ANGLO-SCANDINAVIAN CARDIAC OUTCOMES TRIAL

ASCOT

Factorial Study of the Prevention of Coronary Heart Disease and Vascular Events by Blood Pressure Lowering (comparing beta-blocker-based with amlodipine-based therapy) and by Blood Cholesterol lowering (comparing atorvastatin with placebo)

Working protocol – 23 March 2003
including Amendments 1, 2, 3, 4, 5 & 6

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Principal sponsor: Pfizer Inc, New York
Pfizer trial code: AML-NY-96-008

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I INTRODUCTION AND RATIONALE

I A Blood Pressure and Coronary Heart Disease (CHD)

1. Strength of the relationship between blood pressure and CHD risk

The associations between diastolic blood pressure (DBP) and the incidence of CHD and of stroke have been investigated in several major prospective observational studies.[1] The combined results of nine such studies indicate that the relationship between CHD or stroke risk plotted on a doubling scale and usual diastolic blood pressure is roughly linear (Fig 1). Analyses of these observational studies suggest that a prolonged difference of 5 mmHg in usual DBP is associated with a difference of at least one-fifth in the risk of CHD and at least one-third in the risk of stroke.

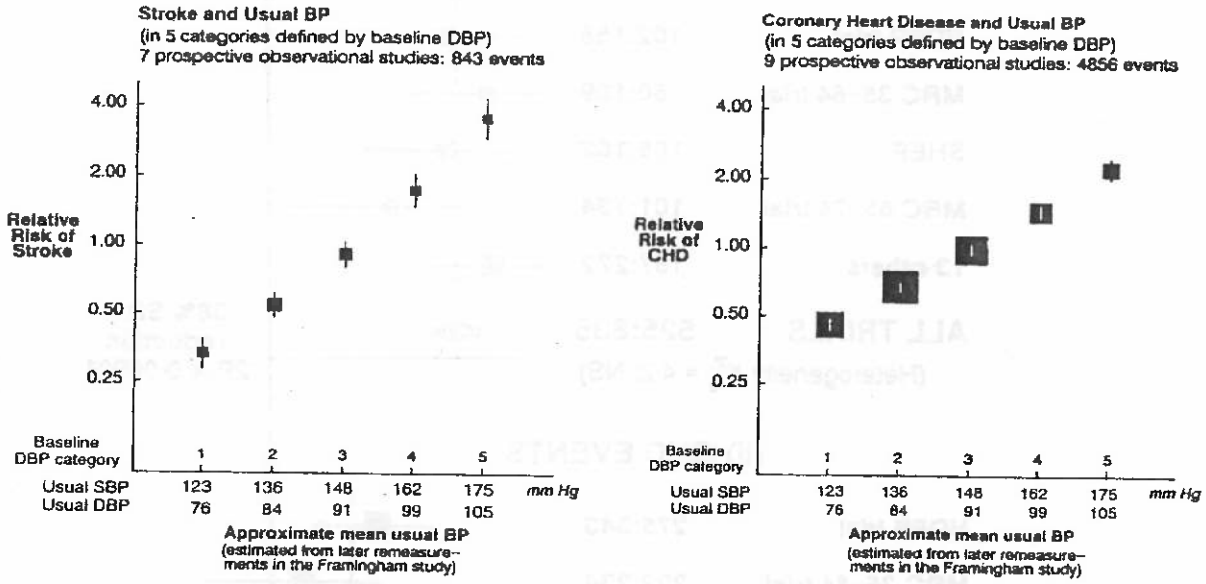


Fig 1: Relative risk of stroke and of CHD. Combined results for nine prospective observational studies among 420,000 individuals with 4,856 CHD events and 843 strokes during a mean of 10 years follow-up. [1]

2. Evidence from randomised trials of the benefits of blood pressure reductions.

The mean difference in DBP between treatment and control groups in trials of hypertension management was about 5-6 mmHg, and the mean treatment duration was 5 years. [2-5] For stroke, an overview of all previous unconfounded randomised trials of antihypertensive therapy suggests that all of the stroke avoidance associated with a prolonged reduction of DBP appears soon after lowering blood pressure (Fig 2). In contrast, the reduction in CHD seen in the trials (16%±5; 95% confidence intervals 7% to 24%: 2P<0.001) falls somewhat short of the difference of about 20-25% that would be

expected from the observational epidemiological evidence to result from a prolonged 5-6 mmHg reduction in DBP (Fig 2).

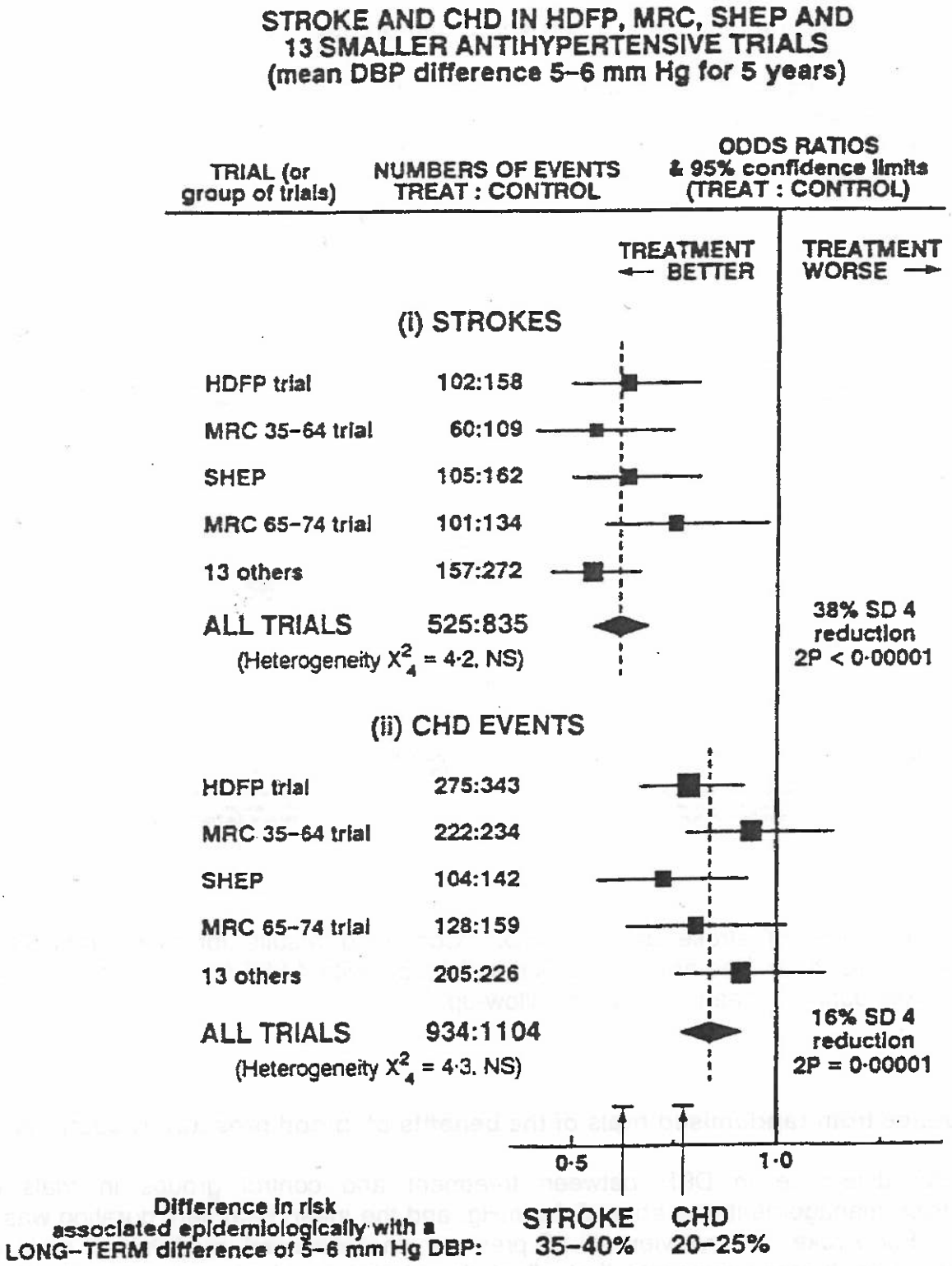


Fig 2: Reduction in the odds of stroke and of CHD in HDFP, MRC, SHEP and 13 other small unconfounded randomised trials of antihypertensive therapy.[2]

3. Rationale for further studies of the effects of lowering blood pressure with converting enzyme inhibitor and calcium channel blocker-based regimens

This apparent shortfall in CHD avoidance may be due to chance and/or to other factors including failure of the drugs to reverse chronic structural changes, or that the agents studied in the previous trials (chiefly diuretics and/or beta-blockers) had some important adverse effects (eg elevation of adverse lipids or falls in serum potassium)[6-7] that limited, but did not abolish, the CHD reduction. Calcium channel blockers (CCB's), and converting enzyme inhibitors (ACE-I) avoid some of these potentially adverse effects of diuretics, and may have some other cardioprotective effects.[8] Hence, antihypertensive regimens based on these agents may produce effects on CHD that are somewhat greater than those of diuretics. Most individual trials had insufficient power to demonstrate a significant reduction in CHD events associated with active BP lowering regimen versus placebo. It is therefore difficult to demonstrate any significant benefit of one antihypertensive regimen over another in terms of CHD prevention since to do so may require the observation of over a thousand coronary heart disease events in directly randomised comparisons. Hence, it is proposed in this study that in order to achieve sufficient power approximately 18,000 hypertensive patients at reasonably high risk of CHD be randomised between a beta-blocker-based regimen versus a calcium antagonist-based regimen and followed for an average of about 5 years depending on the number of events.

I B <u>Cholesterol and Coronary Heart Disease</u>

1. Strength of the relationship between cholesterol and CHD risk

Cholesterol is a major independent risk factor for CHD.[9-10] Across a wide range of increasing serum cholesterol levels, observational data show a clear, marked dose-response relationship with increased CHD mortality (Figs 3 & 4).[11,12,13]

As for DBP, the relationship between CHD risk plotted on a doubling scale and serum cholesterol in observational studies is approximately linear such that a prolonged lower serum cholesterol concentration of about *1mmol/l corresponds to about 50% less CHD*, irrespective of the cholesterol level, down to at least 3mmol/l. Observational studies suggest that a 10% lower cholesterol level which has persisted for decades is associated with about a 30% lower risk of CHD.

2. Evidence from randomised trials of the benefits of cholesterol reduction: A 10% reduction in cholesterol for 2 years or more lowers CHD risk by approximately 25%

In the randomised controlled trials of cholesterol lowering prior to 1995, the average difference in cholesterol between treatment and control was only about 10%, and the mean treatment duration was about 4 years. The benefits of a 10% reduction in total cholesterol achieved in randomised controlled trials by drugs or diet and in primary and secondary prevention, by duration of trial, are shown in Table 1.[14]

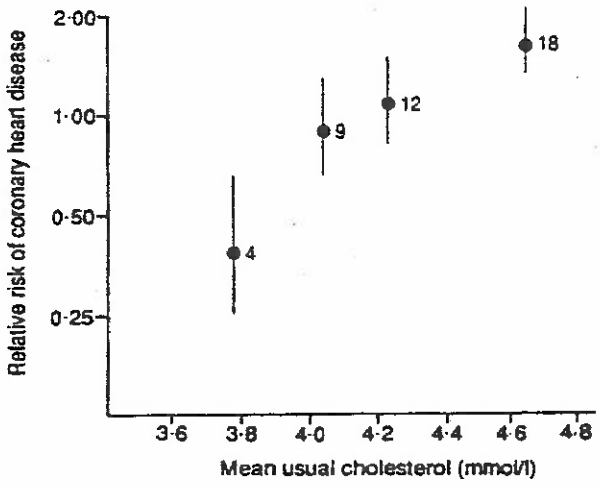


Fig 3: Shanghai prospective study in a low cholesterol population[12]: 9021 Chinese factory workers, subdivided into 4 similar-sized groups with respect to usual serum cholesterol and followed for 8-13 years for death from CHD.

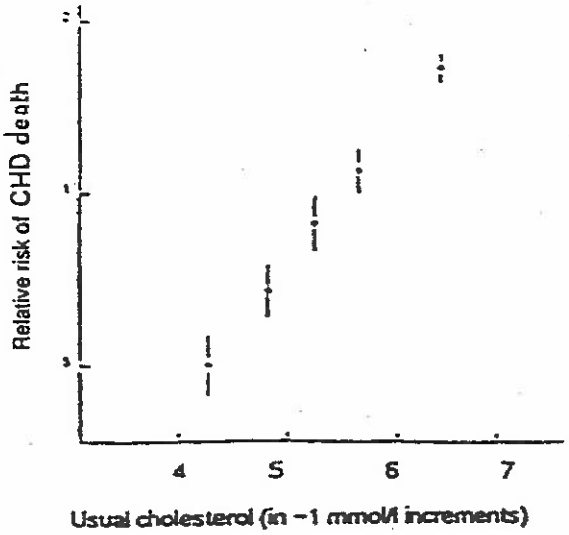


Fig 4: MRFIT prospective follow-up study[9]: 360,000 middle-aged US males, subdivided into 5 similar-sized groups with respect to usual serum cholesterol and followed for 5-10 years for death from CHD

Table 1: Reducing Serum Cholesterol by 0.6mmol/l (10%) and the impact on IHD: Randomised controlled trials (n=45,000)

Trial	% reduction in IHD		
	Duration (years)		
	≤ 2	2.1-5	5.1-12
Drugs	10	21	22
Diet	9	14	37
Men without IHD	11	25	24
Men with IHD	6	20	26
All trials	7	22	25

Moreover, it appears that the larger the cholesterol reduction the larger the CHD reduction (Table2).[14,15,16]

Table 2: CHD reduction by magnitude of cholesterol difference

Cholesterol reduction observed in trial	Reduction in total CHD during, on average, about 4 years of follow up
5-9%	8%
10-15%	19%
20-30%	30-40%

In the POSCH study which was a randomised trial of partial ileal bypass surgery (which reduces cholesterol resorption) versus diet among post-MI patients,[17] a 23% reduction in total cholesterol was maintained for an average of almost 10 years in the surgery group. This was associated with a significant 35±10% reduction in total CHD events with major reductions in all other cardiovascular endpoints. The large blood lipid reductions produced by surgery in the POSCH study are similar to those achieved by drugs such as statins (HMG CoA reductase inhibitors eg. simvastatin, lovastatin and pravastatin). Three large scale trials, evaluating the effects of lipid lowering using statins over a 5 year period, have recently been published. The first, the Scandinavian Simvastatin Survival Study (4S),[16] showed that a reduction in total cholesterol of 25% for 5.4 years in patients with a previous MI reduced major coronary events by 34% (95%CI: 25-41%) and cardiovascular deaths by 35% (95% CI: 20-48%) as well as reducing all-cause mortality by 30% (95% CI: 15-42%). A primary prevention study conducted in Scotland (WOSCOPS)[18] demonstrated a fall of 31% (95%CI: 17-43%) in coronary events, a reduction of 32% (95% CI 3-53%) in cardiovascular deaths and a 22% reduction in all-cause mortality (95% CI:0-40%) as a consequence of reducing total cholesterol by 20% with pravastatin.

In the CARE[19] study a 20% reduction in mean total cholesterol was achieved among post-MI patients using pravastatin. This reduction in cholesterol was associated with a 24% reduction in all coronary events, and a 9% reduction in all-cause mortality.

3. Effects of cholesterol reduction on total and on non-CHD mortality

The early lipid lowering trials had insufficient power to evaluate effects on all-cause mortality and even in combination, these trials were too small to assess the size of such an effect reliably. Furthermore, several of these early studies suggested a small increase in non-CHD mortality in the active treatment groups. This slight excess of non-cardiac deaths has attracted much comment over the years,[20,21] despite the lack of any convincing evidence for a causal relationship. The benefits in terms of all-cause mortality in the 4S

study and the lack of any increase in non-cardiovascular mortality associated with the use of statins in the 4S, WOSCOPS and CARE studies, has helped to resolve the previous concerns which were based on inadequate data from early trials.

I C Rationale for the ASCOT study

1. Insufficient data exist comparing new with conventional hypertension therapy, particularly relating to effects on morbidity and mortality.

2. At least 50% of high risk hypertensives require two or more drugs to provide adequate blood pressure control in the long term.[22] Previous studies have allowed a wide range of possible drug combinations to be used making it impossible to make recommendations about specific combinations. In ASCOT the allowed combinations are clearly specified as are subsequent add-on drugs which will be common to both limbs of the trial, and the agents used have been established as producing effective 24-hour BP control.

3. In the UK, Ireland and Scandinavia, over 40% of those on two drugs for hypertension use diuretics and beta-blockers and hence represent an appropriate standard against which other combinations should be compared.

4. Most recently published national and international guidelines currently recommend diuretics or beta-blockers as first line treatment of hypertension and if monotherapy is not sufficient, a combination of both. This also makes a beta-blocker/diuretic combination a logical standard comparator for patients uncontrolled on monotherapy.

5. ASCOT complements the ALLHAT study[23] which is currently evaluating optimal first line therapy with amlodipine, lisinopril or doxazosin vs. chlorthalidone. Subsequent add-on drugs allowed are very mixed and largely outdated (reserpine, clonidine and atenolol, with hydralazine as 3rd line).

6. There are reasons to believe, particularly from studies of target organ damage, that a combination of the calcium channel blocker, amlodipine and an ACE inhibitor may have advantages for CVD prevention over the standard diuretic/beta-blocker combination.[8]

7. Although hypertensives have been included in previous lipid lowering trials, to date no trials of lipid lowering have been carried out specifically among hypertensives, and particularly among those whose total cholesterol is ≤6.5mmol/l.

8. Eligible hypertensive subjects whose total cholesterol is ≤6.5mmol/l will be randomised to receive atorvastatin or placebo, since few trial data are available in primary prevention to establish the benefits of lipid lowering with a statin in this range of lipid levels.

9. Standard clinical practice in most of Europe does not, in primary prevention, usually involve the treatment of hypertensives with lipid lowering therapy. However, many of the subjects suitable for inclusion in ASCOT (hypertensive with other

cardiovascular risk factors) are likely, according to the most recent European Guidelines[24] to merit lipid lowering therapy if their total cholesterol is >6.5mmol/l. Therefore hypertensive subjects with a cholesterol above 6.5mmol/l will not be randomised to atorvastatin or placebo, but may still be randomised between the antihypertensive regimens.

II OBJECTIVES

II A Primary

1. To assess and compare the long-term effects on non-fatal myocardial infarction [MI] (symptomatic and silent MI) and fatal coronary heart disease (CHD) of the standard antihypertensive regimen (beta-blocker-based + a diuretic if necessary) with a more contemporary regimen (amlodipine-based + an ACE inhibitor if necessary).

2. To compare the effect on non-fatal MI and fatal CHD of 10mg atorvastatin vs placebo among patients with a total cholesterol ≤6.5mmol/l.

II B Secondary

1. To compare the effects of the two antihypertensive regimens on non-fatal MI (symptomatic only) and fatal CHD.

2. To compare the effects of the two antihypertensive regimens on all-cause mortality.

3. To compare the effects of the two antihypertensive regimens on total cardiovascular mortality.

4. To compare the effects of the two antihypertensive regimens on total (fatal and non-fatal) stroke

5. To compare the effects of the two antihypertensive regimens on the development of non-fatal and fatal heart failure.

6. To compare the effects of the two antihypertensive regimens on non-fatal MI, fatal CHD, non-fatal and fatal heart failure and the development of angina (total coronary endpoints).

7. To compare the effects of the two antihypertensive regimens on all cardiovascular events and procedures.

8. To compare the effects of 10mg atorvastatin with placebo on non-fatal MI (symptomatic only) and fatal CHD.

9. To compare the effects of 10mg atorvastatin with placebo on all-cause mortality.

10. To compare the effects of 10mg atorvastatin with placebo on total cardiovascular mortality.

11. To compare the effects of 10mg atorvastatin with placebo on total (fatal and non-fatal) stroke.

12. To compare the effects of 10mg atorvastatin with placebo on the development of fatal and non-fatal heart failure.

13. To compare the effects of 10mg atorvastatin with placebo on non-fatal MI, fatal CHD, non-fatal and fatal heart failure and the development of angina (total coronary endpoints).

14. To compare the effects of 10mg atorvastatin with placebo on all cardiovascular events and procedures.

II C Tertiary

1. To compare the effects of the two antihypertensive regimens and the effects of active lipid-lowering versus placebo on the development of each of the following:
   (a) silent MI
   (b) unstable angina
   (c) chronic stable angina
   (d) peripheral arterial disease
   (e) life-threatening arrhythmias

2. To compare the effects of the two antihypertensive regimens and the effects of active lipid lowering versus placebo on the development of diabetes mellitus or renal impairment.

3. To evaluate whether synergistic effects on the study primary endpoint or cardiovascular events and procedures are observed in association with the use of atorvastatin and amlodipine.

4. To compare the effects of the different antihypertensive and lipid-lowering regimens on health care costs.

5. To compare the effect of the different antihypertensive regimes on all major study endpoints among specific sub-groups of patients (e.g. diabetics, smokers, the obese [>30Kg/m^2], those with LVH, older/younger [≤60/>60 years], male/female, any previous vascular disease [by history or ECG], renal dysfunction [by serum creatinine, urinalysis], with and without metabolic syndrome*).

6. To compare the effects of 10mg atorvastatin with placebo on all major study endpoints among specific subgroups of patients (e.g. diabetics, smokers, the obese [>30Kg/m^2], those with LVH, older/younger [≤60/>60 years], male/female, any previous vascular disease [by history or ECG], renal dysfunction [by serum creatinine, and urinalysis], with and without metabolic syndrome*).

* As defined according to NCEP III except for replacing waist-hip ratio with BMI>30 as patients with triglycerides ≥ 1.69 mmol/l, HDL-C for males <1.03 mmol/l, for women <1.29 mmol/l, BP ≥ 130/85 mmHg, fasting glucose ≥ 6.1 mmol/l.

III STUDY DESCRIPTION

III A Design

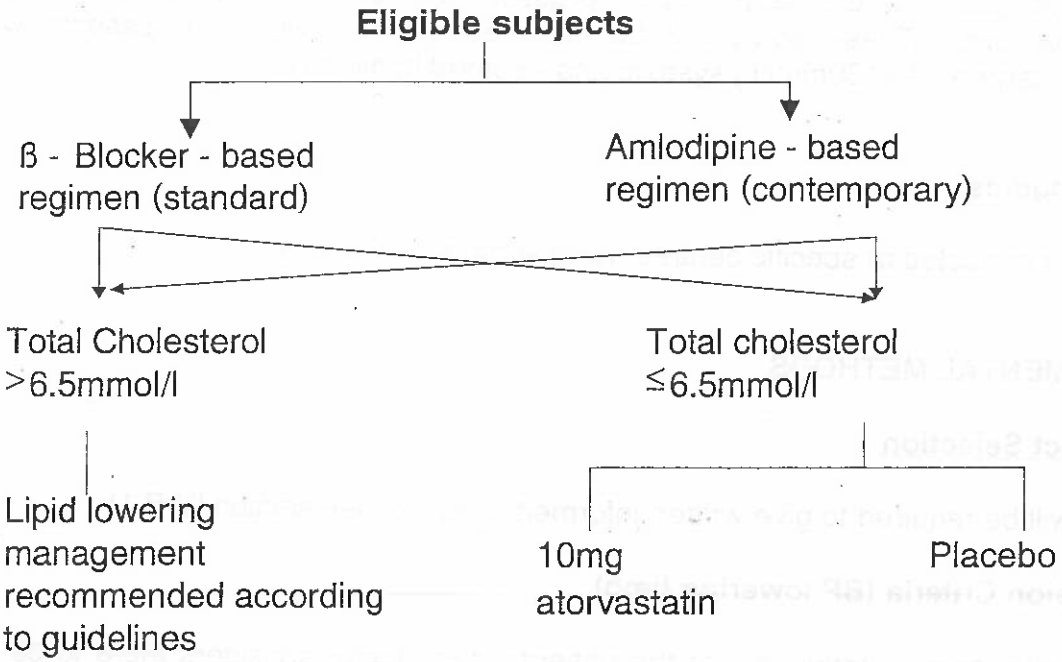
2x2 factorial trial: The two antihypertensive regimens will be compared in a trial using the Prospective Randomised Open Blinded Endpoints (PROBE) design and 10mg atorvastatin will be compared in a double-blinded randomised trial with placebo.

Study treatment will be continued (unless some clear contra-indication or indication develops) until 1150 primary events (fatal CHD or non-fatal MI) have occurred or for an average of 5 years, whichever is the longer. It is estimated that this will require 18000 patients.

III B Antihypertensive and cholesterol lowering regimens

Eligible patients will be randomised using minimisation procedures in a 2x2 "factorial" design to:

- antihypertensive "first-line" regimens:beta-blocker vs calcium antagonist and if total cholesterol is ≤6.5mmol/l to:
  cholesterol lowering: 10mg atorvastatin vs placebo.



III C Sample plan

Estimated numbers in each subgroup are shown in Table 3.

Table 3

Chol level mmol/l	Lipid lowering allocated	ß-blocker	Amlodipine	Total
≤ 6.5	10mg atorvastatin (randomised)	2250	2250	4500
≤ 6.5	Placebo (randomised)	2250	2250	4500
≤ 6.5	Non-randomised lipid lowering agents	500	500	1000
> 6.5	Non-randomised lipid lowering agents	1000	1000	2000
> 6.5	Nil	3000	3000	6000
		9000	9000	18000

It is assumed that 3000 of the total sample will be treated with open lipid-lowering therapy by their physician, of whom 1000 will have a total cholesterol ≤6.5mmol. Thus 9000 will be randomised to 1 of 2 treatments for hypertension as well as atorvastatin versus placebo; this part constitutes the factorial design. The residual 9000 patients will not take part in the factorial design as they will not be randomised to atorvastatin/placebo.

III D Blood pressure targets

In non-diabetic patients, the target blood pressure will be <140mmHg systolic and <90mmHg diastolic. These goals will be more stringent, however, in patients with diabetes, with targets of <130mmHg systolic and <80mmHg diastolic.

III E Sub-studies

These will be conducted at specific centres using separate protocols.

IV EXPERIMENTAL METHODS

IV A Subject Selection

All subjects will be required to give written informed consent (see section IV B 1)

1. Inclusion Criteria (BP lowering limb)

The fundamental entry criterion is that the patient's own doctor considers there to be no clear indications for, or clear contraindications to, any one of the trial treatments. All subjects will be eligible, provided that:

a. They are able and willing to attend the clinic regularly for at least 5 years.

b. (i) At screening and randomisation they have untreated hypertension with a systolic BP maintained at ≥160mmHg and/or a diastolic BP ≥100mmHg;

OR

(ii) At randomisation they have treated hypertension with a systolic BP maintained at ≥140mmHg and/or a diastolic BP at ≥90mmHg on ≥1 drug.

c. They are aged: ≥40, <80 years.

d. They have three or more of the following risk factors for a future cardiovascular event:
i) LVH on echocardiography within 2 months assuming unchanged treatment. Assessed according to ASE criteria or on ECG using either Cornell voltage duration product (>2440) or Sokolow Lyon criteria (>38);

(ii) Any of the following other ECG abnormalities (LV strain pattern, abnormal Q waves, LBBB, ST-T changes compatible with IHD);

(iii) NIDDM as defined by WHO (Appendix IB);

(iv) Peripheral vascular disease according to a standard validated questionnaire (Appendix IA); or has had a recent history of surgical intervention for peripheral vascular disease.

(v) Past history of cerebrovascular event(s) including TIA's ≥three months previously;

(vi) Male sex;

(vii) Age ≥55 years;

(viii) Microalbuminuria/Proteinuria;

(ix) Smoking (ie regular smoker within the last year of ≥20 cigarettes or cigars/week);

(x) Plasma total/HDL cholesterol ratio ≥6.

(xi) A history of a coronary artery disease event occurring in a first degree relative before the age of 55 (males) or 60 years (women).

2. Inclusion Criteria (lipid lowering limb)

The fundamental entry criterion is that the patient's own doctor considers there to be no clear indications for, or clear contraindications to, any one of the trial treatments. All subjects will be eligible, provided that:

a. They are eligible for the BP lowering limb of the trial.

b. They are not currently taking a statin or a fibrate.

c. They have a total cholesterol ≤6.5mmol/l.

3. Exclusion Criteria

a. Any contraindications to, or previous history of, major intolerance to dihydropyridine calcium channel blockers (CCB's), ACE inhibitors, beta-blockers, thiazide diuretics, doxazosin, or statins.

b. A history of secondary hypertension.

c. Malignant hypertension.

d. Previous clinical myocardial infarction or currently treated angina pectoris.

e. Stroke, transient ischemic attacks, or cerebrovascular surgery <3 months before study onset.

f. Patients requiring CCB'S, ACE-I's, beta-blockers or diuretics for concomitant diseases or conditions.

g. Fasting se-triglycerides >4.5 mmol/l.

h. Patients requiring other drugs which are also prescribed for hypertension (eg alpha-blockers for prostatism).

i. Second or third-degree A-V block.

j. Clinical congestive heart failure (NYHA II-IV).

k. Uncontrolled arrhythmias.

l. Concomitant clinically important hematological, gastrointestinal, hepatic (liver function test [ALT] >3x upper normal level), renal (se creatinine >200 µmmol/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.

m. 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.

n. Participation in any other studies involving investigational or marketed products within one month prior to entry into this study or concomitantly with this study.

o. Pregnant or lactating women and those of child bearing potential (i.e. pre-menopausal without appropriate contraception).

IV B Procedures and Measurements

A detailed description of procedures and measurements made in this study are outlined in Appendix IA, C and E and in the study procedures manuals.

1. Informed Consent

Subjects who are considered to be eligible for randomisation will have the study explained to them and will be invited to participate. A written description of the study will be provided in a patient information sheet. Patients will have an opportunity to initiate any discussion they wish during the initial screening visit, and will have time to think about the invitation to

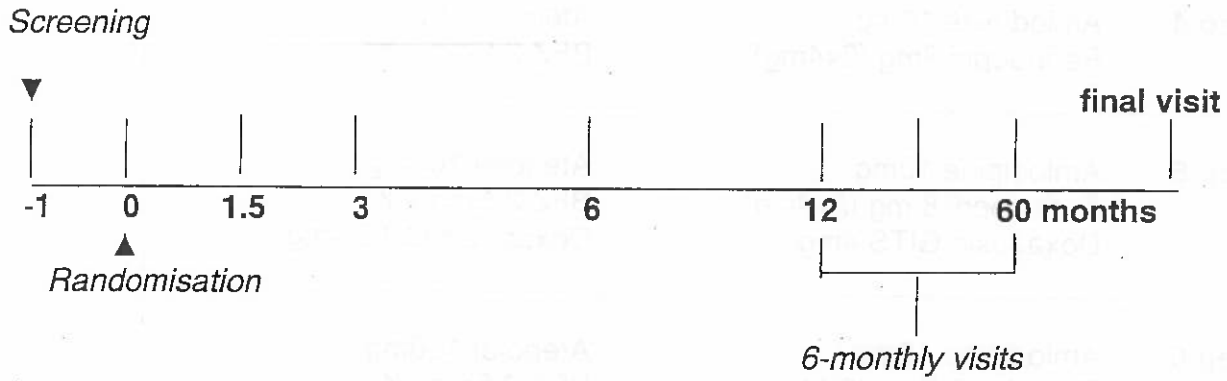
participate in the trial before making a decision. Patients will be discouraged from consenting to participate if it is unlikely that they would wish to contribute for at least 5 years.

Prior to study enrolment, written informed consent, including permission to search available medical records if necessary, will be obtained from each subject in accordance with the recommendation of the revised Declaration of Helsinki (South Africa 1996) and this will be recorded in the case record form; attention is drawn to page 53, points 9-11 concerning freely given consent .

2. Visit Schedule

The schedule for visits outlined below should be adhered to as far as possible. However it is acknowledged that the clinical management of individuals must be judged ad personam. In addition, logistics may prohibit strict adherence to this schedule at some time during a 5-year study. Some flexibility in the timing of routine study visits is therefore allowed, such that more rapid up-titration of medication can be achieved. In addition it may be necessary to arrange extra visits to control or monitor blood pressure or for other reasons. The timing of all visits and any extra visits should be recorded in the case record form, including the reason for the visit and any extra laboratory tests or procedures carried out.

Visit Summary



NB: Every attempt should be made to continue seeing patients in the clinic 6-monthly (or, if this is not possible, following them up by telephone) even if they stop taking the trial treatment.

3. Study drug administration

As mentioned in section IV B2, some flexibility regarding the administration of study drugs must be allowed although ideally the treatment steps outlined below should be followed whenever possible and variations from the schedules outlined should be exceptional. Study drugs will be provided free of charge to all trial participants.

a. *Antihypertensive regimens*

All eligible subjects will be randomised to Step 1 of either regimen A or B (Table 4). Thereafter progression of subsequent steps will be dependent upon not reaching target pressures (<140mmHg systolic and <90mmHg diastolic for non-diabetics or <130mmHg systolic and <80mmHg diastolic for diabetics).

TABLE 4

	Group A	**Group B**
Step 1	Amlodipine 5mg	Atenolol 50 mg
Step 2	Amlodipine 10mg	Atenolol 100mg
Step 3	Amlodipine 10mg Perindopril 4mg	Atenolol 100mg BFZ 1.25mg +K^+
Step 4	Amlodipine 10mg Perindopril 8mg (2x4mg)	Atenolol 100 mg BFZ 2.5mg + K^+
Step 5	Amlodipine 10mg Perindopril 8 mg (2x4mg) Doxazosin GITS 4mg	Atenolol 100mg BFZ 2.5mg + K^+ Doxazosin GITS 4mg
Step 6	Amlodipine 10mg Perindopril 8mg (2X4mg) Doxazosin GITS 8mg	Atenolol 100mg BFZ 2.5mg +K^+ Doxazosin GITS 8mg

- If after step 6, pressures remain above ideal targets (140/90 for non-diabetics:130/80 for diabetics) further treatment modification should be attempted. This modification should involve the addition of a further drug which:

  (a) Is not one of the antihypertensive drug classes used in the other limb of the trial:- (Angiotensin II antagonists should be considered as ACE inhibitors in this context)
  (b) Ideally is a once-a-day drug.

- If after a further antihypertensive agent has been added to either treatment limb after step 6 of the study and blood pressure levels remain below 160mmHg systolic and below 100mmHg diastolic, no further treatment modification need be considered.

- If after the use of 4 different agents, blood pressures remain unacceptably high (eg ≥160mmHg systolic or ≥100mmHg diastolic) the physician in charge should modify therapy further as necessary.

- If the lower dose of amlodipine or atenolol is not tolerated, the patient can be provided with perindopril or bendroflumethiazide respectively instead, to which doxazosin GITS should be added if required.

- If the higher dose of amlodipine or atenolol is not tolerated, trial participants may be down-titrated to receive 5mg or 50mg respectively and proceed to a modified version of step 3, by adding the second drug.

- If the second drug used in each limb - perindopril or bendroflumethiazide is not tolerated, patients should be provided with the third drug - doxazosin GITS.

- If the higher dose of the second drug prescribed in each limb (perindopril or bendroflumethiazide) is not tolerated, this drug dose should be down-titrated and the third drug should be added (doxazosin GITS).

- Ideally all drugs should be taken no more than 24 hours before study visits. No changes to the antihypertensive drugs or doses of these drugs should be made on the basis of elevated blood pressure levels unless it has been confirmed that routine compliance was satisfactory and that study drugs had been taken within 24 hours.

- If, prior to randomisation, patients are taking two or more antihypertensive agents and have either a systolic BP ≥160mmHg or a diastolic ≥100mmHg the patient may be randomised straight into step 2 or step 3 as the physician in charge considers appropriate.

- If after achieving BP targets, BP levels are subsequently found to have risen above target levels, therapy should only be modified after compliance has been established and two sets of readings on separate occasions at least one week apart confirm the need to do so.

b. Lipid-lowering therapy

- The results of blood lipid levels measured at screening will determine whether patients are eligible for randomisation into the lipid arm of the study (see sections III B and III C).

- The patient's own physician will always be advised of their patients' lipid profiles and of local recommendations regarding the use of lipid lowering therapy.

- Patients whose total cholesterol is ≤6.5mmol/l and whose physician does not intend to treat the subject with a lipid lowering agent will be randomised to receive either atorvastatin (10mg) or matching placebo.

- Any lipid lowering therapy other than a fibrate or statin in use prior to randomisation should be continued during the study.

- For subjects whose dyslipidaemia is subsequently considered by their physician to require additional lipid lowering therapy, such therapy may be added.

4. Assessments at baseline and follow-up visits

a. Screening visit (-1 month [-2 months to -2 weeks])

- Written informed consent after full explanation of the study.

- Past medical history, current illnesses, lifestyle variables (smoking and alcohol intake), other factors relevant to eligibility, family history of hypertension, CHD and stroke.

- Height, Weight, BP (see Appendix IC), Heart Rate (HR).

- 12 lead ECG - if required to confirm eligibility, faxed to Scandinavian coordinating centre for evaluation (see Appendix (1E).

- Non-fasting blood sample taken for: Haemoglobin (Hb), se-creatinine, electrolytes, liver function tests (LFT'S), total cholesterol, HDL, triglycerides, blood sugar and some for frozen storage.

- Urine: stix for protein, blood, sugar and microalbuminuria.

- Those on beta-blockers may have the dose down-titrated before randomisation.

- Appointment made for randomisation visit.

- Screening form including inclusion/exclusion criteria transmitted to appropriate co-ordinating centre at least 1 week before randomisation visit.

b. Run-in period prior to randomisation

- The "Run-in period" prior to randomisation is to allow sufficient time to check eligibility, to provide the patient's own doctor with the opportunity to consider the results of the screening lipid values and to help ensure that only those subjects likely to be willing to continue to take their medication for an extended period are

randomised. In the UK those doctors who wish to treat their patient with lipid lowering therapy (statin or fibrate) should inform the relevant study centre before randomisation. Any subjects who wish to drop out for any reason during this early run-in period will be encouraged not to continue in the study. Subjects will be randomised only if, at the end of the run-in, they seem likely to comply with the trial protocol for several more years. By this process it is anticipated that many potential drop-outs will be excluded before becoming part of the randomised comparison, with a consequent improvement in statistical sensitivity.

- Subjects whose triglyceride level was >4.5mmol/l or glucose was >7.0mmol/l at screening will be recalled during this period for a fasting blood sample to evaluate eligibility (see sections IV A1 and IV A3).

c. *Randomisation visit (0 months)*

- Physical examination.
- BP and HR.
- Fasting blood sample: total cholesterol, HDL, triglycerides, and glucose.
- 12 lead ECG (to be posted to ASCOT Scandinavian Co-ordinating Centre, Gothenburg University Clinical Research Institute, Drakegatan 6, 5-41250 Gothenburg, Sweden).
- Eligibility and consent confirmed.
- Randomisation allocated using minimisation procedures by the appropriate co-ordinating centre by telephone.
- All previous antihypertensive medication withdrawn. Continue and record all other existing medication.
- Study medication allocated (see section IV B3).
- Appointment made for next visit.
- Adverse events (including hospitalisation, diagnosis, duration) recorded.

d. *First follow-up visit (6±2 weeks)*

- Endpoints recorded.
- Adverse events (including hospitalization, diagnosis, duration) recorded.
- BP and HR.
- Non-fasting blood sample for electrolytes and creatinine, if started on an ACE inhibitor at 0 months. (This test is required within a few weeks of initiating an ACE inhibitor at any point in the trial).
- BP treatment modified if BP above target (see section IV B3).
- Changes in medication recorded.
- Study medication allocated.
- Appointment made for next visit.

e. *Second follow-up visit (3±1 months)*

- Endpoints recorded.
- Adverse events recorded.
- BP and HR.
- BP treatment modified if BP above target (see section IV B3).
- Changes in medication recorded.
- Study medication allocated.
- Appointment made for next visit.

f. *Third follow-up visit (6±1 month)*

- Endpoints recorded.
- Adverse events recorded.
- BP and HR.
- Fasting blood sample: total cholesterol, HDL, triglycerides, glucose, electrolytes, creatinine and, if randomised to statin/placebo, liver function tests (LFT's).
- Urine: stix for protein, blood and sugar.
- BP treatment modified if BP above target (see section IV B3).
- Changes in medication recorded.
- Study medication allocated.
- Appointment made for next visit.

g. *Subsequent follow-up visit (year 1, 2, 3, 4, 5 ± 1 month)*

- Body weight.
- Endpoints and adverse events recorded.
- BP and HR.
- ECG at year 2 only.
- Fasting blood sample: Hb, total cholesterol, HDL, triglycerides, glucose, electrolytes, creatinine, liver function tests (LFT's), and at year 2 only extra blood for frozen storage.
- Urine: stix for protein, blood and sugar.
- BP treatment modified if BP above target (see section IV B3).
- Changes in medication recorded.
- Study medication allocated.
- Appointment made for next visit.

h. *Follow-up visit (years 1½, 2½, 3½, 4½, 5½ ± 1 month)*

- Endpoints and adverse events recorded.
- BP and HR.
- Smoking and alcohol intake recorded.
- BP treatment modified if BP above target (see section IV B3).
- Study medication allocated.
- Appointment made for next visit.

i. Extra visits

In addition it may be necessary to arrange extra visits to control or monitor blood pressure or for other reasons. The timing of all visits and any extra visits should be recorded in the case record forms, including the reason for the visit and any extra laboratory tests or procedures carried out.

j. Final visit

All participating subjects should have a final assessment at the end of the study. This assessment should include:

- Endpoints and adverse events recorded.
- BP and HR.
- Body weight measurements.
- Smoking and alcohol intake recorded.
- ECG.
- Fasting blood sample for lipid profile; HB, glucose, creatinine, electrolytes and liver function tests (LFT's), and extra blood for frozen storage.
- Urinalysis with stix for microalbuminuria, protein, blood and sugar.
- Changes in medication recorded.

As one arm of the trial has been discontinued before the other, a final visit examination will be performed for the patients involved in the discontinued arm of the trial. These patients will then continue in the remaining arm of the trial until the study is finally terminated, when a final visit for that limb of the trial will also be carried out.

k. 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	X	X•													
Previous Antihypertensive Medication And Side Effects	X														
Current Illness/adverse events[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Morbidity/Mortality Endpoints			X	X	X	X	X	X	X	X	X	X	X	X	X
Informed Consent	X														
Withdrawal Of Antihypertensive Drugs		X													
Height■, Weight	X					X		X		X		X		X	X
BP, Heart Rate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X						X							X
Blood Tests	X∅	X	X*		X◆	X◆		X◆		X◆		X◆		X◆	X
Urine Tests	X				X	X		X		X		X			X
Physical Examination		X													
Extra Visits Optional For Drug Up-Titration When Necessary															

★ bloods for electrolytes, creatinine for those randomised to receive 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 >4.5mmol/l or glucose is >7mmol/l at screening, subjects will be recalled during this period for a fasting blood sample to evaluate eligibility (see section IVB, 4. b).

1 Current illness only is recorded at visit -1.

5. Central ascertainment of biochemical effects, and of cardiovascular events, cancers and cause-specific mortality

a. Assessment of biochemical changes throughout the trial

Two central laboratories will be used for all analyses - one in the UK and Ireland and one in Scandinavia.

b. Ascertainment of cardio-vascular events

The co-ordinating centre will seek additional information (including, if necessary, any pertinent hospital records) from the patient's own doctor about relevant hospital admissions, suspected myocardial infarctions, strokes, coronary angioplasty or vascular surgery which has been recorded on the case record form/worksheet. This will allow central review of any vascular events by the endpoint committee *who will be blind to treatment allocation.*

Standardised criteria for classifying diagnoses will be used by the endpoint committee. These criteria will be defined, a priori, in a manual of operations in conjunction with the endpoint committee members.

c. Follow-up of morbidity and mortality

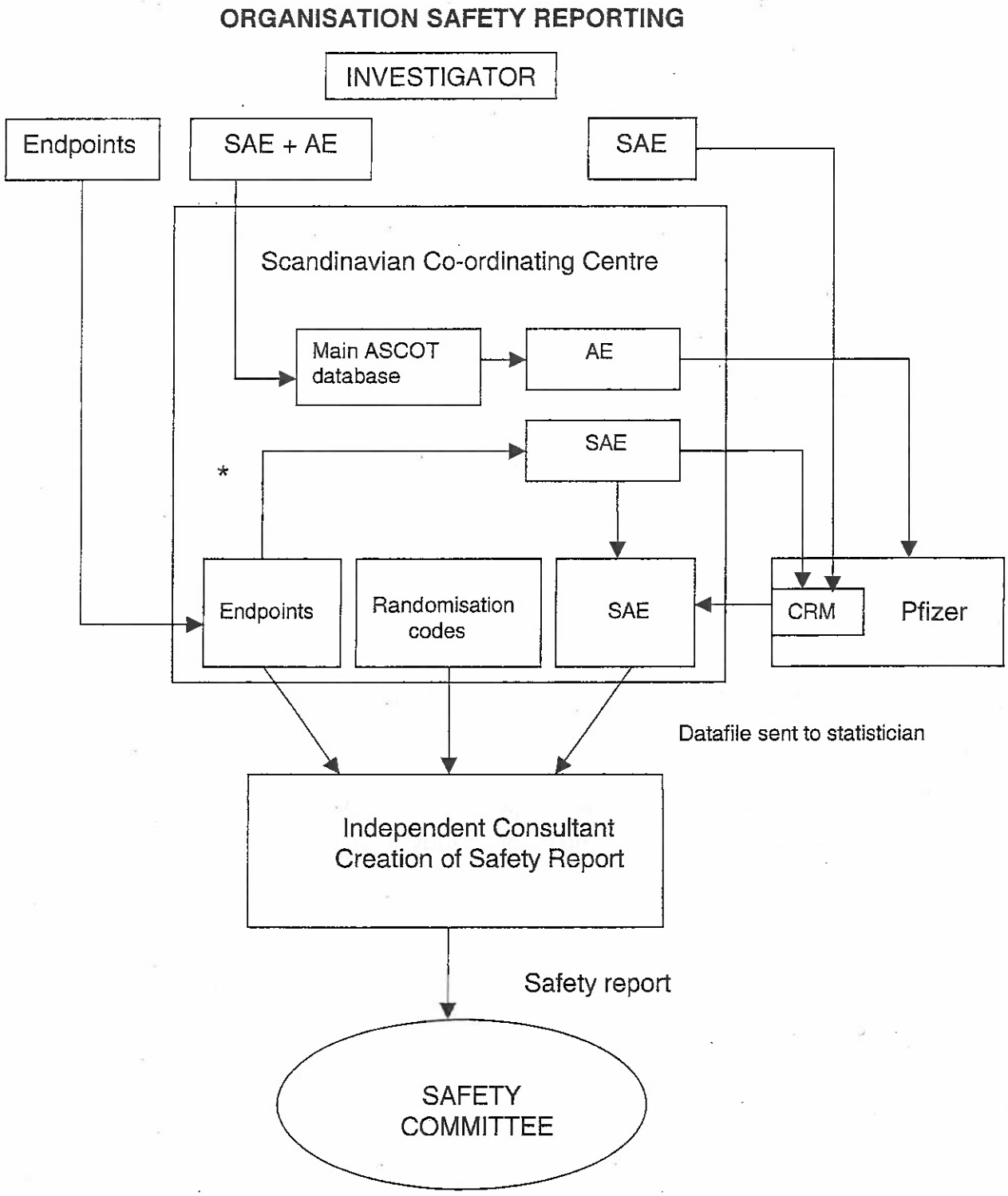
The co-ordinating centre will seek the certified causes of all deaths of randomised patients. For all patients the appropriate National Registries, where available, will be used.

The underlying causes of death will be classified as coronary [ICD-9:410-414], other heart failure [ICD-9:402, 404, 428], cerebrovascular, other vascular, cancer related, or other and unknown causes by the endpoint committee who will be blinded to treatment allocation. From an analysis viewpoint statistical censoring is only enforced at the time of death.

Investigators may be requested by the endpoint committee to provide all relevant documentation to substantiate the diagnosis of a study endpoint.

6. Safety Reporting

A summary of the organisation of reporting adverse events and endpoints is shown in the following figure:



* *Rejected endpoints might potentially be SAE's.*

a. Endpoints

Study endpoints are classified as:

Primary endpoints
(i) Non-fatal MI (symptomatic and silent MI) + fatal CHD

Secondary endpoints
(i) Non-fatal MI (symptomatic only) + fatal CHD
(ii) All cause mortality
(iii) Cardiovascular mortality
(iv) Fatal and non-fatal stroke
(v) Fatal and non-fatal heart failure
(vi) Total coronary endpoints = fatal CHD + non-fatal MI (symptomatic and silent) + chronic stable angina + unstable angina + fatal and non-fatal heart failure
(vii) Total cardiovascular events and procedures = cardiovascular mortality + non-fatal MI (symptomatic and silent) + unstable angina + chronic stable angina + life threatening arrhythmias + non-fatal heart failure + non-fatal stroke + peripheral arterial disease + revascularisation procedures, and retinal vascular thromboses.

Tertiary endpoints
(i) Silent MI
(ii) Unstable angina
(iii) Chronic stable angina
(iv) Peripheral arterial disease
(v) Life threatening arrhythmias (VF or sustained VT or complete heart block)
(vi) Development of diabetes mellitus
(vii) Development of renal impairment
(viii) With and without metabolic syndrome*

* As defined according to NCEP III except for replacing waist-hip ratio with BMI>30 as patients with triglycerides ≥ 1.69 mmol/l, HDL-C for males <1.03 mmol/l, for women <1.29 mmol/l, BP ≥ 130/85 mmHg, fasting glucose ≥ 6.1 mmol/l.

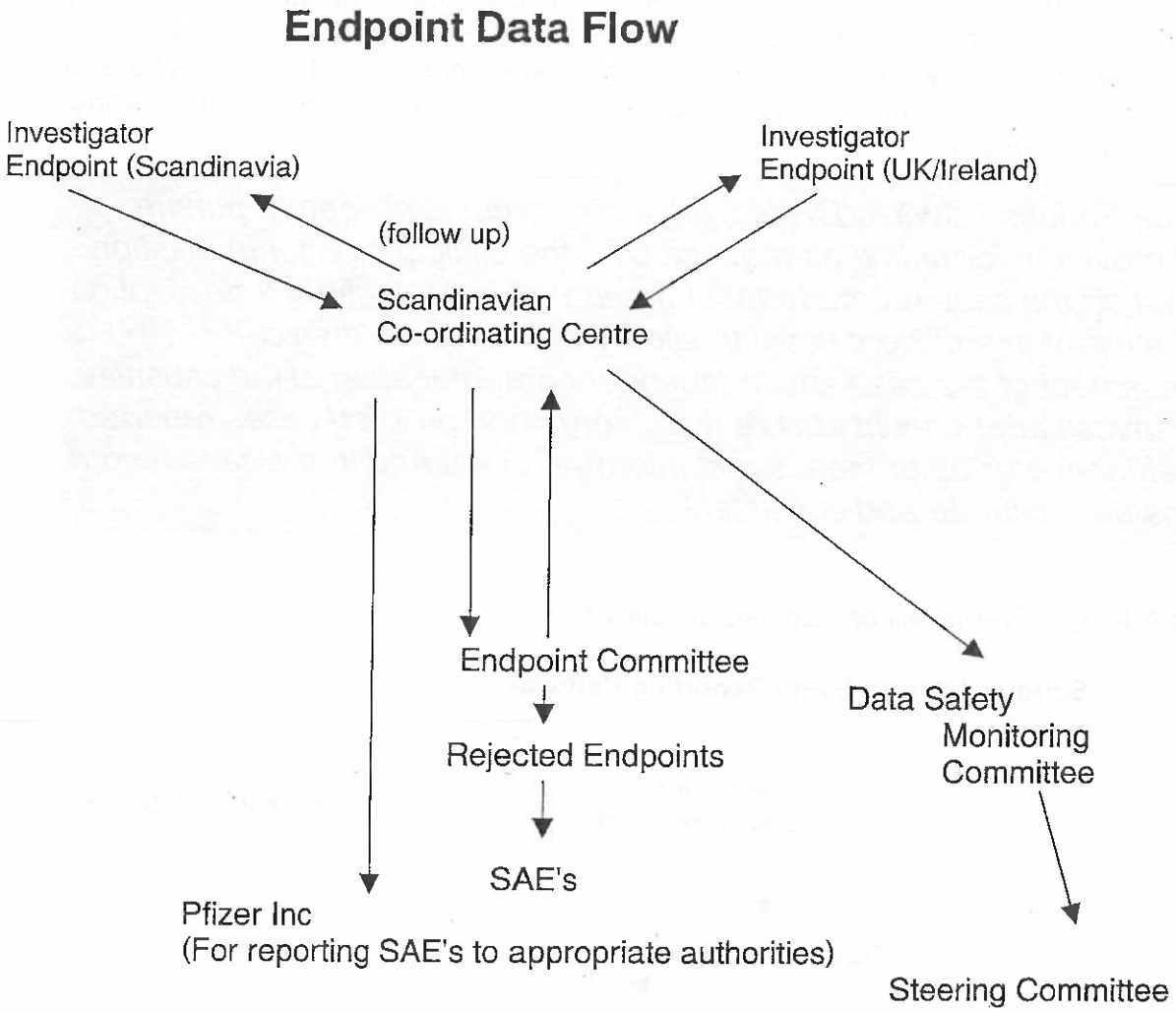
These events are not considered as serious adverse events.
During the study period, an event classified as an endpoint must be reported by mail to the Scandinavian Co-ordinating Centre as soon as the investigator is informed. If an investigator receives information of an endpoint that has occurred within 30 days after the study period this also has to be reported to:

Endpoint Administrator
Scandinavian Co-ordinating Centre/Ascot
Clinical Research Institute
Drakegatan 6
S-41250 Göteborg
Sweden

In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to the Scandinavian Co-ordinating Centre. The investigator should ensure that information on such cases reported by telephone or other means and information entered in the case record forms are accurate and consistent. The endpoints are sent on a continuous basis to the Endpoint Committee for evaluation of whether they qualify for inclusion as an endpoint or not.

The Endpoint Committee, who are blinded as to study therapies, will evaluate and classify the endpoints. Confirmed endpoints will be reported back to the Scandinavian co-ordinating centre who will forward these data to the Data Safety Monitoring Committee (DSMC). Those events considered to be serious adverse events and not endpoints by the Endpoint Committee will be reported immediately to the Scandinavian Co-ordinating Centre for immediate reporting as a serious adverse event to Pfizer Clinical Research Group in the relevant country.

Endpoints will be handled as follows:



b. Serious Adverse Events

Serious Adverse Events includes any experience which is not a study endpoint that suggests a significant hazard, such as events which:

(1) are life threatening
(2) results in a persistent or significant disability/incapacity
(3) require inpatient hospitalisation or prolongation of a hospital stay due to other causes than endpoints (see above)
(4) result in congenital anomaly/birth defect
(5) require medical intervention to prevent any one of the above.(For further details please refer to the Ascot Adverse and Serious Adverse Event manual)

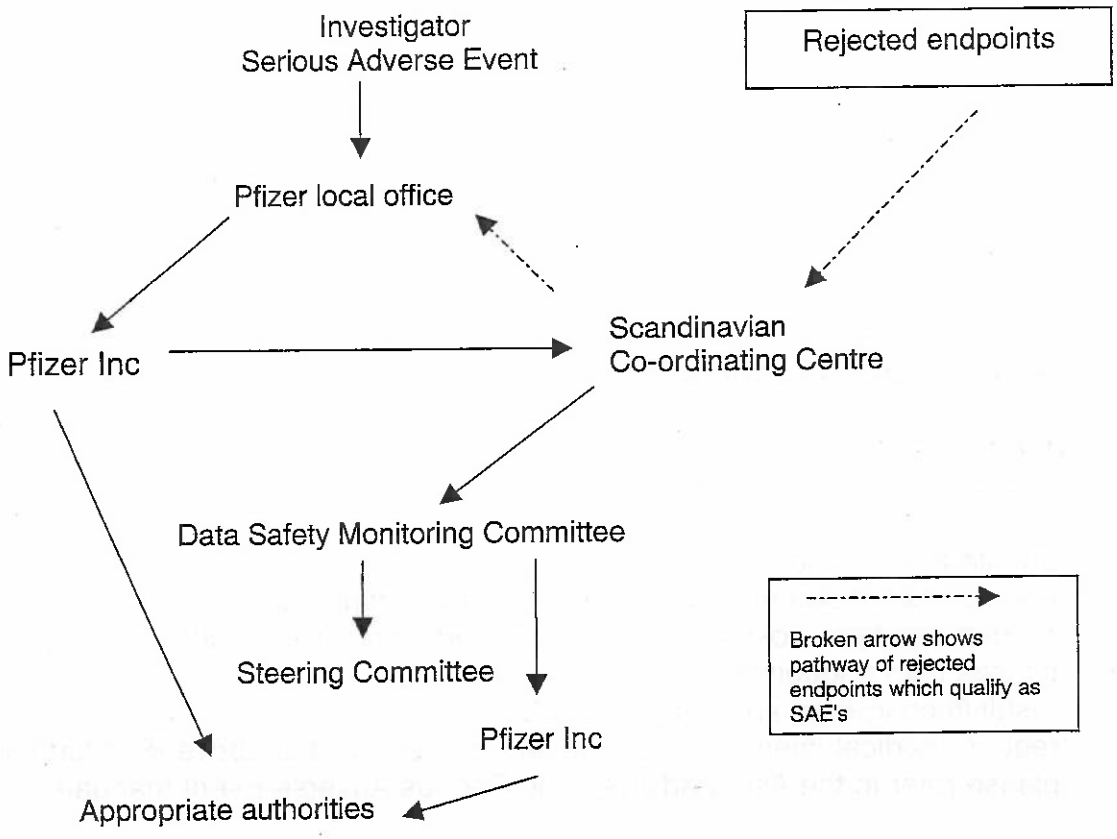
It should be emphasised that, regardless of the above criteria, any additional adverse experience, which the investigator considers serious, should be reported immediately.

An event classified as a Serious Adverse Event occurring during the study period or, if known by the investigator, within 30 days after the patients completion of the study, must as soon as the investigators are informed, be reported by telephone to the appropriate Pfizer Clinical Research Group office regardless of suspected relationship to study drug. (For telephone number please refer to the Ascot Adverse and Serious Adverse Event manual).

For all Serious Adverse Events, the investigator is obliged to pursue and provide information as requested by the clinical monitor in addition to that on the case record form. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of the causality. The investigator should ensure that information on such cases reported by telephone or other means and information entered in the case record forms are accurate and consistent.

Serious Adverse Events will be handled as follows:

Serious Adverse Event Reporting Pathway



The DSMC is responsible for advising the steering committee concerning the protocol amendments or study discontinuation based on this information. The yearly safety report will not contain any information on the treatment arm, if the DSMC has not detected any safety issues. If deemed necessary by the DSMC, safety reports will be issued more frequently than the stipulated 1 year interval.

c. Non Serious Adverse Events

All ongoing Adverse Events at each visit, regardless of treatment, if not a study endpoint will be recorded on the Adverse Event Form. A follow-up of the events is required at each of the following visits until such time that the event is resolved. (For further details please refer to the ASCOT Adverse and Serious Adverse Event manual).

d. Abnormal Laboratory Test Results

The recorded results of all laboratory tests required by the protocol will be attached to the case record form. All clinical important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the clinical monitor, or until a diagnosis that explains them is made. Abnormal laboratory test results that result in a change in study drug dosage should be recorded as adverse events in the case record form.

For patients randomised to atorvastatin or placebo:

Alanine transaminase (ALT) x 4 upper limit of normal (ULN) is to be checked after approximately 1 week, while ALT>2xULN but ≤4xULN is to be checked after approximately 3 weeks. If repeat ALT>4xULN then statin/placebo treatment should be stopped temporarily; whereas if >2 but ≤4xULN, ALT is to be checked again after approximately 3 weeks, with study treatment then stopped temporarily if ALT remains >2xULN. After stopping study treatment temporarily, ALT is to be checked again after approximately 6 weeks and study treatment stopped permanently if still more than 1.5xULN (with 3 week follow up visits) until ALT reverts to normal: ie ≤1.5xULN). If, on the other hand, ALT≤1.5xULN, then the allocated study treatment can be started again, with a further 2 early recall visits at 3-week intervals (at which ALT must remain ≤2xULN, otherwise study treatment is to be stopped permanently).

Creatine kinase (CK): symptoms of myopathy (ie new unexplained muscle pain or weakness) accompanied by an otherwise unexplained elevation of CK>10xULN should result in the study treatment being stopped permanently (with 3-week follow up visits until CK reverts to normal: ie ≤3xULN). CK>4xULN but ≤10xULN that cannot be explained (ie by some trauma, intramuscular injection, heavy exercise, recent myocardial infarction etc) is to be checked after approximately 1 week and, if repeat CK>4xULN then study treatment should be stopped temporarily. CK is to be checked again after approximately 6 weeks and study treatment stopped permanently if still >3xULN. If, on the other hand, CK≤3xULN, then the allocated

study treatment can be started again, with a further 2 early recall visits at 3-week intervals (at which CK must remain ≤3xULN, otherwise study treatment is to be stopped permanently). A flow chart detailing the investigations to be undertaken is located in the Ascot laboratory manual.

e. *Breaking the Randomisation Code: Emergency Procedures*

Individual sealed envelopes including the randomisation code for each subject randomised in the lipid lowering part of the trial will be provided to the investigators. The envelopes must be stored in a secure storage facility. Only the investigator or a person appointed by the investigator will have access to the envelopes. Another set of sealed code envelopes will be kept at the co-ordinating centre in the UK and at the local Pfizer offices for emergency access and security back up to the site.

The envelopes should only be opened in the event of a medical emergency, requiring immediate identification of the therapy. The date and reason for breaking the code should be recorded and signed off by the investigator as follows:

- on the code envelope
- on the appropriate case record form

Such action immediately terminates the double-blind lipid lowering aspect of the study for that patient.

7. Discontinuation from Study Medication

The reason for a patient discontinuing study medication will be recorded in the case record form. A discontinuation occurs when an enrolled patient permanently ceases taking the study medication, regardless of the circumstances, prior to completion of the protocol. A discontinuation must be reported immediately to the appropriate co-ordinating centre if it is due to an endpoint or in the case of a serious adverse event to the local Pfizer office. It may not be necessary for a patient to stop treatment after an endpoint. The investigator will record the reason for study drug discontinuation, provide or arrange for appropriate follow-up for such patients, and document the course of the patient's condition. *The patients should, if at all possible, be followed to the end of the study despite discontinuation of the study drug* as the intention-to-treat analysis includes all patients.

Typically, subjects may discontinue study medication for the following reasons:

a. At the request of the subject.

b. If the investigator considers that a subject's health will be compromised due to adverse events or concomitant illness that develops after entering the study.

c. If a subject is recognized after entry to be uncooperative or a consistent violator of protocol requirements.

For any subject who discontinues therapy before the study is completed, the investigator will:

a. Complete the case record form including any summary sheet, indicating the date of and explanation for the early discontinuation of medication. If possible, provide an overall evaluation of safety of the assigned treatment.

b. Encourage where appropriate the subject to re-start study medication.

c. Arrange for alternative medical care of the discontinued subject if necessary.

d. Follow the patient in the usual way to the end of the study despite discontinuation of the study medication.

IV C Clinical Supplies

The Sponsor will supply the investigator with adequate quantities of the following materials to permit completion of the study:

- Amlodipine 5 and 10mg tablets
- Atenolol 50 and 100mg tablets
- Perindopril 4mg tablets
- Bendroflumethiazide 1.25 and 2.5mg (with potassium) tablets
- Doxazosin GITS 4 and 8mg capsules
- Atorvastatin 10mg tablets
- Matching placebo for atorvastatin tablets

After discontinuation of the lipid-lowering arm of the trial, the sponsor will, where permitted by local rules and regulations, make atorvastatin 10mg available to the patients previously participating in this arm of the trial until the final visit of the main trial.

The investigator should maintain adequate records of the receipt and disposition of all study drugs supplied. Any unused medication will be returned to the Sponsor or designated pharmacies. The investigator shall be responsible for assuring that the study medication is stored in a cool, secure, limited access area, protected from extremes of light, temperature, and humidity (unless otherwise specified). Further details can be found in the drug handling manual.

V ADMINISTRATIVE MATTERS

V A Summary of Study Organization (Appendices III, IV, V)

- Two main co-ordinating centres:

UK and Ireland

Cardiovascular Studies Unit
Dept. Clinical Pharmacology and Therapeutics
Imperial College School of Medicine at St. Mary's
Paddington
London W2 1PG
UK
Tel: +44 (0) 20 7594 3400
Fax:+44 (0) 20 7594 3411

Scandinavia

Scandinavian Co-ordinating Centre/Ascot
Clinical Research Institute
Drakegatan 6
S412 50 Göteborg
Sweden
Tel +46 31 832058
Fax +46 31832790

- Data collection:
  - 9000 patients from the UK and Ireland and 9000 patients from Scandinavia
  - standardised methods in each centre
  - logistics as per local requirements
  - transferred and handled at co-ordinating centres (either London or Gothenburg)
  - transferred between co-ordinating centres

- Randomisation:
  - separately via each co-ordinating centre using identical methods

- Laboratories:
  UK and Ireland:
  Biosys Clinical Ltd
  Royal College of Surgeons in Ireland
  123 St Stephen's Green
  Dublin 2, Ireland.

  Scandinavia:
  Medilab AB
  P O Box 1550 (visiting address: Nytorpsvagen 30, Nasby Park)
  S-183 15 Taby
  Sweden

V B Study committees

- Executive Committee: this consists of the two principal investigators, Peter Sever (UK and Ireland) and Björn Dahlöf (Scandinavia) and Neil Poulter and Hans Wedel.

- The International Steering Committee: this committee is co-chaired by Peter Sever and Björn Dahlöf. The memberships of 15 comprises: one member from each participating country (4 from UK and Ireland, 4 from Scandinavia); the two chairmen; one non-voting Pfizer representative; the 2 other members of the executive; and one non-voting senior member for each of the 2 coordinating centres. Observers may be present at meetings of this committee.

- The working group consists of 6 people, the executive plus 1 senior member from the UK co-ordinating centre and the Scandinavian Clinical Research Co-ordinator. This group should have executive mandate responsibility for day-to-day decisions. For major decisions, the working party will consult the steering committee. Observers may be present at meetings of this committee.

- A national working management group for the UK and Ireland and each of the Scandinavian countries will implement any major decisions. For Scandinavia, regional working groups will also be established.

- A Data Safety Monitoring Committee of experienced clinicians, epidemiologists and statisticians (approximately 5 people) not involved in the study will meet annually or as required.

- An endpoint committee consisting of 4 experienced clinicians will evaluate the blinded endpoints mailed/faxed to them on a running basis.

- An external auditing group will be responsible for ensuring that the participating centres are treating the two treatment groups in a similar fashion and with acceptable adherence to GCP.

- A sub-study committee will determine which sub-studies are acceptable considering the focus of the main study.

V C Monitoring of Study

The study will be monitored periodically by Pfizer CRA's in Scandinavia and by study monitors in the UK and Ireland in accordance with GCP to assess the progress of the study and adherence to the protocol. The investigator should maintain source documents such as laboratory reports, X-rays, ECG's, any consultation reports, complete history and physical examinations, etc. for review by the monitor.

V D Recording of Data

Data from patient visits will be entered using a Remote Data Entry (RDE) system. The methods used by Scandinavia and UK/Ireland differ. In Scandinavia the data is entered onto paper workbooks by the Investigator, then data-entered into the RDE system by the monitors. In the UK/Ireland, data is entered directly into the RDE system by site personnel. An explanation for the omission of any required data should appear on the appropriate page. All data recorded in the CRF will be signed by the Investigator or his/her appropriate designee.

Specific instructions and further detail can be found in the study instruction manual or the RDE/CRF SOP/manuals in each region.

A list of the normal ranges for all laboratory tests conducted will be provided for each of the two central laboratories. The methods employed for each assay should be available on request. Any change in the laboratory, its procedures, normal values, certification, etc. must be reported by the laboratory to the co-ordinating centre.

V E Statistical analyses and power considerations

1. Sample size

a. Comparison of blood pressure treatment

The sample size has been calculated based on several assumptions. Based on the experience from other trials and epidemiological data[1-6, 24-27] the yearly rate of **non-fatal MI and fatal CHD** (later called endpoint rate) is assumed to be 2% before correction and 1.42% after adjusting for withdrawals and dilution from cross-over. (See below).The relative additional benefit of a 'contemporary' drug regimen (per protocol) is estimated to be 20%. This estimate is in part affected by the relatively large reductions in BP anticipated in this trial compared with previous trials. The cumulative non-compliance rate in BP-treatment is estimated to be 20% in 5 years. Including dilution from losses and non-compliance (cross-over) the estimated intention to treat (ITT) effect of the 'contemporary' regimen is 15-16%.

With a significance level of 5% a total sample size of 18000 is needed to get a power of 80% for the primary endpoint (nonfatal MI and fatal CHD) giving a total number of 1150 endpoints.

Dilution effect:
The dilution effect and the effect of losses and statin treatment on endpoint rate in the standard group have been calculated from a Markov model.

Endpoint rates:
The unadjusted endpoint rate (fatal CHD and nonfatal MI) has been calculated from experiences from similar trials (see figure 1, page 4).

Assumptions for blood pressure treatments

Annual endpoint-rate (%) in the control group unadjusted for losses, crossover and statin-effect	2.00
Relative effect of "contemporary" compared with "standard" BP-treatment (per protocol) (%)	20
Relative effect of BP-treatment corrected for losses and crossover Intention to Treat (ITT) %	**15-16**
Proportion statin treated open or randomised (%)	40-45
Treatment effect in endpoint rate by statin (ITT) 10 mg atorvastatin (%)	30
Relative reduction (%) in endpoint rate in the "blood pressure standard" group because of statin treatment effect (%)	18
Cumulative losses of endpoint during 5 year (%)	10
Cumulative cross-over from "standard" to "contemporary" (%)	20
Cumulative cross-over from "contemporary to "standard" (%)	20
Annual endpoint-rate (%) in the "standard" BP treatment group after adjustment for #	**1.42**
Cumulative endpoint rate (%) during 5 years in the control group after adjustment for #	**6.9**
Significance level (alpha) (%) Interim analysis by safety committee will use level 0.005 leaving 0.045 for final test	**5**
Sample size (9000 contemporary + 9000 standard)	**18000**
Power (%)	80

losses and the dilution effect from cross-over and statin effect

b. Comparison of atorvastatin and placebo

These calculations are based on the experience from clinical trials and epidemiological data.[9-19,28,29] It is assumed that 9000 patients (50%) will be randomised to either 10 mg atorvastatin or placebo (see section III C).

The following assumptions are made:

Cholesterol reduction with 10 mg atorvastatin (%)	30
Difference in cholesterol between 10 mg atorvastatin and placebo (mmol/l) 1.7	
Relative (%) effect on endpoint (nonfatal MI and fatal CHD) of 10 mg atorvastatin compared with placebo (40% optimally in long term studies) (ITT)	30
Power for the primary endpoint (nonfatal MI and fatal CHD) given by	
Cumulative endpoint rate (nonfatal MI and fatal CHD) on placebo for five years (%)	6.35
Significance level (%)	1
Sample size	9000
Power (%)	90

2. Statistical analysis

The statistical method for the main analysis will be a log rank test using time to event (nonfatal MI and fatal CHD) as the primary information. The significance level for the primary comparisons of the antihypertensive and the lipid lowering components will be 0.05, both including adjustment for interim looks (for details see section V E.1) and 0.01 for secondary and tertiary analyses. These analyses will be done without adjusting for baseline factors and will be performed according to the intention to treat principles (ITT). 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 done as complementary analyses.

Analyses using information on compliance with treatment (per protocol analyses) will be done as secondary analyses. To some extent these analyses are more sensitive to the rate of cross-over or discontinuation.

Main effect variables will also be analysed in certain subgroups to search for possible interactions. Such analyses will be seen as explanatory, will involve chi-square tests for interaction, and will be foundations for future hypotheses. P-values and confidence intervals will be presented for all comparisons.

The statistical analyses will be performed by the two co-ordinating centres under the supervision of the ASCOT Steering Committee. The unblinded statistical information for the Safety Committee will be provided by one specially named person at the co-ordinating centre in Gothenburg.

V F Disclosure of data and publication

All information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the Sponsors and investigator(s) are completed. Permission from the Executive Committee is necessary prior to disclosing any information relative to this study outside of the Steering Committee. It is proposed that the results relating to the two primary endpoints will be published separately. The results may be published or presented by the investigator(s), but the major Sponsors (Pfizer) will be provided with a complete dataset. All sponsors (Pfizer, Servier, and Lovens) will be given the opportunity to review and comment on any such results for up to 1 month before any presentations or publications are produced.

V I INVESTIGATOR'S APPROVAL

I have carefully read this protocol and agree that it contains all the necessary information required to conduct the study and I agree to conduct it as described. I understand that this trial will not be initiated without appropriate or necessary Ethical Committee approvals and will comply with the administrative requirements of the governing body of the institution.

Informed written consent will be obtained from all participating subjects or their legal guardians and appropriately documented. The undersigned agrees that the trial will be carried out in conformance with the Declaration of Helsinki (attention being drawn to page 53, points 9-11 concerning freely given consent; copy appended) and with the local laws and regulations relevant to the use of new and approved therapeutic agents in patients.

_____

Investigator's name (please print)

_____

Investigator's signature

_____

Date

References

1. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer, A, Stamler J. Blood pressure, stroke and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990; 335: 765-774

2. Collins R, Peto R. Antihypertensive drug therapy: effects on stroke and coronary heart disease. In Textbook of Hypertension, Chapter 69, Part 8 (ed J Swales), Blackwell Scientific Publications 1994, UK.

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APPENDICES

APPENDIX I

MEASUREMENTS AND PROCEDURES

A Intermittent Claudication Questionnaire

B Diabetes Criteria

C Blood Pressure measurement

D Silent Myocardial Infarction: ECG coding

E ECG Flow

APPENDIX IA

Intermittent Claudication Questionnaire

PATIENT DETAILS

Affix label here

(Name, Address, DOB & Study No)

VISIT NUMBER ☐☐

DATE ☐☐ ☐☐ ☐☐

day month year

---

1. Do you get pain or discomfort in you leg(s) when you walk?

   Yes ❑

   No ❑

   I am unable to walk ❑

   If you answered "YES" to question 1 – please answer the following questions. Otherwise you need not continue.

2. Does this pain ever begin when you are standing still or sitting?

   Yes ❑ No ❑

3. Do you get it if you walk uphill or hurry?

   Yes ❑ No ❑

4. Do you get it when you walk at an ordinary pace on the level?

Yes ❑ No ❑

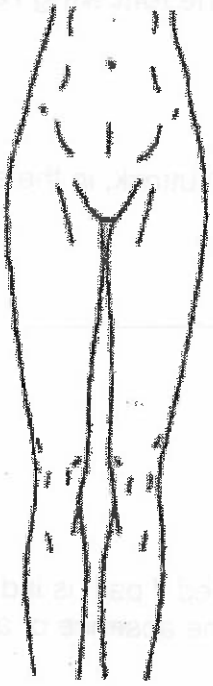
5. What happens to it if you stand still?

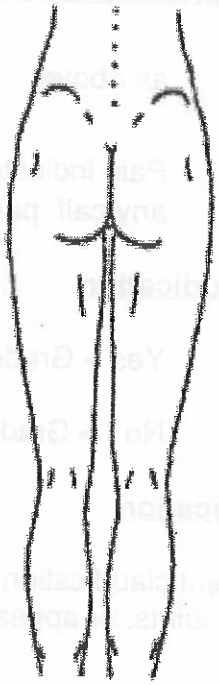
Usually continues more than 10 minutes ❑

Usually disappears in 10 minutes or less ❑

6. Where do you get this pain or discomfort?
Mark the place(s) with "X" on the diagram below.

Front





Back

SCORING THE INTERMITTENT CLAUDICATION QUESTIONNAIRE

A classification of <u>definite claudication</u> requires all the following responses:

Question 1 – Yes

Question 2 – No

Question 3 – Yes

Question 5 – Usually disappears in 10 minutes or less

Question 6 – Pain clearly indicated within the calf muscle, regardless of whether pain is also marked in other sites

A classification of <u>atypical claudication</u> requires all the following responses:

Question 1-5 - as above

Question 6 - Pain indicated in the thigh or buttock, in the absence of any calf pain

<u>Grading degree of claudication</u>

Question 4 - Yes = Grade 2

No = Grade 1

<u>Sites excluding claudication</u>

A diagnosis of intermittent claudication should be excluded if pain is indicated in the hamstrings, feet, shins, joints, or appears to radiate, in the absence of any pain in the calf.

APPENDIX IB

Diabetes criteria

WHO criteria for the diagnosis of diabetes in patients with symptoms are:

a fasting venous plasma glucose concentration of 7mmol/l or more (confirmed on a second measurement) or a 2-hour value of 11.1mmol/l or more following a 75g load.

If the 2-hour value is in the range 7-11 mmol/l the diagnosis is impaired glucose tolerance. Glucose tolerance tests should be performed in all those whose fasting concentration is in the range 6-6.9mmol/l: a fasting concentration of less than 6mmol/l excludes the diagnosis.

Patients who have been diagnosed as having non-insulin dependent diabetes (NIDDM) in the past but who are controlled with a special diet will also be considered as having NIDDM for the purposes of the study.

Subjects currently treated with insulin with a history of onset of diabetes after the age of 40, and body weight in excess of ideal body weight at the time of diagnosis, and treated with oral agents for a period of two years will also be considered to have NIDDM.

APPENDIX IC

BLOOD PRESSURE MEASUREMENT

Responsibilities

Research nurses/Investigators trained in the method are responsible for measuring and recording digital blood pressures from patients.

Equipment

- Digital blood pressure monitor (Omron HEM-705CP with modifications requested for ASCOT))
- Blood pressure cuffs (1 regular and 1 large)
- Rechargeable batteries (R14C)
- Printer paper
- Tape measure

Method

OMRON HEM 705-CP has fulfilled the requirements for accuracy of the protocols of the Association for the Advancement of Medical Instrumentation (AAMI) and the British Hypertension Society (BHS). Moreover the device provides hard copy of the blood pressure measurements and pulse rate together with the time and date of recording

Instructions for using the OMRON HEM 705-CP

Before use

- The nurse/investigator must read the accompanying instruction manual carefully, insert batteries and print paper, and then familiarise him/herself by using the device on one or more volunteers. A step-by-step instruction card as a guide for day-to-day use will be provided with each device.

- Set the time and date.

General Information

- The device should be calibrated at 1 year (± 2 months) intervals by the monitor with the reference equipment supplied.

- Batteries should be replaced when the symbol indicating low battery power is shown. Batteries should provide for 500 measurements.

- The nurse/Investigator should ideally be the same for each individual patient throughout the study. Where this is not possible every effort should be made to

ensure that a consistent type of observer (nurse or doctor) measures blood pressure for each individual throughout the study.

Preparation of patient

- Ensure that the patient is as relaxed as possible with an empty bladder. Instruct the patient to sit with both feet parallel and flat on the floor.
- Ensure that the patients have neither smoked nor consumed alcohol in the 30 minutes before blood pressure measurement.
- Patients should rest for 5 minutes in the sitting position before measurement.
- Patients should not talk during blood pressure measurement.

The cuff

- Arm circumference (AC) should be measured midway between the shoulder tip and the olecranon process.
- If AC <32cm use standard cuff; if AC ≥32cm use large cuff. If arm circumference <24cm use the standard cuff adjusting the velcro strip as illustrated in the OMRON manual page 6 section 4.

Cuff sizes

Arm Circumference	Cuff
24 – 32cm	Standard
32 – 42cm	Large

- The cuffs are designed for blood pressure measurement on the left arm. If the cuff cannot be applied on the left arm, the right arm can be used – but be certain that the green strip on the lower boundary of the cuff is always on the brachial artery. <u>The same arm should be used throughout the study.</u>
  - The cuff can be placed over a shirt or blouse sleeve.
  - See Omron manual (pages 6,7)for correct placement of cuff.
  - Ensure that the arm is supported on a cushion or table top, so the cuff position is in line with the level of their heart (see the manual illustration).
  - Instruct the patient to relax and take 5-6 deep breaths prior to commencing the procedure. This aids in stabilising their blood pressure.

Preparation of equipment and taking the blood pressure

- Insert the air inflation tubing plug from the cuff into the air jack of the monitor. Switch on the device by pressing the SPHYG/CLOCK button, and wait until the display shows a '0'.

- Select range of blood pressure with the PRESSURE VALVE PRESET switch on the AUTO mode the cuff inflates to about 170mmHg If pressures above this level are anticipated put the switch to 240. If the measurement fails, 'EE' will show and if in the AUTO mode, try again with position 240.

- Press the START (inflation) button and immediately release it. A noise will sound and the monitor automatically commences. The screen will flash a heart symbol during the process.

- A sound will indicate the recording has taken place. The cuff then deflates and the BP and pulse will be displayed in the screen. There is a latent period of 3.5 seconds for the BP to be displayed and a further 2 seconds for the pulse.

- If any of the error codes – 'E' – are displayed, refer to page 19 of the instruction manual and after rectifying the source of error, repeat measurement.

Printing the Data

- Press PRINT CURRENT READING button and print-out will give the date and time of measurement, systolic and diastolic pressure and pulse rate.

- After about 1 minute repeat measurement.

- Press PRINT CURRENT READING button

- After about 1 minute repeat measurement.

- Press PRINT CURRENT READING button.

- Calculate the mean of the second and third readings. In the UK the database will automatically calculate the mean. In Scandinavia calculate the mean by adding the two measurements together and divide by two.

- Detach print out, write the date and patient's ID on the front of the print out and attach it to a blood pressure log form (Appendix 1)(with adhesive).

- Take a copy and add the original and the copy to the worksheet/central file.

- Record the last three readings on the CRF.

- Enter the mean of the last two readings on the worksheet. This mean will be used in the analyses.

Additional Information

- Cuff inflation can be terminated by pressing the SPHYG/CLOCK button.
- For insufficient inflation pressure settings, the cuff will automatically re-pressurise to a pressure 40mmHg higher than the previous inflation pressure.
- Do not clean the monitor with detergents; if dirty, wipe with a damp cloth.

Problems

- If you cannot obtain a blood pressure recording with the OMRON HEM-705 CP: a recording should be made using a conventional sphygmomanometer. The measurement should be written into the CRF with an explanatory note.
- If the OMRON HEM 705-CP fails to function: contact the co-ordinating centre, which will provide a replacement device.
- The OMRON will be calibrated at yearly intervals by the Study Monitor. If you have reason to believe that extra calibration is necessary please contact the co ordinating centre.

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APPENDIX ID

SILENT MYOCARDIAL INFARCTION: ECG CODING

Aim

This procedure will identify patients with silent myocardial infarcts as part of the primary endpoint of the study.

The primary aim is to identify patients with newly developed ECG signs of silent myocardial infarction, ie appearance of major Q or QS items during the course of the study.

Appearance of major Q and QS items

The ECG diagnosis of major Q or QS items is based on the appearance of any of Minnesota codes in group 1.1 and 1.2 under the provision that such a code is not present in the same set of leads in the immediately preceding ECG. All ECG's with positive codes 1.1 or 1.2 at conclusion of the study are checked against the original inclusion ECG tracing. According to the specifications of the Minnesota code, a number of pre-evaluation codes are checked for possible suppression of codes 1.1 and 1.2 (see further coding protocol for details).

Silent myocardial infarction is diagnosed when there is appearance of new major Q or QS items without clinical signs of myocardial infarction.

ST segment or T-wave items and intraventricular conduction defects
ST segment changes are diagnosed when any of Minnesota codes 4.1 and 4.2 are present, T-wave changes are diagnosed when any of Minnesota codes 5.1 and 5.2 are present and intraventricular conduction defects are diagnosed when any of codes 7.1, 7.3 and 7.6 are present.

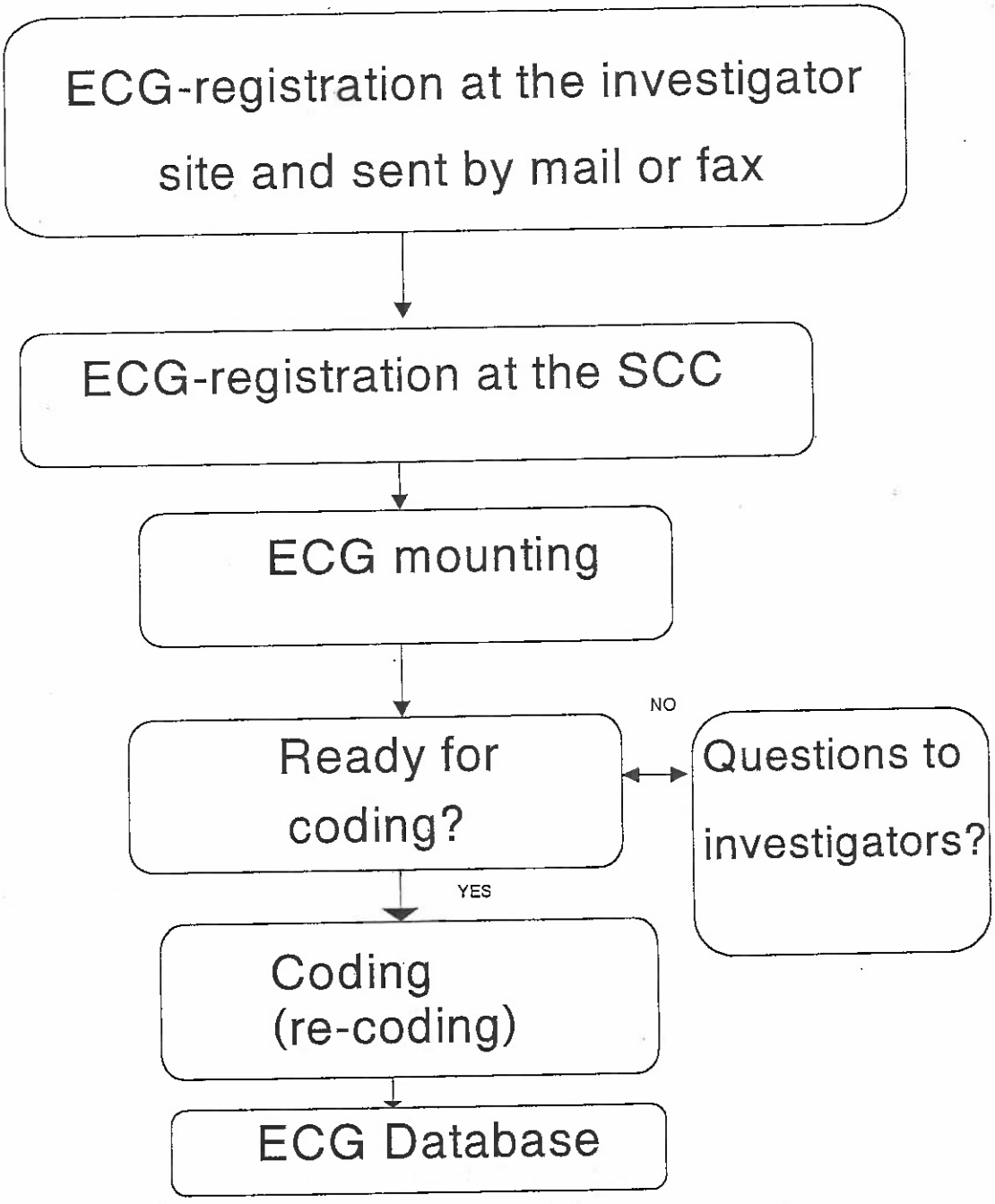
Criteria for sub-group analysis has to be decided by the Steering Committee. Patients could be classified as having possible myocardial ischemia when positive ST segment (codes 4.1 and 4.2) or T-wave (codes 5.1 and 5.2) are present or appear. In addition intraventricular conduction defects (codes 7.1, 7.3 and 7.6) may indicate IHD.

Coding procedure
ECG's are read and coded blindly according to the 'Minnesota code 1982' classification at the Clinical Experimental Research Laboratory, Department of Medicine, Sahlgrenska University Hospital/Östra (ECG Core Centre). Responsible investigator and head of the ECG Core Centre is Associate Professor Sverker Jern MD.

In a second step, serial ECGs with new Q or QS codes are visually compared by two independent coders to determine whether the Q/QS items are definitely new or not.

APPENDIX IE

ECG FLOW



APPENDIX II

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the

subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population

represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

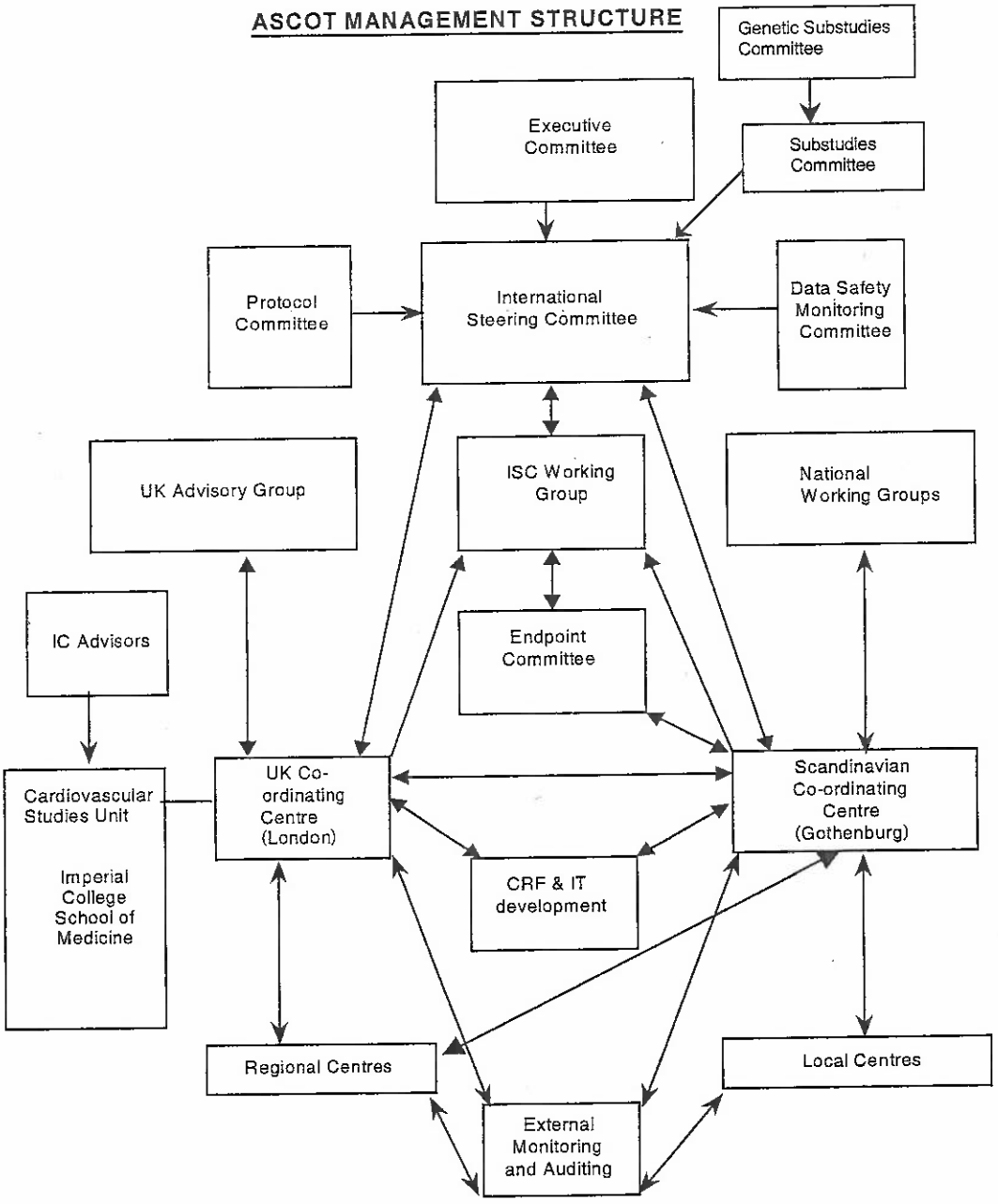
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Appendix III

International Management Structure



APPENDIX IV

Outline of UK and Ireland Study Organisation

The UK and Ireland will be divided into approximately 30 study regions. Each region will be headed by a regional principal investigator (RPI), each responsible for their own region and reporting to the National Principal Investigator (NPI).

For each participating centre in the UK and Ireland a principal investigator is being selected mainly from senior members of the British Hypertension Society.

All RPI's will be members of the UK and Ireland Management Committee, together with the NPI, the Director and Co-ordinators of the UK and Ireland Co-ordinating Centre, a UK and Ireland member of the International Steering Committee, a GP and a nurse. The committee will be chaired by the NPI and will be responsible for the day-to-day management of the study within the UK and Ireland.

Each RPI will be responsible for selecting GP's or hospitals whose patients will be screened for entry into the study. In each region, study nurses and study physicians will be recruited for the duration of the study. All study visits will be conducted by the study physicians and study nurses.

In each region a study centre will be created comprising a regional study office and clinics. The majority of patients will be seen in their regional study centre and other patients in their own practice.

APPENDIX V

Outline of Scandinavian Study Organisation

The Scandinavian countries are divided into 24 different regions: 5 in Norway, 7 in Denmark (including Iceland), 7 in Sweden, and 5 in Finland.

Each region is headed by a Regional Co-ordinator who is a clinician from a centrally located hospital. In some countries a leading GP will assist the Regional Co-ordinator. The Regional Co-ordinator is responsible for the region and is also a member of the National Working Group. The National Working Group will be chaired by the Steering Committee member for the country (one in each country) who is also the National Principal Investigator.

The majority of patients will be recruited from primary health care and each primary care physician will be responsible for including at least 10 patients into the study.

All Scandinavian centres will be monitored regularly by CRA's from Pfizer in accordance with GCP.

APPENDIX VI

ETHICAL ASPECTS

A Ethical Considerations/ Informed Consent

B Advantages and Disadvantages to patients of participation in the trial

C Ethics Committee/Institutional Review Board (IRB)

D Patient Information Sheet

E Patient Consent Form

APPENDIX VI: ETHICAL ASPECTS

APPENDIX VI A: Ethical Considerations/Informed Consent

This study will be performed in accordance with the Revised Declaration of Helsinki (pages 51-55), and will be compatible with the ICH Harmonised Tripartite Guidelines For Good Clinical Practice (GCP), CPMP/ICH/135/95. A physician will inform the patients about the nature, relevance and consequences of the study. They will receive a printed study information sheet and a study brochure, plus additional diet and lifestyle information. All patients will have to give their written consent to participate in this trial. They will be informed that they are allowed to withdraw from the trial at any time without being obliged to give their reasons for doing so and without any disadvantages to their subsequent medical care. An example of the patient information and consent document is shown in Appendix VI D & E. The major study sponsor, Pfizer Inc abides by the current ABPI guidelines on compensation and/or treatment in the event of trial related injury. A copy of the guidelines can be made available to the subjects upon request.

APPENDIX VI B: Advantages and Disadvantages to patients of participation in the trial

a. Advantages

1. Patients will be followed and treated more systematically than is usual for their disease and complications

2. Patients will achieve more stringent BP control than is usually achieved on average in routine clinical procedure

3. Patients will have more complete investigation and evaluation of their cardiovascular health than is usual on average in routine clinical practice

4. The study medication is provided free of charge

b. Disadvantages

1. Treatment choice and administration schedule is theoretically more rigid than in routine practice but total flexibility is permitted within the trial for efficacy or safety reasons

2. Patients with relatively modest elevation in cholesterol or even "normal" blood cholesterol levels may receive low-dose atorvastatin. Although this group of drugs are extremely well tolerated (as well as placebo) and most data suggest benefits may accrue from their use among such patients, the size of the benefits relative to any possible adverse effects has not yet been fully established.

APPENDIX VI C: Ethics Committee / Institutional Review Board (IRB)

Before the start of the study the study protocol and/or other appropriate documents will be submitted to the local or national Ethics committees in accordance with regional legal requirements.

APPENDIX VI D: PATIENT INFORMATION SHEET

Your blood pressure is higher than normal. This is associated with an increased risk of developing cardiovascular side effects such as heart attacks, heart failure and stroke. The risk is further increased if you also have additional risk factors such as smoking and high cholesterol levels. Treatment of high blood pressure has been shown to reduce the risk of these complications. Treatment measures include improving dietary habits, increasing exercise and stopping smoking. However, many patients also require drug treatment for controlling high blood pressure and cholesterol.

The Aim of the Study

You are invited to participate in a study, in which we want to compare the long term effects of blood pressure reduction by using two combinations of antihypertensive drugs. The study is taking place in the UK, Ireland, Denmark Finland, Iceland, Norway and Sweden, and will comprise 18000 patients in total. If you agree to participate in the trial, and we hope you will, you will receive one of two well known drugs used to treat high blood pressure - either atenolol, a beta-blocker or amlodipine, a calcium channel blocker. The decision whether to treat you with atenolol or amlodopine will be made "at random" which means that there is a fifty-fifty chance that you will receive either drug. If the first drug you receive is not enough to lower your blood pressure to an acceptable level, you will get additional treatment. A thiazide diuretic (bendroflumethiazide with potassium supplementation) will be added to those on atenolol, and an ACE inhibitor (perindopril), will be added to those initially supplied with amlodipine. If these treatments are not enough, you will then receive an alpha blocker, (doxazosin),

All the drugs used in the study are well-documented effective blood pressure lowering drugs, and are usually well tolerated by patients. However, each of these drugs may occasionally cause side effects e.g. atenolol may produce cold hands and feet and tiredness; amlodipine may produce swollen ankles; bendroflumethiazide and potassium may cause gout; perindopril may cause coughing and doxazosin may produce dizziness when standing.

All the study drugs will be provided free of charge throughout the study.

Cholesterol Lowering Therapy

If your level of blood cholesterol is below a certain level, you will be invited to participate in a parallel part of the study. In this part of the study we will compare the effects of atorvastatin, a drug which lowers blood cholesterol, with the effect of a placebo (a harmless, inactive substance). If you take the placebo, you will still receive all the advice and medical check-ups included in the study. In order to judge this part of the study fairly, it will be double-blinded (i.e. neither you nor your doctor will know if you are receiving atorvastatin or the placebo, which, like the blood pressure lowering drugs, are assigned randomly). The drugs in this part of the study will also be supplied free of charge.

Advantages and Disadvantages of Joining the ASCOT Study

Advantages

1. Patients will be followed and treated more systematically than is usual for their disease and complications
2. Patients will achieve more stringent BP control than is usually achieved on average in routine clinical procedure
3. Patients will have more complete investigation and evaluation of their cardiovascular health than is usual on average in routine clinical practice.
4. The study medication is provided free of charge

Disadvantages

1. Treatment choice and administration schedule is theoretically more rigid than in routine practice but total flexibility is permitted within the trial for efficacy or safety reasons
2. Patients with relatively modest elevations in cholesterol or even 'normal' blood cholesterol levels may receive low-dose atorvastatin. Although this group of drugs is extremely well tolerated (as well as placebo) and other data suggest benefits may accrue from their use among such patients, the size of the benefits relative to any possible adverse effects has not yet been fully established

Your contribution to this research will help us to select those treatments which are most effective at reducing the level of chronic illness and death caused by cardiovascular illness and will help to improve treatment for patients in the future.

Study Procedure

About one month before the study starts you will be invited to come for a screening visit when a few investigations, including blood and urine tests and an ECG (electrocardiogram) will be carried out. If you are then suitable for inclusion in the study you will be asked to attend for a second visit when you will be supplied treatment with either atenolol or amlodipine. You will also receive information regarding your diet and lifestyle, which will help you to reduce your risk of cardiovascular disease. During the course of the study you will be asked to visit your study doctor and/or nurse about twice each year. At each visit they will measure blood pressure and carry out a general check-up. At some of the visits blood and urine tests will be taken. If the original drugs are not enough to lower blood pressure to an acceptable level, there are possibilities to either increase the dose or to add another drug as described above. All of this will be discussed with you in detail if you decide to join the study. At any time during the trial you can consult the study doctor or nurse if you have any questions about your part in the study (see below).

The study will continue for approximately five years. If you change your address during the study period it may still be possible to remain in the study.

The results of the study will be analysed and reported according to the requirements of official authorities. Your results can only be identified through a special patient number and your birth date, but not by your name, address or any other means of identification. Only your study nurse and study doctor can identify you from the patient number. If you choose to participate in the study your signed consent form will be kept in an archive. Any information that you give will be held in the strictest confidence and used solely for research purposes. Authorised study personnel may occasionally be required to examine your medical files in order to verify that the study in which you are participating is conducted accurately and properly. The study has been approved by the appropriate Ethics Committee.

All significant new findings developed during the course of the research will be made available to you.

Your participation in the study is entirely voluntary and you can withdraw your consent to participate at any time, without giving a reason. In that situation, your own doctor will give you the best alternative treatment, but your study doctor or nurse will still want to keep contact with you until the study is finished. This would not affect your future medical care or your relationship with any of the study staff involved in providing it.

The telephone numbers of the doctor and nurse responsible for the study are listed below. If you have any questions relating to this research project do not hesitate to contact them.

Doctor_____

Telephone_____

Nurse_____

Telephone_____

APPENDIX VI E: PATIENT CONSENT FORM, AGREEMENT TO PARTICIPATE IN THE ASCOT RESEARCH PROJECT

I, [name of subject] _____

Of [address] _____

_____

Agree to take part in the ASCOT research project

I confirm that I have received verbal and written information about participation in the clinical trial called ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial). I have been given time to consider the information and the opportunity to ask questions about this trial. The nature and demands of the research have been explained to me. I fully understand and accept them.

I understand that my medical records relevant to this trial may be examined by authorised ASCOT staff, who have my permission to do so.

I understand that my consent is entirely voluntary, and that I may withdraw from the research project if I find that I am unable to continue for any reason and this will not affect my medical care.

Signed: _____

[print name] _____

Witness _____

[print name] _____

Date _____

Investigator's Statement:

I have explained the study outline, nature, demands and foreseeable risks of the above research project to the subject. I have given the subject time to consider the information. I have received the patient's informed consent to participate.

I will save a copy of this consent form for archive according to the present rules.

To be filled in by responsible doctor/nurse

Signature _____

Date _____

PATIENT CONSENT FORM CHECKLIST

The participant should complete the whole of this checklist him/herself

(please delete as necessary)

- Have you read the patient information sheet? YES/NO
- Have you had an opportunity to ask questions and discuss this study? YES/NO
- Have you received satisfactory answers to all of your questions? YES/NO
- Have you received enough information about the study? YES/NO
- Who have you spoken to?
- Dr/Mrs/Ms/Mr_____
- Do you understand that your decision to consent is entirely voluntary and that you are free to withdraw from the study at any time, without having to give a reason and without affecting your future medical care? YES/NO
- Do you agree to take part in this study? YES/NO

Signed_____Date:_____

Name in block letters_____