Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial

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Objective To test the primary hypothesis that a newer antihypertensive treatment regimen (calcium channel blocker ± an angiotensin converting enzyme inhibitor) is more effective than an older regimen (β-blocker ± a diuretic) in the primary prevention of coronary heart disease (CHD). To test a second primary hypothesis that a statin compared with placebo will further protect against CHD endpoints in hypertensive subjects with a total cholesterol ≤ 6.5 mmol/l.

Design Prospective, randomized, open, blinded endpoint trial with a double-blinded 2 × 2 factorial component.

Setting Patients were recruited mainly from general practices.

Patients Men and women aged 40–79 were eligible if their blood pressure was ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic (untreated) or ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic (treated) at randomization.

Interventions Patients received either amlodipine (5/10 mg) ± perindopril (4/8 mg) or atenolol (50/100 mg) ± bendroflumethiazide (1.25/2.5 mg) +K^+ with further therapy as required to reach a blood pressure of ≤ 140 mmHg systolic and 90 mmHg diastolic. Patients with a total cholesterol of ≤ 6.5 mmol/l were further randomized to receive either atorvastatin 10 mg or placebo daily.

Main outcome measure Non-fatal myocardial infarction (MI) and fatal coronary heart disease (CHD).

Results 19 342 men and women were initially randomized, of these 10 297 were also randomized into the lipid-lowering limb. All patients had three or more additional cardiovascular risk factors.

Conclusions The study has 80% power (at the 5% level) to detect a relative difference of 20% in CHD endpoints between the calcium channel blocker-based regimen and the β-blocker-based regimen. The lipid-lowering limb of the study has 90% power at the 1% level to detect a relative difference of 30% in CHD endpoints between groups.

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Introduction

Meta-analyses of unconfounded randomized trials of antihypertensive therapy [1] indicate that a reduction in diastolic blood pressure of 5–6 mmHg maintained for about 5 years reduced stroke incidence by approximately 38%. The size of this reduction is compatible with that observed for a prolonged 5–6 mmHg difference in diastolic blood pressure in prospective observational studies [2]. However, the 16% reduction in coronary heart disease (CHD) seen in the trials during about 5 years of intervention falls short of the difference of about 20–25% in CHD that would have been predicted from prolonged observational studies for a similar difference in diastolic blood pressure [2].

The shortfall in CHD prevention may have been due to one or more of several possible factors, including chance, the comparatively short duration of the trials, the failure of the drugs to reverse established cardiovascular structural changes, or because the agents used in the trials, most commonly diuretics and β-blockers, exerted adverse effects (e.g. on serum lipids, glucose or potassium) that offset potential benefits from blood pressure lowering [3,4].

Newer agents such as calcium channel blockers and angiotensin converting enzyme inhibitors avoid some of these potential adverse metabolic effects, and may have additional cardiovascular protective effects [5,6]. Thus, antihypertensive treatment regimens that include these agents may produce greater effects on CHD than older drug regimens. Unlike most other trials [7] the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) [8] and the valsartan antihypertensive long-term use (VALUE) trial [9] are the only trials, hitherto designed to compare as a primary endpoint effects on CHD outcomes of different agents, with a diuretic. In addition, it is now clear from at least two trials [10,11] that if recently recommended blood pressure targets [12,13] are to be reached, the majority of patients will require at least two drugs. So far, no trials have evaluated or compared the efficacy of prespecified drug combinations for hypertensive patients.

Cross-sectional studies have frequently reported a high prevalence of dyslipidaemia in hypertensive subjects [14], which considerably increases their risk of a future CHD event. Trials of cholesterol lowering with statins report a 25–40% reduction in CHD events during an intervention period of about 5 years [15–19]. Subgroup analyses suggest that similar benefits might be expected among hypertensive subjects,but with the exception of the ongoing ALLHAT study [8], no study has evaluated the separate and combined effects of antihypertensive and lipid-lowering therapy in a hypertensive population.

The rationale for the ASCOT study is to try to answer several of these important outstanding issues relating to hypertension management, particularly whether a newer combination of antihypertensive agents, a dihydropyridine calcium channel blocker (CCB) and an angiotensin converting enzyme (ACE) inhibitor, produce greater benefits in terms of reducing CHD events than the standard beta-blocker/diuretic combination and whether lipid lowering with a statin provides additional beneficial effects in those hypertensive patients with average or below average levels of serum total cholesterol.

Methods

Study design

The Anglo-Scandinavian cardiac outcomes trial (ASCOT) is a multicentre, international trial which involves two treatment comparisons in a factorial design. The first is a prospective, randomized, open, blinded endpoint (PROBE) design [20] comparing two antihypertensive regimens. The second, in a subsample of those hypertensives studied, is a double-blind placebo-controlled trial of a lipid-lowering agent (Fig. 1).

Study objectives

Primary objectives

(1) To compare the effects on the combined outcome of non-fatal myocardial infarction (MI) and fatal CHD of a β-blocker-regimen (atenolol) (+ a diuretic (bendroflumethiazide-K) if necessary) with a CCB-based regimen (amlodipine) (+ an ACE inhibitor (perindopril) if necessary.)

(2) To compare the effect on the combined outcome of non-fatal MI and fatal CHD of a statin (atorvastatin) with that of placebo among hypertensive patients with total cholesterol ≤ 6.5 mmol/l.

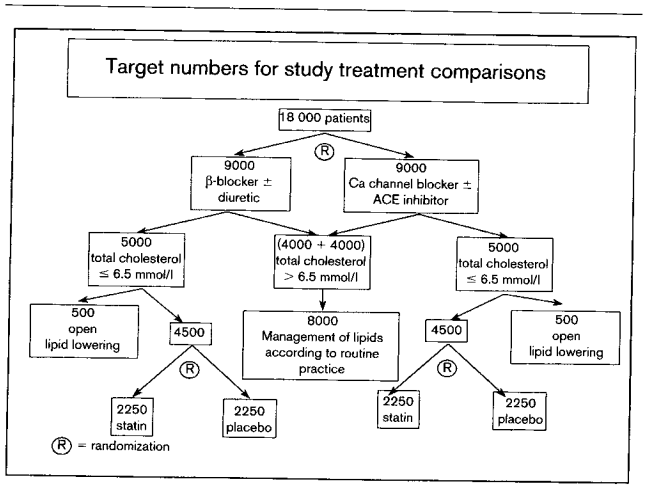
Secondary objectives

To compare the effects of the two antihypertensive regimens, and of statin versus placebo, on the secondary endpoints shown in Table 1.

Tertiary objectives

To compare the effects of the two antihypertensive regimens and of statin versus placebo on the tertiary endpoints (Table 1). The study will also allow an evaluation of whether synergistic effects on the study primary endpoint or on all cardiovascular events and

Fig. 1



Target numbers for study treatment comparisons.

Table 1 Classification of endpoints

Primary endpoints
(1) Non-fatal (MI) + fatal (CHD)

Secondary endpoints
(1) Non-fatal MI (symptomatic only) + fatal CHD
(2) All cause mortality
(3) Cardiovascular mortality
(4) Fatal and non-fatal stroke
(5) Fatal and non-fatal heart failure
(6) Total coronary endpoints = fatal CHD + non-fatal MI (symptomatic and silent) + chronic stable angina + unstable angina + fatal and non-fatal heart failure
(7) Total cardiovascular events and procedures = cardiovascular mortality + non-fatal MI (symptomatic and silent) + unstable angina + chronic stable angina + life threatening arrhythmias + silent non-fatal heart failure + non-fatal stroke + peripheral arterial disease + revascularization procedures, and retinal vascular thromboses.

Tertiary endpoints
(1) Silent MI
(2) Unstable angina
(3) Chronic stable angina
(4) Peripheral arterial disease
(5) Life-threatening arrhythmias (VF or sustained VT or complete heart block)
(6) Development of diabetes mellitus
(7) Development of renal impairment

MI, myocardial infarctions; CHD, cardiac heart disease; VF, ventricular fibrillation; VT, ventricular tachycardia.

procedures are observed between the different antihypertensive regimens and the cholesterol lowering regimen. The study will allow comparisons of the effects of the antihypertensive and lipid-lowering regimens on health care costs, and on all major study endpoints among specific subgroups of patients (e.g. diabetics, smokers, the obese ($> 30\ kg/m^2$), those with LVH, older/younger ($\leq 60 > 60$ years), male/female, any previous vascular disease (by history or electrocardiogram, ECG), and renal dysfunction (by serum creatinine, urinalysis).

Inclusion criteria

Antihypertensive regimen comparison

Men and women aged 40 to 79 years were eligible if they were hypertensive by study definitions and had at least three pre-specified cardiovascular risk factors (Fig. 2). Subjects not already on antihypertensive medication had either systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg at both the screening and randomization visit (see Table 2). Subjects already taking antihypertensive medication had either systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg at randomization.

Fig. 2

Patient eligibility criteria
Any 3 of these risk factors for a CV event required:

- Smoking
- LVH
- ECG abnormalities
- History of early CHD in first degree relative
- Age ≥ 55 years
- Microalbuminuria/ proteinuria
- NIDDM
- Peripheral vascular disease
- History of cerebrovascular event
- Male sex
- Plasma TC/HDL ratio ≥ 6

CV, cardiovascular; NIDDM, non-insulin-dependent diabetes mellitis; LVH, left ventricular hypertrophy; ECG, electrocardiogram; CHD, coronary heart disease; HDL, high-density lipoprotein, TC, total cholesterol.

Lipid lowering comparison

All subjects were eligible for the antihypertensive regimen comparison and had a serum cholesterol at screening of ≤ 6.5 mmol/l.

Exclusion criteria

Table 3 lists the criteria, which exclude patients from the trial.

Study medication

Antihypertensive treatment was initiated, by random allocation, with either amlodipine, or atenolol to which either perindopril or bendroflumethiazide-K, respectively are added to achieve target blood pressures. The treatment sequence, doses used and 'add-on therapy' (the α-blocker doxazosin-gastrointestinal transport system, GITS) of the two antihypertensive regimens being compared are shown in Table 4. Lipid-lowering treatment with atorvastatin,10 mg is compared with placebo in the subgroup of patients with total cholesterol ≤ 6.5mmol/l.

Procedures and measurements

At an initial screening visit, patient eligibility was assessed and an informed consent form was signed. Between 2 and 8 weeks post-screening, certain eligibility criteria were established in anticipation of the second visit, when eligible patients were randomized to

Table 2 Summary schedule of events

Months	−1	0	1.5	3	6	12	18	24	30	36	42	48	54	60†	66/final
Medical history and eligibility	×	×•													
Previous antihypertensive medication and side effects	×														
Current illness/adverse events[1]	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Morbidity/mortality endpoints			×	×	×	×	×	×	×	×	×	×	×	×	×
Informed consent	×														
Withdrawal of antihypertensive drugs		×													
Height■, weight	×					×		×		×		×		×	×
BP, Heart rate	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
ECG	×	×						×							×
Blood tests	×§	×	×*		×◆	×◆		×◆		×◆		×◆		×◆	×
Urine tests	×				×	×		×		×		×			×
Physical examination		×													
Extra visits optional for drug up-titration when necessary															

*Bloods for electrolytes, creatinine for those randomized to receive angiotensin converting enzyme (ACE) inhibitor. This sample should be taken within a few weeks of initiating an ACE inhibitor whenever this occurs during the trial; ◆Bloods to include LFT for those randomised to receive statin/placebo; ■Only at screening; †If this is the final visit see requirements for final; •Eligibility only; §If triglyceride level is > 4.5 mmol/l or glucose is > 7 mmol/l at screening, subjects will be recalled during this period for a fasting blood sample to evaluate eligibility [1]Current illness only is recorded at visit −1.

one of two antihypertensive regimens and, if eligible, to statin or placebo.

Treatment is scheduled to continue for an average period of either 5 years or until 1150 primary events have accrued (whichever is the longer) among the 19 342 patients randomized to the antihypertensive comparison. At each visit, blood pressures are measured using a modified version of the Valwater semi-automated blood pressure machine, (Omron HEM 705CP; Omron Healthcare, Henfield, W. Sussex, UK), [21]. Blood pressure medication is titrated until the target blood pressures are reached. (Non-diabetics: < 140 mmHg systolic and < 90 mmHg diastolic; and diabetics: < 130 mmHg systolic and < 80 mmHg diastolic).

Following randomization, each patient is reviewed at least at 6 weeks, 3 months, 6 months and 6-monthly thereafter until the final visit. (Investigations and procedures carried out at each visit are shown in Figure 2.

In the best interests of the individual patient to deal with side effects and to mimic good clinical practice, flexibility in the drug steps and doses used is allowed (Table 4). If, after step six, pressures remain above the study targets, further antihypertensive therapy which is not one of the classes used in the other limb of the trial, (and is ideally a once-a-day drug), is considered at the physicians discretion.

Ideally, all drugs are taken no more than 24 h before study visits and no changes to the antihypertensive drugs or doses of these drugs made on the basis of elevated blood pressure levels unless it has been confirmed that study drugs had been taken within 24 h and after appropriate repeated readings.

By contrast, the lipid-lowering comparison of atorvastatin 10 mg o.d. or placebo involves no further treatment steps or dose titration. All randomized patients are followed-up according to the protocol, irrespective of whether they have continued study medication.

All screening and in-study ECGs are read at a central ECG coding laboratory, for signs of left ventricular hypertrophy (LVH) [22], ST-T abnormalities (including ST-depression and negative or biphasic T-wave), bundle-branch block and for significant Q-waves. A full Minnesota code is performed [23]

Endpoints

Adverse and serious adverse events excluding study endpoints and all medications ingested are to be recorded at each study visit. Each possible study endpoint (see Table 1) is reviewed by at least two

Table 3 Exclusion criteria

(1) Any contraindications to, or previous history of, major intolerance to dihydropyridine CCBs, ACE inhibitors, β-blockers, thiazide diuretics, doxazosin, or
(2) A history of secondary hypertension.
(3) Malignant hypertension.
(4) Previous clinical MI or currently treated angina pectoris.
(5) Stroke, transient ischemic attacks, or cerebrovascular surgery < 3 months before study onset.
(6) Patients requiring CCBs, ACE-Is, β-blockers or diuretics for concomitant diseases or conditions.
(7) Fasting serum-triglycerides > 4.5 mmol/l.
(8) Patients requiring other drugs which are also prescribed for hypertension (e.g. alpha-blockers for prostatism).
(9) Second or third-degree A-V block.
(10) Clinical congestive heart failure (NYHA II–IV).
(11) Uncontrolled arrhythmias.
(12) Concomitant clinically important hematological, gastrointestinal, hepatic (liver function test (ALT) > 3x upper normal level), renal (serum creatinine > 200 μmol/l), or other disease which, in the opinion of the investigator, will interfere with the treatment or the patient's ability to complete the study.
(13) A history of alcoholism, drug abuse, psychosis, antagonistic personality, poor motivation or other emotional or intellectual problems that are likely to invalidate informed consent, or limit the ability of the subject to comply with the protocol requirements.
(14) Participation in any other studies involving investigational or marketed products within 1 month prior to entry into this study or concomitantly with this study.
(15) Pregnant or lactating women and those of child-bearing potential (i.e. pre-menopausal without appropriate contraception).

CCBs, calcium channel blockers; ACE, angiotensin-converting enzyme; MI, myocardial infarction; NYHA, New York Heart Association; ALT, alanine transaminase.

Table 4 Two antihypertensive regimens being compared

	Calcium channel blocker-based regimen	β-blocker-based regimen
Step 1	Amlodipine 5 mg	Atenolol 50 mg
Step 2	Amlodipine 10 mg	Atenolol 100 mg
Step 3	Amlodipine 10 mg Perindopril 4 mg	Atenolol 100 mg BFZ 1.25 mg + K^+
Step 4	Amlodipine 10 mg Perindopril 8 mg (2 × 4mg)	Atenolol 100 mg BFZ 2.5 mg + K^+
Step 5	Amlodipine 10 mg Perindopril 8 mg (2 × 4mg) Doxazosin GITS 4 mg	Atenolol 100 mg BFZ 2.5 mg + K^+ Doxazosin GITS 4mg
Step 6	Amlodipine 10 mg Perindopril 8 mg (2 × 4 mg) Doxazosin GITS 8 mg	Atenolol 100 mg BFZ 2.5 mg + K^+ Doxazosin GITS 8 mg

BFZ, bendroflumethiazide; GITS, gastrointestinal transport system.

members of an independent Endpoint Committee blinded to the study treatments following standardized study criteria, definitions and algorithms.

Before the start of the study, the protocol and/or other appropriate documents were submitted to the local or national ethics committees in accordance with regional legal requirements. The Declaration of Helsinki [24] for the conduct of clinical studies is followed and the study is performed according to ICH/GCP guidelines [25].

Organizational structure

In the Nordic countries, 686 general practices were responsible for randomizing 10 244 patients. In the UK and Ireland, a further 9098 patients were recruited through 33 regional centres to which patients were referred by their general practitioners. The first patient was randomized on 18 February 1998 and recruitment was completed on 26 May 2000.

Two co-ordinating centres, in London and Gothenburg, are responsible for the overall management of the trial in UK/Ireland and the Nordic countries respectively. An independent International Steering Committee is responsible for the scientific conduct and publication of the trial, with a smaller executive committee and working group responsible for day-to-day decisions.

Sample size, data analysis and statistics

The sample size calculation assumes a yearly rate of non-fatal myocardial infarction (MI) and fatal CHD events of 2% among patients allocated to β-blocker-based therapy which, after adjustment for withdrawals and dilution from crossover, this estimate falls to 1.42% per year. If the CCB-based regimen reduces this risk by 20%, then, after estimated adjustment for withdrawals and cumulative non-compliance (20% over 5 years), the intention to treat effect (ITT) is estimated to be 15–16% reduction in risk. It was estimated that a sample size of 18 000 was required to generate 1150

primary endpoints, which would provide 80% power to detect such an effect ($\alpha = 0.05$).

Comparison of lipid lowering

The expected 30% reduction in cholesterol due to 10 mg atorvastatin translates into a difference of about 1.7 mmol/l between the atorvastatin and placebo groups. The 5 year cumulative rate of non-fatal MI and fatal CHD events in the placebo group is estimated to be 6.35%, and it is anticipated that the cholesterol reduction with atorvastatin might produce a reduction in these events of 30% (ITT). Under these conditions a sample of 9000 patients with a (total cholesterol $\leq$ 6.5 mmol/l) would have 90% power to detect such an effect ($\alpha = 0.01$).

Statistical analysis

The statistical method used for the main analysis will be a log-rank test using time to the primary event without adjusting for baseline factors and will be performed according to intention to treat principles (ITT). The significance level will be 0.01 for all secondary and tertiary analyses. Confidence intervals will be calculated by Cox proportional hazards model [26]. All analyses using 'time to particular event' will be analysed in the same way. The Cox proportional hazards model with adjustment for important prognostic variables will be used for complementary analyses. Secondary analyses derived from information on compliance with treatment (per protocol analyses) will also be carried out.

Analyses in predefined subgroups will be conducted to search for possible interactions using standard tests of heterogeneity of effects. Such analyses will be seen as exploratory and will provide the basis of future hypotheses. Two-tailed tests will be used, with *P*-values or confidence intervals presented for all comparisons. The details will be outlined in a Data Analysis Plan. The final statistical analyses will be performed by the two co-ordinating centres under the supervision of the ASCOT Steering Committee.

Interim analyses

The Data Safety Monitoring Committee (DSMC) will monitor unblinded interim results during the conduct of the trial with analyses provided by one specifically named person at the co-ordinating centre in Gothenburg. The DSMC will use a Haybittle–Peto statistical boundary as a guideline for deciding whether or not to recommend early termination [27]. The DSMC will use symmetric boundaries for the comparison of antihypertensive regimes as well as for the lipid-lowering comparison, with independent stopping rules for the antihypertensive and lipid-lowering components.

Baseline data and demographics of randomized population

Patient recruitment ended in May 2000, by which time 19 342 patients had been randomized to the two antihypertensive treatment regimens (Table 5). Of these 10 297patients were further randomized to lipid-lowering treatment or placebo (Table 5). The demographics of this patient population are given in Table 6.

The average age of recruits was 63 years with a predominance of males). Of the patients, 5% represented ethnic minority groups (mainly Afro-Caribbean or South Asian). Of those previously untreated with antihypertensive therapy the mean BP levels were 179 ± 16 mmHg systolic and 102 ± 10 mmHg diastolic. Approximately two-thirds were taking antihypertensive drugs prior to randomization. The drug classes used by those on treatment are shown in Table 7 and in these patients mean blood pressure levels were 162 ± 20 mmHg systolic and 93 ± 11 mmHg diastolic. Table 8 gives details of the risk factor profile of those randomized, reflecting the patient inclusion criteria for ASCOT.

Discussion

ASCOT randomized in excess of 19 000 patients between February 1998 and May 2000, of whom 53% were recruited into the lipid-lowering limb.

If ASCOT runs its full course it should report in the

Table 5 Number of patients randomized by country

Country	Number randomized
Denmark (including Iceland)	1567
Finland	2382
Norway	2226
Sweden	4069
UK and Ireland	9098
Total randomized to antihypertensive limb	19342
Total randomized to lipid lowering treatment or placebo	10297

Table 6 Baseline characteristics of randomized patients (mean ± SD)

	Antihypertensive limb	Lipid lowering limb
Age (years)	62.9 ± 8.5	63.1 ± 8.5
Sex (%): male	76.5	81.2
Weight (kg): male	87.5 ± 14.8	87.2 ± 14.8
female	75.2 ± 14.8	76.0 ± 15.4
SBP overall DBP mmHg	165 ± 21	165 ± 20
	95 ± 11	95 ± 11
Pulse beats/min	73 ± 14	72 ± 14
Caucasian (%)	95.4	94.6
Total cholesterol	6.00 ± 1.10	5.48 ± 0.69
HDL-cholesterol (mmol/)l	1.29 ± 0.37	1.29 ± 0.36

SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein.

Table 7 Drug use prior to randomization for those on treatment

	(%)
β-blockers	39.3
Diuretics	34.7
Calcium channel blockers	35.1
Angiotensin converting enzyme inhibitors	31.8
Angiotensin receptor blockers	7.9
Other	2.2

Spring of 2004. ASCOT will help to define the place of two different treatment strategies for the lowering of blood pressure, both alone and in combination with lipid-lowering therapy in the prevention of CHD and other cardiovascular outcomes.

In trials in which different active treatment regimens are being compared, differences in outcome will be less than those observed in studies comparing active therapy with placebo. Hence, large numbers of patients with high event rates are required to test the hypothesis that new treatments are better than old treatments with regard to CHD outcome. With the exception of ALLHAT [8], and VALUE [9], ASCOT is the only intervention trial in hypertension that specifically addresses the question of potential treatment benefits for CHD as a primary endpoint. Given that the majority of higher risk hypertensive patients require two or more drugs to provide adequate blood pressure control long term [10,11] ASCOT is particularly important since it is the only trial designed to compare the effects on major cardiovascular morbidity and mortality of two prespecified combination treatments.

ASCOT is timely with regard to the place of dihydropyridine CCBs in the management of hypertension and in light of reports that CCBs may increase cardiovascular risk [28–32]. Contrary evidence was provided, however, by the SYST-EUR study [33] which showed that antihypertensive therapy initiated with the dihydropyridine, nitrendipine reduced the risk of fatal and non-fatal stroke and all cardiovascular events; an observation confirmed in the subgroup with diabetes [34]. The HOT trial, in which treatment was initiated with felodipine also provided no indication of harm for patients with diabetes [10]. However, unlike ASCOT, neither SYST-EUR nor HOT allow conclusions to be drawn on the potential differential benefit of initiating therapy with a dihydropyridine CCB versus the standard therapy of a β-blocker and a diuretic. ASCOT recruited over 4000 patients with non-insulin-dependent diabetes (NIDDM) and will therefore provide much needed evidence with regard to the optimal antihypertensive drug combination for this group of patients.

Although hypertensive patients have been included in previous lipid-lowering trials, to date no trials of lipid lowering have been carried out in sufficiently large numbers of hypertensives without pre-existing CHD to allow a robust estimate of potential benefits in such patients. Given that both high blood pressure and hypercholesterolemia frequently co-exist and are known to induce vascular damage and endothelial dysfunction [35] assessment of effects of lowering both is an important outcome evaluable by virtue of the factorial design of ASCOT.

This combined approach to reduce CHD risk incorporated in the ASCOT design will help validate the recommended optimal approach to reducing cardiovascular risk [12,13,36].

In summary, ASCOT is designed with several features, which together produce a unique trial. Perhaps most importantly it is the first and only large-scale comparison of the effects on CHD morbidity and mortality of a specific combination of newer antihypertensive drugs compared with the most commonly used standard drug combination for the treatment of hypertension at a time when it is clear that most patients need at least two blood pressure-lowering drugs.

Table 8 Percentage of patients with additional cardiovascular risk factors

	Patients (%)
No. of additional risk factors = 3	50.2
> 3	49.8

Risk factor	Patients (%)	Risk factor	Patients (%)
Age ⩾ 55 years	84	Cerebrovascular event	11
Male	76	Microalbumin/proteinuria	62
LVH	13	Smoker	31
Abnormal ECG	14	Plasma total/HDL ⩾ 6	24
NIDDM	22	Family history of coronary disease	28
Peripheral vascular disease	6		

LVH, left ventricular hypertrophy; ECG, electrocardiogram; HDL, high density lipoproteins; NIDDM, non-insulin-dependent diabetes mellitus.

Arising from the main trial a number of substudies are in progress, details of which will be incorporated into a separate publication. Together with the main outcome trial these studies address six of the eight key objectives for future research highlighted in the 1999 World Health Organization-International Society of Hypertension Guidelines for the Mangement of Hypertension [36].

Acknowledgement

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Appendix

ASCOT Committee Members

Steering committee

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