

STATISTICAL ANALYSIS PLAN

Protocol Number: AML-NY-96-008

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)

AMENDMENT 1

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**Statistical Analysis Plan
Protocol Number: AML-NY-96-008 (ASCOT)**

Table of Contents

1.0	STUDY OBJECTIVES / HYPOTHESES TESTING	1
1.1	PRIMARY OBJECTIVES	1
1.2	SECONDARY OBJECTIVES	1
1.3	TERTIARY OBJECTIVES.....	1
2.0	BACKGROUND / INTRODUCTION	2
2.1	INTRODUCTION.....	2
2.2	STUDY DESIGN	4
2.3	TREATMENT GROUPS	4
2.4	STUDY POPULATION.....	4
2.5	STUDY DRUG AND DOSING.....	5
2.6	SAMPLE SIZE	6
2.7	SCHEDULE OF TIME AND EVENTS	9
2.8	RANDOMIZATION.....	12
3.0	POPULATIONS OF ANALYSIS SETS.....	12
3.1	INTENT-TO-TREAT POPULATION.....	12
4.0	VARIABLES OF ANALYSIS.....	12
4.1	PRIMARY EFFICACY VARIABLE	12
4.2	SECONDARY EFFICACY VARIABLES.....	12
4.3	TERTIARY EFFICACY VARIABLES	13
4.4	SAFETY VARIABLES.....	14
4.5	DEMOGRAPHIC VARIABLES	14
5.0	STATISTICAL METHODOLOGY.....	14
5.1	BASELINE DEMOGRAPHICS	14
5.2	PRIMARY EFFICACY ANALYSIS.....	15
5.3	SECONDARY EFFICACY ANALYSIS.....	16
5.4	TERTIARY EFFICACY ANALYSIS.....	18
5.5	GENERAL METHODOLOGY.....	19
5.6	SAFETY ANALYSIS.....	19
6.0	TABLES, DATA LISTINGS & FIGURES	20
6.1	LISTING OF TABLES	20
6.2	DATA LISTINGS.....	21
6.3	FIGURES	22
	REFERENCES:	24

1.0 Study Objectives / Hypotheses Testing

1.1 Primary Objectives

Antihypertensive Regimen:

- 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).

Lipid-Lowering Therapy:

- To compare the effect on non-fatal MI (symptomatic and silent MI) and fatal CHD of combination therapy (10mg atorvastatin + antihypertensive therapy) vs antihypertensive therapy alone among patients with a total cholesterol ≤ 6.5 mmol/l.

1.2 Secondary Objectives

Antihypertensive Regimen:

- To compare the effects of the two antihypertensive regimens on:
 1. non-fatal MI (symptomatic only) and fatal CHD;
 2. all-cause mortality;
 3. total cardiovascular mortality;
 4. total (fatal and non-fatal) stroke;
 5. the development of non-fatal and fatal heart failure;
 6. non-fatal MI, fatal CHD, non-fatal and fatal heart failure and the development of angina (total coronary endpoints); and
 7. all cardiovascular events and procedures.

Lipid-Lowering Therapy:

- To compare the effects of 10mg atorvastatin with placebo on:
 1. non-fatal MI (symptomatic only) and fatal CHD;
 2. all-cause mortality;
 3. total cardiovascular mortality;
 4. fatal and non-fatal stroke;
 5. the development of non-fatal and fatal heart failure;
 6. total coronary endpoints; and
 7. all cardiovascular events and procedures.

1.3 Tertiary Objectives

Antihypertensive Regimen:

- To compare the effects of the antihypertensive regimens on the development of each of the following:
 - Silent MI;
 - Unstable angina;
 - Chronic stable angina;
 - Peripheral arterial disease; and
 - Life-threatening arrhythmias.

- To compare the effects of the two antihypertensive regimens on the development of diabetes mellitus or renal impairment.
- To compare changes in blood pressure, lipids, blood sugar & creatinine.
- To compare the effects of the different antihypertensive regimens on health care costs.
- To compare the effect of the different antihypertensive regimes on all major study endpoints (i.e., primary & secondary efficacy variables) among specific sub-groups of patients:
 - diabetics, smokers, the obese [$>30\text{Kg/m}^2$], those with LVH, older/younger [$\leq 60/>60$ years], male/female, any previous vascular disease [by history or ECG], renal dysfunction [by serum creatinine, urinalysis], with and without metabolic syndrome*.

Lipid-Lowering Therapy:

- To compare the effects of the lipid-lowering regimens on the development of each of the following:
 - Silent MI;
 - Unstable angina;
 - Chronic stable angina;
 - Peripheral arterial disease; and
 - Life-threatening arrhythmias.
- To compare the effects of the two lipid-lowering regimens on the development of diabetes mellitus or renal impairment.
- 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.
- To compare changes in blood pressure, lipids, blood sugar & creatinine.
- To compare the effects of the different lipid-lowering regimens on health care costs.
- To compare the effects of 10mg atorvastatin with placebo on all major study endpoints (i.e., primary & secondary efficacy variables) among specific subgroups of patients:
 - diabetics, smokers, the obese [$>30\text{Kg/m}^2$], those with LVH, older/younger [$\leq 60/>60$ years], male/female, any previous vascular disease [by history or ECG], renal dysfunction [by serum creatinine, 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 $\geq 130/85$ mmHg, fasting glucose ≥ 6.1 mmol/l.

2.0 Background / Introduction

2.1 Introduction

The associations between blood pressure and the incidence of CHD and of stroke have been investigated in several major prospective observational studies. These studies indicate a strong relationship between blood pressure and the risk of CHD and stroke with those patients having elevated blood pressure levels to be at increased risk of CHD and stroke. Calcium channel blockers (CCB's), and converting enzyme inhibitors (ACE-I) avoid some of the potentially adverse effects of diuretics, and may have some other cardioprotective effects. 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 CHD events in directly randomized comparisons.

Cholesterol is a major independent risk factor for CHD. Across a wide range of increasing serum cholesterol levels, observational data show a clear, marked dose-response relationship with increased CHD mortality.

Rationale for the ASCOT Study:

- Insufficient data exist comparing new with conventional hypertension therapy, particularly relating to effects on morbidity and mortality.
- At least 50% of high-risk hypertensives require two or more drugs to provide adequate blood pressure control in the long term. 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.
- 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.
- 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.
- ASCOT complements the ALLHAT study, 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).
- 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.
- 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 ≤ 6.5 mmol/l.
- Eligible hypertensive subjects whose total cholesterol is ≤ 6.5 mmol/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.
- 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 to merit lipid lowering therapy if their total cholesterol is >6.5 mmol/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.

2.2 Study Design

This is a phase IV multicenter, randomized 2x2 factorial study design with the two antihypertensive regimens being compared 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 1,150 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 18,000 patients.

2.3 Treatment Groups

A planned total of 18,000 patients will be randomly assigned antihypertensive and cholesterol lowering regimens as follows:

- All 18,000 patients will be randomized to receive either amlodipine or a β -blocker as a "first-line" antihypertensive.

"First-line" Antihypertensive		TOTAL
Amlodipine	β -blocker	
9,000	9,000	18,000

- Out of these 18,000 patients, it is expected that 9,000 will have total cholesterol ≤ 6.5 mmol/l and be eligible for the 2x2 factorial part of the study. In addition to being randomized to either amlodipine or a β -blocker as a "first-line" antihypertensive, these patients will further be randomized to either atorvastatin or placebo.

		Cholesterol Lowering		TOTAL
		Atorvastatin	Placebo	
"First-Line" Antihypertensive	Amlodipine	2,250	2,250	4,500
	β -blocker	2,250	2,250	4,500
TOTAL		4,500	4,500	9,000

2.4 Study Population

The study population is planned to consist of 18,000 male and female outpatients between 40 and 80 years of age with untreated hypertension defined as SBP > 160 mmHg and/or DBP > 100 mmHg or treated hypertension with a SBP > 140 mmHg and/or a DBP > 90 mmHg on more than 1 drug. Further, the population is considered to be at increased risk for a future cardiovascular event. Namely, each patient had to have at least 3 of the following risk factors for a future cardiovascular event:

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

- Peripheral vascular disease according to a standard validated questionnaire; or has had a recent history of surgical intervention for peripheral vascular disease.
- Past history of cerebrovascular event(s) including TIA's \geq three months previously;
- Male sex;
- Age \geq 55 years;
- Microalbuminuria/Proteinuria;
- Smoking (i.e., regular smoker within the last year of \geq 20 cigarettes or cigars/week);
- Plasma total/HDL cholesterol ratio \geq 6; and
- A history of a coronary artery disease event occurring in a first degree relative before the age of 55 (males) or 60 years (women).

For the estimated 9,000 patients eligible for the lipid-lowering arm of the trial, the patients must meet all of the above criteria and they must have a total cholesterol \leq 6.5 mmol/l and not be currently taking a statin or a fibrate.

All subjects will be required to give written informed consent.

2.5 Study Drug and Dosing

Antihypertensive Regimen:

All eligible subjects will be randomised to Step 1 of either regimen A (amlodipine based) or B (β -blocker based). Thereafter, progression of subsequent steps will be dependent upon not reaching target pressures ($<$ 140 mmHg SBP and $<$ 90 mmHg DBP for non-diabetics or $<$ 130 mmHg SBP and $<$ 80 mmHg DBP for diabetics).

	Regimen A	Regimen 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:

- 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) and is ideally 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 160 mmHg systolic and below 100 mmHg diastolic, no further treatment modification need be considered.

Additional Drug Dosing Considerations:

- If after the use of 4 different agents, blood pressures remain unacceptably high (e.g., ≥ 160 mmHg systolic or ≥ 100 mmHg 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 ≥ 160 mmHg or a diastolic ≥ 100 mmHg 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.

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. 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 ≤ 6.5 mmol/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.

2.6 Sample Size

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, 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. 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 18,000 is needed to get a power of 80% for the primary endpoint (nonfatal MI and fatal CHD) giving a total number of 1,150 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.

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)	18,000
Power (%)	80
# losses and the dilution effect from cross-over and statin effect	

Assumptions for Lipid Lowering Treatments

These calculations are based on the experience from clinical trials and epidemiological data. It is assumed that 9,000 patients (50%) will be randomised to either 10 mg atorvastatin or placebo.

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 9,000

Power (%) 90

2.7 Schedule of Time and Events

Study Visits: The study flow chart below presents the procedures at each of the study visits:

MONTHS	-1	0	1.5	3	6	12	18	24	30	36	42	48	54	60 ¹	66
Medical History And Eligibility	X	X ²													
Previous Antihypertensive Medication And Side Effects	X														
Current Illness/adverse events ³	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 ⁴ , 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 ⁵	X	X ⁶		X ⁷	X ⁷		X ⁷		X ⁷		X ⁷		X ⁷	X
Urine Tests	X				X	X		X		X		X			X
Physical Examination		X													
Extra Visits Optional For Drug Up-Titration When Necessary															

¹ If this is the final visit see requirements for final

² Eligibility only

³ Current illness only is recorded at visit -1

⁴ Only at screening

⁵ If triglycerides 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.

⁶ Bloods for electrolytes, creatinine for those randomized to receive ACE inhibitor. This sample should be taken within a few weeks of initiating an ACE inhibitor whenever this occurs during the trial.

⁷ Bloods to include LFT for those randomized to receive statin/placebo.

VISIT DETAILS:

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, Heart Rate (HR).
- 12 lead ECG - if required to confirm eligibility, faxed to Scandinavian coordinating centre for evaluation.
- 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.

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 triglycerides level was $>4.5\text{mmol/l}$ or glucose was $>7.0\text{mmol/l}$ at screening will be recalled during this period for a fasting blood sample to evaluate eligibility.

Randomisation visit (0 months)

- Physical examination.
- BP and HR.
- Fasting blood sample: total cholesterol, HDL, triglycerides, and glucose.
- 12 lead ECG.
- Eligibility and consent confirmed.
- Randomisation allocated using minimisation procedures by the appropriate coordinating centre by telephone.
- All previous antihypertensive medication withdrawn. Continue and record all other existing medication.
- Study medication allocated
- Appointment made for next visit.
- Adverse events (including hospitalisation, diagnosis, duration) recorded.

First follow-up visit (6 \pm 2 weeks)

- Endpoints recorded.
- Adverse events (including hospitalisation, 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
- Changes in medication recorded.
- Study medication allocated.
- Appointment made for next visit.

Second follow-up visit (3 \pm 1 months)

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

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
- Changes in medication recorded.
- Study medication allocated.
- Appointment made for next visit.

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
- Changes in medication recorded.
- Study medication allocated.
- Appointment made for next visit.

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
- Study medication allocated.
- Appointment made for next visit.

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.

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.

2.8 Randomization

Patients eligible for the lipid lowering arm of the study (i.e., total cholesterol \leq 6.5 mmol/l) will be randomized using minimization procedures in a 2x2 “factorial” design to:

- Antihypertensive “first-line” agent: amlodipine vs atenolol
- Cholesterol lowering agent: atorvastatin vs placebo.

Patients that are only eligible for the antihypertensive arm of the study will be randomized to amlodipine or atenolol as the “first-line” antihypertensive agent.

3.0 Populations of Analysis Sets

3.1 Intent-to-Treat Population

All patients who were randomized comprise the intent-to-treat (ITT) population. Patients will be analyzed according to their randomly allocated treatment group, regardless of their compliance with the study medication regimen.

All efficacy analyses will be performed on the ITT population defined in Section 3.1. All safety analyses will be performed on the ITT population defined in Section 3.1.

4.0 Variables of Analysis

4.1 Primary Efficacy Variable

Antihypertensive Regimen:

The primary efficacy variable is the occurrence of the following primary endpoint:

- Non-fatal MI (symptomatic and silent MI) + fatal CHD.

Lipid-Lowering Therapy:

The primary efficacy variable is the occurrence of the following primary endpoint:

- Non-fatal MI (symptomatic and silent MI) + fatal CHD.

4.2 Secondary Efficacy Variables

Antihypertensive Regimen:

The secondary efficacy variables consist of the occurrence of the following secondary endpoints:

- 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 + revascularization procedures, and retinal vascular thromboses;
- Total coronary endpoints = fatal CHD + non-fatal MI (symptomatic and silent) + chronic stable angina + unstable angina + fatal and non-fatal heart failure;
- Non-fatal MI (symptomatic only) + fatal CHD;
- All cause mortality;
- Cardiovascular mortality;

- Fatal and non-fatal stroke;
- Fatal and non-fatal heart failure.

Lipid-Lowering Therapy:

The secondary efficacy variables consist of the occurrence of the following secondary endpoints:

- 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 + revascularization procedures, and retinal vascular thromboses;
- Total coronary endpoints = fatal CHD + non-fatal MI (symptomatic and silent) + chronic stable angina + unstable angina + fatal and non-fatal heart failure;
- Non-fatal MI (symptomatic only) + fatal CHD;
- All cause mortality;
- Cardiovascular mortality;
- Fatal and non-fatal stroke;
- Fatal and non-fatal heart failure.

4.3 Tertiary Efficacy Variables**Antihypertensive Regimen:**

The tertiary efficacy variables consist of the occurrence of the following tertiary endpoints:

- Silent MI;
- Unstable angina;
- Chronic stable angina;
- Peripheral arterial disease;
- Life threatening arrhythmias (VF or sustained VT or complete heart block);
- Development of diabetes mellitus;
- Development of renal impairment.

Other tertiary efficacy variables include health care costs and changes in blood pressure, lipids, blood sugar & creatinine. Subgroup variables include the following: diabetic status, smoking status, obesity, those with LVH, age, gender, any previous vascular disease, renal dysfunction, and those with and without metabolic syndrome.

Lipid-Lowering Therapy:

The tertiary efficacy variables consist of the occurrence of the following tertiary endpoints:

- Silent MI;
- Unstable angina;
- Chronic stable angina;
- Peripheral arterial disease;
- Life threatening arrhythmias (VF or sustained VT or complete heart block);
- Development of diabetes mellitus;
- Development of renal impairment.

Other tertiary efficacy variables include health care costs and changes in blood pressure, lipids, blood sugar & creatinine. Subgroup variables include the following: diabetic status, smoking status, obesity, those with LVH, age, gender, any previous vascular disease, renal dysfunction, and those with and without metabolic syndrome.

4.4 Safety Variables

Antihypertensive Regimen:

- Treatment emergent adverse events;
- Study completion / discontinuation status;
- Laboratory measurements;
- Vital signs and body weight measurements;
- Use of concomitant medication.

Lipid-Lowering Therapy:

- Treatment emergent adverse events;
- Study completion / discontinuation status;
- Laboratory measurements;
- Vital signs and body weight measurements;
- Use of concomitant medication.

4.5 Demographic Variables

Antihypertensive Regimen:

Demographic variables measured at baseline include age, gender, height, weight, race and education level.

Lipid-Lowering Therapy:

Demographic variables measured at baseline include age, gender, height, weight, race and education level.

5.0 Statistical Methodology

The population used for the efficacy analysis will be the ITT patients defined in Section 3.1. All planned exploratory analyses will be performed according to a separate Statistical Analysis Plan (SAP). The analyses pertaining to health care costs will be discussed in a separate protocol and SAP. There are a large number of substudies that are planned for the ASCOT Trial and each will have their own protocol and analysis plan.

The ASCOT Steering Committee endorsed the Data and Safety Monitoring Committee (DSMC) recommendation that the lipid-lowering portion of the ASCOT trial be discontinued while the blood pressure lowering portion of the study continue as originally planned. Thus, the analyses of the lipid-lowering portion of the trial will be done before the analyses of the antihypertensive portion of the trial are known. Furthermore, analyses for the lipid-lowering portion of the trial will not be able to be performed using the 2x2 factorial structure until the hypertensive portion of the trial has ended.

The DSMC decided, a priori, to use a Haybittle-Peto statistical boundary as a guideline for deciding whether or not to recommend early termination. According to this rule, a large critical value $Z_1 = \pm 3$ is used for all interim analyses of main endpoints. The adjustment of the p -value for the final test depending on repeated testing is negligible.

5.1 Baseline Demographics

Antihypertensive Regimen:

Descriptive statistics of the demographic and baseline characteristics will be presented for each antihypertensive regimen (amlodipine vs. β -blocker). Although no formal statistical tests will be carried out on any demographic or baseline characteristic, the adequacy of the randomization will be addressed via informal statistical looks.

Lipid-Lowering Therapy:

Descriptive statistics of the demographic and baseline characteristics will be presented for each arm in the lipid-lowering part of the study (combination therapy vs. antihypertensive therapy alone). Although no formal statistical tests will be carried out on any demographic or baseline characteristic, the adequacy of the randomization will be addressed via informal statistical looks.

After completion of the antihypertensive portion of the trial, descriptive statistics of the demographic and baseline characteristics will be presented for all four treatment groups (i.e., amlodipine + atorvastatin, amlodipine + placebo, β -blocker + atorvastatin and β -blocker + placebo).

5.2 Primary Efficacy Analysis

Antihypertensive Regimen:

The null hypothesis is that the probability of experiencing the primary endpoint [Non-fatal MI (symptomatic and silent MI) + fatal CHD] is equal for both antihypertensive regimens. The time to 1st event (non-fatal MI or fatal CHD) will be compared for both antihypertensive regimens using a log rank test. Furthermore, this analysis will be performed without adjusting for baseline factors and will be undertaken using the intent-to-treat population. A Kaplan-Meier plot depicting both antihypertensive regimens will also be produced.

Patients that do not experience the event of interest will be considered censored with the censoring time being the study termination time. The Endpoint Committee will have adjudicated all endpoints used in this analysis. The significance level for testing the primary hypothesis will be 0.05, including adjustment for interim analyses. Note that the ECGs are done at baseline, year 2 and the final visit and the date of the ECG will be used as the date of the silent MI, if it is present.

A complimentary analysis will be undertaken using a Cox proportional hazards regression model. If there appears to be imbalance between the treatment groups with regard to relevant baseline demographics (prognostic factors), then the proportional hazards model will adjust for these imbalances as well as other important prognostic variables. This analysis will be performed on the intent-to-treat population. In the case that blood pressure differences exist between the treatment groups, an updated Cox model (i.e., time-dependent) will be utilized.

Lipid-Lowering Therapy:

The null hypothesis is that the probability of experiencing the primary endpoint [Non-fatal MI (symptomatic and silent MI) + fatal CHD] in the lipid-lowering arm compared to the non-lipid-lowering arm. The time to 1st event (non-fatal MI or fatal CHD) will be compared for combination therapy (antihypertensive therapy + lipid-lowering therapy) and antihypertensive therapy alone using a log rank test. Furthermore, this analysis will be performed without adjusting for baseline factors and will be undertaken using the intent-to-treat population. A Kaplan-Meier plot depicting both lipid-lowering arms will also be produced.

Patients that do not experience the event of interest will be considered censored with the censoring time being the study termination time. The Endpoint Committee will have adjudicated all endpoints used in this analysis. The significance level for testing the above analyses will be 0.05, including adjustment for interim analyses. The date used to indicate a silent MI, if present, will be the date that the ECG was performed.

A complimentary analysis will be undertaken using a Cox proportional hazards regression model. If there appears to be imbalance between the treatment groups with regard to relevant baseline demographics (prognostic factors), then the proportional hazards model will adjust for these imbalances as well as other important prognostic variables. This analysis will be performed on the intent-to-treat population.

After completion of the antihypertensive portion of the trial, the time to 1st event (non-fatal MI or fatal CHD) will be compared using a Cox proportional hazards model that takes into account the full 2x2 factorial structure of this group of patients. Furthermore, this analysis will be performed without adjusting for baseline factors and will be undertaken using the intent-to-treat population. Ninety-five percent confidence intervals for combination therapy will also be provided combined over antihypertensive strata and for each antihypertensive stratum. The Cox model will include effects for antihypertensive therapy, lipid-lowering therapy and the interaction term between antihypertensive therapy and lipid-lowering therapy. This interaction will be used to investigate the consistency of the atorvastatin effect across antihypertensive strata. The trial was not powered for testing this interaction, so that, a clinically relevant difference between the combination regimens may not be statistically detected. Thus, the following approach is being adopted. If the primary endpoint [Non-fatal MI (symptomatic and silent MI) + fatal CHD] is significant for the overall atorvastatin effect, the above analytical procedure will be repeated for the composite endpoint [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 + revascularization procedures, and retinal vascular thromboses]. Namely, conditioned on finding a significant difference in the primary endpoint, a Cox proportional hazards regression model taking into account the full 2x2 factorial design will be undertaken looking at the composite endpoint. Thus, 95% confidence intervals will be presented and the interaction between antihypertensive therapy and atorvastatin will be explored.

After completion of the antihypertensive portion of the trial, a complimentary analysis will be undertaken using another Cox proportional hazards regression model. If there appears to be imbalance between the treatment groups with regard to relevant baseline demographics (prognostic factors), then the proportional hazards model will adjust for these imbalances as well as other important prognostic variables while still accounting for the 2x2 factorial structure. This analysis will be performed on the intent-to-treat population. In the case that blood pressure differences exist between the treatment groups, an updated Cox model (i.e., time-dependent) will be utilized.

5.3 Secondary Efficacy Analysis

Antihypertensive Regimen:

All secondary cardiovascular end-point efficacy variables will be analyzed in the same manner. The time to the 1st event of each secondary efficacy variable will be compared for both antihypertensive regimens using a log rank test. A Kaplan-Meier plot depicting both antihypertensive regimens will also be produced. In addition, a Cox proportional hazards regression model adjusting for relevant baseline characteristics will be performed.

The following secondary efficacy variables will be compared between the two antihypertensive regimens using the previously stated methodology:

- 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 + revascularization procedures, and retinal vascular thromboses;
- Total coronary endpoints = fatal CHD + non-fatal MI (symptomatic and silent) + chronic stable angina + unstable angina + fatal and non-fatal heart failure;
- Non-fatal MI (symptomatic only) + fatal CHD;
- All cause mortality;
- Cardiovascular mortality;
- Fatal and non-fatal stroke;
- Fatal and non-fatal heart failure.

The significance level for testing the secondary efficacy parameters will be 0.01. The choice of 0.01 is due to the fact that a large number of secondary and tertiary hypotheses are planned. Thus, this acts as a crude way of guarding against the multiple testing problem. All secondary analyses will be performed on the intent-to-treat population.

Lipid-Lowering Therapy:

All secondary cardiovascular end-point efficacy variables will be analyzed in the same manner. The time to the 1st event of each secondary efficacy variable will be compared for both lipid-lowering arms using a log rank test. A Kaplan-Meier plot depicting both atorvastatin and placebo will also be produced. In addition, a Cox proportional hazards regression model adjusting for relevant baseline characteristics will be performed.

The following secondary efficacy variables will be compared between the two lipid-lowering therapies using the previously stated methodology:

- 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 + revascularization procedures, and retinal vascular thromboses;
- Total coronary endpoints = fatal CHD + non-fatal MI (symptomatic and silent) + chronic stable angina + unstable angina + fatal and non-fatal heart failure;
- Non-fatal MI (symptomatic only) + fatal CHD;
- All cause mortality;
- Cardiovascular mortality;
- Fatal and non-fatal stroke;
- Fatal and non-fatal heart failure.

The significance level for testing the secondary efficacy parameters will be 0.01. The choice of 0.01 is due to the fact that a large number of secondary and tertiary hypotheses are planned. Thus, this acts as a crude way of guarding against the multiple testing problem. All secondary analyses will be performed on the intent-to-treat population.

After completion of the antihypertensive portion of the trial, an analysis will be undertaken where the time to 1st event of each secondary efficacy variable will be compared for both lipid-lowering arms using a Cox proportional hazards regression model that takes into account the full 2x2 factorial structure of this group of patients. Furthermore, this analysis will be performed without adjusting for baseline factors and will be undertaken using the intent-to-treat population.

5.4 Tertiary Efficacy Analysis

Antihypertensive Regimen:

All tertiary efficacy variables will be analyzed in the same manner. The time to the 1st event of each tertiary efficacy variable will be compared for both antihypertensive regimens using a log rank test. A Kaplan-Meier plot depicting both antihypertensive regimens will also be produced. In addition, a Cox proportional hazards regression model adjusting for relevant baseline characteristics will be performed.

The following tertiary efficacy variables will be compared between the two antihypertensive regimens using the previously stated methodology:

- Silent MI;
- Unstable angina;
- Chronic stable angina;
- Peripheral arterial disease;
- Life threatening arrhythmias (VF or sustained VT or complete heart block);
- Development of diabetes mellitus;
- Development of renal impairment.

A mixed model approach will also be utilized to compare the treatment effect on change in blood pressure, lipids, blood sugar and creatinine. The mixed model will make use of the repeated measurements within each subject over the length of the study. The mixed model will include factors for treatment, time and the time by treatment interaction. Furthermore, any other variables found to be unbalanced at baseline or important in predicting the change in blood pressure, lipids, blood sugar and creatinine will be included in the mixed model. The mixed model will assume a compound symmetric covariance structure. In the event that this covariance structure seems unrealistic, other covariance structures will be investigated.

The significance level for testing the tertiary efficacy parameters will be 0.01. The choice of 0.01 is due to the fact that a large number of secondary and tertiary hypotheses are planned. Thus, this acts as a crude way of guarding against the multiple testing problem. All tertiary analyses will be performed on the intent-to-treat population.

Subgroup Analyses:

For each subgroup defined in Section 1.3, all major study endpoints will be compared between the different antihypertensive regimens. The time to the 1st event of each major study endpoint (i.e., primary & secondary efficacy variables) will be compared for both antihypertensive regimens using a log rank test. A Kaplan-Meier plot depicting both antihypertensive regimens will also be produced for the primary endpoint. If the number of endpoints in a subgroup is small, the result should be interpreted with care. Furthermore, the result should only be discussed if consistent findings are present.

Lipid-Lowering Therapy:

All tertiary efficacy variables will be analyzed in the same manner. The time to the 1st event of each tertiary efficacy variable will be compared for both lipid-lowering arms using a log rank test. A Kaplan-Meier plot depicting both atorvastatin and placebo will also be produced. In addition, a Cox proportional hazards regression model adjusting for relevant baseline characteristics will be performed.

The following tertiary efficacy variables will be compared between the two lipid-lowering therapies using the previously stated methodology:

- Silent MI;
- Unstable angina;
- Chronic stable angina;
- Peripheral arterial disease;
- Life threatening arrhythmias (VF or sustained VT or complete heart block);
- Development of diabetes mellitus;
- Development of renal impairment.

A mixed model approach will also be utilized to compare the treatment effect on change in blood pressure, lipids, blood sugar and creatinine. The mixed model will make use of the repeated measurements within each subject over the length of the study. The mixed model will include factors for treatment, time and the time by treatment interaction. Furthermore, any other variables found to be unbalanced at baseline or important in predicting the change in blood pressure, lipids, blood sugar and creatinine will be included in the mixed model. The mixed model will assume a compound symmetric covariance structure. In the event that this covariance structure seems unrealistic, other covariance structures will be investigated.

The significance level for testing the tertiary efficacy parameters will be 0.01. The choice of 0.01 is due to the fact that a large number of secondary and tertiary hypotheses are planned. Thus, this acts as a crude way of guarding against the multiple testing problem. All tertiary analyses will be performed on the intent-to-treat population.

After completion of the antihypertensive portion of the trial, a complimentary analysis will be undertaken where the time to 1st event of each tertiary efficacy variable will be compared for both lipid-lowering arms using a Cox proportional hazards regression model that takes into account the 2x2 factorial structure of this group of patients. Furthermore, this analysis will be performed without adjusting for baseline factors and will be undertaken using the intent-to-treat population.

Subgroup Analyses:

For each subgroup defined in Section 1.3, all major study endpoints will be compared between the different lipid-lowering arms. The time to the 1st event of each major study endpoint (i.e., primary & secondary efficacy variables) will be compared for both lipid-lowering arms using a log rank test. A Kaplan-Meier plot depicting both lipid-lowering arms will also be produced for the primary endpoint. If the number of endpoints in a subgroup is small, the result should be interpreted with care. Furthermore, the result should only be discussed if consistent findings are present.

5.5 General Methodology

All hypothesis tests will be two-sided. Results will be considered statistically significant if a p -value of less than 0.05 is obtained for primary hypotheses and less than 0.01 for secondary and tertiary hypotheses. When statistically significant results are found when comparing composite endpoints, the results will be broken down by each component of the composite endpoint in order to ascertain which component(s) are contributing to the statistical significance.

SAS version 8.2 will be used for all calculations and statistical summaries.

5.6 Safety Analysis

Safety data will be summarized using the worldwide safety standards (WSS), if appropriate. The serious adverse events, as defined in the protocol, will be discussed in

detail. WSS standard safety tables will be produced for adverse events leading to discontinuation of study medication and laboratory tests pertaining to liver function.

Non-serious adverse events will not be reported. Furthermore, concomitant medications will only be reported when the concomitant medication is an antihypertensive, lipid-lowering medication or aspirin.

6.0 Tables, Data Listings & Figures

6.1 Listing of Tables

Table	Title	WSS Reference
Antihypertensive Regimen:		
1.1	Subject Evaluation Groups (Summary)	Table 1.1
2.1	Demographic Characteristics	Table 2.1
2.2	Drug Treatments Prior to Start of Study	Table 2.4
3.1	Duration of Treatment (Summary)	Table 3.1
3.2	Concomitant Drug Treatments – Summary	Table 3.2
4.1	Discontinuations from Study	Table 4.1
4.2	Discontinuations Due to Adverse Events	Table 4.2.1
5.1	Cardiovascular Events	
5.2	Change In Mean Office Blood Pressure and Heart Rate Over Time	
5.3	Change In Lipids, Blood Sugar and Creatinine Over Time	
5.4	Cardiovascular Events for Subgroups	
6.1	Serious Adverse Events by Body System	
7.1	LAB Incidence Table (Without Regard to baseline Abnormality)	Table 7.3
7.2	LAB Median Change Table	Table 7.4
Lipid-Lowering Therapy:		
1.1	Subject Evaluation Groups (Summary)	Table 1.1
2.1	Demographic Characteristics	Table 2.1
2.2	Drug Treatments Prior to Start of Study	Table 2.4
3.1	Duration of Treatment (Summary)	Table 3.1
3.2	Concomitant Drug Treatments – Summary	Table 3.2
4.1	Discontinuations from Study	Table 4.1
4.2	Discontinuations Due to Adverse Events	Table 4.2.1
5.1	Cardiovascular Events	
5.2	Change In Mean Office Blood Pressure and Heart Rate Over Time	
5.3	Change In Lipids, Blood Sugar and Creatinine Over Time	
5.4	Cardiovascular Events for Subgroups	
6.1	Serious Adverse Events by Body System	
7.1	LAB Incidence Table (Without Regard to baseline Abnormality)	Table 7.3
7.2	LAB Median Change Table	Table 7.4
Combination Therapy:		
1.1	Subject Evaluation Groups (Summary)	Table 1.1
2.1	Demographic Characteristics	Table 2.1
2.2	Drug Treatments Prior to Start of Study	Table 2.4
3.1	Duration of Treatment (Summary)	Table 3.1
3.2	Concomitant Drug Treatments – Summary	Table 3.2

Table	Title	WSS Reference
4.1	Discontinuations from Study	Table 4.1
4.2	Discontinuations Due to Adverse Events	Table 4.2.1
5.1	Cardiovascular Events	
5.2	Change In Mean Office Blood Pressure and Heart Rate Over Time	
5.3	Change In Lipids, Blood Sugar and Creatinine Over Time	
5.4	Cardiovascular Events for Subgroups	
6.1	Serious Adverse Events by Body System	
7.1	LAB Incidence Table (Without Regard to baseline Abnormality)	Table 7.3
7.2	LAB Median Change Table	Table 7.4

6.2 Data Listings

All data listings will be produced in electronic form only.

Listing	Title	WSS Reference
Antihypertensive Regimen:		
1.1	Subject Evaluation Groups (Listing)	Section 13, Table 5
2.1	Demographic Characteristics (Listing)	Section 13, Table 6
2.2	Drug Treatments Prior to Start of Study Treatment	Section 13, Table 9
3.1	Administration Schedule	Section 13, Table 15
3.2	Concomitant Drug Treatments – Listing	Section 13, Table 11
4.1	Reasons for Discontinuations – Listing	Section 13, Table 13
5.1	Cardiovascular Events	
5.2	Vital Signs – Listing	Section 13, Table 18
6.1	Listing of Serious Adverse Events (All Reported)	
7.1	LAB Data Listing	Section 13, Table 17
Lipid-Lowering Therapy:		
1.1	Subject Evaluation Groups (Listing)	Section 13, Table 5
2.1	Demographic Characteristics (Listing)	Section 13, Table 6
2.2	Drug Treatments Prior to Start of Study Treatment	Section 13, Table 9
3.1	Administration Schedule	Section 13, Table 15
3.2	Concomitant Drug Treatments – Listing	Section 13, Table 11
4.1	Reasons for Discontinuations – Listing	Section 13, Table 13
5.1	Cardiovascular Events	
5.2	Vital Signs – Listing	Section 13, Table 18
6.1	Listing of Serious Adverse Events (All Reported)	
7.1	LAB Data Listing	Section 13, Table 17
Combination Therapy:		
1.1	Subject Evaluation Groups (Listing)	Section 13, Table 5
2.1	Demographic Characteristics (Listing)	Section 13, Table 6
2.2	Drug Treatments Prior to Start of Study Treatment	Section 13, Table 9
3.1	Administration Schedule	Section 13, Table 15
3.2	Concomitant Drug Treatments – Listing	Section 13, Table 11
4.1	Reasons for Discontinuations – Listing	Section 13, Table 13
5.1	Cardiovascular Events	

Listing	Title	WSS Reference
5.2	Vital Signs – Listing	Section 13, Table 18
6.1	Listing of Serious Adverse Events (All Reported)	
7.1	LAB Data Listing	Section 13, Table 17

6.3 Figures

Figure	Title
Antihypertensive Regimen:	
5.1.1	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD
5.1.2	Kaplan-Meier Plot Of Non-Fatal MI (Symptomatic Only)+ Fatal CHD
5.1.3	Kaplan-Meier Plot Of All-Cause Mortality
5.1.4	Kaplan-Meier Plot Of Fatal And Non-Fatal Stroke
5.1.5	Kaplan-Meier Plot Of Fatal And Non-Fatal Heart Failure
5.1.6	Kaplan-Meier Plot Of Total Coronary Endpoints
5.1.7	Kaplan-Meier Plot Of Total Cardiovascular Events And Procedures
5.1.8	Kaplan-Meier Plot Of Silent MI
5.1.9	Kaplan-Meier Plot Of Unstable Angina
5.1.10	Kaplan-Meier Plot Of Chronic Stable Angina
5.1.11	Kaplan-Meier Plot Of Peripheral Arterial Disease
5.1.12	Kaplan-Meier Plot Of Life Threatening Arrhythmias
5.1.13	Kaplan-Meier Plot Of Development Of Diabetes Mellitus
5.1.14	Kaplan-Meier Plot Of Development Of Renal Impairment
5.2.1	Change in Systolic Blood Pressure Over Time
5.2.2	Change in Diastolic Blood Pressure Over Time
5.3.1	Change in LDL-C Over Time
5.3.2	Change in Total Cholesterol Lipids Over Time
5.3.3	Change in Triglycerides Over Time
5.3.4	Change in HDL Over Time
5.3.5	Change in Blood Sugar Over Time
5.3.6	Change in Creatinine Over Time
5.4.1	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Diabetes Status)
5.4.2	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Smoking Status)
5.4.3	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Obesity)
5.4.4	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By LVH Status)
5.4.5	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Age)
5.4.6	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Gender)
5.4.7	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Previous Vascular Disease)
5.4.8	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Renal Dysfunction)
5.4.9	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Metabolic Syndrome)
Lipid-Lowering Therapy:	
5.1.1	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD
5.1.2	Kaplan-Meier Plot Of Non-Fatal MI (Symptomatic Only)+ Fatal CHD
5.1.3	Kaplan-Meier Plot Of All-Cause Mortality
5.1.4	Kaplan-Meier Plot Of Fatal And Non-Fatal Stroke
5.1.5	Kaplan-Meier Plot Of Fatal And Non-Fatal Heart Failure
5.1.6	Kaplan-Meier Plot Of Total Coronary Endpoints
5.1.7	Kaplan-Meier Plot Of Total Cardiovascular Events And Procedures

5.1.8	Kaplan-Meier Plot Of Silent MI
5.1.9	Kaplan-Meier Plot Of Unstable Angina
5.1.10	Kaplan-Meier Plot Of Chronic Stable Angina
5.1.11	Kaplan-Meier Plot Of Peripheral Arterial Disease
5.1.12	Kaplan-Meier Plot Of Life Threatening Arrhythmias
5.1.13	Kaplan-Meier Plot Of Development Of Diabetes Mellitus
5.1.14	Kaplan-Meier Plot Of Development Of Renal Impairment
5.2.1	Change in Systolic Blood Pressure Over Time
5.2.2	Change in Diastolic Blood Pressure Over Time
5.3.1	Change in LDL-C Over Time
5.3.2	Change in Total Cholesterol Lipids Over Time
5.3.3	Change in Triglycerides Over Time
5.3.4	Change in HDL Over Time
5.3.5	Change in Blood Sugar Over Time
5.3.6	Change in Creatinine Over Time
5.4.1	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Diabetes Status)
5.4.2	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Smoking Status)
5.4.3	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Obesity)
5.4.4	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By LVH Status)
5.4.5	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Age)
5.4.6	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Gender)
5.4.7	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Previous Vascular Disease)
5.4.8	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Renal Dysfunction)
5.4.9	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Metabolic Syndrome)
Combination Therapy:	
5.1.1	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD
5.1.2	Kaplan-Meier Plot Of Non-Fatal MI (Symptomatic Only)+ Fatal CHD
5.1.3	Kaplan-Meier Plot Of All-Cause Mortality
5.1.4	Kaplan-Meier Plot Of Fatal And Non-Fatal Stroke
5.1.5	Kaplan-Meier Plot Of Fatal And Non-Fatal Heart Failure
5.1.6	Kaplan-Meier Plot Of Total Coronary Endpoints
5.1.7	Kaplan-Meier Plot Of Total Cardiovascular Events And Procedures
5.1.8	Kaplan-Meier Plot Of Silent MI
5.1.9	Kaplan-Meier Plot Of Unstable Angina
5.1.10	Kaplan-Meier Plot Of Chronic Stable Angina
5.1.11	Kaplan-Meier Plot Of Peripheral Arterial Disease
5.1.12	Kaplan-Meier Plot Of Life Threatening Arrhythmias
5.1.13	Kaplan-Meier Plot Of Development Of Diabetes Mellitus
5.1.14	Kaplan-Meier Plot Of Development Of Renal Impairment
5.2.1	Change in Systolic Blood Pressure Over Time
5.2.2	Change in Diastolic Blood Pressure Over Time
5.3.1	Change in LDL-C Over Time
5.3.2	Change in Total Cholesterol Lipids Over Time
5.3.3	Change in Triglycerides Over Time
5.3.4	Change in HDL Over Time
5.3.5	Change in Blood Sugar Over Time
5.3.6	Change in Creatinine Over Time
5.4.1	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Diabetes Status)

5.4.2	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Smoking Status)
5.4.3	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Obesity)
5.4.4	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By LVH Status)
5.4.5	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Age)
5.4.6	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Gender)
5.4.7	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Previous Vascular Disease)
5.4.8	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Renal Dysfunction)
5.4.9	Kaplan-Meier Plot Of Non-Fatal MI + Fatal CHD (By Metabolic Syndrome)

References: