Clinical Study Report Synopsis

Drug Substance	Not applicable
Study Code	D3560L00092
Edition Number	Version 1.0
Date	29 August 2011

Prevalence of Atherosclerotic Disease in Asian subjects not on lipid lowering agents, but with at least two CVD risk factors

Study dates:	First subject enrolled: 23 October 2009 Last subject last visit: 11 August 2010
Phase of development:	Prevalence study , Interventional
International Co-ordinating Investigator:	Professor Byung-Hee Oh Director of Cardiovascular Center, Professor of Medicine/Cardiology
Sponsor's Responsible Medical Officer:	Dr. Namrata Bahadur Regional Medical Affairs Director, Crestor and RITA, AstraZeneca Asia Pacific

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

The study was conducted at 33 centers in 8 countries; China, Korea, Taiwan, Thailand, Indonesia, Philippines, Malaysia, Vietnam. The first patient entered the study on 23 October 2009 and the last patient finished the study on 11 August 2010.

Publications

None at the time of writing of this report.

Objectives and criteria for evaluation

The primary objective of this study was to obtain the distribution of measurements of CIMT in Asian individuals with at least 2 or more CVD risk factors, but not on any lipid-lowering agents.

The secondary objectives of the study were:

1. To examine the association between CIMT values and demographic characteristics; CIMT values and CVD risk factors; CIMT values and lipid profiles; CIMT and hs-CRP levels; CVD risk factors and hs-CRP levels.

2. To determine subjects' prevailing knowledge, attitudes and behaviors toward CVD risks and treatment.

Details of Primary and secondary objectives and outcome variables are provided in Table S1.

Table S1: Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
Distribution of measurements of CIMT in Asian individuals with at least 2 or more CVD risk factors, but not on any lipid-lowering agents.	Distribution of mean-mean CIMT: the mean of mean region IMT values Distribution of mean-max CIMT: the mean of max region IMT values	Statistical Analysis
Secondary	**Secondary**	
1. To examine the association between CIMT values and demographic characteristics; CIMT values and CVD risk factors; CIMT values and lipid profiles; CIMT and hs-CRP levels; CVD risk factors and hs-CRP levels.	Association of mean-mean CIMT and mean-max CIMT with other variables (countries, demographic characteristics, CVD risk factors, lipid profiles and hs-CRP) Existence of plaque or not hs-CRP Lipid profile data including total cholesterol, HDL-C, LDL-C and triglycerides	Statistical Analysis
2. To determine subjects' prevailing knowledge, attitudes and behaviors toward CVD risks and treatment.	Patient questionnaire	

Study design

This was a multi-centre, cross-sectional study of Asian subjects with at least two CVD risk factors, with no overt cardiovascular diseases. Physicians were invited to recruit subjects aged 20 to 70 years old (30 to 69 years old in Protocol Version 2).

Data collection for each subject took place at one visit or two visits depending on the availability of a sonographer at site. If only one visit was performed, informed consent and all study procedures were done at that one visit. If two visits were performed, at visit 1 to the physicians' clinics, subjects' informed consent was taken, physical examination and demographic data of eligible patients were collected, subjects' fasting blood samples were taken for analysis of total cholesterol, triglyceride, high- and low density lipoprotein cholesterol, fasting glucose, and hs-CRP. Subjects were asked to complete a Patient Questionnaire. At visit 2, the subjects were scheduled for measurements of CIMT on the left and right carotid arteries by a certified sonographer. If subject had not given a fasting blood sample at visit 1, this was done at visit 2.

Target subject population and sample size

Asian subjects of either gender, aged 20 to 70 years (aged 30 to 69 years in Protocol Version 2), with at least two CVD risk factors but not on lipid-lowering agents. Subject who demonstrated his or her willingness to participate in the survey and comply with its procedures by signing a written consent was included in the study.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Not applicable.

Duration of treatment

Not applicable.

Statistical methods

Descriptive statistical analysis was performed in terms of mean, standard deviation, median, minimum and maximum values. The association between carotid intima media thickness (CIMT) values and demographic characteristics, cardiovascular diseases (CVD) factors, lipid values and hs-CRP were examined by one-way analysis of variance (ANOVA) models or simple regression models in a univariate approach and by general linear models in a multivariate approach. All statistical analyses were performed by using the SAS® package (SAS® Institute Inc., USA, and Version 9.2).

The per protocol analysis set (PPS) was used for analysis. It included subjects who did not violate inclusion (except age criteria) and exclusion criteria and whose CIMT values were available.

Subject population

A total 2627 subjects were enrolled from 8 countries (China, Indonesia, Korea, Philippines, Malaysia, Taiwan, Thailand and Vietnam) out of which 2531 were included for PPS analysis.

Summary of results

Statistical Analysis Results:

Out of 2531, 1462 (57.76%) and 1068 (42.24%) of the subjects were male and female respectively. The mean (SD) age of the subjects was 55.1 yrs (9.0) with a minimum of 20 yrs and maximum of 81 yrs. Overall 2530 (99.9%) of the subjects were of Oriental ethnic group. According to the Body Mass Index (BMI), 1044 (41.31%) of the subjects were overweight and 279 (11.04%) subjects were obese.

Most commonly prevalent CHD risk factors included older age (Men ≥ 45 years; Women ≥ 55 years) in 2079 (82.1%), hypertension in 1903 (75.2%), cigarette smoking (any cigarette smoking in the past month) in 1001 (39.6%) and family history of premature CHD in 622 (24.6%) subjects. Diabetes in 202 (8.0%) subjects was the most commonly prevalent CHD risk equivalents. The risk factors for metabolic syndrome included blood pressure (≥130 / ≥85mmHg) in 1774 (70.2%), abdominal obesity in 1407 (55.7%) and fasting glucose in 473 (20.8%) subjects. Overall 2393 (94.55%) of the subjects were treatment naive and did not take any lipid-lowering drug treatment within the last 3 months, prior to study entry. Out of 137 (5.41%) non treatment naïve subjects 102 (4.03%) subjects used statins as the lipid lowering drugs but stopped treatment 3 months or longer prior to the study.

Primary endpoint results: Mean-mean CIMT

The mean of mean-mean CIMT (mm) in the study was found to be 0.66 mm with a SD of 0.16 mm for 20-70 years age group. The minimum and maximum value of mean-mean CIMT (mm) was 0.13 mm and 1.92 mm respectively in the study as presented in Table S2. The same values were obtained for mean-mean CIMT for 30-69 years age group as given in Table S3.

Table S2: **Summary of mean-mean CIMT (20-70 years age group)**

							95% CI of mean	
	N	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**	**Lower**	**Upper**
Mean-mean CIMT (mm)	2511	0.661	0.1583	0.660	0.127	1.921	0.655	0.667

Mean-mean CIMT: the mean of mean region IMT values

Table S3: Summary of mean-mean CIMT (30-69 years age group)

							95% CI of mean	
	N	Mean	SD	Median	Minimum	Maximum	Lower	Upper
Mean-mean CIMT (mm)	2462	0.664	0.1575	0.662	0.127	1.921	0.658	0.670

Mean-mean CIMT: the mean of mean region IMT values

The mean of mean-max CIMT (mm) in the study was found to be 0.85 mm with a SD of 0.16 mm for 20-70 years age group. The minimum and maximum value of mean-max CIMT (mm) was 0.27 mm and 2.23 mm respectively in the study as presented in Table S4. The same values were obtained for mean max CIMT for 30-69 years age group as given in Table S5.

Table S4: **Summary of mean-max CIMT (20-70 years age group)**

							95% CI of mean	
	N	Mean	SD	Median	Minimum	Maximum	Lower	Upper
Mean-max CIMT (mm)	2511	0.846	0.1590	0.834	0.268	2.229	0.840	0.852

Mean-max CIMT: the mean of max region IMT values

Table S5: Summary of mean-max CIMT (30-69 years age group)

							95% CI of mean	
	N	Mean	SD	Median	Minimum	Maximum	Lower	Upper
Mean-max CIMT (mm)	2462	0.849	0.1580	0.836	0.268	2.229	0.843	0.855

Mean-max CIMT: the mean of max region IMT values

Secondary endpoint results

Mean-mean CIMT and its association with other variables

A statistical significant difference in mean-mean CIMT values was seen in different Asian countries with Taiwan having the maximum (0.769 mm) and Thailand (0.567 mm) having the minimum value. A statistical significance in another factor was age group which showed corresponding increase in mean-mean CIMT as the age increased ($p<0.0001$, 30-39 yrs: 0.527 mm, 40-49 yrs: 0.614 mm, 50-59 yrs: 0.665 mm and 60-69 yrs: 0.715 mm). Other factors/variables with statistical significant difference in mean-mean CIMT value included demographic variables like gender ($p=0.0193$), BMI ($p=0.0060$); all the CHD risk factors

(p<0.0001) excluding low and high HDL-cholesterol; number of risk factors (p=0.0010); all the risk factors of metabolic syndrome (p<0.0001) other than abdominal obesity (p=0.1820).

Mean-mean CIMT was found to positively correlate with age (r=0.344, p<0.0001), sitting SBP (mmHg) (r=0.186, p<0.0001), and negatively correlated with high density lipoprotein - cholesterol (HDL-C) (mg/dL) (r=-0.081, p<0.0001). The correlation observed between the variables and mean-mean CIMT was found to be very weak. Summary of correlation coefficients between mean-mean CIMT and continuous variables is provided in Table S6.

Table S6: Correlation coefficient between mean-mean CIMT and continuous variables

	N	Correlation Coefficient (r)	p-value
Age (years)	2531	0.344	<.0001
Weight (kg)	2528	0.032	0.1059
BMI (kg/m^2)	2527	-0.005	0.7896
Waist circumference (cm)	2525	0.038	0.0561
Sitting SBP (mmHg)	2525	0.186	<.0001
Sitting DBP (mmHg)	2525	0.034	0.0904
TC (mg/dL)	2513	-0.030	0.1277
LDL-C (mg/dL)	2513	0.009	0.6595
HDL-C (mg/dL)	2513	-0.081	<.0001
TG (mg/dL)	2513	-0.031	0.1177
Glucose (mg/dL)	2507	0.020	0.3194
log(hs-CRP)	2513	-0.018	0.3564

In univariate regression analysis with mean-mean CIMT as the dependent variable the following risk factors were found to be significantly associated with increased mean-mean CIMT: increasing unit of age and decreasing unit of HDL-C (mg/dL). In multivariate regression analysis, increasing age, low HDL-C, fasting glucose (≥100 mg/dL) and male sex were found to be associated with increasing mean-mean CIMT after adjustment of the other variables.

Mean-max CIMT and its association with other variables

A statistical significant difference in mean-max CIMT values was seen in different Asian countries with Taiwan having the maximum (0.926 mm) and Thailand (0.765 mm) having the minimum value. A statistical significance in another factor was age group which showed corresponding increase in mean-max CIMT as the age increased (p<0.0001, 30-39 yrs: 0.700 mm, 40-49 yrs: 0.799 mm, 50-59 yrs: 0.850 mm and 60-69 yrs: 0.902 mm). Other

factors/variables with statistical significant difference in mean-max CIMT value included demographic variables like gender (p=0.0152), all the CHD risk factors (p<0.0001) excluding low and high HDL-cholesterol; number of risk factors (p<0.0001); CHD risk equivalent diabetes (p=0.0160); all the risk factors of metabolic syndrome (p<0.0001) other than abdominal obesity (p=0.0835).

Mean-max CIMT was found to have a weak positive correlation with age, sitting SBP (mmHg), waist circumference, sitting DBP, LDL-C, glucose, log (hs-CRP) and negatively correlated with HDL-C (mg/dL). In univariate regression analysis with mean-max CIMT as the dependent variable the following risk factors were found to be significantly associated with increased mean-max CIMT: increasing unit of age, waist circumference, LDL-C, glucose, log (hs-CRP) and decreasing unit of HDL-C (mg/dL). In multivariate regression analysis, increasing age, high LDL-C, high log (hs-CRP), male sex, low HDL-C and high blood pressure were found to be associated with increasing mean-max CIMT after adjustment of the other variables.

Plaque

Overall 451 (17.82%) of the subjects were found to have plaque in the study. A statistical significant difference (p<0.0001) in plaque existence was seen in different Asian countries. Other factors which showed a statistical significant difference (p<0.0001) were age and BMI. In univariate logistic regression analysis, it was found that increase in age; decrease in BMI and waist circumference was associated with the formation of plaque. In multivariate analysis using logistic model for plaque suggested an increase in plaque formation with the increase in fasting glucose (≥100 mg/dl) and with BMI<27.

hs-CRP

In the study overall 2513 subjects were used for analysis for hs-CRP since 18 subjects in the PPS analysis set had missing values in hs-CRP. A statistical significant difference in hs-CRP values was seen in different Asian countries with Malaysia having maximum (0.191 mg/dL) and Korea (0.094 mg/dL) having the minimum values. Other factors which showed significant difference in hs-CRP values were BMI, CHD risk factors: hypertension, family history of premature CHD, other "risk equivalent conditions and all the risk factors of metabolic syndrome.

Log (hs-CRP) was found to positively correlate with weight (r=0.144, p<0.0001), BMI (r=0.248, p<0.0001), waist circumference (r=0.250, p<0.0001), sitting SBP (mmHg) (r=0.116, p<0.0001), sitting DBP (mmHg) (r=0.106, p<0.0001), Total Cholesterol (TC) (mg/dL) (r=0.112, p<0.0001), LDL-C (mg/dL) (r=0.141, p<0.0001), TG (mg/dL) (r=0.087, p<0.0001) and glucose (mg/dL) (r=0.159, p<0.0001) and negatively correlate with HDL-C (mg/dL) (r=-0.165, p<0.0001).

In univariate regression analysis with log (hs-CRP) as the dependent variable the following risk factors were found to be significantly associated with increased log (hs-CRP): increasing unit of weight, BMI, waist circumference (mg/dL), TC, LDL-C (mg/dL), TG (mg/dL),

glucose (mg/dL) and decreasing unit of HDL-C (mg/dl). In multivariate regression analysis waist circumference, high LDL-C (mg/dL), high glucose (mg/dL), increasing unit of BMI, cigarette smoking, hypertension, decreasing unit of weight and low HDL-C (mg/dL) were associated with increasing log (hs-CRP) after adjustment of the other variables.

Lipid profile data

The mean TC (mg/dL), LDL-C (mg/dL), TG (mg/dL) level of the subjects enrolled in the study was borderline high level and the mean HDL (mg/dL) level was 49.8 mg/dL (more than the desirable of >40 mg/dL).

Patient awareness

Awareness among Asian population on the various CVD risk factors, their control and treatments was found to be diverse in nature but appeared sufficient in some parameters. The source of about CVD risk factors were health care professionals and TV/ internet/ radio/ newspapers/ magazines. Most of the subjects were satisfied with the current treatment and were motivated towards controlling the prevalent CVD risk factors.

Summary of pharmacokinetic results

Not applicable

Summary of pharmacodynamic results

Not applicable

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable

Summary of pharmacogenetic results

Not applicable

Summary of safety results

This study was without any drug administration i.e. AstraZeneca did not supply any investigational product for this survey. Only serious AEs related to study procedures was collected and an assessment of causality to study procedure was planned to be performed.

No SAE related to study procedures was reported during the study.