AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: None
ACTIVE INGREDIENT: None

Study No: NIS-CVN-CRE-2007/1
InPractice Survey on the treatment of hypercholesterolemia

Developmental phase: Epidemiological study
Study Completion Date: May 2008
Date of Report: May 2008

OBJECTIVES:

Primary

- To establish the proportion of patients on lipid-lowering pharmacological treatment reaching the LDL-C goals according to Vietnamese/updated 2004 NCEP ATP III guidelines.

Secondary

- To establish the proportion of patients on lipid-lowering pharmacological treatment reaching the LDL-C goals according to the Vietnamese/updated 2004 NCEP ATP III guidelines in the following sub-populations: primary/secondary prevention patients, and patients with metabolic syndrome.
- To establish the proportion of patients on lipid-lowering pharmacological treatment reaching the LDL-C goals according to the NCEP ATP III and Vietnamese/ updated 2004 NCEP ATP III guidelines, in the survey population and in the following sub-populations: primary/secondary prevention patients, and patients with metabolic syndrome.
- To identify determinants (e.g patient and physician characteristics) for undertreatment of hypercholesterolemia. Undertreatment is defined as receiving lipid-lowering pharmacological treatment and not reaching the LDL-C goals according to the Vietnnmese/NCEP ATP III/ updated 2004 NCEP ATP III guidelines.
- To explore physician characteristics associated with the allocation of treatment regime.

SURVEY DESIGN

This is a multi-centre survey of patients who are currently on lipid-lowering pharmacological treatment. Data collection for each patient took place at one visit. Before assessment of the first patient, the investigator filled in one investigator questionnaire on his/her experience and perception of the management of hypercholesterolemia seen in his/her patients. Before assessment by the investigator, patients recorded on a patient questionnaire their awareness of hypercholesterolemia, their current treatment schedule and perception, and compliance.
The investigator completed a Patient Record Form (PRF) with the patient's demographics, the presence of the known cardiovascular risk factors, cardiovascular medical history, current lipid-lowering drug treatment and the reason for the current therapy. Results of lipid laboratory profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, and glucose) within the past week were recorded.

TARGET SUBJECT POPULATION

The target survey population is comprised of subjects of either gender, aged above 18 years, and on lipid-lowering drug treatment for at least 3 months, with no dose change for a minimum of 6 weeks.

TARGET VARIABLES

Primary variable

- The number and percentage of subjects achieving the LDL-C goals, according to the Vietnamese/2004 updated NCEP ATP III guidelines.

Secondary variables

- The number and percentage of subjects achieving the LDL-C goals, according to the Vietnamese/2004 updated NCEP ATP III guidelines for several subject subsets.
- The number and percentage of subjects achieving LDL-C goals according to the NCEP ATP III and Vietnamese/2004 updated NCEP ATP III guidelines, overall and for several subject subsets.
- The association between achievement of LDL-C goals, according to the Vietnamese/NCEP ATP III / 2004 updated NCEP ATP III guidelines, and patient and physician variables. Multivariate logistic regression models will be used to assess this association.

STATISTICAL METHODS

Analyses of primary and secondary endpoints were performed using the same models. For each patient, the NCEP ATP III and 2004 updated NCEP ATP III risk categories were determined and a dichotomous variable was computed indicating whether the patient had achieved the target LDL-C goal corresponding to the risk category. The number and percentage of subjects achieving the LDL-C goals according to each of the lipid-lowering guidelines was then presented.

Furthermore, a logistic regression analysis was performed to determine the prognostic factors of achieving the LDL-C goals, according to each of the lipid-lowering guidelines. Prognostic factors were identified among several patient and physician independent variables.
Firstly, a crude association of each of the potential predictors with the outcome (i.e. achievement of LDL-C goals according to the corresponding lipid-lowering guidelines) was investigated. This was done by multilevel logistic regression with the following:

- Dependent variable = achievement of LDL-C goals according to the corresponding guidelines (yes vs. no)
- Fixed effects = the potential predictor

The association was appraised by estimated odds ratio with associated 95% confidence intervals and p-values in the fixed-effects part of the models. All predictors with a p-value<0.10 (using the Wald-type test) in this crude association analysis were further included in an adjusted multilevel logistic regression model, provided that at least 90% of data was non-missing.
The adjusted association was assessed by means of a random intercept logistic model using the following backward stepwise procedure. First, a full model with all independent variables selected based on the univariate analysis as fixed effects and for which at least 90% of data was non-missing was run. At each step, the least significant independent variable was removed until all parameters reached a level of significance of at least 0.05. Logistic regression models were fit by means of generalised linear mixed models (GLMM) with random intercepts.
For the final models, the following results were provided: parameter estimates, standard error and p-values for each effect, as well as estimated odds ratio with associated 95% confidence intervals.
Summary statistics (e.g., number and percentage) were produced for the primary and secondary endpoints for several subgroups defined according to all patients' characteristics, such as age, gender, type of therapy, patients having the metabolic syndrome or reasons for being treated.
No safety analyses were done.

RESULTS:

The main analysis (*i.e.*, the analysis of the primary and secondary variables) as well as baseline assessments and analysis of patient survey data were based on 2,429 patients. Analysis of the investigator questionnaire was based on the returned questionnaires.
The main demographic and disease-related data are shown in the table below.

Table Patient demographics and baseline characteristics

	N	% *Mean±SD
Age	2,403	59.1 ± 11.3*
Gender		
Male	11661	49%
Female	1221	51%
History of CHD	990	42%)
History of PAD	145	7%
History of CAD	237	10%
Current smoker	507	23%

	N	% *Mean±SD
Diabetes	830	36%
Arterial hypertension	1707	72%
Family history of premature CV disease	435	18%
Being on treatment for (years)	1922	2.31 ± 2.72*
Reason of LLD		
Primary prevention	1236	54%
Secondary prevention	859	38%
Familial hypercholesterolemia	190	8%
Single LLD	2235	94%
Statins	1821	82%
Fibrates*	407	18%
Other	7	0.3%
Multiple therapy	163	6%

Patient Questionnaire

100% (n=2429) patients filled at least one question of patient questionnaire. All data presented here have been calculated taking into account only patients answering the corresponding item in the questionnaire.
According to patients:

- 75% of patients (n=1826) have been informed about their cholesterol levels.
- 85% of patients have been informed about purpose of cholesterol lowering treatment.
- 66% (n=1598) replied that they were advised to change their lifestyle and were prescribed a tablet
- Since being first prescribed a lipid-lowering drug (LLD), about 40% (n=927) of patients were still taking the same drug and the same dose, 14% (n=318) had increased the dose, 34% (n=780) had changed the drug once or twice and 13% (n=301) had changed the drug several times.
- 61% (n=1483) of patients were satisfied about the way their cholesterol was being treated to continue taking their lipid-lowering therapy.
- 28% (n=661) of the patients were not sure about the current situation of their cholesterol level, 17% (n=406) thought that they had not achieved the target cholesterol level and 25% (n=1185) of the patients claimed not to have been given a target cholesterol level at all.
- When asked about the frequency with which the patient was seen by the physician for a check-up of their cholesterol, 32% (n=744) indicated to have more than one check-up every three months, 43% (n=1002) of them reported one every three months, 15% (n=344) one every six months, 2% (n=45) one every year and 1% (n=21) less than one a year.
- The majority of patients (n=1795; 74%) agreed in being satisfied with the level of information about high cholesterol provided to them by physicians. 22% (n=541) of people frustrated for not knowing about the effectiveness of their treatment.
- When asked about how often they forget to take their treatment, 28% (n=658) of responders said no more often than once a month, while 14% (n=329) said once every two weeks, 12% (n=278) once a week and 14% (n=321) more than once a week.
- 37% (n=892) of patients agreed to have stopped taking their tablets when cholesterol returned to normal levels.

Investigator Questionnaire

100% of the 467 physicians participating in the study filled the investigator questionnaire and returned it. Most investigators were cardiologists (n=292; 64%), GPs (n=79; 17%) and Endocrinologists (n=73; 16%). 52% investigators were female (n=241; 52%).
According to investigators:

- They set individual target cholesterol levels to 83.7% of their patients.
- Most of them (n=459; 99%) use guidelines to establish individual target cholesterol levels.
- The lipid-lowering guidelines used are: The National lipid-lowering and NCEP ATP III guidelines (57% [n=266 and 268]). Joint European guideline (SCORE) (n=141; 30%), individual practice guidelines (n=9; 2%). The guidelines mostly used were the NCEP ATP III guidelines (n=126; 26%) and the National lipid-lowering guidelines (n=49; 10%).
- Most investigators reported to schedule a visit for reviewing the cholesterol levels once every three months (n=289; 64%) or more often than once every 6 months (n=104; 23%), while only 12% (n=55) schedule a visit once every 6 months, and 1% (n=6) once a year.
- The lipid-lowering drug most frequently recommended to patients were statins (to 69.1% of patients), followed by fibrates (to 29.3% of the patients), bile acid sequestrants (to 5.63% of patients) and other drugs to (8.16% of patients).
- 50.1% of the patients achieve their target level and stay at this concentration, while 21.4% of patients generally stay at their target level but sometimes their cholesterol concentration gets too high. 13.7% of patients reached their target level in the past but have since relapsed and 14.7% of patients never reach their target level.

Patients attaining the LDL-C goals recommended by the different lipid-lowering guidelines

The percentage of patients attaining the LDL-C goal recommended by the different lipid-lowering guidelines was analysed among those patients within the FAS population who had all the information required to be assigned a cardiovascular risk category.
The percentages of patients reaching the LDL-C goal according to the NCEP ATP III and the Vietnamese/2004 updated NCEP ATP III guidelines are presented in the table below.

Table. Patients attaining the LDL-C goal recommended by the different lipid-lowering guidelines

		2001-NCEP (n=2042)	2004 NCEP (n=1962)
		N (%)	N (%)
Overall survey		970 (48%)	808 (41%)
Age	<40	40 (56%)	39 (58%)
	40-54	333 (50%)	303 (46%)
	55-69	416 (46%)	319 (37%)
	≥70	179 (48%)	145 (40%)
Gender	Male	469 (48%)	348 (36%)
	Female	492 (47%)	452 (45%)
BMI	Normal weight (<25 kg/m^2)	609 (47%)	506 (41%)
	Overweight (25-29 kg/m^2)	291 (46%)	238 (40%)
	Obese (≥30kg/m^2)	38 (50%)	34 (46%)
Type of prevention	Primary prevention	510 (48%)	433 (42%)

		2001-NCEP (n=2042)	2004 NCEP (n=1962)
		N (%)	N (%)
	Secondary prevention (after a cardiovascular event)	351 (48%)	277 (40%)
	Familial hypercholesterolemia	65 (41%)	56 (37%)
Metabolic syndrome (IDF 2005)	Yes	278 (42%)	229 (37%)
	No	614 (51%)	514 (44%)
Type of therapy	Statin monotherapy	761 (49%)	629 (42%)
	Fibrates monotherapy	131(39%)	111 (35%)
	Other monotherapy	4 (67%)	4 (67%)
	Combination therapy	49 (43%)	42 (39%)
Risk category	High/Very high	323 (30%)	50 (16%)
	Medium/High but	412 (62%)	207 (29%)
	Low/Medium high	235 (82%)	84 (27%)
	-------/Medium low		232 (65%)
	--------/Low		235 (82%)

The percentages of patients at goal according to 2004 NCEP guidelines for diabetes, CAD, PAD were 28%, 19% and 14%, respectively.

Predictors of attaining the LDL-C goals recommended by the different lipid-lowering guidelines

When adjusted for all the other univariate significant predictors ($p<0.10$), the predictors of attaining the LDL-C goal that proved to be significant ($p<0.05$) in the multivariate model were:

- **According to the 2001-NCEP ATP III guideline:**

When adjusted for all the other univariate significant predictors ($p<0.10$), the likelihood of reaching the LDL-C goals recommended by the 2001-NCEP guideline was increased by 1.91-fold (95% CI: [1.38; 2.65]) for patients treated with rosuvastatin compared with patients treated with other statins.

The chance to attain the LDL-C goal recommended by the 2001-NCEP guideline was decreased by 0.61-fold ([0.37; 1.00]) for PAD patients, by 0.64-fold (95% CI: [0.42; 0.96]) for CAD patients and by 0.32-fold (95%CI: [0.24; 0.42]) for diabetes patients and by 0.64-fold (95%CI: [0.50; 0.84]) for patients with hypertension when compared without PAD, CAD or diabetes patients and without hypertensive patients, respectively.

Patients being current smoking had a lower chance 0.66-fold (95% CI: [0.47; 0.92]) to reach the LDL-C goal recommended by the 2001-NCEP ATP III guideline compared with patients being not smoking.

The chance to reach the LDL-C goals according to the 2001-NCEP guideline was increased by 1.55-fold (95% CI: [1.11; 2.16]) for patients affirming to have reached their target cholesterol level in the patient questionnaire compared with patients answering not to have been given a target cholesterol level.

The chance to reach the LDL-C goals according to the 2001-NCEP guideline was reduced by 0.65-fold (95%CI: [0.46; 0.92]) if physicians having 10-15 years of practice, by 0.37-fold ([0.20; 0.67]) if physicians having > 20 years of practice compared with physicians having <10 years of practice.

- **According to the Vietnamse/2004-NCEP ATP III guideline:**

When adjusted for all the other univariate significant predictors ($p<0.10$), the likelihood of reaching the LDL-C goals recommended by the 2004-NCEP guideline was decreased by 0.43-fold (95% CI: [0.21;0.85]) for patients 55-70 years old compared with patients

<40years of age. Otherwise, when compared with male patients, female patients had an adjusted chance increased by 1.47-fold (95% CI: [1.12; 1.92]) to meet the LDL-C goal level recommended by the 2004-NCEP guideline.

The chance to attain the LDL-C goal recommended by the 2004-NCEP guideline was increased by 1.54-fold (95% CI: 1.12; 1.92) for patients treated with rosuvastatin compared with patients treated with other statins.

The chance to attain the LDL-C goal recommended by the 2004-NCEP guideline was decreased by 0.28-fold ([0.15; 0.53]) for PAD patients, by 0.40-fold (95% CI: [0.24; 0.64]) for CAD patients and by 0.45-fold (95%CI: 0.34; 0.59) for diabetes patients and by 0.66-fold (95%CI: [0.51; 0.86]) for patients with hypertension when compared without PAD, CAD or diabetes patients and without hypertensive patients, respectively.

Patients being current smoking had a lower chance 0.46-fold (95% CI: [0.32; 0.65]) to reach the LDL-C goal recommended by the 2004-NCEP ATP III guideline compared with patients being not smoking.

The chance to reach the LDL-C goals according to the 2004-NCEP guideline was increased by 1.65-fold (95% CI: [1.18; 2.32]) for patients affirming to have reached their target cholesterol level in the patient questionnaire compared with patients answering not to have been given a target cholesterol level.

The chance to reach the LDL-C goals according to the 2004-NCEP guideline was reduced by 0.55-fold (95%CI: [0.38; 0.78]) if physicians having 10-15 years of practice, by 0.37-fold ([0.20; 0.69]) if physicians having > 20 years of practice compared with physicians having <10 years of practice.

Apart from years of practice, none of the physician determinants assessed in the survey were found to be significant multivariate predictors.

Safety analysis

This was not a therapeutic or a safety study. Only serious adverse events were to be registered throughout the study. No serious adverse event was experienced by any of the included subjects.