# ABC OF HYPERTENSION

Fifth Edition

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# Contents

# Preface

The first edition of the *ABC of Hypertension*, published in 1981, rose out of a series of review articles published in the *British Medical Journal* under the titles of *ABC of blood pressure measurement* and *ABC of blood pressure reduction*. Since that time there have been a great many advances in our understanding of clinical aspects of hypertension that have necessitated regular updating. In particular there have been major improvements in the measurement of blood pressure with increasing awareness of the relative importance of 24 hour ambulatory blood pressure monitoring versus casual office blood pressure readings. In addition, the focus of the management of hypertensive patients has moved to encompass a measure of total cardiovascular risk rather than just the blood pressure. This has been helped by the ready availability of simple risk charts, particularly those published by the British Hypertension Society and the joint British Societies. Along with this there has been an increasing awareness that the height for systolic blood pressure is a better predictor of cardiovascular risk than the diastolic blood pressure and that isolated systolic hypertension, with its high risk, is well worth treating. Even today, however, many clinicians who were originally taught that the diastolic pressure was more important than the systolic are finding this radical change in emphasis to be somewhat startling.

The first edition of the *ABC of Hypertension* was published before the era of angiotensin converting enzyme inhibitors. There is no doubt that these agents, together with the more recently synthesised angiotensin receptor blockers are by far the most tolerable antihypertensive drugs. They have transformed the treatment of diabetic hypertensives and hypertensives with concomitant heart disease or nephropathy. Since the publication of the fourth edition of the *ABC of Hypertension*, we have seen publication of the Losartan Intervention For Endpoint (LIFE) study and the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT). In both of these trials the drugs that block the renin-angiotensin system were found to be superior to previous standard regimes of atenolol with or without a thiazide diuretic. These two trials have heralded the end of the supremacy of $\beta$ blockers in the treatment of uncomplicated hypertension. Again, this will be a radical turnaround for those clinicians who have put their faith in $\beta$ blockers for uncomplicated essential hypertension in the hope that they might be better at preventing first coronary events than other agents.

Thus, since 1980 we have become better at assessing our patients' blood pressure, better at assessing their cardiovascular risk, and we have more effective and more tolerable antihypertensive agents. In previous years a clinician, when faced with a patient where the value of treatment was open to question, might have taken the view "when in doubt, don't treat." Nowadays the same clinician, when faced with a similar patient, is more likely to say "when in doubt, treat." This view, together with the arrival of the statins, means that lives are being saved and people are living longer.

Publication of the LIFE trial and ASCOT brings us to a sort of plateau in the topic of clinical hypertension research. Although there is no doubt that there are many advances to be looked forward to in the topic of the basic cardiovascular sciences, it is unlikely that we will have much more information on clinical care for a few years. Perhaps the biggest problem now is to improve the quality and efficiency of the delivery of the various validated treatments to individual patients. We are acutely aware that this healthcare delivery is mainly the responsibility of the primary healthcare team based in general practice. We hope that this fifth edition of the *ABC of Hypertension* provides sufficient evidence based material to guide clinicians in the correct manner of investigating and managing hypertensive patients while providing pragmatic guidance on good clinical practice that can be applied in any healthcare delivery system. Things have changed so much over the last 25 years that the *ABC of Hypertension* remains necessary to help clinicians manage the most common chronic medical condition world-wide. We hope therefore that this edition will provide useful guidance for clinicians in developing as well as developed countries.

DG Beevers
GYH Lip
E O'Brien

# 1 Prevalence and causes

G Y H Lip, D G Beevers

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. This means that much of the burden of renal disease and cardiovascular disease related to blood pressure can be attributed to blood pressures within the so called "normotensive" or average range for Western populations.

The main concern for doctors 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 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.

**"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. *Br Med Bull* 1971;27:37–42**

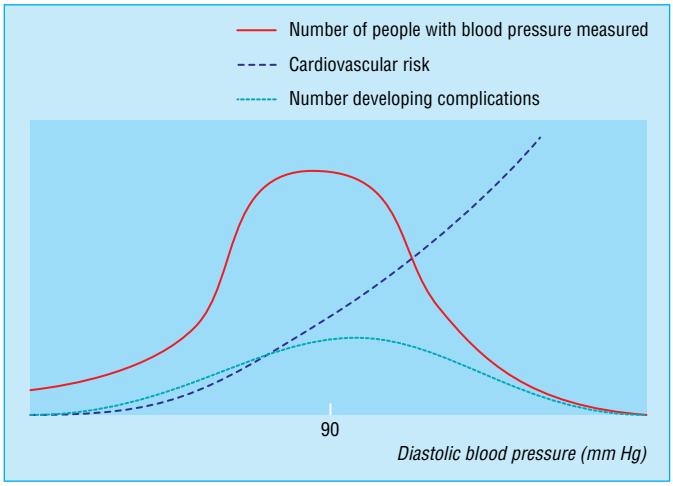
Systolic blood pressure has a strong tendency to increase with advancing age, so the prevalence of hypertension (and its complications) also increases with age. Hypertension thus is as much a disorder of populations as of individual people. Globally, high blood pressure accounts for more deaths than many common conditions and is a major burden of disease.

As hypertension is the most important risk factor for cardiovascular disease, achievement of a universal target systolic blood pressure of 140 mm Hg 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 non-fatal 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.

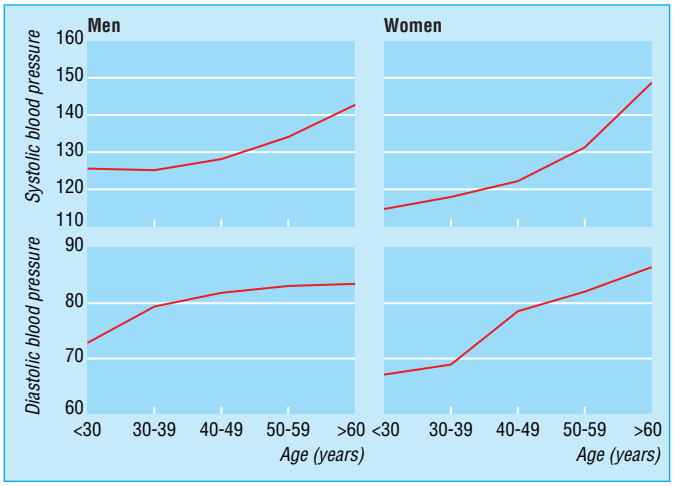
A recently published analysis of pooled data from different regions of the world estimated the overall prevalence and absolute burden of hypertension in 2000 and the global burden in 2025. Overall, 26.4% of the adult population in 2000 had hypertension and 29.2% were projected to have this condition 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 thus is 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.

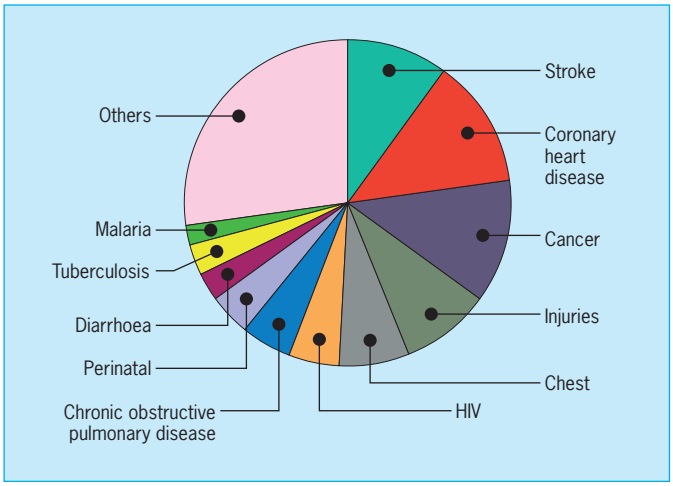
Studies have investigated Japanese people migrating from Japan to the west coast of America. In Japan, high blood




Hypertension: a disease of quantity not quality




Birmingham Factory Screening Project (figure excludes data from 165 patients on drugs that lower blood pressure). Adapted from Lane D, et al. *J Human Hypertens* 2002;16:267–73




Worldwide causes of death. Adapted from Mackay J, Mensah GA, WHO 2004

pressure is common and the incidence of stroke is high, but coronary heart disease is rare. When Japanese people moved across the Pacific Ocean, a reduction in the incidence of hypertension and stroke was seen, but the incidence of coronary heart disease 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.

## Prevalence

The prevalence of 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.

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 current treatment for hypertension). The prevalence of hypertension varies 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. 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.

## Incidence

Unfortunately, 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 two 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. Some authorities argue that high normal blood pressure should be reclassified as "prehypertensive."

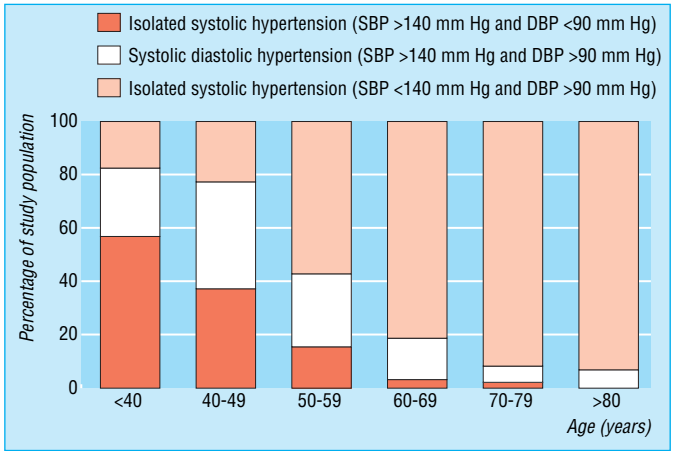
"High normal" blood pressure is one of the strongest predictors for the later development of hypertension. At the individual level, however, blood pressure in childhood is poorly predictive of later levels of blood pressure or the risk of hypertension.

## Age

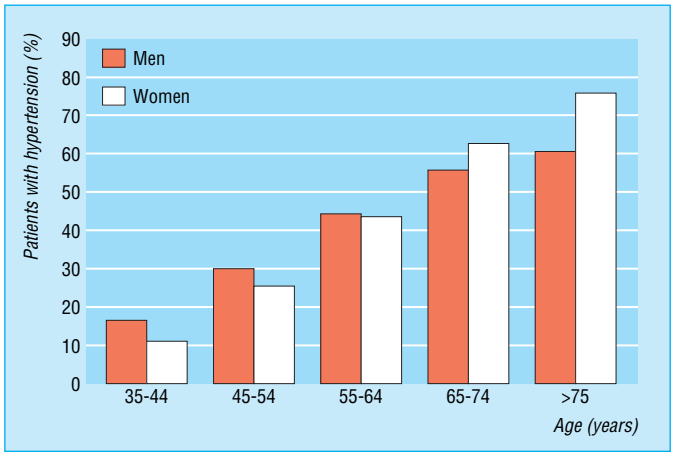
In western societies, blood pressure rises with increasing age, and people with high baseline blood pressures have a faster increase than those with normal or below average pressures. In rural non-Westernised societies, however, hypertension is rare, and the increase in pressure with age is much smaller. The level of blood pressure accurately predicts coronary heart disease and stroke at all ages, although in very elderly people, the

**Prevalence of hypertension (>160/95 mm Hg or treated) in the Birmingham Factory Screening Project**

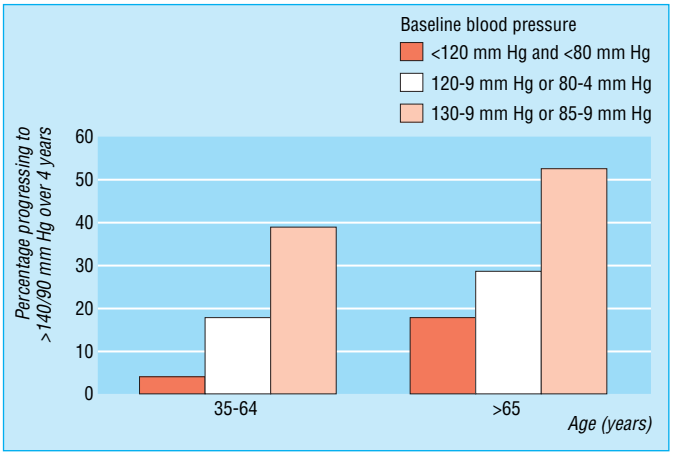
| Population | Men (%) | Women (%) |
|---|---|---|
| African-Caribbean | 30.8 | 34.4 |
| European | 19.4 | 12.9 |
| South Asian | 16.0 | – |




Hypertension subtypes from the NHANES III study (DBP = diastolic blood pressure, SBP = systolic blood pressure). Adapted from Franklin SS, et al. *Hypertension* 2001;37:869–74




Prevalence of hypertension in US citizens aged ≥35 years by age and sex in the NHANES III study (1988–94). Those classified as having hypertension had a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg, were taking antihypertensive drugs. Adapted from Wolz M, et al. *Am J Hypertens* 2000;13:104–4




Patients progressing to develop new hypertension in the Framingham Heart Study. Adapted from Vasan RS, et al. *Lancet* 2001;358:1682–6

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. All studies of people of African origin from urban communities, however, show a higher prevalence than in Caucasian people. 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. 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. 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.

### Sex

Before the age of about 50 years, hypertension is less common in women than men. 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 a harmful effect of androgens on vascular risk.

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

## Causes of hypertension

In around 5% of people with hypertension, the high blood pressure is explained by underlying renal or adrenal diseases. 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.

### Environmental and lifestyle causes of hypertension

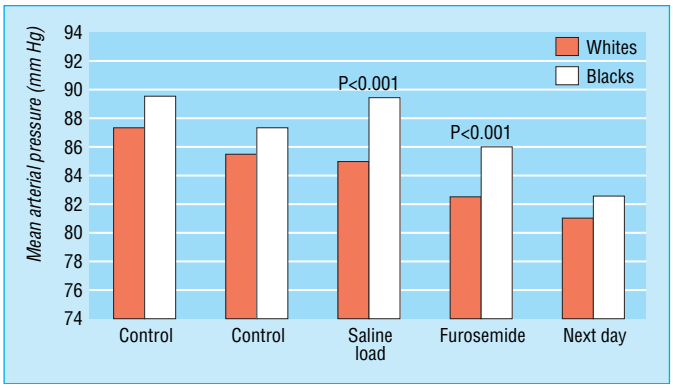
*Salt*

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.

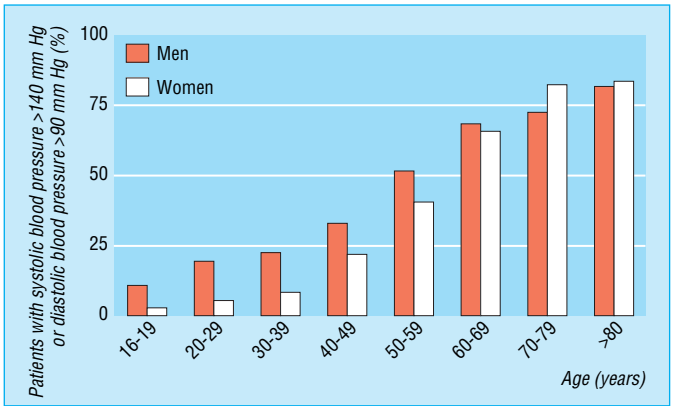
Many potential mechanisms for how salt causes hypertension have been suggested. Evidence from observational

**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 | 10 of 12 |
| Diastolic higher than Europeans | 11 of 14 | 10 of 12 |
| Hypertension more common | 8 of 10 | 8 of 9 |




Effect of salt loading in black and white normotensive people. Adapted from Luft FC, et al. *Circulation* 1979;59:643–50




Prevalence of secondary hypertension in the Health Survey for England 1998. Adapted from Primatesta P, et al. *Hypertension* 2001;38:827–32

**Prevalence of secondary hypertension in three published surveys**

| Type of hypertension | Study | | |
|---|---|---|---|
| | Rudnick, 1977 | Sinclair, 1987 | Anderson, 1994 |
| Essential hypertension | 94.0% | 92.1% | 89.5% |
| Renal disease | 5.0% | 5.6% | 1.8% |
| Renal artery disease | 0.2% | 0.7% | 3.3% |
| Cushing’s syndrome | 0.2% | 0.1% | – |
| Oral contraceptives | 0.2% | 1.0% | – |
| Phaeochromocytoma | – | 0.1% | 0.3% |
| Coarctation | 0.2% | – | – |

**How does salt cause 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

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 thus is 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 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.

This finding was supported by a meta-analysis of the many individual population surveys of blood pressure in relation to salt intake. Law et al performed a meta-analysis of 78 trials of 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 countries would reduce the incidence of stroke by 25% and the incidence of ischaemic heart disease by 15%.

A number of clinical trials also show reductions in blood pressure after restriction of salt intake (see chapter 8). In a recent study in the United Kingdom, a reduction in daily salt intake from 10 g to 5 g over one 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.

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 prevalance of hypertension.

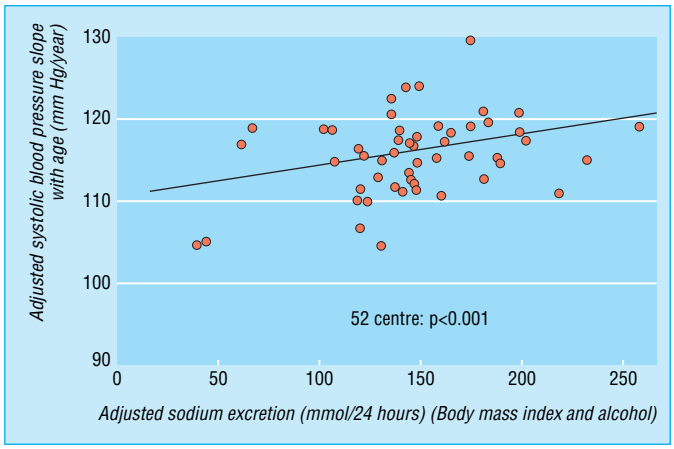
### Potassium

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.

The Intersalt project showed that high intake of potassium was associated with a lower prevalence of hypertension. 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 also has 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.

### 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.




Intersalt project. Adapted from INTERSALT cooperative research group. *BMJ* 1988;297:319–28

**INTERSALT project: sodium excretion and systolic blood pressure in individual centres**

| Variable | Adjusted for | |
|---|---|---|
| | Age, sex | Age, sex, body mass index (kg/m$^2$), alcohol, and potassium |
| Centres with positive change | 39 | 33 |
| Centres with significantly positive change | 15 | 8 |
| Combined centre coefficient per mm Hg per 100 mmol of sodium | 1.63* | 1.00* |
| Combined centre coefficient corrected for reliability | 3.54 | 2.17 |

*$P < 0.001$.

Adapted from INTERSALT cooperative research group. *BMJ* 1988;297:319–28

**INTERSALT project: within centre coefficients for potassium in 24 hour urine sampling adjusted for age and sex**

| Variable | Blood pressure | |
|---|---|---|
| | Systolic | Diastolic |
| Positive coefficients: | 24 | 29 |
| Significant | 0 | 2 |
| Negative coefficients: | 28 | 23 |
| Significant | 2 | 2 |
| Centres | 52 | 52 |

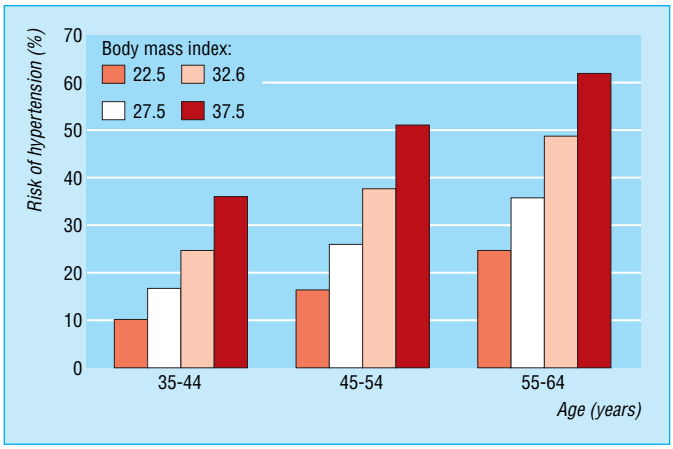
Adapted from INTERSALT cooperative research group. *BMJ* 1988;297:319–28

### Weight

People who are obese or overweight tend to have higher blood pressures than thin people. 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 body mass index (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 (for example, high intake of sodium). 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 cardiovascular disease.

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.




Hypertension and body mass index (BMI) observed in the NHANES III study. Adapted from Thompson PD, et al. *Arch Intern Med* 1999;159:2177–83

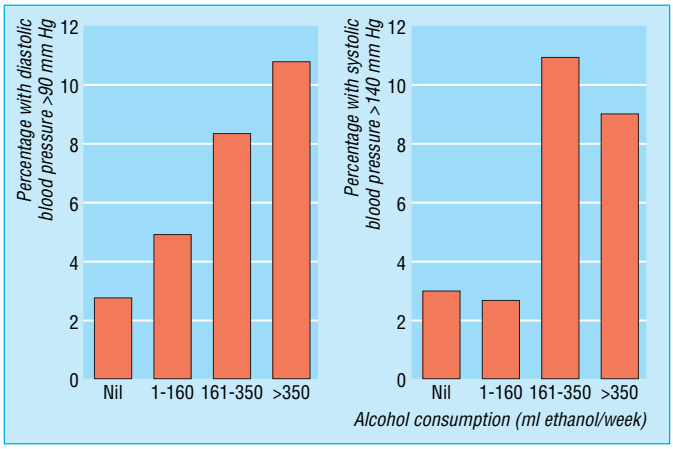
### Alcohol

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. 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 body mass index or salt intake. The effects of alcohol on blood pressure may include:

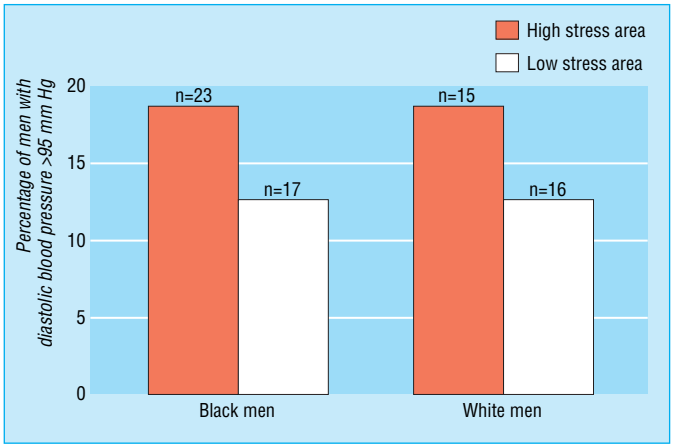
- A direct pressor effect of alcohol
- Sensitisation of resistance vessels to pressor substances
- Stimulation of the sympathetic nervous system (possibly as a result of fluctuating levels of alcohol in blood)
- Increased production of adrenocorticoid hormones.




Alcohol and hypertension. in a working population. Adapted from Arkwright P, et al. *Circulation* 1982;66:60–6

### 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, 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).




Stress, ethnicity, and hypertension in men. Stress was classified by residential area and crime rates. Adapted from Harburg E, et al. *J Chronic Dis* 1973;26:595–611

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. In a recent meta-analysis of trials that involved stress management techniques such as meditation and biofeedback with at least six 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).

**Exercise**

Blood pressure increases sharply during physical activity, but people who undertake regular exercise are fitter and healthier and have lower blood pressures. Such people, however, also may have a healthier diet and more sensible drinking and smoking habits.

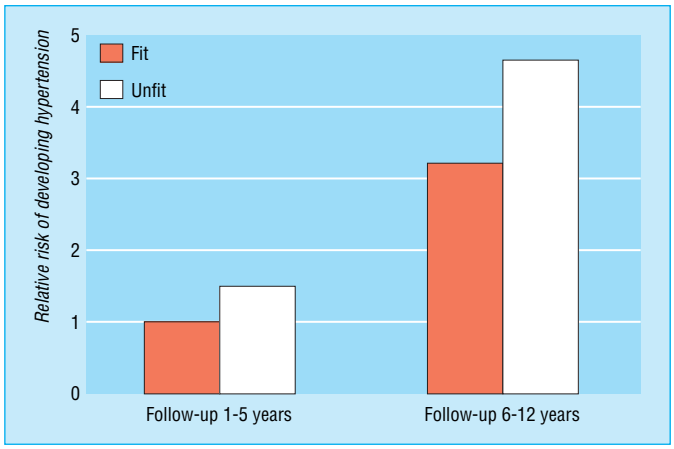
Recent studies suggest an independent relation between increased levels of exercise and lower blood pressures; vigorous exercise might be harmful, but all other grades of exercise increasingly are beneficial. Observational epidemiological studies also show that physical activity reduces the risk of heart attack and 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, body mass index, social class, smoking status, total levels of cholesterol, and levels of high density lipoprotein cholesterol.

**Other dietary factors**

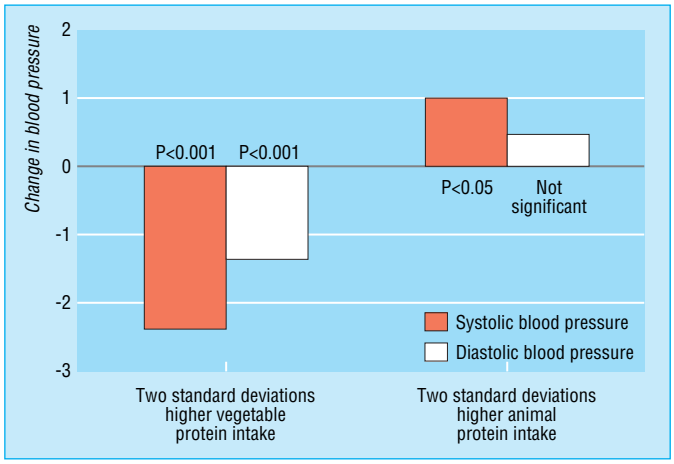
Blood pressure in vegetarians is generally lower than in non-vegetarians. Substitution of animal products with vegetable products reduces blood pressure. The mechanisms of this beneficial effect of a vegetarian diet are uncertain. It may, in part, be related to a lower intake of dairy products or salt. Alternatively the lower blood pressures may be related to a higher dietary intake of potassium, fibre, flavinoids, or vegetable protein (see Elliott P, et al. *Arch Intern Med* 2006;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.




Physical fitness and later hypertension. Adapted from Blair SN, et al. *JAMA* 1984;252:487–90




Vegetable protein and blood pressure in the INTERMAP study. Adapted from Elliot P, et al. *Arch Intern Med* 2006;166:79–87 and Stamler J, et al. *J Human Hypertens* 2003;17:591–608

The table of prevalence of hypertension is adapted from Lane D, et al. *J Human Hypertens* 2002;16:267–73. The table of blood pressure in populations of African origin in the UK is adapted from Agyemang C, Bhopal, RS. *J Human Hypertens* 2003;17:523–34. The table of secondary hypertension is adapted from Rudnick NR, et al. *CMAJ* 1977;117:492–7; Sinclair AM, et al. *Arch Intern Med* 1987;147:1289–93; and Anderson GH, et al. *J Hypertens* 1994;12:609–15.

# 2 Hypertension and vascular risk

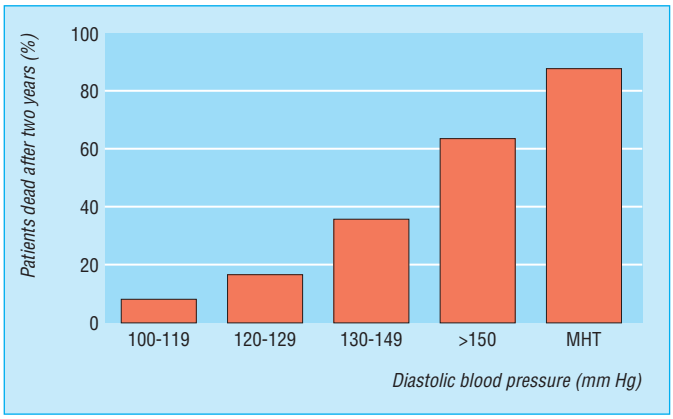
G Y H Lip, D G Beevers

A close dose-response relation exists between the height of systolic and diastolic blood pressures and the risk of stroke or coronary heart disease. This effect is seen in all ages, both sexes, and all ethnic groups.

## Malignant hypertension

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 more rare, being seen in about three per 100 000 population. Malignant hypertension carries a very grave prognosis when untreated, with nearly 90% of patients dying within two years. Most patients die of renal failure, stroke, or left ventricular failure. With modern treatment, survival is much improved, with >80% of patients surviving five years.

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.




Severe hypertension in untreated patients. MHT=malignant hypertension

## Blood pressure and risk

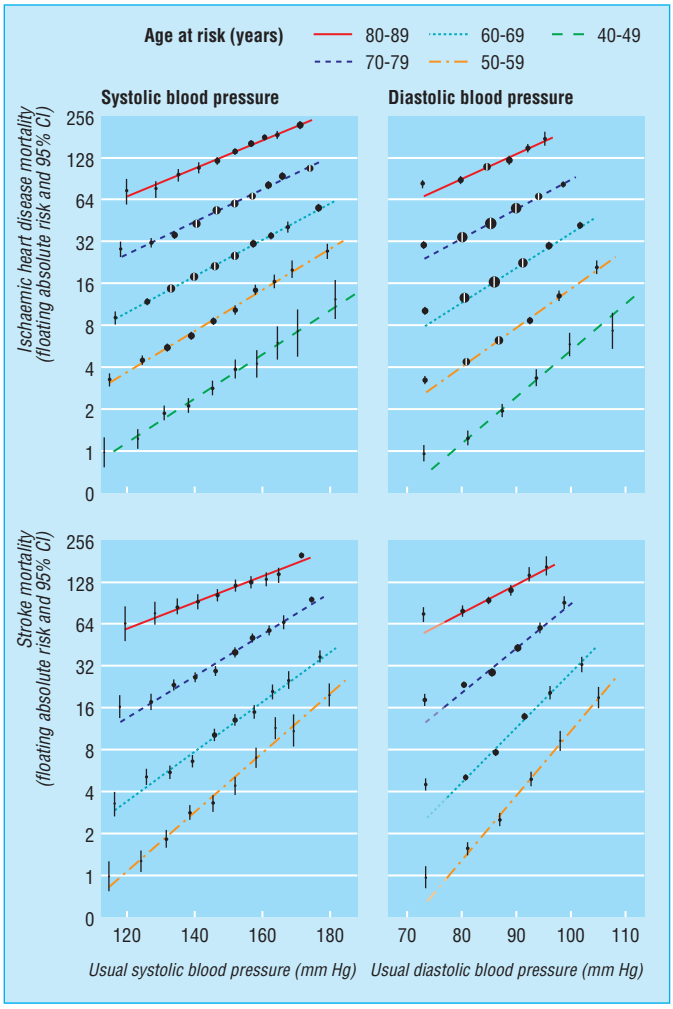
The close relation between the height of the blood pressure and the risk of heart attack and stroke continues down to pressures that are average or even less than the average for the general population. This means that people with systolic blood pressures as low as 130 mm Hg are at greater risk than 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.

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

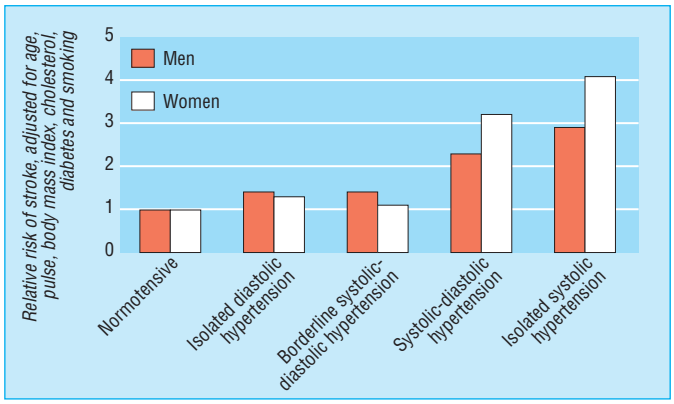



Mortality from coronary heart disease and usual blood pressure (top) and mortality from stroke and usual blood pressure (bottom)

present in people with isolated systolic hypertension and systolic diastolic hypertension, while isolated diastolic hypertension seems to carry a lower risk. 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.

Many patients are unaware that they have hypertension until they develop its complications: stroke, heart disease, peripheral vascular disease, renal failure, and retinopathy. The effective detection and treatment of hypertension is vital to reduce the incidence of cardiovascular disease. Special efforts have to be made to improve the efficiency of healthcare delivery.



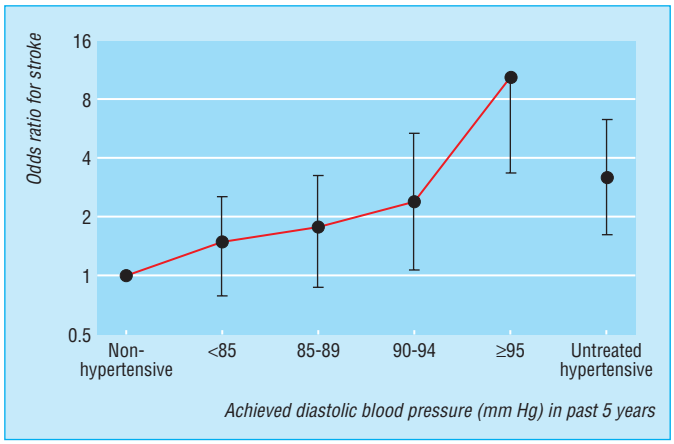

Copenhagen city heart study—relative risk of stroke with normotension, isolated diastolic hypertension, isolated systolic hypertension, and systolic-diastolic hypertension, and isolated systolic hypertension

## 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 eight years than men with systolic blood pressures of 140–159 mm Hg.

Hypertension also is 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 is 8% per year.

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 $\beta$ blockers are less effective at preventing stroke than other antihypertensive agents.




Blood pressure control and odds ratio for stroke in study of 267 cases and 534 controls

## 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. Evidence as to whether lowering blood pressure leads to a reduction of dementia or loss of cognitive function is conflicting.

## 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 $\beta$ blockers rather than newer antihypertensive agents. Hypertension may lead to coronary heart disease because of its contribution to the formation of coronary atheromas, with an interaction with other risk factors such as hyperlipidaemia and diabetes mellitus.

## Left ventricular hypertrophy

Left ventricular hypertrophy occurs as a result of increased afterload on the heart, caused by more peripheral

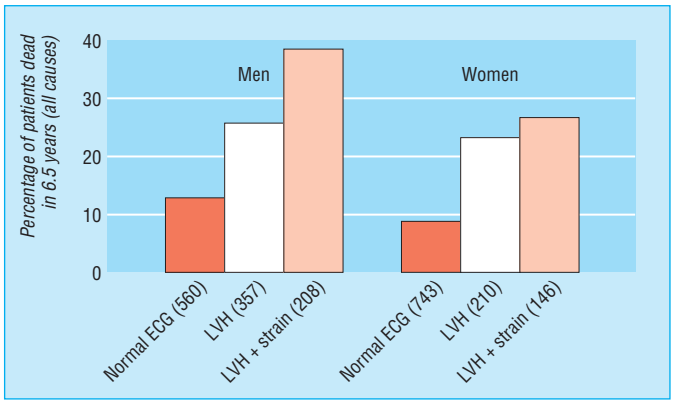
**Stroke versus heart attack in long-term outcome trials**

| Trial | Mean age (years) | Event | |
|---|---|---|---|
| | | Stroke | Heart attack |
| CAPPP | 53 | 340 | 327 |
| HOT | 61 | 294 | 209 |
| INSIGHT | 67 | 141 | 138 |
| LIFE | 67 | 541 | 386 |
| NICS | 70 | 20 | 4 |
| NORDIL | 60 | 355 | 340 |
| SHEP | 72 | 269 | 165 |
| STONE | 67 | 52 | 4 |
| STOP | 76 | 82 | 53 |
| Syst-China | 67 | 104 | 16 |
| Syst-Eur | 70 | 124 | 78 |
| STOP-2 | 76 | 452 | 293 |

CAPPP = Captopril Prevention Project; HOT = Hypertension Optimal Treatment; INSIGHT = International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment; LIFE = Losartan Intervention For Endpoint Reduction; NICS = National Intervention Cooperative Study; NORDIL = Nordic Diltiazem; SHEP = Systolic Hypertension in the Elderly Program; STONE = Shanghai Trial of Hypertension in the Elderly; STOP-Hypertension = Swedish Trial in Old Patients with Hypertension; Syst-China = Systolic Hypertension in the Elderly: Chinese trial; Syst-Eur = Systolic Hypertension in Europe.

vascular resistance. Subsequently, the increased muscle mass outstrips its blood supply and this, coupled with the decreased coronary vascular reserve, can result in myocardial ischaemia—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 left ventricular hypertrophy. The angiotensin blocking drugs reduce left ventricular hypertrophy more than other classes of drug. The prevalence of left ventricular hypertrophy is similar in patients with isolated systolic hypertension and systolic-diastolic hypertension.

Left ventricular hypertrophy 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 left ventricular hypertrophy are at increased risk of cardiac arrhythmias (atrial fibrillation and ventricular arrhythmias) and atherosclerotic vascular disease (coronary and peripheral artery disease). When left ventricular hypertrophy is accompanied by repolarisation abnormalities (also called "strain" pattern), morbidity and mortality are even higher.




Mortality in patients with left ventricular hypertrophy with repolarisation abnormalities (strain) on echocardiograms in the blood pressure clinic at Glasgow. (ECG = echocardiogram, LVH = left ventricular hypertrophy)

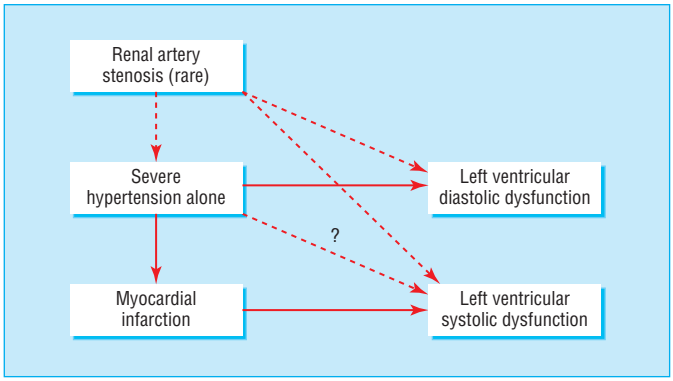
### Heart failure

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.

The presence of left ventricular hypertrophy on an electrocardiogram itself significantly increases the risk of heart failure. The development of atrial fibrillation can precipitate heart failure, especially if left ventricular hypertrophy and diastolic dysfunction are present. The presence of gross left ventricular hypertrophy can result in impaired ventricular compliance and relaxation, which leads to diastolic heart failure or "heart failure with normal systolic function."

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.




Mechanisms of heart failure in hypertension

### 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. 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. 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 also is more common in people with hypertension.

**Blood pressure and risk of intermittent claudication**

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

Adapted from Hughson M. *BMJ* 1978;1:1379–81

**Prevalence of abdominal aortic aneurysm in patients with hypertension**

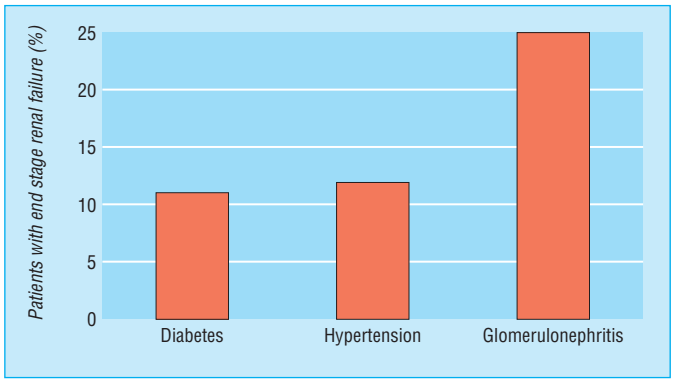
| Study | Prevalence (%) |
|---|---|
| Scriffen, 1995 | 11.9 |
| Vardulaki, 2000 | 4.8 |
| Spittel, 1997 | 6.5 |
| Lindholt, 1997 | 17.8 |
| Williams, 1996: | |
| Men | 5.2 |
| Women | 0.1 |
| Grimshaw, 1994 | 7.7% |

Adapted from Makin AJ. *J Human Hypertens* 2001;15:447–54

**Renal disease**
Renal dysfunction commonly is associated with hypertension, although some controversy exists as to whether mild to moderate essential hypertension 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 angiotensin, as well as sodium and water retention.

**Retinopathy**
Hypertension leads to vascular changes in the eye, which is referred to as hypertensive retinopathy. 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 two years—mainly from heart failure, renal failure, or stroke.

**Hypertension and anaesthesia**
Patients with severe hypertension are at increased risk of events during the intraoperative and postoperative periods, with a high incidence of myocardial infarction and arrhythmias. Some evidence shows that $\beta$ blockers given immediately before anaesthesia reduce this risk. If patients have only mild asymptomatic hypertension and are otherwise generally fit with no evidence of target organ damage (for example, no electrocardiographic evidence of left ventricular hypertrophy), the risk in the perioperative period is likely to be minimal. Thus, many non-urgent surgical operations in such patients are postponed unnecessarily.




Causes of end stage renal disease in Europe

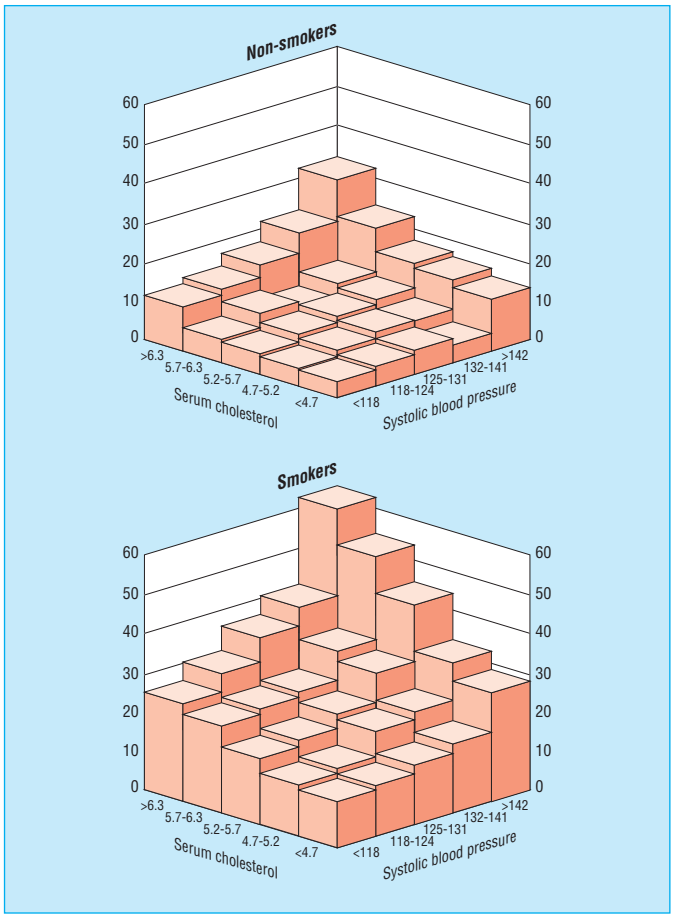
# Multiple risk factors

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.

The treatment of people with hypertension should not focus solely on blood pressure but must also assess total risk for cardiovascular disease 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, left ventricular hypertrophy, previous heart attack, and stroke are all major contributors to premature death.

**How do we assess risk of cardiovascular disease?**
The risk of cardiovascular disease can be assessed in many different ways. These include "gut feeling" (commonly practised 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 British Hypertension Society's guidelines recommend the use of a total cardiovascular disease risk chart that was initially issued by the Joint British Societies (the British Cardiac Society, British Hyperlipidaemia Association, British




Risks of coronary heart disease and stroke in relation to smoking status, serum cholesterol levels, and systolic blood pressure mortality per 10 000 person years in MRFIT screenees

Hypertension Society, and endorsed by the British Diabetic Association) to estimate the risk of cardiovascular disease at 10 years. These risk charts quantify three levels of risk at 10 years, which are represented by three colour bands on the accompanying colour chart.

The Joint British Societies cardiovascular risk prediction charts (see appendix) are based on the long term follow up of people in the town of Framingham, Massachusetts. Whether the charts are applicable to populations of non-European origin in whom patterns of cardiovascular disease are different is uncertain. In people of African and Far Eastern origin, strokes outnumber heart attacks, and these important differences in cardiovascular disease may not be explained by the risk factors measured in the Framingham study. These charts, however, do at least take into account multiple risk factors and can be used to explain risk status to patients and their doctors. They can be used as a rough guide in patients of non-European origin.

**Problems inherent in the total cardiovascular risk chart recommended by the British Hypertension Society**

- The chart predicts absolute risk at 10 years, which results in a tendency to undertreat young people at high relative risk and overtreat older people at lower relative risk
  - —For example, a woman aged 32 years—even with diabetes, a current smoking history, a total cholesterol:high density lipoprotein cholesterol ratio of 8, and a systolic blood pressure of 170 mm Hg—does not reach the 30% threshold of risk of cardiovascular disease at 10 years
  - —Most elderly men would have qualified for intervention simply on account of their age and sex
- Until 2005, the colour charts published in the *British National Formulary* showed the risk of coronary heart disease (CHD) not the total risk of cardiovascular disease
  - —This meant the risk of stroke was ignored
  - —This serious error has now been corrected to quantitate total cardiovascular disease (CVD) risk

## Risk factor assessment in the clinic

*Smoking and hyperlipidaemia*

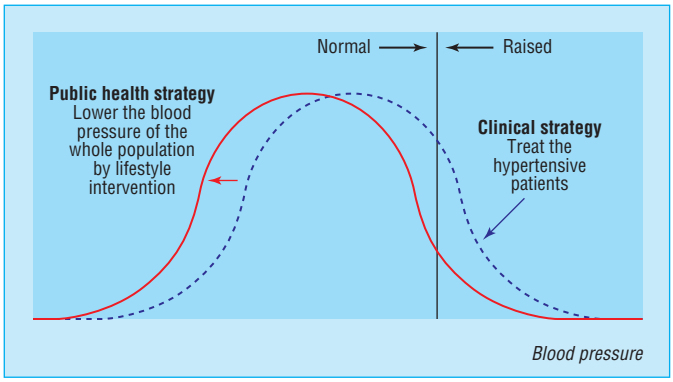
The two most important independent risk factors that need to be taken into consideration are smoking and hyperlipidaemia. In combination with hypertension, these two risk factors have a synergistic effect. Thus, a patient with mild hypertension who does not smoke and has a normal ratio of serum total cholesterol to high density lipoprotein cholesterol has a much lower risk of cardiovascular disease than a patient with mild hypertension who also smokes and has an increased serum cholesterol/high density lipoprotein cholesterol ratio.

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 cardiovascular disease in a young man with mild hypertension is increased, the absolute risk of him sustaining a stroke or 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 cardiovascular disease than men.

## Public health approach

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 cardiovascular disease 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.

Two strategies thus exist for prevention of cardiovascular disease. 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. 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.




Public health and clinical reductions in blood pressure

The figure showing severe hypertension in untreated patients uses data taken from Leishman AWD. *BMJ* 1959;1:1361–3. The figures showing mortality from coronary heart disease and usual blood pressure and mortality from stroke and usual blood pressure are adapted from the Prospective Studies Collaboration. *Lancet* 2002;360:1903–13. The figure of relative risk of stroke with normotension, isolated diastolic hypertension, isolated systolic hypertension, and systolic-diastolic hypertension, and isolated systolic hypertension uses data from the Copenhagen city heart study and adapted from Nielsen N, et al. *Am J Hypertens* 1997;10:634–9. The figure of blood pressure and odds ratio for stroke is adapted from Du X, et al. *BMJ* 1997;314:272. The figure showing mortality in patients with left ventricular hypertrophy with repolarisation abnormalities on echocardiograms is adapted from Dunn FG, et al. *J Hypertens* 1990;8:775–82. The figure showing causes of end stage renal disease in Europe is adapted from United States renal data system 1991. *Nephrol Dialysis Transplant* 1995;10:1–25. The figure showing risks of coronary heart disease in relation to smoking status, serum cholesterol levels, and systolic blood pressure in the MRFIT study is adapted from Stamler J, et al. *JAMA* 1986;256:2823–8

# 3 Pathophysiology of hypertension

G Y H Lip, D G Beevers

A few patients (2–5%) have an underlying renal or adrenal disease as the cause for their increased blood pressure. In the remaining patients, no cause is found, and such cases are referred to as having "essential hypertension." This is clearly illogical, as all diseases have a cause or causes. 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.

## Balance between cardiac output and peripheral resistance

Blood pressure is normally dependent on the balance between cardiac output and peripheral resistance. 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. In the end stages of hypertension, left ventricular damage becomes so severe that 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.

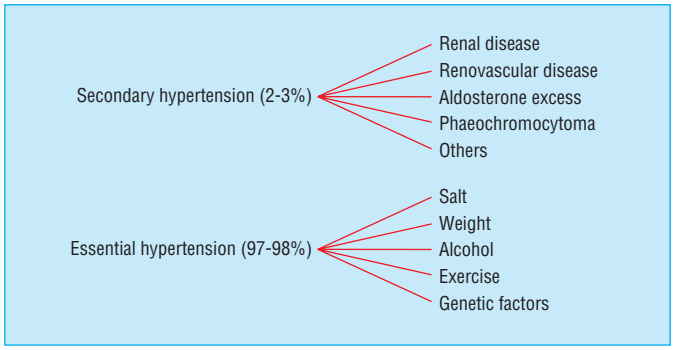
Peripheral resistance is not determined by the large arteries or the capillaries but by the small arterioles. The walls of these arterioles contain smooth muscle cells. Extrinsic influences result in contraction of these smooth muscle cells, probably mediated ultimately by a rise in intracellular levels 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.

## Renin-angiotensin-aldosterone system

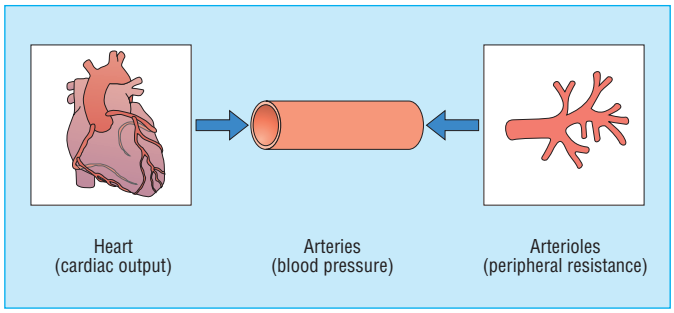
The renin-angiotensin-aldosterone system is one of the major hormonal systems that influence blood pressure. Two of the main drug classes for the treatment of hypertension—the angiotensin converting enzyme inhibitors and the angiotensin receptor blockers—specifically target this system. The hormone aldosterone also can be antagonised by drugs such as spironolactone, but despite beneficial effects in patients with heart failure, little evidence shows a benefit when they are used alone in patients with essential hypertension.

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.

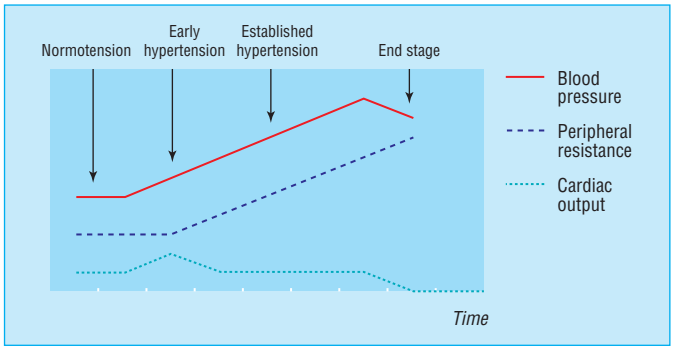
Angiotensin II is a potent vasoconstrictor that leads to an increase in blood pressure. Angiotensin II may also cause some of the manifestations of hypertensive target organ damage,



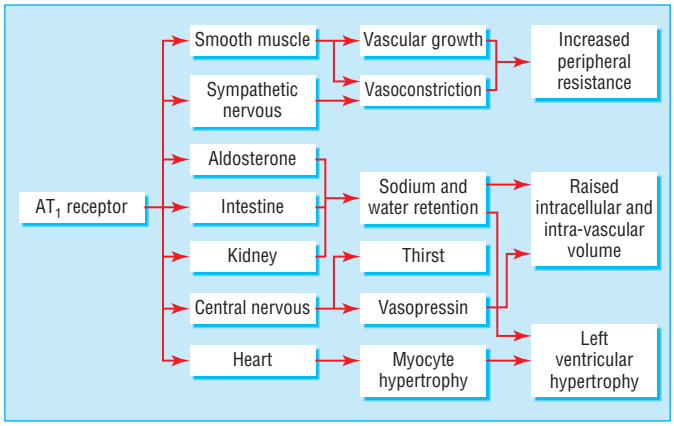

Aetiology of hypertension




Heart, arteries, and arterioles in hypertension




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




Actions of angiotensin II mediated by the angiotensin I ($AT_1$) receptor

such as left ventricular hypertrophy and atherosclerotic vascular disease. Hypertension that results directly from excess renin and aldosterone is seen in patients with renin secreting tumours and in some cases of renal artery stenosis.

Angiotensin II also stimulates release of aldosterone from the zona glomerulosa of the adrenal gland. Aldosterone causes fluid and sodium retention, and this results in a further increase in blood pressure.

The renin-angiotensin system, however, is not thought to be 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 renin-angiotensin-aldosterone system tend to be less effective.

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, which have important roles in the regulation of regional blood flow. Although some drugs have particular affinity for angiotensin converting enzyme in tissue, differences in affinity have not translated to marked differences in clinical outcomes.

**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 is also seen in patients with primary excess of aldosterone (for example, Conn's syndrome) and type 2 diabetes.

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 an interplay between blood volume and renin-angiotensin mediated vasoconstriction.

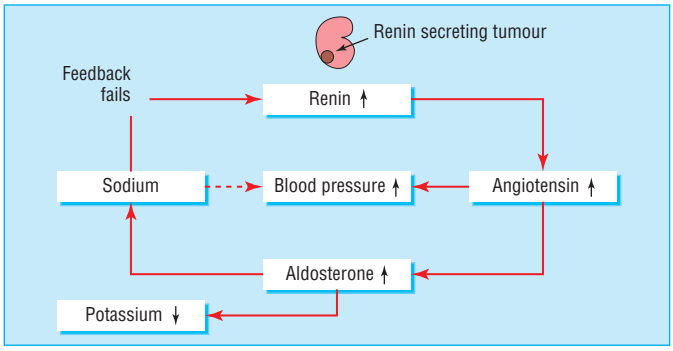
## Autonomic nervous system

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 important role in maintaining a "normal" blood pressure, including the physiological responses to changes in posture, as well as physical and emotional activity.

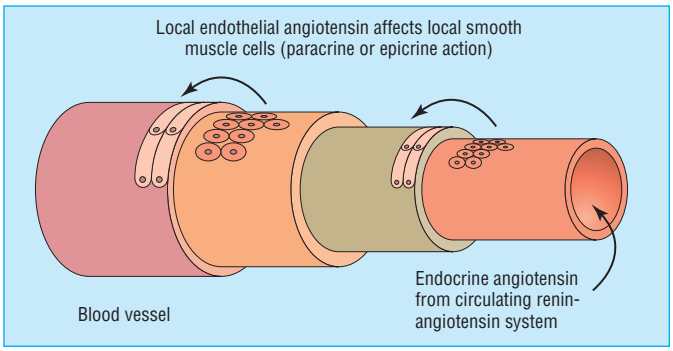
Stimulation of the sympathetic nervous system can cause arteriolar constriction and arteriolar dilatation. After stress and physical exercise, such changes mediate short term changes in blood pressure.

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.

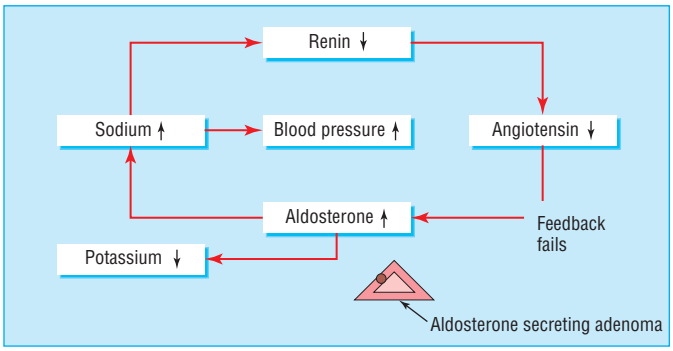
Nevertheless, the effects of the sympathetic nervous system are important, as drugs that act on this system decrease blood pressure. The importance of activation of the sympathetic system in heart failure as a result of systolic dysfunction and in progression of and mortality from renal insufficiency is well established. For example, the role of $\beta$ blockers in patients with chronic heart failure is well established to improve mortality and morbidity.



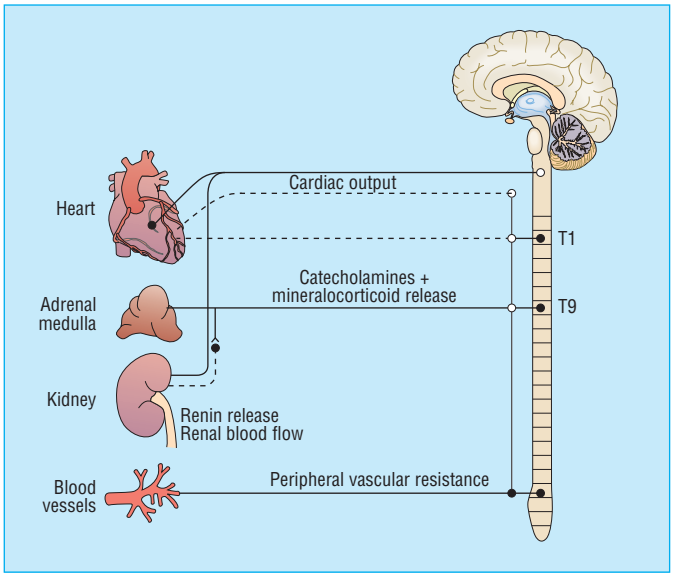

Hypertension as a result of isolated excess of renin as seen with renin secreting tumours, renal artery stenosis, and some primary renal diseases




Local versus systematic renin-angiotensin systems




Hypertension caused by an isolated excess of aldosterone




Autonomic nervous system and its control of blood pressure

## 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."

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.

## Endothelial function

Interest in the role of the endothelium 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, 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.

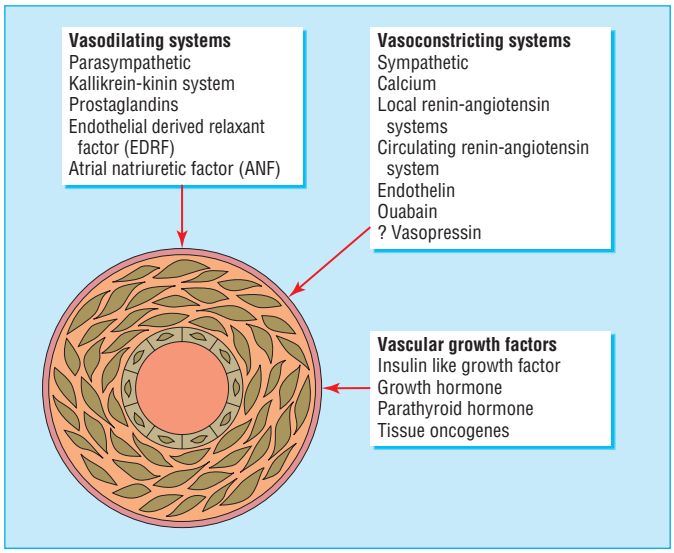
## Prothrombotic state in hypertension

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." 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-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.

### Angiogenesis

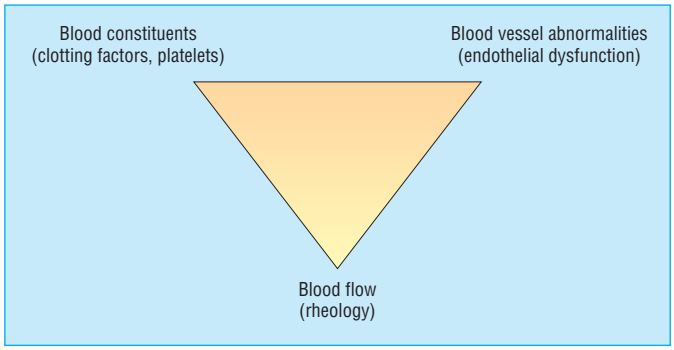
Angiogenesis is increasingly recognised as an important aspect of the pathophysiology of cardiovascular disease and has an impact on thrombogenesis and atherogenesis. The process of thrombogenesis is related intimately to atherogenesis. A common feature is loss of integrity of the endothelial cells.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




Control of peripheral arteriolar resistance

**Thrombotic paradox of hypertension (Birmingham Paradox)**

Although the blood vessels in patients with hypertension are exposed to increased internal pressure, the main complications of hypertension—namely heart attack and stroke—are thrombotic rather than haemorrhagic in origin



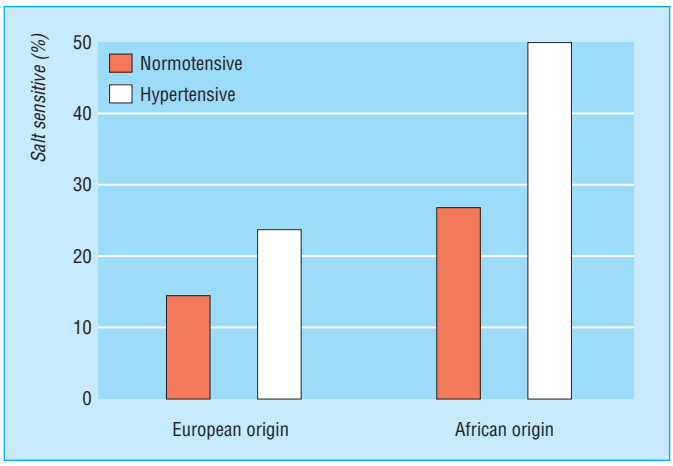

Virchow's triad and prothrombotic state in hypertension

**Essential hypertension is characterised by an impaired capacity for vascular growth, as well as structural alterations of microvascular beds**

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

The precise mechanism of salt induced increases in blood pressure—a phenomenon known as "salt sensitivity"—is understood incompletely. Indeed, the effect of salt in essential hypertension is not predicted by the level of salt intake, but perhaps by the salt sensitivity. Recent evidence suggests that salt sensitivity is an independent risk factor for hypertensive target organ damage and cardiovascular morbidity and mortality. Certainly, restriction of salt intake reduces blood pressure and increases sensitivity to antihypertensive drugs during treatment of hypertension, but wide differences in salt sensitivity are seen when individuals are compared.




Salt sensitivity in black and white US citizens

**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**

## 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 atrial natriuretic peptide 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. Brain natriuretic peptide has been promoted as a "blood test" with a high negative predictive value for heart failure secondary to systolic dysfunction. Increased levels of brain natriuretic peptide have been related to left ventricular hypertrophy and reduced ventricular compliance (so called "diastolic dysfunction").

## 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 genomewide screens are available for genes that control blood pressure. Some autosomal dominant genetically inherited forms of hypertension exist, but they are very rare.

## 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 cardiovascular disease may be the consequences of "programming," whereby a stimulus or insult at a specific, critical, sensitive period of early

**Examples of specific genetic mutations that cause 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$\beta$-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$\beta$-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$\alpha$-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$\alpha$-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

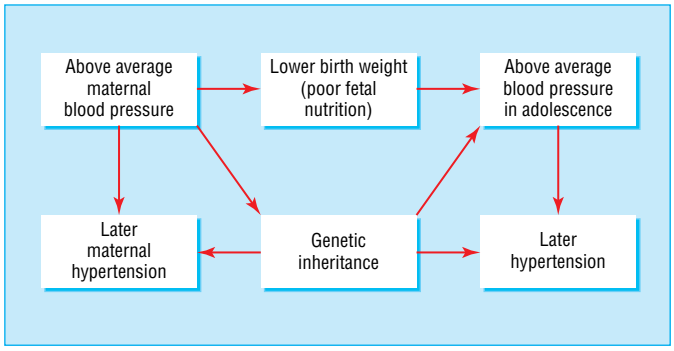
**Other associations**

- Angiotensinogen gene may be related to hypertension
- Angiotensin converting enzyme gene may be related to left ventricular hypertrophy or hypertensive nephropathy
- $\alpha$-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

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 cardiovascular disease, as well as increased risk of cardiovascular disease 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.

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 cardiovascular disease 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.




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

The figure of the autonomic nervous system and its control of blood pressure is adapted from Swales J, et al. *Clinical atlas of hypertension*. London and New York: Gower Medical Publishing, 1991. The figure of control of peripheral arteriolar resistance is adapted from Beevers DG, MacGregor GA. *Hypertension in practice*. London: Martin Dunitz, 1999. The figure of salt sensitivity in black and white US citizens is adapted from Sullivan JM, et al. *Am J Med Sci* 1998;295:370–7