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Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy

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NHS R&D HTA Programme

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Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure was replaced in 2000 by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme will continue to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

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Abstract

Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy

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Objectives: To investigate the screening performance of measuring blood pressure and other variables in identifying those who will develop, or die from, ischaemic heart disease and stroke. To quantify by how much drugs that lower blood pressure will reduce the risk of ischaemic heart disease and stroke in those designated 'screen positive'.
Data sources: MEDLINE, Cochrane collaboration and Web of Science databases; Stroke registries; Health Survey for England; Office of National Statistics; BUPA (British United Provident Association) study.
Review methods: Relevant cohort studies and randomised trials were identified and analysed. Statistical analysis was used to determine drug efficacy and adverse effects.
Results: Lowering blood pressure by 5 mmHg diastolic reduces the risk of stroke by an estimated 34% and ischaemic heart disease by 21% from any pre-treatment level; there is no threshold. These estimates, from cohort studies, have been corroborated by the results of randomised trials in persons with high, average and below average levels of blood pressure. In spite of its importance in causing cardiovascular disease blood pressure is a poor predictor of cardiovascular events. Its poor screening performance is illustrated by the findings that in the largest cohort study, persons in the top 10% of the distribution of systolic blood pressure experienced only 21% of all ischaemic heart disease events and 28% of all strokes at a given age. Combining several reversible risk factors adds little to the screening performance of blood pressure alone; for example the 25% of men aged 55–64 at highest computed risk (≥ 1%) experience only 46% of all ischaemic heart disease events. The main methods of screening should be to identify all persons with a history of cardiovascular disease events (for example identifying patients at the time of hospital discharge following a first myocardial infarction detects 50% of all heart disease deaths in a population at a false positive rate of 12%), and to use a person's age. Identifying everyone with a history of myocardial infarction or stroke in a population and everyone aged 55 or more would include 98% of all deaths from ischaemic heart disease and stroke. The five main categories of blood pressure lowering drugs, thiazides, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists and calcium channel blockers, significantly reduce blood pressure from all pre-treatment levels though the extent of the blood pressure reduction increased with pre-treatment blood pressure. The reductions were similar at standard dose for the five categories; average reduction was 9.1 systolic and 5 diastolic. The effect of combinations of two drugs on blood pressure was additive. No effect of age was apparent, given blood pressure. There were no serious metabolic consequences of using these drugs in standard dose.
Conclusions: The evidence presented indicates that three drugs in combination may reduce stroke by about two-thirds and ischaemic heart disease by half. The report suggests that the term hypertension should be avoided because it is not a disease and it implies another category (normotensives) who would not benefit from lowering blood pressure. Blood pressure reduction using combinations of safe, well-established drugs is effective in preventing cardiovascular events. It is therefore suggested that such preventive therapy be considered more widely in people who by virtue of existing disease or simply age are at risk of a heart attack or stroke regardless of initial blood pressure.

Contents

List of abbreviations

ACE	angiotensin-converting enzyme	HDL	high-density lipoprotein
apo	apolipoprotein	LDL	low-density lipoprotein
BUPA	British United Provident Association	VLDL	very low-density lipoprotein
CI	confidence interval		

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

The traditional approach to the use of blood pressure-lowering drugs has been limited, because intervention has been directed only to the small percentage of people in the upper part of the blood pressure distribution. The term 'hypertension' exacerbates the problem. It suggests a condition that is a disease in itself. It implies that the aim of treatment is to reduce blood pressure to a 'normal' or average level but no lower, and tends to conceal the fact that blood pressure measurement (detecting 'hypertensives') is a poor test to detect persons who will develop stroke or ischaemic heart disease. This approach is misplaced because it focuses on the level of blood pressure rather than a person's overall level of risk of stroke and heart disease, taking all the important determinants of risk into account (notably the presence of existing cardiovascular disease and age). Moreover, the traditional approach to using blood pressure-lowering drugs involves treating no more than a small minority of the population, yet stroke and ischaemic heart disease account for one-third of all deaths, so it will not be possible to make a significant impact on this high mortality without treating a substantial proportion of the population. Although the approach is slowly changing, significant advances in preventing heart disease and stroke will not take place until it is abandoned.

Methods and results

The dose–response relationship between blood pressure and the incidence of stroke and heart disease is continuous. Across the range of values in Western populations there is no evidence of a threshold below which there is no association. Lowering blood pressure reduces the risk of heart disease and stroke whatever the starting blood pressure; a given reduction in blood pressure produces a similar **proportional** reduction in risk from any initial value. Lowering blood pressure by 5 mmHg diastolic reduces the risk of stroke by an estimated 34% and ischaemic heart disease by 21%; these estimates, derived from cohort studies, have been corroborated by the results of randomised trials in persons with high, average and below average levels of blood pressure.

Although blood pressure is an important cause of stroke and heart disease, it is not a good screening test in distinguishing persons who will and will not develop the diseases. Most strokes and ischaemic heart disease events occur in persons who do not have high blood pressure. For example, the 10% of persons with the highest blood pressure experience only 28% of all strokes and 21% of all ischaemic heart disease events. In any age–sex group, the incidence of stroke and myocardial infarction in those whose blood pressure is above any specified level (such as 100 mmHg diastolic) is similar to the incidence in those 10–15 years older whose blood pressure is below this specified level. It may seem paradoxical that blood pressure measurement is a poor screening test for stroke and heart disease even though reducing blood pressure is very effective in reducing the risk from these two diseases. The paradox results from the fact that the average blood pressure is high and the distribution of blood pressure within a given population is relatively narrow – everyone is 'exposed' and the variation in exposure between individuals is small.

Combining several of the 'reversible' cardiovascular risk factors (such as blood pressure, smoking and serum cholesterol) adds little to the screening performance of blood pressure alone. At a 5% false-positive rate, 17% of those who subsequently have ischaemic heart disease events would be identified with screening based on systolic blood pressure alone, 22% with systolic blood pressure and apolipoprotein B (apo B) [a marker for low-density lipoprotein (LDL) cholesterol] in combination, and 28% with six risk factors in combination (including blood pressure, apo B and smoking). It is not possible in this way to identify most people who will develop cardiovascular disease without also identifying many who will not.

Nonetheless, screening has an important role although not through measuring blood pressure. The main method of screening should be to identify systematically all persons with a history of stroke or myocardial infarction at any time in the past, or of angina or transient ischaemic attacks, since they are all at very high risk of death or a recurrent event. However, once a first cardiovascular event has occurred, the ability of blood pressure and other risk factors to predict

recurrent events is very weak. Although a history of past events is an effective way of identifying persons who will have new cardiovascular events and deaths, combining a history of past events with blood pressure and other cardiovascular risk factors is not more effective. Patients who have had a stroke or myocardial infarction have a risk of dying of about 5% per year without treatment; these deaths occurring after a first event account for about half of all deaths from stroke and heart disease, and most of them are preventable.

Among persons without known cardiovascular disease, most, if not all, persons above a specified age need to be treated to ensure that the majority of those who would have had an event will receive preventive treatment; the 'reversible' risk factors, even in combination, are not discriminatory. The principal screening test is determining the age above which treatment would generally be offered (this might be 55 years). With both screening approaches (existing disease and age), blood pressure-lowering drug treatment is offered on the basis of the main determinants of risk, not on blood pressure itself. The two approaches (previous disease and age) would together enable blood pressure-lowering drugs (and other preventive treatment) to be offered to virtually all (98%) persons who would otherwise die of stroke and heart disease.

Studies have shown that realistic changes in diet and lifestyle can reduce average blood pressure levels to only a limited extent (2–3 mmHg diastolic), in the absence of a substantial reduction by the food industry in the salt content of manufactured food. Blood pressure-lowering drugs are needed to achieve larger reductions. Thiazides, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists and calcium-channel blockers are all effective drugs in lowering blood pressure. Meta-analyses of randomised trials showed that the average reductions in systolic blood pressure produced by the five categories of drugs in standard dose were 8.8 mmHg for thiazides, 9.2 mmHg for beta-blockers, 8.5 mmHg for ACE inhibitors, 10.3 mmHg for angiotensin-II receptor antagonists and 8.8 mmHg for calcium-channel blockers. The corresponding diastolic blood pressure reductions were 4.4, 6.7, 4.7, 5.7 and 5.9 mmHg. The drugs significantly reduced blood pressure from all starting levels though the higher the initial level of blood pressure the greater was the reduction in blood pressure. Combinations of drugs from different categories are additive in their blood pressure-lowering effects. From an initial diastolic blood pressure of 90 mmHg (about the average level in persons having a myocardial infarction or stroke), one drug alone on average reduced diastolic blood pressure by 4.7 mmHg, two in combination by 8.9 mmHg and three in combination by 12.6 mmHg. These blood pressure reductions would be expected to reduce the incidence of stroke by 32, 52 and 65% and the incidence of ischaemic heart disease events by 20, 34 and 45%, respectively.

The proportion of persons experiencing any symptom caused by blood pressure-lowering drugs in standard doses (treated minus placebo) was 9.9% for thiazides, 7.5% for beta-blockers, 3.9% for ACE inhibitors, 0.0% for angiotensin-II receptor antagonists and 8.3% for calcium-channel blockers. These symptoms remitted on stopping the drug. The metabolic effects of thiazides and beta-blockers in standard dose (such as changes in serum lipids) are negligible and their use without routine biochemical monitoring is safe. The drugs are inexpensive (the cost to the NHS is £5 per year for hydrochlorothiazide and £9 per year for atenolol). The efficacy of these drugs, their low cost and their safety make them suitable for widespread use.

Conclusions

There are considerable limitations to current guidelines that specify that blood pressure should be lowered only in persons in whom it exceeds a specified level (such as 100 mmHg diastolic). This approach limits the number who can be treated and does not address the inconsistency that an older person with average blood pressure has a substantially greater risk of myocardial infarction or stroke than a younger person with high blood pressure. It also ignores the fact that there is benefit in changing all reversible risk factors (not only blood pressure) in persons who are at high risk for any reason.

The authors have identified a range of policy options in relation to treatment of high blood pressure and considered these in light of the findings of this research. It is suggested that a combination of identifying all people with established cardiovascular disease and offering treatment to all persons above a specified age are likely to have the greatest public health impact (may reduce stroke by about two-thirds and ischaemic heart disease by half), on the basis of the epidemiological evidence presented. Further research into treatment effectiveness and into the economic implications of policy options is required.

Chapter 1
Introduction

Morbidity and death from ischaemic heart disease and stroke are the major health problem in Britain and other Western countries, accounting for one-third of all deaths. Any means of reducing this burden should receive high priority. In this report, we focus on the importance of blood pressure as a cause of cardiovascular disease and the effectiveness of treatment with blood pressure-lowering drugs in preventing morbidity and death.

Developing a rational policy for the use of drugs that lower blood pressure requires quantitative answers to two questions:

1. What is the screening performance of measuring blood pressure and other variables in identifying those who will develop, or die from, ischaemic heart disease and stroke?
2. By how much will drugs that lower blood pressure reduce the risk of ischaemic heart disease and stroke in those designated 'screen positive'?

Neither question has been answered quantitatively, even though it has been standard practice for over 50 years to encourage blood pressure measurements in adults with a view to reducing the associated morbidity and mortality. As a result, blood pressure is commonly measured, but in a manner that is largely haphazard. Various professional guidelines are followed to initiate drug treatment above specified levels of blood pressure, but there is little awareness of the expected reduction in morbidity and mortality, or of the public health implications of alternative, possibly more effective, policies.

In this report, we provide answers to the above two questions, and present a range of policy options which may be helpful in formulating decisions on the most appropriate way of using blood pressure-lowering drugs to prevent blood pressure-related illness and premature mortality.

Chapter 2

The incidence and mortality of ischaemic heart disease and stroke in England and Wales

Key points

- Blood pressure is important in relation to ischaemic heart disease and stroke for two reasons: it is associated with the risk of these disorders and so it is used as a screening test to detect persons who will have future events, and it causes these disorders so reducing it will prevent them. The two are distinct.
- 'Hypertension' should not be considered a disease in itself. The term is best avoided.
- Ischaemic heart disease and stroke cause one-third of all deaths in both men and women.
- Age-specific mortality from ischaemic heart disease and stroke has substantially declined over the past 20 years, but the proportion of people dying from these causes has declined relatively little: the deaths are postponed rather than avoided completely.
- The incidence of stroke and ischaemic heart disease doubles about every 8 years of increasing age. This may be interpreted as indicating that a treatment that halves risk will on average delay an event by 8 years.

Introduction

The objective in using drugs that lower blood pressure is to prevent stroke and ischaemic heart disease. The disorders of interest are, therefore, ischaemic heart disease events and stroke, not hypertension *per se*. It is inappropriate to consider hypertension a disease in itself. The interest in blood pressure arises for two separate reasons:

1. Blood pressure is associated with the risk of heart disease and stroke and so it is used as a screening test to detect persons who will have future events.
2. Blood pressure causes heart disease and stroke, so reducing it will prevent them.

The two are distinct; preventive efficacy does not mean screening efficacy.

In this chapter, we present quantitative data from England and Wales on blood pressure and its distribution according to age and sex, and on the incidence and mortality of the disorder, ischaemic heart disease and stroke.

Blood pressure

Tables 1 and *2* shows the distribution of values of systolic and diastolic blood pressure in 10-year age groups in men and women, taken from the 'Health survey for England'.[1] The data confirm the recognised increase in blood pressure with age. At any age and blood pressure centile the values are similar in men and women; systolic values may be slightly lower in women than men at younger ages and greater at older ages. The oldest age group (75+ years) is open-ended and the women will be older than the men because of their greater longevity; this may contribute to the higher systolic blood pressure of the women than the men in this age group.

TABLE 1 *Distribution of systolic blood pressure (mmHg) according to age and sex*

	Centile of systolic blood pressure					
Age (years)	**5**	**25**	**50**	**75**	**95**	**99**
Men						
16–24	110	122	130	138	150	158
25–34	112	124	132	140	152	160
35–44	109	123	132	141	155	164
45–54	109	126	137	148	165	176
55–64	114	132	144	156	174	187
65–74	114	137	152	167	190	205
75+	115	138	154	170	193	209
Women						
16–24	102	113	121	129	140	148
25–34	103	114	122	130	141	149
35–44	100	114	124	134	148	158
45–54	102	119	132	145	162	175
55–64	108	130	145	160	182	197
65–74	113	136	152	168	191	207
75+	118	143	160	177	202	219

Data from the 'Health survey for England', 1996.[1]

TABLE 2 *Distribution of diastolic blood pressure (mmHg) according to age and sex*

	Centile of diastolic blood pressure					
Age (years)	**5**	**25**	**50**	**75**	**95**	**99**
Men						
16–24	46	57	64	71	82	89
25–34	55	64	71	78	87	94
35–44	60	70	77	84	94	101
45–54	62	73	81	89	100	107
55–64	64	75	83	91	102	110
65–74	63	75	83	91	103	111
75+	56	70	80	90	104	114
Women						
16–24	49	58	64	70	79	86
25–34	53	62	69	76	85	92
35–44	55	65	72	79	89	97
45–54	57	67	75	83	93	101
55–64	58	70	78	86	98	106
65–74	57	69	78	87	99	108
75+	54	69	79	89	104	114

Data from the 'Health survey for England', 1996.[1]

Examination of the increase in blood pressure with age according to blood pressure centile shows a strikingly greater increase at higher blood pressure centiles than lower centiles, in both proportionate terms and absolute terms. For systolic blood pressure in men, for example, the increase from the youngest to the oldest age group is from 158 to 209 (32%) on the 99th centile but from 110 to 115 (5%) on the 5th centile, so the difference in blood pressure between the high and low centiles increases with age. This observation suggests a tendency for blood pressure in individuals to 'track' – to remain on approximately the same centile throughout life. The increase in blood pressure with age is influenced by environmental factors including dietary salt consumption, dietary potassium, body mass index (obesity), alcohol consumption and lack of exercise, and by genetic factors including a person's 'sensitivity' to salt and other environmental factors. It is plausible that these factors would tend to remain similar in an individual throughout adult life, such that blood pressure would track.

The extent to which some individuals deviate from such tracking is an important question – blood pressure may increase substantially over a relatively short period in some persons. It would then be necessary to take repeated blood pressure measurements at regular intervals (say 5-yearly) throughout a person's life if blood pressure were to be used as a screening test. However, if significant deviation from tracking was rare, measurement at one specified year of age to determine a person's blood pressure centile may be sufficient to predict accurately the person's blood pressure throughout life.

This question, although important, cannot be answered. There are no sets of published data on blood pressure recorded in a large group of individuals on repeated occasions over a period of years. Even if there were such measurements, the random fluctuation in blood pressure over time in individuals is so large that it would probably obscure any systematic changes. Blood pressure in an individual fluctuates over time across a 95% range of 18 mmHg systolic and 14 mmHg diastolic either side of a person's long-term average value[2] – random fluctuation is large in relation to the plausible short-term systematic change in a person.

The estimates in this report correspond approximately to the effect of 5-yearly blood pressure measurements, from the duration of the cohort studies and trials on which they are based.

The disorder – ischaemic heart disease and stroke

Table 3 shows the numbers of deaths from ischaemic heart disease (ICD-9 410-4) and stroke (ICD-9 430-8) in England and Wales in 1998, and also shows the smaller numbers of deaths from the other cardiovascular causes that relate to blood pressure and other cardiovascular risk factors.[3] There were about 100,000 deaths in men and 100,000 deaths in women. All the disorders accounted for 38% of all deaths in men and 36% in women; in both sexes ischaemic heart disease and stroke accounted for 33% of all deaths. Age-specific mortality from ischaemic heart disease and stroke has declined substantially in the past 20 years (heart disease by 60%), but the proportion of all deaths caused by the two diseases has changed relatively little over the same period. Ischaemic heart disease has declined from 28% to 22% of all deaths in men and women, and stroke from 13% to 10%. Most deaths are postponed rather than avoided completely.

Table 4 shows the death rates from ischaemic heart disease and stroke in 10-year age groups in men and women recorded in England and Wales in 1998. *Table 5* presents a life table analysis of the death rates in *Table 4*, showing the proportions of men and women who die from ischaemic heart

TABLE 3 *Numbers of deaths from specified cardiovascular causes in men and women aged 15 years and over, and the corresponding proportions of all deaths in men and women aged 15 years and over, England and Wales 1998*

	Men		Women	
Cause of death (ICD-9 code)	**No. of deaths**	**% of all deaths**	**No. of deaths**	**% of all deaths**
Ischaemic heart disease (410-4)	66009	25	55024	19
Stroke (430-8)	21432	8	36046	13
Heart failure (428), myocardial degeneration (429.1) and hypertensive disease (401-5)	5149	2	9172	2
Aortic aneurysm (441)	5829	2	3668	1
Total	**98419**	**38**	**103910**	**36**

From death certification data reported by the Office for National Statistics, 1999.[3]

TABLE 4 *Death rates per 10,000 persons from ischaemic heart disease and stroke according to age and sex, England and Wales 1998*[3]

	Ischaemic heart disease		Stroke	
Age (years)	**Men**	**Women**	**Men**	**Women**
25–34	0.3	0.1	0.2	0.2
35–44	2	0.4	0.6	0.6
45–54	10	2	2	2
55–64	33	10	6	4
65–74	93	41	22	17
75–84	212	122	79	73
85+	393	274	210	230

TABLE 5 *Proportions of men and women who would die from ischaemic heart disease and stroke before specified ages (in the absence of death from other causes), based on 1998 England and Wales death rates (Table 4)*

	Ischaemic heart disease (%)		Stroke (%)		Ischaemic heart disease or stroke (%)	
Age (years)	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
45	0.3	0.1	0.1	0.1	0.3	0.1
55	1	0.3	0.3	0.2	2	0.5
65	4	1	0.8	0.7	5	2
75	13	5	3	2	16	7
85	30	16	10	9	37	22
90	43	26	16	17	51	39

disease, from stroke and from either before specified ages. By the age of 85 years the proportion of people who would die from heart disease or stroke on current rates is 37% in men and 22% in women.

Incidence of myocardial infarction and stroke

Data on the incidence of myocardial infarction and stroke are not routinely collected; unlike cancer, national or regional registries are not maintained. Estimates of incidence are best derived from registries that have been maintained for research purposes in certain localities, usually for periods of 1–3 years, sometimes longer.

The present analysis includes only studies in which the events occurred since 1985, because the incidence of myocardial infarction and stroke has declined over time and was higher in earlier periods. It is based on all published studies from all registries in which all first strokes or all first

TABLE 6 *Studies based on stroke registries, in which all cases of first-ever stroke (fatal or not) occurring in geographically defined populations over specified periods were identified and age- and sex-specific incidence determined (all studies in which the strokes occurred in 1985 or later are included)*

	Population			No. of first strokes	
Locality of registry	**Age range (years)**	**No. of persons (thousands)**	**Duration of observation (years)**	**Male**	**Female**
England					
South London:					
White[6]	0–85+	168	2	221	268
Black[6]	0–85+	49	2	52	50
Lancashire[7]	0–85+	405	1	264	378
Southern England[8]	0–74	322	2	254	202
Oxford[9]	0–85+	105	4	318	357
Italy					
Belluno[10]	35–85+	113	1	203	271
Aosta[11]	0–85+	114	1	112	142
Umbria[12]	0–85+	49	3	183	192
France					
Dijon[13]	0–85+	136	5	477	465
Greece					
Arcadia[14]	28–85+	81	2	309	246
Denmark					
Copenhagen[15]	45–84	13	5	190	185
Frederiksberg[16]	0–85+	87	1	116	146
Norway					
Innherred[17]	0–85+	69	2	197	235
Sweden					
Malmo[18]	0–85+	232	1	244	280
Enköping[19]	0–85+	30	3	125	163
Finland					
Central Finland[20]	25–85+	83	1	79	110
Four rural areas[21]	15–75+	108	2	272	322
USA					
Rochester, NY[22]	0–85+	67	5	201	295
Australia–New Zealand					
Auckland[23]	15–85+	945	1	566	689
Perth[24]	0–85+	139	1.5	281	255
All studies		**3315**		**4664**	**5251**

myocardial infarctions were identified (whether fatal or not and whether admitted to hospital or not), in geographically defined communities in which the incidence of first stroke and first myocardial infarction was determined according to age and sex, using previously defined criteria for identifying studies and for adequate case ascertainment in including studies in the analysis.[4,5] The search was based on MEDLINE (keywords 'myocardial infarction' or 'stroke' and 'incidence' or 'follow-up studies') and on published review articles.

Table 6 lists the 20 stroke registries identified and included in the analysis and shows details of the study populations and follow-up. *Table 7* does the same for the eight myocardial infarction registries.

Figure 1 shows the weighted average incidence of first stroke across all the stroke registry localities (weighting each locality by number of cases) in men and women in 10-year age groups. With incidence plotted on a logarithmic (proportional) scale, the association between incidence and age fits a straight-line relationship well. This indicates that for a specified increase in age (say 10 years) there is a constant proportional increase in the incidence of stroke irrespective of the initial age. In these data, incidence doubled on average with every 8 years increase in age in both men and women. Hence if the number of strokes per 10,000 population is 1 at age 30, it is 2 at age 38, 4 at age 46, 8 at age 54 increasing to 128 at age 86 years. This rate of increase with age varied relatively little across the different localities.

TABLE 7 *Studies based on myocardial infarction registries, in which all cases of first-ever infarct (fatal or not) occurring in geographically defined populations over specified periods were identified and age- and sex-specific incidence determined (all studies in which the infarcts occurred in 1985 or later are included)*

	Population			No. of first myocardial infarctions	
Locality of infarct registry	**Age range (years)**	**No. of persons (thousands)**	**Duration of observation (years)**	**Male**	**Female**
England and Wales					
Brighton, York and S. Glamorgan[25]	35–74	429	2	1864	767
Oxford[26]	25–79	369	1	454	261
Denmark					
Glostrup[27]	30–74	242	3	1026	392
Sweden					
Göteborg[28]	35–64	154	5	1132	293
Malmo[29]	<45–85+	32	7	736	540
Finland					
N. Karelia[30]	25–64	91	3	588	131
Kuopio[30]	25–64	133	3	704	154
Turku[30]	25–64	110	3	425	109
All studies		**1560**		**6929**	**2647**

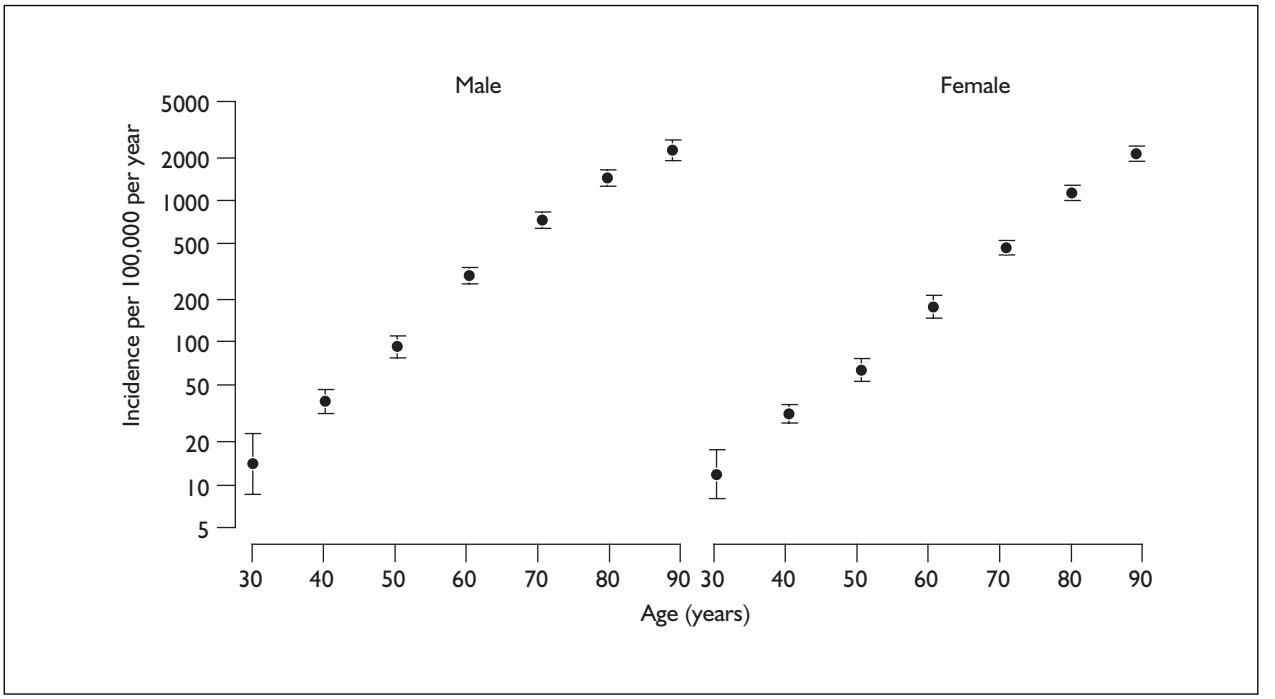

FIGURE 1 *Incidence of stroke in 10-year age groups in men and women (the data in each age and sex group represent a weighted average from the stroke registry studies listed in Table 6)*

Figure 2 shows the weighted average incidence of myocardial infarction across all the registry localities. With incidence plotted on a logarithmic scale, the association with age is again well fitted by a straight line. Incidence doubles every 10 years in men and 6 years in women, 8 years on average.

Table 8 shows the age-specific incidence of first myocardial infarction and stroke in England and Wales, based on a linear regression analysis of the data from the myocardial registries[6–10,25,26] located in England and Wales. *Table 9* presents a life table analysis of the incidence data for England and

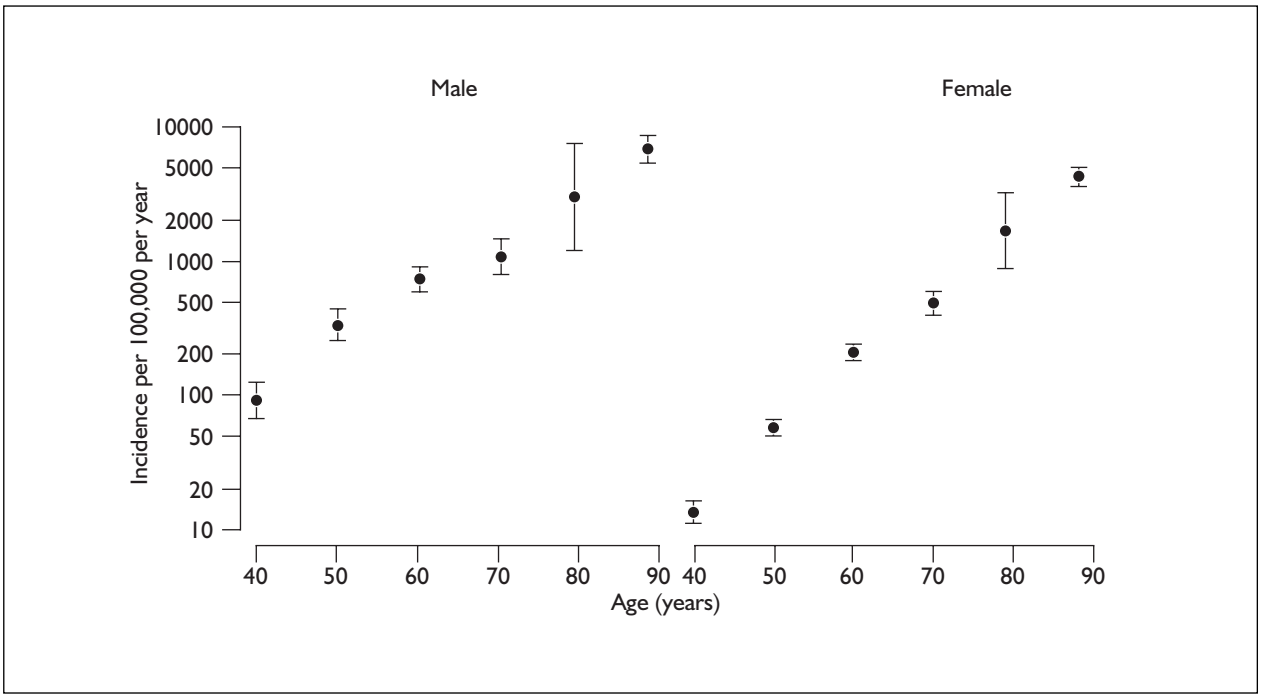

FIGURE 2 *Incidence of myocardial infarction in 10-year age groups in men and women (the data in each age and sex group represent a weighted average from the myocardial infarction registry studies listed in Table 7)*

TABLE 8 *Estimates of the incidence per 10,000 persons per year of first myocardial infarction and first stroke according to age and sex, England and Wales*

	Myocardial infarction		Stroke	
Age (years)	**Men**	**Women**	**Men**	**Women**
25–34	0.8	<0.1	2	1
35–44	5	2	4	3
45–54	29	6	9	7
55–64	54	17	23	18
65–74	99	48	54	43
75–84	182	133	130	107

Based on the registries located in England and Wales listed in *Tables 6* and *7*.

TABLE 9 *Proportions of men and women who have a myocardial infarction or stroke (fatal or not) before specified ages (based on data for England and Wales in Table 8)*

	Myocardial infarction (%)		Stroke (%)		Either or both (%)	
Age (years)	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
45	0.4	0.13	0.5	0.4	0.9	0.5
55	3	0.6	1	0.9	4	1
65	7	2	3	2	10	4
75	15	6	7	6	21	11
85	28	15	15	13	39	26

Wales shown in *Table 8*. By the age of 65 years the cumulative incidence of either a stroke or a myocardial infarct is 10% in men and 4% in women, and by the age of 85 it is 39% in men and 26% in women. Despite the reduction in age-specific incidence and mortality of heart disease and stroke in recent years, they remain important because of the longevity of the population.

Chapter 3

Blood pressure in relation to ischaemic heart disease and stroke: the dose–response relationship and its reversibility

Key points

- The dose–response relationship between blood pressure and the risk of ischaemic heart disease and stroke is continuous across the range of blood pressure values in Western populations without evidence of a threshold. A specified absolute reduction in blood pressure (of, say, 5 mmHg) from any point on the blood pressure distribution produces a constant **proportional** reduction in risk.
- Randomised trials confirm the same proportional reduction in the incidence of stroke and ischaemic heart disease after a specified blood pressure reduction from any point on the blood pressure distribution.
- For a reduction in blood pressure of 5 mmHg diastolic the cohort studies indicate that the risk of stroke is reduced by 34% and the risk of ischaemic heart disease is reduced by 21%, at age 60–65 years. The summary estimate from all the randomised controlled trials is a reduction in stroke of 33% and a reduction in ischaemic heart disease events of 20% – a remarkably close corroboration.
- These proportional effects of blood pressure reduction on risk are similar at different ages and in patients with and without existing disease.
- Risk is reversible within a few months of starting treatment.

Introduction

In this chapter, we assess the evidence on the dose–response relationships between blood pressure and stroke and ischaemic heart disease. We examine whether, as with serum cholesterol and ischaemic heart disease,[31] there is a continuous relationship across the range of blood pressure values in Western populations such that a given blood pressure reduction from any point on the distribution produces the same proportional reduction in risk, or whether (as has been supposed) there is a blood pressure threshold below which further reduction produces no benefit. We then assess the size of the reduction in the incidence of stroke and ischaemic heart disease produced by a given reduction in blood pressure and the time needed to attain the full reduction in risk.

Cohort studies and trials are complementary in answering these questions. Data from cohort studies, adjusted for the regression dilution bias, estimate the differences in risk of stroke and ischaemic heart disease that result from prolonged differences in blood pressure,[32] since the blood pressure differences between individual people in cohort studies will have been present for decades before the data were collected. Cohort studies also best show dose–response relationships.[31,32] Data from randomised trials assess the extent to which the excess risk can be reversed after a reduction in blood pressure in middle-aged or elderly people, and how quickly it can be reversed.[33]

Throughout this chapter, the results are necessarily based on diastolic rather than systolic blood pressure. This was because the large overview of the cohort studies reported results for diastolic pressure only,[32] as did the published reports of six of the randomised trials, including the largest.[34] Systolic and diastolic blood pressure are highly correlated and the results are similar whichever is used.

Methods

For cohort studies we based our estimates on the large overview of MacMahon and colleagues;[32] other cohort study data yield quantitatively similar associations.[33,35–39]

We identified randomised trials of drugs that lower blood pressure using MEDLINE and published reviews.[34,40,41] We first identified trials in persons selected as having high blood pressure.[42–64] For trials published up to the end of 1989 we used the review by Collins and

colleagues,[34] who obtained unpublished data for some of the trials and specified reasons for excluding certain trials. Using MEDLINE and review articles we identified trials published since 1989, including two trials that did not have an untreated control group but compared relatively less intensive drug treatment with more intensive treatment.[58,62] Separate analyses were done of persons with and without a history of cardiovascular disease on entry. In the former category, two of these trials of persons with high blood pressure recruited only persons who had had a stroke,[59,60] and for five of the other trials in which some of the patients had had a stroke[44–47,50,52,55,64] separate data have been published on this subset.[65] The remaining patients in these trials generally had no history of cardiovascular disease on entry. We recorded the numbers of ischaemic heart disease events (ischaemic heart disease death and non-fatal myocardial infarction) and the numbers of strokes (fatal or not).

We then identified randomised trials of blood pressure-lowering drugs in persons with average levels of blood pressure (the standard-blood pressure-lowering drugs reduce blood pressure in persons with average blood pressure levels in addition to those with high blood pressure, as quantified in Chapter 7). These trials came from three different sources:

1. Trials in persons selected as having 'mild hypertension': in these the wide individual fluctuation in blood pressure over time,[2] together with the selection process, meant that blood pressure in the control groups fell on average over the duration of follow-up because of regression to the mean.[32] In four of these trials,[61–64] blood pressure fell to an average value that was around the population average values in persons of the same age as shown in *Tables 1* and *2*. The subjects in these trials generally had no history of previous cardiovascular disease on entry.
2. Two randomised trials tested blood pressure-lowering drugs in patients who had recently had a stroke irrespective of the initial level of blood pressure.[66,67]
3. Randomised trials have tested three categories of blood pressure-lowering drugs, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and calcium-channel blockers, in patients with ischaemic heart disease irrespective of the initial level of blood pressure. The effect of beta-blockers has been tested in trials conducted in patients after myocardial infarction. These trials were identified in a recent review by Freemantle and colleagues;[68] we selected trials of minimum duration 6 months. We recorded the numbers of deaths from ischaemic heart disease, published for 18 of the 28 trials (80% of all the patients in all the trials), and deaths from all causes in the remaining trials (a close approximation to the number of ischaemic heart disease deaths in such high-risk patients). We also recorded the numbers of non-fatal reinfarctions, published for 20 of the trials. The effect of ACE inhibitors on ischaemic heart disease mortality has been tested in trials conducted in patients with ischaemic heart disease.[69–79] We identified trials using MEDLINE and review articles and again selected trials of at least 6 months' duration. In these trials we recorded only acute myocardial infarctions (fatal or not) as ischaemic heart disease events, not heart failure as a late complication of an earlier infarct, and not sudden death because the patient selection in these trials means that many sudden deaths will have been from acute heart failure. We identified and analysed trials of calcium-channel blockers after myocardial infarction, of at least 6 months' duration, in the same way.[80–86]

In all these analyses we excluded trials recording less than five events, because substantially larger trials were available and the very small trials limited the sensitivity of the analysis to detect statistically significant heterogeneity between trials. Relative risk estimates from individual trials were combined to yield summary relative risk estimates from groups of comparable trials using a random effects model,[88] although there was no statistically significant heterogeneity between trials in any of the analyses.

Results from cohort studies

Figure 3 summarises the analysis of MacMahon and colleagues of data from nine large cohort studies of blood pressure and cardiovascular mortality.[32] In the figure the subjects in the cohort studies have been divided into five equal groups according to ranked measurements of diastolic blood pressure, and the risk estimates [with 95% confidence intervals (CIs)] in each of these groups are shown. The figure shows that, for both stroke and ischaemic heart disease, the 95% CIs on the risk estimates in each of the five groups do not overlap, confirming that there is no threshold

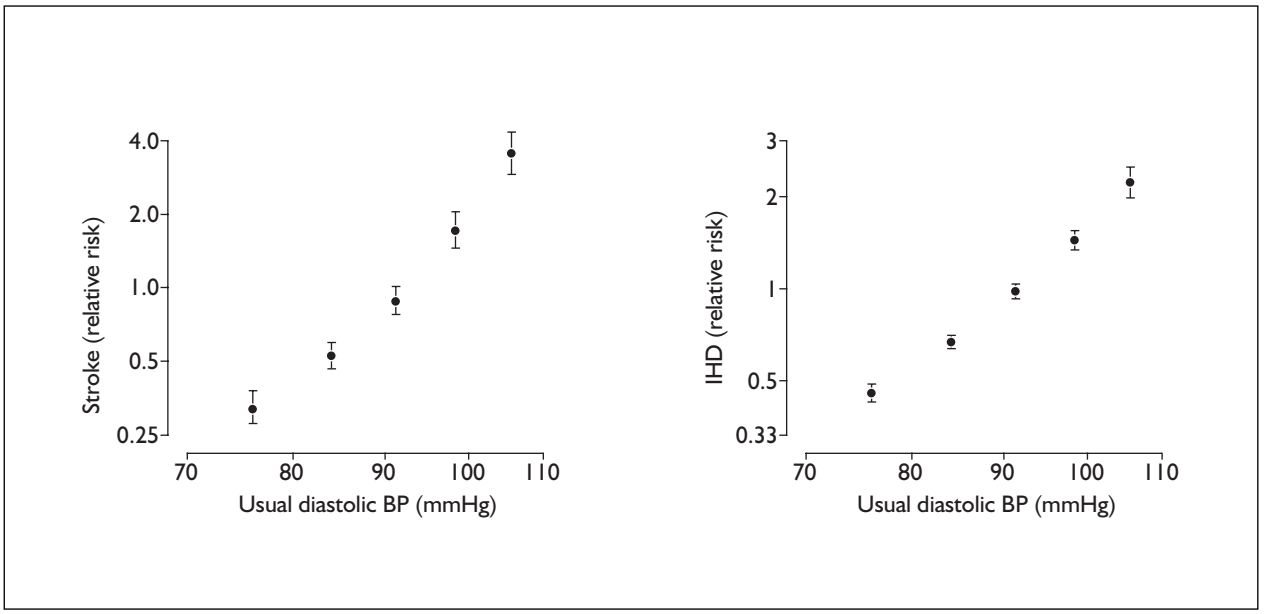

FIGURE 3 *The dose–response relationship between diastolic blood pressure (BP) and mortality from stroke and from ischaemic heart disease (IHD). The data are from a review of cohort studies;[32] the subjects have been divided into five equal groups according to ranked measurements of diastolic blood pressure and the relative risk estimates (with 95% CIs) in each of these groups are shown.*

below which a lower blood pressure is not associated with a lower risk of stroke or heart disease. With incidence plotted on logarithmic (or proportional) scales (a halving in incidence equivalent to a doubling), the associations of blood pressure with stroke and ischaemic heart disease may suggest slight curvature but are nonetheless well fitted by a straight line. The importance of this straight-line relationship is that, like a relative risk, it is generalisable.[31] It indicates that a specified **absolute** difference in blood pressure (say 5 mmHg diastolic) from any point on the blood pressure distribution, and at any level of risk, is associated with a constant **proportional** difference in the incidence of stroke and of ischaemic heart disease events.

This dose–response relationship is inconsistent with the view that drug treatment to lower blood pressure will prevent cardiovascular disease events only when blood pressure is high – towards the upper end of the distribution in Western populations. Average levels of blood pressure in middle-aged and older people in Western populations, as for serum cholesterol, are high in relation to levels in societies typical of our distant ancestors where people led traditional lives obtaining food through hunter–gatherer or subsistence farming means.[31] Blood pressure in such populations is about 110 mmHg systolic and 70 mmHg diastolic throughout life,[31] compared with the average British values at age 60 years of 145 and 80 mmHg (*Tables 1* and *2*).

The summary estimate from the cohort studies was that, after adjustment for the regression dilution bias, a 5 mmHg decrease in diastolic blood pressure was associated with a 34% (95% CI: 32 to 36%) lower risk of stroke and a 21% (95% CI: 19 to 22%) lower risk of ischaemic heart disease.[32] For a blood pressure difference twice as great (10 mmHg diastolic), the percentage reduction is calculated by squaring the relative risk. The 34% lower risk of stroke is equivalent to a relative risk of 0.66; $0.66^2 = 0.44$, a 56% reduction in stroke for double the blood pressure reduction. For ischaemic heart disease, the 21% lower risk is equivalent to a relative risk of 0.79; $0.79^2 = 0.62$, a 38% reduction for double the blood pressure reduction.

Other cohort studies have shown the same linear dose–response relationship between blood pressure and stroke and ischaemic heart disease, and yielded similar estimates of the size of the association.[33,35–39]

Results from randomised trials

The results of the trials of blood pressure-lowering drugs are presented in four categories, trials conducted in persons selected as having high blood pressure and trials conducted in persons with average levels of blood pressure, each separately in persons with and without known cardiovascular disease on entry.

TABLE 10 *Randomised trials of blood pressure reduction and incidence of stroke and ischaemic heart disease events in persons with high blood pressure who generally had no history of cardiovascular disease on entry*

Trial	No. of subjects		Mean age (years)	Main drug used	Mean duration (years)	Average blood pressure (mmHg) in controls		Reduction in blood pressure (mmHg) (treated minus control)		No. of strokes		No. of ischaemic heart disease events[a]	
	Tr	Con				Systolic	Diastolic	Systolic	Diastolic	Tr	Con	Tr	Con
Veterans Administration I[42]	68	63	51	TRH	1.5	186	119	43	27	1	3	0	3
Veterans Administration II[43]	186	194	51	TRH	3.3	165	106	27	17	5	20	11	13
Hypertension Detection and Follow-up Program – stratum III[44–47,65]	521	516	51	TR	5	–	98	–	7	16	31	21	42
US Public Health Service[48]	193	196	44	TR	7	147	98	18	10	1	6	15	18
Oslo Study[49]	406	379	45	T	5.5	150	97	17	10	0	5	14	10
Swedish Trial in Old Patients with Hypertension[50,65]	781	780	76	TB	2.1	188	97	19	8	28	49	26	38
Hypertension Detection and Follow-up Program – stratum II[44–47,65]	1022	979	51	TR	5	–	94	–	7	21	32	56	60
Australian[51]	1721	1706	50	T	4	–	94	–	5	13	22	33	33
European Working Party on High Blood Pressure in the Elderly[52,65]	381	396	72	T	4.7	172	94	21	8	27	39	44	54
Medical Research Council – mild hypertension[53]	8700	8654	52	TB	5	150	91	14	6	60	109	222	234
BBB Study[54]	1063	1063	60	Any	4.9	152	91	–	7	8	11	17	14
Hypertension Detection and Follow-up Program – stratum I[44–47,65]	3806	3822	51	T	5	–	90	–	5	50	79	175	223
Coope[55,65]	408	459	69	TB	4.4	180	88	20	10	18	38	35	36
US Veterans/NHLBI Feasibility Trial[56]	508	504	38	T	1.5	–	88	–	7	0	0	8	5

continued

TABLE 10 *Randomised trials of blood pressure reduction and incidence of stroke and ischaemic heart disease events in persons with high blood pressure who generally had no history of cardiovascular disease on entry (cont'd)*

Trial	No. of subjects		Mean age (years)	Main drug used	Mean duration (years)	Average blood pressure (mmHg) in controls		Reduction in blood pressure (mmHg) (treated minus control)		No. of strokes		No. of ischaemic heart disease events[a]	
	Tr	Con				Systolic	Diastolic	Systolic	Diastolic	Tr	Con	Tr	Con
Medical Research Council – older adults[57]	2183	2213	70	TB	5.8	167	85	15	7	101	134	128	159
UK Prospective Diabetes Study[58]	758	390	56	BA	8.4	154	87	10	5	38	34	107	69
All trials	**22705**	**22314**	**58**		**5.1**					**387**	**612**	**912**	**1011**
Summary relative risk estimates (95% CI)											**0.62[b] (0.54 to 0.70)**		**0.85[b] (0.78 to 0.93)**

Tr, treated, Con, control; –, not reported. T, thiazide; B, beta-blocker; R, reserpine; H, hydralazine; A, ACE inhibitor.
[a] Ischaemic heart disease deaths or non-fatal myocardial infarction.
[b] $p < 0.001$.

Persons with high blood pressure and no history of cardiovascular disease

Table 10 shows data from the trials of drug treatment to lower blood pressure in persons with high blood pressure and generally no history of cardiovascular disease on entry (one of the trials recruited people with diabetes but they were free from known cardiovascular disease[58]). The table shows the average age on entry and the average duration of follow-up (weighting by the total numbers of events in the placebo group in each trial). The average differences in blood pressure between treated and control subjects shown in *Table 10* were generally determined from measurements made only in persons who continued to attend the clinics and does not allow for those who left the trials early and no longer took the tablets. It is important to make this allowance, however, because the numbers of deaths, and where possible the numbers of non-fatal events, were recorded on an intention-to-treat basis, so the difference in incidence of ischaemic heart disease events and stroke between the treated and control groups was smaller than it would have been if no one had left the trial early. This underestimation of the effect can be overcome if the smaller difference in risk is related to the smaller difference in blood pressure between the two groups with all patients originally allocated included in the analysis irrespective of adherence to the trial protocol. The average difference in diastolic blood pressure between all persons **allocated** to the treatment and control groups, over the entire duration of the trials, was 6.6 mmHg with the difference in each trial weighted by the number of strokes in the control groups, and 6.0 mmHg weighted by the number of ischaemic heart disease events in the control groups.

The summary relative risk estimates in *Table 10* show that the above-average differences in diastolic blood pressure reduced the incidence of stroke by 38% (95% CI: 30 to 46%; $p < 0.001$) and ischaemic heart disease events by 15% (95% CI: 7 to 22%; $p < 0.001$).

Persons with high blood pressure and cardiovascular disease

Table 11 shows data from the trials in persons with high blood pressure who had had strokes. (There are no published data on persons with high blood pressure who had known ischaemic heart disease on entry.) The average difference in diastolic blood pressure between patients allocated to the treated and control groups in these trials was 5.7 mmHg weighting by the numbers of strokes and 8.1 mmHg by ischaemic heart disease events. The summary relative risk estimates show that treatment reduced the incidence of stroke by 31% (95% CI: 20 to 41%), a statistically highly significant reduction, but the result on ischaemic heart disease events is uninformative because the 95% CI is wide (35% decrease to 51% increase), due to small numbers.

Persons with average levels of blood pressure and no history of cardiovascular disease

Table 12 shows data from the randomised trials of blood pressure reduction in persons with no history of cardiovascular disease on entry and average levels of blood pressure (about the same as the population average values in persons of the same age shown in *Tables 1* and *2*). The relatively small difference in blood pressure between the treated and control groups in some of these trials arose because some control subjects also received drug treatment. The average difference in diastolic blood pressure between persons allocated to the treated and control groups in these trials was 4.2 mmHg weighting by the numbers of strokes and 4.1 mmHg by ischaemic heart disease events. The summary relative risk estimates show that the above differences in blood pressure reduced the incidence of stroke by 38% (95% CI: 25 to 49%; $p < 0.001$) and the incidence of ischaemic heart disease events by 29% (95% CI: 14 to 41%; $p < 0.001$).

Persons with average blood pressure and cardiovascular disease

Randomised trials of drugs that lower blood pressure in persons with average levels of blood pressure who had cardiovascular disease on entry fall into various categories. *Table 13* shows data from three trials in which the subjects had had strokes. The average differences in diastolic blood pressure were 3.5 mmHg weighting by the numbers of strokes and 3.9 mmHg by ischaemic heart disease events. The summary relative risk estimates show that treatment reduced the incidence of stroke by 24% (95% CI: 13 to 34%; $p < 0.001$) and the incidence of ischaemic heart disease events by 18% (95% CI: 37% reduction to 6% increase, not significant).

Randomised trials have been conducted in patients with ischaemic heart disease, not selected according to their blood pressure level, testing three different categories of drugs that lower blood pressure: beta-blockers, ACE inhibitors and calcium-channel blockers.

TABLE 11 *Randomised trials of blood pressure reduction and incidence of stroke and ischaemic heart disease events in persons with high blood pressure who had had strokes*

Trial	No. of subjects		Mean age (years)	Main drug used	Mean duration (years)	Average blood pressure (mmHg) in controls		Reduction in blood pressure (mmHg) (treated minus control)		No. of strokes		No. of ischaemic heart disease events[a]	
	Tr	Con				Systolic	Diastolic	Systolic	Diastolic	Tr	Con	Tr	Con
Hypertension Stroke Cooperative Study Group[59]	233	219	59	TR	2.3	165	99	25	12	43	52	7	12
Carter[60]	49	48	64	T	4	–	~105	–	~8	10	21	2	2
Hypertension Detection and Follow-up Program[44–47,65]	136	138	51	TR	5	–	92	–	6	15	16	23	18
Swedish Trial in Old Patients with Hypertension[50,65]	31	35	76	TB	2.1	188	97	19	8	1	4	3	2
European Working Party on High Blood Pressure in the Elderly[52,65]	35	28	72	T	4.7	172	94	21	8	5	9	4	5
Coope[55,65]	11	6	69	TB	4.4	180	88	20	10	2	1	0	2
Progress Collaborative Group[66b]	1464	1452	64	A	3.9	159	94	9	4	163	235	–	–
All trials	**1959**	**1926**	**63**	**3.7**						**239**	**338**	**39**	**41**
Summary relative risk estimates (95% CI)										**(0.59 to 0.80)**	**0.69[c]**	**(0.65 to 1.51)**	**0.99**

Tr, treated, Con, control, –, not reported. T, thiazide; B, beta-blocker; R, reserpine; A, ACE inhibitor.
[a] Ischaemic heart disease deaths or non-fatal myocardial infarction.
[b] Data on stroke were published separately for patients with high and average levels of blood pressure on entry.
[c] $p < 0.001$.

TABLE 12 *Randomised trials of blood pressure reduction and incidence of stroke and ischaemic heart disease events in persons with average levels of blood pressure who generally had no history of cardiovascular disease on entry*

Trial	No. of subjects		Mean age (years)	Main drug used	Mean duration (years)	Average blood pressure (mmHg) in controls		Reduction in blood pressure (mmHg) (treated minus control)		No. of strokes		No. of ischaemic heart disease events[a]	
	Tr	Con				Systolic	Diastolic	Systolic	Diastolic	Tr	Con	Tr	Con
Systolic Hypertension in Europe[61]	2398	2297	70	C	2	162	85	10	5	47	77	54	73
Hypertension Optimal Treatment[62b]	6262 6564	6264	62	AB	3.8	144	85	4 2	4 2	12 13	17	7 8	14
Systolic Hypertension in the Elderly Program – pilot[63]	443	108	72	T	2.8	155	72	15	4	11	6	15	4
Systolic Hypertension in the Elderly Program[64,65]	2306	2331	72	T	4.5	155	72	13	4	88	142	101	139
All trials	**17973**	**11000**	**71**		**3.6**					**171**	**242**	**185**	**230**
Summary relative risk estimates (95% CI)										**0.62[c] (0.51 to 0.75)**		**0.71[c] (0.59 to 0.86)**	

Tr, treated; Con, control. T, thiazide; B, beta-blocker; A, ACE inhibitor, C, calcium-channel blocker.
[a] Ischaemic heart disease deaths or non-fatal myocardial infarction.
[b] Three randomised groups: the two with the more intensive drug treatment were considered separate 'treated' groups.
[c] $p < 0.001$.

TABLE 13 *Randomised trials of blood pressure reduction and incidence of stroke and ischaemic heart disease events in persons with average levels of blood pressure who had had strokes*

Trial	No. of subjects		Mean age (years)	Main drug used	Mean duration (years)	Average blood pressure (mmHg) in controls		Reduction in blood pressure (mmHg) (treated minus control)		No. of strokes		No. of ischaemic heart disease events[a]	
	Tr	Con				Systolic	Diastolic	Systolic	Diastolic	Tr	Con	Tr	Con
Systolic Hypertension in the Elderly Program[64,65]	59	40	72	T	4.5	155	72	13	4	8	7	3	2
Post-Stroke Antihypertensive Treatment Study[67]	2841	2824	60	T	2	148	88	5.5	3	159	217	25	21
Progress Collaborative Group[66b]	1587	1602	64	A	3.9	136	79	9	4	144	185	–	–
	3051	3054	64	A	3.9	147	86	9	4	–	–	115	154
All trials	**7538**	**7520**	**62**		**3.1**					**311**	**409**	**143**	**177**
Summary relative risk estimates (95% CI)										**0.76[c] (0.66 to 0.87)**		**0.82 (0.63 to 1.06)**	

Tr, treated; Con, control; –, not reported. T, thiazide; A, ACE inhibitor.
[a] Ischaemic heart disease deaths or non-fatal myocardial infarction.
[b] Data on stroke were published separately for patients with high and average levels of blood pressure on entry.
[c] $p < 0.001$.

Beta-blockers

Table 14 shows data from the randomised trials of beta-blockers in patients with myocardial infarction that were of 6 months' or more duration. The average difference in diastolic blood pressure between patients allocated to the treated and control groups in these trials was generally not recorded, but is estimated to have been about 9 mmHg systolic and 5 mmHg diastolic from the analysis of the blood pressure reduction in randomised placebo controlled trials of beta-blockers reported in Chapter 7, taking into account the average dose, the average blood pressure levels in the placebo groups in these trials and the proportion of treated subjects who took the medication. The summary relative risk estimates from these trials show that beta-blockers reduced mortality from ischaemic heart disease (sudden death or fatal reinfarction) by 22% (95% CI: 14 to 29%; $p < 0.001$), and reduced non-fatal reinfarction by 22% (95% CI: 13 to 31%; $p < 0.001$). The reduction in all-cause mortality of 19% (95% CI: 12 to 26%) was similar to the reduction in heart disease mortality.

ACE inhibitors

Table 15 shows data from the trials of ACE inhibitors of 6 months' or more duration in patients with ischaemic heart disease. The average decrease in blood pressure was reported in five of these trials (*Table 15*) and the median decrease was 6 mmHg systolic and 3.5 mmHg diastolic. The summary relative risk estimate shows a 19% (95% CI: 11 to 25%) reduction in the incidence of reinfarction (fatal and non-fatal) ($p < 0.001$). (Because the patients in five of the eight trials were selected as having heart failure, sudden deaths were not included in this analysis because they may have been caused by heart failure rather than reinfarction.) While the reduction in heart failure shown in ACE inhibitor trials has been emphasised,[69–73,89] the reduction in reinfarction is also important.

Calcium-channel blockers

Table 16 shows data from the trials of calcium-channel blockers of 6 months' or more duration in patients with acute myocardial infarction but no evidence of heart failure. The average difference in diastolic blood pressure is estimated to have been about 8 mmHg systolic and 4 mmHg diastolic from measurements published for one trial[86] (it was not reported for the others), and from the analysis of the blood pressure reduction in randomised placebo controlled trials of calcium-channel blockers reported in Chapter 7, taking into account the average dose, the average blood pressure levels in the placebo groups in these trials and the proportion of treated subjects who took the medication. The summary relative risk estimate shows a 21% (95% CI: 10 to 31%) reduction in the incidence of recurrent ischaemic heart disease events ($p < 0.001$).

We have not analysed the reduction in stroke in these three sets of trials. In many of the trials the patients had acute myocardial infarction or severe cardiac failure, so many of the strokes may have been embolic and unlikely to be prevented by blood pressure reduction.

Synthesis of all the evidence on blood pressure lowering

Table 17 summarises the data from the different categories of randomised trials in *Tables 10–16*. The average diastolic blood pressure reduction in the trials varied, so *Table 17* shows the summary relative risk estimates from *Tables 10–16* standardised to a 5 mmHg diastolic blood pressure reduction (if the average blood pressure reduction in one category of trials was x, the corresponding relative risk estimate was raised to the power $5/x$); the resulting relative risk estimate was then subtracted from 1.00 and expressed as a percentage reduction in risk. *Figure 4* shows these summary estimates of risk reduction for a 5 mmHg reduction in diastolic blood pressure from the different categories of randomised trials, and compares them with the estimates from the cohort studies for stroke (34%) and ischaemic heart disease (21%) (shown with their 95% CIs as bands). For both stroke and ischaemic heart disease events the standardised reduction in risk for a 5 mmHg diastolic blood pressure reduction was consistent with the predicted effect from the cohort studies in each of the categories of randomised trials. For most of the estimates the confidence intervals are reasonably narrow, and these estimates in all cases are close to the predicted estimates. There was no evidence of heterogeneity across the estimates from the different groups of trials, either for stroke ($\chi^2 = 5.3$, $p = 0.15$) or ischaemic heart disease events ($\chi^2 = 4.9$, $p = 0.56$). The average reduction in incidence across all the categories of trials was 33% (95% CI: 26 to 39%) for stroke and 20% (95% CI: 16 to 23%) for ischaemic heart disease events, both remarkably close to the cohort study estimates of 34 and 21%, respectively.

TABLE 14 *Randomised trials of 6 or more months' duration comparing beta-blockers with control after myocardial infarction (see Freemantle and colleagues[68] for citations and additional trial data)*

Trial (first author)	No. of subjects		Mean age (years)	Mean duration (years)	All deaths		Ischaemic heart disease deaths		Non-fatal reinfarction	
	Tr	Con			Tr	Con	Tr	Con	Tr	Con
Ahlmark	69	93	57	2.0	5	11	5	11	4	15
Andersen	238	242	60	1.0	61	64	61	64	–	–
Boissel	298	309	65	0.9	17	34	12	30	–	–
Aronow	79	79	81	1.0	44	60	40	56	3	5
Australian and Swedish study	263	266	58	2.0	45	47	40	43	25	28
Baber	355	365	55	0.75	28	27	25	25	15	15
Barber	151	147	64	2.0	41	46	41	46	–	–
Basu	75	71	60	0.5	2	3	2	3	4	8
BHAT	1916	1921	55	2.1	138	188	119	164	103	121
Darasz	23	24	–	0.5	3	1	1	1	0	3
EIS	858	883	55	1.0	57	45	42	31	36	38
Hansteen	278	282	56	1.0	25	37	22	33	16	21
Julian	873	583	55	1.0	64	52	60	49	22	25
Kaul	25	25	49	0.5	3	3	3	3	0	4
LIT Research Group	1195	1200	58	1.5	86	93	66	70	–	–
Manger Cats	273	280	60	1.0	9	16	9	16	–	–
Mazur	101	103	–	1.5	5	11	5	11	5	7
Multicentre international	1533	1520	55	2.0	94	117	83	110	69	89
Norwegian Multicentre Study Group	945	939	60	1.4	98	152	82	142	56	83
Rehnqvist	59	52		1.0	4	6	4	6	–	–
Rehnqvist	154	147	60	3.0	25	31	25	31	18	31
Reynolds	38	39	55	1.0	3	3	3	3	3	2
Salathia	416	348	58	1.0	49	52	43	47	–	–
Schwartz:										
High risk	48	56		1.8	2	12	2	12	0	2
Low risk	437	432		1.8	15	27	15	27		
SSSD	130	123	59	3.0	17	9	15	9	5	6
Taylor	632	471	51	4.0	60	48	52	44	67	58
Wilcox (2 drugs)	127	129	60	1.0	19	19	19	19	–	–
	132				17		17			
Wilhelmsson	114	116	62	2.0	7	14	7	14	16	18
All trials	**11835**	**11245**	**59**	**1.7**	**1043**	**1228**	**920**	**1120**	**467**	**579**
Summary relative risk estimates (95% CI):					**0.81 (0.74 to 0.88)[a]**		**0.78 (0.71 to 0.86)[a]**		**0.78 (0.69 to 0.87)[a]**	

Tr, Treated; Con, control; –, not reported.
[a] $p < 0.001$.

TABLE 15 *Randomised trials of 6 or more months' duration comparing ACE inhibitors with placebo in patients with ischaemic heart disease*

Trial (acronym)	No. of subjects[a]		Mean age (years)	Drug	Mean duration (years)	Reduction in blood pressure (mmHg) (treated minus control), if reported		No. of reinfarctions[b]	
	Treated	Placebo				Systolic	Diastolic	Treated	Placebo
CONSENSUS[69]	127	126	71	E	0.5	10	–	20	19
SOLVD[70]	1285	1284	61	E	3.4	–	–	40	53
SAVE[71]	1115	1116	59	C	3.5	6	3	133	170
AIRE[72]	1004	982	65	R	1.3	–	–	81	88
TRACE[73]	876	873	67	T	3.1	–	–	34	47
HOPE[74–77]	4645	4652	66	R	5.0	10[c]	4[c]	459	570
PART-2[78]	308	309	61	R	4.0	6	4	22	33
SCAT[79]	229	231	61	E	4.0	4	3	8	13
All trials	**9589**	**9573**	**64**		**4.1**			**797**	**993**
Summary relative risk estimate (95% CI)								**0.81 (0.75 to 0.89)**	

E, enalapril; C, captopril; T, trandolapril; R, ramipril.

[a] In three trials all patients were recruited after myocardial infarction,[71–73] and in the other five trials most patients had ischaemic heart disease and some had other arterial disease.

[b] Two trials[69,70] recorded only fatal infarctions, the others non-fatal and fatal.

[c] The average reduction in blood pressure over 24 hours.[77]

TABLE 16 *Randomised trials of 6 or more months' duration comparing calcium-channel blockers with placebo in patients with acute myocardial infarction but no evidence of heart failure*

Trial (acronym)	No. of subjects		Mean age (years)	Drug	Mean duration (years)	No. of reinfarctions	
	Treated	Placebo				Treated	Placebo
DAVIT[80]	649	661	<75	V	0.5	47	72
MDPT[81]	950	959	58	D	2.1	134	154
DAVIT II[82]	587	574	≤ 75	V	1.5	74	97
SPRINT II[83]	396	430	64	Nf	0.5	53	56
CRIS[84]	531	542	56	V	2.0	39	49
DEFIANT II[85]	270	272	58	Ns	0.5	8	21
INTERCEPT[86]	430	444	57	D	0.5	53	81
PREVENT[87a]	417	408	57	A	3.0	19	20
All trials	**4230**	**4290**	**58**		**1.4**	**427**	**550**
Summary relative risk estimate (95% CI)						**0.79**	**(0.69 to 0.90)**

D, diltiazem; V, verapamil; Ns, nisoldipine; Nf, nifedipine; A, amlodipine.
[a] Patients had coronary artery disease but not necessarily infarction.

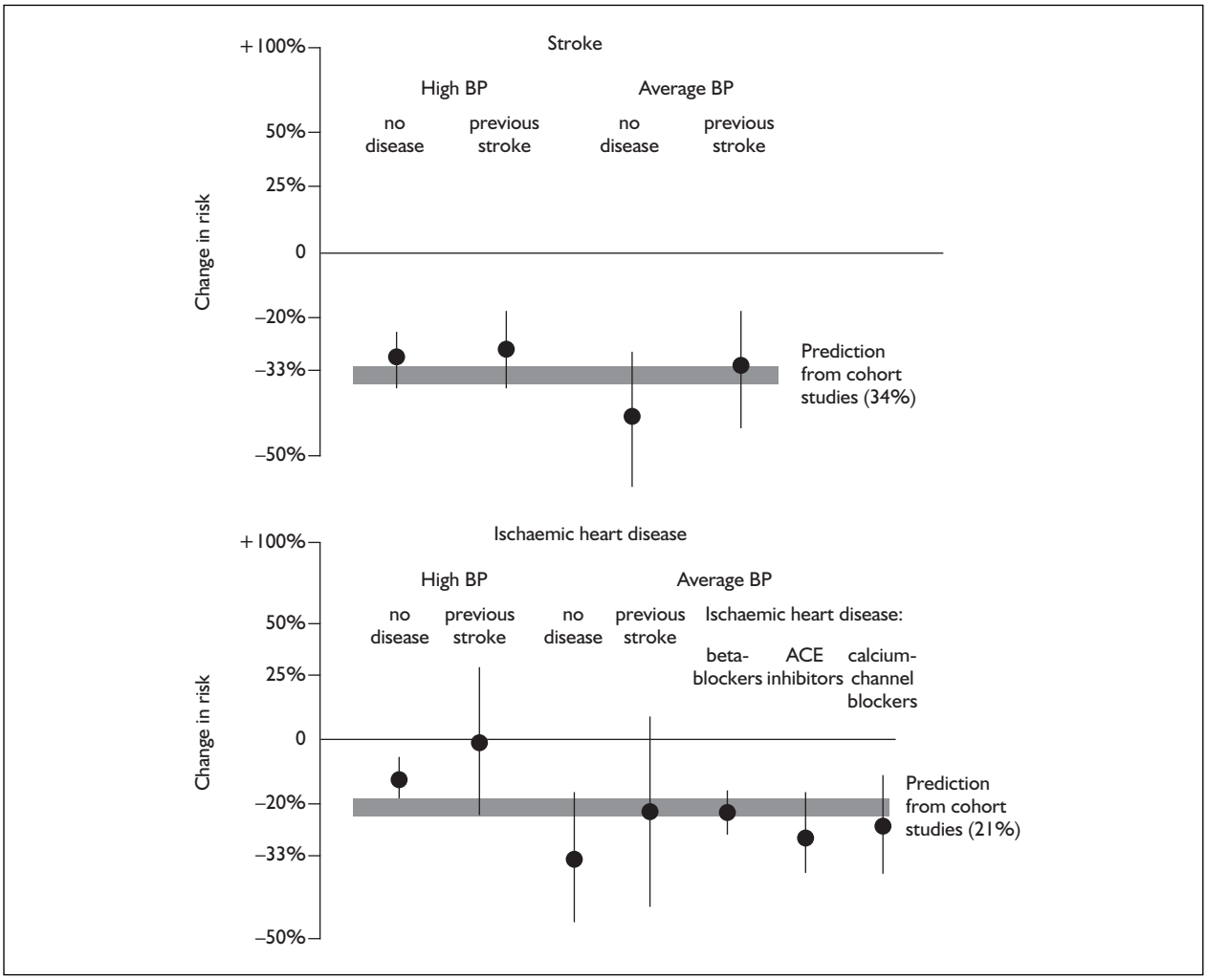

FIGURE 4 *The corroboration between estimates from randomised trials and from cohort studies of the reduction in risk of stroke and ischaemic heart disease events for a diastolic blood pressure reduction of 5 mmHg. The bands show the estimated reduction in risk of stroke (34%) and ischaemic heart disease events (21%), with 95% CIs, from a review of cohort studies.[32] The consistent estimates from different categories of trials of patients with high and average levels of blood pressure, and no disease and previous disease on entry (*Table 17*), are shown with 95% CIs.*

TABLE 17 *Average reduction in diastolic blood pressure in the seven categories of trials listed in Tables 10–16 and the summary relative risk estimates for stroke and ischaemic heart disease (IHD) events standardised to a 5 mmHg diastolic blood pressure reduction and expressed as a percentage reduction in risk*

		Average reduction in diastolic blood pressure (mmHg) weighting by numbers of		Risk reduction (%) for a 5 mmHg diastolic blood pressure reduction (95% CI)	
	Table No.	Strokes	IHD events	Stroke	IHD events
High blood pressure					
No disease on entry	10	6.6	6.0	30 (24 to 37)	13 (6 to 19)
Previous stroke	11	5.7	8.1	28 (18 to 37)	1 (–29 to 23)
Average blood pressure					
No disease on entry	12	4.2	4.1	43 (29 to 55)	34 (17 to 47)
Previous disease on entry:					
Stroke	13	3.5	3.9	32 (18 to 45)	22 (–8 to 44)
Ischaemic heart disease, treated with:					
Beta-blockers	14	–	5.0	–	22 (16 to 28)
ACE inhibitors	15	3.0	3.0	–	29 (17 to 37)
Calcium-channel blockers	16	–	4.0	–	26 (12 to 37)

In all seven categories of trials (*Tables 10–16*) there was relatively little variation between trials in the blood pressure difference between subjects allocated to the treated and control groups. The analyses therefore did not have the statistical power to determine a dose–response relationship. The mean age at the time of an event was 63 years in the cohort studies, and it was close to this in the trials (within 5 years of it in six of the seven categories and within 10 years in the seventh).

The results of the randomised trials corroborate the proportional estimates of effect from the cohort studies, confirm that they apply across the range of values of diastolic blood pressure and show that they apply to persons with and without existing cardiovascular disease. The trials reinforce the conclusion from the cohort studies that a specified absolute reduction in blood pressure from any point on the blood pressure distribution produces a constant proportionate reduction in the risk of stroke and ischaemic heart disease (by 34 and 21%, respectively, per 5 mmHg diastolic blood pressure reduction).

Blood pressure reduction as the mechanism whereby beta-blockers, ACE inhibitors and calcium-channel blockers prevent recurrent ischaemic heart disease events

The reduction in reinfarction and coronary mortality produced by beta-blockers after myocardial infarction has not been accepted as being due to the blood pressure lowering action of beta-blockers. Three observations, however, indicate that beta-blockers exert their protective effect mainly through lowering blood pressure.

1. The reduction in blood pressure produced by beta-blockers is similar to that produced by thiazides (see Chapter 7); the proportional reduction in ischaemic heart disease events is also similar, and it has not been proposed that thiazides prevent ischaemic heart disease events by any means other than lowering blood pressure. Analysis of five large randomised trials that have compared beta-blockers and thiazides in healthy persons with high blood pressure[53,57,90–92] shows this well: the blood pressure reductions were similar (only 0.4 mmHg diastolic different), and the incidence of ischaemic heart disease events was similar (433 events in thiazide-treated patients and 449 events in patients treated with beta-blockers). A greater effect of beta-blockers than thiazides would be expected if they prevented ischaemic heart disease by some other means in addition to lowering blood pressure.
2. Beta-blockers produce no detectable mortality reduction in the short term (1 month) after myocardial infarction.[68] This supports blood pressure lowering as the mechanism of action because (as discussed below) blood pressure lowering may produce little reduction in reinfarction in the first few weeks of treatment despite the significant longer term effect. With other proposed mechanisms by which beta-blockers may reduce mortality, such as by

preventing arrhythmias or preventing myocardial rupture, an immediate mortality reduction would have been expected.
3. In the trials of beta-blockers, the reduction in risk of ischaemic disease events is similar to that expected from the cohort studies of blood pressure and disease events (*Table 17*).

Similar arguments apply for calcium-channel blockers. The reduction in blood pressure that they produce is similar to that produced by thiazides (see Chapter 7). The reduction in the incidence of ischaemic heart disease events (*Table 16*) was commensurate with the blood pressure reduction produced, as it is in trials of thiazide diuretics. Trials of calcium-channel blockers show no reduction in reinfarction in the first month,[80–84,86] yet a short-term mortality reduction would be expected with some proposed mechanisms by which calcium-channel blockers may reduce myocardial infarction.

For ACE inhibitors, it has been claimed that the HOPE trial showed a greater reduction in the incidence of myocardial infarction and stroke than could be explained by the observed blood pressure reduction.[75,76] This analysis was based on the blood pressure reduction recorded at trough (24 hours after the last dose) in the HOPE trial, which was modest (3.8 mmHg systolic and 2.8 mmHg diastolic).[76] However, the blood pressure reduction over 24 hours would be expected to be a better predictor of the reduction in stroke and myocardial infarction, and the average reduction in blood pressure over 24 hours in the HOPE trial was somewhat larger, 10 mmHg systolic and 4 mmHg diastolic.[77] This is consistent with the observed reduction in the incidence of stroke and myocardial infarction. The smaller blood pressure reduction at trough reflects the relatively short duration of action of ramipril taken once daily as in the HOPE trial. The median reduction in blood pressure in all the trials of ACE inhibitors in *Table 15* is 6 mmHg systolic and 3.5 mmHg diastolic, which is similar to that expected from the analysis of the blood pressure reduction in randomised placebo controlled trials of ACE inhibitors reported in Chapter 7, taking into account the average dose, the average blood pressure levels in the placebo group in these trials and the proportion of treated subjects who took the medication. The summary estimate of the reduction in the incidence of ischaemic heart disease events in all the trials of ACE inhibitors in *Table 15* of 19% (95% CI: 11 to 25%) is similar to the expected reduction from the cohort studies of 15% (the reduction of 21% for a 5 mmHg decrease in diastolic blood pressure is equivalent to a 15% reduction for a 3.5 mmHg decrease). Moreover large randomised trials of ACE inhibitors, such as those of beta-blockers and calcium-channel blockers, showed no detectable reduction in reinfarction in the short term (1 month)[93,94] (as distinct from the significant reduction in early mortality through ACE inhibitors ameliorating heart failure). A short-term mortality reduction would be expected with some proposed mechanisms by which ACE inhibitors might reduce myocardial infarction. There is no statistical inconsistency and therefore no necessity to involve a second mechanism other than blood pressure reduction for the prevention of myocardial infarction.

Factors which may influence the reductions in stroke and ischaemic heart disease events in the randomised trials

Previous disease on entry to the trial

Figure 4 shows that the proportional reductions in the incidence of stroke and ischaemic heart disease events were similar in trials in which the subjects generally had no previous disease on entry, had had a stroke and had myocardial infarction or other clinical manifestations of ischaemic heart disease.

Initial blood pressure

Collins and colleagues showed that there were similar proportional reductions in stroke and ischaemic heart disease events in three groups of randomised trials in which the average diastolic blood pressure in the placebo groups was about 100, 95 and 90 mmHg, each group of trials corroborating the cohort study estimates of a 34% reduction in stroke and a 21% reduction in ischaemic heart disease events for a 5 mmHg decrease in diastolic blood pressure.[34] The more recent randomised trial data show this across the entire range of blood pressure values in Western populations (*Tables 12–16*), with trials corroborating the proportional reductions from starting levels as low as 72 mmHg diastolic[63,64] and 120–125 mmHg systolic.[70,71,84,86]

Age

The randomised trial data showed no detectable effect of age. In the trials in *Tables 10–12* in which the average age at sustaining a stroke was over 70 years there was a 36% reduction in risk (95% CI: 28 to 44%) for a 5 mmHg decrease in diastolic blood pressure, and in trials where the average age

at sustaining a stroke was under 70 years the reduction in risk was 38% (95% CI: 28 to 47%). The reductions in ischaemic heart disease events were 24% (95% CI: 17 to 30%) over 70 years and 12% (95% CI: 1 to 22%) under 70 years, a difference that was not statistically significant.

Fatal and non-fatal events

In trials that recorded both, the proportional reductions in fatal and non-fatal strokes and fatal and non-fatal myocardial infarction were similar; there was no suggestion of a difference in either direction.

The duration of treatment

Data on the effect of the duration of the blood pressure reduction on the decrease in the incidence of stroke were available for 10 of the randomised trials listed in *Tables 10–12*. *Table 18* shows these results – the numbers of strokes occurring in treated and control patients in the first year after entering the trials, in the second year and in the third and subsequent years – together with the summary relative risk estimates. The average difference in diastolic blood pressure between treated and control groups in these 10 trials was 5 mmHg. The average reduction in the incidence of stroke in these trials, from *Table 18*, was 24% (95% CI: 8 to 37%) in the first year, 31% (95% CI: 19 to 41%) in the second year, and 37% (95% CI: 28 to 45%) in the third and subsequent years. The trend was statistically significant [p(trend) =0.03]. The maximum effect is not attained in the first year, and the data would be consistent with an interpretation of little reduction in risk in the first few months after lowering blood pressure, but a reduction in risk that is maximal or near maximal after the first year. Equivalent data on ischaemic heart disease events were available from only three of the trials;[53,57,58] the numbers of events each year were small but were consistent with a similar trend. The randomised trials of serum cholesterol reduction and ischaemic heart disease showed a more pronounced effect of duration, with relatively little reduction in risk apparent in the first 2 years after lowering serum cholesterol.[95]

J-shaped associations between diastolic blood pressure and cardiovascular mortality

In some relatively small cohort studies, the incidence of ischaemic heart disease events, and in some studies stroke, was **greater** among persons with the lowest levels of diastolic blood pressure than in persons with average levels of blood pressure.[96–101] The incidence was greater in persons with high levels of blood pressure than in the persons with average levels as expected, so creating a J-shaped association with the lowest incidence occurring at a diastolic blood pressure of about 85 mmHg. A surprising finding is that the J-shaped association in these studies was convincing for diastolic but generally absent for systolic blood pressure,[97–100] a difference that is unlikely to be due to chance. This J-shaped diastolic association with cardiovascular disease is in striking contrast to the continuous association shown in the large-scale cohort studies of healthy adults (*Figure 3*).

It is implausible that low blood pressure should both cause and prevent the same disease. An explanation is that vascular disease can cause a low diastolic blood pressure. The studies showing the J-shaped association included persons with a history of myocardial infarction or other existing vascular disease,[101] most of the disease events were in those with existing vascular disease, and the J-relationship was generally seen only in this subgroup.[99,100] Extensive atheromatous disease increases the risk of death or recurrent events and, through stiffening vessel walls, also lowers diastolic blood pressure.[102,103] Similarly, heart failure increases risk and can lower diastolic blood pressure.[96] The observation that the J-relation tends to be specific for diastolic blood pressure and not systolic supports the explanation that the vascular disease causes low blood pressure rather than vice versa.

The randomised trials of blood pressure reduction summarised in *Table 12* establish that lowering diastolic blood pressure below about 85 mmHg does not increase the incidence of stoke and ischaemic heart disease events as would have been expected from the J-relationship if the low blood pressure caused the disease. In three randomised trials in which the average diastolic blood pressure in the placebo groups was 85 mmHg,[57,61,62] and in two trials in which it was as low as 72 mmHg,[63,64] blood pressure reduction in the treated groups lowered the incidence of stroke and ischaemic heart disease events by about the proportion expected from the continuous association shown in the cohort studies in *Figure 3*. Similarly, in the trials of beta-blockers, ACE inhibitors and calcium-channel blockers in persons with ischaemic heart disease, the average diastolic blood pressure in the placebo groups was below 85 mmHg, and the proportional reduction in reinfarction and ischaemic heart disease mortality was close to the expected value.

TABLE 18 *Randomised trials of blood pressure reduction listed in Tables 10–13 in which data were available on the numbers of strokes occurring in each year of follow-up*[a]

			No. of strokes					
	No. of subjects		Year 1		Year 2		Year 3+	
Trial	**Tr**	**Con**	**Tr**	**Con**	**Tr**	**Con**	**Tr**	**Con**
Swedish Trial in Old Patients with Hypertension[50]	812	815	11	22	12	20	6	11
Medical Research Council – mild hypertension[53]	8700	8654	12	17	14	19	34	72
Coope[55]	419	465	8	5	4	9	8	25
Medical Research Council – older adults[57]	2183	2213	22	17	21	26	57	92
UK Prospective Diabetes Study[58]	758	390	6	3	6	3	26	28
Hypertension-Stroke Cooperative Study Group[59]	233	219	18	21	12	12	7	9
Systolic Hypertension in Europe[61]	1758	1683	10	22	10	17	17	21
Systolic Hypertension in the Elderly Program[64]	2365	2371	28	34	22	42	53	83
PROGRESS Collaborative Group[66]	3051	3054	99	119	92	134	116	167
Post-Stroke Antihypertensive Treatment Study[67]	2434	2418	61	98	64	83	34	36
All trials			**275**	**358**	**257**	**365**	**358**	**544**
Summary relative risk estimates (95% CI)			**0.76 (0.63 to 0.92)**		**0.69 (0.59 to 0.81)**		**0.63 (0.55 to 0.72)**	

Tr, treated; Con, control.

[a] The numbers were published directly for three trials,[59,64,67] provided by the authors for two[53,57] and calculated from published survival curves for the other five.

The evidence allows only one interpretation, that the low diastolic blood pressure is a consequence of the existing cardiovascular disease, not a cause of it.

Conclusions

Average blood pressure levels in Western populations at older ages are high, and a decrease in average levels reduces the risk of cardiovascular disease. A given absolute decrease in blood pressure from any point on the distribution produces a similar proportional reduction in the risk of stroke or ischaemic heart disease events. A reduction in diastolic blood pressure of 5 mmHg reduces the incidence of stroke by about 34% and of ischaemic heart disease by about 21%. A policy of drug treatment to lower blood pressure in high-risk patients irrespective of their level of blood pressure is the rational approach,[35] since the majority of cardiovascular events occur in these patients, as discussed in the next chapter.

Chapter 4

The performance of blood pressure as a screening test for ischaemic heart disease and stroke in persons with no history of cardiovascular disease

Key points

- Blood pressure is an important cause of stroke and ischaemic heart disease and lowering blood pressure substantially lowers risk. However, it is not a good screening test in distinguishing those who will and will not develop the diseases.
- The poor screening performance is illustrated by the findings that in the largest cohort study, persons in the top 10% of the distribution of systolic blood pressure experienced only 21% of all ischaemic heart disease events and 28% of all strokes at a given age.
- Irrespective of the cut-off value used to define high blood pressure, in any age–sex group the risk of stroke and myocardial infarction in those with high blood pressure is similar to the risk in those 10–15 years older who do not have high blood pressure. Risk in men aged 75–84 years without high blood pressure is about six times greater than risk in women age 45–54 years with high blood pressure.
- The underlying problem is that age is a better screening test than blood pressure.
- Data on the risk in untreated persons with very high blood pressure (sustained above 110 mmHg diastolic, the 99.5 centile) are limited but indicate that at age 50 years the annual incidence of myocardial infarction and stroke together is about 7%, and the death rate 3%. This is lower than the risk without treatment in an average patient who has had a myocardial infarct or stroke.

Introduction

The value of blood pressure measurements in screening for cardiovascular disease in the general population is best expressed quantitatively as the detection rate (that is, the proportion of all persons who have a myocardial infarction or stroke within a specified time period whose blood pressure is above a specified cut-off level) set against the false-positive rate (that is, the proportion of all persons who do not have a myocardial infarction or stroke in the time period whose blood pressure is above the same cut-off level). Such data can be obtained from the results of cohort (prospective) studies.

We first present previously unpublished data showing the detection rates and false-positive rates corresponding to various blood pressure cut-off levels using data from a large cohort study, the BUPA (British United Provident Association) study. This cohort consists of 21,520 men aged 35–64 years who attended the BUPA medical centre in London for a medical examination between 1975 and 1982. This study has the advantage that screening performance using blood pressure and other cardiovascular risk factors in combination has also been determined[104] (see Chapter 5). The study has been described previously.[104] The blood pressure measurements were taken in the sitting position after the men had been resting for 5 minutes, using a random zero sphygmomanometer. Serum cholesterol was measured at the time of the visit, a serum sample was stored at –40°C, and we were notified of all deaths by cause from the NHS Central Register. There were 21,188 men with no history of cardiovascular disease on entry and only these men were included in this analysis; among them 751 deaths from ischaemic heart disease and 142 deaths from stroke were recorded to October 1996.

Figures 5 and *6* show the distribution of systolic and of diastolic blood pressure in the 751 men who died of ischaemic heart disease and the men who did not (the blood pressure values were age-adjusted to age 50 years using a linear regression of blood pressure on age, and then fitted to a Gaussian model). *Figures 7* and *8* show the same in the 142 men who died of stroke and the men who did not. A good screening test would be characterised by a wide separation between the distributions in affected and unaffected subjects, but for blood pressure the figures show considerable overlap in the distributions. It is not possible to identify a blood pressure cut-off that would identify most of those who died of heart

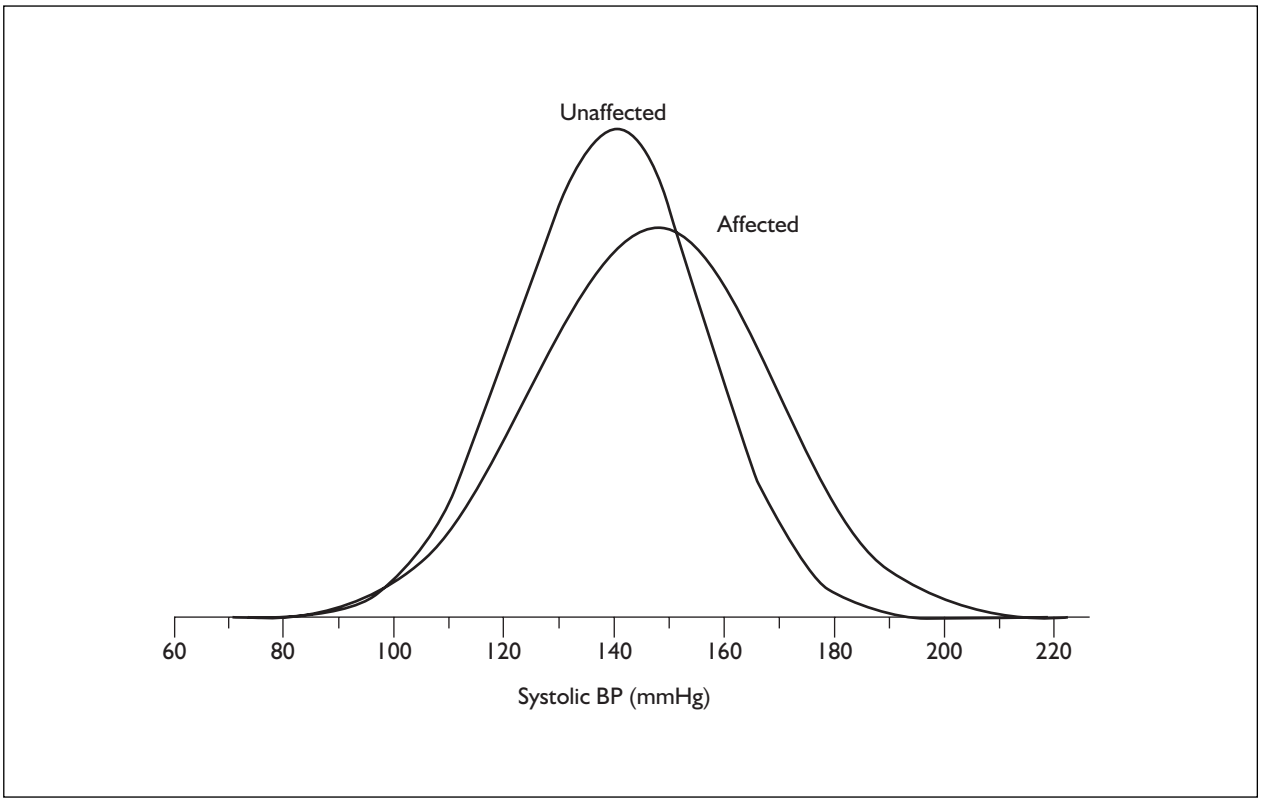

FIGURE 5 *Distribution of systolic blood pressure in men who died of ischaemic heart disease and men who did not; age-adjusted data from the BUPA cohort study*

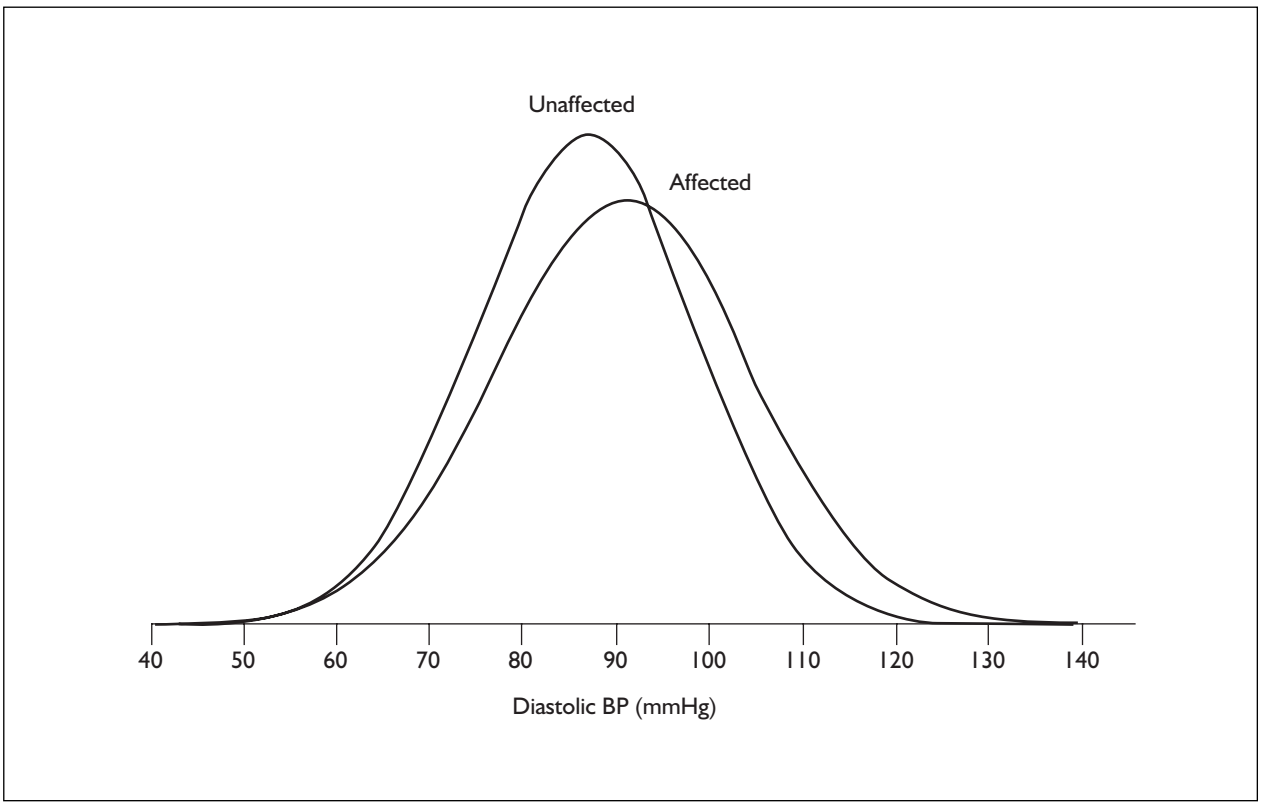

FIGURE 6 *Distribution of diastolic blood pressure in men who died of ischaemic heart disease and men who did not; age-adjusted data from the BUPA cohort study*

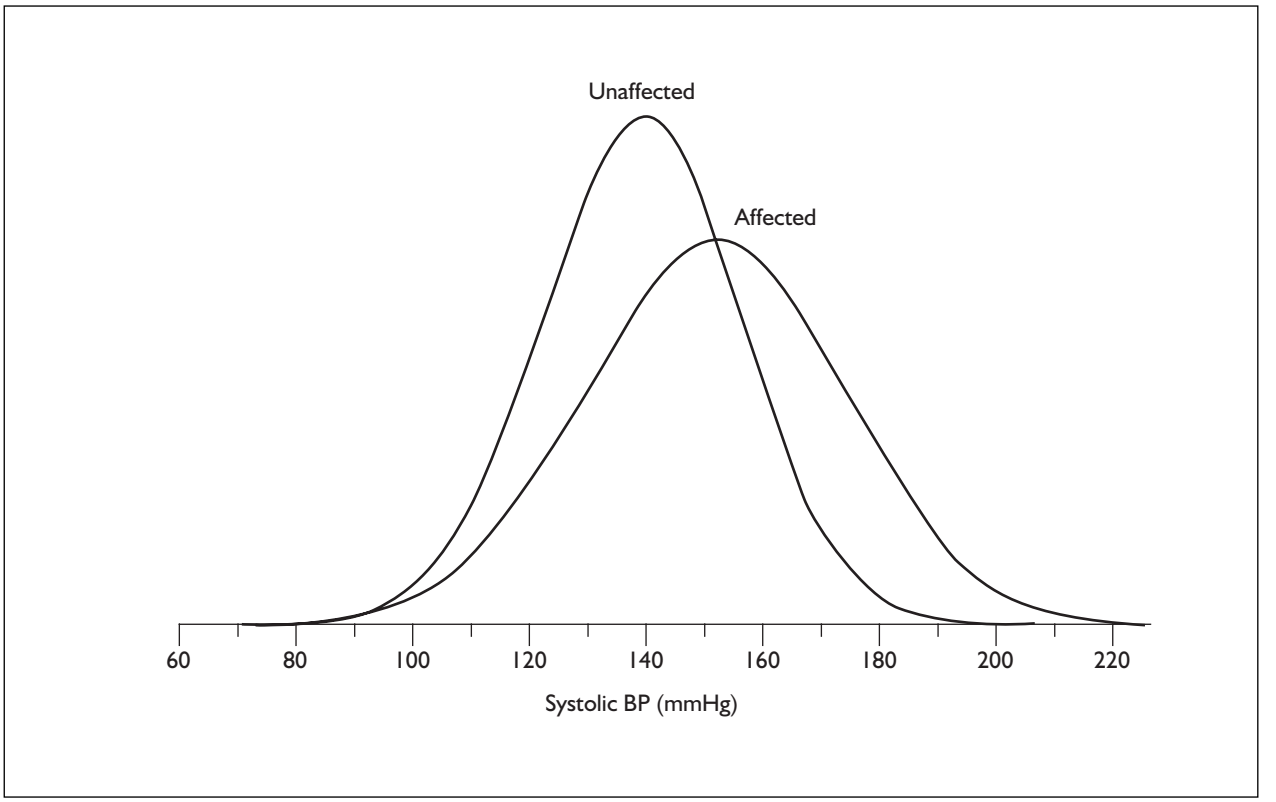

FIGURE 7 *Distribution of systolic blood pressure in men who died of stroke and men who did not; age-adjusted data from the BUPA cohort study*

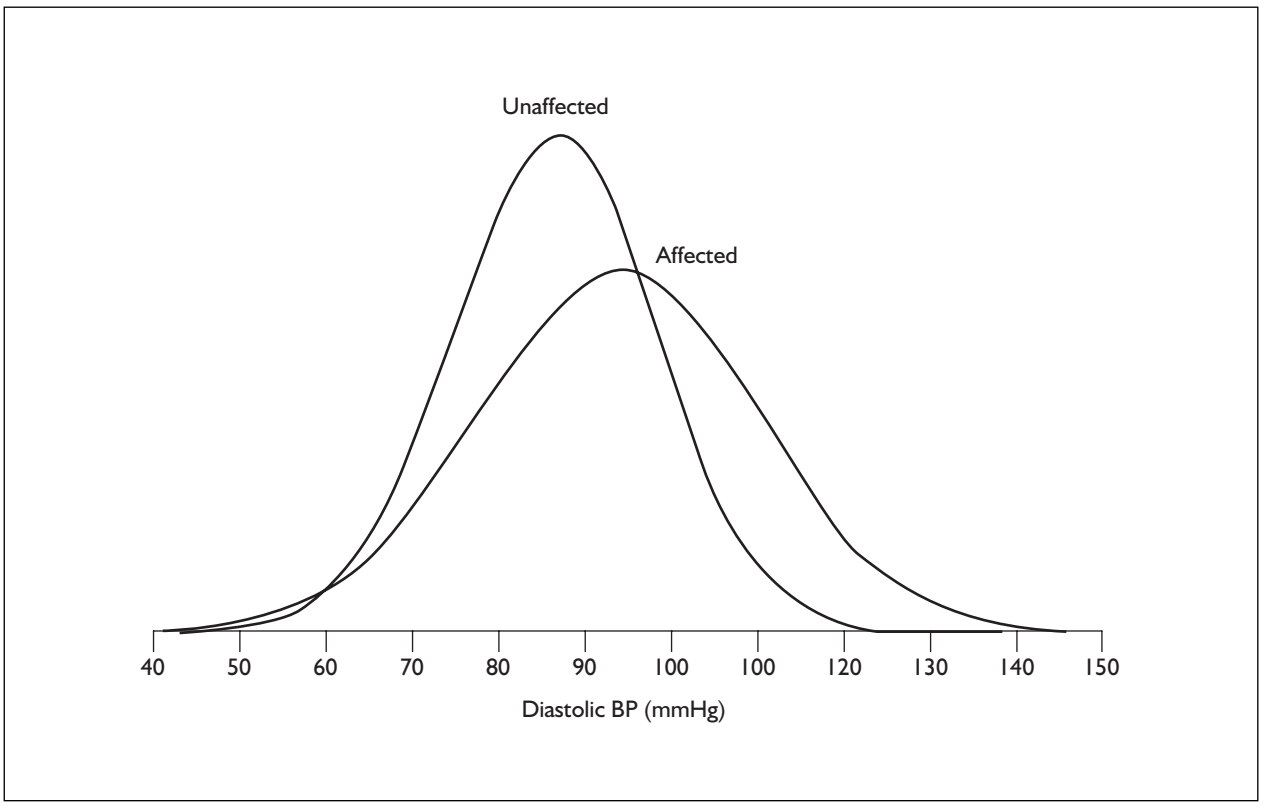

FIGURE 8 *Distribution of diastolic blood pressure in men who died of stroke and men who did not; age-adjusted data from the BUPA cohort study*

TABLE 19 *Estimates of the performance of blood pressure in detecting persons who will die of ischaemic heart disease or stroke: previously unpublished data from the BUPA cohort[1] (the estimates are adjusted for age differences between those who died of cardiovascular disease and those who did not)*

'Screen positive' blood pressure centile	Corresponding blood pressure cut-off (mmHg)	False-positive (%)[a]	Detection rate (%)[b]		
			Ischaemic heart disease	Stroke	Both together
Systolic blood pressure					
≥ 95th	167	5	17	25	19
≥ 90th	160	10	26	35	28
≥ 80th	153	20	39	48	41
≥ 70th	148	30	49	57	50
≥ 60th	143	40	57	65	59
≥ 50th	139	50	65	72	67
≥ 40th	135	60	72	78	73
≥ 30th	130	70	79	84	80
≥ 20th	125	80	86	89	86
≥ 10th	117	90	92	94	92
Diastolic blood pressure					
≥ 95th	106	5	13	24	15
≥ 90th	101	10	21	33	24
≥ 80th	96	20	34	44	36
≥ 70th	93	30	44	53	47
≥ 60th	89	40	54	61	55
≥ 50th	86	50	62	68	64
≥ 40th	83	60	70	74	71
≥ 30th	80	70	78	80	78
≥ 20th	77	80	85	86	85
≥ 10th	72	90	92	92	92

[a] The proportion of all persons who did not die of cardiovascular disease whose blood pressure was above the specified cut-off.
[b] The proportion of all men who died of the specified disease whose blood pressure was above the specified value.

disease or stroke but only a small proportion of those who did not; a large proportion of the population would need to be offered preventive treatment in order that most of those who would have developed stroke or ischaemic heart disease would receive the treatment.

Table 19 summarises the data from the figures, showing the false-positive rate and detection rate corresponding to various blood pressure cut-off values. The table shows that for systolic blood pressure, using the 95th centile as the cut-off value (that is, the false-positive rate, taking age differences into account, was about 5%), the detection rates were 25% for stroke, 17% for ischaemic heart disease and 19% for stroke and heart disease together. At a false-positive rate of 10% the detection rate of stroke and heart disease together was 28% (an additional 9% of the deaths were detected); for a false-positive rate of 20% the detection rate was 40% (an additional 12% of the deaths were detected). To detect half the events, a false-positive rate of 30% would be necessary – 30% of those not developing stroke or ischaemic heart disease would receive treatment. For diastolic blood pressure screening the performance was slightly poorer.

Although the distributions of blood pressure in affected and unaffected persons in the figures were modelled to be Gaussian, this had little effect on the estimates of screening performance. At false-positive rates of 10–20% the directly observed detection rates were 2–3 percentage points lower than the modelled estimates, and at detection rates of 80–90% they were 1–2 percentage points higher.

Table 20 shows published data from the largest cohort study of cardiovascular risk factors and mortality, the cohort of men aged 35–57 years who were screened for recruitment into the Multiple Risk Factor Intervention Trial (the MRFIT screenees).[105] The data in *Table 20* are on the 350,000 men with no history of cardiovascular disease on entry, in whom 7150 deaths from heart

TABLE 20 *Estimates of the screening performance of blood pressure in detecting persons who will die of ischaemic heart disease or stroke: data from the MRFIT screenees cohort*[105]

'Screen positive' blood pressure centile	Corresponding blood pressure cut-off (mmHg)	False-positive (%)	Detection rate (%)	
			Ischaemic heart disease	Stroke
Systolic blood pressure				
≥ 98th	170	2	6	not reported
≥ 90th	151	10	21	28
≥ 80th	142	20	35	43
≥ 70th	137	30	47	55
≥ 60th	132	40	56	65
≥ 50th	129	50	66	73
≥ 40th	125	60	73	78
≥ 30th	121	70	81	87
≥ 20th	118	80	88	92
≥ 10th	112	90	94	97
Diastolic blood pressure				
≥ 90th	98	10	19	25
≥ 80th	92	20	31	40
≥ 70th	89	30	43	51
≥ 60th	86	40	53	62
≥ 50th	84	50	62	69
≥ 40th	81	60	71	77
≥ 30th	79	70	79	84
≥ 20th	76	80	87	90
≥ 10th	71	90	93	95

disease and 733 deaths from stroke were recorded after 12 years of follow-up: the results are adjusted for age and other cardiovascular risk factors. The values of blood pressure corresponding to specified centiles are lower than in the BUPA cohort (*Table 19*) because the MRFITT cohort is younger. The screening performance is similar to that from the BUPA cohort shown in *Table 19*, although slightly weaker. At a 10% false-positive rate using systolic blood pressure, for example, 28% of the stroke deaths were detected and 21% of the deaths from ischaemic heart disease. Detection was again slightly weaker using diastolic than systolic blood pressure.

These results build on concepts set out by Rose in 1981,[106] recognising that intervening only in people in the tail of the risk factor distribution can have only a small impact in preventing diseases caused by the risk factor, and further developed in his 1992 book 'The strategy of preventive medicine'.[107] The results also build on the observation that important risk factors from a causal perspective are usually poor screening tests.[108] Most disease events will occur among the larger number of persons in a population with risk factor levels close to the average and only a minority of the disease events will occur among persons in the tail of the distribution, because despite their greater risk they are few in number.

Table 21 presents estimates of the incidence of myocardial infarction and stroke in men and women of specified ages whose blood pressure is above specified centile values of systolic blood pressure, calculated as follows. From the detection rates and false-positive rate according to various cut-off levels of systolic blood pressure in *Table 19*, the corresponding likelihood ratios are shown. The likelihood ratio (the detection rate divided by the false-positive rate) is the 'concentrating power' of blood pressure as a screening test, the risk in screen positive persons relative to that in the general population. Multiplying the likelihood ratio by the estimates of the incidence of myocardial infarction and stroke according to age and sex in *Table 8* gives an estimate of the average annual incidence of myocardial infarction or stroke in 'screen positive' individuals. In men aged 60 years with blood pressure in the top 5%, the annual risk of myocardial infarction is 1.8% (i.e. 184 per 10,000) and for stroke it is 1.2%. The annual risk for both diseases combined at age 60 years is therefore 3.0%. At age 50 years it is 1.4%.

TABLE 21 *Incidence of myocardial infarction and stroke (rate per 10,000 persons per year in men and women of specified ages) in persons whose systolic blood pressure is above specified centile values*[a]

		Myocardial infarction						Stroke					
				Incidence per 10,000 persons year						Incidence per 10,000 persons per year			
				Men, aged (years)		Women, aged (years)				Men, aged (years)		Women, aged (years)	
'Screen positive' blood pressure centile	False-positive rate (%)	Detection rate (from *Table 19*) (%)	Likelihood ratio[b]	50	60	50	60	Detection rate (from *Table 19*) (%)	Likelihood ratio[b]	50	60	50	60
95th	5	17	3.4	99	184	20	58	25	5.0	45	115	35	90
90th	10	26	2.6	75	140	16	44	35	3.5	32	81	25	63
70th	30	49	1.6	46	86	10	27	57	1.9	17	44	13	34
50th	50	65	1.3	38	70	8	22	72	1.4	13	32	10	25
10th	90	92	1.0	29	54	6	17	94	1.0	9	23	7	18

[a] The data are calculated from the estimates of screening performance in *Table 19* and the estimates of the incidence of myocardial infarction and stroke in England and Wales in *Table 8*.

[b] The detection rate divided by the false-positive rate: the measure of the 'concentrating power' of a screening test.

Guidelines for the management of high blood pressure

Guidelines for the management of high pressure have tended to specify a blood pressure cut-off value that defines 'hypertension', and advocated drug treatment to lower blood pressure in all persons whose blood pressure exceeds that cut-off, irrespective of age or sex.[109–115] Recent guidelines have recommended the use of drugs that lower blood pressure in all people with sustained systolic blood pressure ≥ 160 mmHg or sustained diastolic blood pressure ≥ 100 mmHg, and also recommended that persons with sustained blood pressure of 140–159 mmHg systolic and 90–99 mmHg diastolic be considered for drug treatment, taking other risk factors into account.[115] We derived age- and sex-specific estimates of the incidence of myocardial infarction and stroke in persons whose blood pressure exceeds these blood pressure cut-offs following the approach illustrated in *Table 21*, using the data in *Tables 1* and *2* to translate absolute cut-offs (such as 160 mmHg systolic) into age- and sex-specific blood pressure centiles (as shown in the first column of *Table 21*). Adjustment was made for the fact that the data in *Tables 1* and *2* are based on single blood pressure recordings whereas the above recommendations imply that the average of several recordings is taken, by allowing for regression to the mean using published estimates of the within- and between-person variance in blood pressure.[2]

Table 22 shows the estimates of screening performance derived in this way, according to age and sex, using each of these four recently recommended cut-off values in turn to define 'high blood pressure' – the average of five readings being ≥ 160 mmHg systolic, or ≥ 100 mmHg diastolic , or ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic[115] (shown in *Table 22* in increasing order of the proportion of persons who would be screen positive). Consideration of the recommendation that the values of other risk factors be taken into account in connection with the last two cut-off values is deferred until the next chapter.

Two conclusions arise from the data in *Table 22*. First, the proportions of people classified screen positive varies widely according to the cut-off value: the false-positive rate in men aged 65–74 years, for example, varies between 4% (using 100 mmHg diastolic as the cut-off) and 73% (using 140 mmHg systolic as the cut-off). Second, the risk in persons with and without 'high' blood pressure increases substantially with age, and in any 10-year age group the average risk in those with high blood pressure is about the same as the risk in those without high blood pressure who are about 10 years older for women and about 15 years older for men (for example, the annual risk is 2.2% per year in 65–74-year-old women whose blood pressure is above 160 mmHg systolic and 2.0% per year in 75–84-year-old women whose blood pressure is below that level). Adherence to the current guidelines based on blood pressure cut-offs therefore necessitates the inconsistency of offering drug treatment to a person of given age who has high blood pressure but denying it to a person 10–15 years older with average blood pressure whose risk is similar. The fact that among persons with high blood pressure risk at any age is higher in men than women introduces further inconsistency. Overall, the risk in men aged 75–84 years without high blood pressure (not offered drug treatment) is about six times greater than the risk in women aged 45–54 years with high blood pressure (offered drug treatment). This cannot be justified by the argument that treatment should be started young to prevent an accumulation of risk over many years because, as shown in Chapter 3, risk is reversible within a few months of lowering blood pressure.

The data in *Table 22* confirm that blood pressure is not a good screening test. The differences in risk are too small to justify offering blood pressure-lowering drugs to those with high blood pressure while withholding it from those without. The underlying problem is that age is a better screening test than blood pressure.

The level of risk in untreated persons with very high blood pressure

The prognosis without treatment in persons with very high blood pressure (sustained above the 99.5 centile) is often considered to be extremely poor (it has been said to be 'worse than cancer'[110]). The incidence of stroke and ischaemic heart disease events in the extreme tail of the blood pressure distribution is best taken from direct observation, because projections from observations in persons with lower blood pressure may be inaccurate. Observations on untreated persons with extremely high levels of blood pressure are available only from the medical literature of 35 or more years ago (before effective blood pressure-lowering

TABLE 22 *Estimates of screening performance, by age and sex, using four blood pressure cut-off values to define 'screen-positives' in detecting those who will have a myocardial infarction or stroke over 10 years*

Blood pressure cut-off[a]	Age (years)	False-positive rate (%)[b]	Detection rate (%)[c]	Risk in positives (% per year)[d]	Risk in negatives (% per year)[e]
≥ 100 mmHg diastolic					
Men	45–54	2	6	1.4	0.4
	55–64	3	9	2.7	0.8
	65–74	4	13	5.8	1.7
	75–84	3	16	17.8	3.9
Women	45–54	1	4	0.7	0.2
	55–64	1	5	2.0	0.4
	65–74	1	5	5.8	1.1
	75–84	4	17	15.8	3.2
≥ 90 mmHg diastolic					
Men	45–54	16	32	0.9	0.3
	55–64	22	41	1.7	0.7
	65–74	23	44	3.6	1.3
	75–84	18	45	10.5	3.0
Women	45–54	4	15	0.5	0.1
	55–64	10	26	1.1	0.4
	65–74	12	31	3.0	0.9
	75–84	17	45	9.2	2.4
≥ 160 mmHg systolic					
Men	45–54	2	6	1.4	0.4
	55–64	17	39	2.2	0.7
	65–74	29	55	3.8	1.3
	75–84	45	74	7.4	2.2
Women	45–64	3	9	0.4	0.1
	55–64	12	27	0.9	0.3
	65–74	30	57	2.2	0.7
	75–84	34	63	6.3	2.0
≥ 140 mmHg systolic					
Men	45–54	23	40	0.8	0.3
	55–64	57	79	1.3	0.5
	65–74	73	89	2.4	0.8
	75–84	85	96	5.2	1.3
Women	45–54	37	56	0.2	0.1
	55–64	59	78	0.5	0.2
	65–74	75	91	1.4	0.4
	75–84	78	92	4.2	1.2

[a] That is, the average of five readings is ≥ the specified cut-off.
[b] That is, of all persons in the specified age–sex group who **do not** have myocardial infarction or stroke over the 10 years, the percentage whose blood pressure is ≥ the specified cut-off.
[c] That is, of all persons in the specified age–sex group who **do** have myocardial infarction or stroke over the 10 years, the percentage whose blood pressure is ≥ the specified cut-off.
[d] Risk of myocardial infarction or stroke, without treatment, in those with blood pressure ≥ the specified cut-off.
[e] Risk of myocardial infarction or stroke, without treatment, in those with blood pressure below the specified cut-off.

TABLE 23 *The incidence of stroke and myocardial infarction observed in untreated patients with high blood pressure (85th centile)*[a]

Trial (control group)	No. of subjects	Average duration of follow-up (years)	Diastolic blood pressure (mmHg)	Age-specific centile	Cardiovascular events			Mean age at event (years)	Annual incidence (%)[b]	
					Myocardial infarction	Stroke	Total			
Veterans Administration I[42]	63	1.5	119	99.9	3	3	6	58	6.3	
Hamilton[119]	31	3.5	115	99.9	3	5	8	52	7.4	6.6
Wolff[120]	42	1.4	112	99.7	0	1	1	57	1.7	
Veterans Administration II[43]	194	3.3	106	98	13	20	33	57	5.2	
Hypertension Detection and Follow-up Program – stratum III[44–47]	529	5	98	92	44	34	78	63	2.9	
US Public Health Service[48]	196	7	98	94	18	6	24	52	1.7	
Oslo Study[49]	379	5.5	97	92	10	5	15	49	0.7	
Swedish Trial in Old Patients with Hypertension[50]	815	2.1	97	88	40	53	93	80	5.4	
Hypertension Detection and Follow-up Program – stratum II[47,48]	1004	5	94	86	63	36	99	63	2.0	
Australian[51]	1706	4	94	86	33	22	55	63	0.8	
MRC mild hypertension study[53]	8654	5	91	87	234	109	343	47	0.8	

[a] Data are from the control groups of trials of drug treatment of high blood pressure; trials in which more than 5% of persons in the control groups received drug treatment are excluded.

[b] Total number of events divided by average duration of follow-up.

drugs became available), and from two types of study – observational studies of patients attending clinics and the control groups of trials.

In the observational studies of patients with very high blood pressure attending hospital clinics, many of the patients had been referred to the clinics because they had associated diseases, such as chronic renal failure, heart failure or stroke, and these diseases contributed to the high mortality.[116–118] Patients with uncomplicated high blood pressure were often not referred to the clinics. We identified only one such study in which mortality was reported separately for the patients who had no associated morbidity on entry.[118] In this one study, of 53 patients with uncomplicated very high blood pressure [initial diastolic blood pressure 110 mmHg diastolic (99.5 centile) or higher] the average age was about 50 years, and 14 of the 53 died from cardiovascular causes over 9 years of follow-up,[118] a death rate of 3% per year. This rate is similar to that in untreated patients with angina (see *Table 28*), lower than that in untreated patients after myocardial infarction and much lower than the 'worse than cancer' assessment.

Table 23 shows data from the control groups of trials of drug treatment to lower blood pressure in which the average blood pressure in the placebo group during the trial exceeded the 85th age-specific centile, and in which fewer than 5% of the persons in the control group received drugs to lower blood pressure. In three of the studies the average blood pressure was sustained above 110 mmHg diastolic (the 99.5 age-specific centile).[42,119,120] There were a total of 15 strokes and myocardial infarcts (fatal or not) in these three control groups, and the average age at the time of the event was 55 years. The 15 events corresponded to an average annual incidence of 7% per year, consistent with the above estimate of the death rate of 3% per year.

In summary, in untreated patients with very high blood pressure (>99.5 centile) but no history of cardiovascular disease, at the age of about 50–55 years the combined incidence of stroke and myocardial infarction is about 7% per year and the death rate is about 3% per year. At older ages the risk is likely to be higher but there are no direct estimates.

Conclusions

While blood pressure is an important cause of stroke and ischaemic heart disease and lowering blood pressure (from any level) substantially lowers risk, measuring blood pressure is not an effective method of screening to identify persons at high risk who should be offered blood pressure-lowering drugs.

Chapter 5

Screening performance using multiple cardiovascular risk factors in combination in persons with no history of cardiovascular disease

Key points

- Using multiple cardiovascular risk factors in combination does not add substantially to the poor screening performance of blood pressure alone.
- Among persons in a specified age group, the 5% at highest risk experience 17% of all heart disease deaths with risk computation based on blood pressure alone, 22% when based on blood pressure and apolipoprotein (apo) B [or low-density lipoprotein (LDL) cholesterol] in combination, and 28% using these two, smoking and three other cardiovascular risk factors all in combination.
- In order to offer preventive treatment to the majority of persons who would have a myocardial infarct or stroke in an age group, it is necessary to categorise such a high proportion of the population as high risk that screening serves little purpose. The preventive treatment would have to be so simple and cheap that it might as well be offered to all in the age group.
- As with blood pressure alone, the underlying problem is that age is a better screening test than the reversible risk factors.

Introduction

Over the past few years, there has been a move away from policies for cardiovascular disease prevention that are based on developing "separate guidelines for each risk factor with treatment recommended when that factor is above a specified level".[121] More recent guidelines tend to be based on estimations of a person's probability of developing a cardiovascular disease event over a specified period, this estimation of absolute risk being based on measurements of individual levels of several risk factors including age and sex.[121–125] It has seemed intuitive that combining information on several risk factors must be substantially more informative than one.[125,126] Perhaps surprisingly, the improvement in screening performance is smaller than might be expected.

In the previous chapter it was shown that the BUPA cohort study, like other cohort studies, confirms the poor screening performance of blood pressure measurement in detecting persons who will develop ischaemic heart disease and stroke. In the BUPA cohort study the extent to which screening performance was improved by taking the values of other cardiovascular risk factors into account in combination with blood pressure has been determined in a previously published analysis based on the 229 men who had died from ischaemic heart disease by the end of 1987.[104] In this analysis, the serum concentration of apolipoproteins was measured on stored serum samples, including apo B (the protein component of LDL cholesterol, used as a measure of serum LDL cholesterol concentration), apo AI and apo AII (the protein components of HDL cholesterol) and apo (a) [the protein component of lipoprotein (a)]. Data on smoking and family history had been collected and were used. The results are shown in *Table 24*.

Using either systolic blood pressure or apo B in isolation, the detection rate was 17% (single measurement) for a 5% false-positive rate (that is, the cut-off value that defines the 5% of men who did **not** die of ischaemic heart disease identifies only 17% of those who did). Using systolic blood pressure and apo B in combination, the detection rate increased to 22%. Additional risk factors added relatively little to screening performance, and with six risk factors in combination the detection rate was only 28% for a 5% false-positive rate. The same trends are observed with a 10% false-positive rate. Multiple measurements of the same risk factor also add little to screening performance. The cardiovascular risk factors even in combination cannot be used to identify the majority of persons who will develop cardiovascular disease without also identifying a large proportion of those who will not.

TABLE 24 *Estimates of the detection rate of men who died of ischaemic heart disease, using various combinations of one, two and three measurements of cardiovascular risk factors, at 5% and 10% false-positive rates*[104]

	No. of measurements		
Screening variable	**1**	**2**	**3**
5% false-positive rate			
SBP alone	17	18	19
Cholesterol alone	12	12	13
Apo B alone	17	18	19
SBP and apo B	22	23	23
SBP, apo B, apo A1, apo (a)	24	25	25
SBP, apo B, apo A1, apo (a), smoking	27	28	29
SBP, apo B, apo A1, apo (a), smoking, family history	28	29	29
10% false-positive rate			
SBP alone	26	27	28
Cholesterol alone	20	21	22
Apo B alone	28	29	30
SBP and apo B	34	35	36
SBP, apo B, apo A1, apo (a)	36	38	38
SBP, apo B, apo A1, apo (a), smoking	40	41	42
SBP, apo B, apo A1, apo (a), smoking, family history	41	42	43

SBP, Systolic blood pressure.

Adding other risk factors in combination in persons with no history of cardiovascular disease does not overcome the problem of the weak screening performance of blood pressure alone because all the known risk factors are relatively weak markers of risk, so that adding a second or a third marker adds little to the ability to separate individuals who will develop ischaemic heart disease from those who will not. For example, both systolic blood pressure alone and apo B alone detected 17% of those who died of heart disease at a 5% false-positive rate. If both were used together and a person was designated screen positive if either or both were positive, the detection rate would be slightly less than twice as great [31%, calculated as $1 - (1 - 0.17)^2$], but the false-positive rate would also be about twice as great (10%) (actually 9.75%). The critical question is whether this detection rate of 31% is substantially higher than those from using either blood pressure or apo B alone at a 10% false-positive rate. In fact it is not: the detection rate is 26% for systolic blood pressure alone and 28% for apo B alone (*Table 24*), setting the false-positive rate at 10% in each case. Hence the 'gain' in using both together rather than either one alone is an increase of only about 3–5% in the detection rate. Adding the second adds relatively little to the first, and adding a third or fourth adds even less.

It may appear counter-intuitive that blood pressure, serum cholesterol and other cardiovascular risk factors are so important aetiologically yet show weak screening performance. This paradox has been explained.[108] In screening for disease in general, to detect half the disease events at a false-positive rate of 5%, for example, there must be about a 100-fold difference in risk between the fifth of the population with the highest values of the screening variable and the fifth with the lowest.[108] As a general rule, this tends to be attained in practice only with risk markers that are a consequence of the presence of disease and rarely with risk markers that are of aetiological importance in healthy persons. *Figure 3* shows that when a population is ranked according to blood pressure, the fifth of the population with the highest blood pressure, relative to the fifth with the lowest, have only about a 10-fold risk of stroke and a five-fold risk of heart disease. The fact that drugs can lower blood pressure by an amount equivalent to about half of this 10th to 90th centile range (see Chapter 7) explains their importance in prevention.

Screening based on individual risk estimates from combinations of risk factors

Table 21 shows estimates of the combined incidence of myocardial infarction and stroke in persons above specified blood pressure centiles

TABLE 25 *Incidence of myocardial infarction and stroke (rate per 10,000 persons per year in men and women of specified ages) in smokers and in non-smokers whose systolic blood pressure is above specified centile values (data calculated as those in Table 21)*

	Blood pressure centile			
	≥ 95th		≥ 90th	
	Smokers	Non-smokers	Smokers	Non-smokers
Stroke				
Age 45–64 years				
Men	67	27	56	22
Women	52	21	43	17
Age 65–84 years				
Men	289	242	233	194
Women	249	209	198	166
Myocardial infarction				
Age 45–64 years				
Men	129	47	115	42
Women	33	15	30	13
Age 65–84				
Men	335	238	294	209
Women	217	164	189	142
Both				
Age 45–64 years				
Men	196	74	171	65
Women	86	36	73	31
Age 65–84 years				
Men	623	480	526	403
Women	466	373	387	309

according to age and sex. *Table 25* extends this by showing incidence separately for smokers and non-smokers. The highest incidence is seen in men in the older age group (65–84 years) who are smokers with blood pressure above the 95th centile. The incidence of stroke and myocardial infarction combined in this group is 623 per 10,000 per year, or about 6% per year. Since about one-third of first events are fatal, this corresponds to a death rate of about 2% per year.

To obtain individual risk estimates according to a person's age, sex, blood pressure and smoking status, we modified the calculations used in *Table 25* to provide estimates of the combined incidence of stroke and myocardial infarction for persons **on** specified blood pressure centiles (as opposed to the incidence in all persons whose blood pressure is **above** a specified blood pressure centile as shown in *Table 25*). The resulting estimates of individual risk according to specified values of age, sex, smoking status and blood pressure centile are shown in *Table 26*. The data indicate that age is the single most important determinant of risk. There is a 2–3-fold increase in risk with each 10 years of advancing age in any group defined by sex, smoking status and blood pressure centile. This exceeds the proportional difference between smokers and non-smokers (except in the youngest age group) and exceeds the variation in risk across the greater part of the distribution of blood pressure.

The risk estimates in *Table 26* were validated by using them to predict the incidence of stroke and myocardial infarction in the control groups of the trials shown in *Table 23*; the predicted incidence in each group was calculated taking into account the average age, sex ratio, proportion of smokers and age-specific blood pressure centile. In the 11 studies combined the predicted number of events (stroke and myocardial infarction) was 685 and the observed number was 755 – a close correlation validating the methodology.

Screening using the cardiovascular risk factors to predict which persons will have cardiovascular disease events would be most effectively done using risk estimates such as those in *Table 26*. The risk estimate itself would then be considered the screening variable, and drug treatment to lower blood pressure (and other preventive measures)

TABLE 26 *Estimates of the combined incidence of first stroke and first myocardial infarction (% per year) in England according to age, sex, smoking and blood pressure*

Sex	Age (years)	Smokers (S) or non-smokers (NS)	Blood pressure centile						
			1	5	25	50	75	95	99
Men									
	45–54	S	0.3	0.4	0.6	0.8	1.0	1.4	1.7
		NS	0.09	0.1	0.2	0.2	0.3	0.4	0.5
	55–64	S	0.5	0.7	1.1	1.4	1.8	2.6	3.2
		NS	0.2	0.3	0.5	0.6	0.8	1.1	1.4
	65–74	S	0.8	1.1	1.6	2.1	2.8	4.2	5.4
		NS	0.5	0.7	1.1	1.4	1.8	2.8	3.6
	75–84	S	1.2	1.7	2.8	4.0	5.6	9.2	12.5
		NS	0.9	1.4	2.3	3.2	4.6	7.6	10.4
Women									
	45–54	S	0.09	0.1	0.2	0.2	0.3	0.5	0.6
		NS	0.03	0.04	0.06	0.08	0.1	0.2	0.2
	55–64	S	0.2	0.3	0.4	0.6	0.8	1.2	1.6
		NS	0.09	0.1	0.2	0.3	0.4	0.6	0.7
	65–74	S	0.4	0.6	0.9	1.2	1.7	2.6	3.5
		NS	0.3	0.4	0.6	0.8	1.1	1.8	2.4
	75–84	S	0.8	1.3	2.2	3.1	4.5	7.6	10.5
		NS	0.7	1.1	1.8	2.6	3.7	6.4	8.9

might be offered to all those whose annual risk exceeded a specified level (say 2% per year), as currently advocated.[121–125] *Table 27* shows the results of screening using risk as the screening variable: risk is computed from age, sex, smoking status and blood pressure (*Table 27a*); the effect of also including serum cholesterol is shown in *Table 27(b)*. For risk estimates of myocardial infarction or stroke of 0.25, 0.5, 1 and 2% per year, the positive rate (the percentage of the population whose risk exceeds these specified limits) and the detection rate (the percentage of all persons who will have a stroke or myocardial infarction whose risk estimate exceeds these specified limits) are shown. Few of the cardiovascular events occur in persons with a high computed risk (≥ 4% per year or even ≥ 2% per year), and as with screening using blood pressure alone, screening performance is poor: the detection rate does not greatly exceed the false-positive rate.

The results reinforce those in *Table 24*; it is not possible to identify a high-risk minority who will experience most of the events, even when all these variables are taken into account. For example, 5% of all men aged 55–64 years have a computed annual risk of ≥ 2% but they experience only 16% of all the events in men in that age group; 28% of the men have a computed risk of ≥ 1% but they experience only 52% of the events (*Table 27b*). In order to predict the majority of events in an age group it is necessary to categorise such a high proportion of the population as high risk (81% of men aged 65–74 years to detect 91% of the events, for example) that screening serves little purpose. The preventive treatment, if aimed at 81% of all men in the age group, would have to be simple and inexpensive. It would be more cost-effective to offer the preventive treatment to **all** the men in the age group than to 81% of them; the remaining 9% of the events would be targeted, and the cost of the screening procedure and the large number of medical consultations would be avoided.

Table 27 illustrates the limitations in the expectation that screening using a sufficiently large number of risk factors must be effective. Comparison of the data in *Table 27(a)* and *(b)* shows that the addition of serum cholesterol has very little effect. In older age groups there is little increase in either the positive rate or the detection rate. At younger ages there is a small increase in the detection rate but a similar proportionate increase in the positive rate. The reason is that, because serum cholesterol is a weak marker of risk, its inclusion in the risk equation will involve no

TABLE 27 *Screening using individual risk estimates as the screening variable: risk is computed from a person's age, sex, smoking status and blood pressure (a); the effect of also including serum cholesterol is shown in (b)*[a]

		Percentage with annual risk									
		≥ 0.25%		≥ 0.5%		≥ 1%		≥ 2%		≥ 4%	
Sex	**Age (years)**	**Positive rate (%)**	**Detection rate (%)**	**Positive rate (%)**	**Detection rate (%)**	**Positive rate (%)**	**Detection rate (%)**	**Positive rate (%)**	**Detection rate (%)**	**Positive rate (%)**	**Detection rate (%)**
(a)											
Men	45–54	57	81	28	58	7	22	0	1	0	0
	55–64	99	100	74	87	25	46	4	12	0	0
	65–74	100	100	99	100	82	92	27	44	2	6
	75–84	100	100	100	100	99	100	84	94	36	57
Women	45–54	15	37	1	6	0	0	0	0	0	0
	55–64	66	84	22	43	3	10	0	0	0	0
	65–74	100	100	89	96	41	61	5	14	0	1
	75–84	100	100	100	100	96	99	69	85	23	43
(b)											
Men	45–54	60	86	30	64	11	36	2	10	0	1
	55–64	98	99	73	88	28	52	5	16	0	1
	65–74	100	100	99	100	81	91	29	48	3	8
	75–84	100	100	100	100	99	100	84	94	38	59
Women	45–54	17	42	3	12	0	1	0	0	0	0
	55–64	67	85	24	46	4	12	0	1	0	0
	65–74	100	100	89	96	43	63	7	16	0	1
	75–84	100	100	100	100	96	99	70	86	25	46

[a] For risk estimates of stroke and myocardial infarction combined of 0.25, 0.5, 1 and 2% per year the positive rate (the percentage of the population whose risk estimate exceeds these limits) and the detection rate (the percentage of persons who will have a myocardial infarction or stroke whose risk estimate exceeds these limits) are shown.

more than a modest interchange of persons designated screen-positive and screen-negative. Some persons whose computed risk on the basis of age, sex, smoking status and blood pressure was a little below the specified cut-off (say, 1.9% per year when the specified value is 2% per year) will have above-average serum cholesterol so that the readjustment of their risk calculation means that they cross the risk cut-off to lie slightly above it. These persons will replace a slightly smaller number of people with below-average serum cholesterol whose risk computation was slightly above the cut-off value without, but below it with, the inclusion of serum cholesterol. The overall effect in detecting persons who will have stroke or myocardial infarction is small. The same applies when high-density lipoprotein (HDL) cholesterol and other lipids or lipoproteins, and other cardiovascular risk factors such as family history, are included in the risk equation.

Enthusiasm for cardiovascular screening based on multiple risk factors is based on the premise that persons with relatively high values of several risk factors must be at increased risk. What is perhaps overlooked is that such persons are very uncommon. A person who smokes, has blood pressure in the top 5% of the distribution and has serum cholesterol in the top 5% of the distribution will have about a 12-fold increase in risk on average [an absolute risk of a myocardial infarction or stroke (fatal or not) of about 9% per year in men aged 60 years] with no history of cardiovascular disease. However, the low prevalence of such persons is not widely appreciated; it is about 0.0008 ($0.3 \times 0.05 \times 0.05$) – less than one in 1000. Moreover, as described in the next chapter, even this risk is lower than the average risk without treatment in a person who has had a myocardial infarction or stroke.

Conclusions

Using multiple cardiovascular risk factors in combination does not materially improve the poor screening performance of blood pressure alone. In order to offer preventive treatment to the majority of persons who would have a myocardial infarct or stroke in an age group, it is necessary to categorise such a high proportion of the population as being at high risk that screening serves little purpose: the treatment might as well be offered to all in the age group.

Chapter 6

Patients with cardiovascular disease: existing disease as a screening test

Key points

- Identifying patients at the time of hospital discharge following myocardial infarction or stroke is the most effective screening test to identify those who will die of cardiovascular disease. For myocardial infarction the detection rate is 50% and the false-positive rate 12%.
- In patients with a history of myocardial infarction or stroke the cardiovascular death rate in the absence of treatment is about 5% per year, a high risk that has been observed to persist for at least 15 years.
- In the absence of treatment, about half of all deaths from heart disease in a population occur after hospital discharge following the first infarct. This estimate applies at age 65 years; the proportion is slightly higher at younger ages (about 60% at age 55 years) and lower at older ages (40% at age 75 years).
- In patients with a clinical history of cardiovascular disease, the associations of blood pressure and other cardiovascular risk factors with recurrent events or cardiovascular death are much weaker than in healthy persons. This is because the risk factors do not directly predict cardiovascular events; they predict the underlying arterial disease which must already be present in persons who have had an event.
- Hence reducing the risk factors decreases risk in all such persons, but the risk factors have virtually no discriminatory value as screening tests.

Introduction

A screening test can be a simple enquiry, such as asking people if they have already had an event of the disorder being screened for, since for many disorders recurrence rates are far higher than occurrence rates. Identifying everyone in a population who has had a first myocardial infarction or stroke, or other clinical evidence of existing disease, is a remarkably effective screening method to identify future deaths, although necessarily unsatisfactory if the prime objective is to identify all events.

A review of published studies following patients after myocardial infarction has shown that after a first myocardial infarction, from the time of hospital discharge onwards (about 1 month after the event), the annual death rate from ischaemic heart disease and stroke in the absence of any preventive treatment is 10% in the first year and 5% in all subsequent years.[127] The 5% cardiovascular death rate in subsequent years showed no tendency to attenuate over time in studies that had followed patients for 15 years or more – an important result. After a second (or subsequent) myocardial infarction, the death rate after hospital discharge is twice as high – 20% in the first year and 10% in subsequent years. Again, the high death rate of 10% per year shows no tendency to attenuate over time. In patients with angina but no infarction, the annual cardiovascular death rate is 3%. *Table 28* summarises these estimates of the annual death rate from ischaemic heart disease in patients with a history of existing disease, and shows that mortality in patients with a clinical history of cerebrovascular disease is remarkably similar to that in patients with coronary artery disease. After a first stroke, the annual death rate from stroke and ischaemic heart disease is 5%, and after a transient ischaemic attack without permanent neurological damage it is about 3%. All patients with known cardiovascular disease are at high risk.

Persons with existing disease represent a large group; *Table 29* shows the proportions of English men and women in specified age groups with a history of angina, previous myocardial infarction or previous stroke.

Figure 9 presents estimates that 31 out of every 100 people in England and Wales will have a myocardial infarction at some time in their life. Of these 31, 11 will die of the first acute event (within the first month), a further 11 will eventually die of ischaemic heart disease or stroke and nine will die of some other cause. [These estimates follow algebraically from the following observations. Ischaemic heart disease accounts for 22% of all deaths in England and Wales (*Table 3*). Of all deaths from ischaemic heart disease about half

TABLE 28 *Annual death rates and event rates from ischaemic heart disease and stroke in persons with existing cardiovascular disease*

	Ischaemic heart disease and stroke combined	
Clinical history	**Death rate (%)**	**Event rate (%)**
No history of cardiovascular disease, age 60 years[a]		
men	0.4	0.8
women	0.14	0.35
One previous myocardial infarct[127]	5	10
More than one previous myocardial infarct[127]	10	17
Angina without infarction[127]	3	6
Previous stroke[128–131]	5	10
Transient ischaemic attack without stroke[130,131]	3	8

[a] Data from *Tables 4* and *8*.

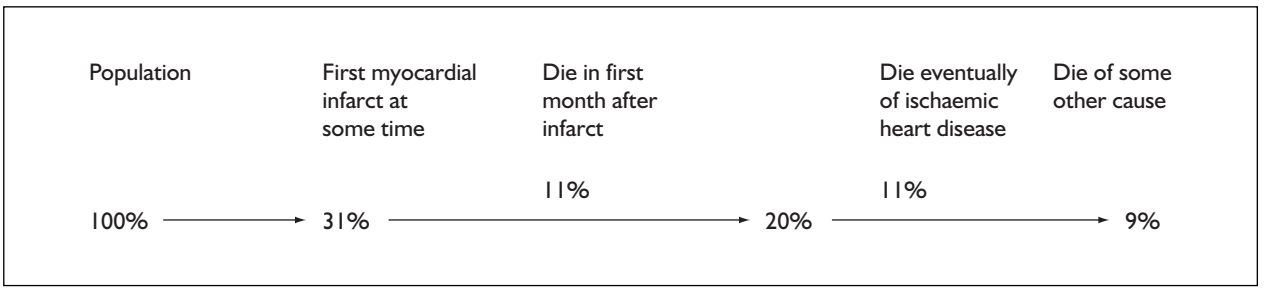

FIGURE 9 *The proportion of persons who have a myocardial infarction at some time in their life, and the outcome in these persons (data from a review of studies of consecutive patients who have a myocardial infarct[127])*

TABLE 29 *The percentages of men and women in specified age groups who give a history of angina, previous myocardial infarction or previous stroke*

	Age (years)			
	45–54	**55–64**	**65–74**	**75+**
Angina				
Men	3	11	16	18
Women	1	6	10	17
Heart attack				
Men	3	8	12	14
Women	1	2	6	7
Stroke				
Men	1	3	6	10
Women	1	2	5	9

Data from the Health survey for England, 1998.[132]

occur in the first month after the first infarct, and half occur at some time after hospital discharge (generally following a subsequent infarct).[127] Hence of the 22 heart disease deaths in 100 people, 11 occur in the first month after the first infarct and 11 occur subsequently. After a first myocardial infarction about 36% die in the first month, so 31 infarcts are necessary to produce the 11 deaths in the first month (11 is 36% of 31).] The resulting estimate in *Figure 9* that over a lifetime 20% of people have an infarct and survive the acute phase is consistent with the numbers with previous myocardial infarction in different age groups in *Table 29*.

It follows from the numbers in *Figure 9* that if preventive treatment were offered to all patients at the time of hospital discharge after their first myocardial infarct, half of all deaths from ischaemic heart disease might be anticipated (detection rate 50%). Of the 100 people in *Figure 9*, 22 died of ischaemic heart disease so 78 died of some other cause and nine of these had a non-fatal infarct. Thus nine out of 78 persons (12%) would be given the treatment but would not have died of ischaemic heart disease (false-positive rate 12%). A detection rate of 50% for a false-positive rate of 12% represents a good screening performance for such a common cause of death.

The above calculations apply to persons aged about 65 years. At older ages relatively more heart disease deaths will occur in the first month after the first infarct because the 1-month case fatality is higher and life expectancy is shorter (and

therefore there are fewer years of exposure to the 5% death rate). From age-specific mortality estimates,[127] at the age of 75 years the proportion of heart disease deaths that occur after hospital discharge following the first infarct is about 40% rather than 50%. At the age of 55 years, on the other hand, it is about 60%.

Similar calculations apply to stroke. The 1-month case fatality is on average about 24% (this was the median estimate from the studies listed in *Table 6*), slightly less than for myocardial infarction. The increase with age is similar to the case fatality after myocardial infarction, and the death rate after hospital discharge is also similar (*Table 28*). In summary, about half of all deaths from heart disease and stroke occur after hospital discharge following the first event.

In determining a policy for selecting those persons who should receive drug treatment to lower blood pressure, this high death rate in persons with a clinical history of cardiovascular disease, and the fact that they account for about half of all the deaths, are of paramount importance. Among apparently healthy people living in the community, often not under medical care, there is no other group that is subject to such a high risk of death. In spite of this, such patients are not, as a group, collectively identified as being at very high risk and treated accordingly.[133–135] Identifying people who have cardiovascular disease (and offering them intensive preventive treatment) is by far the most important screening test in preventing subsequent events and deaths from cardiovascular disease.

The presence of existing cardiovascular disease places a person at far higher risk than persons without known cardiovascular disease but high levels of coronary risk factors, at whom preventive measures tend to be focused.[136] As shown in *Table 26*, the incidence of myocardial infarction or stroke in, say, a 50-year-old man with no clinical history of cardiovascular disease but who smokes and is on the 95th centile of blood pressure is about 1.8% per year. Since about one-third of first events are fatal in the acute phase, the corresponding death rate will be about 0.6% per year. The risk in those with a previous infarct or stroke is about 10 times higher. The first priority in preventing heart disease deaths should be to identify people who have had a myocardial infarct or stroke at any time in the past and offer them the full armament of preventive treatment, including drug treatment to lower blood pressure.

Can blood pressure and other risk factors be used to predict reinfarction and cardiovascular deaths in patients with existing disease?

There is a mistaken view that after a myocardial infarction or stoke, blood pressure and other risk factors that predict these events in the general population remain predictive of recurrent events and cardiovascular death, despite the fact that the event the risk factor is intended to predict has occurred.

In patients with a history of myocardial infarction or stroke, the association between blood pressure and other risk factors and recurrent events is substantially attenuated, in comparison with the association with first events.[36,137,138] Similarly risk does not vary significantly with age or sex.[127] Patients who have had an infarct are all at high risk, and blood pressure and other risk factors cannot usefully discriminate between them. The weak association between cardiovascular risk factors and disease events is a general phenomenon: for example, the association between atrial fibrillation and recurrent stroke is weak,[139] yet randomised trials show that warfarin is beneficial in these patients.[140]

The substantial loss of the relationship between the risk factors and subsequent cardiovascular events occurs because these risk factors do not directly predict reinfarction or death; they predict the underlying arterial disease which must already be present in patients who have had a cardiovascular event, so there is little for the risk factors to predict. Blood pressure and other cardiovascular risk factors, of limited value in screening healthy persons (Chapter 5), have no discriminatory value in persons with existing disease. The weak relationships should not, however, be taken to indicate that interventions that favourably change the risk factors are not worthwhile in patients with existing disease; there is much evidence to show that changing the risk factors can substantially reduce the rate of recurrent events, as summarised for blood pressure in Chapter 3.

Conclusions

Identifying patients after discharge from hospital following a myocardial infarction is by far the most effective screening test to identify persons who will

die of ischaemic heart disease, with a detection rate of 50% for a 12% false-positive rate. Patients with a past history of myocardial infarction, or of angina, stroke or transient ischaemic attack, are by far the most important high-risk group. They are at substantially higher risk than healthy persons with relatively high values of blood pressure and other cardiovascular risk factors. There is no useful way of discriminating between these patients in offering them preventive treatment, they are all at high risk whether they are older or younger, men or women, smokers or non-smokers, fat or thin, or have high or low values of blood pressure and serum cholesterol. Taking into account the evidence presented in Chapter 3, and elsewhere,[36] we conclude that drug treatment to lower blood pressure should be offered to these high-risk patients irrespective of whether their starting level of blood pressure is high or average.

Chapter 7

By how much do blood pressure-lowering drugs lower blood pressure?

Key points

- The efficacy of five categories of blood pressure-lowering drugs, thiazides, beta-blockers, ACE inhibitors, angiotensin-II receptor antagonists and calcium-channel blockers, was estimated quantitatively from meta-analyses of the results of 354 randomised placebo-controlled trials.
- The average reductions in blood pressure were similar for the five categories of drugs in standard dose. The reductions in systolic pressure (placebo adjusted) were 8.8 mmHg for thiazides, 9.2 mmHg for beta-blockers, 8.5 mmHg for ACE inhibitors, 10.3 mmHg for angiotensin-II receptor antagonists and 8.8 mmHg for calcium-channel blockers. The corresponding reductions in diastolic pressure were 4.4, 6.7, 4.7, 5.7 and 5.9 mmHg, respectively. Within each category there was no evidence that any specific drug was materially better than the others.
- The drugs significantly reduced blood pressure from all pretreatment levels though the extent of the blood pressure reduction increased with pretreatment blood pressure. No effect of age was evident, given pretreatment blood pressure.
- The blood pressure-lowering effects of different categories of drugs used in combination were independent and additive.
- From an initial blood pressure level of 150/90 (about the average level in persons having a myocardial infarction or stroke), the average diastolic blood pressure reduction with one drug alone (4.7 mmHg), two drugs in combination (8.9 mmHg) and three drugs in combination (12.6 mmHg) would reduce stroke mortality by 32, 52 and 65% and ischaemic heart disease mortality by 20, 34 and 45% respectively.

Introduction

The rise in blood pressure with age that is usual in Western populations does not occur in communities living in Stone Age (pre-agricultural) conditions; their blood pressure remains at around 110/70 throughout adult life.[31] The higher blood pressure levels in older people in Western communities are attributable to aspects of Western lifestyle, including high dietary salt, obesity, high alcohol consumption, low dietary potassium and low habitual exercise. Reversal of these lifestyle factors could substantially lower the distribution of blood pressure in Western communities. Although an important objective in the longer term, this is not a realistic short-term objective. An individual cannot at present achieve dietary and other lifestyle changes large enough to have a major impact on blood pressure while still leading a reasonably normal life in the community. So many manufactured foods, convenience meals and restaurant and canteen meals have a high salt content and low potassium content, for example, that substantial change by individuals is difficult because of the need to avoid so wide a range of foods. In the short term, only blood pressure-lowering drugs can be expected to reduce blood pressure substantially in large numbers of people.

Many different categories of blood pressure-lowering drugs have been used, but five form the mainstay of current practice. These are thiazides, beta-blockers, ACE inhibitors, angiotensin-II receptor antagonists and calcium-channel blockers. Despite the widespread use of these drugs, there has been no systematic review quantifying the reduction in blood pressure that they produce in standard doses, of the effect of two or more drugs in combination or of the long-term reduction in mortality from stroke and ischaemic heart disease to be expected from using the drugs in standard doses separately or in combination. In this chapter, we aim to answer these questions from an analysis of all published randomised, placebo-controlled trials of all drugs in these five categories used in any fixed dose in which the change in blood pressure was reported.

Methods

Identification of studies

We sought randomised, placebo-controlled trials that recorded the change in blood pressure in persons receiving a specified fixed dose of any thiazide, beta-blocker, ACE inhibitor, angiotensin-

II receptor antagonists or calcium-channel blocker. We identified trials published in English from a MEDLINE search covering the years 1966–2000 (extended to 2001 for angiotensin-II receptor antagonists because these trials are the most recent). We used the generic and trade names of drugs as keywords or textwords, and within the resulting citations identified randomised trials as (i) those of MEDLINE publication type 'clinical trial', (ii) those under subject headings 'random allocation', 'double-blind method' or 'randomised controlled trials', or (iii) those containing textwords 'randomised' or 'randomized'. We also searched the Cochrane collaboration and Web of Science databases, examined all relevant citations in the reports of the trials identified and in review articles, and asked pharmaceutical companies to identify trials of drugs that they manufactured. Not all the trials recruited patients with high blood pressure, some trials tested the drugs for beneficial effects in various non-vascular disorders (thiazides for renal calculi, for example), and these trials provided useful estimates of the effect of these drugs at lower levels of blood pressure.

We excluded the following types of trial:

1. Trials of less than 2 weeks' duration, because a preliminary analysis suggested that, for some categories of drug at least, the full blood pressure lowering effect is not attained in under 2 weeks.
2. Trials in which the dose of the drug was not fixed but titrated according to subsequent blood pressure measurements so that different individuals received different doses.
3. Trials in which some placebo patients took drugs to lower blood pressure.
4. Trials that tested drugs only in combination with other drugs, including potassium, or with exercise.
5. Cross-over trials in which the placebo period was always either before or after the treatment period (rather than the order being randomised).
6. Trials in which more than a minority of the participants were black (of African origin) because of their different responses on average to some blood pressure-lowering drugs.[141]
7. Trials in which patients were recruited because of heart failure or other cardiovascular disorders as these may alter the effect of the drugs on blood pressure.

Definition of outcome

The blood pressure reductions recorded in the trials were categorised as 'peak' (blood pressure measurements 2–6 hours after the last dose of the drug) or 'trough' (22–26 hours after the last dose). In calculating the fall in blood pressure at trough we excluded the results from trials of drugs recommended to be taken more than once daily (see *Table 30*) unless they were administered in a sustained release preparation. In some trials the time period was not explicitly stated but was necessarily peak, either because the medication was taken in the morning and the blood pressure recorded at a clinic during the day, or because the medication was taken three times per day. Some trials reported only the peak or only the trough fall in blood pressure, but we used both if reported. Blood pressure was recorded either sitting or supine (similar numbers of trials reported each). Drug efficacy was the change in blood pressure in the treated group minus that in the placebo group (in cross-over trials it was simply the blood pressure at the end of the treatment period minus that at the end of the placebo period).

In combining the trial data, it was necessary to specify equivalent daily dosages of different drugs within each of the five categories. We based equivalent daily dosages on the usual maintenance dose of each drug recommended in reference pharmacopoeias (such as the British National Formulary or Martindale).[142–144] We refer to this as the standard dose. For some drugs a range between two dosages was listed (the second usually double the first); we took the lower to be the standard dose. These standard doses are determined by pharmaceutical companies from (i) studies in dogs and other animals that indicate the pharmacological and toxicological effects at various blood concentrations of the drug, (ii) pharmacokinetic studies of blood concentration according to dose in human volunteers, (iii) dose escalation efficacy studies in human volunteers and (iv) clinical trials. These experiments are often unpublished.

Statistical methods

The standard error of the change in blood pressure (treated minus placebo), if not reported directly, was calculated (in parallel group trials) from the variances of the change in blood pressure in the treated and the placebo groups. When only the standard error of blood pressure before and after the intervention was available, the standard error of the change was estimated as described previously.[145] In 45 trials no data were reported from which the standard error could be determined; it was estimated, given the number of participants, from the average in all parallel group

and in all cross-over trials that reported standard error or variance.

The data were analysed using STATA software. Parallel group and cross-over trials yielded similar results, so we combined them. Random effects regression models were fitted (separately for systolic and diastolic blood pressure), relating the change in blood pressure in each treatment arm (treated minus placebo), weighted by the inverse of its variance, to the category of the drug, the dose of the drug (expressed as a proportion of the standard dose), the usual pretreatment blood pressure (estimated as the blood pressure in the placebo group at the end of the trial to avoid regression to the meant), whether the blood pressure measurements were taken at peak or trough and the average age. The model took the distribution of the residual errors to be Gaussian, with additive within-study variance (taken as the variance of the placebo-adjusted change of blood pressure) and between-studies variance (estimated within STATA by the maximum likelihood method). The model was therefore equivalent to a random effects meta-analysis,[88] but with additional covariates. Covariates which did not contribute significantly to the variance of the model were removed sequentially.

We compared the fit of four different models to the data, based on expressing the dose of the drug on a logarithmic or arithmetic scale, and on the association between dose and reduction in blood pressure as either a straight-line relationship or a quadratic (curving) function with the increase in the blood pressure reduction flattening at higher doses. The fit of the model was significantly better (that is, more of the variance was explained) by expressing dose on a logarithmic (proportional) scale than on a linear scale; the proportional scale meant that the effect of a halving of a dose was taken as equivalent to that of a doubling. The linear and quadratic models for the association between the dose of the drug and decrease in blood pressure both fitted the data well; we used the straight-line model because it was simpler and the fit of the quadratic model was no better. For each of the five categories of drug the regression analysis yielded the average reduction in blood pressure at standard dose, and we used as the measure of effect the average reduction over 24 hours by combining the peak and trough estimates with equal weighting for each.

We also analysed data on whether the combined effect of two drugs of different categories is additive. Within the 354 trials there were 50 trials in which the effect on blood pressure of drugs of two different categories were each tested separately and both were tested in combination, in different randomised placebo-controlled treatment arms or cross-over periods. Some of these trials included randomised sub-groups testing different doses of one or both of the drugs, and considering these separately there was a total of 119 randomised comparisons testing specified doses of two drugs each separately and both in combination. The 119 comparisons involved 238 treatment groups, of which 84 tested thiazides, 26 beta-blockers, 71 ACE inhibitors, three angiotensin-II receptor antagonists and 44 calcium-channel blockers (the analysis was limited to trials in which at least one of the drugs was in one of these five categories); in addition, 10 treatment groups tested other drugs. The 119 comparisons were combined, weighting each result by the inverse of its variance.

The drugs tested in trials, their recommended doses and costs

Table 30 lists the individual thiazides, beta-blockers, ACE inhibitors, angiotensin-II receptor antagonists and calcium-channel blockers tested at fixed dose in randomised trials. The table shows the total number of randomised treatment groups testing each individual drug and the total number of participants in them, the standard (present recommended) daily dose of each drug,[142–144] and the present cost to the NHS of a 1-year supply of each drug.[142] In general, the more expensive drugs (over £100 per year) are those that are still on patent. The least expensive thiazide (hydrochlorothiazide) costs £5 per year and the least expensive beta-blocker (atenolol) £9 per year.

Table 31 shows details of the randomised trials identified. In total there were 354 trials, and these are listed separately from the general references[r1–r343] (343 papers report 354 trials because some reported two or three separate trials). Each trial had one placebo group, and there was a total of 791 treatment groups (about two per trial on average), testing different drugs or different doses of the same drug. There were about 40,000 (39,879) participants allocated treatment and about 16,000 (15,817) allocated placebo. The median duration of the 354 trials was 4 weeks; the range was 2–15 weeks except for nine trials lasting 5–36 months.[r32,r50,r57,r102,r151, r158,r169,r199,r202]

TABLE 30 *Randomised placebo-controlled trials testing five categories of blood pressure-lowering drugs in fixed dose: numbers of participants and treatment arms testing each drug, present standard daily dose of each drug, and cost to the NHS of 1 year's supply at standard doses*[142]

Drug	Total no. of participants (treatment arms) in trial	Standard daily dose (mg)	Cost of 1 year's supply (£)
Thiazides			
Hydrochlorothiazide[r1–34]	2458 (56)	25	5
Chlorthalidone[r35–46]	908 (18)	25	11
Indapamide[r47–55]	668 (11)	2.5	37
Bendroflumethiazide[r56–60]	285 (9)	2.5	10
Metolazone[r61]	78 (3)	2	37
Chlorothiazide[r38,r62]	64 (4)	250	–[a]
Cyclopenthiazide[r63]	41 (3)	0.25	17
Beta-blockers			
β_1 selective			
Atenolol[r14,r39,r43,r60,r64–88]	1276 (38)	50	9
Bisoprolol[r17,r25,r29,r89–93]	950 (15)	10	125
Betaxolol[r94–96]	601 (6)	20	98
Metoprolol[r36,r43,r75,r77,r87,r97–104]	547 (16)	100	22
Celiprolol[r105,106]	70 (3)	200	222
Acebutolol[r60,107]	43 (3)	400	261
Non-selective			
Nebivolol[r71,108–110]	619 (10)	5	128
Pindolol[r11,r51,r60,r77,r86,r104,r111–114]	384 (12)	15	87
Propranolol[r13,r60,r80,r84,r98,r101,r115–119]	339 (15)	160[b]	12
Bopindolol[r120]	86 (3)	1	–[a]
Oxprenolol[r84,r87]	73 (3)	80[b]	37
Timolol[r12,r60]	50 (3)	10	30
Nadolol[r121,r122]	33 (2)	80	68
α-Blocking action			
Carvedilol[r123,r124]	70 (4)	25	164
Labetalol[r58,r60]	48 (3)	400[b]	84
ACE inhibitors			
Enalapril[r10,r13,r65,r66,r76,r125–150]	1682 (49)	10	68
Perindopril[r5,r150–157]	1054 (21)	4	159
Captopril[r6,r7,r86,r158–167]	1048 (22)	50[b]	38
Trandolapril[r168–177]	1001 (18)	1	135
Cilazapril[r23,r178–186]	871 (23)	2.5	107
Ramipril[r4,r187–193]	737 (18)	2.5	98
Lisinopril[r34,r137,r194–202]	651 (14)	10	126
Quinapril[r20,r203–207]	625 (15)	20	117
Fosinopril[r16,r21,r208–210]	619 (14)	10	157
Spirapril[r3,r211–r214]	583 (13)	6	–[a]
Benazepril[r18,r26,r215,r216]	334 (7)	20	–[a]
Moexipril[r15,r217]	145 (3)	15	122
Angiotensin-II receptor antagonists			
Candesartan[r144,r218–r228]	2894 (33)	8	195
Valsartan[r19,r139,r158,r195,r229–232]	2880 (18)	80	205
Losartan[r9,r140–142,r224,r225,r229,r233–240]	2296 (24)	50	225
Olmesartan[r241]	2243 (6)	20	–[a]
Irbesartan[r30,233,r242–246]	1143 (19)	150	214
Telmisartan[r234,r247,r248]	661 (14)	40	164
Tasosartan[r249–252]	417 (7)	50	–[a]
Eprosartan[r253–255]	306 (4)	600	192

continued

TABLE 30 *Randomised placebo-controlled trials testing five categories of blood pressure-lowering drugs in fixed dose: numbers of participants and treatment arms testing each drug, present standard daily dose of each drug, and cost to the NHS of 1 year's supply at standard doses[142] (cont'd)*

Drug	Total no. of participants (treatment arms) in trial	Standard daily dose (mg)	Cost of 1 year's supply (£)
Calcium-channel blockers			
Dihydropyridines			
Felodipine[r135,r150,r193,r256–272]	1335 (37)	5[b]	106
Isradipine[r273–287]	1151 (30)	5[b]	178
Nifedipine[r31,r37,r42,r83,r88,r167,r268,r288–303]	1082 (31)	40[b]	105
Amlodipine[r215,r216,r288,r304–310]	631 (17)	5	154
Nicardipine[r311–318]	358 (11)	90[b]	175
Lercandipine[r319]	161 (3)	10	127
Nisoldipine[r320]	148 (3)	20[b]	171
Lacidipine[r8,r79,r321–324]	145 (7)	4	199
Nitrendipine[r70,149]	71 (2)	20[b]	–[a]
Non-dihydropyridines			
Diltiazem[r2,r24,r28,r74,r136,r194,r199,r325–r333]	1668 (33)	240[b]	77
Verapamil[r43,r65,r116,r117,r138,r170,r171,r173,r177,r305,r334–343]	1248 (35)	240[b]	27

[a] Not marketed in Britain.
[b] Should be taken more than once daily in divided doses, or a sustained-release preparation used.

TABLE 31 *Details of the 354 trials of blood pressure-lowering drugs*

	Treatment	Placebo
No. of participants (number of different drugs) in trials of:		
Thiazides (7)	4502	2636
Beta-blockers (15)	5189	2701
ACE inhibitors (12)	9350	4712
Angiotensin-II receptor antagonists (8)	12840	5100
Calcium-channel blockers (11)	7998	3976
All trials	39879	15817[a]
No. of treatment groups within trials of:		
Thiazides	104	64
Beta-blockers	136	76
ACE inhibitors	217	114
Angiotensin-II receptor antagonists	125	54
Calcium-channel blockers	209	122
All trials	791	354[a]
Trial design		
Cross-over	219	125
Parallel group	572	229
Pretreatment blood pressure (mmHg): mean (90% range)		
Systolic	154 (139–170)	154 (139–170)
Diastolic	97 (87–106)	97 (87–106)
Duration (weeks): median (90% range)	4 (2–12)	4 (2–12)
Age (years): mean, (90% range)	53 (43–68)	53 (43–68)

[a] Less than the total of the five categories because some trials compared drugs from two or more categories with the same placebo group.

The average fall in blood pressure produced by the drugs

Table 32 shows the average placebo-adjusted fall in blood pressure over 24 hours produced by the five categories of drug in standard dose. The estimates are remarkably similar for the five categories: 8.8, 9.2, 8.5, 10.3 and 8.8 mmHg systolic and 4.4, 6.7, 4.7, 5.7 and 5.9 mmHg diastolic. Generally the differences between categories were <1 mmHg. The average fall in blood pressure across the five categories of drug was 9.1 mmHg systolic and 5.5 mmHg diastolic.

Estimates for individual drugs

The degree of consistency in the blood pressure reductions across both different categories of drug and different drugs within each category is striking (taking the confidence intervals into account). This is shown in *Figure 10*, which gives the estimates of the peak fall in diastolic blood

TABLE 32 *Average reductions in blood pressure over 24 hours (treated minus placebo) according to category of drug and dose*

Drugs		Fall in blood pressure (mmHg)[a]
Thiazides	Systolic	8.8 (8.3 to 9.4)
	Diastolic	4.4 (4.0 to 4.8)
Beta-blockers	Systolic	9.2 (8.6 to 9.9)
	Diastolic	6.7 (6.2 to 7.1)
ACE inhibitors	Systolic	8.5 (7.9 to 9.0)
	Diastolic	4.7 (4.4 to 5.0)
Angiotensin-II receptor antagonists	Systolic	10.3 (9.9 to 10.8)
	Diastolic	5.7 (5.4 to 9.0)
Calcium-channel blockers	Systolic	8.8 (8.3 to 9.2)
	Diastolic	5.9 (5.6 to 6.2)

[a] In each category, the fall in blood pressure is standardised to the average starting blood pressure across all trials of 154 mmHg systolic and 97 mmHg diastolic; the estimates are the average over 24 hours from combining separate peak and trough estimates, with 95% CIs in parentheses.

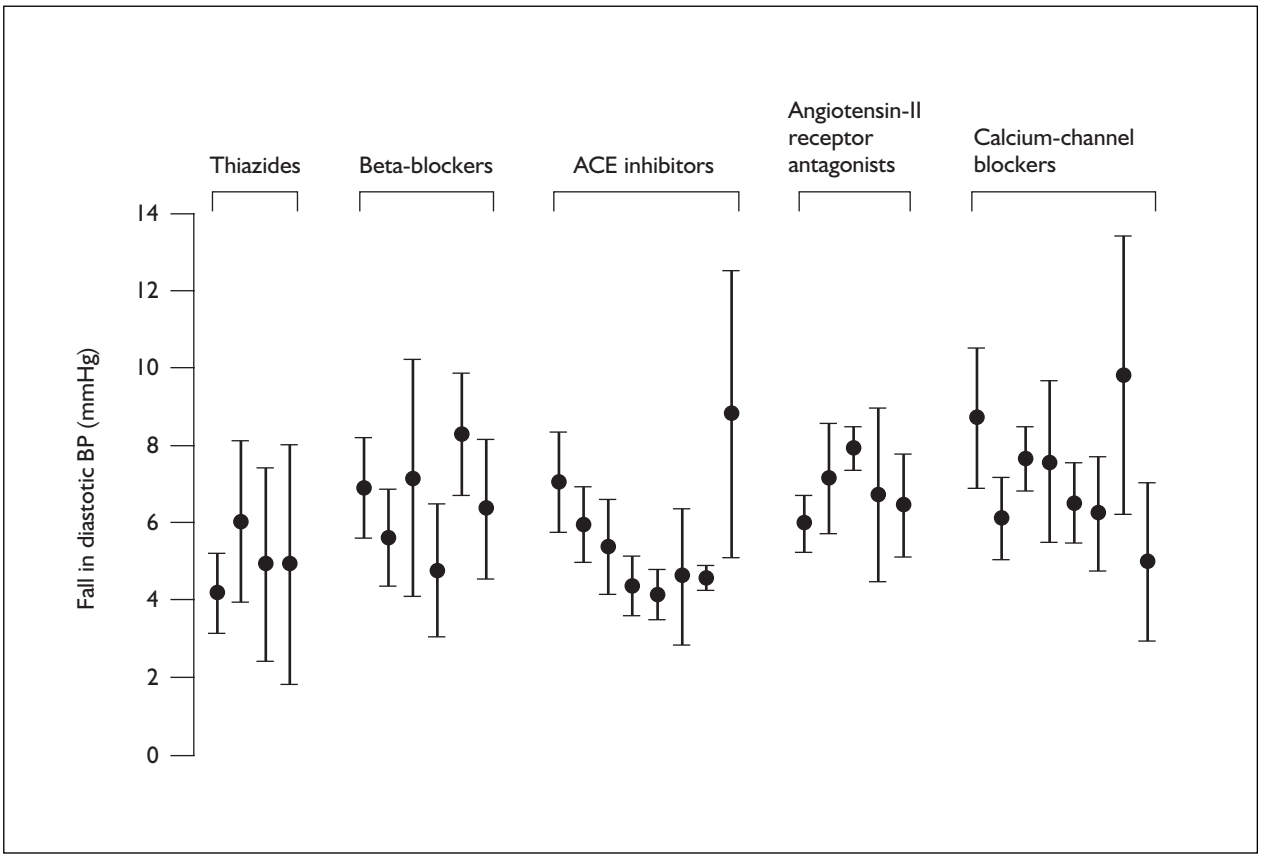

FIGURE 10 *Estimates of the reduction in diastolic blood pressure at standard dose at peak (2–6 hours after last dose) from randomised trials of specific blood pressure-lowering drugs (results are shown only for drugs tested in six or more trials). The drugs are, from left to right, hydrochlorothiazide, chlorthalidone, bendroflumethazide, indapamide; atenolol, metoprolol, propranolol, pindolol, bisoprolol, nebivolol; enalapril, captopril, cilazapril, perindopril, quinapril, trandolopril, lisinopril, spirapril; losartan, irbesartan, telmisartan, candesartan, tasosartan; isradipine, nifedipine, felodipine, verapamil, diltiazem, amlodipine, nicardipine and lacidipine.*

pressure at standard dose for all of the individual drugs having at least six trials that contributed data: four thiazides, six beta-blockers, eight ACE inhibitors, five angiotensin-II receptor antagonists and eight calcium-channel blockers. There were some 'statistically significant' differences between drugs, but with so many comparisons available this is expected by chance alone. In the absence of any prior hypothesis that some of the drugs might be expected to be better than others, our analysis should not be used to interpret the statistically significant differences observed as evidence of specific drug preferences. If some drugs genuinely were better it is not possible to identify them from this analysis. Perhaps the most important result in this context is that the efficacy of the less expensive drugs listed in *Table 30* was similar to that of the more expensive drugs.

Within each of the five categories, the average systolic and diastolic blood pressure reductions recorded showed statistically significant heterogeneity across trials (that is, greater variation than expected through chance alone). The heterogeneity was largely explained by factors recognised as influencing the blood pressure response. On average, 78% of the variance between trials in the reduction in systolic blood pressure and 69% of the variance in diastolic blood pressure were explained by the combined effects of (i) difference between trials in dose of drug (as a proportion of standard dose), (ii) pretreatment blood pressure (see below), (iii) whether blood pressure was recorded at peak or trough and (iv) differences between individual drugs within a category (since the standard doses of different drugs within a category will not correspond exactly to equivalent pharmacological effects and some drugs within a category may genuinely be better than others). Two further sources of variation could not be quantified: (i) differences between trials in the proportion of participants who did not take all their allocated medication and in the extent to which blood pressure measurements on persons known not to have taken the treatment were included in the results and (ii) the effect of age (our analysis had little power to examine this).

Fall in blood pressure in the placebo group

In trials in which the participants had been selected as having high blood pressure, blood pressure fell in the placebo groups over the duration of the trials by an average of 4.8 mmHg systolic (95% CI: 4.1 to 5.4 mmHg) and 5.0 mmHg diastolic (95% CI: 4.6 to 5.3 mmHg). This is attributable to regression to the mean; blood pressure fluctuates randomly over time in an individual and persons selected as having high blood pressure will tend to have been seen at a time period when their blood pressure was (for them) unusually high. When seen at a later date, the blood pressure will tend to be lower. The fact that the selection was generally based on diastolic rather than systolic pressure accounts for the large fall in diastolic relative to systolic pressure. Our analysis overcomes this bias since it was based on the differences between treated and placebo groups.

Effect of pretreatment starting blood pressure and age on the reduction in blood pressure

Table 33 shows the average fall in blood pressure (treated minus placebo) at standard doses of the drugs according to pretreatment blood pressure (taken as the blood pressure in the placebo group at the end of the trial to allow for regression to the mean). The drugs significantly reduced blood pressure from all pretreatment levels, but there was a greater reduction with higher pretreatment levels. This was the case for all five categories of drug. However, the analysis lacked the statistical power to determine whether this trend varied

TABLE 33 *Average reductions in blood pressure (treated minus placebo) produced by five categories of blood pressure-lowering drugs at standard dose, according to the 'pre-treatment' blood pressure*

	Pretreatment blood pressure (mmHg)	Fall in blood pressure (mmHg)
Systolic	120–9	6.8
	130–9	7.7
	140–9	8.6
	150–9	9.4
	160–9	10.3
	170–9	11.2
	180–9	12.1
Diastolic	70–9	2.9
	80–9	4.1
	90–9	5.4
	100–9	6.6
	110–9	7.8

quantitatively for the five different categories of drug [because most of the trials tested participants with blood pressure in a relatively narrow range (150–169 mmHg systolic and 90–99 mmHg diastolic), comparatively few trials tested higher or lower pretreatment values]. The reduction in blood pressure with one drug at standard dose increased by 1.0 mmHg (95% CI: 0.7–1.2 mmHg) systolic and 1.1 mmHg (95% CI: 0.8–1.4 mmHg) diastolic for each 10 mmHg increment in pretreatment blood pressure.

Given pretreatment blood pressure, no effect of age on the reduction in blood pressure produced by the drugs was evident, although the statistical power of the analysis was small because there was little variation between the trials in average age.

Assessing whether the combined effect of two drugs of different categories is additive

Table 34 shows the combined estimates from the 119 comparisons, weighting each result by the inverse of its variance. The table shows the observed average reduction in blood pressure (treated minus placebo) when the 'first' drug was used alone (the result presented first by the authors), when the 'second' drug was used alone and the average observed reduction in blood pressure when the two drugs were used in combination. The latter was close to the expected reduction using the two drugs in combination if the effect were additive. *Figure 11* shows the close linear correlation across a wide range between the observed and expected reduction in blood pressure in the individual trials.

With five categories of drug there are 10 possible combinations of any two, and in the trials we examined there was direct trial evidence for an additive effect for six of these combinations. There were insufficient data on beta-blockers and ACE inhibitors (only one trial and its results are inconclusive[r76]). For angiotensin-II receptor antagonists there was direct trial evidence for an additive effect only in combination with thiazides with no trial data on combinations with the other three drugs.

Effect of blood pressure-lowering drugs in combination on cardiovascular mortality

Table 35 shows the expected reductions in blood pressure using one, two or three drugs of different categories at standard dose in combination together with the corresponding reductions in stroke and ischaemic heart disease events. The blood pressure reductions are based on data in *Figures 5–8* (which show that the average blood pressure in persons who die of ischaemic heart disease or stroke is about 150 mmHg systolic and 90 mmHg diastolic), and the data in *Table 33*. The reductions in the incidence of stroke and ischaemic heart disease events in *Table 35* are based on the estimates of effect given in Chapter 3, namely that lowering blood pressure by 5 mmHg diastolic reduces stroke by 34% and heart disease by 21%.[32] Using two drugs in combination lowers blood pressure by an

TABLE 34 *The effects of two different drugs on blood pressure separately and in combination (summary results from 119 randomised placebo-controlled comparisons)*

Treatment	Average fall in blood pressure (mmHg) (treated minus placebo)	
	Systolic	Diastolic
Observed		
'First' drug alone[a]	7.0 (0.4)	4.1 (0.3)
'Second' drug alone[a]	8.1 (0.3)	4.6 (0.3)
Both drugs together[a]	14.6 (0.5)	8.6 (0.4)
Expected		
Sum of first and second drugs alone	15.1	8.7
Difference between observed and expected[b]	–0.5 (–1.4 to 0.4)	–0.1 (–1.0 to 0.8)

[a] Standard error in parentheses.
[b] 95% CI in parentheses.

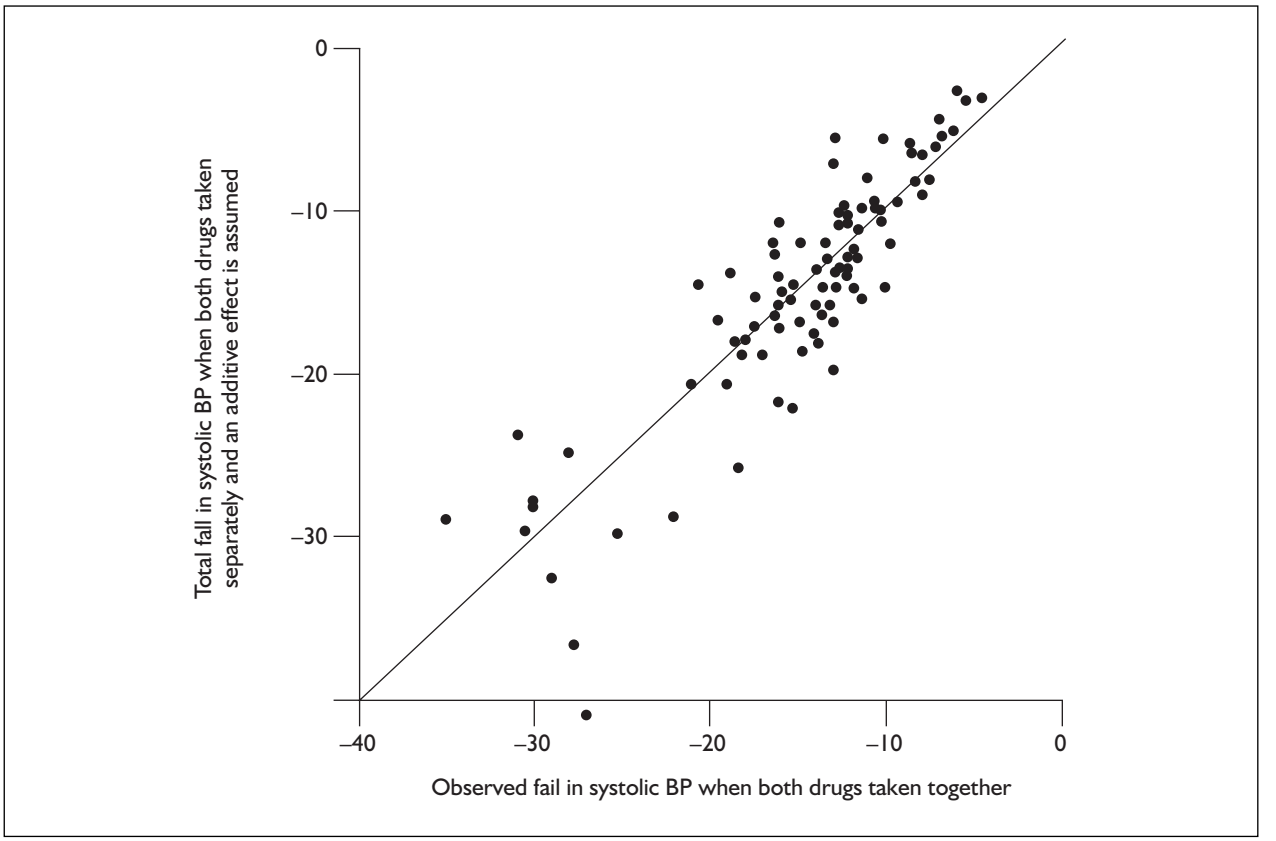

FIGURE 11 *Trials testing two blood pressure-lowering drugs separately and in combination: observed reduction in systolic blood pressure (treated minus placebo) with the two drugs used in combination plotted against the expected reduction in blood pressure (from adding the two reductions when each drug was tested alone)*

estimated 16.6 mmHg systolic and 8.9 mmHg diastolic [based on the additive model in *Table 34* allowing for the slightly smaller decline in blood pressure expected with a second drug because of the lower initial blood pressure from the action of the first drug (from *Table 33*)]. This blood pressure reduction results in an estimated 52% reduction in stroke and 34% reduction in ischaemic heart disease events. Using three drugs in combination is predicted to reduce the incidence of stroke by 65% and the incidence of ischaemic heart disease events by 45% – a substantial effect.

TABLE 35 *Estimated effects of blood pressure-lowering drugs separately and in combination in lowering blood pressure and in reducing the incidence of stroke and ischaemic heart disease events*

	One drug	Two drugs	Three drugs
Blood pressure reduction in persons with average blood pressure[a]			
Approximate reduction in systolic blood pressure (mmHg)[b]	9.0	17.2	24.7
Approximate reduction in diastolic blood pressure (mmHg)[b]	4.7	8.9	12.6
Corresponding reduction in:			
Stroke (%)	32	52	65
Ischaemic heart disease events (%)	20	34	45

[a] 150 systolic and 90 diastolic, about the average level in persons having a first myocardial infarction or stroke in the age range 50–69 years (*Figures 5–8*); blood pressure reductions from *Table 33*.

[b] Based on the additive model shown in *Table 34* but adjusted for the fact that the first and second drugs lower the 'initial' blood pressure for subsequent drugs and therefore the reduction in blood pressure they produce.

Conclusions

The effect of thiazides, beta-blockers, ACE inhibitors, angiotensin-II receptor antagonists and calcium-channel blockers in reducing cardiovascular mortality is substantial. The expected effects of one, two or three of these drugs in combination is, on average, to lower diastolic pressure by 4.7, 8.9 and 12.6 mmHg, which in turn is expected to reduce stroke mortality by 32, 52 and 65% and to reduce ischaemic heart disease mortality by 20, 34 and 45%, respectively.

Chapter 8

Adverse effects of blood pressure-lowering drugs

Key points

- The prevalence of adverse effects (symptomatic and metabolic) of blood pressure-lowering drugs was estimated quantitatively from meta-analyses of randomised placebo-controlled trials.
- Thiazides, beta-blockers, ACE inhibitors, angiotensin-II receptor antagonists and calcium-channel blockers caused symptoms in 9.9, 7.5, 3.9, 0.0 and 8.3%, respectively, of patients treated with standard doses. The prevalence of symptoms severe enough for the patient to stop taking the tablets was 0.1, 0.8, 0.1, 0 and 1.4%, respectively.
- There were no serious metabolic consequences of using these drugs in standard dose. The effect of thiazides on serum cholesterol was small and did not affect the atherogenic LDL and HDL subfractions.
- The drugs are suitable for widespread use in lowering blood pressure. Routine specific enquiry should be made to identify symptoms recognised as being caused by the drugs.
- Use of thiazides, beta-blockers and calcium-channel blockers without routine biochemical monitoring is safe. Measurement of potassium and creatinine before and after taking ACE inhibitors or angiotensin-II receptor antagonists is probably over-cautious; the case has not been made.

Introduction

In Chapter 7 we quantified the **efficacy** of five categories of blood pressure-lowering drugs: thiazides, beta-blockers, ACE inhibitors, angiotensin-II receptor antagonists and calcium-channel blockers. In this chapter we estimate the prevalence of **adverse effects** (symptoms and metabolic effects) of the five categories of drugs. These, like the effects of the drugs on blood pressure, have not previously been quantified in an overview. Our analysis is based on the same 354 randomised, placebo-controlled trials testing specified fixed doses of single drugs that we used in Chapter 7.[r1–r343]

Methods

From the published reports of the 354 randomised, double blind, placebo-controlled trials cited in the previous chapter, we sought data on adverse effects – both symptoms and adverse metabolic effects.

Definition of outcomes

We estimated the prevalence of symptoms caused by the drugs as the difference in prevalence between the treated and placebo groups, since symptoms not caused by the drug would on average be as frequent in the treated and control groups and cancel out. We identified trials where the symptoms recorded included all those that the authors considered might plausibly be caused by the drug, and determined the difference between the treated and placebo groups in the proportion of participants experiencing one or more symptoms. However, one symptom, headache, was excluded from this analysis because of published evidence,[146] supported by our analysis of these trials, that **fewer** treated than placebo participants reported headache; blood pressure reduction prevents headache. Data on all symptoms (excluding headache) were reported in 313 of the 354 trials (88% of all the participants in the 354 trials). Data on the prevalence of specified individual symptoms recognised as being caused by the drugs were reported in 164 trials (59% of all participants in the 354 trials). Trials varied in the extent to which they recorded mild or self-limiting symptoms, so the overall difference between treated and placebo groups indicates the prevalence of drug-related symptoms considered significant on average in all the trials. Lastly, as an indication of the prevalence of more severe effects of the drugs, we identified the proportions of participants in the treated and placebo groups who stopped taking the tablets because of illness or new symptoms, reported in 305 trials (84% of all participants in the 354 trials). Adverse metabolic effects recorded were the placebo-adjusted average changes in the serum concentration of potassium, uric acid, glucose (non-fasting) and total cholesterol and its subfractions.

Some trials did not report adverse effects, but there was no reason to expect that the prevalence

TABLE 36 *Percentages of persons taking blood pressure-lowering drugs in standard dose with one or more symptoms attributable to the drugs[a] according to category*

Category of drug	No. of trials	No. of participants		Percentage with symptoms (treated minus placebo) (95% CI)
		Treated	Placebo	
Thiazides	59	3907	2257	9.9 (6.6 to 13.2)
Beta-blockers	62	4276	2178	7.5 (4.0 to 10.9)
ACE inhibitors	96	8387	4492	3.9 (–0.5 to 8.3)
Angiotensin-II receptor antagonists	44	10775	3804	0.0 (–5.4 to 5.4)
Calcium-channel blockers	96	7118	3668	8.3 (4.8 to 11.8)

[a] Calculated as the difference between treated and placebo groups in the proportion of participants who developed one or more symptoms. Headaches, which are significantly less common in treated persons, are excluded from this analysis.

would have been higher in these trials than in those that did: trials not reporting adverse events tended either to report that there was little or no suggestion of toxicity without quantifying the statement, or not to record adverse effects because they were concerned primarily with other considerations such as physiological effects of the drugs besides the change in blood pressure. As in our blood pressure analysis in the previous chapter, as a means of deriving equivalent doses of the different drugs within each of the five categories, the dose of the drug tested in each treatment arm was expressed as a proportion of the usual maintenance dose recommended in reference pharmacopoeias;[142–144] we refer to this as the 'standard' dose.

Statistical analysis

As in the analysis of efficacy in Chapter 7, we compared the fit of four different models according to whether the dose of the drug was expressed on a linear or a logarithmic scale and whether the association between dose and reduction in blood pressure was a straight-line relationship or a quadratic function. The fit of the model was again significantly better with dose expressed on a logarithmic (proportional) scale than on a linear scale, the proportional scale indicating that the effect of a halving of dose was equivalent to that of a doubling. The linear and quadratic models for the association between the dose of the drug and the prevalence of adverse effects both fitted the data well and we used the linear model because it was simpler and the fit of the quadratic model was no better. In the analyses, the differences between the treated and placebo groups in the biochemical changes were weighted by the inverse of variance, and the difference in the proportions developing symptoms were weighted by the numbers of participants [that is, the inverse of the square root of $(1/n_1^2 + 1/n_2^2)$ (n_1 and n_2 being the numbers of participants in the treated and placebo groups, respectively)].

The prevalence of symptoms caused by the drugs

Table 36 shows that at standard doses of thiazides, beta-blockers, ACE inhibitors and calcium-channel blockers, 9.9, 7.5, 3.9 and 8.3% respectively, more treated than placebo patients developed any symptom or symptoms (excluding headache). With angiotensin-II receptor antagonists there was no excess of symptoms.

Table 37 shows the prevalence of specified symptoms recognised as being caused by the drugs. The average dose of the drugs used in these trials was close to the standard dose of thiazides and beta-blockers. With thiazides the commonest symptoms were dizziness (1.7% excess in the treated compared with the placebo groups) and impotence (0.7%). The other symptoms recorded in *Table 37* are recognised adverse effects of thiazides, but in these trials using doses of the drugs that were around standard they were uncommon: the excess was not statistically significant and the upper confidence limits on their prevalence estimates are generally below 1.5%.

With beta-blockers, the commonest symptoms were cold extremities (Raynaud's syndrome) (2.7%) and fatigue (1.4%). Psychological testing in three of the trials showed no adverse effects of beta-blockers on cognitive function and a beneficial effect on anxiety.[r13,r75,r78] The prevalence of some symptoms recorded in these trials is likely to depend on the extent to which minor symptoms are recorded. For example, in the beta-blocker trials only 1.4% more treated than placebo patients mentioned fatigue,

TABLE 37 *Percentages of persons in whom five categories of blood pressure-lowering drugs caused specified symptoms recognised as being caused by the drug in randomised trials (calculated as the difference between treated and placebo groups in the proportion of participants who developed each symptom)*

Category of drugs	No. of trials[a]	No. of participants		Average dose as multiple of standard	Percentage with symptom (treated with placebo) (95% CI)
		Treated	Placebo		
Thiazides	22				
Total no. of patients[b]		2420	1345		
Patients with:				0.9	
Dizziness		105	39		1.7 (0.5 to 2.8)
Impotence		14	1		0.7 (0.2 to 1.2)
Nausea		38	15		0.7 (–0.4 to 1.8)[c]
Muscle cramp		19	8		0.4 (–0.7 to 1.4)[c]
Skin rash		10	4		0.2 (–0.4 to 0.9)[c]
Fatigue		72	43		0.0 (–1.3 to 1.3)[c]
Beta-blockers	19				
Total no. of patients[b]		2274	1167		
Patients with:				1.2	
Cold extremities		40	11		2.7 (1.4 to 4.1)
Fatigue		126	64		1.4 (–0.2 to 3.0)
Nausea		39	18		0.2 (–1.3 to 1.8)[c]
Dizziness		81	42		0.1 (–1.6 to 1.9)[c]
Dyspnoea		18	14		–0.1 (–1.1 to 1.0)[c]
Vivid dreams		28	28		–0.6 (–1.8 to 0.5)[c]
ACE inhibitors	38				
Total no. of patients[b]		4326	2536		
Patients with:				1.8	
Cough		208	30		4.1 (3.2 to 5.0)
Skin rash		37	21		1.0 (–0.2 to 2.1)[c]
Nausea		41	14		0.7 (–0.1 to 1.6)[c]
Dizziness		122	56		0.6 (–0.4 to 1.5)[c]
Fatigue		100	44		0.6 (–0.5 to 1.7)[c]
Abdominal cramps		17	5		0.5 (–0.2 to 1.2)[c]
Angiotensin-II receptor antagonists	26				
Total no. of patients[b]		7701	2803		
Patients with:				1.2	
Back pain		39	20		0.8 (–0.3 to 2.0)[c]
Cough		124	127		0.0 (–0.5 to 0.4)[c]
Dizziness		177	162		–0.3 (–1.1 to 0.4)[c]
Upper respiratory tract infection		204	205		–0.4 (–1.6 to 0.8)[c]
Fatigue		111	121		–0.9 (–1.9 to 0.2)[c]
Calcium-channel blockers	72				
Total no. of patients[b]		5790	3133		
Patients with:				1.0	
Flushing		190	36		6.6 (4.7 to 8.5)
Ankle oedema		529	136		6.5 (4.8 to 8.2)
Headaches		764	617		3.4 (1.1 to 5.8)
Dizziness		209	139		1.7 (0.2 to 3.2)
Nausea		36	18		0.7 (–1.0 to 2.3)[c]
Rash		42	32		0.3 (–0.9 to 1.5)[c]

[a] Reference numbers: thiazides, r19–26,r28–30,r33–36,r46–49,r53,r56,r63;
beta–blockers, r22,r25,r29,r36,r39,r66–72,r92,r95,r96,r105,r108,r114,r119,r120;
ACE inhibitors, r15,r20,r21,r23,r26,r34,r66,r135–140,r155–159,r175–182,r193–196,r203,r210–217;
angiotensin-II receptor antagonists, r9,r19,r30,r139,r140,r158,r195,r225–230,r239–245,r247–250,r253, r254;
calcium-channel blockers, r9,r24,r28,r31,r65,r79,r82,r136,r138,r170,r171,r182,r215,r216,r257–302,r305–324, r326–340.
[b] This varied; some symptoms were not recorded in every trial.
[c] Not statistically significant; however, the upper CI is informative.

TABLE 38 *Randomised trials of patients who had previously experienced cough while taking an ACE inhibitor, allocated to take an ACE inhibitor again, an angiotensin-II receptor antagonist or to a control group*

Trial (first author)	Duration (weeks)	No. with cough/total no. of participants		
		ACE inhibitor	Antiotensin-II receptor antagonist	Control
Paster 1998[152a]	8	28/32 (88%)	11/30 (37%)	11/35 (31%)
Lacourcière 1999[153a]	8	15/25 (60%)	5/32 (16%)	3/31 (10%)
Tanser 2000[154a]	8	45/66 (68%)	22/62 (35%)	7/26 (27%)
Rake 2001[155a]	6	9/39 (23%)	2/39 (5%)	2/41(5%)
Lacourcière 1994[156]	8	33/46 (72%)	14/48 (29%)	14/41 (34%)
Benz 1997[157]	6	32/45 (71%)	9/42 (21%)	8/42 (19%)
Chan 1997[158]	10	27/28 (96%)	5/28 (18%)	6/28 (21%)
Average difference in prevalence of cough between treated and control (95% CI)		47% (32 to 62%)	1.5% (–45% to 7.6%)	

[a] In these four trials the controls took a placebo; in the other three trials the controls took a thiazide (not associated with cough).

but it may be that most patients taking beta-blockers are prone to excess fatigue on exercise but many people rarely do sufficient exercise to perceive it. Two trials showed that the average duration of exercise on a cycle ergometer in all participants before fatigue enforced cessation was shorter on a beta-blocker than placebo [in one trial, testing a beta-blocker in standard dose in athletes, duration of exercise was 25 minutes on the beta-blocker and 39 minutes on the placebo ($p < 0.01$),[r72] and in a second trial (testing 1.5 times the standard dose) it was 11 minutes on the beta-blocker and 13 minutes on the placebo[147]]. The other symptoms in *Table 37* were uncommon, the excess risk was not statistically significant and the upper CIs excluded an excess of more than 2%. Some symptoms may have been uncommon because susceptible patients were not recruited; for example, the prevalence of dyspnoea was low but the trials mostly tested selective beta-blockers and excluded patients with known chronic airways obstruction.

With ACE inhibitors, the average dose was almost double the standard dose for ACE inhibitors (*Table 37*), but the prevalence of the main symptom, cough, varied little with dose. There was a statistically significant excess of only one symptom – cough (with or without other upper respiratory symptoms), the excess was 4.1%. As with beta-blockers, the proportion of patients taking ACE inhibitors who develop any degree of cough may have been underestimated; it is likely to depend on how assiduously minor symptoms are sought. Experimentally, almost everyone taking ACE inhibitors experiences an increase in sensitivity to cough induced by physical and chemical stimuli, with a reversible shift to the left of the dose–response curve between cough frequency (recorded by pneumotachograph) and the dose of chemical stimuli.[148–150] Angioneurotic oedema is a recognised complication of ACE inhibitors; it was not detected in these randomised trials but review of studies of patients prescribed ACE inhibitors indicated that it affects between 2 and 10 per 10,000 treated patients.[66,150,151] It is mild and not life threatening, and is reversible on cessation of the drug.[151]

Angiotensin-II receptor antagonists did not cause a significant excess prevalence of any symptoms (*Table 37*), and the upper CIs on the risk estimates generally excluded an excess risk of more than about 1%. In particular, the trials showed no excess risk of cough in patients treated with angiotensin-II receptor antagonists. This finding is confirmed in *Table 38* by a meta-analysis of seven randomised trials conducted in patients who had previously experienced cough while taking an ACE inhibitor; the patients were either allocated to take an ACE inhibitor again, an angiotensin-II receptor antagonist or to a control group [the controls took a placebo in four of the trials and a thiazide (not associated with cough) in three]. The summary result shows that, adjusted for the prevalence of cough in the control groups, ACE inhibitors caused cough in 47% (95% CI: 32 to 62%) of treated patients but there was no significant excess risk with angiotensin-II receptor antagonists (1.5%; 95% CI: –4.5 to 7.6%). The cough associated with ACE inhibitors is thought to be caused by the accumulation of kinins (bradykinin is metabolised

TABLE 39 *Percentages of persons taking blood pressure-lowering drugs who developed symptoms attributable to the drugs that were sufficient to stop taking the tablets*

Category of drugs	No. of trials[a]	No. of participants		Average dose as multiple of standard	Percentage who stopped taking tablets because of symptoms[a] (95% CI)
		Treated	Placebo		
Thiazides	57	3530	2079	1.0	0.1 (–0.7 to 0.9)[b]
Beta-blockers	62	4265	2176	1.3	0.8 (0.3 to 1.4)
ACE inhibitors	92	7645	4181	1.9	0.1 (–0.3 to 0.6)[b]
Angiotensin-II receptor antagonists	44	10775	3804	1.3	–0.2 (–0.5 to 0.2)[b]
Calcium-channel blocker	92	6564	3384	1.0	1.4 (0.4 to 2.4)

[a] Calculated as the difference in prevalence between treated and placebo groups in randomised trials.
[b] Not statistically significant; however, the upper CI is informative.

by ACE), and angiotensin-II receptor antagonists would be expected not to cause cough because they do not increase bradykinin levels.[159] For the same reason, angiotensin II receptor antagonists would be expected not to cause angioneurotic oedema (a complication of ACE inhibitors as discussed above); however, there have been two case reports suggesting that angioneurotic oedema may be a rare complication of angiotensin-II receptor antagonists.[159]

For calcium-channel blockers there were sufficient trial data to estimate the prevalence of symptoms caused by the drug at exactly standard dose (*Table 37*). The commonest symptoms were caused by the vasodilatory action of the drug: flushing (6.6%), ankle oedema (6.5%), dizziness (1.7%) and headaches (3.4%). Assessing the prevalence of headache is compounded by the fact that headache is more common in the placebo than treated groups in trials of other blood pressure-lowering drugs.[146] Allowing for this, by estimating the expected reduction in the prevalence of headaches in the treated groups attributable to the blood pressure reduction and increasing the observed prevalence in the treated groups by this amount, suggested that calcium-channel blockers caused headache in about 6.5% of treated persons at standard dose.

The trials of cross-over design showed that the symptoms were reversible on stopping the drugs. Of the different categories of drug, only thiazides had a detectable effect on sexual function in these trials, a finding confirmed in a long-term (4-year) trial.[160]

Table 39 shows the estimates of the proportions of persons in whom the drugs caused symptoms that resulted in the treatment being stopped, as an indication of the prevalence of more serious effects of the drugs. In trials of beta-blockers, 0.8% (95% CI: 0.3 to 1.4%) more treated than placebo patients left the trial because of symptoms (at an average dose of 1.3 times the standard dose), and for calcium-channel blockers (at standard dose) the proportion was 1.4%. For thiazides, ACE inhibitors and angiotensin-II receptor antagonists, however, there was no statistically significant excess, and the upper CIs indicate that <0.9% (thiazides), <0.6% (ACE inhibitors) and <0.2% (angiotensin-II receptor antagonists) of treated patients developed symptoms attributable to treatment and serious enough to leave the trial.

The trials lasted only a few weeks on average, so the question arises as to whether the prevalence of symptoms might have increased with longer duration of treatment. One randomised placebo-controlled trial offers an opportunity to assess this; it tested treatment regimes based on a thiazide and on a beta-blocker in separate randomised treatment arms. The prevalence of symptoms caused by both drugs (treated minus placebo) was in general no greater after 2 years than after 12 weeks,[161] suggesting no tendency for symptoms caused by the drugs to accumulate over time.

Metabolic effects of the drugs

Table 40 summarises the biochemical changes in the trials of thiazides at standard dose. The changes were relatively small: a 9% decrease in potassium, 3% increase in glucose and 15% increase in uric acid. The analysis confirmed the recognised increase in total serum cholesterol with thiazides, but showed that it was small. There were no adverse changes in LDL or HDL cholesterol, the subfractions strongly related to heart disease. The increase in total cholesterol lay in the very low density lipoprotein (VLDL) subfraction, associated

TABLE 40 *Average changes in serum concentrations of potassium, uric acid, glucose and total cholesterol and its subfractions, placebo-adjusted, in randomised trials of thiazides, at standard dose*

	Average change (mmol/l) (95% CI)	Change as % of mean
Potassium[a]	–0.38 (–0.44 to –0.33)	–9
Glucose[a]	0.19 (0.10 to 0.27)	3
Uric acid[a]	0.048 (0.043 to 0.053)	15
Cholesterol[a]:		
Total	0.18 (0.10 to 0.27)	3
LDL	0.04 (–0.02 to 0.13)[b]	–1
HDL	0.004 (–0.01 to 0.02)[b]	0
VLDL	0.13 (0.03 to 0.23)	22

[a] Reference numbers: potassium, r4,r25–41,r47–52,r56,r61,r63; glucose, r2,r28,r31–38,r47–50,r56; uric acid, r9,r29–40, r47–51,r56,r63; cholesterol fractions, r2,r22,r28,r31,r33,r36,r44,r47–50,r56,r57
[b] Not statistically significant; however, the upper CI is informative.

TABLE 41 *Average changes in serum concentrations of potassium, glucose and cholesterol and its subfractions, placebo-adjusted, in randomised controlled trials of beta-blockers, at standard dose*

	Average dose (multiple of standard)	Average change (mmol/l) (95% CI)	Change as % of mean
Potassium[a]	1.8	0.11 (0.05 to 0.17)	2
Glucose[a]	1.4	0.09 (–0.13 to 0.31)[b]	2
Cholesterol[a]:			
Total	1.5	–0.16 (–0.28 to 0.03)[b]	–3
LDL	1.3	–0.03 (–0.28 to 0.22)[a]	–1
HDL	1.7	–0.04 (–0.11 to 0.03)	–3

[a] Reference numbers: potassium, r29,r36,r39,r51,60,r64–67,r115 (20 treatment arms in 10 trials); glucose, r36,r64–66, r80,r97–99 (11 treatment arms in 8 trials); cholesterol fractions, r36,r60,r64,r85,r99,r102 (12 treatment arms in 6 trials).
[b] Not statistically significant.

only weakly (or not at all) with atherogenesis, and this was confirmed by a parallel increase in serum triglyceride (measured in seven of the trials).

In view of published evidence, mainly from non-randomised studies,[162–165] suggesting that the increase in total serum cholesterol caused by thiazides does not persist in the long term, we examined five randomised controlled trials that reported changes in total serum cholesterol in the long term (2–4 years after the initiation of thiazides).[r50,r57,166–168] At standard doses there was no detectable long-term increase in serum cholesterol [the average change was –0.04 mmol/l (95% CI: –0.24 to +0.16 mmol/l].

Table 41 summarises the biochemical changes in trials of beta-blockers and the average dose in these trials as a proportion of standard. There was a statistically significant increase in serum potassium, of 0.11 mmol/l (2%) on average. One of the long-term trials showed that a similar increase was evident after 3 years, indicating that this change is persistent.[166] There was no significant change in blood glucose. The results on serum cholesterol and its subfractions in *Table 41* show a small (3%) decrease in total cholesterol, comprising separate small decreases in both the LDL and HDL subfractions. A large long-term (4 years) trial of acebutolol showed similar results – a statistically significant decrease in serum total and LDL cholesterol of 0.17 mmol/l (95% CI: 0.11 to 0.23 mmol/l), a decrease in HDL cholesterol of 0.03 mmol/l (95% CI: –0.00 to 0.06) and no significant change in VLDL cholesterol.[169] It has been suggested, mainly from the results of uncontrolled or non-randomised studies, that the changes in serum cholesterol induced by a beta-blocker may differ according to whether it has intrinsic sympathomimetic activity (that is, a partial agonist effect – acebutolol, pindolol and oxprenolol have this activity).[163] Any such difference is likely to be small, however, because the trial data examined here showed no statistically significant difference between beta-blockers with and without this activity.

ACE inhibitors and angiotensin-II receptor antagonists increase serum potassium because of their effect on aldosterone. In 18 trials of either (28 treatment arms) the average increase was 0.13 mmol/l (95% CI: 0.07 to 0.19 mmol/l), or 3%. The increase with ACE inhibitors (15 trials, 20 treatment arms) was 0.16 mmol/l (95% CI: 0.08 to 0.23 mmol/l), or 4%, and with angiotensin-II receptor antagonists (five trials, eight treatment arms) it was 0.07 mmol/l (95% CI: –0.04 to 0.18 mmol/l), or 2%. There was no statistically significant change in glucose, uric acid or cholesterol.

It has been suggested that calcium-channel blockers may increase blood glucose, but the trials showed no significant increase in treated patients [95% CI: 0.1 mmol/l (2%) lower to 0.2 mmol/l (5%) higher, from 13 treatment arms in 10 trials[r2,r24,r28,r37,r65,r295,r311,r315,r317,r322]].

Adverse effects in trials testing combinations of drugs

Of the 50 placebo-controlled trials testing drugs of two different categories separately and in combination reported in Chapter 7, 33 reported adverse effects. In 66 trial arms, single drugs caused symptoms in 5.2% (95% CI: 3.6 to 6.6%) on average (prevalence in treated group minus placebo). In 33 trial arms, two drugs together caused symptoms in 7.5% (95% CI: 5.8 to 9.3%), significantly lower than the value of 10.4% (twice 5.2%) expected with an additive effect ($p = 0.03$). One drug does not therefore potentiate the adverse effects of another. The lower than expected prevalence with two drugs may suggest that some individuals are more likely than others to either experience or report symptoms.

In trials testing different drugs separately and together the serum potassium lowering effect of thiazides was offset by beta-blockers,[r29,r36,r39,r51] ACE inhibitors[r4,r26,r34] and angiotensin-II receptor antagonists.[r30]

The risk of hazard arising from the metabolic effects of the drugs

Thiazides

Thiazides in standard doses reduced serum potassium concentration from an average pretreatment value of 4.2 mmol/l by 9% on average (*Table 40*). It has been established that the loss of potassium is not progressive over time (balance is reattained after about 1 week[165]). Serum potassium is a poor marker of total body potassium (most potassium being intracellular) and the loss of total body potassium associated with thiazides is small (about 200 mmol).[170–172] The relatively small potassium loss (*Table 40*) confirms that potassium supplementation with thiazides is unnecessary in terms of safety,[173] although potassium supplements do augment the blood pressure reduction.[173,174]

Thiazides increased the serum concentration of uric acid by 0.048 mmol/l on average at standard dose. From the results of a cohort study in men, this would be expected to about double the incidence of gout.[175] In women, gout is less common and the excess risk would be about one-tenth of the increase in men[166] (about 10%). Observational differences in serum urate seen in cohort studies, however, will have been present for many years before the start of the observation, so it may require an accumulation of several years of treatment with thiazides before the excess risk is manifest. In a study of persons commencing a thiazide (at twice the standard dose) to lower blood pressure the incidence of gout over the first 5 years was 0.4% (15 out of 3693),[176] similar to the population average rate.[175] Blood glucose increased from an average pretreatment level of 5.4 mmol/l by 3% (*Table 40*). Follow-up studies of patients taking thiazides have also shown a progressive increase in blood glucose, both fasting and 2 hours after a glucose load, but it reversed on stopping the thiazide.[177] There was no excess risk of overt diabetes after 6 years.[178]

The randomised trial data in *Table 40* establish that the increase in serum cholesterol caused by thiazides is small and does not adversely affect the atherogenic LDL or HDL subfractions; any increase in cardiovascular risk is likely to be negligible.

An advantage of thiazides is that they reduce urinary calcium and slow the rate of bone loss in older people.[179] Case–control studies show a lower risk of hip fracture in users of thiazides, by one-third in one study[180] and by 20% in another after 2–5 years of use and by half after more than 5 years of use.[181]

Beta-blockers

Beta-blockers given in conjunction with thiazides will partly counter the decrease in serum potassium caused by the thiazides. The net effects on cardiovascular risk of the changes in serum cholesterol subfractions produced by beta-blockers (*Table 41*) are likely to be negligible.

ACE inhibitors and angiotensin-II receptor antagonists

There is uncertainty over the need to monitor renal function in healthy people taking ACE inhibitors or angiotensin-II receptor antagonists. These drugs have no significant general adverse metabolic effects but they may substantially decrease glomerular filtration rate in a post-stenotic kidney.[182] In people with bilateral renal artery stenosis or renal artery stenosis of a solitary kidney, this can induce acute renal failure.[182,183] The fall in glomerular filtration rate is reversible on stopping the drugs, as is the acute renal failure. People with elevated serum creatinine therefore benefit from taking ACE inhibitors or angiotensin-II receptor antagonists, and this benefit may counter the above hazard of acute renal failure. Measuring serum creatinine and serum potassium before treatment and at intervals during treatment is recommended,[142,143] but such monitoring may be over-cautious. The case has not been made, and it is probably unnecessary.

Taking ACE inhibitors or angiotensin-II receptor antagonists may be advantageous in diabetes (insulin dependent and non-insulin dependent); they retard the onset of microalbuminuria, its progression to overt proteinuria and subsequent loss of renal function, and they do so across all levels of blood pressure.[184] Progression of non-diabetic renal disease is also delayed.[185,186]

Calcium-channel blockers

Metabolic effects are not a problem. There was no increase in the incidence of diabetes in a 6-year follow-up study,[178] consistent with the lack of any effect on blood glucose in the trials reviewed here.

Adverse effects of lowering blood pressure

The symptom most likely to be caused by blood pressure reduction itself (rather than a specific effect of a drug) is dizziness. In the same 50 placebo-controlled trials in which drugs of two different categories were tested separately and in combination, 20 reported on dizziness. The proportion of trial participants experiencing dizziness when taking one drug (prevalence in treated group minus that in placebo) was on average 0.2%, and when taking two drugs it was 2.0% – significantly higher than the value of 0.4% expected with an additive effect ($p = 0.03$). The result therefore suggests that adding a second blood pressure-lowering drug causes dizziness in about 1.6% of people. There were insufficient data to examine the trend with pretreatment blood pressure.

In the randomised trials of drug treatment to lower blood pressure, Collins and colleagues in their 1990 review showed that there was no suggestion of increased non-vascular mortality.[34] The death rate from all non-vascular causes was similar in the treated and control groups. The trials of blood pressure-lowering drugs published since that review (*Table 10*) confirm that there is no excess mortality from non-vascular causes. Apart from the adverse effects of specified blood pressure-lowering drugs discussed above, there is no evidence that low blood pressure *per se*, or lowering blood pressure, is hazardous.

In some cohort studies, mortality from non-vascular causes was higher in persons with the lowest values of diastolic blood pressure than in persons with average diastolic pressure.[96,97] Similar cohort study findings have been reported among persons with the lowest values of body mass index and of serum cholesterol, and it has been shown that these associations arise indirectly because cancer and other non-vascular diseases may lower body weight and serum cholesterol and also increase the overall risk of death.[187,188] The same phenomenon arises in relation to blood pressure. The sub-group with the lowest values of blood pressure in a cohort tend to include those with manifestations of disease including weight loss, anaemia and heart failure; low blood pressure is a marker of poor general health and the low blood pressure is a consequence of the disease rather than a cause of it.[96,97]

Conclusions

Thiazide diuretics cause adverse effects in about 10% of treated patients but these are reversible on stopping the drug. Thiazides are inexpensive (£5 per year; *Table 30*), and are ideal drugs for widespread use in lowering blood pressure. With beta-blockers some of the drugs are cheap (£9 per year for atenolol; *Table 30*), symptoms are fairly common (about 7%) but reversible and could be identified with routine monitoring. ACE inhibitors are generally safe apart from causing a cough in some people. Angiotensin-II receptor antagonists avoid the cough and cause remarkably few adverse effects, and are effective in lowering blood pressure, but they are more expensive (*Table 30*) because they are 'on patent'; the patents have some years to run. Calcium-channel blockers cause

adverse effects fairly commonly (8.3%) at standard dose but they are reversible on stopping the drug. The occurrence of symptoms recognised as being caused by the drugs should be identified through routine specific enquiry by the doctor. Certain symptoms are particularly important to monitor because they are common and may not be volunteered, either through embarrassment (such as impotence with thiazides) or because they may be confused with getting older (fatigue with beta-blockers) or intercurrent illness (cough with ACE inhibitors).

Chapter 9

Conclusions and recommendations

We have identified five policy options in choosing persons at sufficiently high risk to offer them drugs that lower blood pressure:

1. Patients with existing disease are the most important high-risk group. Selecting only persons with established disease, irrespective of their existing blood pressure level, would identify all those who have recurrent events and identify about half of all persons who die from heart disease and stroke, in time to offer preventive treatment. 'Persons with established disease' would include those with a history of myocardial infarction, stroke, angina or transient ischaemic attack.
2. Treating healthy persons above a specified blood pressure cut-off. Blood pressure is too poor a screening test to justify this strategy, and it leads to the inconsistency that older persons with average blood pressure have higher risk than younger persons with high blood pressure.
3. Treating healthy persons above a specified 'absolute risk' cut-off calculated from combining the values of several risk factors, age and sex. The problem is that the discriminatory potential of a number of risk factors in combination is not substantially stronger than that of blood pressure alone. The strategy does not offer a solution to the problem that to prevent the majority of preventable cardiovascular events in an age–sex group it would be necessary to categorise such a high proportion of the population as high risk that screening would serve little purpose. Treatment might as well be offered to all persons above a specified age.
4. Offering treatment to all persons above a specified age, for example to everyone aged 55 years and over, or to men aged 55 years and over and women aged 60 years and over.
5. A combination of options 1 and 4. This strategy (adopting an age cut-off in option 4 of 55 years or more) would include virtually all (98%) deaths from stroke and heart disease that would occur in the absence of preventive treatment.

We conclude that option 5 is the preferred option. Under this option, blood pressure-lowering drugs, preferably in combination to maximise efficacy, would be offered to all persons after a first myocardial infarction or stroke and to everyone aged 55 years and over without known cardiovascular disease. This would have a substantial public health impact. The evidence presented indicates that three drugs in combination may reduce stroke by about two-thirds and ischaemic heart disease by half.

We have proposed radical policies based on the epidemiological evidence presented. The term 'hypertension' should be avoided; it is misleading because blood pressure is a poor screening test and 'hypertension' is not a disease. Since blood pressure reduction by using simple drugs is effective in preventing cardiovascular events regardless of initial blood pressure, we conclude that such preventive therapy should be considered in all persons at increased risk. The identification of all persons at increased risk should be based first on the presence of existing disease alone. In persons without existing disease it may be best based on age and sex alone, because these risk factors dwarf the others in categorising people as being at risk of a heart attack or a stroke.

Recommendations for further research

1. A review of trials testing blood pressure-lowering drugs according to dose as a proportion of standard would determine whether the benefit-to-hazard ratio is better at lower doses.
2. Additional short-term trials are needed to determine whether the effects of beta-blockers and ACE inhibitors are additive in lowering blood pressure, and whether angiotensin-II receptor antagonists are additive with beta-blockers, ACE inhibitors and calcium-channel blockers, and to confirm estimates of the prevalence of adverse effects of treatment.
3. This review has focused on epidemiological and randomised trial evidence. Further research into the economic consequences of the proposed preventive strategies would be useful.

4. We have suggested that the widespread practice of blood pressure monitoring with titration of the doses of blood pressure-lowering drugs is unlikely to be worthwhile. A review of the effectiveness and cost-effectiveness of this practice would be useful. A study could be conducted as to how fixed triple blood pressure therapy (perhaps a thiazide, beta-blocker and ACE inhibitor) with no 'target' blood pressure compares with titrated blood pressure therapy (adjusting drugs and dose aiming for a target blood pressure) in terms of blood pressure reduction, adverse effects of treatment and general acceptability to patients.
5. Additional long-term randomised trials with disease end-points are **not** necessary and should not be conducted in view of their cost. It is already well established that lowering blood pressure from any point on the distribution in Western populations reduces the risk of coronary events and stroke.

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The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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