mechanisms of hypertension following renal transplantation

Found in about 50% of patients
Related to ciclosporine and prednisolone
Transplant renal artery stenosis
Ischaemic renal damage during transfer
Transplant rejection
Recurrence of recipient renal or systemic disease
Hypertension from transplanted kidney
Activation of the renin-angiotensin system
Sodium and water retention

angiotensin, as well as sodium and water retention. There is increasing evidence of the prognostic importance of proteinuria, microproteinuria and mild elevations of serum creatinine in patients with hypertension and no clear evidence of intrinsic renal disease (Table 2.5).

It has also become clear that patients with renal failure, with or without dialysis or transplantation, have a greatly increased risk of developing coronary heart disease or strokes. This excess appears not to be explained by the conventional cardiovascular risk factors (blood pressure, cholesterol, smoking and diabetes). There is also marked excess of hypertension in patient following renal transplantation (Table 2.6).

Retinopathy

Hypertension leads to vascular changes in the eye, which is referred to as hypertensive retinopathy, comprising of generalised and focal retinal arteriolar narrowing, arteriovenous nipping or nicking, retinal hemorrhages, microaneurysms and, in severe cases, optic disc and macular oedema.

These changes were classified by Keith, Wagener and Barker into four grades that correlate with prognosis. The most severe hypertension – that is, malignant hypertension – is defined clinically as increased blood pressure in association with bilateral retinal flame-shaped haemorrhages and cotton wool spots or hard exudates, or both, with or without papilloedema. If untreated, 88% of patients with malignant hypertension die within 2 years – mainly from heart failure, renal failure or stroke.

Mild hypertensive retinopathy signs are seen in nearly 10% of the general adult non-diabetic population. Hypertensive retinopathy is closely associated with other indicators of end-organ damage (e.g. LVH, renal impairment) and may be a risk marker of future clinical events, such as stroke, congestive heart failure and cardiovascular mortality.

Several retinal diseases such as retinal vascular occlusion (artery and vein occlusion), retinal arteriolar emboli, macroaneurysm, ischaemic optic neuropathy and age-related macular degeneration are also related to hypertension, although there is no evidence that treatment of hypertension prevents vision loss from these conditions.

Hypertension and anaesthetic risk

Patients with hypertension are at increased risk of heart attacks, stroke and atrial fibrillation during general anaesthetics and the immediate post-operative period. In addition, quite marked surges in blood pressure are seen during the induction of anaesthesia and endotracheal intubation. Many of these problems can be overcome in emergency situations by expert anaesthetists. There is now no convincing evidence that any particular group of antihypertensive drugs, including the β blockers, convey any specific advantage. In patients who are receiving treatment with drugs which block the renin–angiotensin–aldosterone system (the ACE inhibitors or the angiotensin receptor blockers), the height of the blood pressure is highly dependent on their intravascular volume and hydrational status. Careful and accurate fluid replacement in mandatory.

In patients with surgical emergencies who have very high blood pressures, a diagnosis of phaeochromocytoma should be considered, although this is very rare. Emergency blood pressure reduction is best achieved either with intravenous nitrates or sodium nitroprusside infusion. Occasionally, oral nifedipine 30 mg can be used in hypertensive urgencies, but not in emergencies.

Patients for non-emergency surgery with known and treated hypertension should continue their antihypertensive therapy until the morning of operation. Treatment should usually be restarted as soon as the patients are able to swallow their pills.

Many patients who are to undergo elective surgery are not surprisingly very anxious and may develop raised blood pressures, not unlike the so-called white-coat effect. It is crucial therefore that the blood pressure is measured accurately in a quiet, conversation-free room with the patient seated, preferably using an automatic manometer. Up to five of six blood pressure readings should be taken at 5 min intervals. If the systolic blood pressure settles to below 160 mm Hg and there is absolutely no LVH or any other abnormality on the ECG, surgery can proceed as planned. In the past, a great many elective surgical operations were postponed on the basis of a single one-off raised blood pressure reading in stressed patients.

If prior to non-urgent surgery the blood pressure remains above 160 mm Hg or the ECG shows LVH, the operation should be postponed pending the achievement of good pressure control by the patient's family doctor or in a specialist blood pressure clinic.

Multiple risk factors

High blood pressure should not be viewed as a risk factor in isolation. Instead, patients with hypertension very often have many additional risk factors, including hyperlipidaemia, diabetes mellitus and impaired glucose tolerance. Patients with hypertension who smoke cigarettes are at particularly high risk.

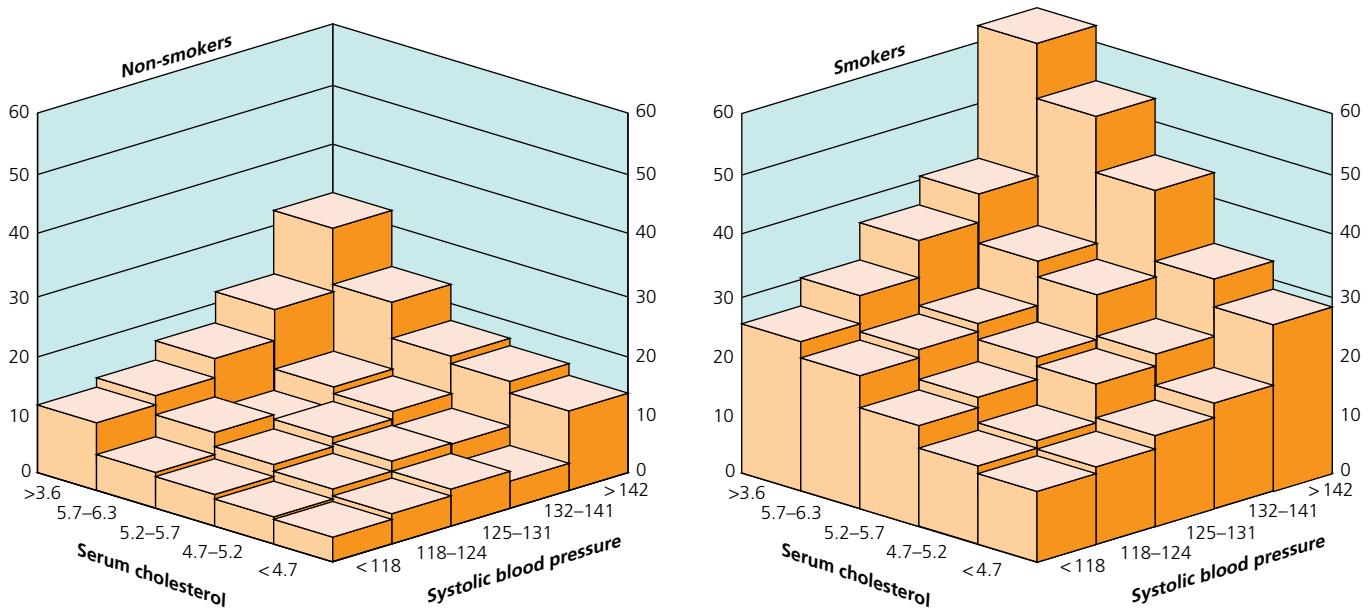


Figure 2.10 Risk of death from coronary heart disease and stroke in men in relation to smoking status, serum total cholesterol levels, and systolic blood pressure; rated per 1000 patient years in the MRFIY screenees. Source: Data from Stamler, J., *et al*. (1986) *Journal of the American Medical Association*, 256, 2823–2828.

A good example of the multiplicative rather than additive effect of multiple risk factors comes from the US 1986 study of 356 222 examinees for the MRFIT trial (see Further Reading). A man with a systolic blood pressure of more than 141 mm Hg and a serum total cholesterol of less than 4.7 mmol/l (i.e. one risk factor) has an expected total cardiovascular mortality risk of around 12 per 10 000 person years. If, however, his serum total cholesterol was more than 6.3 mmol/l (i.e. two risk factors), his expected mortality would be around 35 per 10 000 person years.

If this same individual also had the misfortune to be a cigarette smoker (i.e. three risk factors), his expected mortality would be 64 per 10 000 person years (Figure 2.10).

The treatment of people with hypertension should not focus solely on blood pressure but must also assess total risk for CVD and use multifactorial interventions to reduce their risk in a 'holistic' approach.

The treatment of blood pressure alone in the presence of other risk factors may be relatively ineffective at preventing stroke and myocardial infarction. Coexistent signs of cardiovascular end organ damage also confer a high degree of cardiovascular risk on a patient. For example, LVH, previous heart attack and stroke are all major contributors to premature death

How do we assess risk of cardiovascular disease?

The risk of CVD can be assessed in many different ways. These include 'gut feeling' (commonly practiced in the clinic but not very scientific), various complex algorithms (used more as research tools than for everyday clinical use) and simple colour charts that are based on established risk scores.

The Joint British Societies' (the British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, and endorsed by the British Diabetic Association) risk assessment has the advantage of a more accurate lipid profile, including serum HDL cholesterol as well as systolic pressure and smoking habit (Figure 2.11). This also provides a measure of total cardiovascular risk (fatal and nonfatal) over 10 years, in a manner which is easily explicable to patients. The presence or absence of concomitant diabetes mellitus is not included in the charts as all patients with this condition have a cardiovascular risk of more than 20% in 10 years.

For these charts to be used in clinical practice, it is crucial to measure both serum total cholesterol and HDL cholesterol and calculate the ratio (TC: HDL). Unlike the measurement of serum triglycerides, blood samples do not need to be taken in the fasting state unless the TC: HDL is borderline. A normal nonfatty meal only affects cholesterol by about 10%.

Figure 2.11 Cardiovascular (CVD) risk charts for men (upper panel) and women (lower panel) published by the Joint British Societies. CVS includes both heart attacks and strokes. Source: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart 2005; 91 (suppl 5). Reproduced with permission from BMJ Publishing Group Ltd.

The Joint British Societies cardiovascular risk prediction charts are based on the long-term follow up of people in the town of Framingham, Massachusetts. Whether the charts are equally applicable to populations of non-European origin in whom patterns of CVD are different is uncertain. In people of African and Far Eastern origin, strokes outnumber heart attacks, and these important differences in CVD may not be explained by the risk factors measured in the Framingham study. However, the risk charts do provide an easily accessible risk assessment relevant to all people.

Another factor to take into consideration when deciding about whether to treat hypertension is the patient's age. Although the relative risk of mortality from CVD in a young man with mild hypertension is increased, the absolute risk of him sustaining a stroke or

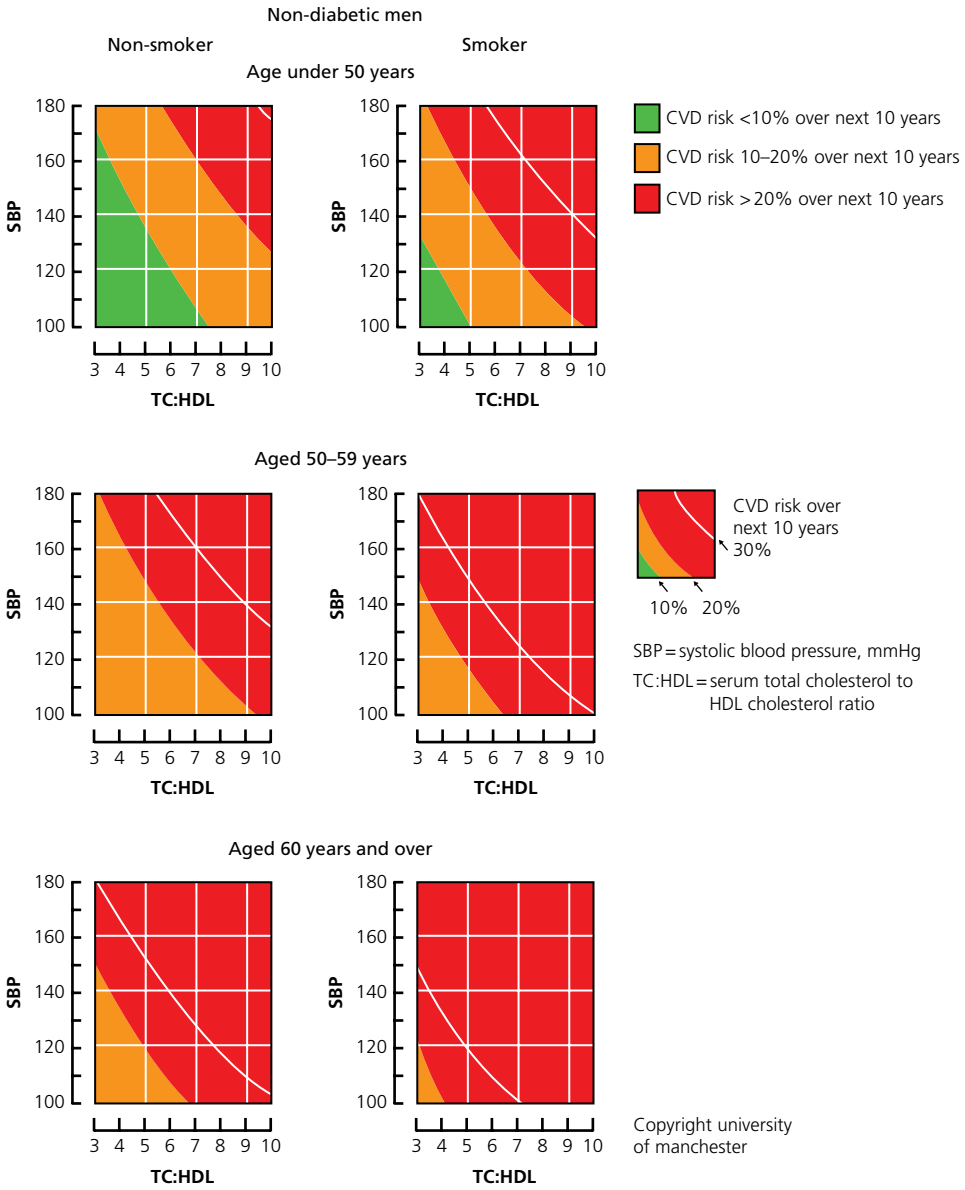


Figure 2.11 Cardiovascular (CVD) risk charts for men (upper panel) and women (lower panel) published by the Joint British Societies. CVS includes both heart attacks and strokes. Source: Reproduced with permission from Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. (2005) *Heart*, 91 (suppl 5), v1–52. © BMJ Publishing Group Ltd.

myocardial infarction within the next 10 years may be low. For an elderly patient with the same degree of hypertension, however, the absolute risk of stroke or heart attack is much higher, as the prevalence of these conditions increases with age. In addition, up to the age of about 50 years, women have a lower risk of CVD than men.

Assessing cardiovascular risk and target organ damage based in the 2011 guidelines from the National Institute of Health and Clinical Excellence

- Estimate cardiovascular risk using the colour charts based on The Framingham Heart study. In the United Kingdom, these are readily available in the last pages of the British National Formulary (BNF). Use these charts to discuss prognosis and treatment options with people with blood pressures of 140/90 mm Hg or more. The estimate of risk should also take into account the individual's age and family history of premature heart attack or stroke.
- Discuss with the patient the benefits managing the other modifiable risk factors (cigarette smoking and lipid-lowering drugs).
- Assess target organ damage
  - Use a reagent strip to test the urine for proteinuria and haematuria.
  - Send a urine sample to the laboratory for estimation of the albumin:creatinine ratio.
  - Take a blood sample to measure plasma glucose, urea, creatinine, estimated glomerular filtration rate (eGFR), sodium, potassium and serum total and HDL cholesterol.
  - If the blood pressure exceeds 160/100 mm Hg, examine the optic fundus for arteriovenous nipping/nicking, cotton wool spots and retinal haemorrhages.

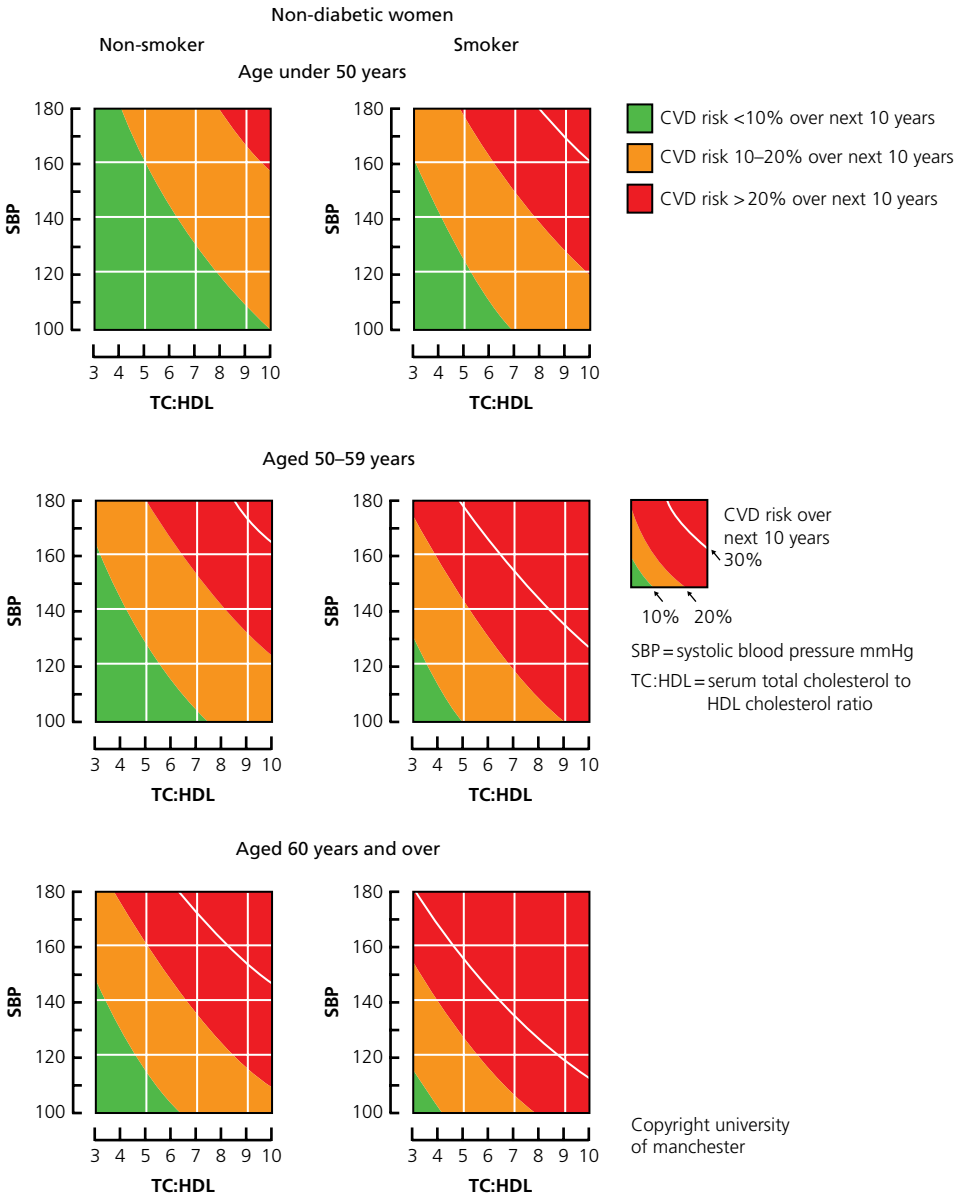


Figure 2.11 (*Continued*)

- Carry out a standard 12 lead echocardiograph to test for LVH, atrial fibrillation and ischaemic heart disease.
- For people under age 40 and those with abnormal urine or blood tests, consider seeking specialist evaluation for underlying renal and adrenal causes for their hypertension.

The public health approach and the high-risk approach to raised blood pressure

In contrast to the strategy of assessing a patient's personal risk when making the decision to start treatment, the public health approach to hypertension means that we should consider community risk on the basis of evidence that the risk of CVD increases with blood pressures even within the normotensive range. Most heart attacks and strokes occur in people with blood pressures that are around average for the general population and below the threshold at which drug treatment would be reasonable. It seems appropriate to try to reduce the blood pressure of the community as a whole. A shift in the entire bell-shaped distribution curve of blood pressure by 5 mm Hg to the left would be expected to produce about a 40% reduction in the incidence of stroke and a 20–25% reduction of coronary heart disease (Table 2.7).

Two strategies thus exist for the prevention of CVD. Patient care is the strategy of treating people with a high risk. In contrast, the public health strategy can be achieved only by public education and manipulation of the nation's habits – sometimes by means of legislation on food labelling (Figure 2.12). This population-based approach aims to produce radical alterations in the national diet, with lower intakes of salt and animal fat and higher intakes of fruit and vegetables. More people should be encouraged to take more exercise and moderate their alcohol consumption, and, of course, benefits can be gained from a reduction of passive and active smoking.

Table 2.7 Meta-analysis of the expected percent reduction in coronary heart disease and stroke following a 2, 5–6 or 7.5 mm Hg reduction in population average diastolic blood pressure

DBP reduction mmHg	CHD %		Stroke %	
	Observational studies	Clinical trials	Observational studies	Clinical trials
7.5	29	21	46	46
5–6	20–25	16	35–40	38
2	9	6	15	15

Source: Data from Cook, N.R., *et al*. (1995) *Archives of Internal Medicine*, 155, 701–709.

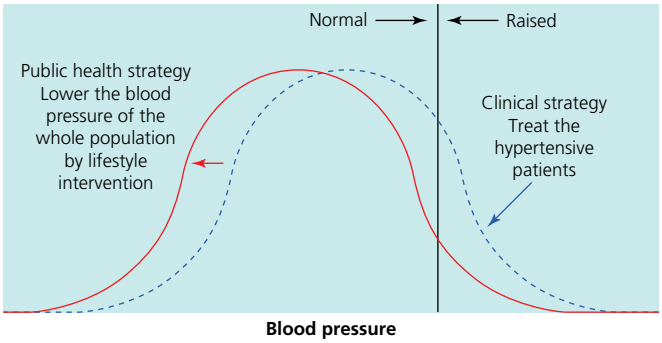


Figure 2.12 The public health strategy (reduce the blood pressure of the whole population) and the clinical strategy (treat hypertensive patients) for preventing heart attacks and strokes. Both strategies are necessary.

Further Reading

(2002) American College of Cardiology/American Heart Association (2002) Guideline update for peri-operative cardiovascular evaluation for non-cardiac surgery-executive summary. *Journal of the American College of Cardiology*, 39, 542–553.

Bhargava, M., Ikram, M.K. & Wong, T.Y. (2012) How does hypertension affect your eyes? *Journal of Human Hypertension*, 26, 71–83.

Cuspidi, C., Sala, C., Negri, F., Mancia, G. & Morganti, A. (2012) Prevalence of left-ventricular hypertrophy in hypertension: an updated review of echo-cardiographic studies. *Journal of Human Hypertension*, 26, 343–349.

Drazner, M.H. (2011) The progression of hypertensive heart disease. *Circulation*, 123, 327–334.

Gorelick, P.B., Scuteri, A., Black, S.E., *et al.* & American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia (2011) Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, 42, 2672–2713.

Kaplan, N.M. & Opie, L.H. (2006) Controversies in hypertension. *Lancet*, 367, 168–176.

Kuhl, M., Lip, G.Y. & Varma, C. (2007) Management of hypertension in relation to acute coronary syndromes and revascularization. *Current Pharmaceutical Research*, 13, 2556–2566.

MacMahon, S., Peto, R., Cutler, J., *et al.* (1990) Blood pressure, stroke and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for regression dilution bias. *Lancet*, 335, 765–774.

McGuinness, B., Todd, S., Passmore, P. & Bullock, R. (2009) Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database of Systematic Reviews*, 4, CD004034.

Perk, J. (2011) ESC/EAS guidelines for management of dyslipidaemia. *European Heart Journal*, 32, 1769–1818.

Sharp, S.I., Aasland, D., Day, S., Sønnesyn, H. & Alzheimer Society Vascular Dementia Systematic Review Group (2011) Hypertension is a potential risk factor for vascular dementia: systematic review. *International Journal of Geriatric Psychiatry*, 26, 661–669.

CHAPTER 3

Pathophysiology of hypertension

OVERVIEW

- The height of the blood pressure in maintained by the interplay between the cardiac output and the total peripheral vascular resistance.
- Cardiac output is usually normal in hypertension, if the heart is undamaged. A high intravascular volume, as is seen in aldosterone excess, also raises blood pressure.
- The main factor controlling peripheral resistance is angiotensin II, generated by the renin-angiotensin system.
- Angiotensin II also stimulates the secretion of aldosterone by the adrenal cortex, causing sodium and water retention.
- The sympathetic nervous system also influences blood pressure and also regional blood flow. Its role in the pathogenesis of hypertension is uncertain.
- Other vasodilating and vasoconstricting hormones also affect blood pressure. Some have both circulating (endocrine) and local (paracrine) effects.
- Arteriolar narrowing is also influenced by structural changes to the vessel wall with vasoconstriction and remodelling.
- There is good evidence that salt intake and salt sensitivity substantially influences blood pressure.
- Whilst a tendency to develop hypertension is clearly genetically inherited, no single gene polymorphism has been found in hypertension. A great many genes are associated with hypertension.

A minority of patients (2–5%) have an underlying renal or adrenal disease as the cause for their increased blood pressure (Figure 3.1). They are classified as having secondary hypertension. In the remaining patients, no cause is found, and such cases are referred to as having primary or 'essential hypertension'. This is clearly illogical, as all diseases have a cause or causes. It is however clear that there is no single cause of essential hypertension. A great many factors influence blood pressure and cause it to be clinically high in some individuals

A wide variety of pathophysiological mechanisms are involved in the maintenance of blood pressure, and their derangement thus may result in the development of essential hypertension.

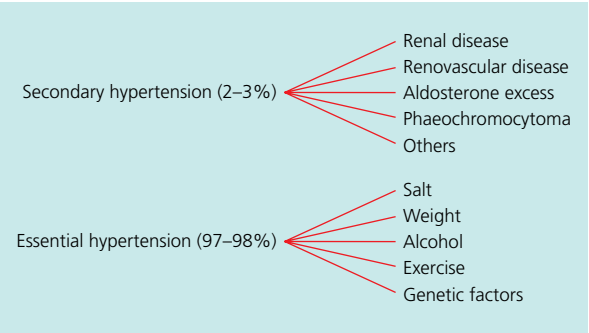


Figure 3.1 Aetiology of hypertension.

Balance between cardiac output and peripheral resistance

Blood pressure is normally dependent on the balance between cardiac output and peripheral resistance (Figure 3.2). Most patients with essential hypertension have increased peripheral vascular resistance and a normal cardiac output. The cardiac output may be increased in the early stages of essential hypertension so that the peripheral resistance gradually increases in order to maintain normal tissue perfusion and cardiac output returns to normal (Figure 3.3). In the later stages of hypertension, left ventricular dysfunction develops and cardiac output decreases so that blood pressure is maintained solely by increased peripheral vascular resistance. At the final stage, the cardiac output may be so impaired that blood pressure then decreases, rendering the patient frankly hypotensive.

Peripheral resistance is not determined by the large arteries or the capillaries but by the small arterioles. The walls of these arterioles contain smooth muscle cells. Extrinsic influences result in contraction of these smooth muscle cells, probably mediated ultimately by a rise in intracellular levels of calcium. Drugs that block the calcium channels thus have a vasodilatory effect that decreases blood pressure. In people with chronic hypertension, the prolonged constriction of smooth muscle results in structural changes to the arterioles, with thickening of the walls and a further increase in arterial blood pressure.

ABC of Hypertension, Sixth Edition. D. Gareth Beevers, Gregory Y. H. Lip and Eoin O'Brien.

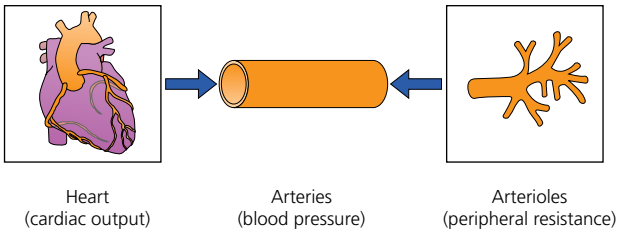


Figure 3.2 Heart, arteries, and arterioles in hypertension.

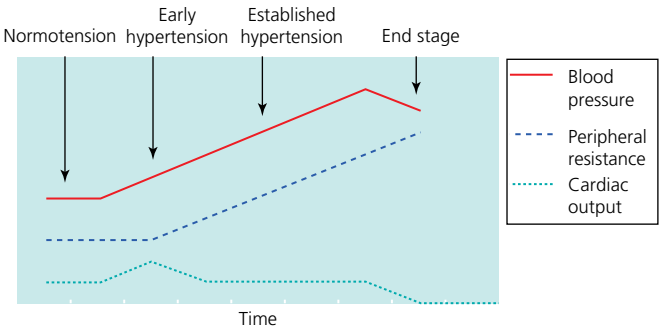


Figure 3.3 Proposed interaction between cardiac output and peripheral vascular resistance in pathogenesis of essential hypertension.

Renin–angiotensin–aldosterone system

The renin–angiotensin–aldosterone system (RAAS) is one of the major hormonal systems that influence blood pressure by the interplay of the vasoconstrictor, angiotensin II and sodium and water retention mediated by aldosterone from the adrenal cortex (Figure 3.4).

Renin is secreted from the juxtaglomerular apparatus of the kidney in response to glomerular underperfusion, reduced intake of salt or stimulation from the sympathetic nervous system. Renin results in the conversion of renin substrate (angiotensinogen) to angiotensin I, which is a physiologically inactive substance. A key enzyme, angiotensin converting enzyme (ACE), results in the conversion of angiotensin I to angiotensin II, which is a powerful vasoconstrictor.

Angiotensin II may also cause some of the manifestations of hypertensive target organ damage, such as left ventricular hypertrophy and atherosclerotic vascular disease (Figure 3.5).

Two of the main drug classes for the treatment of hypertension – the angiotensin converting enzyme inhibitors (ACE-I) and the angiotensin receptor blockers (ARB) – specifically target this system.

The hormone aldosterone also can be antagonised by the non-selective aldosterone receptor antagonist (ARA), spironolactone. This drug has been shown to be beneficial in patients with heart failure. Two open label surveillance studies have shown beneficial effects of spironolactone in resistant hypertension, but there are no long-term studies demonstrating beneficial effects on morbidity or mortality in hypertension

The RAAS, however, is not responsible directly for the increase in blood pressure in patients with essential hypertension. Many patients with hypertension have low levels of circulating endocrine renin and angiotensin II, and, in these patients, the drugs that block the RAAS tend to be less effective.

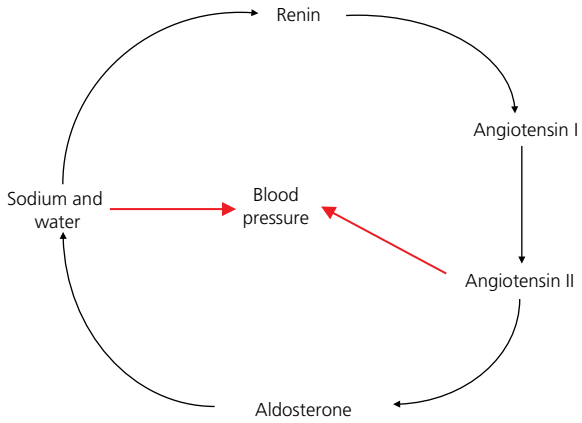


Figure 3.4 The renin–angiotensin–aldosterone system and the control of blood pressure.

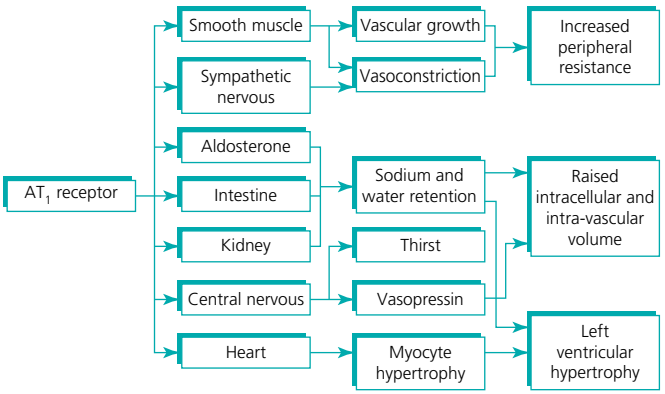


Figure 3.5 Actions of angiotensin II mediated by the angiotensin I (AT1) receptor

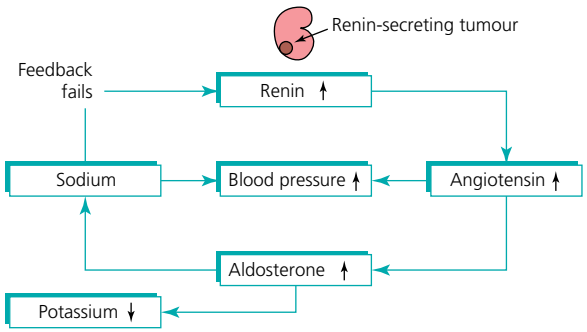


Figure 3.6 Hypertension as a result of isolated excess of renin as seen with renin secreting tumours, renal artery stenosis, and some primary renal diseases.

Hypertension that results directly from excess renin and angiotensin is seen in patients with the extremely rare condition of renin-secreting juxtaglomerular cell tumours and, in some cases, of renal artery stenosis and renal disease (Figure 3.6).

Evidence shows that non-circulating levels of 'local' or 'tissue' angiotensin contribute to control of blood pressure; these hormones are classified as epicrine or paracrine rather than endocrine. Examples are the local renin systems in the kidney and arterial tree,

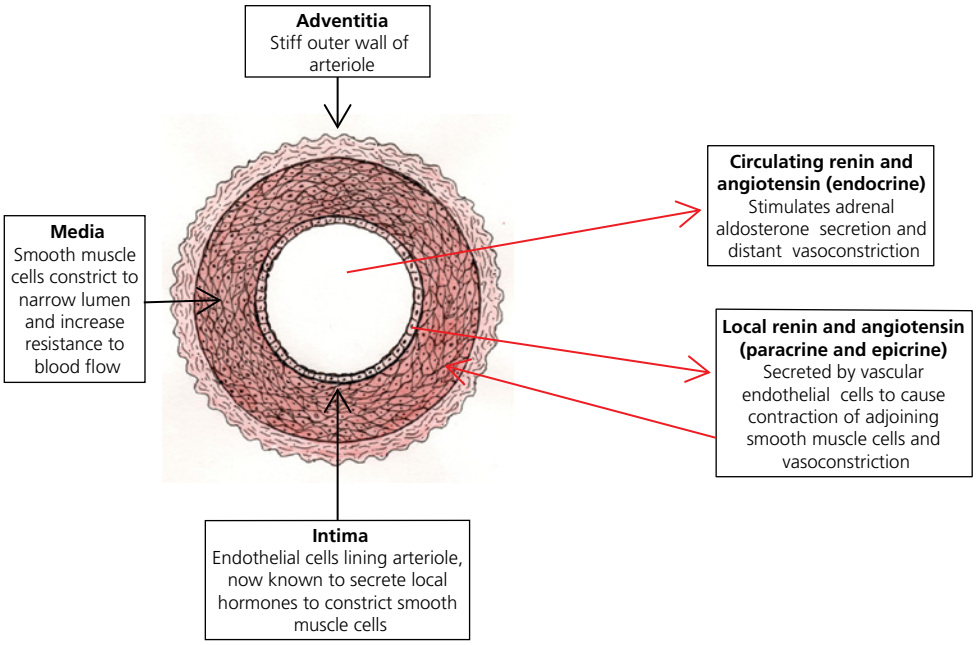


Figure 3.7 Cross-section of an arteriole showing the local and circulating renin–angiotensin systems.

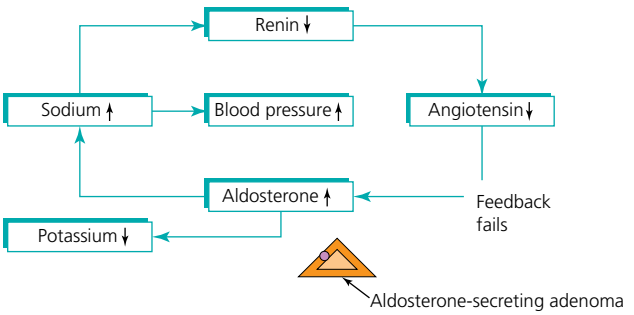


Figure 3.8 Hypertension caused by an isolated excess of aldosterone.

which have important roles in the regulation of regional blood flow (Figure 3.7).

Volume-mediated hypertension

Patients with hypertension and low levels of renin and angiotensin tend to be older and more often of African origin. In these patients, volume overload may cause hypertension. Volume-mediated hypertension due to aldosterone excess alone is seen in primary aldosteronism (Conn's syndrome) (Figure 3.8).

In most other patients, plasma levels of renin, angiotensin and aldosterone are not increased, and circulating blood volume, total body water and total exchangeable sodium are normal. In these people, hypertension may be related to the interplay between blood volume and renin-angiotensin mediated vasoconstriction.

Autonomic nervous system

The second main neurohumeral system that influences blood pressure is the sympathetic nervous system and the corresponding plasma catecholamines. The autonomic nervous system thus has an

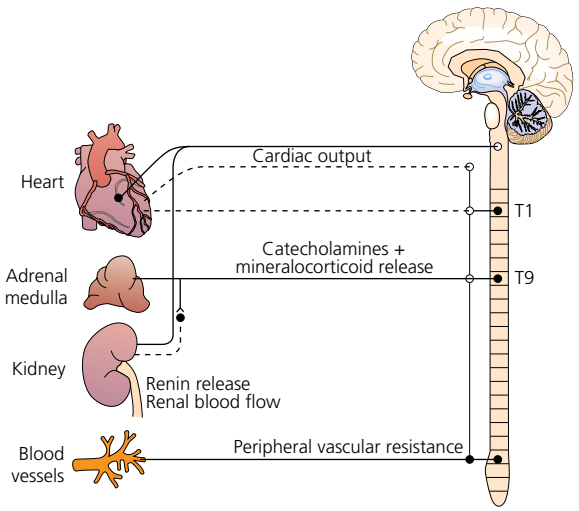


Figure 3.9 Autonomic nervous system and its control of blood pressure. Source: Reproduced with permission from Swales, J., *et al.* (1991) *Clinical Atlas of Hypertension*. London/New York: Gower Medical Publishing. © Elsevier.

important role in maintaining a 'normal' blood pressure, including the physiological responses to changes in posture, as well as physical and emotional activity (Figure 3.9).

Stimulation of the sympathetic nervous system can cause arteriolar constriction and arteriolar dilatation. After stress and physical exercise, such changes mediate short-term changes in blood pressure.

Only limited evidence suggests that the catecholamines (adrenaline and noradrenaline) have a clear role in essential hypertension. Exceptions are the rare catecholamine-secreting tumours, such as phaeochromocytoma, which can cause severe secondary hypertension.

Nevertheless, the effects of the sympathetic nervous system are important, as drugs that act on this system decrease blood pressure. The importance of activation of the sympathetic system in heart

failure as a result of systolic dysfunction and in progression of and mortality from renal insufficiency is well established. For example, the role of β blockers in patients with chronic heart failure is well established to improve mortality and morbidity.

Nonetheless, the neurogenic component to primary hypertension has attracted recent attention given recent developments in the therapeutic targeting of the sympathetic nervous system to control hypertension (e.g. catheter-based renal denervation and carotid baroreceptor stimulation) Chronic activation of the sympathetic nervous system in hypertension leads to raised vasomotor tone and increased cardiac output, as well as interactions of angiotensin II on inflammation and vascular dysfunction/brain hypoperfusion in the pathogenesis and progression of neurogenic hypertension.

Interlocking vasoconstrictor and vasodilator systems

There are a great many neural and hormonal factors which influence peripheral vascular resistance (Table 3.1). This includes various tissue growth factors promoting influencing vascular smooth muscle proliferation and rarefaction. Their role in hypertension remains uncertain and their control is not clinically feasible at present. Two endothelin receptor antagonists are available (bosentan and ambrisentan) and they do lower blood pressure. They are not licensed for systemic hypertension but are used in some patients with pulmonary arterial hypertension (primary primary hypertension).

Insulin sensitivity and metabolic syndrome

In 1988, Reaven highlighted the frequent clustering of multiple risk factors, particularly increased blood pressure, dyslipidaemia, abnormal glucose regulation and obesity. This cluster of cardiovascular risk factors was termed 'syndrome X', 'insulin resistance syndrome', 'metabolic syndrome' or sometimes 'Reaven's syndrome' (Figure 3.10).

Metabolic syndrome is common in high-risk populations, and an alarming prevalence of 24% has been documented in the American population. Mortality from cardiovascular and peripheral vascular disease is higher in people with metabolic syndrome than in those without. Metabolic syndrome particularly is prevalent in people of South Asian (Indian, Pakistani and Bangladeshi) and African-Caribbean origin, who have high morbidity and mortality from vascular disease. Other associations with insulin resistance are non-alcoholic fatty liver disease (NAFLD), hyperuricaemia and low HDL cholesterol. Metabolic syndrome is not a disease entity in itself but rather a unifying hypothesis about the mechanisms of cardiovascular disease. It associated with a raised cardiovascular morbidity and mortality. There is no specific treatment, although individual components, including hypertension, should be treated on the basis of their severity.

Endothelial function

There is increasing interest in the role of the endothelium in the control of blood flow. There are a great many neural and hormonal factors which influence peripheral vascular resistance (Figure 3.11).

Table 3.1 Factors affecting total peripheral vascular resistance

Vasoconstricting systems
Circulating renin–angiotensin system
Local renin–angiotensin systems
Sympathetic nervous system
Circulating and local endothelin
Intracellular calcium
Intracellular sodium
Ouabain
Vasopressin
Tissue plasminogen activator
Chymase
Vasodilating systems
Parasympathetic nervous system
Kallikrein–kinin system
Prostaglandins
Nitric oxide (NO), previously called endothelial derived relaxing factor (EDRF)
Atrial natriuretic peptides, including BNP.
Vascular growth factors
Insulin-like growth factor
Growth hormone
Parathyroid hormone
Tissue oncogenes

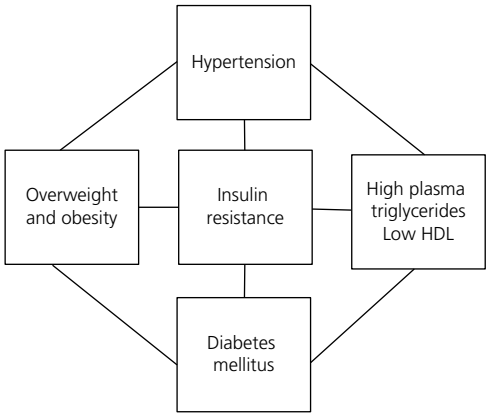


Figure 3.10 The interlocking components of the metabolic syndrome. Other features associated with the metabolic syndrome are nonalcoholic fatty liver disease, hyperuricaemia, polycystic ovary syndrome, and a history of gestational diabetes or hypertension or having given birth to a baby weighing 4 kg or more.

This includes various tissue growth factors influencing vascular smooth muscle proliferation and rarefaction. Their role in hypertension remains uncertain and their control is not clinically feasible at present. Two endothelin receptor antagonists are available (bosentan and ambrisentan) and they do lower blood pressure. They are not licensed for systemic hypertension but are used in some patients with pulmonary arterial hypertension (primary pulmonary hypertension).

Research into the vascular endothelium and its role in vascular disease has been extensive, and the traditional belief that the endothelium is an inert interface between blood and the vessel wall is no longer held. The endothelium produces an extensive range of substances that influence blood flow and, in turn, is affected by changes in the blood and the pressure of blood flow. For example,

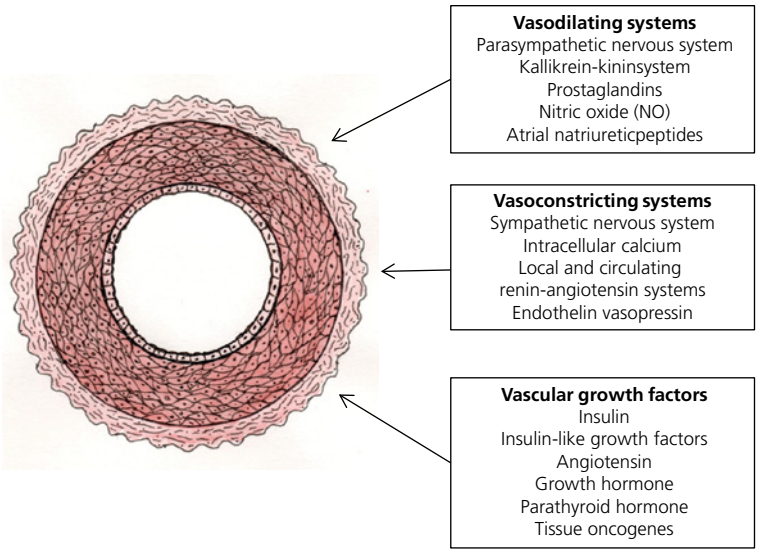


Figure 3.11 Cross section of an arteriole showing some of the vasodilating and vasoconstricting systems and the influence of vascular growth factors.

local nitric oxide and endothelin, which are secreted by the endothelium, are the major regulators of vascular tone and blood pressure.

In patients with essential hypertension, the balance between the vasodilators and the vasoconstrictors is upset, which leads to changes in the endothelium and sets up a 'vicious cycle' that contributes to the maintenance of high blood pressure. In patients with hypertension, endothelial activation and damage also lead to changes in vascular tone, vascular reactivity, and coagulation and fibrinolytic pathways. Alterations in endothelial function are a reliable indicator of target organ damage and atherosclerotic disease, as well as prognosis.

Such macro- and micro-vascular dysfunction may persist for many years, even in patients with treated malignant hypertension who have good blood pressure control.

Prothrombotic state in hypertension

Although patients with high blood pressure have high intra-arterial pressures, their vessels tend more often to thrombose than burst. Cerebral infarction is therefore much more common than cerebral haemorrhage.

Nearly 150 years ago, Virchow postulated a triad of abnormalities that predispose to thrombus formation (thrombogenesis). These are abnormalities in blood flow, blood constituents and the vessel wall. These are referred to as 'Virchow's triad' (Figure 3.12). Evidence suggests that hypertension fulfils the prerequisites of Virchow's triad for thrombogenesis, which leads to a prothrombotic or hypercoagulable state. For example, hypertension leads to changes in platelets, the endothelium and the coagulation and fibrinolytic pathways that promote the induction and maintenance of this prothrombotic state. These changes can be reversed, to a certain extent, by the treatment of hypertension, although different antihypertensive agents may have variable effects in reversing these changes.

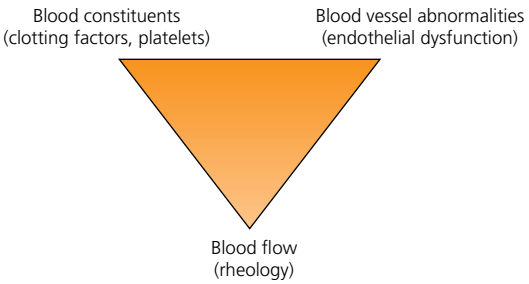


Figure 3.12 Virchow's triad and prothrombotic state in hypertension.

Angiogenesis

Angiogenesis is increasingly recognised as an important aspect of the pathophysiology of cardiovascular disease (CVD) and has an impact on thrombogenesis and atherogenesis. The process of thrombogenesis is related intimately to atherogenesis. A common feature is loss of integrity of the endothelial cells. Certainly, endothelial damage or dysfunction is crucial in the formation of atherosclerosis (atherogenesis).

Angiogenesis is another pathophysiological process that is also evident in atherosclerotic vascular disease: vasa vasorum in the adventitia and media are at a higher density in atherosclerotic tissue and often greater neovascularisation is seen, which leads to stenoses or collateral growth to bypass obstructions, or both.

Salt sensitivity

It is clear that some individuals' blood pressures are more sensitive to salt loading or salt restriction than others. The exact mechanisms of the variations in salt sensitivity are uncertain but are related to circulating levels of renin and angiotensin. There is a tendency for plasma renin activity (PRA) or concentration to fall with increasing age: between the ages of 20 and 60, PRA is roughly halved. In addition, mean PRA in African-origin individuals is about half of that seen in other ethnic groups. Patients with overt hypertension are also more sensitive than normotensive individuals.

Table 3.2 Genetic causes and associations in hypertension.

Liddle's syndrome: a disorder associated with hypertension, low plasma levels of renin and aldosterone, and hypokalaemia: all of which respond to amiloride, an inhibitor of the distal renal epithelial sodium channel.
Glucocorticoid remediable aldosterone: a disorder that mimics Conn's syndrome, in which a chimeric gene is formed from portions of the 11 β-hydroxylase gene and the aldosterone synthase gene. This defect results in hyperaldosteronism, which is responsive to dexamethasone and has a high incidence of stroke.
Congenital adrenal hyperplasia due to 11 β-hydroxylase deficiency: a disorder that has been associated with 10 different mutations of the CYP11B1 gene.
Syndrome of apparent mineralocorticoid excess: this disorder arises from mutations in the gene that encodes the kidney enzyme 11 α-hydroxysteroid dehydrogenase. The defective enzyme allows normal circulating levels of cortisol (which are much higher than those of aldosterone) to activate the mineralocorticoid receptors.
Congenital adrenal hyperplasia due to 17 α-hydroxylase deficiency: a disorder with hyporeninaemia hypoaldosteronism, absent secondary sexual characteristics and hypokalaemia.
Gordon's syndrome (pseudo-hypoaldosteronism): familial hypertension with hyperkalaemia, which possibly is related to the long arm of chromosome 17. Sporadic case reports of familial inheritance of phaeochromocytoma (multiple endocrine neoplasia (MEN-2) syndrome), Cushing's syndrome, Conn's syndrome, and renal artery stenosis as a result of fibromuscular dysplasia.
Other associations
Angiotensinogen gene may be related to hypertension
Angiotensin converting enzyme gene may be related to left ventricular hypertrophy or hypertensive nephropathy
α-Adducin gene may be related to salt-sensitive hypertension
Autosomal dominant polycystic kidney disease (PKD-1 and PKD-2): a primary renal disease that frequently causes hypertension

Salt sensitivity is likely to be distributed in a Gaussian or 'normal' distribution rather than a dichotomous division of patients who are salt sensitive or salt resistant, and there is considerable overlap between all groups.

There is reliable evidence that salt restriction to lower blood pressure is more rather effective in older patients, those of African origin and also patients with hypertension compared with normotensives.

There is also evidence that salt restriction is more effective in hypertensive patients who are receiving treatment with drugs, which block the renin-angiotensin system, when compared with other agents like diuretics or calcium channel blockers.

Natriuretic peptides

Atrial natriuretic peptide (ANP) is a hormone secreted from the atria of the heart in response to increased blood volume. Increased levels of ANP result in an increase in excretion of sodium (and fluid) from the kidney. A defect in this system theoretically may cause fluid retention and hypertension.

Brain natriuretic peptide (BNP) is a hormone produced by the left ventricle and has gained much interest as a marker for the presence of left ventricular systolic dysfunction. BNP has been promoted as a 'blood test' with a high negative predictive value for heart failure secondary to systolic dysfunction. Increased levels of BNP have been related to left ventricular hypertrophy and reduced ventricular compliance (so called 'diastolic dysfunction').

Nonetheless, natriuretic peptide levels can be influenced by atrial fibrillation, renal impairment, valvular heart disease and so on.

Genes and hypertension

Each person's variance in blood pressure is under an important degree of genetic control, but quantitative estimates range from 35 to 70%. About 50% of patients with hypertension have a family history of high blood pressure or premature death from cardiac problems in first-degree relatives. People with normal blood pressure but a strong family history of hypertension are at a greater risk than those with no such history.

The precise identification of 'genes that cause hypertension' has not been clear, however, because of the multifactorial nature of the disease and the presence of many major pathogenetic pathways. Indeed, major genes that definitely cause essential hypertension have yet to be discovered, although more than 20 published genome wide screens are available for genes that control blood pressure.

Some autosomal dominant genetically inherited forms of hypertension exist, but they are very rare (Table 3.2).

Intrauterine growth and hypertension

The 'Barker hypothesis' postulates that hypertension and related risk factors for cardiovascular disease – including central obesity, hyperlipidaemia, glucose intolerance and type 2 diabetes – can originate through impaired growth and development during fetal life. The hypothesis suggests that hypertension and related risk factors for CVD may be the consequences of 'programming', whereby a stimulus or insult at a specific, critical, sensitive period of early life results in long-term changes in specific aspects of physiology and metabolism.

Low birth weight and other indices of abnormal growth in utero are related to higher blood pressure, glucose intolerance and other risk factors for CVD, as well as increased risk of CVD events and mortality in later life. People who were small and thin at birth are therefore at particularly high risk of hypertension if they become obese in adult life (Figure 3.13).

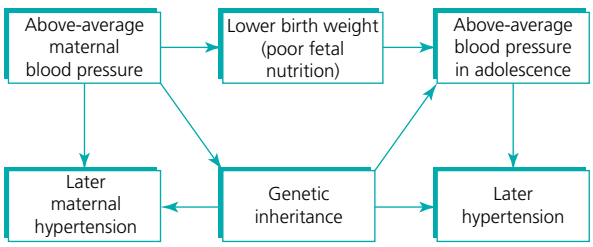


Figure 3.13 Possible mechanisms to explain why low birth weight babies are more likely to develop hypertension in later life.

The Barker hypothesis cannot fully explain observations from many cross-population studies of the effects of migration and acculturation on blood pressure and cardiovascular risk. Many other influencing confounding factors are still unaccounted for, including social class at birth and maternal risk factors for CVD during pregnancy, such as maternal blood pressure. For example, high-normal maternal blood pressure during pregnancy is associated with low-normal birth weight and plausibly with hypertension in later life through the genes and environment shared by a mother and her offspring.

Further Reading

Brown, M.J. (2007) Renin: friend or foe. *Heart*, 93, 1026–1033.

Fisher, J.P. & Paton, J.F. (2012) The sympathetic nervous system and blood pressure in humans: implications for hypertension. *Journal of Human Hypertension*, 26, 463–475.

Schmieder, R.E., Hilgers, K.F., Schlaich, M.P. & Schmidt, B.M.W. (2007) Renin-amgiotensin system and cardiovascular disease. *Lancet*, 369, 1208–1219.

Shantsila, A., Dwivedi, G., Shantsila, E., Butt, M., Beevers, D.G. & Lip, G.Y. (2011) Persistent macrovascular and microvascular dysfunction in patients with malignant hypertension. *Hypertension*, 57, 490–496.

CHAPTER 4

Blood pressure measurement

Part I: Factors influencing all techniques of blood pressure measurement

OVERVIEW

- Hypertension can only be diagnosed by measurement and the device used to measure blood pressure must be accurate.
- Ambulatory blood pressure measurement should be offered to all patients suspected of having hypertension.
- Many factors that affect the accuracy of measurement are common to all techniques of measurement.
- Use of an inappropriate bladder that is too large or too small for the arm is a major cause of inaccurate measurement.
- Patient characteristics, such as obesity and age, must be taken into account when measuring blood pressure.
- Advancing technology will influence greatly the way blood pressure is measured in the future.

Advances in technology and blood pressure measurement

Traditionally, blood pressure has been assessed with the auscultatory technique introduced into clinical medicine at the end of the nineteenth century. Despite being prone to inaccuracy because of inattention to the requirements needed to obtain accurate measurement, this technique has survived largely unchanged for over 100 years. It is salutary to reflect that since Riva-Rocci and Korotkoff introduced the technique, we have landed men on the moon, encircled Mars, invented the automobile and airplane and, most importantly, revolutionised the technology of science with the microchip. Clinical practice has been criticised for ignoring scientific evidence and thereby perpetuating a measurement technique that is likely to be misleading. However, this criticism has been addressed with publication of the recommendations of the National Institute of Clinical Excellence (NICE) in August 2011, which states that ambulatory blood pressure measurement 'should be implemented for the routine diagnosis of hypertension in primary care' (Figure 4.1).

The NICE recommendation is based not only on the large irrefutable evidence base that ambulatory blood pressure measurement is superior to all other measurement techniques for the diagnosis and management of patients with hypertension but also on the fact that it been shown to be a more cost-effective technique than either conventional measurement or self-measurement of blood pressure.

Selection of an accurate device

An accurate device is fundamental to all measurements of blood pressure. If a device is inaccurate, attention to the detail of measurement methods is of little relevance. The accuracy of devices for measurement of blood pressure should not be judged on the sole basis of claims from manufacturers, which can be extravagant. Instead devices should be validated according to international protocols in peer-reviewed journals.

A number of websites provide updated assessments of all devices used to measure blood pressure and indicate which have passed or failed independent validation.

Variability of blood pressure

No matter which measurement device is used, blood pressure is always a variable haemodynamic phenomenon. Modification of the factors that influence variability is not always possible, but we can minimise their effect. When optimum conditions are not possible, this should be noted with the reading.

ABC of Hypertension, Sixth Edition. D. Gareth Beevers, Gregory Y. H. Lip and Eoin O'Brien.

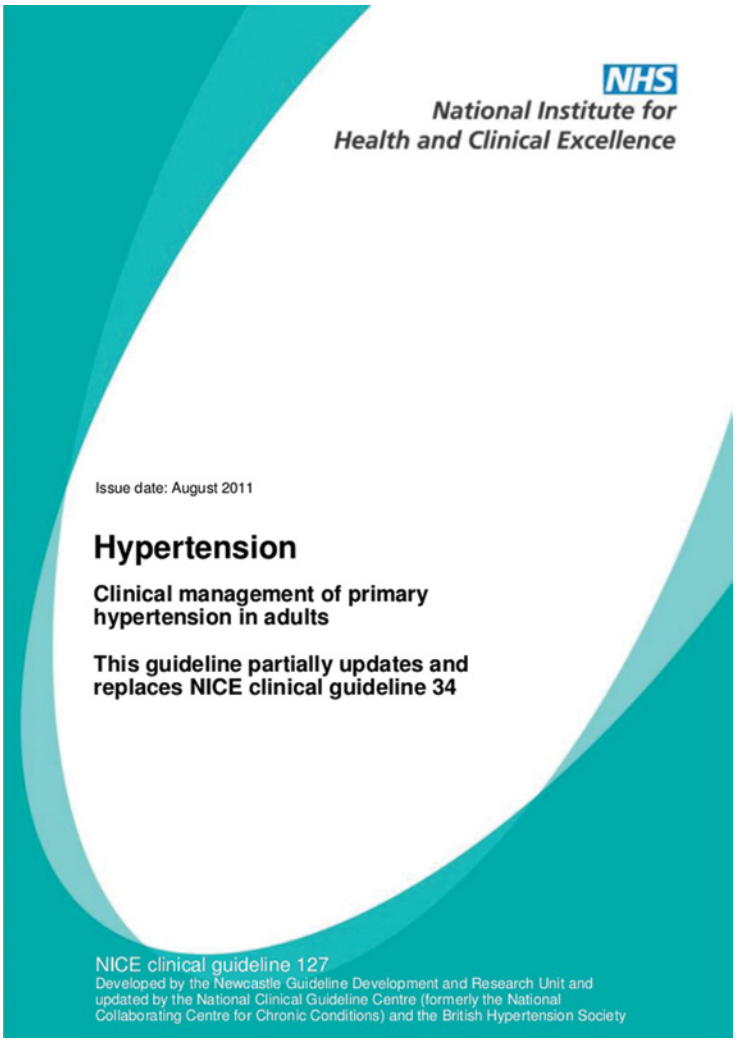


Figure 4.1 NICE guideline.

Box 4.1 **Factors that influence blood pressure variability**

- Circumstances of measurement
- Temperature
- Respiration
- Bladder distension
- Emotion
- Pain
- Exercise
- Age
- Meals
- Race
- Tobacco
- Diurnal variation (blood pressure lowest during sleep)
- Alcohol

White coat hypertension

White coat hypertension is a condition where people with normal blood pressure outside the medical environment have hypertension during measurement by doctors and nurses. White coat hypertension is shown best by ambulatory blood pressure measurement.

White coat effect

This phenomenon, which occurs in both treated and untreated subjects, is present when the office blood pressure is higher than self-measured blood pressure and/or the daytime ambulatory blood pressure but the latter is also above normal.

These white coat phenomena are important because a decision to initiate drug treatment or to modify drug dosage should never be made on the basis of conventional measurement of blood pressure.

Posture

Posture affects blood pressure, with a general tendency for it to decrease when a person moves from the lying position to the sitting or standing positions. Some patients may have postural hypotension, especially those who are taking certain antihypertensive drugs and elderly people. When this is likely, blood pressure should also

Box 4.2 **Definitions of white coat and masked hypertension phenomena**

White coat hypertension
Untreated subjects with elevated office BP ≥ 140/90 mm Hg **and**
Awake ABPM < 135/85 mm Hg **or**
Home BP < 135/85 mm Hg

White coat effect
Treated or untreated subjects with elevated office BP ≥140/90 mm Hg **and**
Awake ABPM ≥135/85 mm Hg **or**
Home BP ≥135/85 mm Hg

Masked hypertension
Untreated subjects with office BP <140/90 mm Hg **and**
Awake ABPM ≥ 135/85 mm Hg **or**
Home BP ≥135/85 mm Hg

Box 4.3 **Posture and position**

- Measure blood pressure routinely with patient in sitting position.
- Back should be supported.
- Legs should be uncrossed.
- Feet should be flat on the floor.
- Patient should be relaxed.
- Measure after 2 min of standing if indicated.

be measured when the patient is standing, but ambulatory blood pressure measurement is the most effective way of diagnosing symptomatic hypotension.

Arm support

If the arm in which blood pressure is being measured is unsupported – as tends to happen when the patient is sitting or standing – the patient will perform isometric exercise, which can increase blood pressure by as much as 10%. The arm therefore must be supported during measurement of blood pressure, especially when the patient is in the standing position. This is achieved best in practice by the observer holding the patient's arm at the elbow (Figure 4.2).

Arm position

The forearm should be at the level of the heart – that is, the mid-sternum. Measurement in an arm lower than the level of the heart leads to an overestimation of systolic and diastolic pressures, while measurement in an arm above the level of the heart leads to underestimation. Such inaccuracy can be as much as 10 mm Hg, especially when the patient is in the sitting or standing position, when the arm is likely to be below heart level by the side. Arm position is important for self-measurement of blood pressure, especially with devices for wrist measurement.

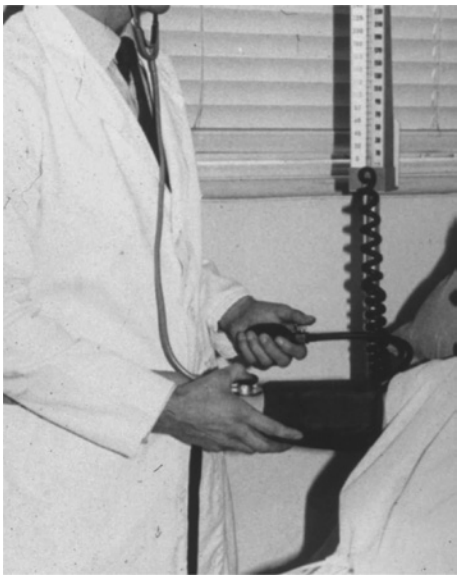


Figure 4.2 Arm support during blood pressure measurement.

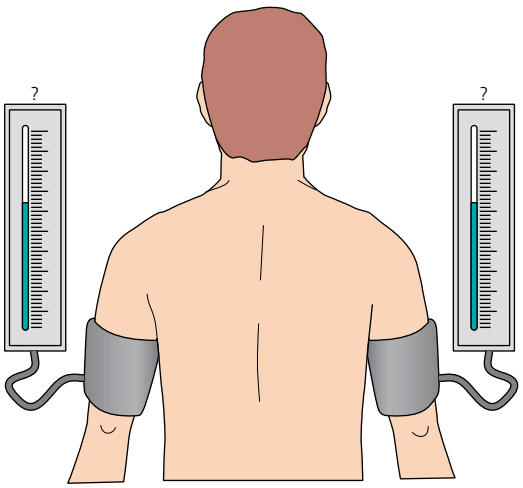


Figure 4.3 Which arm?

Which arm?

Arterial disease can cause differences in blood pressure between arms, but because blood pressure varies from beat to beat, any differences may simply reflect blood pressure variability or measurement errors, or both. Bilateral measurement should be made at the first consultation; if differences >20 mm Hg for systolic or 10 mm Hg for diastolic blood pressure are present on consecutive readings, the patient should be referred to a cardiovascular centre for further evaluation with simultaneous bilateral measurement and for the exclusion of arterial disease (Figure 4.3).

Crossing legs

Crossing legs has been shown to increase blood pressure and when measurement is made both feet should be flat on the floor with the legs uncrossed.

Cuff and bladder

The cuff is an inelastic cloth that encircles the arm and encloses an inflatable rubber bladder. The cuff is secured around the arm most often by means of Velcro on the adjoining surfaces of the cuff. Velcro surfaces must be effective; when they lose their grip, the cuff should be discarded. It should be possible to remove the bladder so that the cuff can be washed.

Cuff hypertension

All devices in clinical use are dependent on cuff occlusion of the arm and are prone to the inaccuracy of miscuffing. Firstly, a bladder that is too long for the arm may result in underestimation of blood pressure, but more commonly, a bladder that is too short and does not encircle the arm will overestimate blood pressure – so-called cuff hypertension. Miscuffing is a serious source of error that leads inevitably to incorrect diagnosis in clinical practice and erroneous conclusions in research into hypertension.

Whatever cuff is used, the centre of the bladder should be placed over the brachial artery, to minimise the occurrence of cuff hypertension (Figure 4.4).

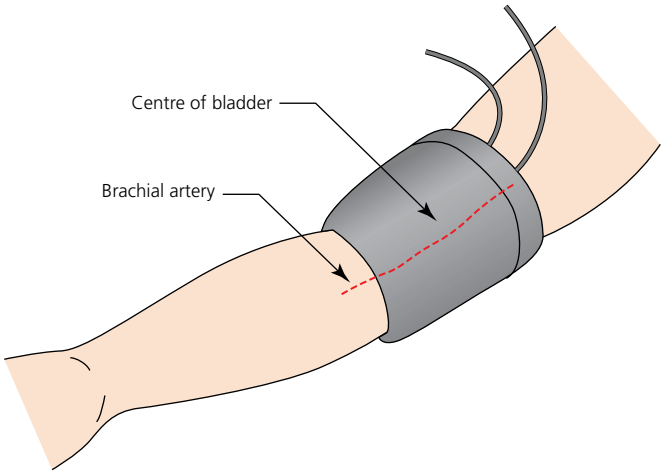


Figure 4.4 Placement of cuff.

Box 4.4 **Recommended bladder dimensions for adults**

British Hypertension Society

Cuff type	For whom	Dimensions (cm)
Small	Lean adult arms and children	12 × 18
Standard	Most adult arms	12 × 26
Large	Arms of obese patients	12 × 40

American Heart Association

Cuff type	Arm circumference (cm)	Dimensions (cm)
Small adult	22–26	12 × 22
Adult	27–34	16 × 30
Large adult	35–44	16 × 36
Adult thigh	45–52	20 × 42

Many national bodies now recommend a range of cuffs to cater for all eventualities, which presupposes that the user will measure the arm circumference and, having done so, will have access to an adequate range of cuffs. In practice, neither of these requirements is easily fulfilled.

Societies differ in their recommendations. The striking difference between the American and British recommendations is not so much the length of the bladders but the width: most European arms will comfortably accommodate a bladder with a width of 12 cm, but a bladder with a width of 16 cm is likely to encroach on the antecubital fossa – particularly if (as often happens in practice) the sleeve of the patient's shirt or blouse is rolled up.

Special management of blood pressure

Certain groups of people merit special consideration for the measurement of blood pressure because of age, body habitus or disturbances of blood pressure related to haemodynamic alterations in the cardiovascular system.

Children

Measurement of blood pressure in children presents a number of difficulties. Variability of blood pressure is greater than in adults, and any one measurement is less likely to represent the true blood pressure. Systolic pressure is more accurate and reproducible than diastolic pressure. A cuff with proper dimensions is essential for accurate measurement. The widest cuff practicable should be used. Ideally, blood pressure should be measured after a few minutes of rest. Values obtained during sucking, crying or eating will not be representative. As with adults, a child's blood pressure status should be decided only after it has been measured on a number of separate occasions. Ambulatory blood pressure measurement is being used increasingly in children.

Elderly people

In epidemiological and interventional studies, blood pressure predicts morbidity and mortality in elderly people as effectively as in the young.

Elderly people have considerable variability in blood pressure, which can lead to a number of diurnal blood pressure patterns that are identified best with ambulatory blood pressure measurement. These *patterns include* isolated systolic hypertension, white coat hypertension and hypotension.

Elderly patients may also have pseudohypertension, a condition in which there is a large discrepancy between cuff and direct measurement of blood pressure in elderly patients. When conventional measurements seem to be out of proportion with the clinical findings, referral to a specialist cardiovascular centre for further investigation may be an appropriate option.

Obese people

The association between obesity and hypertension has been confirmed in many epidemiological studies. Obesity may affect the accuracy of measurement of blood pressure in children, young

and elderly people, and pregnant women. The relation of arm circumference to bladder dimensions is particularly important. If the bladder is too short for the arm as often happens with obese arms, blood pressure will be overestimated – 'cuff hypertension'. The increasing prevalence of the metabolic syndrome (obesity, hypertension and hyperglycaemia) makes accurate measurement of blood pressure in obese people increasingly important. In some obese patients, the arm circumference is so great that upper arm measurement is not possible and forearm measurement may be the only option. For conventional measurement, the Korotkoff sounds are auscultated over the radial artery and for devices that measure blood pressure by oscillometry (devices for self-measurement and ambulatory blood pressure measurement), the cuff is placed on the forearm.

Patients with arrhythmias

Large variations in blood pressure from beat to beat make it difficult to obtain accurate measurements in patients with arrhythmias. In patients with arrhythmias, such as atrial fibrillation, blood pressure varies depending on the preceding pulse interval. No generally accepted method of determining auscultatory end points in patients with arrhythmias exists. Devices for measuring blood pressure with oscillometry vary in their ability to accurately record blood pressure in patients with arrhythmias. Measurements of blood pressure at best will constitute a rough estimate in those with atrial fibrillation, particularly when the ventricular rhythm is rapid or highly irregular, or both. The rate of deflation should be no faster than 2 mm Hg per heartbeat, and repeated measurements may be needed to overcome variability from beat to beat (Figure 4.5).

Two potential sources of error exist when patients have bradyarrhythmia. If the rhythm is irregular, the same problems as with atrial fibrillation will apply. When the heart rate is extremely slow – for example, 40 beats/min – it is important that the rate of deflation used is less than for people with normal heart rates, as too rapid deflation will lead to underestimation of systolic blood pressure and overestimation of diastolic blood pressure.

Pregnant women

Clinically, relevant hypertension occurs in more than 10% of pregnant women in most populations. High blood pressure is a key factor in making medical decisions in pregnancy.

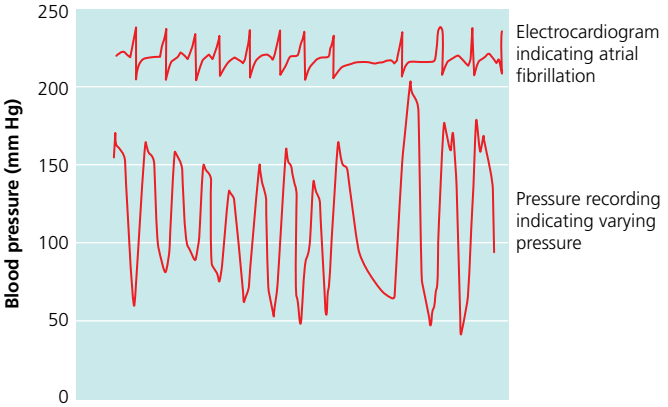


Figure 4.5 Atrial fibrillation.

Disappearance of sounds (fifth phase) is the most accurate measurement of diastolic pressure, except when sounds persist to zero, in which case the fourth phase of muffling of sounds should be used.

Patients who take antihypertensive drugs

In patients who take antihypertensive drugs, the timing of measurement may have a substantial influence on the blood pressure. The time of taking antihypertensive drugs should be noted.

Patients who are exercising

Systolic blood pressure increases with increasing dynamic work as a result of increasing cardiac output, whereas diastolic pressure usually remains about the same or moderately lower. An exaggerated blood pressure response during exercise may predict development of future hypertension.

The impact of future technological advances

The advancing development of technology is likely to bring further innovative changes in blood pressure measurement.

Box 4.5 **Technological advances**

- **Central blood pressure measurement** – the use of techniques that measure blood pressure in the central aorta non-invasively suggests that central BP may give different and important information that cannot be obtained with measurement of BP in a peripheral artery.
- **Blood pressure variability** – recent studies have shown that measures of blood pressure variability may provide additional information to mean blood pressure levels, and attention is now been given to finding an index of variability within ABPM that is equivalent to visit-to-visit variability.
- **Arterial function** – function of the arterial organ can be assessed by techniques, such as pulse wave velocity and measures of arterial stiffness. The ambulatory arterial stiffness index (AASI), which is readily obtainable from a single ABPM, provides a prognostic measure of outcome even in normotensive subjects.
- **Information technology and management** – the development of communication technology offers vast potential for the transmission of data and the establishment of centrally hosted registries to provide valuable research and audit resources so as to give accurate demographic information relating to blood pressure and its control in the community.

Further Reading

National Clinical Guideline Centre (2011) *Hypertension. Clinical Management of Primary Hypertension in Adults (Clinical Guideline; no. 127)*. National Institute for Health and Clinical Excellence (NICE), London.

O'Brien, E. (2011) 24-hour ambulatory blood pressure measurement in clinical practice and research: a critical review of a technique in need of implementation. *Journal of Internal Medicine*, 269, 478–495.

O'Brien, E., Asmar, R., Beilin, L., *et al.* & on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring (2003) European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *Journal of Hypertension*, 21, 821–848.

Part II: Conventional blood pressure measurement

OVERVIEW

- Conventional blood pressure measurement is the measurement of blood pressure with a sphygmomanometer in the medical setting.
- Automated oscillometric devices are replacing auscultatory measurement of blood pressure with a sphygmomanometer and stethoscope.
- Mercury sphygmomanometers are being removed from clinical practice because of the international move to ban mercury from the environment but hybrid devices that do not contain mercury are now available.
- The auscultatory technique is likely to live on for some time, but because it is fraught with potential inaccuracies, attention to the correct procedure is important.
- Automated oscillometric devices, which are being increasingly used as replacements for mercury and aneroid sphygmomanometers, must be independently validated for accuracy.

Definition

The term 'conventional blood pressure measurement' is open to misinterpretation unless clearly defined. It is sometimes applied to the traditional auscultatory technique of blood pressure measurement using a stethoscope and mercury sphygmomanometer, whereas it can also be applied to any method of measurement used in the setting of clinical practice. For the purpose of this book, it is the measurement of blood pressure by whatever means in a medical setting, such as a doctor's office or surgery, a hospital clinic or outpatient department, or a pharmacy. It is distinguished, therefore, from what are often referred to as 'out-of-office' measurements, such as self-measurement or ambulatory blood pressure measurement.

Conventional measurement of blood pressure will remain the initiating measurement technique for most patients. However, accurate automated devices, some of which can give repeated measurements and thereby minimise the likelihood of misdiagnosis, are replacing the auscultatory technique.

The auscultatory technique of blood pressure measurement

Conventional measurement of blood pressure with a mercury sphygmomanometer and stethoscope, which was first introduced to medicine by Scipione Riva-Rocci and Nicolai Korotkoff at the end of the nineteenth century, is now used decreasingly in clinical practice for a number of reasons (Figure 4.6).

However, apart from what might be termed a sentimental desire to retain a century-old method that is the last measurement technique used regularly in clinical examination, there are two reasons why the technique should be retained. Firstly, in patients with arrhythmias, blood pressure measurement with automated techniques may not be possible, and in this circumstance the average of a number of auscultatory measurements may be the best estimate of blood pressure. Secondly, in some patients it is not possible (for reasons that are not apparent) to measure blood pressure with oscillometric techniques and the auscultatory technique has to be used.

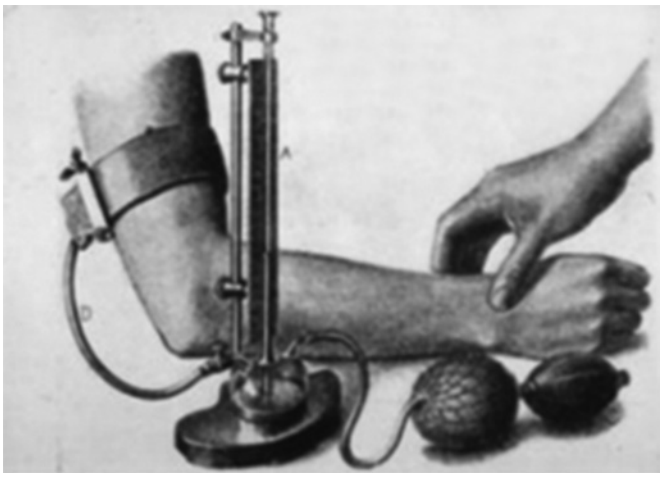


Figure 4.6 Riva-Rocci sphygmomanometer. Source: Reproduced with permission from O'Brien, E. & Fitzgerald, D. (1991) The history of indirect blood pressure measurement. In: *Blood Pressure Measurement* (eds E. O'Brien & K. O'Malley). Elsevier, Amsterdam. © Elsevier.

Box 4.6 **Decreasing use of auscultatory sphygmomanometry**

- The technique is fraught with errors that include terminal digit preference, bias and inattention, leading to erroneous measurement.
- The technique is more likely to mislead than guide doctors and their patients by inducing white coat hypertension in as many as 25% of patients and missing hypertension in perhaps as many as 20% of patients – so-called masked hypertension.
- Mercury is being increasingly banned from use in clinical practice because of the risks of environmental pollution and toxicity.
- With the increasing replacement of mercury sphygmomanometers by automated devices, the skill of auscultating the Korotkoff sounds is disappearing from practice.

Sphygmomanometers for auscultatory measurement

Mercury Sphygmomanometers

The mercury sphygmomanometer is a simple, accurate and reliable device that can be serviced easily, but concerns rightly exist about the toxicity of mercury for people who use mercury sphygmomanometers and those who service them. The greatest concern about mercury, however, is its toxic effect on the environment, and mercury increasingly is being banned from use in medicine.

Figure 4.7 Hybrid sphygmomanometer. Source: Reproduced with permission from A&D Company.

Hybrid sphygmomanometers

Alternative devices to the mercury sphygmomanometer, which combine the features of electronic and mercury devices by using an electronic pressure gauge as a substitute for the mercury column, are now available. These devices, which are known as hybrid sphygmomanometers, display cuff pressure as a simulated mercury column with a digital readout on a liquid crystal display. An aneroid scale may be used instead of a mercury-like column.

The cuff is deflated in the normal way; when systolic and diastolic pressure are heard, a button next to the deflation knob is pressed, which freezes the digital display to show systolic and diastolic pressures. This offers the potential of eliminating terminal digit preference, which is a major problem with the clinical use of any auscultatory monitor. The observer is therefore able to measure blood pressure with the traditional auscultatory technique without necessarily having to rely on automated readings. This is achieved without the risk of mercury toxicity (Figure 4.7).

Aneroid sphygmomanometers

Aneroid sphygmomanometers register pressure through a bellows and lever system that is more intricate mechanically than the mercury reservoir and column. The jolts and bumps of everyday use affect accuracy over time, which usually leads to falsely low readings and thus underestimations of blood pressure. They are therefore less accurate in use than mercury or hybrid sphygmomanometers. As mercury sphygmomanometers are removed from clinical practice, they are often replaced with aneroid devices on the false assumption that they are equally accurate. Remarkably little literature exists on the accuracy of aneroid devices and what does is generally negative.

Problems common to all methods of auscultatory measurement

Observer inaccuracy

All sphygmomanometric methods that are dependent on the auscultatory technique are prone to all the problems of observer inaccuracy. The major cause of observer error is the variability of blood pressure and the misleading measurements that constitute the phenomenon of white coat hypertension and masked hypertension may now be added to this list. Training of observers in the technique of auscultatory measurement of blood pressure is often taken for granted. Instruction to medical students and nurses has not always been as comprehensive as it might be, and assessment for competence in the measurement of blood pressure has been a relatively recent development. A number of training methods exist; they include: direct instruction with a binaural or multi-aural stethoscope; manuals, booklets and guidelines; electronic instruction in which the trainee can be assessed by visually watching a falling mercury and listening to Korotkoff sounds.

Box 4.7 **Observer influences**

- Systematic error – intraobserver and interobserver error.
- Terminal digit preference – rounding off to favoured digit, usually 0.
- Observer prejudice – choice of measured pressure influenced by what observer wishes it to be.
- White coat hypertension – high office and normal daytime ambulatory blood pressure.
- White coat effect – office blood pressure higher than high daytime ambulatory blood pressure.
- Masked hypertension – normal office and high daytime ambulatory blood pressure.

Box 4.8 **Weaknesses common to mercury, aneroid and hybrid sphygmomanometers**

- Defective control valve – leakage:
  - — Underestimation of systolic blood pressure.
  - — Overestimation of diastolic blood pressure.
- Leaks as a result of cracked or perished rubber:
  - — Mercury fall cannot be controlled.
- Inadequate tubing:
  - — Minimum length of 70 cm between cuff and manometer.
  - — Minimum length of 30 cm between pump and cuff.
- Connections not airtight.

Inflation–deflation system

The inflation–deflation system consists of an inflating and deflating mechanism connected by rubber tubing to an occluding bladder. The standard mercury, hybrid and aneroid sphygmomanometers used in clinical practice are operated manually, with inflation by means of a bulb compressed by hand and deflation by means of a release valve, which is also controlled by hand. The pump and control valve are connected to the inflatable bladder and to the sphygmomanometer. One of the most common sources of error in sphygmomanometers is the control valve.

Stethoscope

A stethoscope should be of high quality, with clean and well-fitting earpieces. Whether the bell or diaphragm is used in routine measurement of blood pressure probably does not matter much, as long as the stethoscope is placed over the palpated brachial artery in the antecubital fossa. As the diaphragm covers a larger area and is

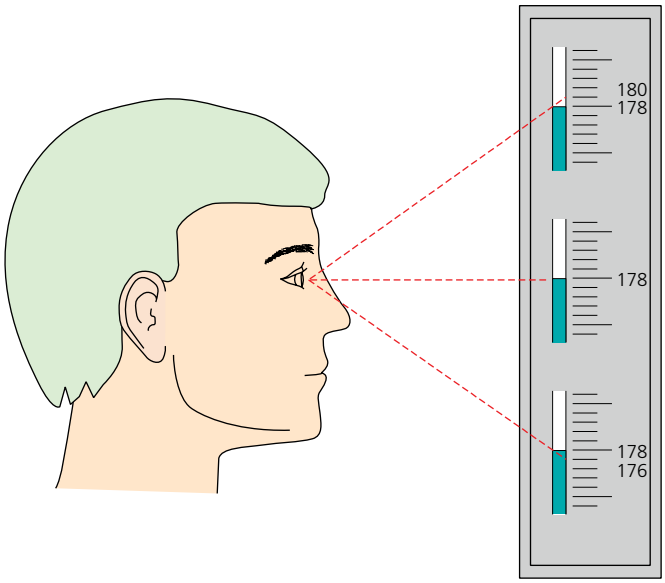


Figure 4.8 Eye level.

easier to hold than a bell end piece, it is reasonable to recommend it for routine clinical measurement of blood pressure. Electronic stethoscopes that amplify the Korotkoff sounds are now commonly used in clinical practice.

Maintenance

To check and maintain mercury sphygmomanometers is easy, but great care should be taken when mercury is handled. Mercury sphygmomanometers need cleaning and checking at least every 6 months in hospital use and every 12 months in general use. In practice, doctors often neglect to have sphygmomanometers checked and serviced. The responsibility for reporting faulty equipment or lack of appropriate cuffs lies with the observer, who should always refuse to use defective or inappropriate equipment.

Aneroid and hybrid sphygmomanometers should be checked every 6 months against an accurate mercury sphygmomanometer over the entire pressure range. If inaccuracies or other faults are found, the instrument should be repaired by the manufacturer or supplier.

Performing auscultatory measurements

Observer skill

The major source of inaccuracy in the technique is observer error. Observers should be trained in the auscultatory technique and should have good hearing.

Position of manometer

The observer should take care to position the manometer so that the scale can be read easily. Accurate measurement is achieved most effectively with stand-mounted models, which can easily be adjusted to suit the height of the observer (Figure 4.8). The mercury manometer has a vertical scale, and errors will occur unless the eye is level with the meniscus. The aneroid scale is a composite of vertical and horizontal divisions and numbers, and it must be viewed straight on, with the eye on a line perpendicular to the centre of the face of the gauge.

Box 4.9 **Manometer position**

- Manometer <3 ft from observer.
- Mercury column should be vertical.
- Mercury column at eye level – standard mounted models can be adjusted to suit the height of the observer.
- Observer's eye should follow the level of the mercury meniscus.
- Aneroid scale must be viewed straight on with eye on a line perpendicular to the centre of the face of the gauge.

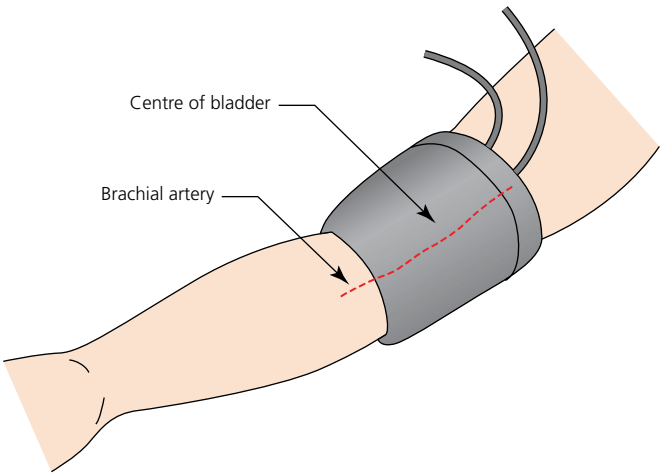


Figure 4.9 Cuff placement.

Placement of cuff

The cuff should be wrapped around the arm, ensuring that the dimensions of the bladder are accurate. If the bladder does not completely encircle the arm, the centre of the bladder must be over the brachial artery. The rubber tubes from the bladder are usually placed inferiorly, often at the site of the brachial artery, but placing them superiorly allows easy access to the antecubital fossa for auscultation. The lower edge of the cuff should be 2–3 cm above the point of brachial artery pulsation (Figure 4.9).

Palpatory estimation of blood pressure

The brachial artery should be palpated while the cuff is inflated rapidly to about 30 mm Hg above the point where the pulse disappears; the cuff is then deflated slowly, and the observer notes the pressure at which the pulse reappears. This is the approximate level of the systolic pressure. Palpatory estimation is important, because phase I sounds sometimes disappear as pressure is reduced and reappear at a lower level (the auscultatory gap), which results in systolic pressure being underestimated unless already determined by palpation. The palpatory technique is useful in patients in whom auscultatory end points may be difficult to judge accurately, for example, pregnant women, patients in shock and those who are exercising. (The radial artery is often used for palpatory estimation of the systolic pressure but use of the brachial artery also allows the observer to establish its location before auscultation begins.)

Diastolic dilemma

For many years, recommendations on blood pressure measurement have been uncertain about the diastolic end point – the so-called diastolic dilemma. Phase IV (muffling) may coincide with or be as much as 10 mm Hg higher than phase V (disappearance), but usually the difference is less than 5 mm Hg. Disappearance of sounds (phase V) should be taken as diastolic pressure. When the Korotkoff sounds persist down to zero, muffling of sounds (phase IV) should be recorded for diastolic pressure, and a note made to this effect.

Recording blood pressure

To make measurement of conventional blood pressure more informative and accurate, it is important to record the circumstances of measurement as well as the levels of blood pressure recorded. Reliability of measurement is improved if repeated measurements are made and measurement of ambulatory blood pressure or self-measurement of blood pressure, or both, give much valuable information that cannot be obtained with measurement of conventional blood pressure.

Automated blood pressure measurement

Sphygmomanometers for automated measurement

Automated devices that are dependent on the oscillometric method for measuring blood pressure are replacing the auscultatory technique. They are being used increasingly in office, clinics and hospitals across the world.

Oscillometric methodology

The oscillometric method measures mean blood pressure, and a specific algorithm (known only to the manufacturer) estimates systolic and diastolic blood pressure.

Accuracy of automated devices

Automated devices for blood pressure measurement should be validated independently using one of the internationally accepted validation protocols. The most commonly used protocol is the European Society of Hypertension International Protocol (ESH-IP). Several oscillometric devices for professional use have been validated and are available on the market.

Advantages and disadvantages of automated measurement

Overall, automated devices are superior to auscultatory measurement of blood pressure, but they also have limitations.

Box 4.10 **Steps in measurement**

- Place the stethoscope gently over the brachial artery at the point of maximal pulsation.
- Hold stethoscope firmly and evenly but without excessive pressure – excess pressure which may distort artery and produce sounds below diastolic pressure.
- Stethoscope end-piece should not touch clothing, cuff, or rubber tubes to avoid friction sounds.
- Inflate cuff rapidly to about 30 mm Hg above palpated systolic pressure.
- Deflate cuff at a rate of 2–3 mm Hg per pulse beat (or per second) during which the Korotkoff sounds will be heard.
- Deflate cuff rapidly after all sounds disappear.
- Make sure cuff is completely deflated before repeating measurement so as to avoid venous congestion of the arm.

Box 4.11 **Korotkoff sounds**

- **Phase I** – the first appearance of faint, repetitive, clear tapping sounds that gradually increase in intensity for at least two consecutive beats is the systolic blood pressure.
- **Phase II** – a brief period may follow phase I, during which the sounds soften and acquire a swishing quality.
- **Auscultatory gap** – in some patients, sounds may disappear altogether for a short time.
- **Phase III** – the return of sharper sounds that become crisper to regain, or even exceed, the intensity of the sound in phase I. The clinical significance, if any, of phases II and III has not been established.
- **Phase IV** – the distinct abrupt muffling of sounds, which become soft and blowing in quality.
- **Phase V** – the point at which all sounds finally disappear completely is the diastolic pressure.

Box 4.12 **Points to be noted**

- Measurements should be noted to the nearest single millimeter of mercury, without rounding off to the nearest 5 or 10 mm Hg.
- Note state of patient – anxious or relaxed.
- Note position of patient for measurement – lying, sitting or standing.
- Note arm (right or left) in which blood pressure is measured; readings should be taken in both arms at the first visit.
- Note arm circumference.
- Note inflatable bladder dimensions.
- Identify Korotkoff phases IV and V for diastolic pressure.
- Note presence of auscultatory gap.
- Note time of drug ingestion, if appropriate.
- At least two measurements should be taken at each visit at intervals of at least 1 min.

Box 4.13 **Advantages and disadvantages of automated devices**

Advantages

- Provides printouts with:
  - — Systolic and diastolic blood pressure.
  - — Mean blood pressure.
  - — Heart rate.
  - — Time of measurement.
  - — Date of measurement.
- Eliminates observer error.
- Eliminates observer bias.
- Eliminates observer digit preference.
- Minimal training needed.
- Some devices can be programmed to take multiple measurements in the absence of an observer so as to minimise the white coat effect.
- Stores data for future analysis and comparison.
- Ability to plot trends.

Disadvantages

- Poor record for accuracy but improving.
- Designed for self-measurement rather than clinical use.
- All use oscillometric measurement.
  - — Point of maximal cuff oscillation – mean blood pressure.
  - — Systolic and diastolic blood pressure derived from algorithm.
  - — Details of algorithm known only to manufacturer.
- Oscillometric technique fails in some individuals.
- Oscillometric technique not accurate in rapid atrial fibrillation.
- Maintenance and calibration – devices are usually discarded if they cease to function.
- Separate validation is required in subgroups of subjects, for example elderly, diabetics, pregnancy, obese, children, and so on.

Some professional oscillometric devices have been programmed to take multiple blood pressure readings in the office or clinic (by manual activation or bluetooth), which allows measurements to be obtained in the absence of an observer, while patients are alone in the examination room (automated office blood pressure measurement). Such devices minimise the office reaction (white coat effect) and give blood pressure values that are closer to those obtained by daytime ambulatory blood pressure monitoring.

Further Reading

O'Brien, E. (2000) Replacing the mercury sphygmomanometer. *British Medical Journal*, 320, 815–816.

O'Brien, E. (2011) What to do when faced with an unmeasurable ambulatory blood pressure? *Journal of Hypertension*, 29, 451–453.

O'Brien, E., Asmar, R., Beilin, L., *et al.* & on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring (2003) European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *Journal of Hypertension*, 21, 821–848.

O'Brien, E. & Fitzgerald, D. (1994) The history of blood pressure measurement. *Journal of Human Hypertension*, 8, 73–84.

Stergiou, G., Karpettas, N., Atkins, N. & O'Brien, E. (2010) European Society of Hypertension International Protocol for the validation of blood pressure monitors: a critical review of its application and rationale for revision. *Blood Pressure Monitoring*, 15, 39–48.

Myers, MG, Valdivieso, M, Kiss, A. (2009) A. Use of automated office blood pressure measurement to reduce the white coat response. *J Hypertens*, 27, 280–286.

Part III: Ambulatory blood pressure measurement

OVERVIEW

- The NICE recommendations have made ABPM an essential investigation for the diagnosis and management of hypertension.
- The technique should be offered to all patients with suspected hypertension.
- Only independently validated devices should be used.
- Training in the technique is necessary.
- ABPMs should be interpreted by experienced personnel.
- Computer generated interpretative reports with standardised plots make the technique more widely acceptable and can be used to involve the patient in management.
- White coat and masked hypertension are best diagnosed by ABPM.
- There are many patterns of ABPM that can improve the management of hypertension.

Box 4.14 **NICE recommendation**

If the clinic blood pressure is 140/90 mm Hg or higher, offer ambulatory blood pressure monitoring (ABPM) to confirm the diagnosis of hypertension.

Box 4.15 **Advantages of ambulatory blood pressure measurement**

- Multiple measurements – real blood pressure is reflected more accurately by repeated measurements.
- A profile of blood pressure away from the medical environment allowing identification of white coat phenomena or masked hypertension.
- Patients with white coat hypertension may be spared blood pressure-lowering drugs.
- Assessment of efficacy of antihypertensive medication throughout the day and night.
- Identify patterns of blood pressure behaviour, such as nocturnal hypertension.
- Stronger predictor of cardiovascular morbidity and mortality.
- Nocturnal blood pressure may be a sensitive predictor of outcome.
- Demonstrates efficacy or otherwise of 24-h blood pressure control.
- More cost-effective than conventional and self-measurement of blood pressure.

Why has NICE chosen ABPM over all other measurements?

Ambulatory blood pressure measurement (ABPM) has been used increasingly in clinical practice over the past two decades, and whereas it was regarded by many as being an indispensible investigation in the diagnosis and management of patients with established and suspected hypertension, it had never been recommended as a mandatory investigation. However, with publication of the recommendations of the National Centre for Clinical Excellence (NICE) in 2011, ABPM has been recommended unequivocally for all patients with suspected hypertension, which means any patient who has had an elevated blood pressure recorded on conventional or with self-measurement of blood pressure.

The NICE recommendation is based on the scientific evidence and the cost-effective superiority of ABPM over conventional measurement and self-measured blood pressure.

Choosing devices and software

The first step in adopting ABPM is to select an accurate device. ABPM in clinical practice is simplified by a standardised graphical presentation of the recording (much as is the case for electrocardiograph recordings) regardless of the type of monitor used. This saves the user having to become familiar with a variety of programs and simplifies the interchange of recordings between hospitals and primary care practices. Interpretive reports provide help for doctors and nurses unfamiliar with the technique, and the time needed for a doctor to report on each measurement is reduced, which lessens the cost of the technique.

Financial considerations

Analysis of the cost-benefit of ABPM by NICE has shown that 'Ambulatory blood pressure measurement is the most cost-effective method of confirming a diagnosis of hypertension in a population suspected of having hypertension based on a conventional blood pressure screening measurement >140/90 mm Hg.... This conclusion was consistent across a range of age/gender stratified sub-groups'.

Training requirements

Measurement of ambulatory blood pressure is a specialised technique and should be approached with the care reserved for any such procedure. An understanding of the principles of the measurement of conventional blood pressure, cuff fitting, monitor function, and analysis and interpretation of the data produced is needed. In practice, a nurse, technician or pharmacist with an interest and experience in hypertension can master the use of devices to measure ambulatory blood pressure after relatively little training. Analysis and interpretation of profiles for ambulatory blood pressure, however, need experience in the technique; this is achieved best by the doctor in charge of a service that provides ABPM.

Using a monitor

Time needs to be allowed to fit the monitor and prepare the patient for the monitoring period if good results are to be obtained. The key to successful measurement of ambulatory blood pressure is

educating the patient on the process of monitoring, and the instructions should be explained and printed on a diary card. Blood pressures recorded during the 24 h can be analysed in a number of ways, which can be selected in the software program. One simple and popular method is to assess the time of awakening and sleeping from entries in diary cards. Another method uses fixed times, in which the retiring period (21:01 to 00:59) and rising period (06:01 to 08:59) during which blood pressure is subject to considerable variation are eliminated. The daytime period lasts from 09:00 to 21:00 and the nighttime period from 01:00 to 06:00. In this way, variations between young and old people and between people of different cultures are eliminated, to some extent, from the analysis (Figure 4.10).

The reproducibility of measurements of ambulatory blood pressure is improved when the measurements are taken on like days – for example, working days or recreational days. A diary card may be used to record symptoms and events that could influence ABPM.

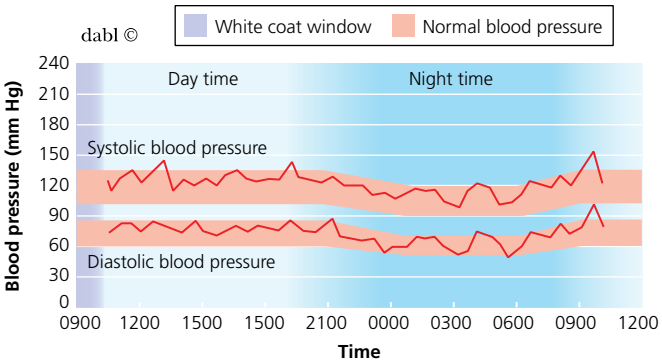


Figure 4.10 Normal ambulatory blood pressure monitoring pattern. The ambulatory blood pressure monitoring pattern shows normal 24-h systolic and diastolic blood pressure (128/78 mm Hg daytime, 110/62 mm Hg nighttime). Plot and report generated by dabl ABPM. © dabl ABPM (www.dabl.eu).

Box 4.16 **Requirements for obtaining a satisfactory ambulatory blood pressure measurement**

- 10–15 min needed depending on first or follow-up recording.
- Patient should be relaxed in quiet room.
- Enter patient details into monitor.
- Choose non-dominant arm.
- Select appropriate cuff.
- Select frequency of measurement – usually every 30 min day and night.
- Inactivate measurement display.
- Give patient oral and written instructions and a diary card.
- Instruct patient to carry on normal activities.
- Instruct patient on how to remove and inactivate monitor after 25 h.
- Allow 25 h recording so as to obtain full 24 h.
- Daytime minimum – 20 measurements of systolic and diastolic blood pressure.
- Nighttime minimum – seven measurements of systolic and diastolic blood pressure.
- If minimum requirement not met, measurement should be repeated.

Editing data

Many statistical techniques exist to describe different aspects of ambulatory records, and no one method is ideal. If sufficient measurements are available, editing is not needed to calculate average values for 24 h, daytime and nighttime. Only grossly incorrect readings should be deleted from recordings.

Normal levels

As with the measurement of conventional blood pressure, normal ranges for ambulatory blood pressures have been the subject of much debate over the years. Levels of ambulatory blood pressure are appreciably lower than normal levels for conventional blood pressure.

Clinical indications

ABPM provides a large number of measurements over a period of time, usually 24 h, which can be plotted to give a profile of the behaviour of a person's blood pressure. In practice, although the

Box 4.17 **Thresholds for hypertension with ambulatory blood pressure measurement**

- Awake ≥ 135/85
- Asleep ≥ 120/70
- 24-hour ≥ 130/80

It must be emphasised that these levels are only a guide to 'normality' and that lower levels may be more appropriate in patients whose total risk factor profile is high, and in whom there is concomitant disease, such as diabetes.

Box 4.18 **Clinical indications for ABPM**

Identifying white coat phenomena
- White coat hypertension in untreated subjects
- White coat effect in treated or untreated subjects

Identifying masked phenomena
- Masked hypertension in untreated subjects
- Masked uncontrolled hypertension in treated subjects

Identifying abnormal 24-h blood pressure patterns
- Daytime hypertension
  - Siesta dipping/postprandial hypotension
- Nocturnal hypertension
  - Dipping status
  - Morning hypertension and morning BP surge
  - Obstructive sleep apnoea

Assessment of treatment
- Increased blood pressure variability
- Assessing efficacy of blood pressure control
- Identifying resistant hypertension

Assessing hypertension in the elderly
Assessing hypertension in children and adolescents
Assessing hypertension in pregnancy
Assessing hypertension in high-risk patients
Identifying ambulatory hypotension
Identifying hypertensive patterns in Parkinson's disease
Endocrine hypertension

average daytime or nighttime values from ABPM are used to make decisions, the clinical use of ambulatory blood pressure has identified a number of phenomena in hypertension.

White coat hypertension

White coat hypertension, also called isolated office hypertension, is present in people who seem to have hypertension from measurement of conventional blood pressure (blood pressure ≥ 140/90 mm Hg) but have normal ambulatory blood pressure throughout the 24 h, except possible during the first hour, when the patient is under the pressor influence of the medical environment while having the monitor fitted (Figure 4.11).

White coat hypertension is present in 10–20% of clinic referrals for ABPM. Patients with white coat hypertension have a higher risk of major cardiovascular events than those with clinically normal blood pressure and a lower risk than those with high pressures during the daytime.

Failure to identify white coat hypertension can result in people being penalised for insurance, pension policies and employment, and lifelong treatment being prescribed unnecessarily with the potential for adverse effects, especially in elderly people.

White coat hypertension may affect young people, elderly people, people with normal blood pressure, those with hypertension and pregnant women.

White coat effect

White coat hypertension should be distinguished from white coat effect, which is the term used to describe the increase in pressure that occurs in the medical environment in people who also have elevated daytime ambulatory blood pressure. It is present in most patients with hypertension, who usually tend to have conventional blood pressures higher than the average daytime ambulatory blood pressure, which is still higher than normal (Figure 4.12).

Masked hypertension

Recently, patients in whom conventional blood pressure is normal but ambulatory blood pressure is high have been identified. Because ambulatory blood pressure gives a better classification of risk than conventional blood pressure, these people should be regarded genuinely as being hypertensive and at risk. The problem for doctors in clinical practice is how to identify and manage these patients, who may number as many as 10 million people in the United States.

Masked hypertension is common in the elderly and it may also be present in pregnancy.

Masked hypertension should be suspected in patients in whom conventional blood pressure has been recorded as high at some time, a young patient with early left ventricular hypertrophy, a family history of hypertension in two parents, and in patients with multiple risks for cardiovascular disease or diabetes.

Nocturnal hypertension

ABPM allows blood pressure to be measured during sleep. People whose blood pressure remains high at night (non-dippers) rather than falling below daytime levels (as in most people) are at higher risk of stroke, heart attack and cardiovascular death. The pattern of non-dipping may provide a useful (although nonspecific) clue to the presence of secondary hypertension (Figures 4.13 and 4.14).

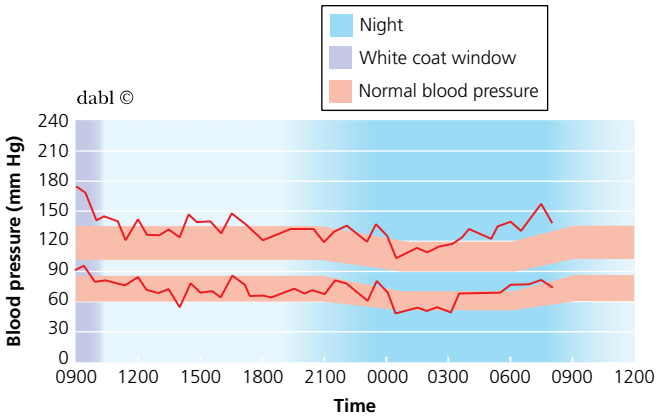


Figure 4.11 White coat hypertension. The ambulatory blood pressure monitoring pattern shows white coat hypertension (175/95 mm Hg) with otherwise normal 24-h systolic and diastolic blood pressure (133/71 mm Hg daytime, 119/59 mm Hg night-time). Plot and report generated by dabl ABPM. © dabl (www.dabl.eu).

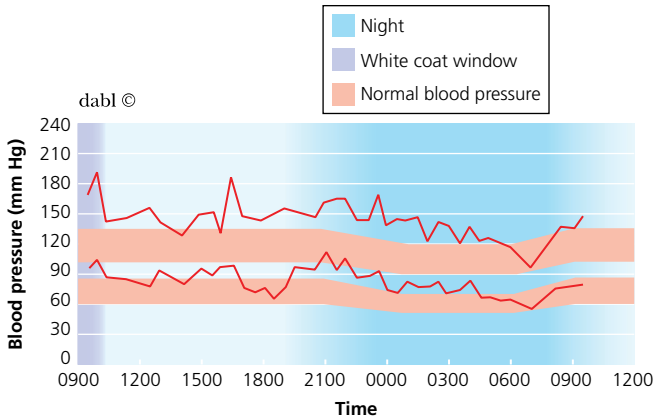


Figure 4.12 White coat effect. The ambulatory blood pressure monitoring pattern shows mild daytime systolic hypertension (149 mm Hg), borderline daytime diastolic hypertension (87 mm Hg), borderline nighttime systolic hypertension (121 mm Hg) and normal nighttime diastolic blood pressure (67 mm Hg) with white coat effect (187/104 mm Hg). Plot and report generated by dabl ABPM. © dabl (www.dabl.eu).

Sleep apnoea

Sleep apnoea is often associated with hypertension, especially nocturnal hypertension, but in practice, patients (or their partners) are rarely asked about their sleeping characteristics, and, in particular, about snoring and daytime sleepiness. The clinical spectrum ranges in severity from snoring at the benign extreme to obstructive sleep apnoea at the other. These conditions are significant risk factors for cardiovascular disease. About 2% of women and 4% of men have sleep apnoea and the prevalence increases with age, reaching a maximum at the age of about 70 years. It is more frequent in patients who are obese and who have the metabolic syndrome. About 60% of patients with sleep apnoea have hypertension and about 30% of patients with hypertension have sleep apnoea. Sleep apnoea may be

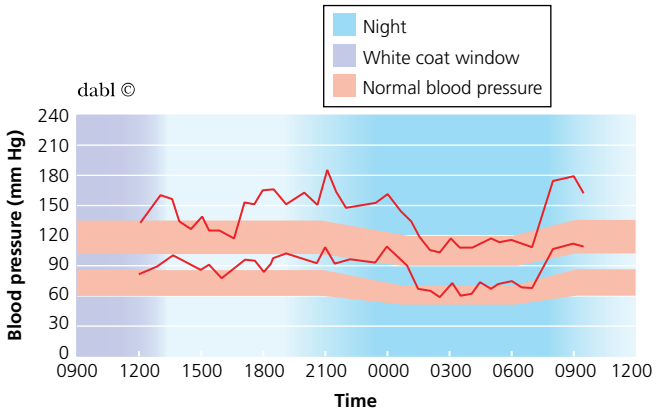


Figure 4.13 Hypertensive dipper. The ambulatory blood pressure monitoring pattern shows mild daytime systolic and diastolic hypertension (147/93 mm Hg) and normal nighttime systolic and diastolic blood pressure (111/66 mm Hg) with white coat effect (158/90 mm Hg). Plot and report generated by dabl ABPM. © dabl (www.dabl.eu).

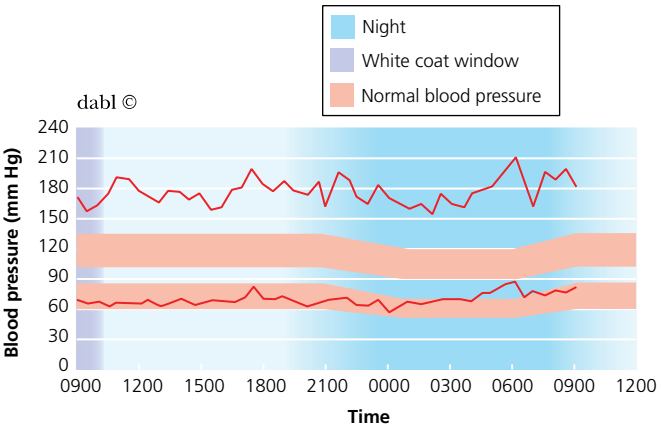


Figure 4.15 Isolated systolic hypertension. The ambulatory blood pressure monitoring pattern shows severe 24-h isolated systolic hypertension (176/68 mm Hg daytime, 169/70 mm Hg nighttime). Plot and report generated by dabl ABPM. © dabl (www.dabl.eu).

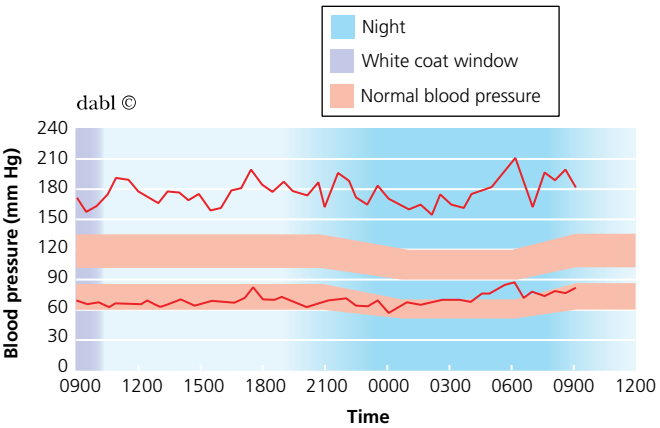


Figure 4.14 Hypertensive non-dipper. The ambulatory blood pressure monitoring pattern shows severe systolic and diastolic hypertension over 24 h (209/135 mm Hg daytime and 205/130 mm Hg at night). Plot and report generated by dabl ABPM. © dabl (www.dabl.eu).

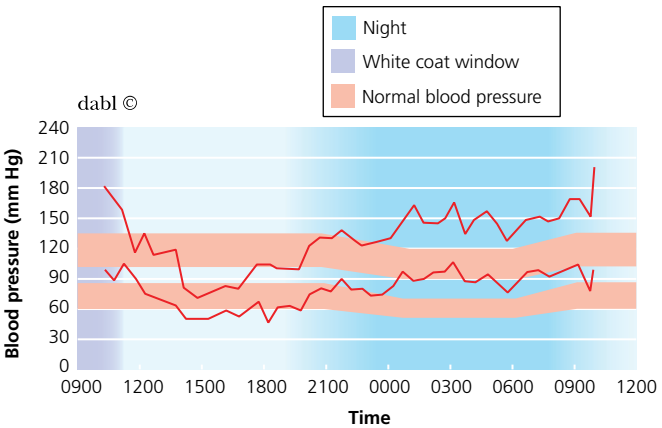


Figure 4.16 Ambulatory hypotension. The ambulatory blood pressure monitoring pattern shows low daytime systolic blood pressure (100 mm Hg) and normal daytime diastolic blood pressure (61 mm Hg) and moderate nighttime systolic and diastolic hypertension (146/89 mm Hg) with white coat effect (200/102 mm Hg). Plot and report generated by dabl ABPM. © dabl (www.dabl.eu).

a factor in making patients resistant to blood pressure lowering treatment. It can be treated effectively by continuous positive airway pressure (CPAP), which maintains the patency of the upper airway during sleep.

Elderly patients

A number of patterns of ambulatory blood pressure may be found in elderly people. Conventional systolic blood pressure in elderly people may be an average of 20 mm Hg higher than daytime ambulatory blood pressure. Isolated systolic hypertension is the most common pattern of hypertension in the elderly and may be present throughout the day and nighttime periods (Figure 4.15).

A number of hypotensive states as a result of baroreceptor or autonomic failure are common in elderly people. Postprandial hypotension is also common. As elderly people particularly can be susceptible to the adverse effects of drugs used to reduce blood pressure, identification of hypotension becomes especially important, although its management may present a considerable therapeutic challenge (Figure 4.16).

Resistant hypertension

Ambulatory blood pressure may be useful in patients with resistant hypertension (conventional blood pressure consistently >150/90 mm Hg despite treatment with three antihypertensive drugs) in whom it may indicate that the apparent lack of response is the result of a white coat effect.

Children and adolescents

ABPM is being used increasingly in children and adolescents to exclude white coat hypertension and to determine the severity of hypertension throughout the 24-h period. This information can be helpful in guiding investigation for secondary causes of

hypertension and in making the difficult decision to start life-long treatment at a young age. The normal levels of ambulatory blood pressure are now available for children.

Hypertension of pregnancy

As in the nonpregnant state, the main use for ABPM in pregnancy is to identify white coat hypertension, which may occur in nearly 30% of pregnant women. Its recognition is important so that pregnant women are not admitted to hospital or given antihypertensive drugs unnecessarily or excessively. Normal values for ambulatory blood pressure in the pregnant population are available, and changes in pressure, which occur during the trimesters of pregnancy and the postpartum period, have been defined.

Diabetes

In people with diabetes, a blunted or absent drop in blood pressure from day to night is an even more serious predictor for increased cardiovascular complications than in patients with hypertension without diabetes. The aim of antihypertensive drugs should be to achieve lower levels of 24-h blood pressure in diabetic than in non-diabetic patients.

Parkinson's disease and other neurological disorders

A non-dipping pattern of nocturnal blood pressure, frank nocturnal hypertension and postprandial hypotension may be seen in a number of neurological disorders that include Parkinson's disease, patients with other extrapyramidal syndromes, such as multiple system atrophy and supranuclear palsy and diabetic patients with autonomic neuropathy.

Ambulatory hypotension

ABPM is helpful in identifying hypotensive episodes in elderly people, but it also may be used in young patients in whom hypotension is suspected as a cause of symptoms. ABPM may also show drug-induced decreases in blood pressure in patients being treated for hypertension.

Ambulatory blood pressure can vary greatly in elderly patients with autonomic failure, with periods of hypotension interspersed with hypertension. As elderly people especially can be susceptible to the adverse effects of antihypertensive drugs, identification of postural hypotension particularly becomes important. Some elderly patients experience quite a marked decrease in blood pressure after lunch – a siesta dip – and this may be symptomatic (Figure 4.16).

Assessment of drug treatment

The role of ambulatory blood pressure in guiding drug treatment is the subject of much research, and recent reviews have highlighted the potential of ABPM over 24 h in guiding the use of antihypertensive drugs so as to avoid excessive lowering of blood pressure while achieving smooth control of both day and nighttime blood pressures. ABPM is particularly valuable in indicating those patients with white coat hypertension in whom treatment may be avoided, and for identifying those with masked hypertension in whom treatment is needed.

Box 4.19 **Suggested frequency for repeat ambulatory blood pressure measurement**

- White coat hypertension pattern – confirm diagnosis in 3–6 months.
- White coat pattern and low risk profile – repeat ABPM every 1–2 years.
- White coat hypertension pattern and high-risk profile – repeat ABPM every 6 months to detect possible transition to sustained hypertension requiring treatment.
- To determine efficacy of treatment
  - If low risk and controlled without target organ damage – annual ambulatory blood pressure measurement.
  - If high risk and/or poorly controlled with target organ damage – more frequent ABPM.

The presence of nocturnal hypertension on ambulatory monitoring may prompt the prescribing doctor to administer a long-acting drug or to prescribe mediation in the evening rather than in the morning.

Who should be re-monitored

ABPM may be inconvenient to patients and should be used, therefore, with discretion. The decision as to when to repeat ABPM is largely one of clinical judgment. The frequency of repeat ABPM must be guided by the response to treatment, the stability of blood pressure control and the overall cardiovascular risk profile. Where the risk for cardiovascular complications is high, the frequency is more than justified by the need for tight blood pressure control, whereas when the risk is low, less frequent measurement is needed. Recently, a special software program has enabled pharmacists to provide ABPM, thereby increasing the accessibility of the technique to a larger number of hypertensive patients. Self-measurement of blood pressure may be combined with ABPM to reduce the frequency of the latter.

Further Reading

National Clinical Guideline Centre (2011) *Hypertension. Clinical Management of Primary Hypertension in Adults (Clinical Guideline; no. 127)*. National Institute for Health and Clinical Excellence (NICE), London.

O'Brien, E. (2008) Ambulatory blood pressure measurement. The case for implementation in primary care. *Hypertension*, 51, 1435–1441.

O'Brien, E. (2011) 24-hour ambulatory blood pressure measurement in clinical practice and research: a critical review of a technique in need of implementation. *Journal of Internal Medicine*, 269, 478–495.

O'Brien, E., Parati, G., Stergiou, G.S. & on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring (In press) Expert recommendations for ambulatory blood pressure measurement. *Journal of Hypertension*.

O'Brien, E., Parati, G., Stergiou, G., et al. (2013) on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension Position Paper on Ambulatory Blood Pressure Monitoring. *J Hypertens*, 31, 1731–1767.

Lovibond, K., Jowett, S., Barton, P., *et al.* (2011) Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: a modelling study. *The Lancet*, 378, 1219–1230.

Part IV: Self-blood pressure measurement

OVERVIEW

- Self-blood pressure measurement is popular with patients and is often performed without medical supervision.
- Devices for self-blood pressure measurement that have not been independently validated should not be used as they may give inaccurate measurements.
- Self-blood pressure measurement is superior to conventional (office) measurement of blood pressure but is not a substitute for ambulatory blood pressure measurement.
- Occasional self-blood pressure measurements are often misleading and are not recommended.
- The recommended procedure is that blood pressure is measured twice in the morning and evening for 7 days, that the first day's measurements are discarded and the remaining days' measurements averaged so as to obtain a measurement that approximates to the mean daytime blood pressure on ambulatory blood pressure measurement.

Self-measured blood pressures outside of the medical setting (out-of-office blood pressures) have been popular with patients for many years as indicated by the huge sales of self-monitoring devices. The discrepancy between pressures recorded in the home and the clinic, which has been confirmed repeatedly, is primarily a result of the white coat effect, and is present regardless of whether patients or their relatives measure the blood pressure. Doctors have tended to be cautious in their use of the technique, but it now recognised as being a useful adjunct to conventional office measurement and guidelines for the procedure have been issued.

Advantages of self-measurement

Self-measurement of blood pressure has several advantages but the technique is not as good as ambulatory blood pressure measurement, and the National Centre for Clinical Excellence (NICE) guideline recommends the technique only when ambulatory blood pressure measurement is not possible or is unavailable.

General considerations

Devices and validation

Monitors for self-measurement of blood pressure include mercury column sphygmomanometers, aneroid manometers and electronic semi-automatic or automatic devices. Mercury sphygmomanometers are no longer recommended for self-blood pressure measurement and aneroid devices that are dependent on the auscultatory technique are only occasionally used in patients in whom oscillometric measurement is unsatisfactory.

The sale of electronic devices designed for self-measurement of blood pressure is not necessarily subject to any medical influence. This freedom from medical control, coupled with a growing public desire to know more about health and illness, has resulted in the manufacture and marketing of a vast array of such devices, many of which have not been evaluated according to the procedures considered necessary for equipment that may influence management of hypertension in clinical practice.

Automated devices available for self-measurement all use the oscillometric technique.

Devices for finger measurement have been manufactured in the past but because of the susceptibility of the small arteries in the finger to vasoconstriction and the inaccuracy associated with the device not being kept at heart level, such devices are no longer available.

Box 4.20 **Advantages and limitations of self-blood pressure measurement**

Advantages	Limitations
Relatively low cost.	Less cost-effective than ambulatory blood pressure measurement.
Vast array of devices available	Relatively few devices validated according to international protocols – many inaccurate.
Digital storage, printout, PC download or teletransmission of blood pressure, heart rate, date and time of measurement possible.	Isolated measurements are misleading and a 5- to 7-day schedule is necessary.
Provides a number of measurements of blood pressure and heart rate during the day and also over several days, weeks or month.	Technique subject to bias by patients unless data is electronically stored or transmitted.
Facilitates diagnoses of white coat and masked hypertension.	Induction of anxiety, resulting in excessive monitoring.
Reproducibility is good.	Risk of treatment changes made by patients on the basis of casual home measurements without doctor's guidance.
Can be used to assess blood pressure variability over time.	Normality thresholds and therapeutic targets still debated – more research needed.
Eliminates terminal digit preference.	Lack of nighttime recordings.
Involves patients in management – educational role.	Not suitable for patients with certain disabilities.
Compliance to treatment may be improved.	
Blood pressure control may be improved.	

Devices that measure blood pressure at the wrist are more accurate than finger measuring devices, but there are reservations about the correct use of wrist devices. If the wrist is not held at heart level during measurement, inaccurate measurements will be obtained, and measurement is also influenced by flexion and hyperextension of the wrist. However, wrist measuring devices are useful in obese or elderly individuals, in whom self-measurement using the upper arm may be more difficult to perform. Because correct placement of the cuff at heart level is essential for accurate measurement with wrist devices, some devices have an inbuilt position sensor to indicate the correct position. Despite their many limitations, automatic wrist monitors are popular among patients, because measurement is readily obtained without the need to remove clothing.

Monitors that measure blood pressure in the upper arm (brachial artery) have been shown to be the most reliable devices, both in clinical practice and in the major hypertension trials; therefore, their use is recommended for self-measurement.

Box 4.21 **Device requirements**

- Devices must be independently validated preferably with the International Protocol of the European Society of Hypertension.
- Devices that claim suitability for special patients, such as children, the elderly, pregnant and patients with arrhythmias should have been validated in these patients.
- Upper arm (brachial artery occluding) devices are preferred to wrist devices.
- Devices with memory facility to prevent patient misreporting of results.
- Auscultatory (aneroid or mercury) devices are not recommended except under specific circumstances.
- Finger cuff devices not recommended.
- Wrist cuff devices are not recommended at present, except in patients with extremely obese arms.
- Appropriately sized cuffs (small, standard or large) should be available.

User procedure

The same principles apply to self-measurement as to measurement in general. Some points, however, need emphasis.

Use in primary care

At present, self-measurement of blood pressure is performed mostly by patients on their own initiative, with devices bought on the free market without medical control. Primary care doctors should see self-measurement as a means of gaining further insight into control of blood pressure and the effects of management strategies in motivated and informed patients who remain under medical supervision.

Device requirements

Devices for self-measurement must be independently validated. There are three internationally used validation protocols – the International Protocol of the European Society of Hypertension, the standard of the Association for the Advancement of Medical Instrumentation and the British Hypertension Society protocol. The International Protocol is the most popular because compared to the other protocols it simplifies the validation procedure without compromising the validity of the results.

Patient training

Little training is required for the correct use of automated devices, but a doctor, nurse of pharmacist should explain the interpretation of results to the patient. In some patients with motor or cognitive impairment, self-measurement of blood pressure may not be suitable. Telephonic support and telemonitoring facilities are useful adjuncts for self-measurement, which may improve adherence to treatment regimens and thereby improve blood pressure control.

Conditions of measurement

Conditions under which self-measurement is performed can affect the measured blood pressure levels. Patients must be informed about the importance of adhering to these instructions.

Box 4.22 **Conditions of measurement**

- At least 5-min rest.
- Abstain from smoking, eating, caffeine or physical exercise for 30 min.
- Seated position in a quiet room, back supported, arm supported (e.g. resting on the table).
- Subject immobile, legs uncrossed, not talking and relaxed.
- Correct cuff bladder placement at heart level.
- Results immediately reported in a specific logbook or stored in device memory.
- Patient diaries may be unreliable.
- Reading from first day should be discarded.

Cuff size

Devices for self-measurement should be supplied with a range of cuffs for varying arm sizes. Patients with obese arms should be advised of the importance of cuff hypertension.

Patient reporting of blood pressure

Bias in recording the results of self-measured blood pressure has been reported and devices equipped with an automated memory have the potential to prevent misreporting of blood pressure measurements.

Frequency and timing of self-measurement

The frequency of self-measurement may vary according to the indication and the information that is sought. Frequent measurement may be recommended for individual patients (such as those with poor compliance) or for participants in pharmacological studies.

Diagnostic thresholds

The threshold level of 135/85 mm Hg (average of multiple readings taken on several days) for self-measurement of blood pressure is the same as that for mean daytime ambulatory blood pressure. Optimal measurements are less than 130/80 mm Hg (average of multiple

Box 4.23 **Scheme for self-measurement**

Phase	Directions
Start	Initial period of 7 days (minimum 3 days). Two measurements in the morning. Two measurements in the evening. Discard readings from first day of measurement, which are unrepresentative because of anxiety and unfamiliarity. Use average measurements as reference for treatment and follow-up.
Treatment	Repeat the above when the patient is on treatment. Morning measurements should be made before drugs are taken (trough levels of drug). Average of 2 weeks on treatment should be compared with average of commencement phase to determine efficacy. Averages of 2 weeks on each treatment regimen should be compared to determine efficacy after a change in treatment.
Follow-up	Two measurements on one day a week in patients with good control of blood pressure. More frequent measurements in patients with poor control of blood pressure or poor compliance.

Box 4.24 **Factors that influence self-measurement**

- Device accuracy – use only validated devices.
- Observer prejudice (can be overcome with printouts and devices equipped with memory).
- Training of patients by doctors or nurses.
- Training should focus on:
  - — Use of device
  - — Correct procedure
  - — Interpretation of results
  - — Need for maintenance and calibration
  - — Essentials of hypertension
  - — Management and treatment
- Seasonal variation (blood pressure is higher in winter and lower in summer).

readings taken on several days). Casual, isolated home measurements can be very misleading and should not by themselves constitute the basis for clinical decisions.

Clinical indications

The clinical applications of self-measurement of blood pressure are beginning to become apparent only as the technique is used more widely and scientific data is gathered.

White coat hypertension

Self-measurement has been proposed as a useful alternative to measurement of ambulatory blood pressure to detect white coat hypertension. The finding of normal blood pressure on self-measurement, however, does not rule out the possibility that the blood pressure may be higher at other times of the day. Self-measurement, which is less costly and more convenient than measurement of ambulatory pressure, may be appropriate for long-term follow up of patients with white coat hypertension.

Guiding antihypertensive treatment

Self-measurement may have a role in assessing the response to antihypertensive drug treatment outside the medical environment and over time. Measurement of blood pressure in the home environment under similar everyday conditions avoids the white coat effect and reduces variability. Self-measurement can improve the assessment of blood pressure control in the management of hypertension and in clinical trials.

Elderly patients

The feasibility of self-measurement in elderly patients may be influenced by physical and intellectual limitations and the complexity of the chosen device. Studies in elderly people have shown that automatic equipment is more precise and easier to use than semi-automatic equipment.

Pregnancy

As in the general population, blood pressures recorded by self-measurement are lower than conventional blood pressures. Self-measurement may be useful for the diagnosis of white coat responders and to monitor the effect of antihypertensive drugs. Data storage and electronic transmission of data may have a particular role for patients who live at distance from the maternity clinic.

Diabetes

Increasing evidence shows that stringent control of blood pressure reduces the cardiovascular and microvascular complications of diabetes. Self-measurement of blood pressure may be an additional means of ensuring that such control is achieved, although no data are available yet to guide the use of self-measurement in patients with diabetes.

Resistant hypertension

Patients with apparently uncontrolled blood pressure according to conventional monitoring may have adequate control at home. It may be possible to identify at least some of these patients by self-measurement, although ambulatory blood pressure is the preferred technique.

Improving compliance to treatment

One of the most important causes of refractory hypertension is poor compliance or adherence to treatment. Self-blood pressure measurement may provide patients with an understanding of increased blood pressure and its response to treatment, thereby improving adherence to treatment.

Predicting outcome

Self-measurement may offer some advantage over measurement of conventional blood pressure in predicting cardiovascular outcome in hypertension, but data are limited. The results of cross-sectional studies have shown that the degree of left ventricular hypertrophy determined by electrocardiography and echocardiography is correlated more strongly with self-measurement than conventional measurement.

Further Reading

Parati, G., Stergiou, G.S., Asmar, R., *et al.* & on behalf of ESH Working Group on Blood Pressure Monitoring (2010) European Society of Hypertension Practice Guidelines for home blood pressure monitoring. *Journal of Human Hypertension*, 24, 779–785.

O'Brien, E., Asmar, R., Beilin, L., *et al.* & on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring (2003) European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *Journal of Hypertension*, 21, 821–848.

O'Brien, E., Parati, G., Stergiou, G., et al. (2013) on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension Position Paper on Ambulatory Blood Pressure Monitoring. *J Hypertens*, 31, 1731–1767.

CHAPTER 5

Screening and management in primary care

OVERVIEW

- As hypertension in usually a symptomless risk factor for heart attacks and strokes, it frequently goes undiagnosed until a late stage in the disease.
- In the general population, hypertension (140/90 mm Hg or more) in found on screening in 10–75% of people, depending on their age.
- Routine screening of all adults is the only way to improve the detection and management of hypertension. This is best achieved within the primary health care team.
- The most efficient method of detention of hypertension is by opportunistic screening when patients visit their General Practice Health Centre for any reason. By this method, up to 75% of the population can be screened in 3 years.
- Different health care systems in different countries will have different methods of well-population screening. The system in the United Kingdom has proved reasonably effective.
- Screening will indentify three groups of patients:
  - — People with normal blood pressures where no action is needed in the short term
  - — People with overt hypertension who require urgent investigation and anti-hypertensive drug therapy
  - — An intermediate group where drug therapy should be considered if moderately raised pressures do not settle on rescreening, or there are concomitant other risk factors for cardiovascular disease (CVD).

Detection in general practice

Hypertension is usually a symptomless condition, so, unless special efforts are made, it goes undetected. It is sometimes described as 'the silent killer'. The state of awareness of hypertension in the general population was said to follow the 'rule of halves' so that only a small minority of patients was receiving adequate care (Figure 5.1).

It is now generally agreed that the detection and management of hypertension is primarily the responsibility of the primary health-care team based on general practice (known in some countries as family medicine). All countries have different ways of delivering good primary care. In this chapter, we concentrate on the system developed in the United Kingdom. However, the principals of health-care delivery are universal and the UK system is one of many. Of the 25 wealthiest nations, all but one (the United States) have some form of universal health-care coverage, which incorporates the management of common chronic diseases like hypertension.

The size of the problem

In the screening survey of the town of Renfrew, Scotland, 37.7% of 45- to 64-year-old men and women were found to have a diastolic blood pressure of 90 mm Hg or more at first screening. In many cases, these pressures settled at second screening but the act of rescreening can be regarded as an act of clinical management. Most of the hypertensives detected had mild hypertension (Table 5.1). The 1215 hypertensives of the town were attached to the lists of nine general practitioners.

In the last decade, guidelines for the detection and management of hypertension have been published in the United Kingdom, Europe and the United States. Differences between these guidelines are minor and there is general agreement on who and how to treat. The remainder of this chapter concentrates on the British guidelines

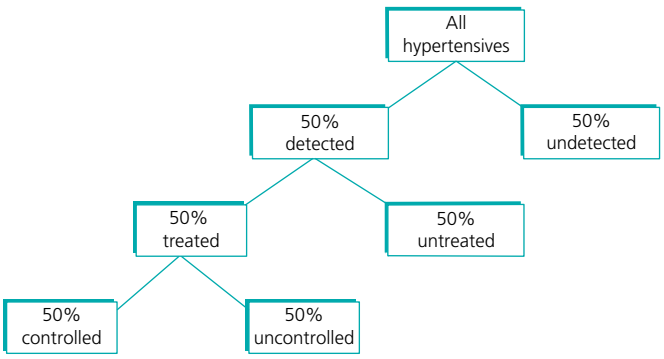


Figure 5.1 The 'rule of halves'; the frequency of undetected, untreated and uncontrolled hypertension in the days before systematic screening programmes in primary care. Only about 12.5% of hypertensive patients were receiving adequate care. Source: Data from Hart, J.T. (1992) *British Journal of General Practice*, 42, 116–119

ABC of Hypertension, Sixth Edition. D. Gareth Beevers, Gregory Y. H. Lip and Eoin O'Brien.

produced jointly by the British Hypertension Society and the National Institute of Health and Care Excellence (BHS/NICE).

Patient involvement

All guidelines on hypertension management advocate the importance of patient involvement in the successful management and control of hypertension. This includes non-pharmacological or lifestyle changes, as well as patient involvement when considering drug treatment, including education about the drugs patients should take and the drugs' proven benefits and possible side effects.

Patients also need to be warned that, on average, 75% of patients with hypertension need two or more drugs and that one-third will need three or more drugs to achieve good control of blood pressure. The number of drugs needed may be even higher in patients with diabetes, in view of the lower thresholds for treatment in this group (Table 5.2).

Whilst clinicians should do all they can to minimise the number of tablets to be swallowed every day for years to come, the treatment of comorbidities may need the use of antidiabetic drugs, statins and aspirin.

Many patients are generally keen to help with the management of their hypertension with home recording of blood pressure. Many high street chemists now sell inexpensive semi-automatic devices for the measurement of blood pressure, but as many of these have not been validated for accuracy, it is important to check this when purchasing a devise.

Table 5.1 The prevalence of mild, moderate and severe hypertension in Renfrew

3060 randomly selected 45–64-year-old man and women	
Normotensive (DBP ≤ 89)	1846 (60.3%)
Mild hypertensive (DBP 90–109)	1069 (34.9%)
Moderate hypertensive (DBP 110–129)	130 (4.2%)
Severe hypertensive (DBP ≥ 130)	16 (0.5%)

Source: Data from Hawthorne, V.M., et al. (1974) *British Medical Journal*, 3, 600–603.

Blood pressures measured at home (HBPM) probably resemble ambulatory blood pressures measured automatically (ABPM) over 24 h more closely than conventional pressures measured in the clinic, and they provide a more reliable index of cardiovascular risk than casual clinical or office readings (CBPM). Indeed, HBPM features highly in the 2011 BHS/NICE guidelines on hypertension. Patients should be encouraged to buy their own blood pressure machines. For more information, see Chapter 4, Part IV.

The Blood Pressure Association in the United Kingdom (now renamed *Blood Pressure UK*) was set up specifically to provide information and support to people with high blood pressure. Cards that record blood pressure that are held by patients can improve compliance with treatment, particularly if the patient is attending a secondary referral clinic.

Health-care systems

National service frameworks

The national service framework provides health-care service standards in relation to various diseases and patient groups, such as coronary artery disease, elderly people and patients with diabetes. These frameworks have led to targets of achievement that have broadly led to improvements in care. The 2011 BHS/NICE guidance provides a simple algorithm for the follow-up and management of hypertension in primary care (Figure 5.2).

The importance of the prevention of CVD is recognised, including the detection and treatment of hypertension. The framework is broadly consistent with the Joint British Societies' recommendations and the current guidelines of the British Hypertension Society. One exception is that the national service framework defines 'high risk primary prevention' as 'people without diagnosed (coronary heart disease) or other occlusive arterial disease but with a 10-year (coronary heart disease) risk >30%', which equates to a risk of CVD over 10 years >40%. This confusion about the risk of coronary heart disease and the risk of CVD is unfortunate, but most guideline committees now accept that total cardiovascular risk should be assessed (i.e. including stroke and heart attack).

The guidelines of the National Institute for Health and Clinical Excellence (BHS/NICE) do not address when aspirin and statin

Table 5.2 Formulation of an individual patient management plan

- Explain that high blood pressure is a major cause of heart attacks and strokes but add that well-organised antihypertensive treatment, usually with drugs, is highly effective at preventing these events.
- Explain that hypertension is almost always managed in GP health centres by doctors and practice nurses. Specialist hospital referral is only rarely necessary.
- Show the patient the risk colour charts in the colour charts for cardiovascular risk in 10 years in the back pages in the British National Formulary or similar systems in other publications. Explain that these charts show the chance that a patient will develop a heart attack or stroke in the next 10 years if the blood pressure is not reduced.
- Use absolute risk (i.e. 10% in the next 10 years) rather than relative risk (i.e. twice as likely)
- Explain that all drug therapies have some sort of side effect, the most common being inconvenience.
- Modern antihypertensive drugs have far fewer side effects that more traditional drugs. If the first choice drug causes problems, there are plenty of alternatives with different modes of action.
- Encourage the patient to purchase their own blood pressure machine and explain how to use it. Explain that home blood pressure rules.
- Give out information leaflets provided by the British Heart Foundation.
- Encourage online contact with Blood Pressure UK.
- Discuss how the patient can help with the management of their hypertension with modifications to diet and lifestyle as well as home blood pressure measurement

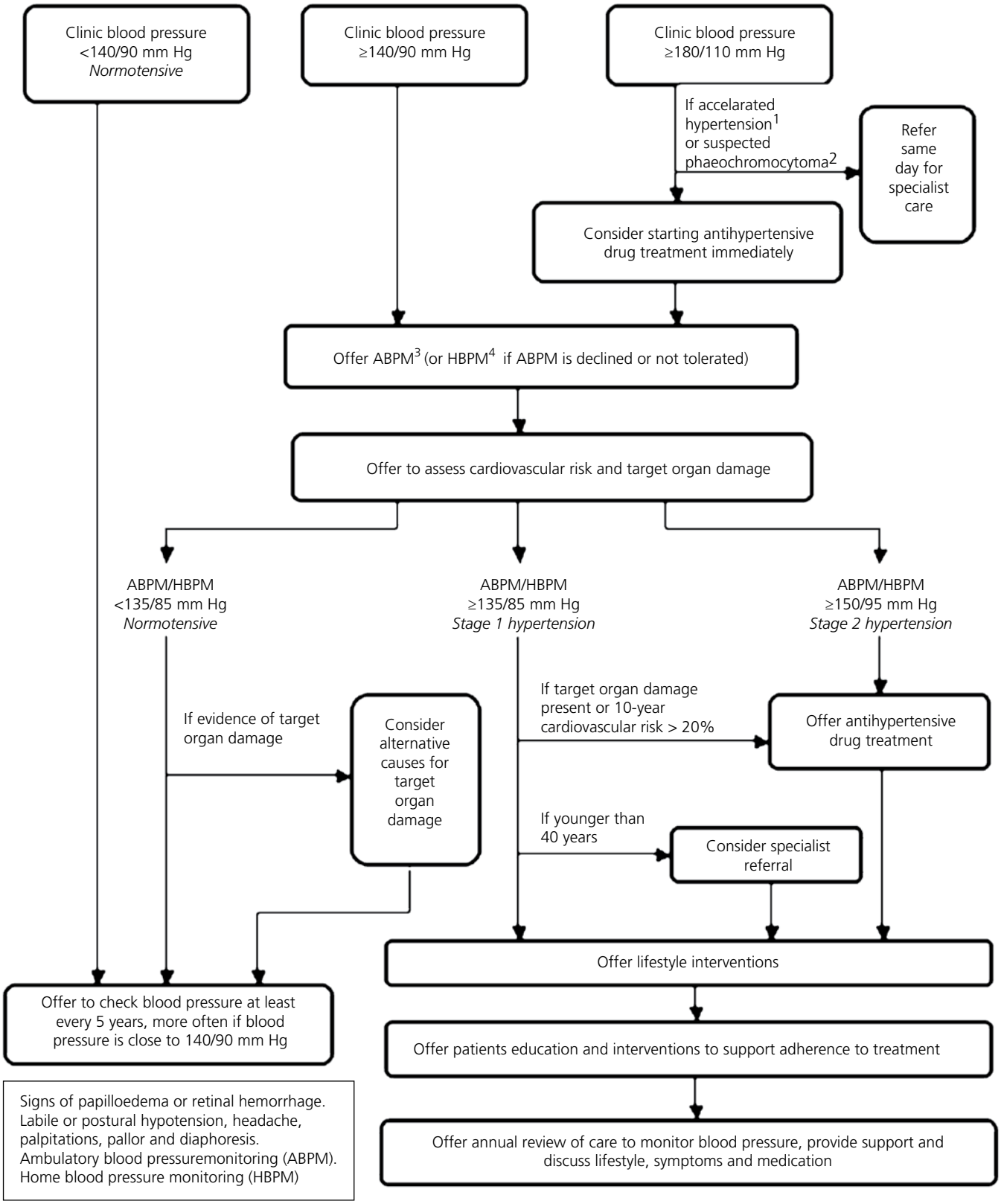


Figure 5.2 BHS/NICE recommendations for the management of hypertension in primary care. From National Institute of Health and Clinical Excellence. Hypertension; clinical management of primary hypertension in adults. Source: NICE clinical guideline 127, 2011. Krause, T., et al. (2011) *British Medical Journal*, 343, d489. Reproduced with permission from BMJ Publishing Group Ltd.

drugs should be used to reduce the total burden of cardiovascular risk in people with high blood pressure. Optimal management of blood pressure needs assessment of these risk factors and a 'package of care' of multifactorial intervention to reduce cardiovascular risk, including all risk factors and not just blood pressure.

Primary care

Most patients with hypertension are managed in primary care, and general practitioners and practice nurses are responsible for measurement of blood pressure and the detection, treatment, and control of hypertension. The management of millions of patients with hypertension can therefore be achieved only within primary health care.

Only a minority of patients with hypertension need to be referred to blood pressure clinics based in hospitals. The accurate detection, assessment and treatment of patients with hypertension lead to considerable reductions in the rates of stroke and heart attack. Unfortunately, many patients with hypertension are not receiving the management they need.

Doctors also seem to overestimate their own compliance with current guidelines on hypertension, especially with regard to the proportion of patients who have adequately controlled blood pressure. This limited awareness may represent a barrier to successful implementation of management guidelines. In addition, doctors tend to underestimate the adverse effects of blood pressure and its treatment on their patient's quality of life.

Screening

Between 70 and 80% of a practice's population will visit their general practitioner at least once in 3 years, and screening can take place at the same time. This is 'opportunistic screening'. Blood pressure should therefore be checked in all patients who visit their general practitioner if they have not attended for more than 12 months. When screening for hypertension, it is important to check for concomitant factors for CVD as well as for hypertension (Figure 5.3).

Opportunistic screening has the advantage that it requires no special appointments or documentation. The primary health-care team and particularly the practice nurses need to check that all patients allocated to their practice have had a recent blood pressure check when they attend for whatever purpose or medical condition.

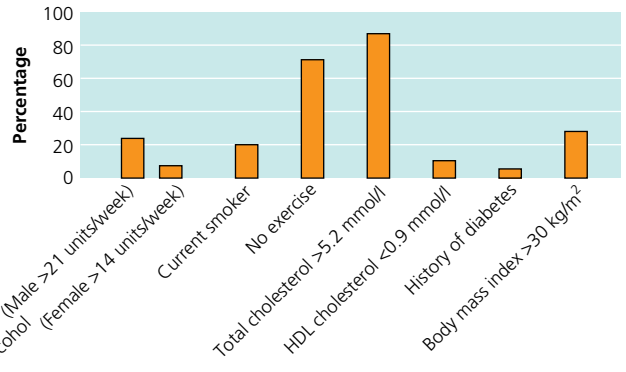


Figure 5.3 Concomitant risk factors in hypertension in primary care. Source: Data from Poulter, N.R., et al. (1996) *Blood Press*, 5, 209–215.

This approach was validated in urban and rural settings in Scotland. Just under 80% of eligible male patients were checked over 3 years (Figure 5.4). In almost all screening surveys, it has proved very difficult to examine the remaining 20% of the population.

Patients with blood pressures >140/95 mm Hg should be advised that their blood pressures are not quite normal and recalled for re-examination a few weeks later. They should be assessed fully for cardiovascular risk according to the guidelines of the British Hypertension Society. For confirmation of the diagnosis, the use of Ambulatory Blood Pressure Monitoring (ABPM) should be routine. If ABPM facilities are not available or cannot be tolerated, HBPM is recommended in the 2011 NICE/BHS guidelines.

When screening for hypertension, certain 'high risk' patient groups should be targeted specifically rather than waiting for them to attend for some other reason. This 'selective' or 'targeted' screening should be conducted in those at particular risk of developing hypertension or its vascular complications – for example, patients with diabetes (Table 5.3).

In the primary care setting, high-risk patients who stand to benefit most from control of blood pressure seem to be least likely to be controlled, despite being on a higher number of antihypertensive drugs. In one analysis, higher risk scores according to the Framingham study, female sex, diabetes and impaired fasting glucose seemed to correlate negatively with control of blood pressure in primary care. Patients' knowledge of hypertension and the number of comorbid conditions seemed to correlate positively with control of blood pressure.

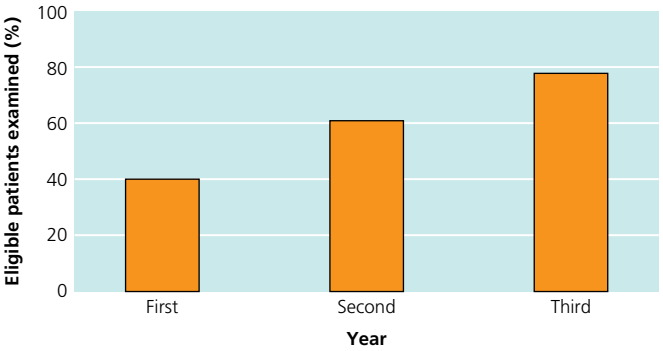


Figure 5.4 Opportunistic screening for hypertension in primary care in Scotland; men aged 35 to 69. Source: Data taken from Barber, J.H., et al. (1979) *British Medical Journal*, 1, 843–846.

Table 5.3 High-risk patients who need targeted screening

Pregnant women
Patients with:
Strong family history of hypertension, heart attack or stroke
Existing cardiovascular disease
Previous cardiovascular disease
Diabetes mellitus
Renal impairment
Systemic disease (including rheumatoid arthritis, polyarteritis and systemic lupus erythematosus)
Corticosteroid therapy
History of pre-eclampsia or hypertension in pregnancy
Oral contraceptive use
Overweight or obesity

Specialist referral

About 10% of patients with hypertension in primary care have an underlying cause for their high blood pressure or have very severe or resistant hypertension. Such patients should be referred for specialist assessment (Table 5.4). Many general practitioners themselves have established dedicated hypertension clinics, which also can be run by appropriately trained nurse practitioners. A patient-held record card can aid liaison and encourage HBPM (Figure 5.5).

Hypertension and NHS resources

Heart and circulatory disease remain major causes of mortality in the United Kingdom. In 2002, CVD caused 39% of deaths in the United Kingdom and killed just fewer than 238 000 people. Coronary heart disease, the main form of CVD, causes more than 117 000 deaths a year; this equates to about one in five deaths in men and one in six deaths in women.

Importantly, 35% of premature deaths in men and 27% in women are from CVD, which caused more than 67 000 premature deaths in the United Kingdom in 2002.

Table 5.4 Suggestions for patients who should be referred for specialist investigation and management

Hypertension below age 30 years
Paroxysmal symptoms suggestive of phaeochromocytoma or paroxysmal arrhythmia
Hypokalaemia (serum potassium less than 3.5 mmol/l) not associated with diuretic therapy
Serum creatinine above 120 µmol/l or eGFR less than 60
Hypertension resistant to triple antihypertensive therapy

Important reductions in death rates for coronary heart disease and stroke have been seen since the late 1970s. Despite this, the United Kingdom has rates that are still among the highest in Western Europe. Death rates are higher in Scotland than the south of England, in manual workers than in non-manual workers, and in certain ethnic groups.

Although mortality from heart disease is falling rapidly, the morbidity associated with heart and circulatory disease is not decreasing. Recent estimates are that just fewer than 2.7 million people in the United Kingdom have coronary heart disease: about 1.51 million men who have or have had coronary heart disease (angina or heart attack) and about 1.16 million women. A general practitioner with a list of 2000 patients is estimated to have about 400 consultations each year for about 200 patients with hypertension.

Recent prescribing of drugs that affect blood pressure in England and Wales shows that the thiazides, β blockers, angiotensin-converting enzyme inhibitors and calcium channel blockers are used in similar quantities in primary care, although their costs vary by a factor of 10. The NHS writes more than about 90 million scripts annually, at a cost of £840 million; this is nearly 15% of the total annual cost of drugs in primary care (Table 5.5).

Hypertension in primary care in developing countries

This chapter has concentrated on the delivery of hypertension care in developed countries and particularly the United Kingdom. However, hypertension is rapidly becoming a major hazard to health in the developing countries and particularly in Africa. This is largely due to urbanisation, the adoption of Western-style fast foods (which are very salty) and the increasing prevalence of obesity. The health-care systems in these developing countries must be

Hypertension Cooperation Card

Name David Jenkins

DOB 7/12/12

Address 25 Main Street, Anytown, AT13 4BS

General Practitioner Dr Bristow

First diagnosed hypertensive 14/12/12

Cigarette smoker Yes/No Yes Number per day 20

Alcohol intake 9 u/wk

- No smoking
- Avoid being overweight
- Avoid salty foods to reduce your salt intake
- Moderate alcohol consumption
- Take moderate exercise
- Bring this card to all visits to your doctor or practice nurse
- Do not stop taking your tablets unless advised to by your doctor or nurse

Contact Blood Pressure UK

Wolfson Institute, Queen Mary University of London

London EC1M 6BQ

Tel, 020 7822 6355/5793

www.bloodpressureuk.org

Date	16/2/13	19/3/13	17/5/13	27/8/13	13/2/14	4/8/14	7/2/15
BP1	172/106	169/100	156/89	148/83	142/86	139/81	137/79
BP2	168/98	171/98	152/88	146/82	146/84	136/80	135/80
Weight	84.2	-	-	-	-	-	-
Urine	nad	-	-	-	-	-	-
Cholesterol/HDLC	5.2/1.3	-	-	-	-	-	-
Serum Creatinine	132	-	-	139	-	143	-
Serum Na/K	140/4.1	-	-	138/3.3	-	139/3.8	-
Drug 1 Indapamide	-	Start 2.5	2.5	Stop	-	-	-
Drug 2 Lisinopril	-	-	-	Start 10	20 mg	20 mg	20 mg
Drug 3 Simvastatin	-	-	-	-	-	Start 10	10 mg
Drug 4	-	-	-	-	-	-	-
Next visit	1/12	2/12	3/12	3/12	6/12	6/12	6/12
Signed	GB	GB	GL	GB	GL	GL	GB

Figure 5.5 An example of a patient-held hypertension cooperation card used in Birmingham.

Table 5.5 Antihypertensive drugs in common use in the United Kingdom

	Usual daily dose	Cost of 28 days' supply (£)
Angiotensin-converting enzyme inhibitors		
Lisinopril	20 mg	1.19
Perindopril	5 mg	6.28
Ramipril	5 mg	1.21
Angiotensin receptor blockers		
Losartan	100 mg	1.67
Valsartan	160 mg	18.41
Candesartan	16 mg	12.72
Calcium channel blockers		
Nifedipine LA	20 mg	5.27
Amlodipine	5 mg	1.22
Felodipine	5 mg	4.21
Verapamil MR	240 mg	5.55
Thiazide-type diuretics		
Bendroflumethiazide	2.5 mg	0.88
Indapamide	2.5 mg	1.40
Chlortalidine	50 mg	1.64
Beta adrenergic receptor blockers		
Atenolol	50 mg	0.85
Bisoprolol	5 mg	1.15
Metoprolol	200 mg	2.38
Alpha adrenergic receptor blockers		
Doxazocin	4 mg	1.22
Aldosterone receptor antagonists		
Spironolactone	50 mg	1.88
Centrally acting imidazoline receptor antagonists and alpha agonists		
Moxonidine	400 µg	£3.49
Methyldopa	750 mg	£9.74

Prices extracted from British National Formulary; 66 (September 2013).

organised in a manner depending on local facilities. The increasing prevalence of hypertension may be minimised with the adoption of national guidelines to reduce the salt content of prepared foods.

At a clinical level, with a relative shortage of medically qualified health-care professionals, there is a clear role for primary care nurses, community pharmacists and in some countries, partially-trained but supervised para-medical staff, sometimes referred to as 'bare foot doctors'. Educational classes for these health-care professionals is mandatory.

The Blood Pressure Association is a UK charity dedicated to improving the prevention, detection, diagnosis and treatment of high blood pressure. Their experts provide information on all aspects of the condition for people with high blood pressure and for health-care professionals.

Further Reading

Hart, J.T. (1974) Milroy lecture: the marriage of primary care and epidemiology: continuous anticipatory care of whole populations in a state medical service. *Journal of Royal College of Physicians of London*, 8, 299–314.

Hart, J.T. (1985) Practice nurses: an underused resource. *British Medical Journal*, 290, 1162–1163.

Ibrahim, M.M. & Damasceno, A. (2012) Hypertension in developing countries. *Lancet*, 380, 611–619.

The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (2007) 2007 guidelines for the management of arterial hypertension. *Journal of Hypertension*, 25, 1105–1187.

VIPER-BP study investigators (2012) Effect of intensive structured care on individual blood pressure targets in primary care: multicentre randomised controlled trial. *British Medical Journal*, 345, e7156.

Blood Pressure UK

FIGHTING HIGH BLOOD PRESSURE TO BEAT STROKE
AND HEART DISEASE
Registered charity: 1058944
Wolfson Institute of Preventive Medicine
Queen Mary, University of London, London, EC1M 6BQ
tel (+44) 020 7882 6255/ 5793www.bloodpressureuk.org

CHAPTER 6

Clinical assessment of patients with hypertension

OVERVIEW

- Most people with hypertension are symptomless and only become ill when they develop a heart attack or stroke.
- Once hypertension has been diagnosed, patients may develop symptoms more closely related to anxiety. Antihypertensive treatment with accurate blood pressure control may ameliorate some of these symptoms.
- New patients with hypertension should be assessed for previous cardiovascular events, concomitant diabetes mellitus, hyperlipidaemia, tobacco habit and renal disease. In women, a past obstetrical history may reveal a previous pregnancy complicated by hypertension.
- A family history may reveal parental hypertension, which may, in part, be due to genetic factors.
- The total lack of familial hypertension raises the possibility of there being an underlying renal or endocrine cause for the raised blood pressure.
- Examination of the optic fundi should be carried out if the blood pressure is ≥200/110 mm Hg.

A full and careful clinical history is essential to assess the aetiology, causes and complications of hypertension. Initial evaluation should also include measurement of total cardiovascular risk with the Joint British Societies' colour charts to be found at the back of the British National Formulary. These charts are based on the Framingham equation, which calculates risk on the basis of routine characteristics (age and sex), smoking habit, levels of total and high density lipoprotein cholesterol and systolic blood pressure.

Symptoms

Most patients with uncomplicated hypertension are asymptomatic or present with non-specific (occasionally vague) symptoms. Most cases of hypertension are diagnosed as an incidental finding at a routine medical examination or after visiting the doctor for another condition.

The perception that patients with hypertension have frequent (and severe) headaches, epistaxis and lethargy is a misconception. Even patients with severe hypertension may have no symptoms until they present with a vascular complication, such as myocardial infarction, stroke or heart failure. When patients with hypertension are symptomatic, this is usually the result of anxiety and stress after diagnosis or 'labelling', (Figure 6.1) or the side effects of some of the older antihypertensive drugs.

In symptomatic untreated hypertensive patients, the introduction of antihypertensive therapy may lead to a reduction of their symptoms. In a meta-analysis of 94 placebo-controlled trials of the antihypertensive effects of the thiazides, β blockers, ACE inhibitors and angiotensin receptor blockers, all these drugs were associated with a statistically significant reduction of headache, this effect being most noticeable with the β blockers.

Almost all patients with malignant hypertension are symptomatic, however, with visual deterioration or breathlessness as a result of heart failure. Headache is common but not universal, but many patients feel generally, non-specifically unwell, particularly if they have renal failure.

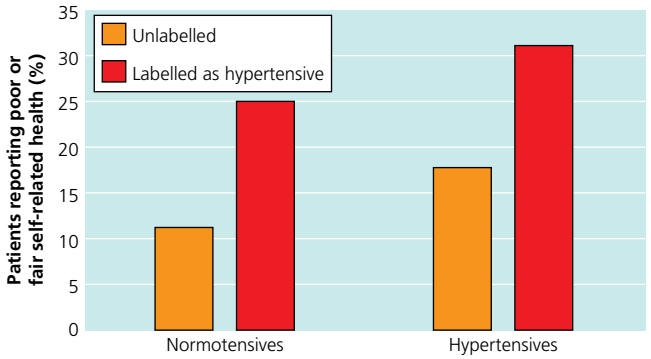


Figure 6.1 The adverse effects of being diagnosed with hypertension. Source: Data from Barger, S.D. (2006) *Journal of Human Hypertension*, 20, 117–123.

ABC of Hypertension, Sixth Edition. D. Gareth Beevers, Gregory Y. H. Lip and Eoin O'Brien.

Clinical History

Attention should be directed to common associates of hypertension, such as diabetes mellitus, dyslipidaemia and renal disease, as well as a past history of complications associated with hypertension. In women who present with hypertension, the obstetric history should be ascertained, including use of oral contraceptives, previous pre-eclampsia or pregnancy-induced hypertension (Table 6.1).

Family history

Many patients with essential hypertension report a family history of hypertension. Any family history of coronary or cerebrovascular disease or premature vascular death should be determined, as this may help assess the patient's cardiovascular risk profile. Younger patients with hypertension and absolutely no family history need detailed investigations to detect possible underlying renal, renovascular and adrenal causes of hypertension that are not familial. A family history of disease that may cause hypertension, such as autosomal dominant polycystic kidney disease, should be ascertained.

Drug history

Current or previous use of antihypertensive drugs should be assessed. Some drugs, such as oral contraceptives, may exacerbate hypertension. Drugs that cause sodium retention can exacerbate or impede control of hypertension and heart failure. Others may interact with antihypertensive drugs – for example, the effects of angiotensin-converting enzyme inhibitors may be attenuated by non-steroidal anti-inflammatory drugs (Table 6.2).

Table 6.1 Important comorbidities in hypertensive patients

History	Comment
Angina, myocardial infarction or stroke	Complications of hypertension Angina may improve when blood pressure is controlled, especially with β blockers
Asthma, obstructive airways disease	Preclude the use of β blockers
Heart failure	ACE inhibitors or ARB are indicated β Blockers indicated once stable
Diabetes	ACE inhibitors preferred
Polyuria or nocturia	Suggests renal impairment
Claudication	May be aggravated by β blockers Atheromatous renal artery stenosis may also be present
Gout	May be caused by diuretics
Arthritis	Some NSAIDS increase blood pressure
Past history of hypertension in pregnancy	Increased risk of hypertension in later life
Family history of hypertension	Important risk factor
Family history of premature death	May have been the result of hypertension
Family history of diabetes	Patient also may be diabetic
Cigarette smoker	Independently causes coronary heart disease and stroke
High alcohol intake	A cause of high blood pressure
High salt intake and use of convenience foods	Important to advise restriction of salt
Stressful lifestyle	Usually not relevant in long term

Table 6.2 Drugs affecting blood pressure

Drug raising blood volume	Corticosteriod and ACTH Liquorice Indomethacin and NSAIDS Erythropoetin
Drug causing vasoconstriction	Ephedrine nose drops and pseudoephedrine Ciclosporin Ergot alkaloids Appetite suppressants
Oestrogens	Oral contraceptives Hormone replacement therapy (unconfirmed)
Intraction with antihypertensive drugs	Tricyclic antidepressants Indomethacin and all NSAIDS Grapefruit juice with calcium channel blockers
Drug withdrawal	Clonidine Opiates Cocaine

Social history

The social history should include risk factors for hypertension and cardiovascular disease, such as high intake of alcohol, high consumption of salt and fat, lack of exercise and smoking history. Some patients may report stressful lifestyles and domestic stress. Somewhat surprisingly, smoking is less common in patients with hypertension than the general population, but, when present, it greatly increases the risk of heart attack or stroke. The only exceptions are in patients with malignant hypertension and renal artery stenosis, which are closely associated with cigarette smoking (Table 6.2).

Physical examination

Physical examination of patients with hypertension should assess the causes and seek evidence of target organ damage (e.g. in the brain, heart, kidneys and peripheral arteries). Cardiovascular risk factors and complications that may influence management should also be assessed. Height and weight should be measured so that body mass index (weight (kg)/(height (m)^2)) can be calculated to measure obesity. Body weight should be checked at every clinic visit.

Blood pressure should be measured as accurately as possible (see Chapter 4). Current guidelines recommend that it is measured routinely in all adults at least every 5 years. It should be measured annually in patients with high-normal blood pressure (systolic 130–139 mm Hg; diastolic 85–89 mm Hg) and those with previously high readings that have settled. More frequent readings should also be taken in those with existing cardiovascular disease and/or diabetes mellitus. Recent interest has been directed towards BP variability as a predictor of complications from hypertension. In one analysis, visit-to-visit variability in SBP and maximum SBP are strong predictors of stroke, independent of mean SBP. Increased residual variability in SBP in patients with treated hypertension is associated with a high risk of vascular events (Figure 6.2)

Single one-off raised blood pressure readings can be misleading. Regular measurement of blood pressure gives a truer picture of a patient's blood pressure over time. Ambulatory blood pressure measured (APBM) over 24 h is now recommended in all patients with blood pressures of 140/90 mm Hg at first screening. Many will be found to have a 'white coat' effect with pressures raised only when consulting their primary care doctors or nurses. Most of them do not need antihypertensive therapy in the short to medium term. If 24-h ABPM is not available, patient-activated home blood pressure monitoring (HBPM) is a reasonable alternative.

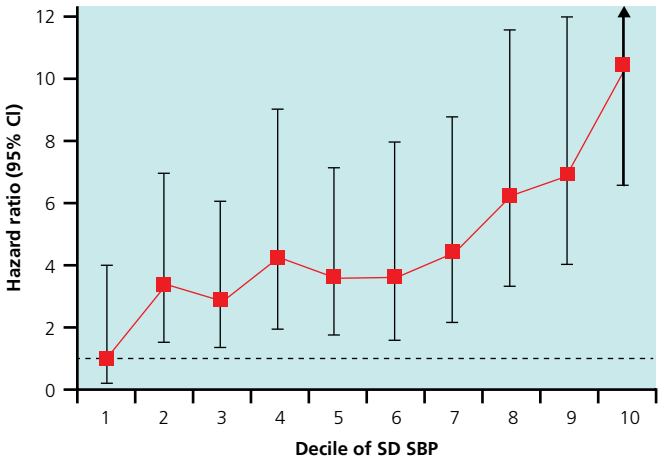


Figure 6.2 Hazard ratio for risk of stroke by deciles of standard deviation of systolic blood pressure (an index of systolic blood pressure variability) based on the first seven measurements over 2 years in the UK-TIA trial. Source: Reproduced with permission from Rothwell, P.M., *et al*. (2010) *Lancet*, 375, 895–905. © Elsevier.

General

Physical examination may show typical facies of systemic disease, such as thyroid disease, acromegaly or Cushing's syndrome. Other clues include xanthomas or xanthelasmas (associated with hyperlipidaemia), nicotine staining of the fingers and facial plethora, which may indicate polycythaemia or excessive intake of alcohol.

Cardiovascular

Examination of the pulse may show a full volume pulse and, occasionally, atrial fibrillation. Absent pulses or arterial bruits suggest atherosclerotic vascular disease in the femoral or carotid circulation. Such patients may also have undiagnosed atheromatous renal artery stenosis, which will affect the choice of antihypertensive therapy.

Examination of the praecordium may show a displaced apex beat or a left ventricular heave. Cardiac auscultation may show a loud second heart sound. Any systolic or diastolic murmurs require further investigation. For example, aortic regurgitation results in a soft blowing early diastolic murmur, which is associated with a wide pulse pressure ('collapsing pulse') and isolated systolic hypertension. Haemodynamically significant aortic stenosis can be present in patients with hypertension

One rare vascular cause of hypertension is suggested by the presence of a loud systolic murmur across the chest and back, with delayed femoral pulses and a difference in blood pressure recorded in the arms and legs as a result of coarctation of the aorta. The femoral pulses should be checked for radio-femoral delay in all patients with newly diagnosed hypertension. With modern blood pressure monitors, it is now possible to measure blood pressure in the lower leg without removing trousers.

Chest

Examination of the chest may suggest obstructive airway disease (such as asthma, chronic bronchitis or emphysema) so that β blockers should not be used. Fine basal crackles suggest pulmonary oedema or fibrosingalveolitis.

Abdomen

Examination of the abdomen may provide additional clues to associates of hypertension. For example, a renal arterial bruit is suspicious of renal artery stenosis. Almost 50% of patients with severe hypertension and peripheral artery disease have evidence of renal artery stenosis on renal angiography. Occasionally, such patients present with flash pulmonary oedema. Stigmata of chronic liver disease may be present as a result of high intake of alcohol. Enlarged kidneys may also be palpable on abdominal examination and are likely to be due to autosomal dominant polycystic kidney disease (AD-PKD)

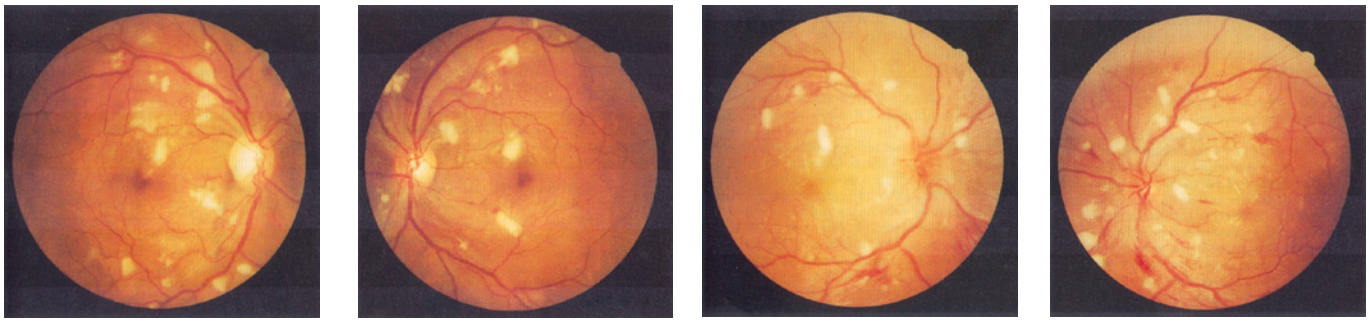
Central nervous system

Examination of the central nervous system may show cerebrovascular disease. Cognitive function is rarely tested in hypertension clinics, but informal assessment may show impairment in patients with vascular dementia.

Fundus

Fundoscopy should be part of the initial clinical assessment of all patients with moderate to severe hypertension. Patients with severe hypertension and retinal haemorrhages, cotton wool spots, hard exudates, with or without papilloedema are diagnosed as having malignant phase hypertension (Figure 6.3). Without treatment, 90% of patients with this condition die within 2 years. These patients need immediate hospital referral. Many have renal impairment or heart failure, although some present clinically with only visual symptoms.

If the blood pressure is <200/110 mm Hg, routine examination of the optic fundi is not particularly helpful, as retinopathy of grades 1–2 on the Keith, Wagner and Barker scales is more closely related to age and generalised cardiovascular status than the level of the blood pressure. Diabetic retinopathy and the changes that result from hypertension may be difficult to assess. Fundal photography through dilated pupils should be performed if retinopathy is present or suspected. The implications of the physical signs described above are summarised in Table 6.3



(a) (b) (c) (d)

Figure 6.3 Retinal features in two patients with malignant-phase hypertension a and b right and left fundus of a patient with bilateral cotton wool spots and one small haemorrhage but no papilloedema (Keith Wagener & Barker grade III retinopathy): c and d right and left fundus of a patient with bilateral cotton wool spots, haemorrhages and papilloedema (Keith, Wagener & Barker grade IV retinopathy. The differentiation between these two grades of retinopathy is not important as both conditions share the same terrible prognosis if left untreated. Source: Reproduced with permission from Lip, P.L, *et al*. (1997) *Journal of Human Hypertension*, 11, 395–396. © Nature Publishing.

Table 6.3 The implications of abnormal physical signs in patients with hypertension

Finding	Comment
Retinal haemorrhages and cotton wool spots with or without papilloedema	Malignant/accelerated hypertension Urgent admission to hospital
Corse facial features, greasy, shiny skin	Consider acromegaly
Plethoric appearance	Consider Cushing's syndrome or high intake of alcohol
Overweight and obesity	Body mass index 25–30 kg/m^{2}indicates overweight; >30 kg/m^{2}indicates obesity. May have hypothyroidism.
Intermittent palpitations, sweating, anxiety attacks, pallor or weight loss	Consider phaeochromocytoma
Myxoedema or thyrotoxicosis	Both can give rise to hypertension
Tachycardia	Consider anxiety but exclude thyrotoxicosis and phaeochromocytoma
Left ventricular apical heave	Left ventricular hypertrophy is an ominous sign Urgent treatment needed
Loud aortic second sound	Present in patients with long-established hypertension
Mitral incompetence murmur	May be the result of left ventricular failure
Aortic outflow murmur	May be a flow murmur, but aortic stenosis may be present May be aortic sclerosis if aortic second sound is loud
Pulmonary fine crackles	Suggests heart failure Use diuretics first Consider angiotensin-converting enzyme inhibitors
Pulmonary wheezes	Avoid β blockers
Delayed or weak femoral pulses with or without precordial murmurs	Consider coarctation of the aorta Measure blood pressure in the legs
Absent ankle and foot pulses	Peripheral vascular disease
Ankle swelling	May be due to congestive cardiac failure Dihydropyridine calcium blockers (particularly amlodipine) cause ankle swelling
Abdominal mass	Autosomal dominant polycystic kidney disease (AD-PKD) Abdominal aortic aneurysm if pulsatile
Corneal arcus or xanthelasmae	Associated with hyperlipidaemia. Xanthelasmae are highly predictive of coronary heart disease, corneal arcus less so.

Further Reading

Beevers, D.G. & Aitchison, F.A. (2011) Screening for aortic coarctation by comparing blood pressure in the arms and legs is more convenient and reliable than examination of the femoral pulses. *Journal of Hypertension*, 29, 1465–1467.

Kakar, P. & Lip, G.Y. (2006) Towards improving the clinical assessment and management of human hypertension: an overview from this Journal. *Journal of Human Hypertension*, 20, 913–916.

Kaplan, N.M. (1993) Essential workup of the hypertensive patient. *Heart Disease and Stroke*, 104–108.

Law, M., Morris, J.K., Jordan, R. & Wald, N. (2005) Headaches and the treatment of blood pressure: results from a meta-analysis of 94 randomized placebo-controlled trials with 24,000 participants. *Circulation*, 112, 2301–2306.

Rothwell, P.M. (2010) Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet*, 375, 938–948.

CHAPTER 7

Investigation in patients with hypertension

OVERVIEW

- Patients who have been diagnosed as having hypertension need detailed clinical assessment.
- Clinical assessment has three functions:
  - — Identification of the severity of cardiovascular risk due to the blood pressure, plasma lipid profile and where relevant, cigarette smoking and concomitant diabetes mellitus.
  - — Identify evidence of existing 'end-organ' cardiac, cerebral or renal damage.
  - — Identify underlying renal or endocrine causes of hypertension
- All hypertensive patients should undergo:
  - — Dipstick urine test for proteinuria
  - — Serum urea and creatinine to assess renal involvement
  - — Serum sodium and potassium to identify adrenal disease
  - — Random blood glucose
  - — Random serum total and HDL cholesterol
  - — 12 lead ECG
- Patients where initial clinical assessment suggests renal or endocrine disease should be referred to specialist centres for further more detailed investigation.
- About 5% of hypertensive patients will be found to have underlying renal or endocrine causes for their raised blood pressure. These include:
  - — Concomitant type 1 or type 2 diabetes mellitus
  - — Underlying renal damage either as a cause or a consequence of hypertension
    - ■ Glomerulonephritis
    - ■ Pyelonephritis
  - — Evidence of aldosterone excess including Conn's syndrome
  - — Other endocrine diseases associated with hypertension
    - ■ Thyroid disease
    - ■ Cushing's disease or syndrome
    - ■ Acromegaly
  - — Other conditions to be excluded are aortic coarctation and phaeochromocytoma

Routine investigations

Investigations are needed in all patients with hypertension to detect any underlying cause (e.g. to exclude secondary hypertension), assess for the consequences of hypertension (target organ damage) and test for other cardiovascular risk factors (Table 7.1). Very thorough investigations should be performed in young patients (those younger than 40 years), patients who present with severe or resistant hypertension and patients in whom secondary hypertension is suspected. Chestxray, urine microscopy and culture and echocardiography are not 'routine' investigations and are not needed in most patients. The NICE guidelines suggest the following routine tests.

Urinalysis

In addition to the BHS/NICE recommendations above, we strongly advocate the routine dipstick testing of the urine in all hypertensive patients in primary and secondary care. Proteinuria and microscopic haematuria suggest intrinsic renal disease, including glomerulonephritis, particularly immunoglobulin A (IgA) nephropathy, autosomal dominant polycystic kidney disease (ADPKD) or pyelonephritis. In patients with proteinuria, the risk of mortality and morbidity is roughly doubled for a given blood pressure. Proteinuria is a powerful predictor of all-cause mortality in hypertensive patients

Table 7.1 BHS/NICE guidance for the initial assessment for target organ damage in hypertensive patients

Test for the presence of protein in the urine by sending aurine sample for estimation of the albumin: creatinine ratio and test for haematuria using a reagent strip.
Take a blood sample to measure plasma glucose, electrolytes, creatinine, estimated glomerular filtration rate (eGFR), serum total cholesterol and HDL cholesterol.
Examine the fundi for the presence of hypertensive retinopathy.
Arrange for a12-lead electrocardiograph to be performed.

Source: Reproduced with permission from Krause, T., *et al.* (2011) *British Medical Journal*, 343, d4891. © BMJ Publishing Group Ltd.
Some of these tests can be conducted in primary care.

ABC of Hypertension, Sixth Edition. D. Gareth Beevers, Gregory Y. H. Lip and Eoin O'Brien.

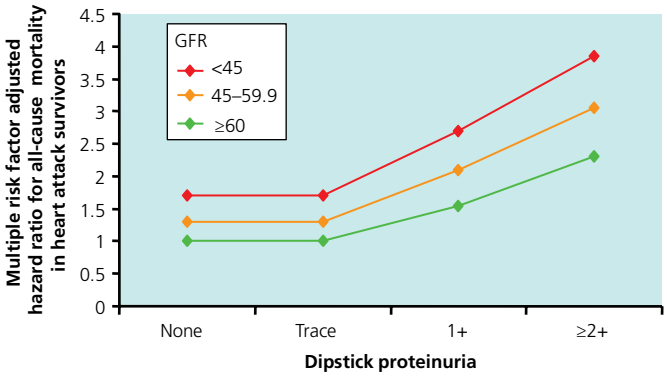


Figure 7.1 The relationship between dipstick proteinuria and all-cause mortality in patients with existing coronary heart disease. Similar trends are found in patients with no end-organ damage. Source: Data from Tonelli, M, *et al*. (2006) *British Medical Journal*, 332, 1426–1429.

with or without cardiovascular damage. This effect is independent of the amount of renal impairment (Figure 7.1).

Microalbuminuria (urine albumin less than 300 mg/24 h) or urine albumin: creatinine ratio also predicts all-cause and cardiovascular mortality.

By contrast, microscopic haematuria does not appear to predict end-organ damage. It may occur in severe uncomplicated essential hypertension. However, it may be a marker for underlying primary renal disease. When haematuria is persistent and marked, renal and renal tract malignancies should be excluded and urological referral may be necessary.

Biochemistry

Serum potassium

Serum levels of potassium are usually low or low-normal in patients with primary hyperaldosteronism (Conn's syndrome). This is often associated with high or high-normal serum levels of sodium.

Low levels of potassium sometimes occur in patients who take diuretics, but usually, thiazide diuretics only lower potassium by 0.5 mmol/l. If hypokalaemia is marked, it is possible that it is related to underlying aldosterone excess. Patients with malignant hypertension may have mild hypokalaemia because of aldosterone excess, secondary to high levels of renin caused by juxtaglomerular cell ischaemia. As blood pressure is brought under control, this hypokalaemia often normalises. If serum levels of potassium remain low without diuretic treatment despite good control of blood pressure over a few months, primary hyperaldosteronism should be excluded.

Hyperkalaemia may develop in patients with renal failure and those who take drugs such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and potassium sparing diuretics (e.g. spironolactone and amiloride). Spironolactone is increasingly used as third-line treatment in patients with resistant hypertension, and potassium and renal function need to be monitored regularly. Low table salt alternatives, which contain potassium salts, should be used cautiously with angiotensin-blocking drugs as dangerous hyperkalaemia can occur, particularly if spironolactone is also being used. This is a problem which is becoming more common as angiotensin-blocking drugs and spironolactone are frequently used together in both hypertension and heart failure.

Serum sodium

Serum levels of sodium may be high or high-normal in patients with primary hyperaldosteronism (Conn's syndrome). This is usually associated with low or low-normal serum levels of potassium. In patients with secondary hyperaldosteronism as a result of malignant hypertension or renal disease, serum levels of sodium can be low or low-normal. Low levels of sodium may also be present with overuse of diuretics.

Profound hyponatraemia, which may cause confusion and hypotension, is occasionally seen in patients even on low doses of diuretics.

Serum urea and creatinine

Non-malignant essential hypertension only rarely causes renal impairment, but associated co-morbid disease (such as diabetes mellitus) and concomitant treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers can lead to renal impairment.

Almost all intrinsic renal diseases can cause hypertension, and levels of urea and creatinine in serum should be part of the initial work up in a patient with newly diagnosed hypertension. Even a modest increase in levels of creatinine in serum needs more detailed investigation.

Estimated glomerular filtration rate

In recent years, it has become fashionable to assess renal function using a formula devised from the US Modification of Diet in Renal Disease (MDRD) study. This has proved a little controversial. It has long been recognised that serum creatinine levels do not rise above the so-called normal range until renal function is about halved. The MDRD study attempted to correct for this. The estimated glomerular filtration rate (eGFR) formula takes into account age, gender, body weight (as a surrogate for muscle bulk) and ethnicity (African American vs. non-African American). The grade of renal impairment can then be calculated but this should also take into account the presence of other abnormalities including proteinuria and haematuria. Taking these criteria, patients with a eGFR above 90 ml/min (excellent) will be labeled as having grade 1 chronic kidney disease (CKD) (Table 7.2). It would appear that all patients, regardless of their eGFR, have some form of CKD.

Table 7.2 The MDRD classification of chronic kidney disease

eGFR		CKD stage
>90 ml/min	Without other abnormality otherwise regard as normal	1
60–89 ml/min	With other abnormality otherwise regard as normal	2
30–59 ml/min	Moderate impairment	3
15–29 ml/min	Severe impairment	4
<15 ml/min	Established renal failure	5

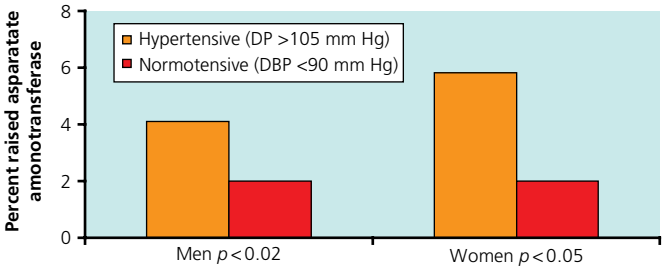


Figure 7.2 Serum aspartate aminotransferase in normotensives and hypertensives in the Renfrew Community study. Source: Data from Beevers, D.G. (1977) *Lancet*, 2, 114–115.

This has presented a particular problem in older patients with serum creatinine levels that are about average or near average for their age. Once labeled as having CKD, they are subjected to renal imaging and often unnecessary nephrological referral. It is to be hoped that the use of serum creatinine levels to measure eGFR will be refined over the coming years.

Serum uric acid

High levels of uric acid in serum are found in about 40% of patients with hypertension, especially in association with renal impairment. Increased ingestion of alcohol and the use of thiazide diuretics can also lead to higher levels of uric acid. Whether high levels of uric acid are harmful in their own right, or only by association with hypertension, hyperlipidaemia and diabetes remains uncertain. There is no information as to whether the treatment of hyperuricaemia with allopurinol in symptomless hypertensive patients with normal renal function is of any value.

Liver function tests

There is an increased prevalence of abnormal liver function tests (LFTs) in patients with hypertension. (Figure 7.2). This is partly explained by the association between excess alcohol intake in the causation of hypertension. However, abnormal LFT are also seen in people who consume no alcohol at all. Such patients are often overweight and/or have type 2 diabetes, as part of Non-Alcoholic Fatty Liver Disease (NAFLD). This syndrome is usually reversible with weight reduction but may progress to Non-Alcoholic Steato-Hepatitis (NASH) or even cirrhosis.

Serum calcium

A low serum level of calcium with a high level of phosphate may be found in patients with renal failure. Hypertension is closely associated with primary hyperparathyroidism, which results in a high level of calcium and a low serum level of phosphate. Serum levels of calcium are also slightly higher in patients who use thiazide diuretics.

Plasma lipid profile

Assessment of serum levels of lipids is mandatory in all patients with hypertension as part of the assessment of cardiovascular risk. In outpatient clinics, a simple random level of serum cholesterol together with high density lipoprotein (HDL) cholesterol will suffice. The ratio of total cholesterol to high density lipoprotein cholesterol (TC:HDL) can therefore be calculated.

Haematology

A full blood count is not needed in most patients with hypertension. Macrocytosis may suggest associated alcohol abuse or hypothyroidism. Erythrocytosis with a raised haemoglobin level is also a feature of alcohol excess.

In patients with impaired renal function a normochromic, normocytic anaemia may be present; almost all patients with renal failure are anaemic. There may also be thrombocytopenia.

Electrocardiography

12-Lead electrocardiography is a mandatory part of the assessment of all patients with hypertension. It provides a baseline with which later changes may be compared, but, more importantly, it may show evidence of the presence of left ventricular hypertrophy (LVH) – the most common manifestation of hypertensive target organ damage.

LVH is commonly diagnosed when the sum of the S wave in lead V1 and the R wave in leads V5 and V6 is 35 mm or more (the Sokolow–Lyon criteria). The prognosis is even worse if the 'strain' pattern is present with T wave inversion in leads V5 or V6 (Figures 7.3 and 7.4).

The 'strain' changes are due to ischaemia where the hypertrophied left ventricle has 'outgrown' its blood supply. All the ECG changes of LVH are reversible with accurate blood pressure control. There is reliable evidence that the angiotensin-blocking drugs are more effective at reducing LVH than other agents.

In very obese patients, the chest lead criteria for LVH may be absent due to the thick chest wall. LVH should be suspected if there is left axis deviation and/or a tall R wave (12 mm or more) in lead aVL.

In addition, the 12-lead electrocardiography may show underlying ischaemic heart disease, including previous myocardial infarction. Common arrhythmias, such as atrial fibrillation, may also be documented.

Investigations for selected patients

If clinical assessment or the initial simple investigations suggest the need for further detailed investigation, specialist advice may be needed to facilitate management and further tests.

Echocardiography

Paradoxically, echocardiography should be considered in patients where the ECG shows an unexpected lack of LVH. This is commonly seen in obese patients. If the ECG shows convincing LVH in a hypertensive patient who is not breathless, then an echocardiogram may not be needed as it will merely confirm the LVH. False positives on ECG testing may be seen in slim, athletic patients. False negatives are common and the usual cause is obesity. If an obese patient has convincing LVH on ECG, the cardiovascular prognosis is poor.

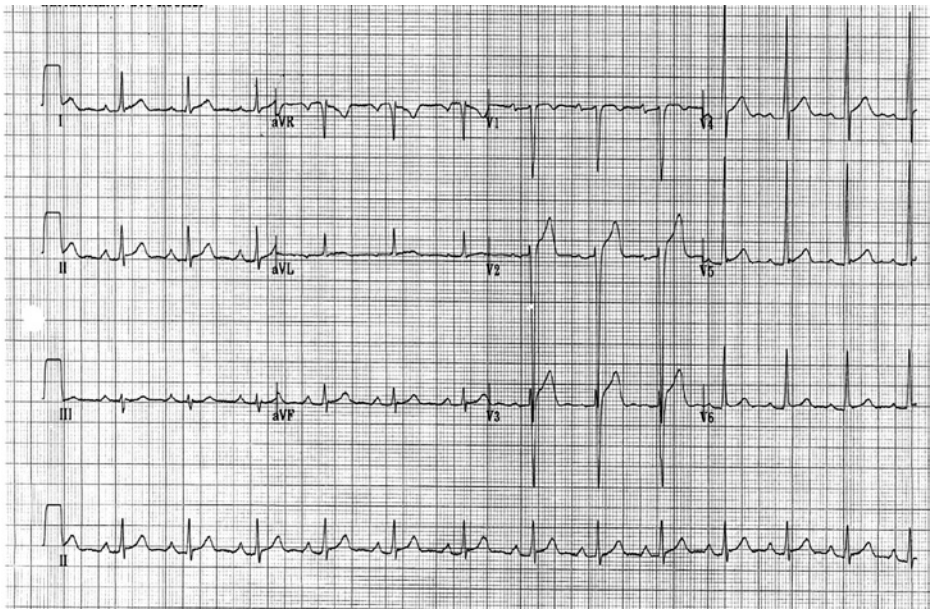


Figure 7.3 12-lead ECG in a hypertensive patient with left ventricular hypertrophy. The S wave in lead V1 is 16 mm; the R wave in V5 is 24 mm, making a total of 40 mm (normal less than 35 mm). Note also the biphasic P wave in lead V1, indicating left atrial stretch. There is no left axis deviation here.

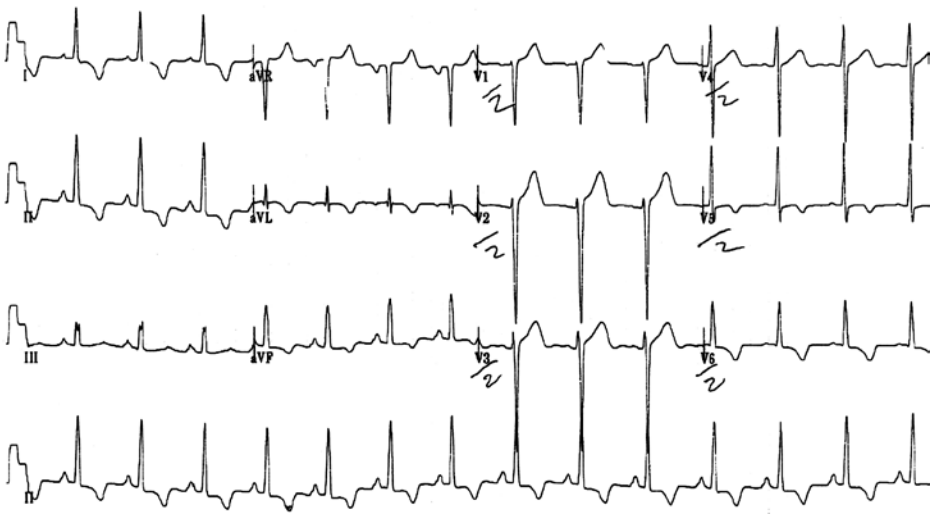


Figure 7.4 12-lead ECG in a hypertensive patient with left ventricular hypertrophy and 'strain'. The calibration marks on the left of the trace indicate that the voltages are normal in the limb leads but are halved in the chest leads. The S wave in lead V1 is, therefore, 30 mm, as in the R wave in lead V5. The Sokolow sum is therefore 60 mm, indicating gross left ventricular hypertrophy. In addition, the T waves are inverted in leads V5 and V6, indicating repolarisation abnormalities, sometimes called 'strain'.

The echocardiographic features of LVH are symmetrical or asymmetrical thickening of the left ventricle (Figure 7.5).

Echocardiography should be performed in patients with breathlessness to assess cardiac function. Hypertension can lead to heart failure as a result of systolic dysfunction alone or secondary to associated myocardial infarction, when regional abnormalities of wall motion may be present.

In patients with hypertension who develop atrial fibrillation (AF), assessment of left atrial size and the mitral valves is necessary, as well as ventricular size and function. Patients with hypertension are at high risk of developing AF. In addition, AF is particularly common in patients with hypertension due to aldosterone excess (Conn's syndrome).

Echocardiography may also show impaired diastolic function with reduced diastolic filling but normal contractive (systolic) function. The significance of left ventricular diastolic dysfunction has been debated, but long-term outcomes include the development of AF and a worsened prognosis compared to patients with normal (systolic and diastolic) cardiac function. Quantification of left atrial size has been regarded as a surrogate for the chronicity of left ventricular diastolic dysfunction.

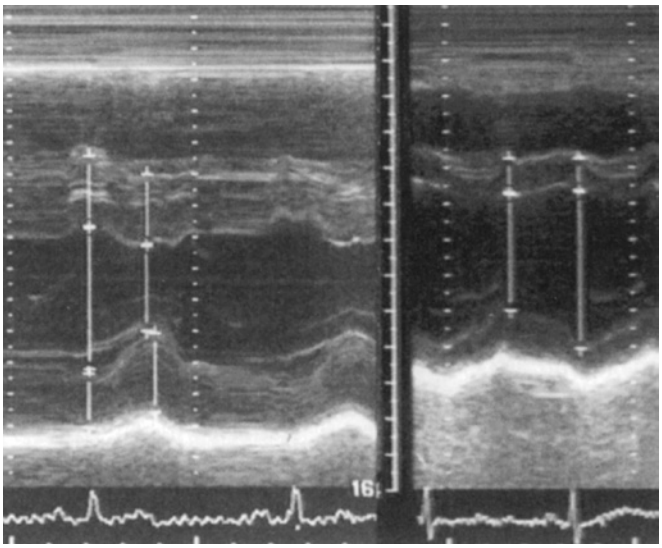


Figure 7.5 Two-dimensional and M mode echocardiograms showing severe left ventricular hypertrophy with marked thickening of the intraventricular septum and posterior wall (left) and normal echocardiogram (right).

Twenty-four hour urine collection

At least one urine collection over 24 h should be taken to test for urine catecholamines in young, thin patients with hypertension and those with paroxysmal symptoms, including blanching attacks, panic attacks and marked variability of blood pressure. Routine estimation of creatinine clearance is not necessary unless the serum creatinine is raised.

Measurement of sodium excretion in urine over 24 h may give some indication of the intake of salt and provide a basis for education and counseling.

If dipstick urinalysis shows proteinuria, 24-h collection of urine allows this to be quantified. If the patient has >1 g proteinuria per 24 h, referral to a nephrologist may be needed for consideration of renal biopsy.

Radiology and imaging

Chest radiography

Chest X rays are not helpful in most patients with hypertension – unless they are breathless. Inferior rib notching may be seen in patients with coarctation of the aorta.

Renal imaging

Renal ultrasound is the best imaging test for suspected renal disease and should be performed in all patients with malignant hypertension, proteinuria or raised serum levels of creatinine. All patients younger than 40 years with hypertension and those with severe or resistant hypertension should also undergo renal ultrasound scans. A unilateral small kidney raises the suspicion of renal artery stenosis, although unilateral renal parenchymal disease cannot be ruled out. In patients with some forms of glomerulonephritis, the kidney may seem 'bright' or echogenic on ultrasound images. More often, chronic renal parenchymal disease, in which the renal cortex is thinned or the renal pelvis is distorted and dilated, or both, can be diagnosed. Hydronephrosis or polycystic kidneys can also be diagnosed (Figure 7.6). Improvements in renal ultrasound techniques mean that intravenous urography is no longer used.

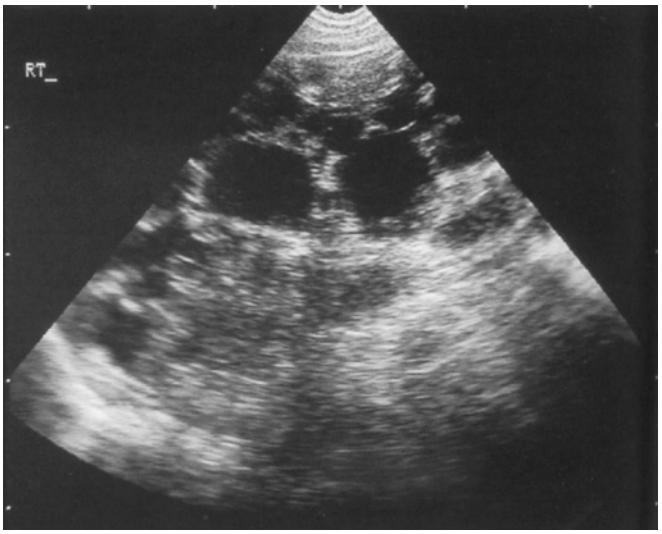


Figure 7.6 Ultrasound showing polycystic kidney.

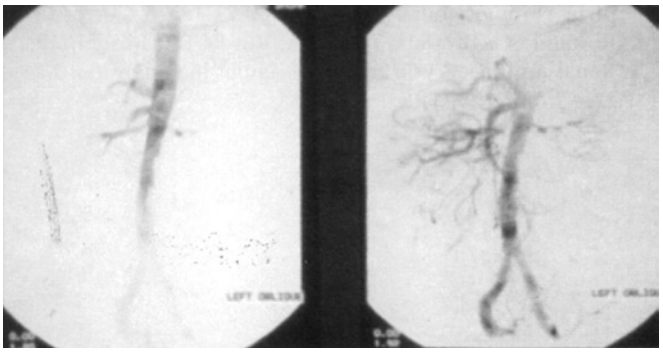


Figure 7.7 Renal angiograms showing atheromatous renal artery stenosis (left) and extensive aortic atheroma (right).

Magnetic resonance renal angiography is the most useful test for renal artery stenosis. If this is positive, conventional renal angiography may be needed for more detailed assessment of the renal arteries. Renal artery stenosis may be the result of atheroma (Figure 7.7) in elderly patients and fibromuscular dysplasia in younger usually female patients (Figure 7.8)

Computed tomography and magnetic resonance imaging

Computed tomography and magnetic resonance imaging are the investigations of choice for detecting phaeochromocytomas and adrenal tumours that cause cortisol or aldosterone excess. These tests may miss small tumours in patients with Conn's syndrome and may not pick up generalised adrenal hyperplasia.

Radioisotope imaging

Renal radioisotope imaging has a limited role in the investigation of hypertension. The captopril renogram was previously used for the diagnosis of renal artery stenosis but has been superceded by magnetic resonance renal angiography.

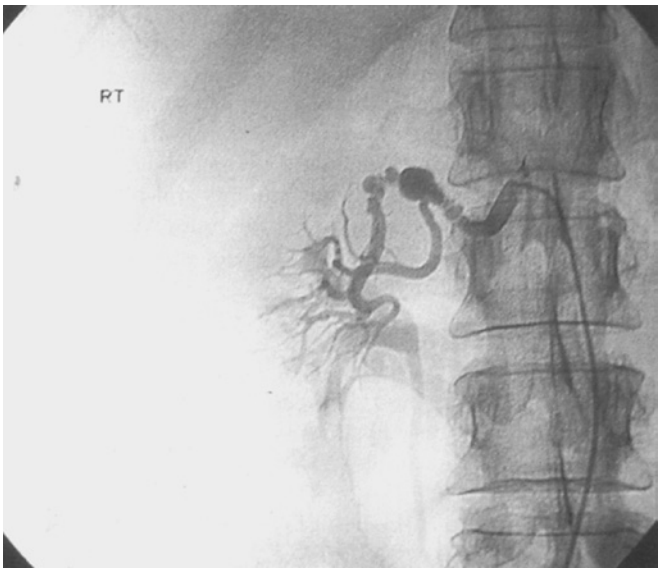


Figure 7.8 Fibromuscular dysplasia on renal angiography.

Plasma levels of hormones

Plasma levels of hormones must be assessed in patients with suspected endocrine causes of hypertension. Many of these hormones are labile and the blood must be taken carefully with special blood tubes – often with the patient fasting and supine and preferably before they rise in the morning. Such tests are performed best in specialist centres.

Conn's syndrome is diagnosed by high plasma levels of aldosterone and suppressed plasma renin activity. More recently, the aldosterone–renin ratio has been used to detect aldosterone excess at an earlier stage, when absolute levels of hormone are equivocal. Secondary hyperaldosteronism causes high plasma levels of aldosterone in association with high plasma renin activity. This is seen in some patients with renal or renal artery disease and those who use diuretics. It is also seen in young patients with renin-secreting tumours.

Cushing's syndrome is investigated by the overnight dexamethasone suppression test (Table 7.3). An elevated random cortisol measurement is of no value as false positives are seen in obesity, anxiety and alcohol excess.

Table 7.3 The overnight dexamethasone (DMZ) suppression test to detect Cushing's syndrome

Patient takes 1 mg of dexamethasone at 22:00
At 8:00 the next morning, the patient's plasma cortisol level should be <50 mol/l
Failure to suppress suggests Cushing's disease or Cushing's syndrome
If the plasma cortisol is 'normal' with the overnight DMZ test, Cushing's is likely

Acromegaly is suspected from the typical facies and is investigated with a glucose tolerance test and plasma levels of growth hormone. A skull X-ray may show an enlarged pituitary fossa, which can be confirmed on computed tomography.

In patients with phaeochromocytoma, secretion of adrenaline, noradrenaline and dopamine may be intermittent. These hormones or their metabolites (metanephrines) thus are usually measured in a collection of urine over 24 h. This test should be done in young, thin patients with hypertension, who have variable blood pressures, tachycardia, blanching attacks or other episodic symptoms.

Further Reading

Bausch, B., Boedeker, C.C., Berlis, A., *et al.* (2006) Genetic and clinical investigation of pheochromocytoma: a 22-year experience, from Freiburg, Germany to international effort. *Annals of the New York Academy of Sciences*, 1073, 122–137.

Giles, P.D. & Fitzmaurice, D.A. (2007) Formula estimation of glomerular filtration rate: have we gone wrong? *British Medical Journal*, 334, 1198–1200.

Kaplan, N.M. (2004) The current epidemic of primary aldosteronism: causes and consequences. *Journal of Hypertension*, 22, 863–869.

Manolis, A.J., Hamodraka, E.S. & Poulimenos, L.E. (2012) Electrocardiography for the diagnosis of left ventricular hypertrophy: revisiting an old friend in times of austerity. *Journal of Hypertension*, 30, 1325–1327.

Peters, D.J. & Breuning, M.H. (2001) Autosomal dominant polycystic kidney disease: modification of disease progression. *Lancet*, 358, 1439–1444.

Pietrobelli, D.J., Akopian, M., Olivieri, A.O., *et al.* (2001) Altered circadian blood pressure profile in patients with active acromegaly. Relationship with left ventricular mass and hormonal values. *Journal of Human Hypertension*, 15, 601–605.

CHAPTER 8

Non-pharmacological treatment of hypertension

OVERVIEW

- There is a close relationship between hypertension and being overweight or obese, and weight reduction lowers blood pressure at a rate of about 1 mm Hg/kg lost.
- A great many trials have shown that a moderate and achievable reduction in salt intake causes an important fall in blood pressure in hypertensive patients.
- Amongst heavy alcohol drinkers, moderation or discontinuation causes a significant fall in blood pressure.
- There is no convincing evidence that chronic stress causes hypertension, although acutely stressful stimuli may cause transient rises in blood pressure.
- There is no evidence that cigarette smoking raises blood pressure. Smoking is an important and independent reversible cause of premature death.
- The DASH diet (low in dairy products and high in fruit and vegetables) also lowers blood pressure.
- All these non-pharmacological maneuvers also lower blood pressure in normotensive individuals. A small reduction in blood pressure in the general population could greatly reduce the number of heart attacks and strokes in the population at large.

Many lifestyle factors increase blood pressure, and their modification can reduce blood pressure in patients with or without hypertension. Changes that lead to such reductions include restriction of salt intake, weight reduction, reduced intake of dairy products, increased intake of fruit and vegetables, moderation of alcohol intake and increased exercise. These approaches may reduce the need for drug treatment, add to or complement the effect of antihypertensive drugs and even occasionally allow antihypertensive drugs to be stopped. Effective non-pharmacological lifestyle modification may reduce blood pressure as much as a single antihypertensive drug. Combinations of two or more lifestyle modifications produce even better results.

In patients with mild hypertension but no cardiovascular complications or target organ damage, the response to non-pharmacological measures should be observed for 4–6 months. If antihypertensive drugs are introduced – for example, in patients with more severe hypertension – non-pharmacological lifestyle measures should be started concurrently. Most management guidelines recommend that verbal and written advice on lifestyle measures be given to all patients with hypertension as well as those with high-normal blood pressure or a strong family history of hypertension.

These non-pharmacological approaches should also be applied in a population-based strategy to manage blood pressure in the community. Such a strategy could theoretically minimise the increase in blood pressure with age and thus reduce the prevalence of hypertension, as well as the burden of cardiovascular disease to the community.

- All people who are having their blood pressure measured should be provided with lifestyle advice in order to facilitate blood pressure reduction or prevent hypertension developing in future years.
- Patients with blood pressures that are above average for their age but not high enough to warrant drug therapy should be reviewed about once per year for reinforcement of lifestyle advice.
- Patients who are overweight or obese should be advised on the benefits of weight reduction on blood pressure and referred for expert dietetic advice.
- Patients should be questioned on the amount of exercise they take. Those who take little exercise should be advised to increase gradually by avoiding lifts and escalators where possible and regularly walking about 1 mile/day. Vigorous static or dynamic exercise should not be recommended.
- The salt intake of all patients should be assessed by detailed questioning. Patients should be warned on the hazards of a high salt intake and the proven benefits of reducing salt intake. Dietary salt can be reduced by avoiding 'junk' or convenience foods and salty processed foods and snacks. Expert dietetic advice should be recommended. Do not recommend salt substitutes.
- Alcohol intake should be assessed; those who consume more than 14 units per day (women) or 21 units per day (men) should be advised to reduce

ABC of Hypertension, Sixth Edition. D. Gareth Beevers, Gregory Y. H. Lip and Eoin O'Brien.

- All smokers should be advised on the dangers of this habit and should be referred to local antismoking facilities.
- Do not recommend dietary supplements of potassium, magnesium or calcium.
- Patients should be advised that yoga or relaxation therapies are of little value.
- Advise patients to enter the Blood Pressure UK website for more information (see chapter 7).

Obesity and weight reduction

Obesity and hypertension are closely related; the mechanisms of this relationship are complex. Firstly, there is a tendency to overread blood pressure with an upper arm cuff. This source of error can be reduced by using larger blood pressure cuffs when the arm circumference exceeds 35 mm. Other true mechanisms include a higher salt intake associate with obesity, insulin resistance, increased sympathetic tone and sodium and water retention. Obesity is also closely related to obstructive sleep apnoea (OSA), which also causes a rise in blood pressure.

There is increasing anxiety about the rising prevalence of overweight (BMI 25–30) and obesity (BMI ≥ 30) in the general population. In some populations in the developed countries, obesity is seen in 30% of adults. Clearly, therefore, obesity must be seen as a public health issue, which needs to be solved by public heath means, if necessary with legislation.

At I clinical level, weight reduction does cause a significant fall in both systolic and diastolic blood pressure. Most of these controlled trials have been relatively short term and have required a lot of effort by the research trialists (Figure 8.1). Sadly some of the reductions in weight achieved in the short term have not been maintained on a longer term basis. Taking into account all studies, a simple rule of thumb for patients is that if they can reduce their weight by 1 kg (roughly 2 lb) the diastolic pressure will fall by about 1 mm Hg; a 5 kg (roughly 10 lb) reduction will reduce diastolic pressure by 5 mm Hg and so on.

There is evidence that dietary advice and support provided by nutritionalists and dietitians is more effective than advice by a doctor in a routine clinical setting. Technical advice, information of healthy versus unhealthy foods and their availability, together with information leaflets and Internet access to Blood Pressure UK may also prove beneficial.

Weight reduction also has beneficial effects on other risk factors associated with hypertension, including insulin resistance, type 2 diabetes mellitus, dyslipidaemia and left ventricular hypertrophy. The blood pressure-reducing effect of weight reduction should be complemented by an increase in physical exercise and a reduction in the intake of salt and alcohol.

Salt intake and salt restriction

Many studies confirm a clear and causal relation between dietary intake of salt and blood pressure. Conversely, a strategy of salt restriction to <100 mmol/day (<6 g/day) significantly reduces blood pressure. A reduction in salt intake from an average of 10 g/day (about two teaspoons) to 5 g/day can result in an average reduction in blood pressure of 5/2 mm Hg (Figure 8.2). Reductions in salt intake can result in larger decreases in blood pressure in the elderly, African-Caribbean people (who are more salt sensitive), and those with higher initial blood pressures. On average, one-third of such patients who reduce their intake of salt will achieve a reduction in blood pressure of 5/5 mm Hg.

The effects of salt restriction add to the beneficial effects of a healthy diet in reducing blood pressure. For example, in the Dietary Approaches to Stop Hypertension (DASH) trial, salt restriction further lowered blood pressure in patients who had already obtained benefit from a diet low in dairy products and rich in fruit and vegetables.

Modest salt restriction can be achieved by not adding salt at table or when cooking. However, this 'discressionary' salt intake only accounts for 10–20% of total salt intake. A greater reduction of salt intake can be achieved by reducing intake of salty foods, such as crisps, hamburgers, sausages and salty bacon. A large amount of salt is also present in common everyday processed foods, such as bread, breakfast cereals, canned soups, 'ready meals' and flavour enhancers, such as stock cubes. Unfortunately, in many countries,

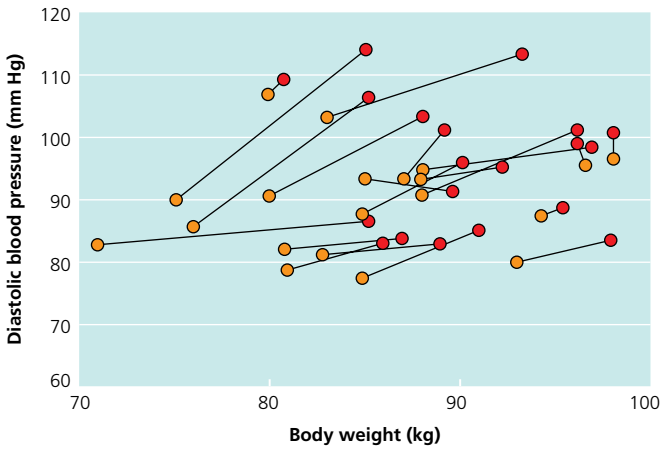


Figure 8.1 Overview of short term trials of weight reduction on blood pressure. Source: Reproduced with permission from Staessen, J., *et al*. (1988) *Journal of Human Hypertension*, 2, 207–217. © Nature.

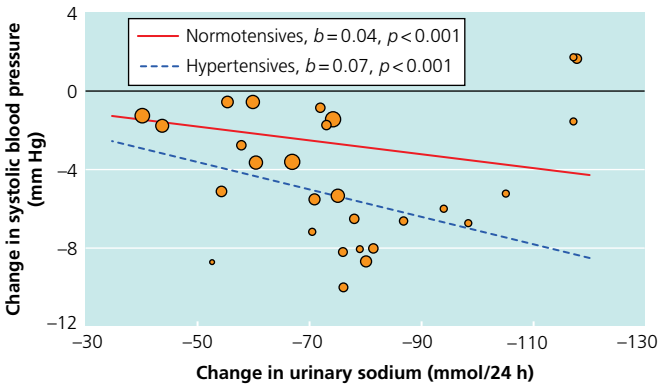


Figure 8.2 Dose response of salt restriction: meta-analysis of trials lasting 1 month or longer. A 6 g/day reduction in intake of salt predicts a fall in systolic blood pressure of 7 mm Hg in hypertensives and 4 mm Hg in normotensives. Source: Reproduced with permission from He, F.J. *et al*. (2002) *Journal of Human Hypertension*, 16:761–770. © Nature.

food labeling is inadequate, so it is difficult for patients to judge whether some processed foods are salty.

The substitution by salt substitutes (which contain potassium chloride instead of some sodium chloride) is another option, but care is needed when angiotensin inhibitors or potassium sparing diuretics are being prescribed, as life-threatening hyperkalaemia may result. It is better to persuade patients that they should avoid adding any chemical substances to their food.

Alcohol

High intake of alcohol can be related to hypertension, as well as obesity and other problems, including cardiac arrhythmias, alcoholic cardiomyopathy, peripheral neuropathy, liver disease and pancreatitis. In patients with hypertension, even a moderately high intake of alcohol of 80 g/day (equivalent to four pints of beer a day) can significantly increase blood pressure. Binge drinking has been associated with an increased risk of stroke.

Conversely, reducing intake of alcohol to fewer than 21 units a week reverses any increase in blood pressure associated with alcohol, and blood pressure remains low in those who continue to abstain (Figure 8.3). Patients with hypertension should therefore be advised to limit their alcohol intake to fewer than 21 units a week in men and 14 units a week in women.

Exercise and physical activity

Epidemiological studies on exercise and blood pressure are often confounded by 'healthy lifestyle' changes, including changes in diet and weight reduction. It generally is accepted, however, that a graduated exercise programme beneficially can reduce mean blood pressure in patients with hypertension. Such physical activity should be regular and aerobic (such as brisk walking) and, importantly, should be tailored to each patient. For example, three vigorous training sessions a week may be appropriate for fit younger patients, and brisk walking for 20 min a day may be more appropriate in older patients. Such regular aerobic exercise reduces systolic and diastolic blood pressures by about 2–3 mm Hg, but a combination of exercise and a healthy diet may reduce systolic and diastolic blood pressures by 5–6 mm Hg. A reasonable strategy is perhaps one that includes regular aerobic exercise (such as brisk walking) for at least 30 min, ideally on most, but at least three, days of the week (Figure 8.4)

By contrast, isometric exercise (such as heavy weight lifting) is not recommended because of the pressor effects on blood pressure. Obese patients with newly diagnosed hypertension and heart disease should not suddenly take up heavy exercise, although a sensibly administered physical exercise programme may be beneficial.

In observational studies, physical activity – at work or in leisure time – is associated with a lower risk of coronary heart disease in men and women. This cardioprotection is lost when exercise is discontinued. The greatest reduction in risk is seen between sedentary and moderately active individuals; the difference between those who take moderate and vigorous activity is more modest.

Healthy diet

The dietary approaches to stop hypertension (DASH) trial clearly shows a beneficial effect on blood pressure of a diet high in fruit and vegetables and low in dairy products. Increased consumption of fruits and vegetables has a beneficial effect on blood pressure. An increase from two to seven portions of fruits and vegetables a day reduces average blood pressure by about 7/5 mm Hg in patients with hypertension. Increased fruit and vegetable consumption and decreased consumption of dairy products and total and saturated fats can cause larger reductions – perhaps 11/6 mm Hg – in patients

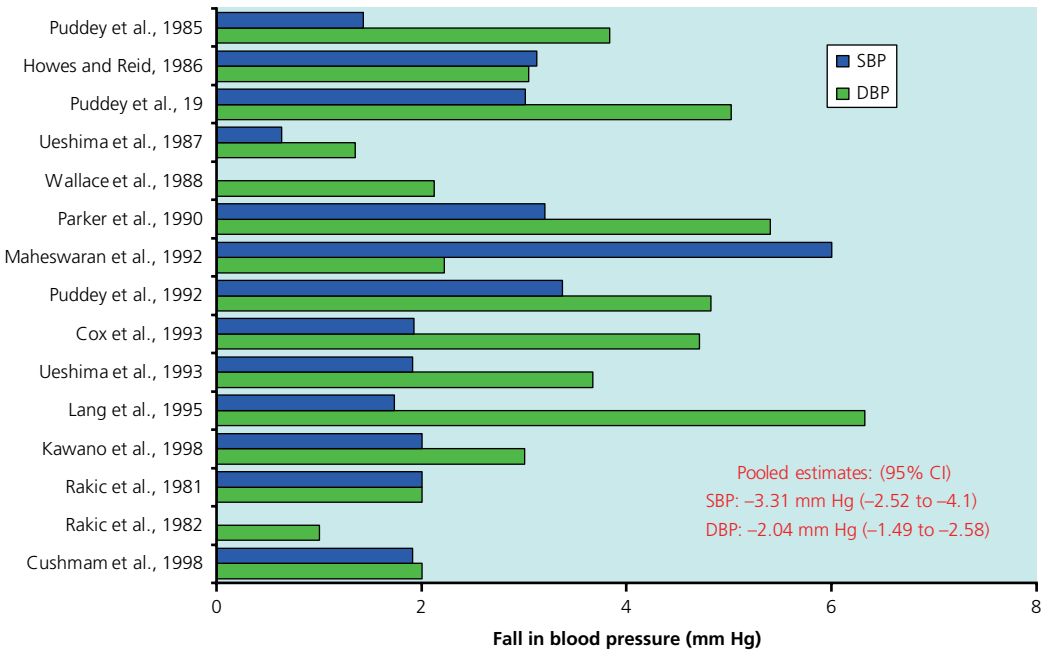


Figure 8.3 Overview of 15 trials of alcohol reduction in hypertensive patients. Source: Data from: Xin X, *et al*. (2001) *Hypertension*, 38, 1112–1117.

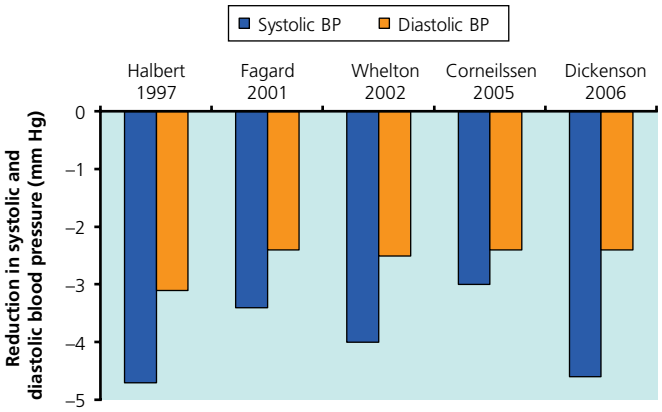


Figure 8.4 The effects of exercise and blood pressure: analysis of five overview studies in 105 trials. Source: Data from Arroll, B. (1992) *Journal of Clinical Epidemiology*, 45, 439–447.

with hypertension. This beneficial effect may be partly the result of increased intake of potassium.

Total dietary intake of fat should be reduced to ≤35% of total energy intake. Intake of saturated fats should be limited to one-third of the total intake of fats; saturated fats can be replaced by an increased intake of monounsaturated fats. In clinical practice, such diets reduce serum levels of cholesterol by only about 6% on average.

Increases in dietary intake of potassium through increased consumption of fruits and vegetables may reduce blood pressure. The use of potassium tablets to supplement intake of potassium is not recommended, however, especially if angiotensin-converting enzyme inhibitors or potassium sparing diuretics are used.

Other lifestyle interventions

Stress management

Approaches to reduce stress can result in short-term reductions in office blood pressure, but they have little effect on ambulatory blood pressure over 24 h (i.e. the more usual blood pressure). Only limited evidence supports the use of garlic, yoghurts, herbal and other complementary medicines as strategies to reduce blood pressure.

Cigarette smoking

Chronic and heavy cigarette smoking may be associated with hypertension. Indeed, blood pressure can increase acutely during smoking. Importantly, smoking has a graded adverse effect on cardiovascular risk, increasing it even more than mild hypertension. People who stop smoking rapidly reduce their risk by as much as 50% after 1 year, although 10 years may be needed before the level of risk reaches that of people who have never smoked.

Patients with hypertension who smoke should therefore be encouraged to stop smoking. Interventions with doctor's advice and encouragement can reduce smoking by 21%, which will be reinforced by smoking cessation clinics. Nicotine replacements can help smoking cessation and are generally safe in people with hypertension.

Blood pressure reduction: patients and populations

This book is primarily concerned with the problem of hypertension as a clinical condition, where antihypertensive strategies have been shown to be very effective at preventing heart attacks and strokes. However, this approach can only benefit those patients who have been detected as having a clinical condition.

The problem of the high incidence of heart disease and strokes in westernised populations and the rising incidence in the developing nations cannot be solved by a clinical approach alone. There also needs to be a population-based solution concerning the public health of all nations.

There is good evidence of the harmful effects of the rising prevalence of obesity and high intakes of salt in populations. There is reasonable evidence that reversing these trends has beneficial effects on the health of populations. It is necessary for all nations to introduce strategies to reverse the rising problem of obesity and the trend for national salt intakes to rise. Public health information campaigns are necessary for the maintenance of healthy diets and a reduction of the consumption of sugary drinks and fatty foods. With the increasing consumption of ready-made (manufactured) foods, snacks with their high salt, sugar and fat content, urgent action is necessary, with pressure on food 'manufacturers' to make their products less unhealthy. This must include better food labeling so that consumers can identify which products are high in salt and fat.

In 2014, in the United Kingdom there is now an agreement by many (but not all) supermarkets to improve the quality and comprehensibility of food labels. Most public health bodies favour the 'traffic lights' system with salt and fat contents classified as high (red), moderate (orange) and low (green).Customers can then make their own choice. Furthermore, this system may encourage food manufacturers to modify their products so that they have fewer red lights.

Whilst there is no evidence that the prevalence of obesity is falling, there is evidence that the UK national salt intake has fallen. The Food Standards Agency (FSA) accepted the harmful effects of a high salt intake and recommended that the national salt intake should be reduced to 6.0 g/day (Since then, the WHO have followed suit but recommend an average salt intake of 5.0 g/day.) by 2015. Recent evidence strongly suggests that British salt consumption has fallen (Table 8.1). It is hoped that this trend will be maintained. This will only be achieved with continued pressure from health-care professionals.

Table 8.1 The fall in average salt intake in gram per day in England 2000–2012

	Men	Women	All
2000–2001	10.96	8.1	9.5
2008	9.68	7.66	8.64
2012	9.3	6.8	8.1

Source: Data from Consensus Action on Salt and Health (CASH) 2013.

Obstructive sleep apnoea

Patients with OSA are usually overweight and complain of excessive snoring and sleep disturbance. They have a high prevalence of hypertension. Reliable controlled trials have demonstrated that continuous nasal positive airway pressure (nCPAP) improves symptoms and also reduces blood pressure. Being overweight, diets that help in reducing body weight should also be employed. All patients with symptoms suggestive of OSA should be referred for sleep studies and consideration for nCPAP.

Further Reading

Appel, L.J., Frohlich, E.D., Hall, J.E., *et al.* (2011) The importance of population-wide sodium reduction as a means to prevent cardiovascular disease and stroke: a call to action from the American Heart Association. *Circulation*, 123, 1138–1143.

Coxson, P.G., Cook, N.R., Joffres, M., *et al.* (2013) Mortality benefits from US population-wide reduction in sodium consumption. *Hypertension*, 61, 564–570.

Neaton, J.D., Grimm, R.H., Prineas, R.J., *et al.* (1993) Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. *Journal of the American Medical Association*, 270, 713–724.

Peperell, J.C.T., Ramdassingh-Dow, S., Crosthwaite, N., *et al.* (2001) Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet*, 359, 204–210.

Whelton, P.K., Appel, L.J., Sacco, R.L., *et al.* (2012) Sodium, blood pressure and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations. *Circulation*, 126, 2880–2889.

CHAPTER 9

The pharmacological treatment of hypertension and endovascular renal sympathetic denervation

OVERVIEW

- Antihypertensive drug therapy causes a 40% reduction in strokes and a 20% reduction in coronary events. They also reduce new-onset atrial fibrillation and heart failure. There is also some evidence that blood pressure lowering reduces dementia and declining cognitive function.
- Drugs used as monotherapy are all about equally effective but the β blockers, the angiotensin-converting enzyme inhibitors and the angiotensin receptor antagonists are less effective than the diuretics and the calcium channel blockers in African-origin patients and the elderly, both groups tending to have lower plasma renin levels.
- The latest guidelines in the United Kingdom recommend starting treatment in all patients with blood pressures persistently 160/100 mm Hg or more.
- Currently, recommended first-line drugs are the angiotensin-blocking drugs (A) in younger patients and calcium blockers (C) in older patients. Second-line therapy is A + C. Thiazide-type diuretics (D) are now used as third-line agents.
- For patients with existing target organ damage, concomitant diabetes mellitus, renal damage or a total cardiovascular risk of 20% or more over 10 years, the threshold for starting drug therapy is 140/90 mm Hg.
- All blood pressures should be reduced to below 140/90 mmHg with a slightly higher target in patients over the age of 80 years.
- More aggressive pressure control is recommended in patients with diabetes.
- There is no consensus on the optimum drugs to add in to the A + C + D regime if blood pressure is genuinely uncontrolled.
- In patients with hypertension resistant to triple therapy, catheter-based renal sympathetic denervation has produced impressive antihypertensive effects in highly selected patients. The long-term value of this procedure is unknown.

When to use drugs

The commonly accepted definition of hypertension is 'that level of blood pressure above which investigation and treatment do more good than harm'. Reliable evidence now shows that patients whose blood pressure is consistently >160/90 mm Hg will obtain benefits from drugs that reduce blood pressure. Such treatment reduces the rate of stroke by about 40% and of heart attacks by about 20% (Figure 9.1). Thresholds are lower in high-risk patients, particularly those with existing cardiovascular damage (left ventricular hypertrophy, angina pectoris, prior myocardial infarction, heart failure, transient ischaemic attack (TIA) or stroke), as well as existing diabetes mellitus or chronic renal impairment.

Despite efforts by the National Institute of Health and Clinical Excellence (NICE), British Hypertension Society (BHS) and other scientific societies, many patients with hypertension still have poor control of blood pressure, many are not receiving any treatment, and inappropriate drugs are often used. All too often, low drug doses are started with no subsequent dose titration, and unsuitable drug combinations are used. Two (or more) drugs that synergistically reduce blood pressure are better than high-dose monotherapy, which also has a higher risk of side effects. Randomised clinical trials consistently show that a large majority of patients with hypertension need two or more drugs to achieve targets for blood pressure.

Monotherapies reduce blood pressure by an average of 7–8%, with some inter-individual variation (Figures 9.2 and 9.3). This is largely a reflection of individual pathophysiological mechanisms, with low renin states being more common in elderly people and Afro-Caribbeans (see Chapter 12).

Thresholds

Decisions to start treatment in patients with mild hypertension are made on the basis of careful history taking, including family history of premature heart attack or stroke, 12-lead electrocardiography

ABC of Hypertension, Sixth Edition. D. Gareth Beevers, Gregory Y. H. Lip and Eoin O'Brien.

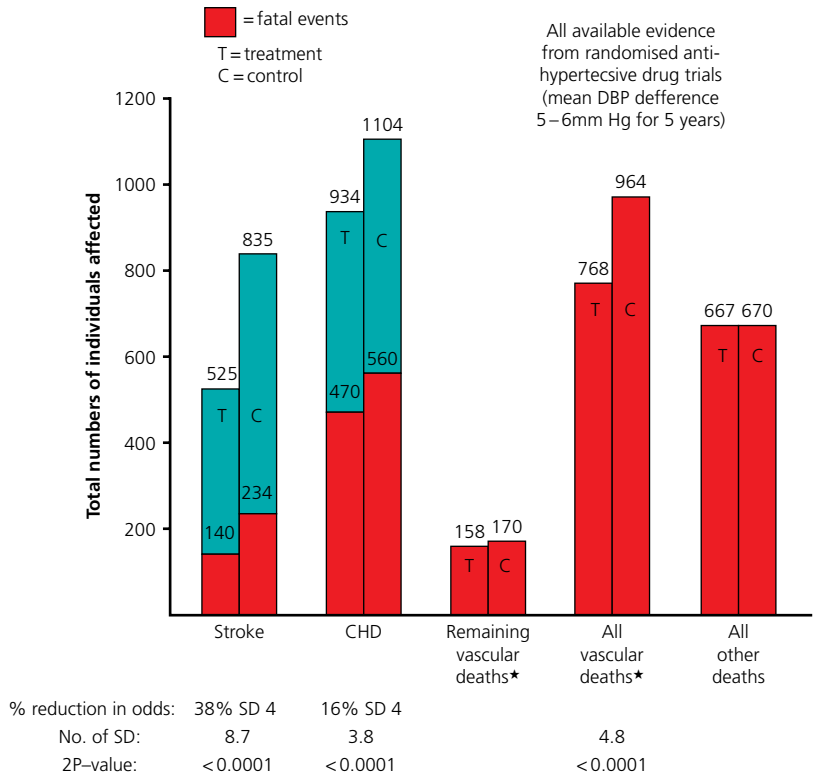


Figure 9.1 Meta-analysis of results in 17 randomised placebo-controlled trials of the treatment of hypertension in 47 667 individuals. The mean diastolic BP difference during follow-up was 5–6 mm Hg, mean time from entry to vascular event 2–3 years. In later trials, the reduction in coronary heart disease was nearer to 20%. *Includes any deaths from unknown causes. Source: Reproduced with permission from Collins, R. (1994) *British Medical Bulletin*, 50, 272–290. © Oxford University Press.

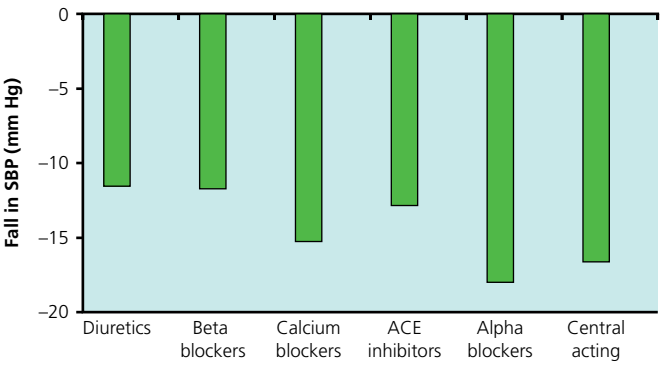


Figure 9.2 Non-placebo-adjusted fall in systolic blood pressure with monotherapy using six different classes of antihypertensive drugs. Source: Data from Sehgal, A.R. (2004) *Hypertension*, 43, 566–572.

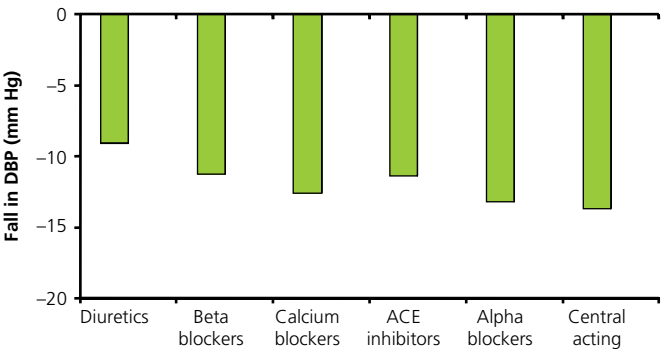


Figure 9.3 Non-placebo-adjusted fall in diastolic blood pressure with monotherapy using six different classes of antihypertensive drugs. Source: Data from Sehgal, A.R. (2004) *Hypertension*, 43, 566–572

and levels of total and high density lipoprotein cholesterol (TC:HDL). Decisions should be influenced by the patient's attitude to taking drugs for life, their motivation and their awareness of the risks of hypertension and the benefits of treatment.

Guideline committees all stress that patients whose untreated blood pressures are near to thesthresholds for starting treatment or whose pressures settle to below the thresholds on rechecking need careful monitoring about once per year. As blood pressures rise with increasing age, one would expect that 5-10% of these patients would develop hypertension at a level worth treating within 5 years.

Decisions on treatment at lower levels of cardiovascular risk should be influenced by the patient's attitude towards taking anti-hypertensive medication, possible drug side effects, the proven benefits of blood pressure reduction as well as compliance with dietary and lifestyle modifications. Blood pressures increase within 5 years to levels that clearly need treatment in about 10–15% of such patients. In addition, cardiovascular risk will increase with age, so risk should be reassessed annually. All of these patients should be encouraged to continue with lifestyle measures to reduce blood pressure and cardiovascular risk.

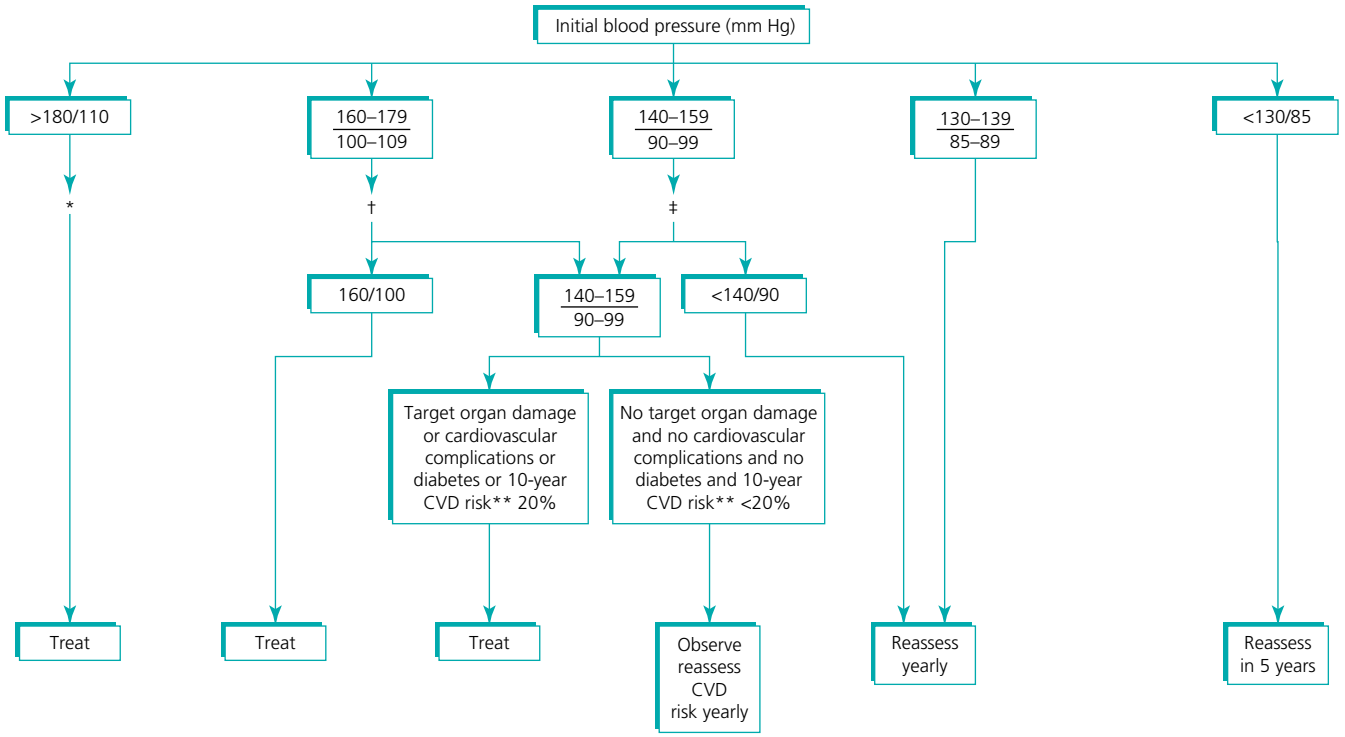


Figure 9.4 The thresholds for starting antihypertensive therapy are recommended by the British Hypertension Society. *Unless malignant phase of hypertensive emergency, confirm over 1–2 weeks, then treat. †If cardiovascular complications, target organ damage or diabetes is present, confirm over 3–4 weeks, then treat; if absent, remeasure weekly and treat if blood pressure persists at these levels over 4–12 weeks. ‡If cardiovascular complications, target organ damage or diabetes is present, confirm over 12 weeks, then treat; if absent, remeasure monthly and treat if these levels are maintained and if estimated 10 year CVD risk is 20%. **Assessed with CVD risk chart. Source: Reproduced with permission from Williams, B., *et al*. (2004) *Journal of Human Hypertension*, 18, 139–185. © Nature.

The threshold for starting drug treatment is also based on the total cardiovascular risk status. In high-risk patients, the threshold is a blood pressure consistently above 140/90 mm Hg. In low-risk patients, the threshold is 160/100 mm Hg (Figure 9.4).

The 2011 NICE/BHS guideline recommendations

Initiating Treatment

The guideline recommends that antihypertensive drug treatment should be offered to people aged 80 years or less with **stage 1 hypertension** who have one or more of the following:

- Target organ damage including left ventricular hypertrophy
- Established cardiovascular disease
- Renal disease/impairment
- Diabetes mellitus
- A 10-year total cardiovascular risk equivalent to 20% or greater.

Antihypertensive drug treatment should be offered to people of any age with **stage 2 hypertension**.

For people aged under 40 years with stage 1 hypertension and no evidence of target organ damage, cardiovascular disease, renal disease or diabetes, specialist evaluation to detect underlying causes of hypertension is recommended. There is some evidence that the currently used 10-year cardiovascular risk assessments can underestimate the lifetime risk of cardiovascular events in these people.

Table 9.1 Targets for antihypertensive drug therapy

	Clinic or office BP	Daytime ambulatory or home BP
Under age 80	140/90	130/85
Over age 80	150/90	145/85
Diabets or TOD	130/80	—

TOD, target organ damage.

Monitoring treatment and blood pressure targets

The 2011 NICE guidance recommends target blood pressure levels in relation to age and whether the pressure is measured in the clinic or at home (Table 9.1). The 2011 NICE guidance provides no recommendations on how far to lower blood pressure in patients with concurrent diabetes or who are at high risk. However, in their 2004 guidelines, the British Hypertension Society recommended lowering blood pressure to 130/80 mm Hg or less.

A review of antihypertensive drugs

Most antihypertensive drugs work primarily by relaxing the smooth muscle cells in the media of the arterioles, leading to a fall in peripheral vascular resistance. This is mainly achieved by blocking the generation or effects of the powerful vasoconstrictor,

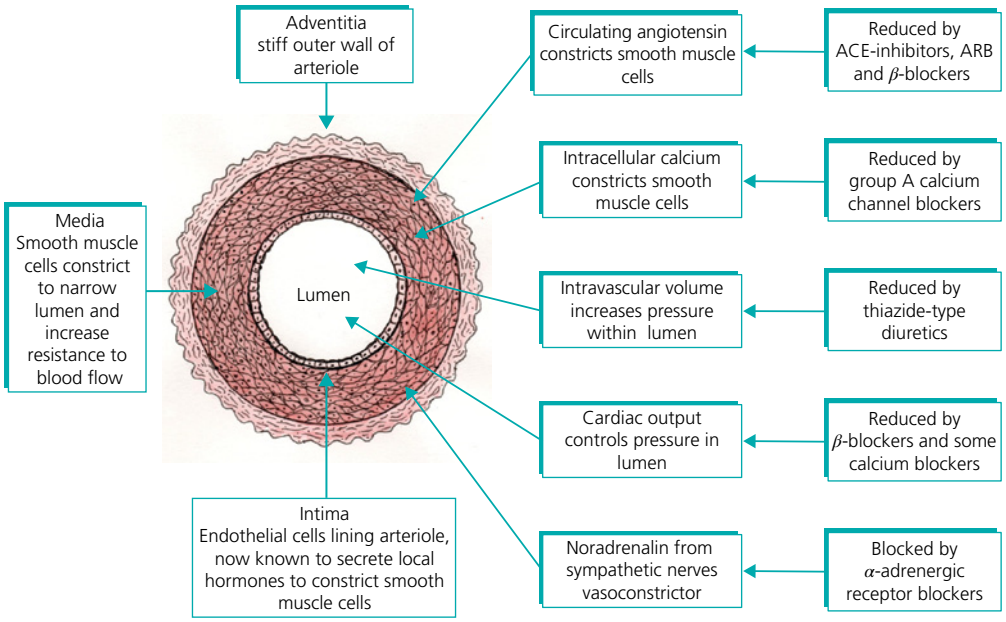


Figure 9.5 Schematic cross section of a peripheral arteriole showing pressor mechanisms and their blockade by antihypertensive drugs.

angiotensin II. The smooth muscle cells also constrict in response to a rise in intracellular calcium, which is blocked by the calcium channel blockers. The β blockers reduce circulating renin and angiotensin levels but they also reduce cardiac output. The diuretics reduce circulating blood volume but also have a direct effect on the arterioles, causing vasodilatation (Figure 9.5).

It is now becoming clear that the endothelial cells, lining the arterioles, have local humeral properties, producing both vasoconstrictor (angiotensin and endothelin) and vasodilator (nitric oxide and bradykinin) hormones, which affect the adjacent smooth muscle cells.

Angiotensin-converting enzyme (ACE) inhibitors

The ACE inhibitors are a major class of drugs that has transformed the treatment of cardiovascular disease. As the name implies, these drugs block ACE, which converts angiotensin I to angiotensin II, mainly in the lungs. Angiotensin II is a potent arteriolar vasoconstrictor and also stimulates aldosterone release from the adrenal cortex. Aldosterone causes retention of sodium and water. The ACE inhibitors thus cause vasodilatation and reduced renal reabsorption of sodium and water. In addition, angiotensin II has many other properties that may be harmful in vascular disease, and its inhibition (at the local tissue and systemic levels) leads to additional benefits. ACE is also responsible for the breakdown of bradykinin, so the ACE inhibitors increase levels of bradykinin, which enhances vasodilatation.

In patients who are fluid depleted, usually because of high doses of diuretics, and those with severe heart failure, bilateral renal artery stenosis and malignant phase hypertension, acute administration of ACE inhibitors may cause a sudden decrease in blood pressure and deterioration in renal function, so caution is needed. Increases in serum levels of creatinine <20% are the result of reversible reductions in intra-glomerular pressure, however, and are acceptable. In the long term, ACE inhibitors preserve renal function and are indicated in most patients with hypertension and renal impairment.

The ACE inhibitors also have additional trial evidence for some benefits in coronary artery disease (e.g. perindopril), diabetic retinopathy, systolic heart failure, diabetic and non-diabetic nephropathy, and (possibly) atrial fibrillation. In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), 25% fewer patients randomised to an amlodipine/perindopril-based regimen developed new onset type 2 diabetes mellitus, compared to the β blocker/thiazide regimen.

The most common side effect of ACE inhibitors is a persistent, frequently nocturnal, dry cough, which occurs in 10–20% of users. It is more common in women and patients who do not smoke. The cough may not be particularly troublesome, although the complaint sometimes comes from the patient's partner. Many patients do not realise that their cough is due to their medication, so this symptom is worth enquiring about routinely.

All the ACE inhibitors can cause life-threatening acute or subacute angiooedema, with swelling of the tongue and lips. This occurs in about one in 4000 white patients but is about four times more common in black people (Figure 9.6).

The ACE inhibitors are absolutely contraindicated in women who are pregnant or are likely to become pregnant. They have been reported to be associated with a significant excess frequency of developmental anomalies. However, some detailed studies have not been able to confirm this.

Angiotensin receptor blockers

The angiotensin receptor blockers (ARB) block the type-I angiotensin II receptors (AT_1), which leads to vasodilatation and reductions in blood pressure. Like the ACE inhibitors, the ARB are not only excellent drugs for hypertension but have benefits in stroke reduction,

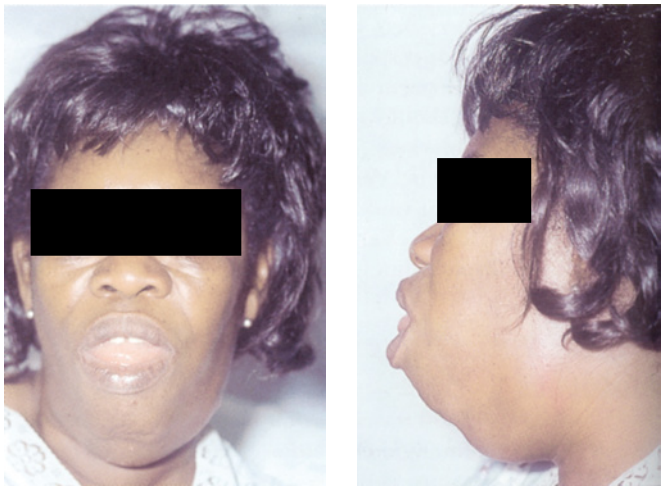


Figure 9.6 Acute angio-oedema in an Afro-Caribbean patient with hypertension.

heart failure with left ventricular dysfunction, nephropathy (diabetic and non-diabetic) and after myocardial infarction, where they are at least as good as the ACE inhibitors.

In relation to long-term outcomes in hypertension, the ARB are superior to theβ blockers. In the losartan intervention for endpoint (LIFE) study, losartan was superior to atenolol in reducing strokes and there were 25% fewer cases of new-onset type 2 diabetes mellitus. In the valsartan antihypertensive long-term use evaluation (VALUE) trial, a regimen based on valsartan was not superior to a regimen based on amlodipine, although valsartan was associated with fewer cases of new-onset diabetes.

There a very limited number of reports of acute angiooedema associated with ARB therapy. Cough does not occur; however, if a patient changes to an ARB because of a cough related to ACE inhibitors, the cough may persist for up to 6 weeks. There is very little information about ARB use in pregnancy, but at the present state of knowledge, they should not be used in women who are pregnant or are likely to become pregnant.

Calcium channel blockers

Calcium channel blockers (CCB) act by inhibiting the transfer of calcium ions across smooth muscle cell membranes, which produces arteriolar vasodilatation. The systolic hypertension in Europe (SYST-EUR) trial and two other long-term outcome trials validated their use as first-line drugs in patients with hypertension.

CCB are useful antianginal and antihypertensive drugs. Non-dihydropyridine CCB (diltiazem and verapamil) block calcium channels in cardiac myocytes. This reduces cardiac output and may have some antiarrhythmic action on the atrioventricular node.

The dihydropyridineCCB (such as nifedipine, amlodipine and felodipine) block L type calcium channels in vascular smooth muscle cells. This causes vasodilatation and reductions in vascular resistance and arterial blood pressures. These agents have little effect on the atrioventricular node but do have some mild diuretic effects.

Some formulations of dihydropyridine CCB (such as short acting nifedipine capsules) have a rapid onset of action and unpredictable effects on blood pressure, and they may cause reflex sympathetic stimulation, tachycardia and activation of the renin-angiotensin-aldosterone system. Nifedipine capsules bitten or swallowed should never be used in the treatment of hypertensive emergencies and urgencies, and may result in significant cerebral or cardiac ischaemia. Longer acting formulations of dihydropyridine CCB (such as chlortalidone, indapamide bendroflumethiazide and hydrochlorothiazide) cause less neurohumoral activation. Amlodipine is a slow-onset, slow-offset, long-acting calcium blocher, so it is not suitable for use in hypertensive emergencies and urgencies. Dose titration from 5 to 10 mg once daily should be employed at 1–2-week intervals.

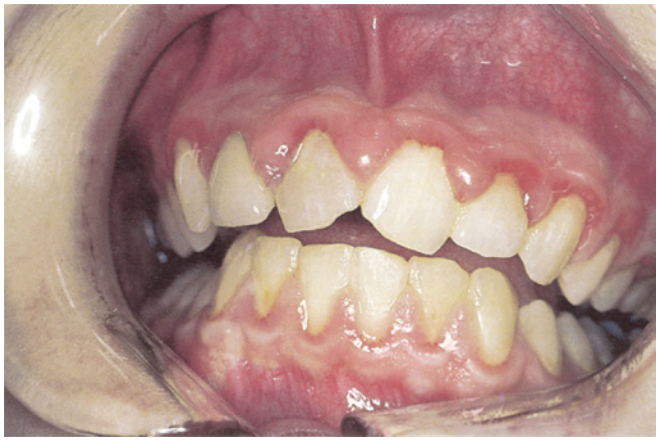


Figure 9.7 Gum hypertrophy caused by amlodipine.

Side effects include headache and flushing, but the most troublesome side effect is dose-dependent peripheral oedema. This is the result of transudation of fluid from the vascular compartments into the dependent tissues because of precapillary arteriolar dilatation. It is not responsive to diuretics and is common when amlodipine 10 mg is used.

Gum hypertrophy is common with dihydropyridineCCB but is less commonly seen with verapamil or diltiazem (Figure 9.7). This gum hypertrophy can be minimised with scrupulous dental hygiene. If, despite this, the gum hypertrophy is troublesome, it is best to consider changing to diltiazem or verapamil.

Whilst non-dihydropyridine CCB cause less peripheral oedema, they are negatively inotropic (especially verapamil) and negatively chronotropic. Thus, diltiazem and verapamil are contraindicated in left ventricular systolic dysfunction, but may be useful to control the ventricular response in patients with atrial fibrillation. These two drugs should not be used in patients already receiving a β blockers.

All CCB, but particularly verapamil, can alter bowel habit and occasionally cause troublesome constipation. This side effect can be turned to a benefit in some patients with irritable bowel syndrome and hypertension.

Diuretics

Thiazide diuretics and thiazide-like diuretics

The thiazide and thiazide-like diuretics (chlortalidone and indapamide) are cheap, easy to use and can be given once daily. They are effective and are drugs of choice in elderly people and those of African origin who cannot tolerate a CCB. They are also useful in combination with ACE inhibitors, ARB and β blockers.

These drugs reduce blood pressure by increasing excretion of sodium and water, which lowers blood volume, but they also have

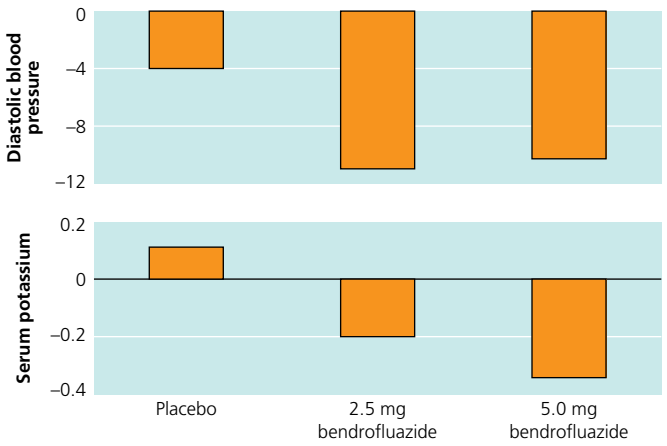


Figure 9.8 Effects of placebo and bendroflumethiazide (2.5 or 5 mg daily) on diastolic blood pressure and serum potassium levels. Source: Data from Carlson, M., *et al*. (1990) *British Medical Journal*, 300, 975–978.

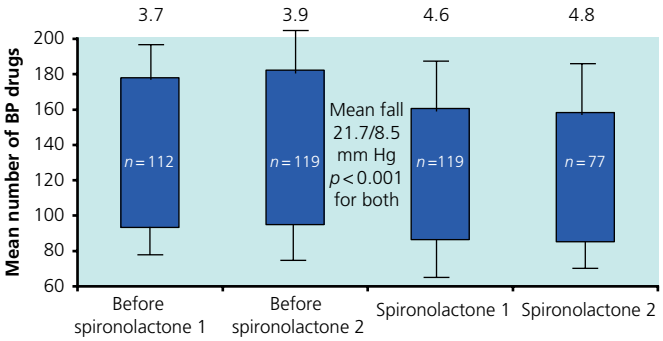


Figure 9.9 Effects of adding spironolactone 25 mg in 119 patients with severe resistant hypertension. All were taking an angiotensin-blocking drug. Source: Data from Lane, D.A., *et al*. (2007) *Journal of Hypertension*, 25, 891–894

some vasodilating properties. The reduction in blood volume results in reflex activation of the renin-angiotensin-aldosterone system, which leads to an increase in peripheral vascular resistance that may attenuate the reduction of blood pressure. This effect is smaller in patients with low baseline plasma levels of renin (such as in elderly people and those of African origin).

The antihypertensive effect of thiazides is slow, and when used as monotherapy, the dose-response curve is relatively flat, so increasing doses give limited additional reductions in blood pressure (Figure 9.8). This dose-response curve may alter when thiazide diuretics are added to the angiotensin blocking agents (ACE inhibitors or ARB), where higher doses do have an added antihypertensive effect. The adverse metabolic effects of the thiazides are, however, increased at higher doses, with more hypokalaemia, hyperuricaemia and hyperglycaemia. The lowest possible doses are therefore used (e.g. indapamide 1.5 mg).

Marked hypokalaemia is very uncommon with the use of thiazides in low doses. If profound hypokalaemia occurs, therefore, other causes must be considered, particularly underlying aldosterone excess (as in patients with Conn's syndrome).

Impairment of glucose tolerance and development of overt type 2 diabetes are more common when thiazides (particularly in high doses) are combined with β blockers. Minor changes in plasma levels of lipids and uric acid may also be seen; these are of limited clinical importance if low doses are used.

Activation of the renin-angiotensin-aldosterone system can be reduced with the concomitant use of drugs that block this system, particularly the ACE inhibitors and ARB. This explains why there is useful synergy of diuretics with drugs that block the renin-angiotensin-aldosterone system.

Erectile dysfunction develops in up to 25% of men who take thiazide diuretics in higher doses, although this may be less of a problem with indapamide.

Potassium sparing diuretics

The potassium sparing diuretics: spironolactone, amiloride and triamterene; control sodium and potassium exchange in the distal renal tubes. They limit the loss of potassium in patients treated with other diuretics.

Spironolactone is a non-selective aldosterone receptor antagonist (ARA). This non-selectivity means that it has anti-androgenic properties, leading to gynaecomastia and/or breast tenderness in men. This side effect is uncommon if the dose is less than 50 mg daily. Eplerenone is a more selective ARA with almost no anti-androgenic properties. It is, however, very expensive and should only be used in exceptional circumstances. Spironolactone in high dose is associated with an excess frequency of gastro-duodenal ulceration and upper gastrointestinal bleeding.

There are now two studies that have demonstrated impressive reductions in systolic (~20mm Hg) and diastolic (~10 mm Hg) blood pressure when spironolactone 50 mg daily is used as a forthline antihypertensive drug (Figure 9.9). Hyperkalaemia (serum potassium 6.0 mmol/l) was uncommon.

Amiloride 20 mg has been championed by some experts as an alternative to spironolactone. The main problem is that this requires four extra tablets daily on top of all other tablets. The addition of amiloride 5 mg daily to spironolactone 50 mg daily has been claimed to be effective in resistant hypertension.

Spironolactone is also used in the treatment of patients with aldosterone excess and the preoperative management of patients with Conn's syndrome. Spironolactone and eplerenone, used in combination with ACE inhibitors, reduce mortality and morbidity in patients with left ventricular impairment as a result of myocardial ischaemia.

Loop diuretics

The loop diuretics (such as furosemide) are powerful diuretics but are less potent at reducing blood pressure than the thiazides. They should be used only when a patient has cardiac or renal failure. They have no place in the management of hypertension otherwise.

Beta (β) blockers

Most β blockers reduce cardiac output through negative chronotropic and inotropic effects. The short-term haemodynamic responses are partly offset by reflex activation of vasoconstrictor mechanisms, which may attenuate reductions in blood pressure. Release of renin from the kidneys is also partly blocked. As with the thiazide diuretics, the β blockers have a relatively flat dose-response curve for reductions in blood pressure. As their mechanism of

action involves suppression of renin release, they tend to be less effective than monotherapy with a diuretic or calcium blocker in elderly people and African-Caribbeans.

β Blockers are no longer first-line drugs for treating hypertension, and are recommended only in patients with specific indications, such as atrial fibrillation, coronary artery disease or left ventricular systolic dysfunction. Carvedilol, bisoprolol and metoprolol are beneficial in patients with heart failure due to left ventricular systolic impairment. Otherwise, the *β* blockers should rarely be used in the management of asymptomatic and uncomplicated hypertension.

Recent evidence from clinical trials suggests that *β blockers* may increase the likelihood of new-onset diabetes, especially when combined with thiazide diuretics. In patients with electrocardiographically confirmed left ventricular hypertrophy, the *β blockers* atenolol was less effective than the ARB losartan in reducing stroke. In addition, the blood pressure lowering arm of the Anglo-Scandinavian cardiac outcomes trial (ASCOT) was stopped early because of the inferiority of treatment based on a thiazide and the *β blockers* atenolol compared with treatment based on amlodipine and perindopril. The 10-year outcome data from ASCOT show that these benefits are maintained.

Side effects of *β blockers* include lethargy, aching limbs on exercise, impaired concentration and memory, erectile dysfunction, vivid dreams, sleep disturbance and exacerbation of symptoms of peripheral artery disease and Raynaud's syndrome. *β* blockers are contraindicated absolutely in patients with bronchospasm or heart block. They may cause minor adverse metabolic effects, including impairment of blood glucose tolerance and lipid abnormalities (such as reduced levels of high-density lipoprotein cholesterol and high levels of triglycerides), although the clinical significance is likely to be limited. They should not be used in conjunction with verapamil.

The newer *β blockers*, carvedilol, nebivolol and bisoprolol have not been tested in long-term outcome trials in hypertension, although some data are available for these drugs in heart failure (carvedilol, bisoprolol) and elderly heart failure patients (nebivolol). Whether they share the inferiority of the older *β blockers* in hypertension is therefore unknown.

Alpha (*α*) blockers

The *α* blockers block the activation of alpha-1 adrenoceptors in the vascular tree, which results in vasodilatation. Prazosin, the early *α* blocker, was short acting and had to be given three times a day, so it is no longer recommended. Longer acting agents, such as doxazosin and terazosin, are now available. The doxazosin arm in the antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT) was terminated early, however, because of the suggestion of more adverse outcomes with *α* blockers than with thiazide-type diuretics – principally a 25% excess in alleged heart failure. Alpha-blockers thus are considered to be third- or fourth-line drugs for hypertension and should be used with caution in patients at risk of heart failure.

Postural hypotension is a problem, especially with prazosin. All members of this drug class often cause stress or urge incontinence in women, who may not volunteer this adverse effect unless asked (Figure 9.10). By contrast, *α* blockers may be useful in men with prostatism. Minor benefits on levels of lipids and coagulation factors have not translated into clinically significant benefits.

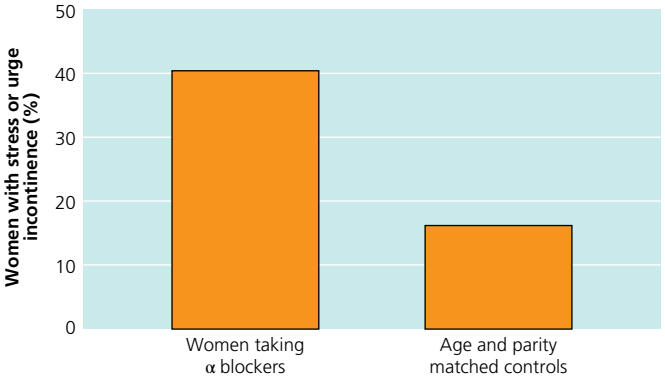


Figure 9.10 The prevalence of stress or urge incontinence of urine in women treated with *α* blockers and age- and parity-matched controls. Source: Data from Marshall, H.J. (1996) *British Journal of Clinical Pharmacology*, 42, 507–509.

Centrally acting agents

Methyldopa, clonidine and moxonidine are centrally acting imidazoline agonists. Their central *α*receptoragonism is thought to be responsible for their side effects: tiredness, lethargy and depression. Almost no long-term data are available on these drugs, which can therefore be justified only as a last resort in patients with resistant hypertension. One study of moxonidine in heart failure was stopped early due to an excess of cardiovascular events.

Methyldopa can be used in pregnant women with hypertension where long-term follow-up studies have reported no excess of unfavourable outcomes. Otherwise these drugs have no place in the management of hypertension, although moxonidine is sometimes used in severe resistant hypertension where all else has failed.

Direct-acting vasodilators

The main drugs in this class are hydralazine and minoxidil. Hydralazine is now rarely used in hypertension but is still used as a second-line drug in the hypertensive disorders of pregnancy. Its main side effect is a lupus-like syndrome with arthralgia. It is effective, when used in conjunction with nitrates, in the treatment of left ventricular failure in African-origin patients.

Minoxidil is a powerful vasodilator, which is still occasionally used in severe resistant hypertension. Because it causes tachycardia and ankle oedema, it can only be used in conjunction with a *β* blocker and a diuretic. The main side effect is prolific facial hair growth, which almost precludes its use in women.

The choice of antihypertensive drugs

Until about the year 2000, there was no consensus on the optimum antihypertensive drugs. The commonly held view was that it did not matter how blood pressure was reduced. The *β* blockers tended to be the mainstay of treatment because of their relative

tolerability and the hope that they might be better than the diuretics at preventing coronary heart disease. At this time, there was little evidence on the comparative ability of the newer antihypertensive drugs (the ACE inhibitors, the ARB and CCB) to reduce heart attacks and strokes. These agents had not been compared with what was then regarded as conventional therapy in long-term controlled outcome studies.

The publication of the Losartan Intervention for Endpoints (LIFE) trial in 2002 and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) in 2005 radically changed opinions and have greatly influenced the guidelines from the British Hypertension Society (BHS) and the UK National Institute for Health and Clinical Excellence (NICE).

The LIFE trial compared the outcomes from using an atenolol 50–100 mg based regime with a regime based on losartan 50–100 mg. The trial was conducted in 5193 hypertensive patients all of whom had ECG evidence of left ventricular hypertrophy. The reduction in systolic and diastolic blood pressure was broadly similar in both arms of the trial. When the trial ended, the losartan patients had sustained 25% fewer strokes and 10% fewer deaths from all causes. There was no significant difference in the heart attack rates comparing the two regimes (Figure 9.11). However, the losartan patients had a 25% lower rate of the development of new-onset diabetes mellitus.

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) of an antihypertensive regime based on amlodipine and perindopril in comparison with one based on atenolol and bendroflumethiazide. It was conducted in 18 965 high-risk hypertensive patients. By the end of the study, the amlodipine/perindopril patients suffered 22% fewer strokes and 10% fewer deaths from all causes. Both these trends were statistically significant. There was also a 10% lower rate of coronary events but this trend was not significant. However, if the data are reanalysed to include all coronary events, including coronary artery revascularisation, the reduction was statistically significant (Figure 9.12). The amlodipine/perindopril patients had a 22% lower rate of new-onset diabetes mellitus.

The choice of first-line antihypertensive drugs depends on the presence or absence of other important underlying medical conditions related to hypertension, pre-existing cardiovascular damage due to the hypertension, or other unrelated conditions. Finally, the choice is greatly influenced by the patient's age and ethnicity – both of which affect release of renin.

Despite these factors, the prime objective is to control the blood pressure by any means. The differences in outcome between the different drug classes are minor compared with the differences attributable to the adequate control of blood pressure. In order to achieve good control of blood pressure, most patients need two or more antihypertensive drugs, so the choice of second- and third-line agent will also be influenced by the considerations above.

Some drug combinations are also sensible ones. For example, significant synergy of action occurs when an angiotensin-blocking drug is added to a thiazide diuretic or a CCB. Conversely, little synergy occurs when a calcium blocker is added to a diuretic or when an angiotensin blocker is added to a β-blocker.

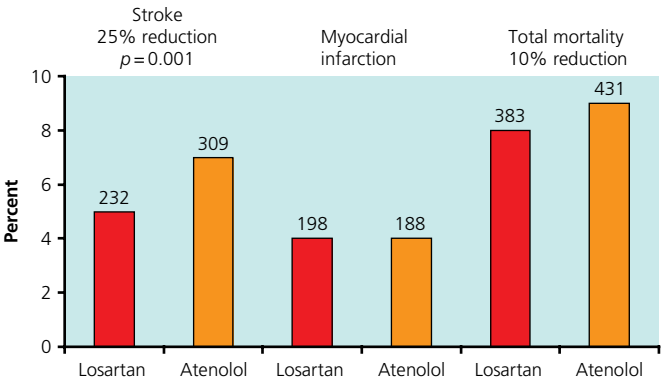


Figure 9.11 Principal results of the Losartan Intervention for Endpoints (LIFE) trial. The 10% lower rate of myocardial infarction in the losartan patients was not statistically significant. Source: Data from Dahlöf B, *et al*. (2002) *Lancet*, 359, 995–1003.

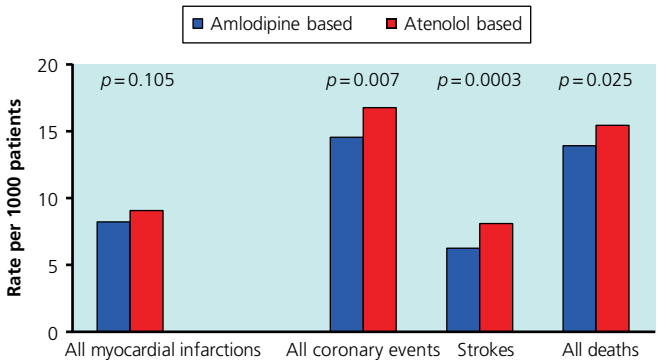


Figure 9.12 Results of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). The reduction in coronary events became statistically significant if coronary revascularisations were included. Source: Data from Dahlof, B., *et al*. (2005) *Lancet*, 366, 895–906.

The use of an ACE inhibitor with an ARB is controversial. It is clear that using these agents together has little effect on blood pressure. However, there is some evidence that the use of an ACE inhibitor with an ARB is associated with a greater reduction in proteinuria in patients with diabetic nephropathy and improved outcomes in patients with heart failure with reduced left ventricular ejection fraction.

Most patients will need two or more drugs to achieve treatment targets for blood pressure. This is true for complex cases in a hospital-based context, as well as in primary care. The general approach is to use several drugs in low doses rather than one drug in high doses. This should minimise the side effects of drugs and give better control of blood pressure.

The UK-NICE guidance provides the following algorithm for the management of hypertension in primary and secondary care (Figure 9.13).

Step 1 treatment

- Offer people aged under 55 years step 1 antihypertensive treatment with an ACE inhibitor or an angiotensin-II receptor blocker (ARB), but not in combination.

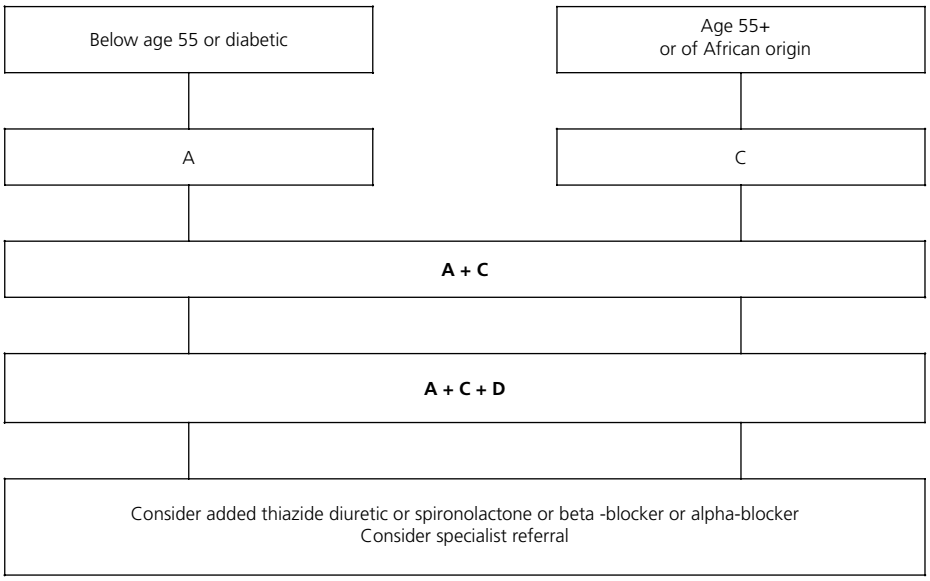


Figure 9.13 National Institute of Health and Clinical Excellence (NICE) algorithm for the management of Hypertension. A, angiotensin blocking drug; C, calcium channel blocker; D, thiazide/thiazide-like diuretic. Source: Reproduced with permission from Krause, T., *et al*. (2011) *British Medical Journal*, 343, d4891. © BMJ Publishing Group Ltd.

- For patients aged over 55 years and to black people of African or Caribbean family origin of any age, a CCB is recommended. If a CCB is not suitable, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. The latter includes either-chlortalidone (12.5–25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide orhydrochlorothiazide.
- Beta-blockers are not a preferred initial therapy for hypertension, although they may be considered in younger people, particularly:
- those with an intolerance or contraindication to ACE inhibitors angiotensin II receptor antagonists
- women of child-bearing potential
- people with evidence of increased sympathetic drive
- other co-morbidities whereby a β blocker is indicated include paroxysmal AF, systolic heart failure, etc
- If therapy is initiated with a β blocker and a second drug is required, CCB rather than a thiazide-like diuretic should be considered to reduce the person's risk of developing diabetes.

Step 2 treatment

- If blood pressure is not controlled by step 1 treatment, offer step 2 treatment with a CCB in combination with either an ACE inhibitor or an ARB.
- If a CCB is not suitable, a thiazide-like diuretic may be considered, although for black people of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.

Step 3 treatment

- If treatment with three drugs is required, the combination of ACE inhibitor or angiotensin II receptor blocker, calcium-channel blocker and thiazide-like diuretic should be used.

Step 4 treatment

- Regard clinic blood pressure that remains higher than 140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
- Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower, but caution is needed in people with a reduced renal function because they have an increased risk of hyperkalaemia.
- High-dose thiazide-like diuretic treatment can be considered if the blood potassium level is higher than 4.5 mmol/l. An α- or β blocker may be considered if BP is still suboptimal.

Strategies for resistant hypertension

Even with assiduous adherence to the recommendations above, a considerable number of patients in primary and secondary healthcare settings fail to reach ideal targets for blood pressure or even audit standards. In such patients, doctors should have a strategy for investigation and management. Many patients with resistant hypertension can be managed by adhering to the advice of the guideline committees. Many such patients, however, may benefit from referral to a specialist hypertension clinic for more detailed investigation and management (Table 9.2).

Table 9.2 Strategies for resistant hypertension

Is the patient actually taking the tablets prescribed?
Ask the patient in a non-confrontational manner
Check the patients requests for repeat prescriptions
Does the patient understand the consequences of uncontrolled hypertension?
Emphasise the high risk of a disabling stroke.
Does the patient understand the proven value of controlling blood pressure?
Emphasise the impressive reduction of strokes and premature death
Lowering blood pressure is usually achieved with no drug side-effects
Has the patient received advice on lifestyle and dietary changes?
If obesity present, emphasise the value of weight loss
Emphasise the value of salt restriction
Enquire about alcohol intake and advise accordingly
Is the patient complying with dietary advice?
Consider referring to a dietitian
Provide leaflets on the avoidance of salty foods
Is the hypertension truly resistant?
Consider the possible diagnosis of white-coat hypertension
Does the ECG show a 'surprising' lack of LVH?
Suggest the patients purchase their own BP monitor
Advise on the required techniques for home BP testing (HBPM)
If home BP is not feasible, consider 24-h ambulatory BP monitoring (ABPM)
Recheck for underlying renal or adrenal causes of hypertension.
Serum potassium low or low-normal suggests aldosterone excess
Raised serum creatinine suggests renal disease
Paroxysmal symptoms suggest phaeochromocytoma
Does the patient's tablet regime comply with the NICE 'A + C + D' system?
Are the correct top doses being prescribed?
Simplify drug regime by using fixed dose drug combinations (FDC).

Table 9.3 The choice of fourth-line antihypertensive therapy used at City Hospital, Birmingham, pending the results of ongoing clinical trials

Women	Men
A	A
A + C	A + C
A + C + D	A + C + D
A + C + D	A + C + D
A + C + D + Spironolactone 25 mg	A + C + D + Doxazocin 2–4 mg

Doxazosin is not used in women because of the risk of loss of bladder control. Spironolactone is not used in men because of the risk of breast tenderness and gynaecomastia.

Fixed-dose drug combination tablets (FDC) have long been frowned upon by some clinical pharmacologists. However, the British, European and American guidelines all endorse their use. Almost all products do comply with the A + C + D system and so are logical. Their use is associated with improved patient compliance and blood pressure control. With some FDCs, there are also some financial savings.

There is no consensus on the optimum choice of fourth-line drugs. Trials are currently underway to compare spironolactone, doxazocin or a β blocker as fourth-line agents. In the meantime, in Birmingham, the following system is used (Table 9.3).

Renal sympathetic denervation

Given the intimate relation between sympathetic modulation and blood pressure, some interest has been directed towards sympathetic denervation as a means to managed resistant hypertension. In the 1950s, bilateral thoraco-lumbar sympathectomy was found to lower blood pressure but was associated with the side effects of severe postural hypotension. The procedure was abandoned following the introduction of effective antihypertensive drugs. More recently, selective catheter-based renal sympathetic denervation has been studied and remarkably good results have been achieved. Apart from minor discomfort during the procedure, there were very few side effects.

In one study, catheter-based renal denervation caused a substantial and sustained blood pressure reduction, without serious adverse events, in patients with resistant hypertension (Figure 9.14)

The study by Krum and colleagues has been confirmed is several further trials but some problems have been encountered. Many of the patients referred to specialist centres for the procedure were found on 24-h ambulatory monitoring to have excellent control of their hypertension. This may, in part, be due to the white-coat effect, but there is also the possibility that patients referred to specialist centres had become worried and therefore improved compliance with their drug regime. In one study, of 1029 patients referred for consideration for possible renal denervation, truly resistant hypertension was confirmed in only 200. Of 113 of these, the hypertension was found to be due to underlying renal or adrenal diseases. Of the remaining 87 patients with resistant essential

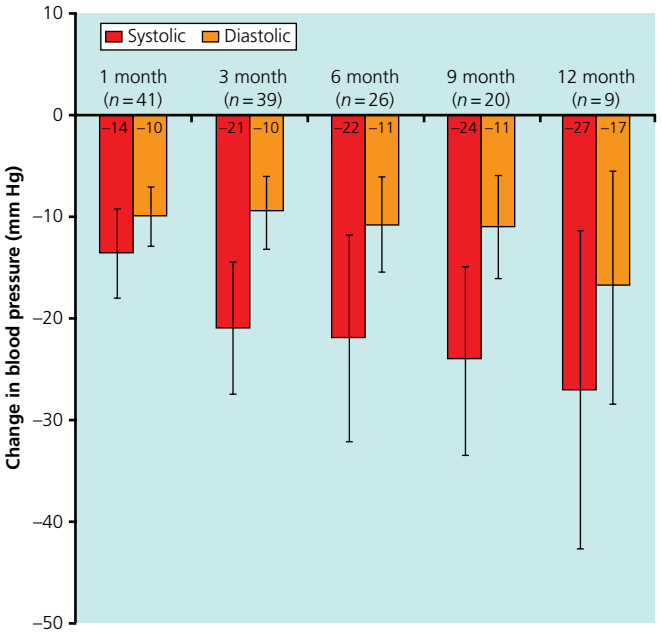


Figure 9.14 Results of catheter-based renal sympathetic denervation for resistant hypertension showing change in office systolic and diastolic blood pressure (95% CI) after 1, 3, 6, 9 and 12 months. Figures in brackets are the number of patients seen at each time period. Source: Reproduced with permission from Krum, H., *et al.* (2009) *Lancet*, 373, 1275–1281. © Elsevier.

hypertension, renal denervation was considered to be indicated or feasible in only 15. Whatever the reasons for the reduction in blood pressure prior to renal sympathetic denervation, it has meant that ramdomised clinical trials have encountered difficulties in recruitment.

In January 2014, the British Hypertension Society called for a moratorium on all renal denervation procedures in both the NHS and the private sector. This followed an announcement by the manufacturers of one renal denervation catheter that, in a randomised trial of renal denervation versus continued medical treatment in 530 patients, there was no difference in blood pressure at follow-up between the two groups. The trial was therefore discontinued. The final results published in April 2014 in the New England Journal of Medicine by Bhatt et al (see Further reading) confirmed that renal angiography with denervation was no more effective at lowering blood pressure than angiography without denervation.

Hypertensive urgencies and emergencies

The classification urgencies and emergencies reflect the fact that it is only very rarely that blood pressure needs to be reduced in a hurry (Table 9.4). Rapid falls in blood pressure can be dangerous, causing strokes, myocardial infrctions and acute renal failure. Sublingual nifedipine capsules, bitten or swallowed, should never be used, as the antihypertensive effect is unpredictable and often excessive.

Urgencies

Initially, malignant phase hypertension with retinopathy of grade III–IV is usually treated with 10–20 mg oral slow release nifedipine. Amlodipine, which has a gradual onset of action, is not suitable. Blood pressure should be monitored every 15 min. Oral atenolol has also been used successfully in hypertensive urgencies, but it is suitable only if no suggestion of phaeochromocytoma exists. Similarly, ACE inhibitors and ARB are best avoided until suspected renal artery stenosis is excluded. Normalisation of blood pressure over a few days or weeks is best achieved with gradual titration of drug doses according to the NICE/BHS treatment algorithm.

Emergencies

True hypertensive emergencies where blood pressure needs to be brought down within minutes is seen in a very small number of patients, either with hypertensive encephalopathy, acute coronary syndromes with concurrent very high blood pressure and very severe acute left ventricular failure. In such cases, intravenous infusions of labetolol or intramuscular hydralazine may be useful. Sodium nitroprusside by intravenous infusion can control blood pressure accurately but should only be used in an intensive care unit.

Patients with severe hypertension and acute myocardial infarction or unstable angina need emergency reduction of blood pressure, particularly if primary angioplasty or thrombolysis is proposed. Intravenous nitrates, nitroprusside or labetolol are best used in the coronary care unit.

Table 9.4 Conditions in which blood pressure needs to be reduced rapidly

Very severe hypertension
Dissecting aortic aneurysm
Severe left ventricular failure due to hypertension
Severe pre-eclampsia
Eclampsia
Hypertensive encephalopathy
Severe hypertension in acute coronary syndromes

Lipid lowering

More than half of all hypertensive patients have adverse lipid profiles. For a given level of blood pressure, a concurrent raised plasma cholesterol triples the risk of cardiovascular events. All patients need to have blood taken for plasma total cholesterol and HDL cholesterol. Then, the total cholesterol/HDL cholesterol (TC/HDL) ratio can be calculated (see appendix). This ratio, together with the systolic blood pressure and the smoking status provides a reasonable index of total cardiovascular risk (heart attack and stroke), based on the Framingham Heart Study. Recent meals have only a small effect on plasma cholesterol levels, so blood specimens do not need to be fasting.

The statin group of drugs has been shown to reduce coronary events and strokes in high-risk patients and heart attack survivors. Side effects are uncommon. The biggest problem is myalgia, which affects around 5% of takers.

Three large long-term outcome trials have been conducted in patients with hypertension (ALLHAT, HPS and ASCOT-LLA). All shows benefits with a reduction in heart attacks and strokes.

The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ACSOT-LLA) investigators examined the value of lipid lowering in high-risk hypertensive patients. They took the view that in the 9037 patients whose non-fasting plasma was above 6.5 mmol/l, treatment should be started with a statin.

The remaining 12 037 patients whose non-fasting total plasma cholesterol was 6.5 mmol/l or less were randomised to receive atorvastatin 10 mg daily or a matching placebo tablet. The trial had to be discontinued earlier than planned because of a highly significant reduction of fatal and non-fatal infarctions and fatal and non-fatal strokes (Figure 9.15). Similar results were obtained in the ALLHAT and HPS studies.

The results of the lipid-lowering arm of the Anglo-Scandinavian cardiac outcomes trial strongly suggest that all patients with hypertension and a total cardiovascular risk of ≥20% in 10 years should receive a statin in addition to antihypertensive drugs, regardless of the serum cholesterol levels.

Aspirin

Despite the recognised increased prothrombotic state found in patients with uncomplicated hypertension, the use of antithrombotic drugs, particularly aspirin, is debatable. Consensus has nearly been reached that patients with hypertension who have coronary heart disease or have had a stroke or a transient ischaemic attack

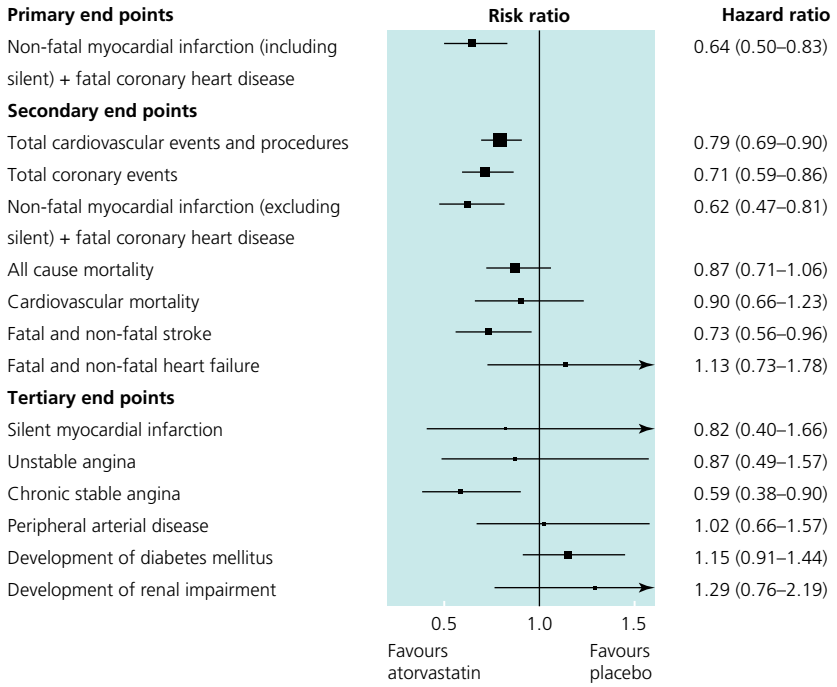


Figure 9.15 Results of the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA). Source: Data from Sever, P.S., *et al.* (2003) *Lancet*, 361, 1149–1158.

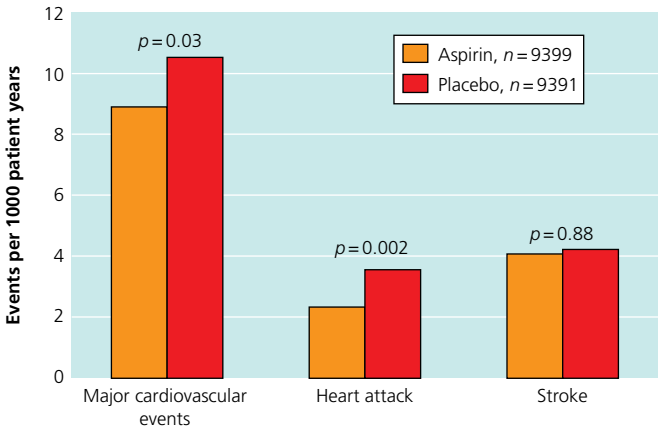


Figure 9.16 The results of aspirin versus placebo in the Hypertension Optimal Treatment (HOT) trial. Source: Reproduced with permission from Hansson, L.H., *et al.* (1988) *Lancet*, 351, 1755–1762. © Elsevier.

should be prescribed aspirin. In the Hypertension Optimal Treatment (HOT) trial, aspirin had no effect in the primary prevention of stroke and only a small effect on coronary prevention (Figure 9.16). However, for every coronary event prevented by aspirin, there was an extra serious haemorrhagic event. It was speculated that aspirin may have prevented ischaemic strokes but increased the number of cerebral haemorrhages.

Despite the greatly increased risk in patients with uncontrollable hypertension, aspirin is best avoided because of the high risk of cerebral haemorrhage. Current guidelines recommend the use of aspirin only when the blood pressure has come under control.

Hypertensive patients who develop atrial fibrillation are at even higher risk of stroke, and should be given thromboprophylaxis with oral anticoagulants (whether with warfarin or one of the new oral anticoagulants, e.g., dabigatran or rivaroxaban). Aspirin is an inferior choice for stroke prevention in atrial fibrillation, and may not be any safer in terms of major bleeding, especially in the elderly (see Chapter 10). Aspirin should not be combined with oral anticoagulation in patients with stable vascular disease, due to a significant increase in the risk of major bleeding and intracranial haemorrhage.

Further Reading

Anekwe, L. (2012) Fasting makes little difference to results of routine lipid level tests. *British Medical Journal*, 345, e7806.

Bangalore, S., Steg, P.G., Deedwania, P., *et al.* (2012) β-blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *Journal of the American Medical Association*, 308, 1340–9.

Bhatt D.L., *et al.* (2014) A controlled trial of renal denervation for resistant hypertension. *New England Journal of Medicine*, 370, 1393–401.

The CAFÉ Investigators, for the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Investigators (2006) Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes. *Circulation*, 113, 1213–25.

Healey, J.S., Baranchuk, A., Crystal, E., *et al.* (2005) Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *Journal of the American College of Cardiology*, 45, 1932–9.

Kaplan, N.M. & Opie, L.H. (2006) Controversies in hypertension. *Lancet*, 367, 168–76.

Lasker, S.S. & Cowdhury, T.A. (2012) Myalgia whilst taking statins. *British Medical Journal*, 345, e5348.

Laurent, S., Schlaich, M. & Esler, M. (2012) New drugs, procedures and devices for hypertension. *Lancet*, 380, 581–600.

Myat, A., Redwood, S.R., Qureshi, A.C., Spectus, J.A. & Williams, B. (2012) Resistant hypertension. *British Medical Journal*, 345, e7473.

Savard, S., Frank, M., Bobrie, G., *et al.* (2012) Eligibility for renal denervation in patients with resistant hypertension. When enthusiasm meets reality in real-life patients. *Journal of the American College of Cardiology*, 60, 2422–4.

Symplicity HTN-2 Investigators (2010) Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomized controlled trial. *Lancet*, 376, 1903–9.

CHAPTER 10

Hypertension in patients with cardiovascular disease

OVERVIEW

- Antihypertensive drug therapy reduces new-onset stroke by about 40%. Immediately following a stroke, there is no convincing evidence that blood pressure lowering improves the short-term outlook. However, there is good evidence that, in stroke survivors, blood pressure lowering does reduce the chances of developing a second stroke.
- Antihypertensive therapy reduces left ventricular hypertrophy (LVH) both on ECG and on echocardiography. There is reliable evidence that the angiotensin-blocking drugs are more effective than other agents at reducing LVH and also are better at reducing strokes and coronary events.
- Antihypertensive drug therapy reduces new-onset coronary heart disease by about 20%. There is little information on the value of antihypertensive drugs following a heart attack, but both the β blockers and the angiotensin-blocking drugs do improve long-term survival, irrespective of blood pressure.
- There is an under-recognised relationship between hypertension and abdominal aortic aneurysm and intermittent claudication. Patients with peripheral vascular disease have an increased prevalence of atheromatous renal artery stenosis.
- Heart failure due to hypertension is usually due to a previous myocardial infarction. The β blockers, the angiotensin-blocking drugs and spironolactone all reduce mortality in patients with heart failure with reduced left ventricular ejection fraction.
- Hypertension is a major cause of atrial fibrillation (AF). Antihypertensive therapy with angiotensin-blocking drugs does reduce new-onset AF. Patients with hypertension and AF need detailed cardiological assessment with a view to anticoagulant therapy as long as the blood pressure is well controlled. Cardiac rate control can be achieved with β blockers or calcium channel blockers.

Introduction

The presence of 'co-morbidities' and previous cardiovascular diseases substantially influences the methods of assessing patients with hypertension, the management of high blood pressure and the most appropriate antihypertensive drugs. As with all patients, total cardiovascular risk rather than just the height of the blood pressure must be taken into account.

Hypertension after stroke

As mentioned in Chapter 1, hypertension is the most important treatable risk factor for stroke, and antihypertensive treatment significantly reduces this risk. Half of all patients with stroke will have a history of hypertension, and up to 40% of patients are taking antihypertensive treatment when their stroke occurs.

Immediately after a stroke, a breakdown in cerebral autoregulation occurs. As a result, rapid decreases in blood pressure can cause a reduction in cerebral perfusion and a further extension of the stroke. For this reason, most authorities recommend that antihypertensive drugs should be withheld until the patient is ambulant; however, very little trial data is available on this point.

In the acute period after a stroke, casual levels of blood pressure are often high, with about 70% of patients having levels ≥140/90 mm Hg within the first 48 h of ictus. These levels usually subside over the next 10–14 days. In part, the increase may be simply the result of the stress of the stroke and of hospitalisation, but other mechanisms may also be responsible, including pre-existing hypertension and neurohumeral activation. The higher the blood pressure at presentation, the worse the outcome, although patients who are hypotensive also do badly. The international stroke trial reported a J-shaped relation between initial blood pressure and outcome, with early deaths increasing by 18% for every 10 mm Hg of admission systolic blood pressure below 150 mm Hg and by 4% for every 10 mm Hg above 150 mm Hg.

On a longer-term basis, in stroke survivors, there is a much closer relationship between the height of the blood pressure (Figure 10.1).

Blood pressure reduction in acute strokes

The value of blood pressure reduction in patients immediately following their stroke is controversial and there are wide international differences in clinical practice. Some studies of β blockers and

ABC of Hypertension, Sixth Edition. D. Gareth Beevers, Gregory Y. H. Lip and Eoin O'Brien.

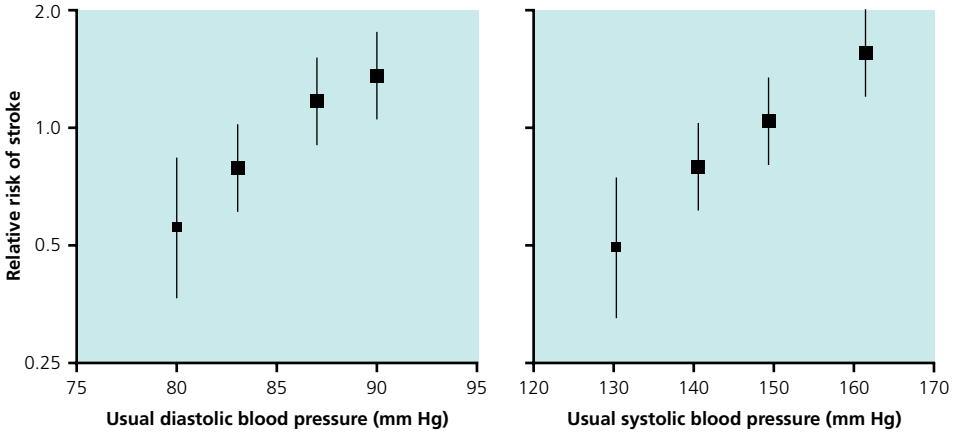


Figure 10.1 Stroke recurrence rate following a minor stroke or a transient ischaemic attack (TIA) in relation to usual blood pressure in 2435 patients attending 23 centres in New Zealand and Scotland. Source: Reproduced with permission from Rodgers, A., *et al*. (1996) *BMJ*, 313, 147. © BMJ Publishing Group Ltd.

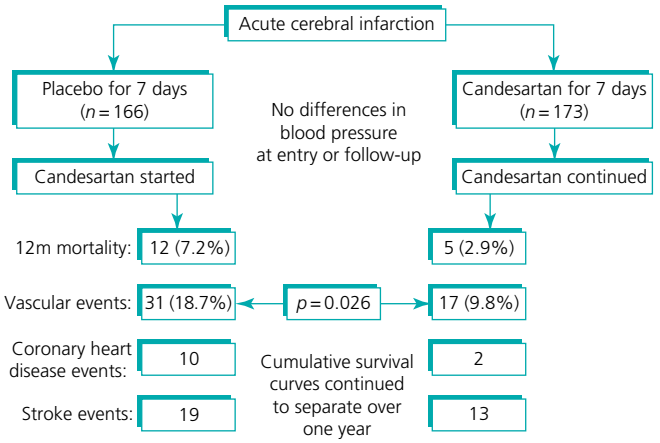


Figure 10.2 Results of the acute candesartan cilexetil therapy in stroke survivors. Source: Data from Schrader, J., *et al*. (2003) *Stroke*, 34, 1699–1703.

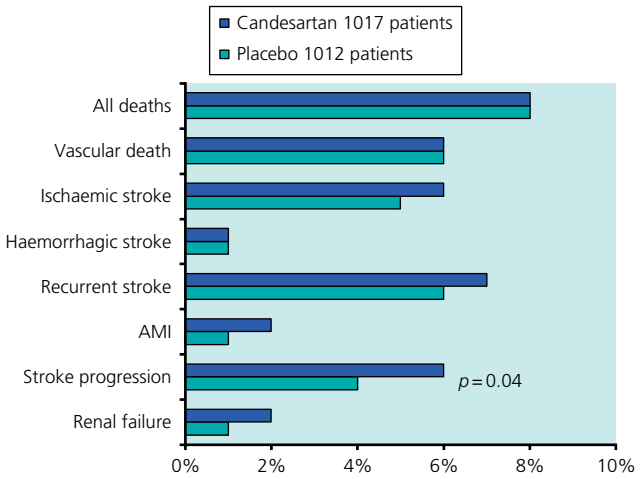


Figure 10.3 A comparison of candesartan versus placebo on outcome following acute stroke. Only the adverse effects of candesartan on stroke progression were statistically significant. Source: Data from Sandset, E.C., *et al*. (2011) *Lancet*, 377, 741–750.

calcium blockers used immediately after a stroke have shown no benefit, but these studies were small. It is possible that any benefits of blood pressure reduction were offset by harmful reductions in cerebral blood flow.

There is some evidence that the angiotensin blocking drugs (ACE inhibitors and ARBs) do not have adverse effects on cerebral blood flow immediately following a stroke, unlike the other antihypertensive drugs. The acute candesartan therapy in stroke survivors (ACCESS) trial suggested that the ARB, candesartan may be of benefit in patients with high blood pressure (200/110 mm Hg) within the first 48 h after cerebral infarction (Figure 10.2).

The results of the ACCESS trial are offset by the larger SCAST trial, which reported adverse outcomes with candesartan versus placebo in 2029 stroke patients (Figure 10.3).The SCAST investigators also included a meta-analysis in their paper of all the trials of blood pressure reduction following an acute stroke. Their conclusion was that there was a non-significant trend for acute blood pressure reduction to be harmful. The treatment to reduce blood pressure in acute stroke (<48 h) is probably only appropriate when blood pressure is persistently very high (>220/110 mm Hg), although no robust outcome data from clinical trials are available on this point.

There is now good evidence that intravenous thrombolysis with tissue plasminogen activators (TPA) does improve outcomes in patients with acute cerebral infarction, but this is only feasible if computed tomography or magnetic resonance imaging of the head is available within 2 h of stroke onset. If thrombolysis is given, then antihypertensive drugs – such as labetolol, nifedipine or intravenous sodium nitroprusside – will be needed if blood pressure is very high. Immediate reductions in blood pressure may also be beneficial in patients with proven cerebral haemorrhage, although there is little information on this point.

Blood pressure reduction after complete or partial recovery from a stroke

High blood pressures that persist for more than a month after a stroke are associated with an increased risk of recurrence, as well as the subsequent development of cardiovascular events. Data

Table 10.1 Results of the PROGRESS trial of perindopril/indapamide versus placebo in stroke survivors

	Active *n* = 3051	Placebo *n* = 3054	Percent reduction (95% CI)
All second strokes	307	420	28% (17–38)
ischaemic stroke	246	319	24% (10–35)
haemorrhagic stroke	37	74	50% (26–67)
Acute myocardial infarction	115	154	26% (6–42)

Source: Data from PROGRESS Collaborative Group. Lancet 2011; 358: 1033–1041.

from seven randomised controlled intervention trials of reductions in blood pressure in patients with stroke or transient ischaemic attacks who were not necessarily hypertensive have shown that treatment significantly reduces the odds ratio for recurrence of fatal and non-fatal stroke by 26% and the odds ratio for cardiovascular events by 16%.

The perindopril protection against recurrent stroke study (PROGRESS) is the largest study to assess the effects of reductions in blood pressure (using the ACE inhibitor, perindopril with or without the thiazide like diuretic, indapamide) on recurrence in patients with a history of stroke or transient ischaemic attack with or without hypertension (Table 10.1). This trial was confined to survivors of stroke seen in follow-up clinics and provides no information on the management of acute stroke. A post-hoc subgroup analysis of this trial suggested that the benefits of treatment were confined to patients who received perindopril with indapamine but not those who received perindopril alone. These findings, however, are controversial.

Patients who have had a transient ischaemic attack or cerebral infarct should receive aspirin (75–300 mg/day). This will reduce the risk of subsequent cardiovascular events by about 11% after acute stroke and by 20% in those with a past history of ischaemic stroke. Aspirin should, however, only be administered once the blood pressure has been controlled.

For patients with AF, anticoagulation will reduce the incidence of a further stroke by >65%, and treatment with statins reduces the risk of subsequent major vascular events by >20%. In patients with symptomatic severe carotid artery stenosis (≥70% but without near occlusion), carotid endarterectomy reduces subsequent stroke by 40%.

Summary of the role of antihypertensive therapy before, during and after stroke

Before
Many randomised controlled trials have shown that the treatment of hypertension reduces stroke incidence by about 40%.

Acute Stroke
Aggressive treatment of hypertension is detrimental to most patients. If the blood pressure is persistently >180/110 mm Hg, prescribe oral 10–20 mg nifedipine or 25 mg atenolol.

After
On a long-term basis, reduction of blood pressure prevents recurrence of stroke.

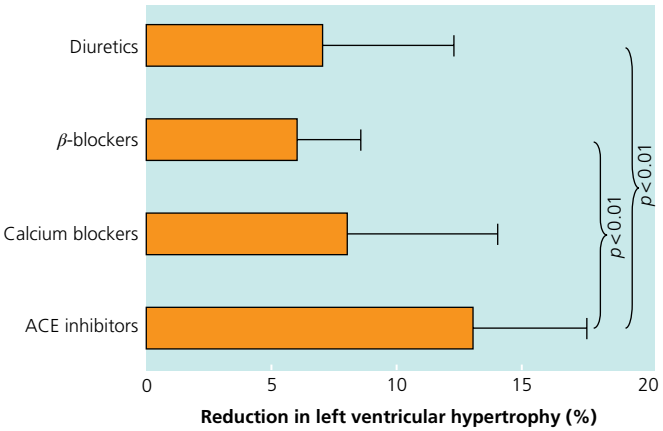


Figure 10.4 Overview of trials of antihypertensive drugs and regression of left ventricular hypertrophy (ACE inhibitors = angiotensin converting enzyme inhibitors). Source: Data from Schmieder, R.E., *et al*. (1996) *Journal of the American Medical Association*, 275, 1507–1513.

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is the most common cardiac manifestation of hypertensive end organ damage and is an independent risk factor for cardiovascular mortality. For a given level of blood pressure, the presence of LVH increases mortality by three to four times, and the risk is even greater if the patient has repolarisation abnormalities (the so-called strain pattern). Patients with LVH have a very high risk of stroke, myocardial infarction, heart failure and AF.

Drugs that block the renin-angiotensin-aldosterone system (ACE inhibitors and ARB) are better at reducing LVH than other drug classes (Figure 10.4). In the losartan intervention for endpoint (LIFE) study, for example, losartan caused more regression of LVH than atenolol. This may partly explain why losartan patients suffered 25% fewer strokes than those randomised to atenolol.

Electrocardiography is highly specific but not very sensitive for the detection of LVH – if an electrocardiogram (ECG) shows LVH, then it is usually present, but a normal electrocardiogram does not exclude LVH on echocardiography, especially in obese people. The only exception is seen in slim athletic adults, in whom chest leads may suggest LVH that is not confirmed on echocardiography. Chapter 7 gives criteria for the diagnosis of LVH.

Coronary heart disease

Patients with hypertension frequently have angina and myocardial infarction. Many antihypertensive drugs, particularly the β blockers, reduce blood pressure and have anti-ischaemic properties. In patients with hypertension, chest pain may result from impaired blood supply as a result of coronary artery disease, but it can also result from 'relative ischaemia', when significant LVH is present and is not accompanied by an increase in the coronary blood supply. Many patients with angina and hypertension have normal coronary arteries on angiography, and effective management of hypertension may improve the patient's symptoms.

All patients should receive aspirin (or clopidogrel, if aspirin is contraindicated) and a β blocker (unless contraindicated). One study showed some benefit from the use of the calcium antagonist verapamil

Table 10.2 Hypertension in patients after a heart attack

If the patient is receiving a thiazide diuretic, serum levels of potassium may be low, which means an increased risk of arrhythmias.
If blood pressure decreases, the outcome is poor.
All patients should receive aspirin (or clopidogrel if aspirin is contraindicated).
If blood pressure is very high, this must be reduced before thrombolysis is started.
All patients should receive a statin.
Dihydropyridine calcium blockers are contraindicated.
If possible, all patients should be given β blockers.
If β blockers are contraindicated, verapamil or diltiazem may be used.
ACE inhibitors should be given if the patient has any evidence of left ventricular systolic dysfunction or clinical heart failure.
All treatments should be given, even if the blood pressure is not high.

after myocardial infarction if β blockers are contraindicated. Diltiazem may be beneficial after non-Q wave myocardial infarction with no evidence of heart failure or left ventricular dysfunction.

Short-acting dihydropyridine calcium blockers (especially short-acting nifedipine) should be avoided, as evidence from trials shows these drugs can be harmful, possibly because of pro-arrhythmic properties related to raised plasma levels of catecholamines. Plasma potassium levels should be checked in patients who are taking thiazide diuretics for hypertension if they are admitted to hospital with an acute myocardial infarction, because hypokalaemia leads to an increased tendency to arrhythmias and sudden death.

If patients with acute myocardial infarction have severe hypertension (>180/110 mm Hg), thrombolysis could be hazardous, with an increased risk of intracerebral bleeding. Before thrombolysis, therefore, blood pressure should be reduced with an oral β blocker, intravenous nitrates or, occasionally, sodium nitroprusside. In many centres, primary angioplasty is used as the preferred option of reperfusion in patients presenting with an acute ST-elevation myocardial infarction. Nonetheless, vascular access via the femoral artery must be performed with caution in patients with severely uncontrolled hypertension, although increasing use of the radial artery access reduces the risk of significant bleeding. Uncontrolled hypertension should be proactively managed, given that multiple antithrombotic agents are administered during the procedure.

ACE inhibitors are increasingly recognised to be of value in patients after myocardial infarction, especially if the patient has impaired left ventricular systolic function. Evidence shows that ramipril and perindopril reduce the rate of cardiovascular events even in patients with existing vascular disease. Following presentation with an acute coronary syndrome (whether an acute ST-elevation myocardial infarction or non-ST elevation MI), all patients require secondary prevention measures, including aspirin plus a thienopyridine (clopidogrel, prasugrel or similar, such as ticagrelor), as well as a statin, a β blocker and an ACE inhibitor. A summary of the management of acute myocardial ischaemia in hypertensive patients appears in Table 10.2.

Peripheral artery disease

A strong association exists between peripheral artery disease and hypertension, which is exacerbated by smoking. Although control of blood pressure is important in these patients, caution needs to be exercised with some drugs, particularly β blockers, which may occasionally worsen symptoms in patients with claudication. Nonetheless, data from trials do not suggest any worsening of the claudication distance in patients randomised to β blockers. Certainly, these drugs should not be used in patients with rest pain or gangrene.

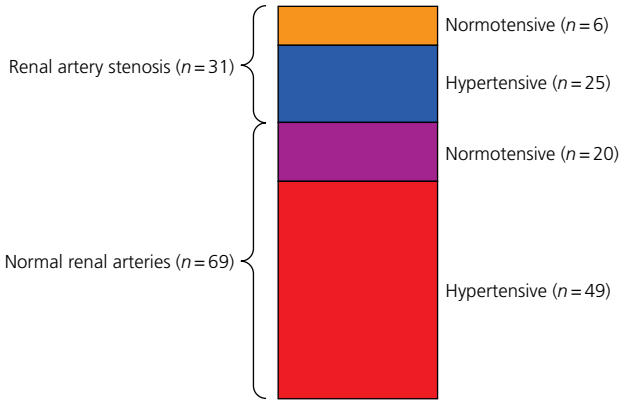


Figure 10.5 The prevalence of renal artery stenosis in patients with peripheral vascular disease and hypertension. Source: Data from Watchell, M., *et al*. (1996) *Journal of Human Hypertension*, 10, 83–85.

Table 10.3 Antihypertensive drugs and peripheral vascular disease

β Blockers may worsen rest pain
ACE inhibitors must be used with caution if renal artery stenosis present
Thiazides increase levels of lipids and glucose (small effect)
Calcium channel blockers may relieve symptoms
Lipid lowering drugs are usually prescribed
Type 2 diabetes mellitus may also present
Smoking cessation is mandatory

Peripheral artery disease may increase the likelihood of undiagnosed atheromatous renal artery stenosis (Figure 10.5). Serum levels of creatinine should therefore be monitored carefully if ACE inhibitors are used. An increase in levels of creatinine <20% is acceptable, however, and not indicative of underlying atheromatous renal artery stenosis.

A recent Cochrane review on the treatment of patients with hypertension and peripheral arterial disease concluded that evidence for various antihypertensive drug classes in peripheral arterial disease was poor. Whether significant benefit or risk accrues from their use is therefore unknown. In view of this, definite recommendations on their use or avoidance cannot be given.

Patients with peripheral arterial disease need full cardiovascular risk assessment (Table 10.3). They should be treated with statins and antiplatelet drugs (aspirin or clopidogrel), although recent randomised trials of primary prevention suggest that the addition of aspirin did not impact on mortality or major cardiovascular events, but caused significant increase in bleeding. This is in contrast to historical trials of aspirin in patients with vascular disease or risk factors, suggesting that in contemporary clinical practice, the incremental impact of aspirin over other measures (statins, ACE inhibitors, etc.) may be small. Thus, good control of hypertension and other associated disorders, such as angina, is needed.

Heart failure

At a population level, hypertension is commonly listed as an aetiological factor for the development of heart failure due to left ventricular systolic dysfunction. Patients with hypertension may develop heart failure because of underlying coronary artery disease or, occasionally, because of severe hypertension alone. Excessive alcohol intake could be a common aetiology for hypertension and alcoholic heart muscle disease – 'alcoholic cardiomyopathy'.

Heart failure with normal systolic function (so-called 'diastolic dysfunction' or 'diastolic heart failure') is also commonly associated with hypertension and reflects impaired ventricular relaxation and poor cardiac compliance. Patients with diastolic heart failure tend to have a better prognosis than those with impaired systolic function (ejection fraction <40%).

In the presence of heart failure as a result of systolic dysfunction, the use of verapamil is contraindicated and caution should be used with diltiazem. Treatment of systolic heart failure with diuretics and ACE inhibitors (or ARB) may control the patient's blood pressure. β Blockers (carvedilol, bisoprolol or metoprolol) introduced slowly and gradually are beneficial – reducing mortality and morbidity. Aldosterone antagonists (spironolactone, eplerenone) are other agents that would impact on blood pressure, and have been shown to improve outcomes in patients with systolic heart failure.

The ACE inhibitors have been proved to prolong life in patients with heart failure (Figure 10.6). They are therefore the drugs of choice for patients with systolic heart failure and hypertension. The use of carvedilol may have a small benefit over the use of metoprolol. The ARB are at least as good as the ACE inhibitors in patients with systolic heart failure and are a suitable alternative.

The non-selective aldosterone receptor antagonist (ARA), spironolactone has been shown to reduce mortality and morbidity in patients with heart failure. Great care must be taken when introducing these drugs, particularly in patients with diabetes or renal impairment, as life-threatening hyperkalaemia may develop. Spironolactone may cause tender breasts and occasionally gynaecomastia in men. Eplerenone, a more selective ARA, has been found to be beneficial in patients with heart failure after myocardial infarction with fewer side effects. It is, however, very expensive and should only be used in exceptional circumstances.

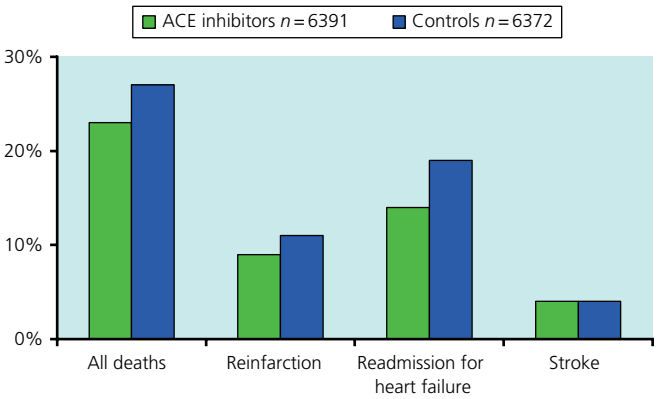


Figure 10.6 Pooled results of long-term ACE inhibition in four outcome trials in patients with heart failure or left ventricular systolic dysfunction. The differences for all deaths, reinfarction and readmission for heart failure are all statistically significant. Source: Data from Flather, M.D., *et al*. (2000) *Lancet*, 355, 1575–1581.

A smaller benefit in patients with heart failure is also seen with a combination of hydralazine and nitrates, which is the treatment choice in African-Caribbean patients with hypertension who develop heart failure, where ACE inhibitors are less effective.

The best treatment for diastolic heart failure is less certain, but it includes treatment of concomitant hypertension and regression of LVH. The ACE inhibitors and the β blockers appear to be less effective than in patients with systolic heart failure. The candesartan in heart failure assessment of reduction in mortality and morbidity (CHARM)-preserved trial showed only a modest benefit of candesartan in patients with heart failure and normal systolic function.

Atrial fibrillation

Hypertension is a common aetiological factor for AF – the most common sustained disorder of cardiac rhythm. Both increase the risk of ischaemic stroke; when both are present, the risk is additive. The risk of stroke is higher in patients with poor control of hypertension, and those on antithrombotic therapy have a higher risk of bleeding complications (Table 10.4).

The presence of uncontrolled blood pressure increases the risk of stroke and major bleeding. Thus, blood pressure control is essential. Hypertension appears as a risk factor in risk stratification schemes for stroke (e.g. $CHADS_2$ and CHA_2DS_2-VASc) and bleeding (HAS-BLED) used in the 2010 European Society of Cardiology guidelines on AF (Table 10.5). Patients with one or more stroke risk factors (and hypertension is an established risk factors, especially if

Table 10.4 The CHA_2DS_2-VASc scoring system for risk factors for stroke and systemic thromboembolism in non-valvular AF

Letter	Risk factor	Score
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A_2	Age > 75 years	2
D	Diabetes mellitus	1
S_2	Stroke/ TIA/ thromboembolism	2
V	Vascular disease	1
A	Age 65-74	1
S	Sex category (i.e. female sex)	1
		Maximum 9 points

Table 10.5 Major and minor risk factors for stroke or thromboembolism in patients with non-valvular AF

"Major" risk factors	"Clinically relevant non-major" risk factors
Previous stroke	Heart failure or moderate LV systolic dysfunction (e.g. LVEF < 40%)
Previous TIA	Hypertension
Previous systemic embolism	Diabetes mellitus
Age > 75 years	Female sex
	Age 65-74 years
	Vascular disease

Table 10.6 Clinical characteristics comprising the HAS-BLED bleeding risk score INR = international normative ratio

Letter	Clinical characteristic	Points awarded
H	Hypertension	1
A	Abnormal renal & liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age > 65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2 Maximum 9 points

suboptimally controlled) should be considered for effective thromboprophylaxis, with oral anticoagulation therapy (OAC), whether with well-controlled warfarin (INR 2–3) or one of the new oral anticoagulants from the oral direct thrombin inhibitor class (e.g. dabigatran) or oral Factor Xa inhibitor class of drugs (e.g. rivaroxaban, apixaban) (Table 10.6).

Patients with permanent AF and hypertension may benefit from drugs that allow control of the rate of fibrillation and reduce blood pressure, such as β blockers and rate-limiting calcium channel blockers (verapamil and diltiazem), in addition to antithrombotic drugs (Table 10.7). β Blockers may reduce paroxysms in some patients with paroxysmal AF, especially if the blood pressure is controlled. Some care is needed when class I and III antiarrhythmic agents are used in the presence of LVH, because of the risk of proarrhythmia. The risk of AF is higher in patients with hypertension and hypokalaemia due to primary aldosteronism (Conn's syndrome).

Table 10.7 The approach to thromboprophylaxis in patients with atrial fibrillation

Risk category	CHA_2DS_2-VASc	Antithrombotic therapy
One major risk factor or 2 or more "clinically relevant non-major" risk factors	>2	Oral anticoagulants (OAC)
One "clinically relevant non-major" risk factor	1	Either OAC or aspirin 75-325 mg daily:- OAC rather than aspirin.
No risk factors	0	No antithrombotic therapy Preferred: no antithrombotic therapy.

OAC, oral anticoagulation therapy.

Further Reading

Camm, A.J., Lip, G.Y., De Caterina, R., *et al.* (2012) focused update of the ESC Guidelines for the management of atrial fibrillation. *European Heart Journal*, 33, 2719–2747.

Robinson, T.G., Potter, J.F., Ford, G.A., *et al.* (2010) Effect of antihypertensive treatment after acute stroke in Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. *Lancet Neurology*, 9, 767–775.

Wilmot, M., Leonardi-Bee, J. & Bath, P.M. (2004) High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension*, 43, 18–24.

CHAPTER 11

Special groups; diabetes mellitus, renal disease, renal artery stenosis and connective tissue diseases

OVERVIEW

- Patients with hypertension and type 2 diabetes are at more than twice the risk of developing cardiovascular complications as those with diabetes alone. Antihypertensive therapy in diabetic patients greatly reduces cardiovascular events. There is reliable evidence that angiotensin-blocking drugs delay deteriorating renal function in patients with diabetic nephropathy. There is also some evidence that they delay diabetic retinopathy.
- Patients with renal disease are usually hypertensive and they have a greatly increased cardiovascular risk compared with those with hypertension alone. Angiotensin-blocking drugs delay end-stage renal disease in all forms of nephropathy.
- In older patients, renal artery stenosis(RAS) is usually due to atheromatous narrowing of the renal arteries. There is no convincing evidence that angioplasty and stenting of the renal arteries is of any benefit in the majority of patients. In young patients, the RAS may be due to fibromuscular dysplasia of the renal arteries angioplasty, and stenting may be effective at normalising the blood pressure.

Diabetes mellitus

Hypertension or type 1 and type 2 diabetes mellitus often coexist. Hypertension (≥140/90 mm Hg) is twice as common in people with diabetes than those without diabetes (Figure 11.1). For example, hypertension is very common (up to 80%) in patients with type 2 diabetes; in women, the increase in systolic blood pressure with age is also steeper. In patients with type 1 diabetes, the presence of hypertension is related strongly to incipient or overt diabetic nephropathy.

Furthermore, hypertension and diabetes are commonly associated with hyperlipidaemia. Hypertension therefore greatly increases the already high risk of coronary disease in people with diabetes – by twofold in men and fourfold in women. Patients with hypertension and diabetes also have double the risk of mortality of people with hypertension but not diabetes (Figure 11.2).

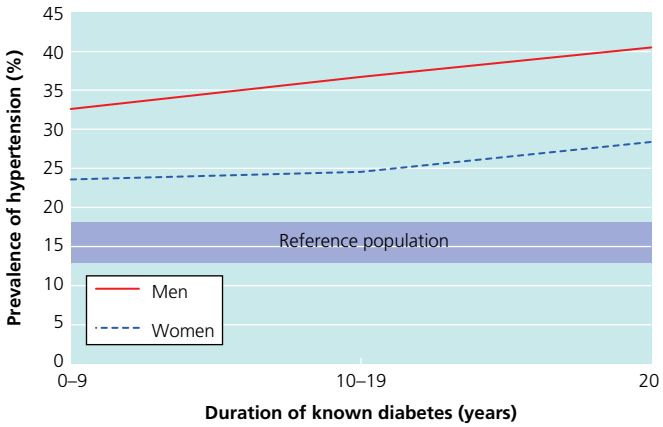


Figure 11.1 The prevalence of hypertension (≥140/90 mmHg) in individuals with type 2 diabetes mellitus. Source: Reproduced with permission from Krolewski, A.S., *et al*. (1985) *Journal of Chronic Disease*, 38, 319–326. © Elsevier.

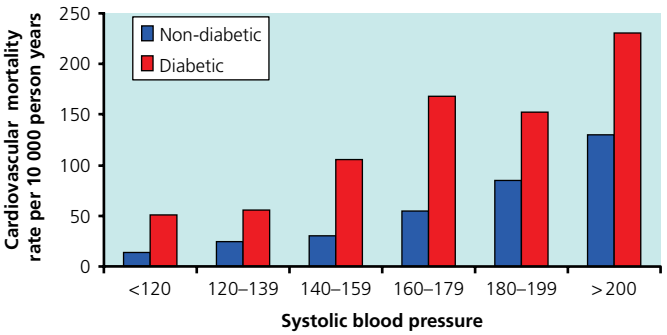


Figure 11.2 Cardiovascular mortality rates in individuals in relation to their systolic blood pressure in the Framingham Heart Study. Source: Data from Vasan, R.S., *et al*. (2001) *New England Journal of Medicine*, 345, 1291–1297.

The aetiology of hypertension in patients with diabetes is multifactorial. In patients with type 1 diabetes, hypertension may be related to diabetic renal disease (early glomerular hypertrophy

ABC of Hypertension, Sixth Edition. D. Gareth Beevers, Gregory Y. H. Lip and Eoin O'Brien.

and hyperfiltration followed by nodular glomerulosclerosis, (the Kimmelstiel-Wilson kidney) and mesangial expansion). These changes are associated with marked activation of the renin-angiotensin-aldosterone system and possibly some fluid retention. Patients with type 2 diabetes have marked volume expansion and sodium retention, perhaps related to hyperinsulinaemia as well as both microvascular and macrovascularischaemia. Plasma levels of renin and angiotensin tend to be low in type 2 diabetes (Figure 11.3).

Reduction of blood pressure in patients with diabetes has marked benefits for major cardiovascular events, including heart failure, cardiovascular death or total mortality (Figure 11.4).

Cardiovascular risk is higher in patients with diabetes than those without at every level of blood pressure – even into the conventional 'normotensive' range. Furthermore, no 'threshold' below which risk substantially declines exists.

A decision to use antihypertensive treatment in patients with diabetes needs to take into account the effects of antihypertensive drugs on glucose and lipid metabolism. Furthermore, reductions in progression of retinopathy, microalbuminuria, albuminuria, and progression of nephropathy occur. For example, hypertension accelerates the decline of renal function in patients with diabetes and established nephropathy; conversely, treatment with antihypertensives slows the progression of nephropathy in patients with type 1 and type 2 diabetes. There is evidence that antihypertensive drugs that block the renin-angiotensin-aldosterone system (e.g. losartan) are better at preventing new-onset diabetes than other therapies (Figure 11.5).

Current guidelines recommend that reduction of blood pressure with drug treatments is indicated in people with type 1 or type 2 diabetes when the systolic blood pressure is ≥140 mm Hg or the diastolic blood pressure is ≥90 mm Hg. Targets for the treatment of blood pressure also are lower in patients with diabetes; the 'optimal target' is <130/80 mm Hg.

Choice of therapy

Angiotensin converting enzyme (ACE) inhibitors are recommended as first-line therapy for people with diabetes and hypertension because of their benefits on cardiac function, vascular disease and possibly neuropathy. There is now also convincing evidence that angiotensin-blocking drugs delay the deterioration in renal function in patients with diabetic nephropathy associated with both type 1 and type 2 diabetes, reducing end-stage renal disease and the need for dialysis and renal transplantation (Figures 11.6 and 11.7).

There is some evidence that the ACE inhibitor, lisinopril reduces the progression of diabetic retinopathy, although more information is needed (Figure 11.8).

Patients with type 2 diabetes are generally older than those with type 1 diabetes. They are more prone to cardiovascular disease (CVD) (heart attacks and strokes and less prone to microvascular complication mainly nephropathy and retinopathy). There is good evidence that antihypertensive drugs do reduce cardiovascular events (Figure 11.4).

Most patients with hypertension and diabetes will need a combination of antihypertensive drugs (often three or more) to reach targets for blood pressure. The combination should include an

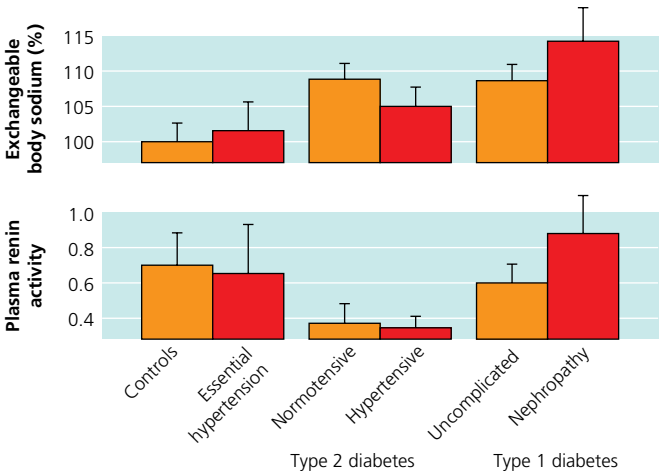


Figure 11.3 Plasma renin activity and total exchangeable sodium in patients with essential hypertension, type 1 and type 2 diabetes. Source: Data from Ferriss, J.B. (1991) *Journal of Human Hypertension*, 5, 245–254.

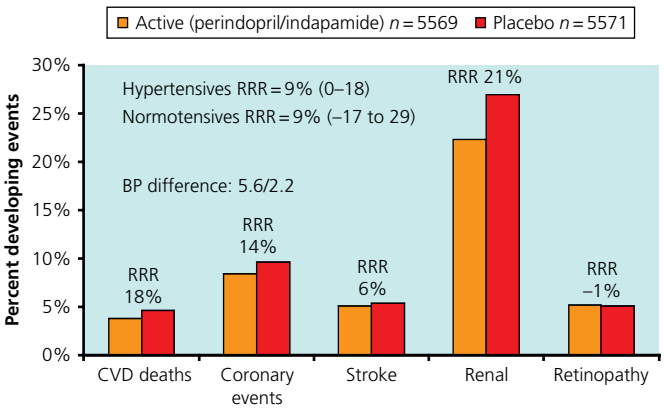


Figure 11.4 The effects of blood pressure reduction with perindopril and indapamide versus placebo in 11,140 patients with type 2 diabetes, data from normotensives and hypertensives combined. RRR; relative risk reduction. Source: Data from Patel A for the ADVANCE Collaborative Group (2007) *Lancet*, 370, 829–840.

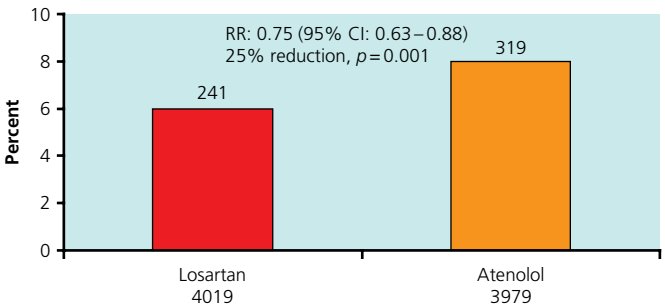


Figure 11.5 Percent of patients developing new-onset diabetes in the LIFE trial. CI confidence intervals; RR, relative risk. Source: Reproduced with permission from Dahlöf, B., *et al*. (2002) *Lancet*, 359, 995–1003. © Elsevier.

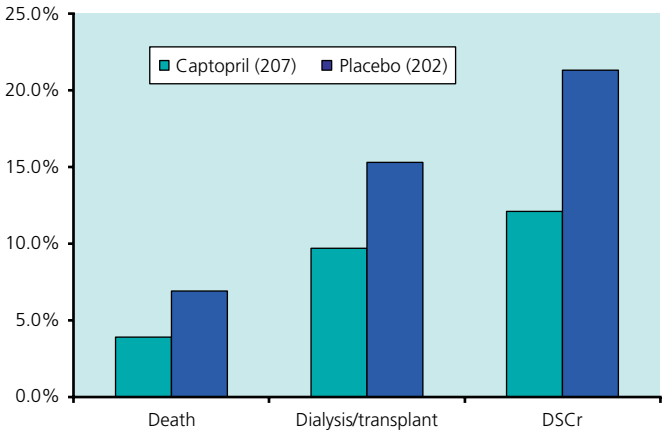


Figure 11.6 Percent of patients developing clinical end points in a trial of captopril versus placebo in type 1 diabetes and nephropathy. DSCr, doubling of serum creatinine. Source: Data from Lewis, E.J., *et al*. (1993) *New England Journal of Medicine*, 239, 1456–1462.

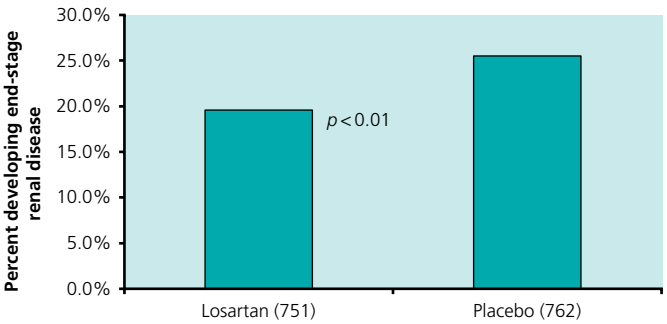


Figure 11.7 Comparison of losartan versus placebo on the progression of renal damage in patients with type 2 diabetes and incipient nephropathy. Source: Data from Brenner, B.M., *et al*. (2001) *New England Journal of Medicine*, 345, 861–869.

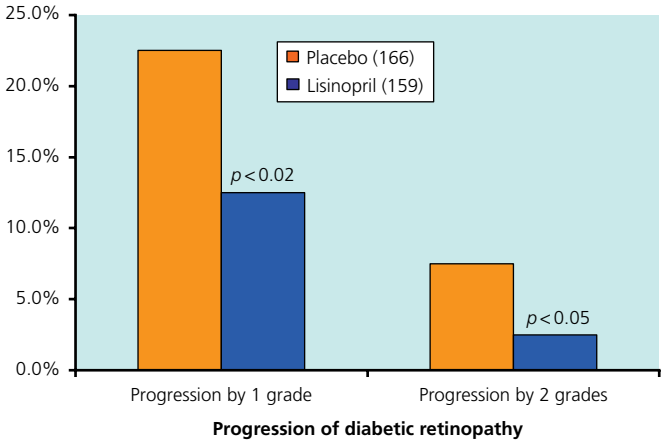


Figure 11.8 The effects of lisinopril versus placebo on the progression of diabetic retinopathy in patients with type 1 diabetes. Source: Reproduced with permission from Chaturvedi, N., *et al*. (1998) *Lancet*, 351, 28–31. © Elsevier.

ACE inhibitor or angiotensin receptor blocker as per the BHS-NICE guidelines (see Chapter 9). Initial therapy should almost always be with an angiotensin-blocking drug, but In most cases, an ACE inhibitor or an ARB alone will not control the blood pressure to below 130/80 mm Hg. If this is the case, the second-line drug should be a calcium channel blocker like amlodipine, nifedipine or verapamil. There remains some controversy on the optimum choice of third-line therapy if two drug classes fail to achieve targets. In theory, the thiazide-type diuretics might not seem the best choice with their tendency to increase glucose intolerance. However, if low doses are prescribed, this effect is small and is significantly offset by the benefits of achieving optimal blood pressure control.

ACE Inhibitors with ARB in diabetes

The co-prescription of ACE inhibitors with ARBs (dual blockade of the renin-angiotensin system) is highly controversial. Analysis of all the limited number of short-term antihypertensive efficacy studied strongly suggests that little added blood pressure control is achieved in patients who do not have concomitant diabetes (Figure 11.9). There is, however, some evidence that this combination may be of use in patients with diabetes with some improvement in pressure control and a reduction of proteinuria. In theory, dual blockade might cause a sharp rise in serum creatinine, so very careful monitoring is mandatory. There are reports that dual blockade of the renin-angiotensin system may provoke acute renal failure.

Patients with type 2 diabetes and hypertension also benefit from treatment with statins – irrespective of their baseline levels of cholesterol. In patients with type 1 diabetes, insufficient data with regard to statins are available, but the high rates of CVD in this population mean they should be treated as for patients with type 2 diabetes.

Aspirin for primary prevention of CVD in patients with diabetes is also controversial. It should only be prescribed – but only when blood pressure is controlled (<150/90 mm Hg) and the underlying total cardiovascular risk is 20% or more over 10 years. Glycaemic control should be optimised, and non-pharmacological lifestyle measures, such as salt restriction, weight reduction and increased exercise, should be implemented.

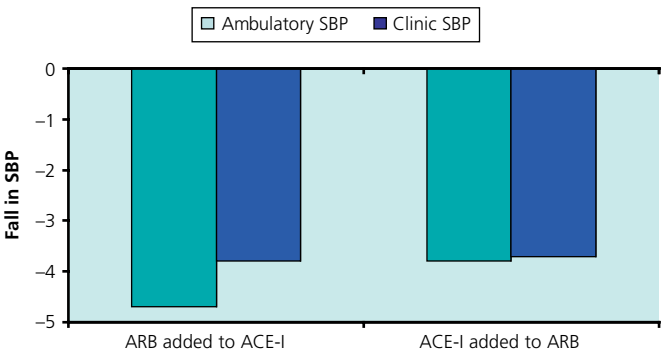


Figure 11.9 Meta-analysis of 14 randomised trials of the effects on systolic blood pressure of the co-prescription of an ACE inhibitor with an ARB. Source: Data from Doulton, T.W., *et al*. (2005) *Hypertension*, 45, 880–886.

Renal disease

The frequency of renal impairment is higher in patients with hypertension – as a cause or effect of the high blood pressure. Renal parenchymal disease is the cause of hypertension in about 5%. Renal impairment itself is now recognised to be a powerful risk factor for CVD, and these patients have an enormously increased chance of developing stroke, heart failure or coronary heart disease (Figure 11.10).

The presence of high serum levels of creatinine or proteinuria at the initial assessment of a patient with hypertension should lead to suspicion of renal parenchymal or obstructive renal disease or renal artery stenosis, as well as retinopathic malignant phase hypertension. High blood pressure can accelerate the age-related decline in glomerular filtration rate in essential hypertension.

Regardless of the cause of renal impairment, hypertension considerably influences its progression. In people with diabetic and non-diabetic renal disease, two factors are important in preserving residual renal function: control of blood pressure and blockade of the renin-angiotensin system with ACE inhibitors or ARBs.

The threshold for antihypertensive treatment in patients with persistent proteinuria or renal impairment is ≥140 mm Hg systolic blood pressure or ≥90 mm Hg diastolic blood pressure, or both. Optimal control of blood pressure is defined as <130/80 mm Hg, although reduction of blood pressure to <125/75 mm Hg may provide additional benefit in patients with chronic renal disease of any aetiology that is associated with proteinuria of ≥1 g/24 h. Nonetheless, the recent African American study of kidney disease did not show that a lower target blood pressure (128/78 mm Hg) was better at preserving renal function in African Americans with non-diabetic chronic renal disease than less tight control of blood pressure (141/85 mm Hg).

Choice of therapy

Any drugs that are excreted by the kidney need to be given initially in small doses. This is particularly true for the ACE inhibitors and the β blockers.

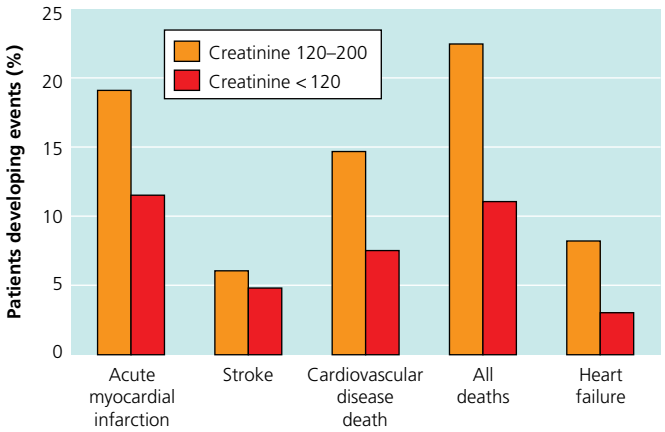


Figure 11.10 Cardiovascular events in patients receiving placebo therapy in relation to serum creatinine levels at entry to the study. Source: Data from Mann, J.F., *et al.* (2001) *Annals of Internal Medicine*, 134, 629–636.

ACE inhibitors have been shown to reduce microproteinuria and macroproteinuria, and some evidence suggests that they preserve renal function. Meta-analyses that examined the renoprotective effect of ACE inhibitors in patients with non-diabetic parenchymal renal disease have all confirmed a benefit of inhibition of ACE beyond that achieved with reductions in blood pressure, particularly in patients with overt proteinuria. When treatment is started with an ACE inhibitor or an ARB, serum creatinine levels may rise. This is not evidence of nephrotoxicity but reflects a small fall in renal artery perfusion pressure as a consequence of a reduction in blood pressure. In addition, angiotensin-blocking drugs selectively dilate the post-glomerular efferent arterioles, leading to a fall in intraglomerular pressure. On a long-term basis, these changes reduce glomerular damage and preserve renal function. Large rises in serum creatinine levels, however, can be serious and may be seen if there is renal artery stenosis or a reduction in intravascular volume due to concomitant diuretic therapy, particularly with furosemide (Table 11.1).

Sub-group meta-analysis suggests that blocking the renin-angiotensin-aldosterone system does not delay progression to end-stage renal failure in patients with autosomal dominant polycystic kidney disease (ADPKD).

Additional antihypertensive treatment is often needed and should include a thiazide diuretic or thiazide-like diuretic. In patients with oedema and those with more advanced renal impairment (serum levels of creatinine >200 µmol/l), thiazide diuretics and thiazide-like diuretics are ineffective, and a loop diuretic (such as furosemide) should be used. Calcium channel blockers are effective and relatively safe in patients who have renal failure.

In patients with end-stage renal failure, hypertension is common but can be controlled with dialysis. In anephric patients, salt and water restriction between dialyses sessions may be enough to control blood pressure, but drug treatment is often still needed. Patients with end-stage renal failure are usually anaemic, and treatment with erythropoietin is usually initiated, although blood pressure may increase with this drug.

A high proportion of dialysis and renal transplant recipients develop hypertension, especially if they have received kidneys from donors with hypertension. Post-transplant hypertension in the early phase may be related to acute rejection or acute tubular necrosis that follows the ischaemic period, as well as some fluid overload if the patient was underdialysed before the operation. The use of

Table 11.1 The effects of angiotensin-blocking drugs on serum creatinine levels

A small increase in serum levels of creatinine with ACE inhibitors is haemodynamic not nephrotoxic.
An increase of up to 20% is not an indication to stop ACE inhibitors or ARBs.
If creatinine increases by >20%, ACE inhibitors and ARBs should be withdrawn temporarily.
An increase of serum creatinine of >20% can be caused by:
Hypotension
High-dose diuretics (furosemide)
Dehydration
Bilateral renal artery stenosis
Non-steroidal anti-inflammatory drugs
Underlying chronic renal failure

corticosteroids as immunosuppressive agents can exacerbate fluid retention, and, in the long term, the use of cyclosporin A may also cause hypertension. Hypertension can develop in response to renin secretion from the patient's own atrophic kidneys, or atheromatous renal artery stenosis may affect the blood supply to the transplanted kidney (Table 11.2). Good control of blood pressure is needed to preserve the function of the transplanted kidney.

Even mild persistent increases in urinary excretion of albumin (even below the threshold currently used to define microalbuminuria) and mild increases in serum levels of creatinine before antihypertensives are started are strong predictors of premature cardiovascular morbidity and mortality. Patients with end-stage renal failure, and those on dialysis or after transplantation, have a particularly high incidence of atheromatous vascular disease, heart attacks, atrial fibrillation, heart failure, and strokes. Most patients with renal disease and treated hypertension are at substantial cardiovascular risk and will benefit from treatment with statins and aspirin (or anticoagulation, if atrial fibrillation is present).

Renal artery stenosis

There are two forms of renal artery stenosis. The commonest form is atheromatous renal artery stenosis (ARAS). The deposition of atheroma in the abdominal aorta, particularly at the origin of the renal arteries, might be regarded as a consequence of hypertensive arterial disease rather than an underlying cause of the hypertension. The other form of renal artery stenosis is due to fibromuscular dysplasia (FMD) of the renal arteries. This condition is a genuine underlying cause of hypertension and its correction by renal angioplasty and stenting can cause normalisation of blood pressure (Table 11.3). FMD is an important cause of hypertension in children; in adult practice, it is most commonly seen in young women (see Chapter 7).

The optimum management of patients with ARAS)remains uncertain. Factors that may lead to its diagnosis are summarised in Table 11.4. Many patients have evidence of atheromatous arterial disease elsewhere (e.g. peripheral vascular disease). ARAS should be considered in patients who develop a marked rise in serum creatinine levels after starting treatment with an angiotensin-blocking drug. These agents should be introduced gradually in older patients with peripheral vascular disease with early monitoring of renal function tests.

Whilst there is little doubt on the value of treating FMD with angioplasty and stenting, there is considerable uncertainty on the usefulness of surgery or angioplasty in patients with ARAS. Several well-conducted randomised controlled trials of angioplasty and stenting versus conventional medical treatment have demonstrated no improvement in blood pressure control, no reduction in serum creatinine levels and no reduction in the high risk of cardiovascular consequences of hypertension or survival (Table 11.5).

However, great care must be taken when interpreting the ASTRAL trial results. A large number of patients with ARAS were considered for inclusion in the study but not randomised. In some patients, the investigators did not consider the hypertension to be severe enough to warrant possible angioplasty. In many patients, the renal artery narrowing was so severe that angioplasty was too difficult to achieve. In some patients with critical renal artery stenosis, the investigators felt that there was a significant risk of total bilateral renal artery occlusion, which might lead to severe ischaemic nephropathy if renal angioplasty was not undertaken. The ASTRAL trial was, therefore, confined to patients where the

Table 11.2 Hypertension following renal transplantation

Found in about 50% of patients
Related to cyclosporin and prednisolone
Transplant renal artery stenosis
Ischaemic damage during transfer
Transplant rejection
Recurrence of renal or systemic disease
Hypertension from transplanted kidney
Activation of the renin-angiotensin system
Sodium and water retention

Table 11.3 Characteristics of patients with renal artery stenosis attending the Mayo Clinic in Rochester, Minnesota

	Atheroma	**Fibro-muscular dysplasia**
Mean age (range)	53 (35–73)	39 (6–64)
M:F ratio	65:35	27:73
Proportion	65%	35%
Abdominal bruit present	40%	80%
Bilateral stenosis	31%	24%
Heart disease or strokes	49%	Rare
Developed renal failure	15%	Rare
5-year survival	67%	92%
Disease progression	28%	—

Source: Data from Hunt, J.C. (1973) *American Journal of Cardiology*, 32, 562–574.

Table 11.4 Factors suggesting a diagnosis of renal artery stenosis (FMD or ARAS)

Onset of hypertension before the age of 30 years, particularly in women
Documented sudden onset of hypertension or sudden worsening of hypertension in middle age
Accelerated (malignant-phase) hypertension
Resistant hypertension (to regimen of more than four drugs)
Renal impairment of unknown cause
Large elevation of serum creatinine, especially with marked reduction in blood pressure with treatment with ACE inhibitors or ARBs (≥30% increase of serum creatinine)
Peripheral vascular disease or severe generalised atherosclerotic disease
Recurrent 'flash' pulmonary oedema or heart failure with no obvious cardiac cause

Table 11.5 Results of the angioplasty and stenting for renal artery lesions (ASTRAL) trial

Serum creatinine at follow up	No benefit
Blood pressure at follow up	No benefit
Need for dialysis/renal transplantation	No benefit
Total mortality	No benefit
Cardiovascular events (fatal and non-fatal)	No benefit

Source: Data from Wheatley, K., *et al*. (2009) *New England Journal of Medicine*, 361, 1953–1962. © ASTRAL Investigators.

investigators were uncertain whether renal angioplasty was indicated or contraindicated.

In practice, all patients with ARAS should be referred to a nephrologist for consideration of undergoing revascularisation. Blood pressure control must be optimised; if the pressure appears to be uncontrolled, checks should be made on patient medication compliance and if compliance is not an issue, 24-h blood pressure monitoring (ABPM) should be carried out to exclude any white coat element in the height of the blood pressure. Although there is no randomised trial evidence on this point, all patients should be prescribed a statin to reduce plasma lipid levels and reduce total cardiovascular risk.

Connective tissue disease

Rheumatoid arthritis, systemic lupus erythematosus, polyarteritis-nodosa and other connective tissue disorders are all associated with hypertension and an increased risk of CVD. In some of these conditions, the hypertension is related to renal vasculitis. The tendency to develop hypertension is increased by the concomitant use of non-steroidal anti-inflammatory drugs, corticosteroids, gold treatment, and, in some cases, immunosuppressive drugs. In patients with progressive systemic sclerosis (scleroderma), hypertension is unusual unless the patient has evidence of renal involvement leading to progressive renal failure.

No clear guidance is available on the best antihypertensive drugs in these patients. In patients with scleroderma kidney, ACE inhibitors are frequently used. In other connective tissue diseases, most doctors opt for ACE inhibitors or calcium channel blockers, or both. The β blockers increase the tendency to develop Raynaud's syndrome and are best avoided. All patients with any connective tissue disease and hypertension, with or without overt renal involvement, need specialist referral.

Further Reading

Beaman, M. & Adu, D. (1988) Mesangial IgA nephropathy: an autoimmune cause of hypertension. *Journal of Human Hypertension*, 2, 139–141.

Brown, J.H., Hunt, L.P., Vites, N.P., *et al.* (1994) Comparative mortality from cardiovascular disease in patients with chronic renal failure. *Nephrology Dialysis Transplantation*, 9, 1136–1142.

Ferrannini, E. & Cudhman, W.C. (2012) Diabetes and hypertension: the bad companions. *Lancet*, 380, 601–610.

Ginzler, E.M., Felson, D.T., Anthony, J.M. & Anderson, J.J. (1993) Hypertension increases the risk of renal deterioration in systemic lupus erythematosis. *Journal of Rheumatology*, 20, 1694–1700.

CHAPTER 12

Ethnicity, age and hypertension

OVERVIEW

- In both developed and developing countries, hypertension is common in people of African origin than in those of South Asian or European origin. African origin hypertensive individuals suffer more strokes and renal failure but less coronary heart disease.
- South Asians living in Europe and in Asia suffer more heart attacks than other groups.
- People of Sino-Japanese origin have a high incidence of cerebrovascular disease.
- Hypertensive patients of African origin have lower levels of plasma renin activity and angiotensin II than other groups. Consequently, drugs that block the renin-angiotensin system tend to be less effective at lowering blood pressure. There is a non-significant trend for calcium channel blockers (CCBs) to be marginally more effective.
- In African-origin patients, the CCBs are recommended as first-line antihypertensive agents, with angiotensin-blocking drugs used as second-line drugs.
- Plasma renin activity falls with advancing age, so antihypertensive drugs that block the renin-angiotensin system tend to be less effective in elderly patients. The CCBs are recommended as first-line agents in older patients with angiotensin-blocking drugs used as second line.
- In all groups, angiotensin-blocking drugs should be used as first-line agents where specifically indicated (diabetic and non-diabetic nephropathy and heart failure).
- Anxieties that blood pressure lowering might be harmful in older patients have been allayed. Controlled blood pressure lowering in the elderly prevents strokes, heart failure and cardiovascular death, and possibly reduces impairment of cognitive function. This has been shown to be true in all ages, including octogenerians.

Ethnic groups

Surveys in the United Kingdom and United States show that black people of African or African-Caribbean origin have higher levels of blood pressure and a greater prevalence of hypertension than white Caucasians. This greater burden of hypertension is associated with higher rates of renal failure, left ventricular hypertrophy and stroke. By contrast, morbidity and mortality from coronary heart disease is lower in black people than in the white population (Figure 12.1).

In general, there is little evidence that black patients consume more salt that other groups. Instead, they seem to be more sensitive to a given salt load than white patients, and advice on salt restriction is particularly important. Most salt intake (90%) derives from processed or ready-made foods rather than salt that is added at table or when cooking (10%), and education on restriction of salt intake should include expert dietary advice. There is evidence that African Americans consume significantly less potassium in fruit and vegetables than white Americans.

The other striking difference between African origin people is that they have lower circulating plasma renin levels than all other groups (Figure 12.2). The reasons for this are uncertain but may be related to differences in renal sodium and water handling, reduced sympathetic nervous system activity and in some cases, possible early nephrosclerosis. From a practical point of view, those drugs that primarily act by blocking the renin-angiotensin-aldosterone system tend to be rather less effective in people with low plasma renin levels.

If drug treatment is needed, black people trend to have different responses to antihypertensive drugs to white people and south Asian people. Blood pressure in black people responds better to thiazide or thiazide-like diuretics and to CCBs and poorly to β blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) (Figure 12.3). In a comparison of the CCB, verapamil and the β blocker, metoprolol in African-Caribbean patients with diabetes, metoprolol was no more effective than placebo but verapamil significantly reduced blood pressure. These trends explain the recommendations of the UK BHS/NICE guidance on the choice of first-, second- and third-line antihypertensive therapy in African-origin versus European-origin patients (see Chapter 9).

These ethnic differences in response to antihypertensive treatment have significant implications for prognosis – for example, among the black (but not white) patients with hypertension in the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT) study, stroke and coronary events were

ABC of Hypertension, Sixth Edition. D. Gareth Beevers, Gregory Y. H. Lip and Eoin O'Brien.

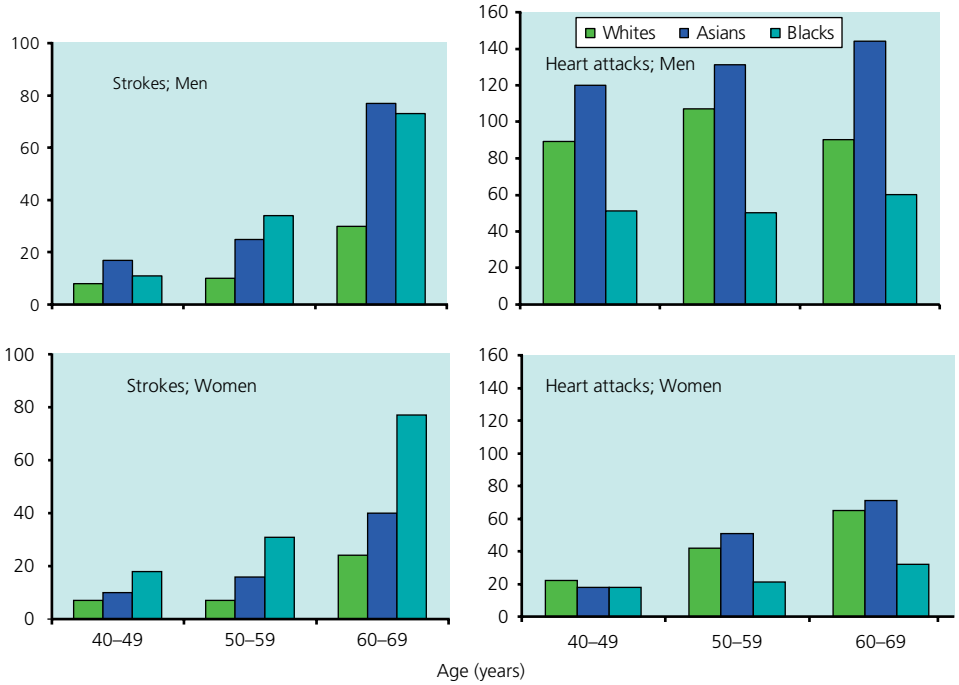


Figure 12.1 Stroke and heart attack admission rates per 1000 admissions for all causes in European whites, South Asians and Afro-Caribbean blacks to Dudley Road Hospital, Birmingham, 1981–1986. Source: Reproduced with permission from Weil, J., Beevers, D.G. (1993) Cardiovascular disease in blacks, whites and Asians in Birmingham. In: *Cardiovascular Disease: Risk Factors and Intervention* (eds. N. Poulter, P. Sever, S. Thom), pp 63–70. Radcliffe Medical Press, Oxford. © Radcliffe Publishing.

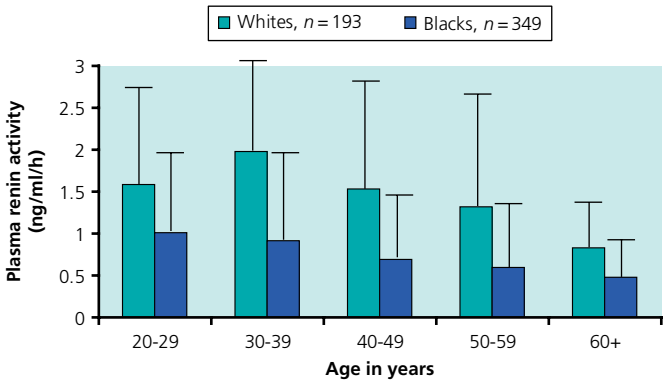


Figure 12.2 Plasma renin activity in relation to age and ethnic origin in hypertensive patients. Source: Data from Freis, E.D., *et al*. (1983) *American Journal of Medicine*, 74, 1029–1041.

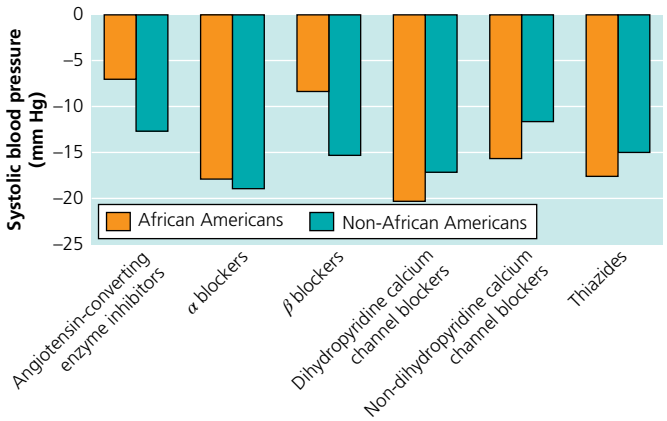


Figure 12.3 Differences in the response of systolic blood pressure to the major classes of antihypertensive drugs in relation to ethnic origin. Source: Data from Wu, J., *et al*. (2005) *American Journal of Hypertension*, 18, 935–942.

significantly more common among patients randomised to an ACE inhibitor than those randomised to chlortalidone. No differences in these end points were seen between those randomised to the thiazide or thiazide-like diuretics and those randomised to the dihydropyridine CCB amlodipine. These differences in outcome are largely explained by the fact that CCBs and thiazides are more effective at controlling blood pressure than ACE inhibitors.

The combination of diuretic treatment with ACE inhibitors, however, is as effective in black people as in white people. Alternatively, very high doses of β blockers or ACE inhibitors (or ARBs) are needed to achieve the same degree of reduction in blood pressure. Nonetheless, in patients with renal impairment, an ACE inhibitor is still needed. For example, the African-American Study of Kidney Disease and Hypertension trial in African-American patients with renal impairment compared the ACE ramipril with amlodipine and with the β blocker metoprolol. The trial was stopped prematurely because of worsening of renal failure in those randomised to amlodipine but not ramipril.

Patients of South Asian origin with hypertension are at very high risk from coronary heart disease and diabetes mellitus. In the United Kingdom, this population has higher mean levels of blood pressure and a higher prevalence of hypertension than the white population, as well as a higher risk of stroke. Sadly, no morbidity or mortality data from hypertension trials that relate to this population are available. In addition, no robust data are available

to suggest that South Asian people respond differently to antihypertensive agents than white Caucasians. The thiazide diuretics, which can worsen glucose intolerance, should therefore be used with some caution. In people from the Far East, some epidemiological and clinical trial data are available. Of note, mean levels of blood pressure in Chinese people in the United Kingdom may be higher than those of people in mainland China. There is insufficient information on the effects of antihypertensive drugs in South Asian and Chinese-origin patients. What little evidence there is suggests that drug response in these groups is similar to European-origin patients.

Elderly people

Coronary heart disease and stroke are the major causes of mortality in elderly people, and hypertension is the most common treatable risk factor. A definition of ≥160/95 mm Hg means that more than half of the 12 million people in the United Kingdom older than 60 years are hypertensive. With a definition of ≥140/90 mm Hg, more than 70% of people will be hypertensive. In this patient group, isolated systolic hypertension is common, and, on an epidemiological basis, the degree of systolic hypertension is related more closely to stroke and coronary heart disease, even when underlying diastolic blood pressure is corrected for. An age-related increase in pulse pressure is also seen.

Multiple measurements of blood pressure should be taken in elderly people to confirm the diagnosis of hypertension, as such patients tend to have greater variability in blood pressure. During the initial assessment, attention to symptoms and total cardiovascular risk should be checked. In addition, measurements of blood pressure with the patient in the seated and standing positions are needed to assess postural or orthostatic hypotension, which is more common in older people. If the latter is significant (e.g., a decrease in systolic blood pressure with standing of ≥20 mm Hg with symptoms), antihypertensive treatment should be titrated to standing values of blood pressure. Ambulatory blood pressure measurement may be of particular value in identifying patterns of 24-h blood pressure behaviour in the elderly (see Chapter 4). All elderly people with hypertension should be given lifestyle advice. In particular, a diet low in salt is more effective in elderly people than in younger patients.

Up until around 1985, there were few data on the value of reducing blood pressure in older patients. There was some anxiety that such treatment might do more harm than good with an excess risk of falls, hip fractures and hypotensive episodes. However, later, randomised trials were reassuring and it was demonstrated that the absolute benefits of antihypertensive treatment are much greater in elderly people with hypertension because of their increased absolute risk (Figure 12.4).

As shown in Figure 12.2, plasma renin levels fall with advancing age and as a result of this, drugs that block the renin-angiotensin system tend to be less effective in the elderly. In elderly patients, the CCBs are now the drugs of first choice, as they reduce cardiovascular morbidity and mortality. Should CCBs prove insufficient to control blood pressure, it is usual to add an ACE inhibitor or an ARB. As per the BHS/NICE guidance, thiazides and thiazide-like

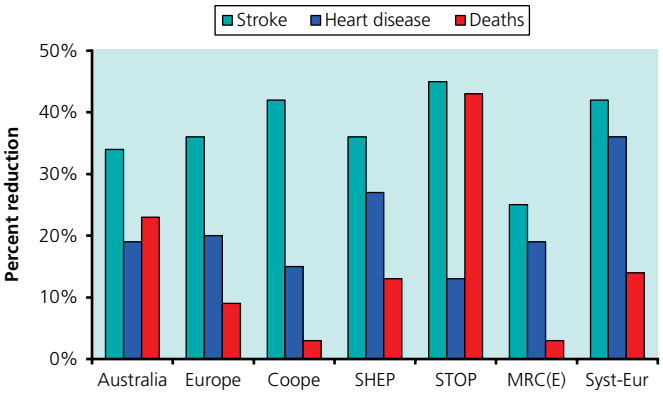


Figure 12.4 Results of seven randomised controlled trials of antihypertensive therapy in elderly patients (Unpublished analysis of data from Australian National Blood Pressure Study, European Working Party on Hypertension in the Elderly, Coope and Warrender UK Trial, Systolic Hypertension in the Elderly Program, Swedish Trial in Old Persons, Medical Research Council (Elderly) and Systolic Europe)

diuretics are now relegated to be third-line agents. β Blockers should now only be used in patients with concomitant heart disease.

The hypertension in the very elderly trial (HYVET) has established the safety and efficacy of antihypertensive treatment in very elderly patients (Figure 12.5). In HYVET, 3845 elderly patients aged >80 years of age with a sustained systolic blood pressure of 160 mmHg or more were randomised to receive either the diuretic indapamide (sustained release, 1.5 mg) or matching placebo. The ACE inhibitor perindopril (2 or 4 mg), or matching placebo, was added if necessary to achieve the target blood pressure of 150/80 mm Hg. During the trial, the systolic blood pressure was 15 mm Hg lower in patients randomised to active treatment compared with those on matching placebo tablets.

The primary end point was fatal or non-fatal stroke. In HYVET, active treatment was associated with the following:

- A 30% reduction in the rate of fatal or non-fatal stroke (95% confidence interval [CI], −1 to 51; $p = 0.06$),
- A 39% reduction in the rate of death from stroke (95% CI, 1–62; $p = 0.05$)
- A 21% reduction in the rate of death from any cause (95% CI, 4–35; $p = 0.02$)
- A 23% reduction in the rate of death from cardiovascular causes (95% CI, −1 to 40; $p = 0.06$)
- A 64% reduction in the rate of heart failure (95% CI, 42–78; $p < 0.001$).

Fewer serious adverse events were reported in the active-treatment group (358, vs. 448 in the placebo group; $p = 0.001$).

In a HYVET sub-study, active treatment was associated with a 13% reduction of new-onset dementia but this trend was not statistically significant. However, when the new-onset dementia data from all the trials of hypertension in the elderly are pooled, the reduction, also of 13%, was significant ($p = 0.045$).

The HYVET study will almost certainly be the last randomised placebo-controlled trial of the treatment of hypertension. It is now clear that high blood pressures are worth reducing in all ages, with a trend for older patients to derive more benefit than younger ones. It is likely that any future trials will be conducted to investigate the

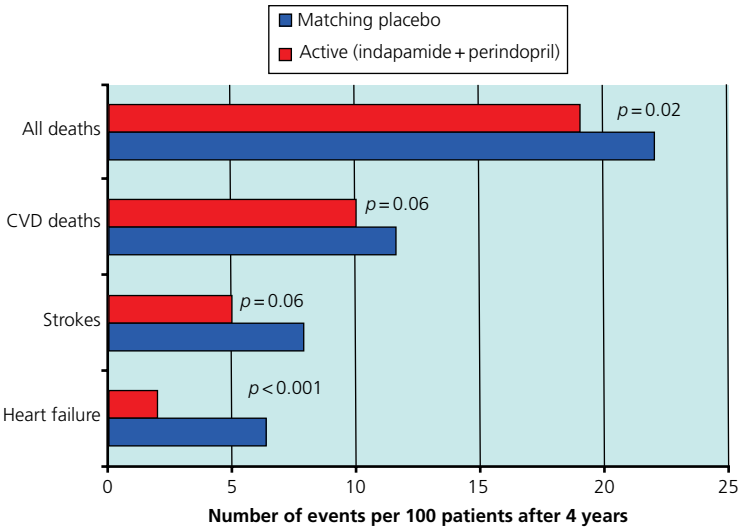


Figure 12.5 Principal results of the hypertension in the very elderly trial (HYVET). Source: Data from Beckett, N.S., *et al*. (2008) *New England Journal of Medicine*, 358, 1887–1898.

Table 12.1 Average systolic and diastolic blood pressures and thresholds for diagnosing hypertension (95th percentile) in children in relation to their age

Age (years)	Mean blood pressure			
	Systolic		Diastolic	
	Normal mean	95th percentile	Normal mean	95th percentile
Birth–6 weeks	75	95	—	—
6 weeks–4 years	35	110	60	70
5–6	105	115	60	75
7–8	105	120	65	80
9–10	110	125	65	80
11–12	115	130	65	85
13–14	120	135	70	85
>14	—	140	—	90

Source: Data from the Report of the Second Task Force on Blood Pressure Control in Children–1987. Task Force on Blood Pressure Control in Children. National Heart, Lung, and Blood Institute, Bethesda, Maryland (1987) *Pediatrics*, 79, 1–25.

relative benefits of different antihypertensive drug classes. In the meantime, after careful assessment, blood pressures should be reduced using the ACD system as recommended by the BHS/NICE guidance.

Hypertension in children

Children's blood pressure is closely related to their age, so the criteria for diagnosing overt hypertension depend on an individual's age. Clinical hypertension is diagnosed if either the systolic or diastolic blood pressure exceeds the 95th percentile. The results from several large surveys are shown in Table 12.1

Hypertension in children appears to be more common in girls than boys. The reasons for this are a matter of speculation but may be related to a greater frequency of ascending urinary tract infection (Figure 12.6)

In children younger than 3 years, measurement of blood pressure can be achieved with Doppler flow equipment, and, of course, the appropriate-sized cuff must be used in children of all ages. Over the age of 3 years, conventional blood pressure measurement with the common oscillometric monitors is usually satisfactory. Children whose blood pressure is higher than the 90th percentile for their age need to be rechecked at a follow-up screening; if blood pressure is higher than the 95th percentile, referral for further assessment by a paediatrician and detailed investigation is mandatory.

Children with blood pressures between the 90th and 95th percentiles are classified as having borderline hypertension. They need regular follow-up but specialist referral is not necessary unless there is some suspicion of an underlying renal disease. When the pressure rises to exceed the 95th percentile, paediatric specialist referral is necessary.

The routine screening for hypertension in all children is not currently justifiable as the number of children with raised readings is very small. However, blood pressure should be measured in all children who present with any systemic illness, especially renal disease or those who require hospital admission for any cause.

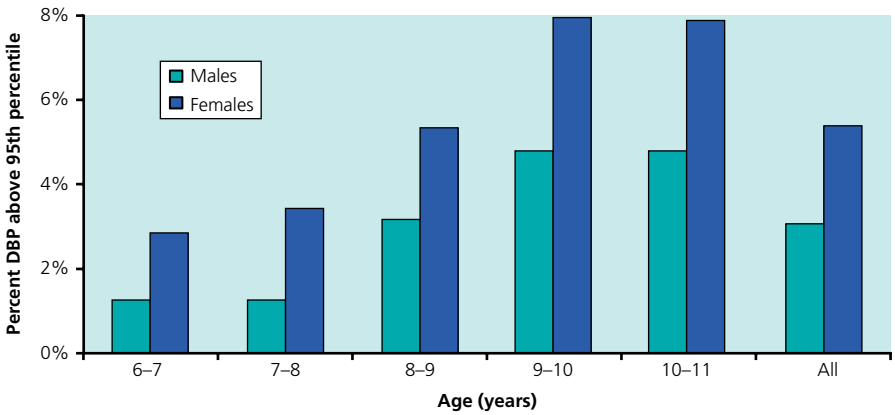


Figure 12.6 The prevalence of diastolic hypertension in male and female school children. Source: Data from Genovesi, S., *et al*. (2005) *Journal of Hypertension*, 23, 493–497.

Table 12.2 The common underlying causes of hypertension in children

Age group	Cause
Newborn infants	Renal artery thrombosis
	Renal artery stenosis due to fibromuscular dysplasia (FMD)
	Congenital renal malformations
	Coarctation of the aorta
Infancy to 6 years	Glomerulonephritis and pyelonephritis
	Coarctation of the aorta
	Renal artery stenosis due to FMD
6–10 years	Renal artery stenosis due to FMD glomerulonephritis and pyelonephritis
	Autosomal dominant polycystic kidney disease (ADPKD)
	Primary (essential) hypertension
Adolescence	Primary (essential) hypertension glomerulonephritis and pyelonephritis
	Renal artery stenosis due to FMD
	Aldosterone excess
	Connective tissue diseases

Raised blood pressure in children can be due to genetic factors related to their parents' pressures. Whilst hypertension runs in families but only about half of this effect is due to true genetic factors. Most 'familial concordance' is due to shared lifestyle factors, including obesity, high salt foods and physical inactivity.

Children with raised blood pressure have a great likelihood of underlying primary causes, such as renal and adrenal disease, aortic coarctation or vasculitis (Table 12.2). Careful evaluation for secondary hypertension is therefore needed. However, with the rapidly rising prevalence of obesity in children and adults, it is probable that obesity itself will overtake all other factors in the causation of hypertension. There is also evidence that children in many countries are now consuming more salt in relation to their body weight than adults. This is mostly in the form of salty snacks and crisps. Many of the cheese snacks targeted at children can be considered to be dangerously salty.

As with the general management of hypertension, the approach to children initially should include non-pharmacological measures, such as weight reduction (if the child is obese), restriction of salt intake, and increased levels of exercise. All children with blood pressures above the 95th percentile should be referred to a paediatric nephrology specialist.

Data from trials on drug treatments in this patient population are limited and there are no long-term outcome studies. However, the CCBs, and the α blockers are generally safe. Theoretically, the thiazide diuretics may have long-term metabolic effects and perhaps should be avoided in children. The ACE inhibitors and ARBs should also be used with care in patients with renal disease, as on a long-term basis, they probably are renoprotective in children as well as adults.

Further Reading

Douglas, J.G., Bakris, G.L., Epstein, M., *et al.* (2003) Management of high blood pressure in African Americans. Consensus statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. *Archives of Internal Medicine*, 163, 525–541.

Report of the Second Task Force on Blood Pressure Control in Children (1987) Task force on blood pressure control in children. National Heart, Lung, and Blood Institute, Bethesda, Maryland. *Pediatrics*, 79, 1–25.

Sagnella, G.A. (2001) Why is plasma renin activity lower in populations of African origin? *Journal of Human Hypertension*, 15, 17–25.

CHAPTER 13

Hypertension, pregnancy and the oral contraceptives

OVERVIEW

- The hypertensive disorders of pregnancy are becoming common as many women are now opting to start their family at a later age, by which time between 5 and 10% will have developed mild hypertension.
- Around 10% of women with chronic essential hypertension develop superadded pre-eclampsia.
- Although women with chronic hypertension have an increased risk of developing pre-eclampsia, there is no convincing evidence that antihypertensive therapy reduces this risk.
- The main reason for prescribing antihypertensive drugs in pregnancy is to prevent maternal strokes, extra hospital admissions and premature delivery.
- There is little trial evidence, but most authorities recommend antihypertensive drug therapy if the systolic blood pressure is consistently 160 mm Hg or more.
- The β blockers cause some intrauterine growth retardation, so should not be used.
- There is some evidence that the use of angiotensin-blocking drugs in pregnancy is associated with excess fetal anomalies. These agents are contraindicated in pregnancy.
- First-line agents in pregnancy are labetolol or methyldopa.
- Pre-eclampsia is an obstetrical emergency and all patients should be referred for expert obstetrical care.
- Women who had *de novo* hypertension or pre-eclampsia are at increased risk of developing hypertension and cardiovascular disease in later life.
- About 5% of women taking the oral contraceptive develop hypertension, which is usually mild. They are usually older, have high-normal blood pressures or have underlying renal or adrenal diseases causing their hypertension. Occasionally, it is necessary to change to another form of contraception.

Pregnancy

Hypertension in pregnancy: An increasing problem

This chapter is primarily concerned with hypertension in women with child-bearing potential as seen from the point of view of physicians and general practitioners. It is not our remit to cover the obstetrical management of late pregnancy, the delivery of the baby and the immediate puerperium. There is, however, a trend for obstetricians to take an increasing interest in hypertension in women wishing to become pregnant as well as the management of hypertension in early pregnancy.

The hypertensive disorders of pregnancy are getting commoner. This is partly due to the trend for women to delay becoming pregnant in order to pursue their careers. The prevalence of pre-pregnancy hypertension (blood pressure of 140/90 mm Hg or more) rises from around 3% in 20-year olds to about 8% in women in their late 30s. The other major cause of the rising prevalence of hypertension in young women is the rising prevalence of obesity and the increasing reliance on convenience foods with their high salt content.

Blood pressure measurement

The topic of the measurement of bold pressure is covered in detail in Chapter 4. There is an increasing trend to abandon the measurement of blood pressure using a stethoscope. However, if this auscultatory method of measuring pressure is employed, it is important to record the diastolic pressure at the disappearance of the Korotkov sounds (phase 5), not their muffling (phase 4).

Most blood pressures are now measured using semi-automatic oscillometric devices. There have been some questions on the accuracy of some of the manometers in pregnancy. Any possible inaccuracy is, however, much less than the inaccuracy caused by hurried, casual, one-off auscultatory measures in a noisy clinic. If the pressure is 140/90 mm Hg or more at the first reading, at least two further readings should be taken, preferably with a semi-automatic device. There is also an increasing interest in 24-h ambulatory blood pressure (ABPM) in pregnancy.

Maternal and perinatal mortality

Hypertension in pregnancy is the most common cause of maternal death, with a risk of around 10 deaths per million pregnancies in the United Kingdom. Hypertension in pregnancy is also the most common cause of stillbirth and neonatal death. Hypertension occurs in 8–10% of pregnancies and may be the first sign of impending pre-eclampsia – a potentially more serious condition in the second half of pregnancy and in the puerperium.

ABC of Hypertension, Sixth Edition. D. Gareth Beevers, Gregory Y. H. Lip and Eoin O'Brien.

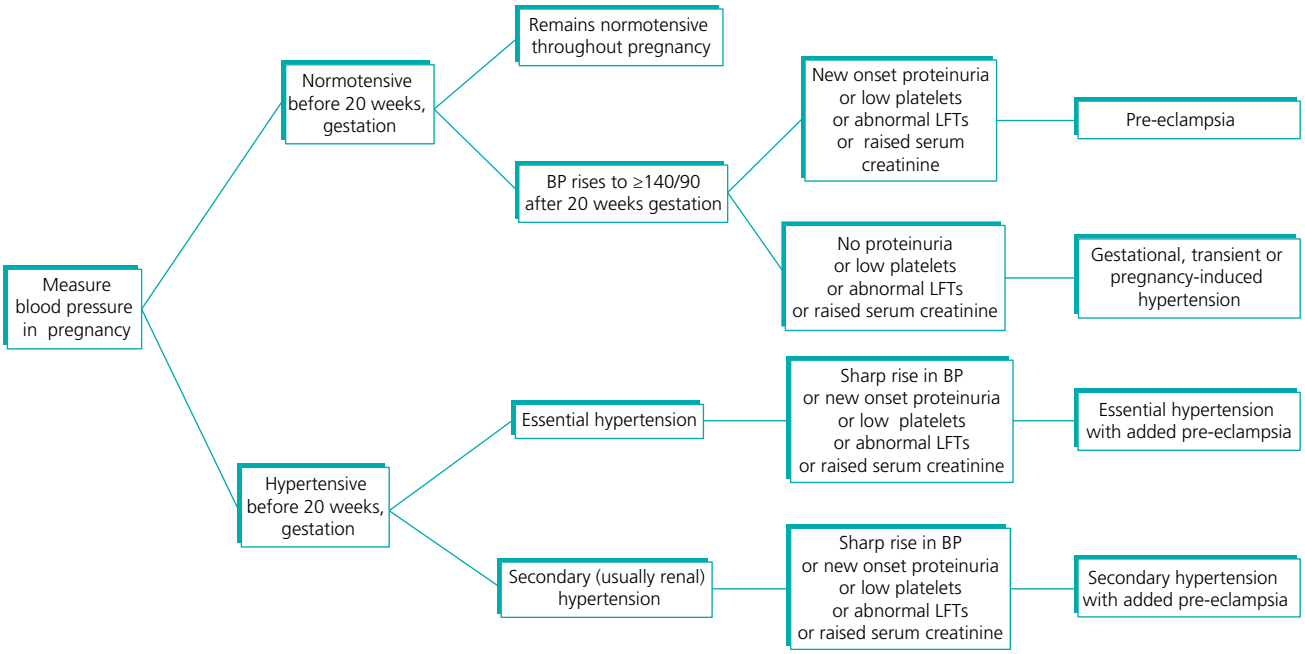


Figure 13.1 The hypertensive disorders of pregnancy.

Recent data from the United States show that pregnancy-induced hypertension was the underlying cause in 16% of maternal deaths. More seriously, pre-eclampsia is responsible for one-sixth of all maternal deaths and a doubling of perinatal mortality. Despite accurate figures on the effects of high blood pressure, its precise causes of hypertension in pregnancy are unknown; eclampsia has been referred to as a 'disease of theories'.

Prevalence of hypertension

In a survey of 6000 women in an unselected obstetric population in Oxford, 0.1% of women had blood pressure ≥160/100 mm Hg before the 20th week of pregnancy. This increased to 3.7% when the maximum antenatal reading at any stage of pregnancy was used. The threshold of ≥140/90 mm Hg was found in 2.0% of women in early pregnancy and 21.5% of women at some stage (usually very near to term). The combined frequency of pre-eclampsia and eclampsia varies between 1 and 6%, depending on parity; the higher figure is seen in first pregnancies. In specialist hypertension obstetric clinics, rates are higher – 11.9 and 16% for women with normal blood pressure and high blood pressure before pregnancy, respectively.

Most women with high blood pressure in early pregnancy (before 20 weeks' gestation) probably have pre-existing or chronic hypertension. This will often be 'essential' hypertension, but clinical evaluation is needed, as secondary (usually renal hypertension) may present for the first time in pregnancy. Most women with high blood pressure in late pregnancy have pregnancy-induced hypertension or pre-eclampsia, which complicate chronic underlying hypertension. Unfortunately, many, usually younger women have never had their blood pressure measured before becoming pregnant and may not attend for antenatal care until after 20 weeks gestation. If they are found to have raised pressures, it is difficult to be certain whether or not they have chronic hypertension or have gestational hypertension.

In the developed world, perinatal mortality is now approaching 10 per 1000 women, and just under half of these deaths are the result of high blood pressure. Furthermore maternal mortality is about 50 deaths per million women and about 20% of these deaths can be attributed to all hypertensive diseases combined. In many cases of death as a result of eclampsia or pre-eclampsia (72% in one series), the care (diagnosis and management) was considered to have been substandard, with half of patients who died of eclampsia having had convulsions despite being admitted to obstetric wards (Figure 13.1).

Hypertensive syndromes in pregnancy

Several attempts have been made at classifying hypertension in pregnancy. None, however, is entirely satisfactory (Table 13.1).

The Working Group of the American National Heart, Lung and Blood Institute classifies hypertension in pregnancy as:

- Chronic hypertension
- Pre-eclampsia
- Pre-eclampsia superimposed on chronic hypertension
- Gestational hypertension.

Gestational hypertension becomes transient hypertension of pregnancy if pre-eclampsia is not present at the time of delivery and blood pressure returns to normal by 12 weeks after birth and chronic hypertension if high levels persist.

There have been a great many attempts to define standardized criteria for the hypertensive syndromes in pregnancy. It has now become clear that gestational or pregnancy-induced hypertension (PIH) is not quite the innocent condition it was once thought to be. The peri-natal mortality in women with PIH is lower than in women with overt pre-eclampsia but is not as low as in women with persistently normal blood pressure. It is possible, therefore, that PIH is simply a mild form of pre-eclampsia. The main problem is pragmatic; if a woman develops *de novo* hypertension in

Table 13.1 Diagnostic criteria for the hypertensive syndromes in pregnancy

Pre-eclampsia Diagnosed on the basis of hypertension with a low platelet count or abnormal liver function tests. If these investigations are not available, the presence of proteinuria may be diagnostic. Ankle swelling is common in late pregnancy, not complicated by pre-eclampsia, and therefore is no longer considered to be a useful diagnostic feature.
Gestational and pregnancy-induced hypertension (PIH) Blood pressure >140 mm Hg systolic blood pressure or >90 mm Hg diastolic blood pressure after 20 weeks in a woman who was normotensive before 20 weeks' gestation Hypertension should be confirmed by two separate measurements
Proteinuria 300 mg/l protein or 30 mg/mmol creatinine in a random specimen or total protein excretion of 300 mg/24 h. This is no longer considered to be a reliable marker for pre-eclampsia as false positive results can occur if the specimen is not clean catch or there has been a recent urinary tract infection. Proteinuria is present in most chronic renal diseases
Chronic hypertension Blood pressure 140/90 mm Hg or more before 20th week of pregnancy or hypertension in late pregnancy, persisting 6 weeks after delivery. Some of these patients have underlying (usually renal) causes of their hypertension.
Pre-eclampsia superimposed on chronic hypertension Regarded as highly likely in women with hypertension alone who develop a low platelet count and/or abnormal liver function tests or new-onset proteinuria or in women with pre-existing hypertension and proteinuria who have sudden increases in blood pressure or proteinuria, thrombocytopenia or increases in hepatocellular enzymes

Table 13.2 Problems with classification of hypertensive disorders of pregnancy

Blood pressure is not measured before pregnancy in many women, and some may have had previous undiagnosed hypertension.
Blood pressure tends to settle in mid-pregnancy.
Differentiation between mild pre-eclampsia and less ominous rises in blood pressure in late pregnancy is difficult. The differentiation between PIH and pre-eclampsia can often only be decided after the pregnancy is over.
Whether increases in blood pressure in late pregnancy may proceed rapidly to severe pre-eclampsia cannot be predicted.
Blood pressure may rise *de novo* after delivery of the baby in a syndrome similar to pre-eclampsia.
Many women are opting for later pregnancies and may have essential hypertension.
Ambulatory blood pressure monitoring is being used increasingly for the various forms of hypertension in pregnancy.

late pregnancy but has no proteinuria, she will be classified as having gestational hypertension. If a week later she is found to have developed proteinuria, the diagnosis will be changed to pre-eclampsia. It is not possible to be sure whether a patient had gestational hypertension rather than pre-eclampsia until well into the puerperium (Table 13.2).

There is the relatively new recognised syndrome of post-partum pre-eclampsia, where the blood pressure rises after delivery and proteinuria appears for the first time.

Pre-Existing Hypertension (Essential Hypertension)

The most benign category is pre-existing mild essential hypertension that is present before the 20th week of pregnancy, when the mother is assumed to have had pre-existing hypertension, although often no data are available. Many of these patients are overweight and are consuming a high salt diet. In these patients, blood pressure follows the normal pattern of pregnancy – it may fall during the first trimester and then increase again later in the pregnancy. This long-term hypertension is not confined to or caused by pregnancy, but it may be noted for the first time during pregnancy, typically towards the end. There is, however, an increased risk of developing super-added pre-eclampsia.

Pre-Existing Hypertension (Secondary Hypertension)

Most women with secondary hypertension have an underlying renal disease (pyelonephritis, glomerulonephritis, reflux nephropathy). Older women with diabetes mellitus may have diabetic nephrosclerosis. Proteinuria or microproteinuria is usually present. Very rarely, young women may have renal artery stenosis due to fibromuscular dysplasia of the renal and other abdominal arteries.

Adrenal causes of hypertension are rare at this age but episodic or very variable blood pressure suggests the diagnosis of phaeochromocytoma. Hypokalaemia not due to diuretics suggests a diagnosis of aldosterone excess.

Aortic coarctation is a very rare cause of hypertension, which is classically seen in children or young people. All women of child-bearing age should have their blood pressure measured in the legs as well as the arms using a standard semi-automatic manometer. In the leg, the cuff is applied round the calf whilst the patient is lying flat.

Pregnancy Induced Hypertension

Pregnancy-induced hypertension develops after the 20th week of pregnancy and usually resolves within 10 days of delivery. This syndrome is common, occurring in up to 25% of first pregnancies, although it is less common (about 10%) in subsequent pregnancies. Some women who develop hypertension de novo early in the second half of pregnancy, however, are likely to progress to pre-eclampsia, with the development of proteinuria, thrombocytopenia and oedema and the need for early delivery.

For diagnosis of pregnancy-induced hypertension to be made, the blood pressure must be documented to be normal before and after pregnancy. The International Society for the Study of Hypertension

Table 13.3 Birth weight and ponderal index in 703 consecutive primiparous women delivered at City Hospital, Birmingham. There were no perinatal deaths

	Normal	Pregnancy-induced hypertension	Pre-eclampsia	Chronic hypertension
No (%) of women	625 (88.9)	55 (7.8)	12 (1.7)	11 (1.6)
Age (years)	23	25	23	28
Booking blood pressure (mm Hg)	107/64	114/68	112/66	131/91
Weight (kg)	3.17	3.07	2.91	2.88
Ponderal index (kg/m^2)	24.6	23.1	23.8	23.3

Source: Data from Perry, I.J. (1994) *Gynaecology*, 101, 587–591.
*Adjusted for gestational age at delivery.

in Pregnancy defines pregnancy-induced hypertension as a single diastolic blood pressure (phase V) of 110 mm Hg or two readings of 90 mm Hg at least 4 h apart after the 20th week of pregnancy. The National High Blood Pressure Education Program of the United States defines pregnancy-induced hypertension as an increase >15 mm Hg in diastolic blood pressure or >30 mm Hg systolic blood pressure compared with readings taken in early pregnancy.

Pregnancy-induced or gestational hypertension is not an entirely innocent condition. In a study of 703 consecutive pregnancies in primiparous women, those with PIH had smaller babies than normotensive women, although they were larger than those with pre-eclampsia (Table 13.3)

Pre-Eclampsia

Pre-eclampsia is diagnosed with an increase in blood pressure >15 mm Hg diastolic or >30 mm Hg systolic from early pregnancy or a diastolic blood pressure of >90 mm Hg on two occasions 4 h apart or >110 mm Hg on one occasion and proteinuria (proteinuria of 1+ is an indication for referral and >300 mg/24 h is the criterion for diagnosis). About 30% of eclamptic convulsions occur in the absence of high blood pressure or proteinuria. Women with pre-eclampsia generally have no symptoms and can be detected only by routine screening. The most frequent symptoms are headache, visual disturbance (often 'flashing lights'), vomiting, epigastric pain and oedema. Women rarely present with a convulsion, but a first seizure in the second half of pregnancy with no other known cause is highly suggestive of eclampsia.

Pre-eclampsia is less common than pregnancy-induced hypertension, occurring in about 5% of first pregnancies. Risk factors for pre-eclampsia include first pregnancy, change of partner, previous pre-eclampsia (particularly if it had developed early in the second half of pregnancy), family history of pre-eclampsia, idiopathic hypertension, chronic renal disease, diabetes, systemic lupus erythematosus, multiple pregnancy and obesity (Figure 13.2). Although the prevalence falls in subsequent pregnancies by the same father, pregnancies by different fathers are said to have the same rate as in primigravidas.

Pre-eclampsia is also more common in women with low socio-economic status. The incidence of pre-eclampsia is increasing with

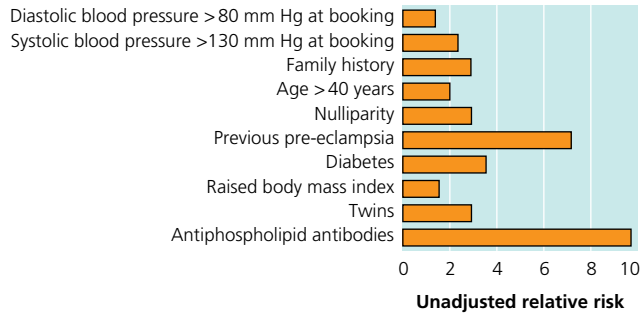


Figure 13.2 Risk factors for pre-eclampsia: systematic review of controlled studies published between 1996 and 2002. Source: Data from Duckitt, K. (2005) *British Medical Journal*, 330, 565–567.

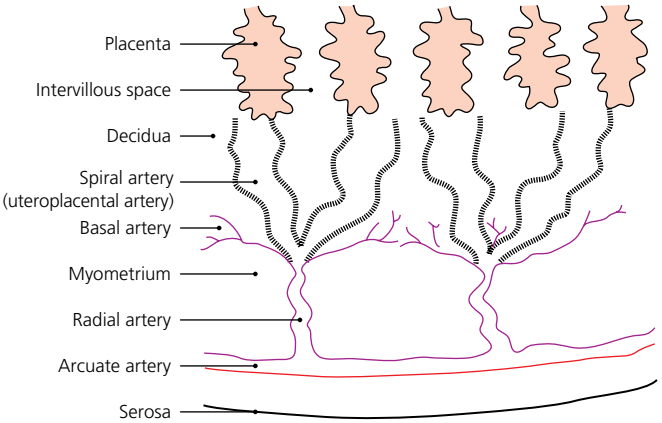


Figure 13.3 The normal process of demuscularisation of the uterine spiral arteries so that they respond less to vasoconstrictor agents and effectively become vein-like conduits. Source: Reproduced with permission from Gerretsen, G., *et al*. (1981) *British Journal of Obstetrics and Gynaecology*, 88, 876–881. © John Wiley & Sons.

advancing maternal age, but, paradoxically, the incidence is high in young teenage mothers. In addition, pre-eclampsia is associated with hydatiform mole and rhesus isoimmunisation.

The origins of pre-eclampsia relate to abnormalities of implantation of the placenta in the first trimester. Failure to demuscularise the utero-placental arteries leads to placental and fetal ischaemia in severe cases and eventually to placental infarctions (Figures 13.3 and 13.4). The fetus may have intrauterine growth retardation as it becomes hypoxic and ischaemic, and it may die. The circulating renin-angiotensin system is less activated than in normal pregnancies and, although disturbances of other vasoactive systems, such as angiogenic factors (vascular endothelial growth factor and its receptor, flt-1), the kallikrein-kinin system, and endothelin occur, the full importance of all of these changes is not understood fully. Although pre-eclampsia has its origins in the first half of pregnancy, it may not become clinically evident until 30 weeks gestation.

Pre-eclampsia occurring early in the second half of pregnancy carries a poor prognosis. By contrast, mild pre-eclampsia developing after 37 weeks gestation does not cause such concern and is best treated by delivery of the baby. However, pre-eclampsia does rank as an obstetric emergency requiring immediate

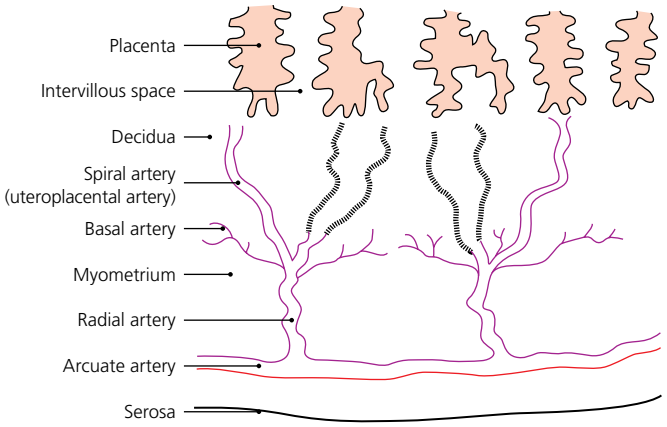


Figure 13.4 Failure of demuscularisation of some or all of the uterine spiral arteries to become wider utero-placental arteries. Source: Reproduced with permission from Gerretsen, G., *et al*. (1981) *British Journal of Obstetrics and Gynaecology*, 88, 876–881. © John Wiley & Sons.

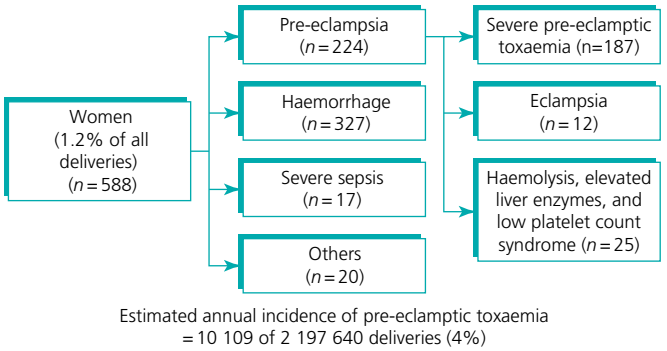


Figure 13.5 The causes of severe obstetric morbidity. Source: Data from Waterstone, M., *et al*. (2001) *British Medical Journal*, 322, 1089–1093.

hospital admission. The outcome of pre-eclampsia in a survey from London is shown in Figure 13.5.

Pre-Eclampsia Complicating Pre-Existing Hypertension

Around 30% of women with chronic pre-existing hypertension develop super-added pre-eclampsia. This may be characterised by a sharp rise in blood pressure but this may not be evident if the patient is already receiving antihypertensive medication. A more useful diagnostic test is the development of new-onset proteinuria. New-onset thrombocytopenia may also occur.

Eclampsia

Full-blown eclampsia is an obstetric emergency that has a very high risk of maternal and fetal mortality. In addition to hypertension and proteinuria, often gross oedema is present. The more serious complications include the HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count), cerebral oedema with convulsions, renal failure, pulmonary oedema, and disseminated intravascular coagulation. Fortunately, this condition is rare, occurring in 1 in 500 pregnancies. Usually, overt eclampsia is a consequence of prior pre-eclampsia but it can occur de novo or even after the baby has been delivered.

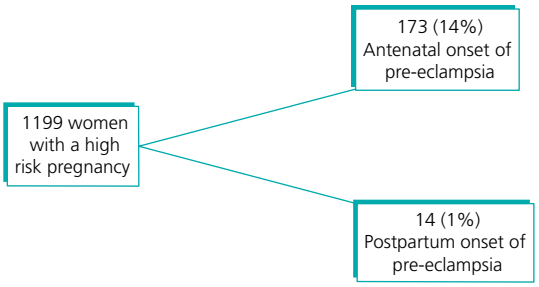


Figure 13.6 The frequency of ante-natal and post-natal pre-eclampsia amongst 1199 high-risk pregnancies. Source: Data from Poston, L., *et al*. (2006) *Lancet*, 367, 1145–1154.

Post-Partum Pre-Eclampsia

This condition has until recently been under-recognised. Women may go through an entirely normal pregnancy but then develop a sustained rise in blood pressure in the early puerperium (Figure 13.6). The pathophysiological mechanisms of this condition are uncertain. Eclamptic fits may rarely be seen.

The Investigation of the Hypertensive Syndromes in Late Pregnancy

All women with hypertension in late pregnancy need detailed assessment. Many need to be admitted to the ante-natal ward for frequent blood pressure measurement pending the result of the laboratory investigations (Table 13.4).

Management of hypertension

Clinical management of hypertension in pregnancy aims to:

- Protect the mother from the effects of high blood pressure
- Prevent progression of the disease and occurrence of eclamptic convulsions
- Minimise risks to the fetus
- Deliver the fetus when the risk to the mother or fetus, if the pregnancy continues, outweighs the risks of delivery and prematurity.

There is no convincing evidence that strict bed rest conveys any benefits in the management of the hypertensive disorders of pregnancy. In theory, bed rest might increase the risk of venous thromboembolism. However, many women with hypertension in late pregnancy do need admission to the ante-natal ward for assessment and regular blood pressure checks.

There is also no convincing evidence that antihypertensive drug therapy delays or ameliorates the development or severity of pre-eclampsia (Figure 13.7). Antihypertensive drugs are therefore only prescribed to prevent maternal morbidity or mortality particularly from strokes. However, during their child bearing years, most women are at very low cardiovascular risk, so the treatment of mild hypertension conveys little value. It is probable that antihypertensive drugs are over-prescribed in pregnancy.

A meta-analysis of trials of antihypertensive drug therapy for chronic hypertension in pregnancy suggests that the main benefits may be some reduction in the risk of progression from mild to severe hypertension and fewer hospital admissions (Figure 13.8). Treatment certainly should be started if levels of blood pressure exceed 150–160 mm Hg systolic or 100–110 mm Hg diastolic.

Table 13.4 Laboratory investigations for hypertension in late pregnancy (Please delete the end periods given in the first two columns)

Investigation	Importance	Implications
Dip-stick test for proteinuria.	Performed daily.	Exclude prior proteinuria and urinary tract infection.
24 h urine protein.	If dip-stick test in positive.	Exclude prior proteinuria.
Full blood count.	Will have been performed in early pregnancy.	Mild anaemia is common in pregnancy.
Platelet count.	Mandatory.	New-onset thrombocytopenia strongly suggests pre-eclampsia.
Serum creatinine.	Mandatory.	Serum creatinine should be below 70 µmol/l in late pregnancy. Higher levels suggest renal disease.
Serum urea.	Mandatory.	Serum urea inappropriately raised compared with creatinine suggests dehydration/intravascular volume depletion.
Liver function tests.	Mandatory.	Raised serum aspartate occurs in HELLP syndrome in severe pre-eclampsia Aspartate also raised in non-alcoholic fatty liver disease (NAFLD).
Serum uric acid.	No longer recommended.	May be raised in severe pre-eclampsia.

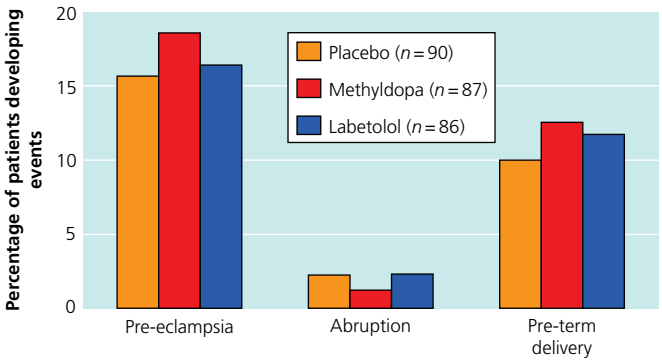


Figure 13.7 Results of a randomised placebo-controlled trial of the treatment of mild chronic hypertension in early pregnancy. Source: Data from Sibai, B.M., *et al*. (1990) *American Journal of Obstetrics and Gynecology;* 162: 960–966.

Similarly, the use of antihypertensive drugs in late pregnancy is mainly of benefit to the mother, with prevention of progression to severer grades of hypertension and importantly the reduction of the number of admissions to hospital (Figure 13.9). There was however a trend for a reduction in the development of proteinuria.

The ultimate treatment of pregnancy-induced hypertension and pre-eclampsia, as well as eclampsia, is delivery – certainly when the fetus is mature enough for the neonatal care facilities available. This option is needed in pregnant women with severe, persisting hypertension, in association with rapid weight gain, decreased creatinine clearance, significant proteinuria, the HELLP syndrome, evidence of fetal growth retardation, or the development of severe headache, papilloedema, hyperreflexia or right upper quadrant (hepatic) pain. In women with milder grades of pre-eclampsia, elective or induced delivery of the fetus before 37 weeks gestation is associated with adverse outcomes, so obstetricians tend to make

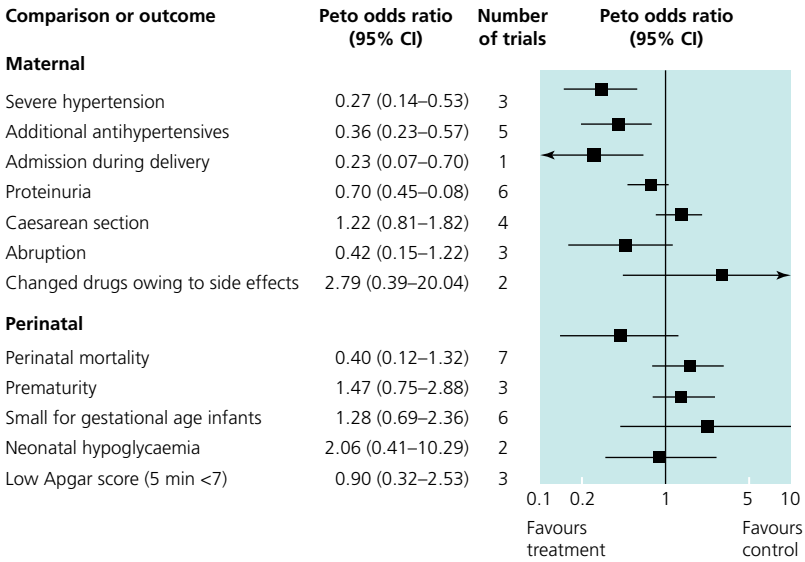


Figure 13.8 Results of a meta-analysis of the trials of antihypertensive drug therapy for mild chronic hypertension in early pregnancy. Source: Adapted by permission from Magee, L.A., *et al*. (1999) *British Medical Journal*, 318, 1332–1336. © BMJ Publishing Group Limited.

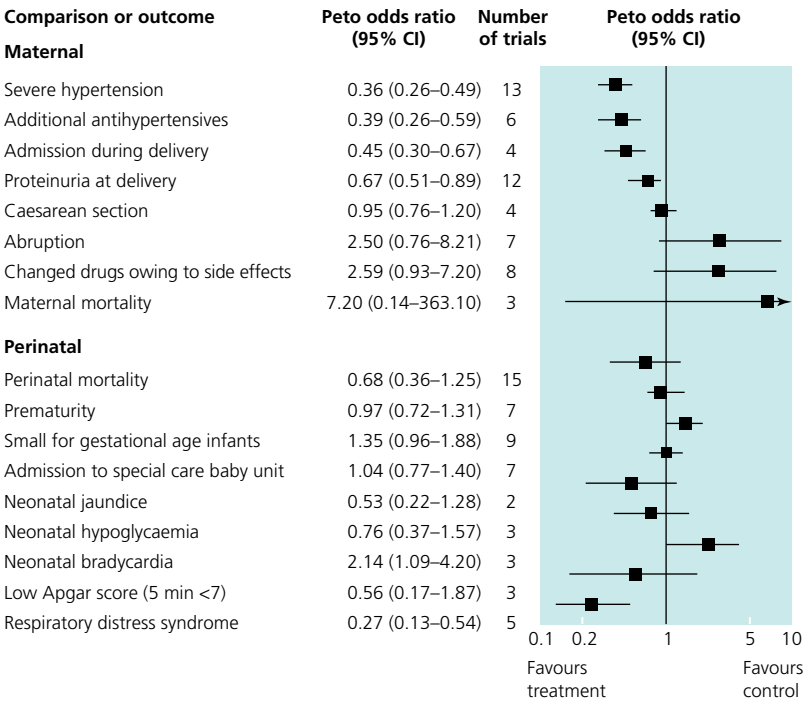


Figure 13.9 Results of a meta-analysis of the trials of antihypertensive drug therapy for hypertension in late pregnancy, including pregnancy-induced hypertension and mild pre-eclampsia. Source: Adapted by permission from Magee, L.A., *et al*. (1999) *British Medical Journal*, 318, 1332–1336. © BMJ Publishing Group Limited.

efforts to delay delivery until this stage if the health of the mother and fetus permits this.

Post-partum blood pressure should continue to be monitored and where necessary treated with antihypertensive drugs. Eclamptic seizures can develop up to about 10 days after delivery, particularly if the blood pressure is uncontrolled. In addition, blood pressure can rise de novo in the puerperium, so careful monitoring remains necessary even after mother and baby have been discharged from hospital.

Non-Pharmacological Blood Pressure Reduction

Obesity in pregnancy can be associated with chronic hypertension, pregnancy-induced hypertension and pre-eclampsia. Mothers should be encouraged to avoid excessive weight gain in pregnancy, but they should not be advised to go on strict diets because of a detrimental effect on birth weight. There is little information on the role of salt intake in the hypertensive disorders of pregnancy. Strict salt restriction should be avoided as this might affect fetal nutrition. All pregnant mothers should be advised to follow a healthy lifestyle, avoiding obesity, fatty foods and very salty foods and snacks. No alcohol should be consumed and active and passive smoking should be avoided.

Aspirin

Low doses of aspirin were previously advocated to prevent pre-eclampsia, although more recent evidence from trials has some inconsistencies because of the heterogeneous nature of the studies. One recent systematic review suggested a small protective effect (Table 13.5). For example, early use of aspirin (150 mg/day) prevented fetal growth retardation and maternal proteinuria in women with fetal growth retardation, fetal death or abruptio placentae in at least one previous pregnancy. In contrast, the Italian study of aspirin in pregnancy found that low doses of aspirin (50 mg/day) did not affect the clinical course or outcome of pregnancy. The large collaborative low-dose aspirin study in pregnancy found that aspirin at a dose of 60 mg/day was associated with a non-significant reduction in the incidence of proteinuric pre-eclampsia, intrauterine growth retardation, stillbirth or neonatal death.

Table 13.5 The effects of low-dose aspirin (60 mg) in the prevention of pre-eclampsia none of these trends were statistically significant

Condition causing risk	Number of women	No (%) of women who developed pre-eclampsia	
		Aspirin	Placebo
Pregestational insulin-treated diabetes	471	18	22
Chronic essential hypertension	774	26	25
Multifetal gestation	688	12	16
Previous pre-eclampsia	606	17	19
Total	**2539**	**18**	**20**

Source: Data from Caritis, S., *et al*. (1998) *New England Journal of Medicine*, 338, 701–705.
No differences in perinatal mortality, preterm birth or infants small for gestational age.

The Australasian Society for the Study of Hypertension in Pregnancy recommends the use of prophylactic low doses of aspirin from early pregnancy in the following groups:

- Women with prior fetal loss after the first trimester, with placental insufficiency

- Women with severe fetal growth retardation in a preceding pregnancy either due to pre-eclampsia or unexplained causes
- Women with severe early-onset pre-eclampsia in a previous pregnancy requiring delivery at or before 32 weeks gestation.

Aspirin is not routinely indicated for healthy nulliparous women, women with mild chronic hypertension and women with established pre-eclampsia

Pre-Eclampsia

Pre-eclampsia indicates urgent transfer to a specialised maternity unit with an adequate special care baby unit, together with antihypertensive and anticonvulsant treatment. Diazepam and magnesium sulphate help prevent fits and reduce levels of blood pressure.

Box 13.1 **Antihypertensive Drug therapy in pregnancy**

Labetolol

- This is used widely as a first- and second-line agent in all stages of pregnancy. There are no reports of adverse outcomes to the fetus and no evidence of penetration into breast milk. The normal dose is 50–400 mg twice daily. If the blood pressure remains uncontrolled on the higher dose, it is better to add in another agent rather than further increases in dosage.
- In small studies in women with severe hypertension, labetolol by intravenous infusion (20–160 mg/h) or intermittent bolus (50–100 mg at 20–30 minute intervals) reduced blood pressure smoothly, although hypotension, oliguria and bradycardia have been reported in neonates when fetal distress or hypoxia was also present.

Methyldopa

- This was the antihypertensive drug of choice during pregnancy, but there is some evidence of penetration into breast milk. Whilst high dose of methyldopa can cause depression and lethargy, there are no reports of it causing post-natal depression. The normal dose is 250 mg twice daily, increasing to 500 mg three times daily.
- Calcium channel blockers (especially long-acting formulations of nifedipine)
- Nifedipine is used as a second- or third-line agent during late pregnancy and is particularly useful in patients of African origin. The usual dose of nifedipine is 30–60 mg daily

Diuretics

- Diuretics are not recommended to treat hypertension in pregnancy, as they theoretically may cause a reduction in circulating volume and uteroplacental blood flow. They may also impair lactation.

α Blockers

- These are probably safe, although doxazosin and terazosin can exacerbate urinary incontinence in women. There is no published evidence of the use of these agents in pregnancy.

β Blockers

- Increasing evidence suggests that atenolol and possibly labetolol cause intrauterine growth retardation, particularly if taken in early pregnancy. Their use is declining rapidly.
- Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs).
- These drugs are contraindicated absolutely in pregnancy because of a possible association with congenital abnormalities, growth retardation, intrauterine death, oligohydramnios and fetal anuria.

The value of magnesium sulphate in the management of eclampsia is increasingly well established. Magnesium sulphate has the benefits of anticonvulsant and antihypertensive properties and is given intravenously or intramuscularly. It works quickly and has a nonsedative effect and wide safety margin. If toxicity occurs, an antidote exists in the form of calcium gluconate.

Severe Pre-Eclampsia/Eclampsia

Women with severe hypertension should be referred to an obstetrical intensive care unit with an associated neonatal special care unit. The Urgency of treatment depends on the severity of the disease and the stage of pregnancy (Table 13.6).

As stated earlier this chapter

The first line of management is to control the seizures. Intravenous diazepam, usually 20–40 mg, is used. Occasionally, phenytoin is used to prevent recurrence of fits. Magnesium sulphate is a popular alternative anticonvulsant for use in women with eclampsia.

Intravenous hydralazine is a useful antihypertensive drug of first choice. It is given as a 5 mg bolus at intervals of 20 min or as an infusion of 25 mg in 500 ml of Hartman's solution, with the dose titrated against the woman's blood pressure. An alternative is intravenous labetolol. Patients should be admitted to well-equipped and staffed obstetric units with adequate facilities for neonatal care.

If the woman is in labour, or induction is considered, an epidural anaesthetic may be helpful – to reduce the blood pressure and the tendency to fit by reducing the pain of uterine contractions. The ultimate treatment of eclampsia, however, is urgent delivery of the baby.

Long-Term Sequelae of Pre-Eclampsia

Women who have had pre-eclampsia or eclampsia are at significantly greater risk of a recurrence in future pregnancies compared with women with no such history (Table 13.7). There is evidence that this occurs more commonly if the pregnancy is by a new father. Special care is necessary in women who have the risk factors shown in Figure 13.2. There is also evidence that these women are at greater risk of developing future chronic 'essential' hypertension.

In addition, there is now good evidence from long-term follow-up studies that women who have had pre-eclampsia are at greater risk of developing coronary heart disease and strokes (Figure 13.10). These findings have implications for the assessment of cardiovascular risk in women of all ages, both in primary and secondary care. A detailed obstetrical history should now be a mandatory component of screening for cardiovascular disease.

Oral Contraceptive Pill

Combined oral contraceptives increase blood pressure by an average of 5/3 mm Hg. Nonetheless, severe hypertension may be induced in a small number of women (1%), many of whom may have above-average blood pressure in the first place. There is some evidence that women who have a history of hypertension in pregnancy are more likely to develop hypertension when taking the oral contraceptive. Blood pressure may increase rapidly many months

Table 13.6 The management of severe pre-eclampsia

	20 weeks (+0 days) – fetal viability	Fetal viability – 29 weeks (+6 days)	30 weeks (+0 days) to 33 weeks (+6 days)	34 weeks (+0 days) to 36 weeks (+6 days)	37 weeks (+0 days) or more
Perinatal prognosis on admission with pre-eclampsia: cohort data of 2128 women admitted to tertiary units with pre-eclampsia	18–50% survival; 2–45% intact survival	60–95% survival; 15–90% intact survival	98% survival; 88–96% intact survival	>99% survival; 96% intact survival	>99% survival; >96% intact survival
Increase in maternal risks (compared with normotensive pregnancy)	Substantial	Substantial	Substantial	Moderate	Minimum
Consider in-utero transfer to tertiary centre with NICU	Optional; centre should be competent with midtrimester termination of pregnancy or expectant management	Yes, if mother stable for transfer	Ideally, but perinatal outcomes might be unchanged if transfer post partum	Optional, but centre should be competent with expectant management if considered as management option	Optional; in case of severe disease
Expectant management	No; although in very few patients at 22–23 weeks' gestation clinician might attempt sufficient pregnancy prolongation to attain perinatal survival	Optional; could be considered in view of possible perinatal gains	Optional; could be considered in view of possible perinatal gains	Optional; could be considered, but in severe disease balance towards delivery	No
Betamethasone for fetal lung maturation	Optional; dependent on gestational age	Yes	Yes	No	No
Suggested route of delivery	Vaginal (misoprostol induction of labour)[85]	Probable caesarean section, unless intrauterine fetal death	Vaginal, depending on fetal and cervical status	Vaginal, depending on fetal and cervical status	Vaginal, depending on fetal and cervical status

Source: Reproduced with permission from Steegers, E.A., *et al*. (2010) The *Lancet*, 376, 631–644. © Elsevier.
NICU, neonatal intensive care unit.
*As defined locally (usually between 23 weeks' (+0 days) and 24 weeks' (+6 days) gestation).
†Unpublised data from PIERS.
‡Chance of living to discharge from a NICU without major morbidity (≥ grade 3 intraventricular haemorrhage, stage 3 or 4 retinopathy of prematurity, necrotising enterocolitis, and chronic lung disease).

Table 13.7 Pre-eclampsia in primigravidae; risk of pre-eclampsia in later pregnancies and later chronic hypertension

Variable	Pre-eclampsia in first pregnancy	Pregnancy with normal blood pressure
No of women	406	409
Pre-eclampsia in second (%) pregnancy	46.8	7.6
Later pre-eclampsia (%)	20.7	7.7
Chronic hypertension (%)	14.8	5.6

Source: Data from Sibai, B.M., *et al*. (1986) *American Journal of Obstetrics and Gynecology*, 155, 1011–1016.
*$p < 0.001$.
**$p < 0.0001$.

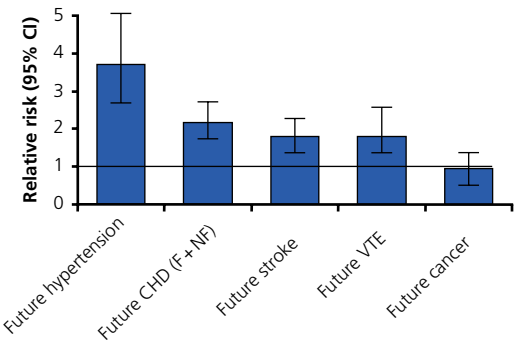


Figure 13.10 The relative risk of future chronic hypertension, cardiovascular disease and stroke in women with a past history of pre-eclampsia; a meta-analysis of 25 follow-up studies. Source: Data from Bellamy, L., *et al*. (2007) *British Medical Journal*, 335, 974–977.

or years after initial use of a combined oral contraceptive pill. Combined oral contraceptives are also associated with a higher risk of stroke and myocardial infarction. Progestogen-only contraceptive pills do not increase blood pressure and are therefore recommended for women with hypertension who want to use oral contraception or those with hypertension induced by the combined oral contraceptive pill.

If a woman is found to have high blood pressure while taking an oral contraceptive pill, alternative methods of contraception should

be considered. If these are unacceptable, it may be necessary to restart a progestogen-only pill, and antihypertensive drugs may be needed. The hazards of an unplanned pregnancy in women are greater than the hazards of a small increase in blood pressure.

Hormone Replacement Therapy

Blood pressure increases with age and after the menopause, and the adjusted increase in blood pressure may be steeper after the menopause. The use of hormone replacement therapy does not cause blood pressure to increase, so it is not contraindicated in women with hypertension. Nonetheless, several large randomised trials have established that 'opposed' hormone replacement therapy (containing oestrogen and progestogen) does not protect from cardiovascular disease or stroke of any type in the context of primary or secondary prevention.

Further Reading

Bramham, K., Nelson-Piercy, C., Brown, M.J. & Chappell, L.C. (2013) Postpartum management of hypertension. *British Medical Journal*, 346, f894.

Brown, M.A. & Buddle, M.L. (1997) What's in a name? Problems with the classification of hypertension in pregnancy. *Journal of Hypertension*, 15, 1049–1054.

Higgins, J.R. & de Swiet, M. (2001) Blood pressure measurement and classification in pregnancy. *The Lancet*, 357, 131–135.

Munjulari, N., Lipman, M., Valentine, A., Hardiman, P. & Maclean, A.B. (2005) Postpartum eclampsia of late onset. *British Medical Journal*, 331, 1070–1071.

National High Blood Pressure Education Working Group on High Blood Pressure in Pregnancy (2000) Report of the national high blood pressure education program working group on high blood pressure in pregnancy. *American Journal of Obstetrics and Gynecology*, 183, S1–S22.

Steegers, E.A., von Dadelszen, Duvekot, J.J. & Pijnenborg, R. (2010) Pre-eclampsia. *The Lancet*, 376, 631–644.

Index

Note: Page numbers in *italics* refer to Figures; those in **bold** refer to Boxes and Tables

ABC of Hypertension, Sixth Edition. D. Gareth Beevers, Gregory Y. H. Lip and Eoin O'Brien.

ABC series

An outstanding collection of resources for everyone in primary care

The *ABC* series contains a wealth of indispensable resources for GPs, GP registrars, junior doctors, doctors in training and all those in primary care

- **Highly illustrated, informative and a practical source of knowledge**
- **An easy-to-use resource, covering the symptoms, investigations, treatment and management of conditions presenting in day-to-day practice and patient support**
- **Full colour photographs and illustrations aid diagnosis and patient understanding of a condition**

For more information on all books in the *ABC* series, including links to further information, references and links to the latest official guidelines, please visit:

www.abcbookseries.com

WILEY-BLACKWELL

BMJ|Books

NEW TITLES

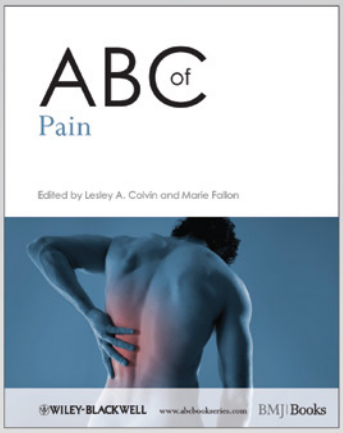
ABC of Pain

Lesley A. Colvin & Marie Fallon
Western General Hospital, Edinburgh; University of Edinburgh

Pain is a common presentation and this brand new title focuses on the pain management issues most often encountered in primary care. *ABC of Pain*:

- Covers all the chronic pain presentations in primary care right through to tertiary and palliative care and includes guidance on pain management in special groups such as pregnancy, children, the elderly and the terminally ill
- Includes new findings on the effectiveness of interventions and the progression to acute pain and appropriate pharmacological management
- Features pain assessment, epidemiology and the evidence base in a truly comprehensive reference
- Provides a global perspective with an international list of expert contributors

JUNE 2012 | 9781405176217 | 128 PAGES | £24.99/US$44.95/€32.90/AU$47.95



ABC of Urology

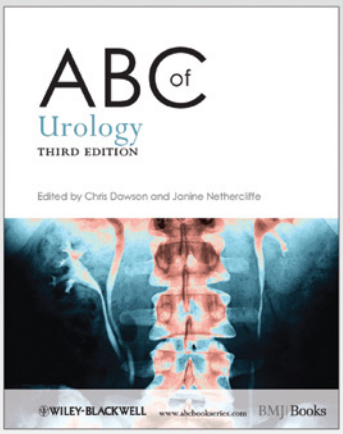
3RD EDITION

Chris Dawson & Janine Nethercliffe
Fitzwilliam Hospital, Peterborough; Edith Cavell Hospital, Peterborough

Urological conditions are common, accounting for up to one third of all surgical admissions to hospital. Outside of hospital care urological problems are a common reason for patients needing to see their GP.

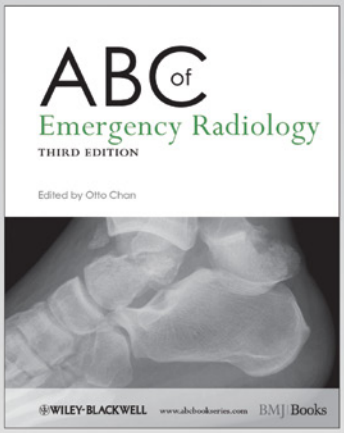
- *ABC of Urology, 3rd Edition* provides a comprehensive overview of urology
- Focuses on the diagnosis and management of the most common urological conditions
- Features 4 additional chapters: improved coverage of renal and testis cancer in separate chapters and new chapters on management of haematuria, laparoscopy, trauma and new urological advances
- Ideal for GPs and trainee GPs, and is useful for junior doctors undergoing surgical training, while medical students and nurses undertaking a urological placement as part of their training programme will find this edition indispensable

MARCH 2012 | 9780470657171 | 88 PAGES | £23.99/US$37.95/€30.90/AU$47.95



For more information on any of these books, please visit the ABC website at **www.abcbookseries.com**

COMING SOON



ABC of Emergency Radiology

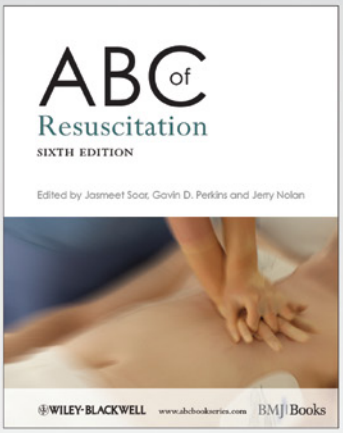
3RD EDITION

Otto Chan
London Independent Hospital

The *ABC of Emergency Radiology, 3rd Edition* an invaluable resource for accident and emergency staff, trainee radiologists, medical students, nurses, radiographers and all medical personnel involved in the immediate care of trauma patients.

- Follows a systematic approach to assessing radiographs
- Each chapter covers a different part of the body, leading through the anatomy for ease of use
- Includes clear explanations and instructions on the appearances of radiological abnormalities with comparison to normal radiographs throughout
- Incorporates over 400 radiographs

JANUARY 2013 | 9780470670934 | 144 PAGES | £29.99/US$48.95/€38.90/AU$57.95



ABC of Resuscitation

6TH EDITION

Jasmeet Soar, Gavin D. Perkins & Jerry Nolan
Southmead Hospital, Bristol; University of Warwick, Coventry; Royal United Hospital, Bath

A practical guide to the latest resuscitation advice for the non-specialist *ABC of Resuscitation, 6th Edition*:

- Covers the core knowledge on the management of patients with cardiopulmonary arrest
- Includes the 2010 European Resuscitation Council Guidelines for Resuscitation
- Edited by specialists responsible for producing the European and UK 2010 resuscitation guidelines

DECEMBER 2012 | 9780470672594| 144 PAGES | £28.99/US$47.95/€37.90/AU$54.95

COMING SOON

ABC of Ear, Nose and Throat

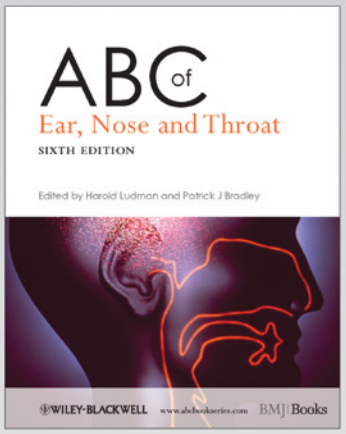
6TH EDITION

Harold S. Ludman & Patrick Bradley
King's College Hospital, London; Queen's Medical Centre, University of Nottingham

This new edition of the established text:

- Provides symptomatic coverage of the most common ear, nose and throat presentations
- Includes additional chapters on tinnitus, nasal discharge, nasal obstruction, facial plastic surgery and airway obstruction and stridor to reflect recent changes in the practice of otolaryngology and new content on thyroid disease, head and neck cancer, rhinoplasty, cosmetic and therapeutic scar
- Has been restructured on a symptom based classification for quick reference
- Incorporates guidance on assessment, treatment and management, and when to refer patients

NOVEMBER 2012 | 9780470671351 | 168 PAGES | £28.99/US$47.95/€37.90/AU$54.95



ABC of Major Trauma

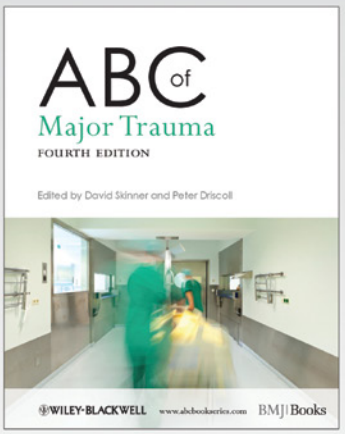
4TH EDITION

David Skinner & Peter Driscoll
John Radcliffe Hospital, Oxford; Hope Hospital, Salford

Prehospital care is a growing area in medicine, and emergency treatments are becoming more sophisticated as the potential to save lives grow. This practical book:

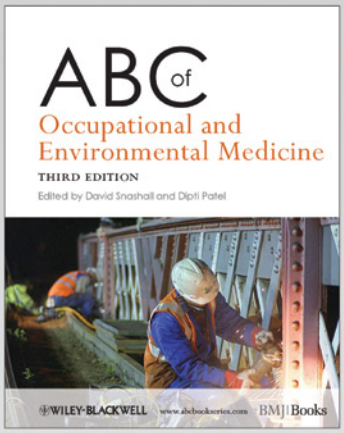
- Is a comprehensive guide to the management of the multiply injured patient during the initial hours after injury
- Includes new chapters on major incidents and nuclear and biological emergencies
- Provides clear and concise guidance with accompanying photographs and diagrams
- Is edited and written by leading UK trauma authorities for everyday use by emergency medicine staff, nurses, hospital doctors, paramedics, and ambulance services

DECEMBER 2012 | 9780727918598 | 224 PAGES | £29.99/US$47.95/€38.90/AU$57.95



For more information on any of these books, please visit the ABC website at **www.abcbookseries.com**

COMING SOON



ABC of Occupational and Environmental Medicine

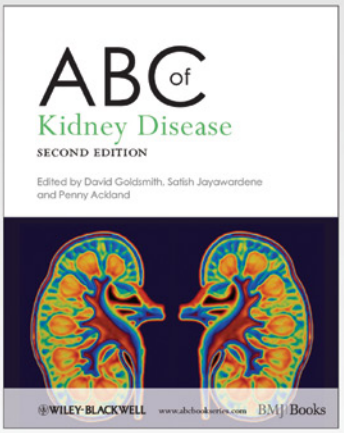
3RD EDITION

David Snashall & Dipti Patel
Guy's & St. Thomas' Hospital, London; Medical Advisory Service for Travellers Abroad (MASTA)

Since the publication of last edition, there have been huge changes in the world of occupational health. It has become firmly a part of international public health, and in Britain there is now a National Director for Work and Health. This fully updated new edition embraces these changes and:

- Provides comprehensive guidance on current occupational and environmental health practice and legislation
- Concentrates on the newer kinds of occupational disease, for example 'RSI', pesticide poisoning and electromagnetic radiation, where exposure and effects are difficult to understand
- Places an emphasis on work, health and well-being, and the public health benefits of work, the value of work, disabled people at work, the aging workforce, and vocational rehabilitation
- Includes chapters on the health effects of climate change and of occupational health and safety in relation to migration and terrorism

NOVEMBER 2012 | 9781444338171 | 168 PAGES | £27.99/US$44.95/€38.90/AU$52.95



ABC of Kidney Disease

2ND EDITION

David Goldsmith, Satish Jayawardene & Penny Ackland
Guy's & St. Thomas' Hospital, London; King's College Hospital, London; Melbourne Grove Medical Practice, London

Nephrology is sometimes considered a complicated and specialized topic and the illustrative ABC format will help GPs quickly and easily assimilate the information needed. *ABC of Kidney Disease, 2nd Edition*:

- Is a practical guide to the most common renal diseases to enable non-renal health care workers to screen, identify, treat and refer renal patients appropriately and to provide the best possible care
- Covers organizational aspects of renal disease management, dialysis and transplantation
- Provides an explanatory glossary of renal terms, guidance on anaemia management and information on drug prescribing and interactions
- Has been fully revised in accordance with new guidelines

OCTOBER 2012 | 9780470672044 | 112 PAGES | £27.99/US$44.95/€35.90/AU$52.95

CURRENT TITLES

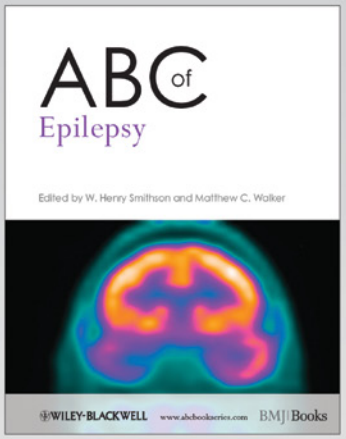
ABC of ABC of Epilepsy

W. Henry Smithson & Matthew C. Walker
University of Sheffield; University College London

In the new, easy to navigate ABC series format *ABC of Epilepsy*:

- Provides a practical guide for general practitioners, and all those working in primary care
- Includes the diagnosis, treatment and management of epilepsy, and for the continued monitoring and long term support
- Covers anti-epileptic drugs and non-drug treatments, as well as self-management and living with epilepsy
- Highly illustrated throughout to clearly present what epilepsy is, its classification, and how to diagnose it

MARCH 2012 | 9781444333985 | 48 PAGES | £19.99/US$33.95/€25.90/AU$37.95



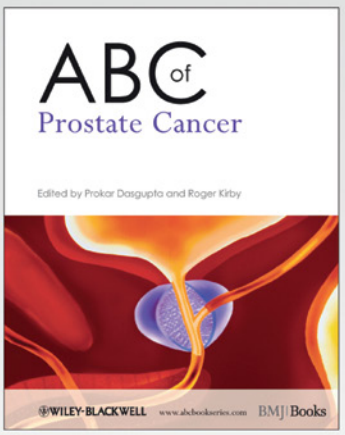
ABC of Prostate Cancer

Prokar Dasgupta & Roger Kirby
Guys & St Thomas' Hospitals, London; The Prostate Centre, London

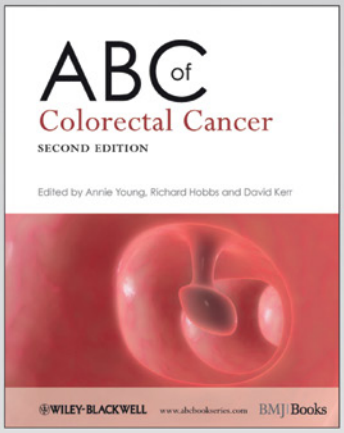
Prostate cancer is the most common cancer in men in the UK and US and the second most common worldwide. *ABC of Prostate Cancer*:

- Provides fully illustrated guidance on the treatment and management of prostate cancer
- Covers the biology, anatomy, and pathology of prostate cancer, screening, and active surveillance and monitoring
- Presents an assessment of treatment options including prostatectomy, bracytherapy, chemotherapy and immunotherapy, along with modern diagnostic tests and an overview of new approaches to prostate cancer
- With an international author team, *ABC of Prostate Cancer* is ideal for GPs, family physicians, specialist nurses, junior doctors, medical students and others working with prostate cancer patients and their families

DECEMBER 2011 | 9781444334371 | 80 PAGES | £22.99/US$35.95/€39.95/AU$44.95



For more information on any of these books, please visit the ABC website at **www.abcbookseries.com**



ABC of Colorectal Cancer

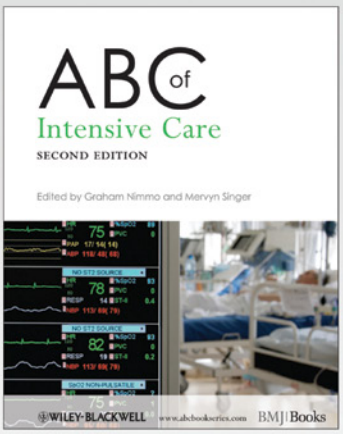
2ND EDITION

Annie Young, Richard Hobbs & David Kerr
University of Warwick; University of Oxford; University of Oxford

Colorectal cancer is the third most common cancer in men and the second most common cancer in women worldwide. The second edition to this practical guide:

- Provides an invaluable guide for the non-specialist on the diagnosis and treatment of colorectal cancer and is ideal for GPs, junior doctors, nurses and allied health professionals
- Covers core knowledge on therapy, management, and supportive care interventions, diagnosis follow up and advanced and innovative treatment and highlights the evidence base throughout
- Includes key information on new drug treatments and the new UK screening program and guidelines
- Maps the "real life" treatment pathway to enhance the resources' practical use

NOVEMBER 2011 | 9781405177634 | 88 PAGES | £19.99/US$30.95/€25.90/AU$37.95



ABC of Intensive Care

2ND EDITION

Graham R. Nimmo & Mervyn Singer
Western General Hospital, Edinburgh; University College London

Intensive care is an increasingly important medical specialty and has a strong multidisciplinary component with a common stem for initial training.

This practical guide to intensive care:

- Provides the core knowledge of intensive care patient management with best practice management in the intensive care unit
- Covers topics from general principles through to critical care outreach and end of life care, key organ system support, monitoring, sepsis, brain-stem death, and nutrition in intensive care and organ donation
- References key evidence, and further reading and resources for comprehensive coverage in each chapter
- Is endorsed by the Intensive Care Society
- Is ideal for junior doctors, medical students and specialist nurses working in an acute hospital setting and for anyone involved in the management and care of intensive care patients

SEPTEMBER 2011 | 9781405178037 | 88 PAGES | £19.99/US$30.95/€25.90/AU$37.95

CURRENT TITLES

ABC of Sexually Transmitted Infections

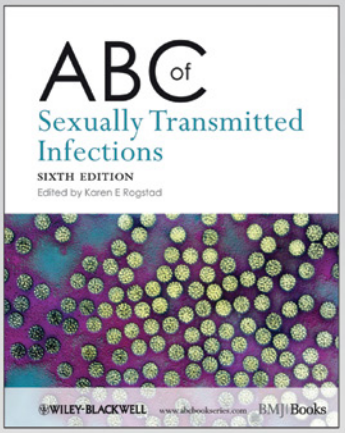
6TH EDITION

Karen E. Rogstad
Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield

With sexually transmitted infections (STIs) a major cause of morbidity and mortality throughout the world, the new edition of *ABC of Sexually Transmitted Infections* is a much-needed introduction and reference guide. This sixth edition:

- Includes the latest guidance on the prevalence, prevention and treatment of STIs, screening programmes and new testing methods
- Features new chapters on service modernization and new care providers, high risk and special needs groups, systemic manifestations, and sexually transmitted infections in resource-poor settings
- Covers contraception in depth and reflects the increasing integration of STI and contraceptive services
- Is ideal for those providing community based STI diagnosis and management such as GPs, primary care physicians, pharmacists and contraceptive service providers. Those in the voluntary sector, junior doctors, medical students, and nurses working in community or specialist services will also find it a valuable resource

APRIL 2011 | 9781405198165 | 168 PAGES | £26.95/US$42.95/€34.90/AU$52.95



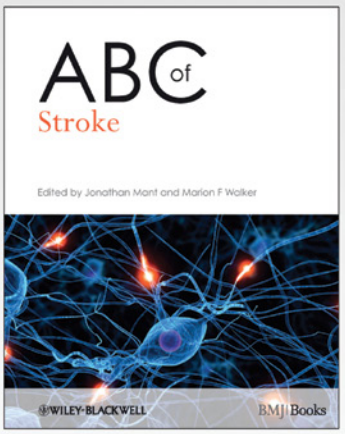
ABC of Stroke

Jonathan Mant & Marion F. Walker
UK Stroke Research Network and Addenbrooke's Hospital, University of Cambridge; UK Stroke Research Network and University of Nottingham

Stroke is the most common cause of adult disability and is of increasing importance within ageing populations. This practical guide to stroke:

- Covers the entire patient journey, from prevention through to long-term support
- Includes primary prevention and management of risk factors for stroke and secondary prevention including pharmaceutical, lifestyle and surgical intervention
- Addresses the general principles of stroke rehabilitation as well as mobility, communication and psychological problems, stroke in younger people and long-term support for stroke survivors and their carers
- Is invaluable to all aspects of stroke for health care professionals and is of particular relevance to GPs, junior doctors, nurses and therapists working with stroke patients and their careers

MARCH 2011 | 9781405167901 | 72 PAGES | £20.95/US$32.95/€26.90/AU$39.95



For more information on any of these books, please visit the ABC website at **www.abcbookseries.com**

WILEY END USER LICENSE AGREEMENT

Go to www.wiley.com/go/eula to access Wiley’s ebook EULA.