AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA

FINISHED PRODUCT: None
ACTIVE INGREDIENT: Not applicable. This was a non-therapeutic study.

Study No: NCT01075594
Centralized pan-Bulgarian Survey on the undertreatment of hypercholesterolemia

Developmental Phase: Non-Interventional Study
Study Completion Date: 26.08.2010
Date of Report: 07.07.2011

Number of patients and sites

Total 2500 patients all over Bulgaria were enrolled as planned. Patient enrolment took place between February and August 2010. The study has been conducted in 23 centres in Bulgaria.

OBJECTIVES:

Primary

- To establish the proportion of Bulgarian patients on lipid-lowering pharmacological treatment reaching the LDL-C goals according to the Fourth Joint European Task Force guidelines.

Secondary

- To establish the proportion of patients on lipid-lowering pharmacological treatment reaching the LDL-C goals according to the Fourth Joint European Task Force guidelines in the following sub-populations:
  - Primary/secondary prevention patients
  - Patients with metabolic syndrome (according to NCEP III definition).
- To establish the proportion of patients on lipid-lowering pharmacological treatment reaching the LDL-C goals according to the NCEP ATP III / updated 2004 NCEP ATP III / national guidelines, in the survey population and in the following sub-populations:
  - Primary/secondary prevention patients
  - Patients with metabolic syndrome.
- To establish the proportion of patients on lipid-lowering pharmacological treatment reaching the non HDL-C goals according to the NCEP ATP III / updated 2004 NCEP ATP III / national guidelines [<3.37 mmol/L], in the following sub-population: patients with fasting triglycerides > 2.26 mmol/L.
- 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 Fourth Joint European Task Force/ NCEP ATP III/ updated 2004 NCEP ATP III guidelines.

- To explore physician characteristics associated with the allocation of treatment regimen.

Study design

Multi-centre, cross-sectional non-interventional survey study.

Study Flow-chart

The study included a single visit.

Patient population

Patients on lipid-lowering pharmacological treatment for at least 3 months prior to inclusion and with no dose change for a minimum of 6 weeks. Written informed consent was required for inclusion in the study.

METHODS:

Before recruitment of any patient, the investigator filled the investigator questionnaire on his/her experience and perception of the management of the hypercholesterolemia seen in his/her patients. The investigator was asked to indicate his/her general attitude on the diagnosis of hypercholesterolemia, the existing lipid-lowering guidelines and goals, and the various treatment options for hypercholesterolemia.
Before being assessed by the investigator, patients recorded on the patient questionnaire their awareness of hypercholesterolemia, their current lipid-lowering treatment schedule and their perception about it, and compliance.
Afterwards, the investigator completed the Patient Record Form (PRF) with the patient‟s demographics, current lipid-lowering drug treatment and the reason for their therapy. In addition, the investigator recorded the presence of the known cardiovascular risk factors and the cardiovascular medical history. A fasting blood sample was drawn to evaluate the blood lipid profile and the glucose blood level. Blood samples for total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose and HbA1c were collected within 7 days after the visit and analysed by a central laboratory in Bulgaria.
Within 2 days after sample collection, the investigator was able to access the lab results on the laboratory web site and assessed them to the target levels as stated in the European guidelines. This allowed the investigator to determine the patient‟s risk profile and to take the appropriate measures, if any, with respect to the future treatment of the patient.

Statistical Analysis

All statistical analyses were performed using SAS package (Version 9.2).

Analyses of primary and secondary endpoints were performed using the same models for estimation of proportions of patients on lipid-lowering pharmaceutical treatment reaching the LDL-C goals. For each patient, the FJETF, 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 LDL-C target level corresponding to the risk category. Additionally, a dichotomous variable was computed indicating whether the patient had

achieved the non HDL-C target level corresponding to the NCEP ATP III and 2004 updated NCEP ATP III risk categories. The number and percentage of subjects achieving the LDL-C and non HDL-C goals according to the relevant lipid-lowering guidelines was then presented. Furthermore, a two-level logistic regression analysis was performed to determine the prognostic factors of achieving the LDL-C goals, according to each of the lipid-lowering guidelines, with patients at the first-level and investigators at the second-level. 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 relevant guidelines (Yes vs. No)
- Fixed effects = the potential predictor
- Random effect = investigator.

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. The adjusted association was assessed by means of a random intercept logistic model using the following method. First, a full model with all independent variables with a p-value < 0.10 selected based on the univariate analysis as fixed effects and investigator as the random effect 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 **generalized linear mixed models** (GLMM) with random intercepts. Discrete variables with more than 2 categories were taken into account in the model through series of binary variables by means of the CLASS statement. In cases where a too small number of answers per category was observed (frequency of answers per category < 5%), categories were pooled together with the closest relevant category, if applicable, or the predictor was removed from the analysis. 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. The type III effects Wald-type test was used to assess the significance of a variable. 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. All continuous variables were summarized using descriptive statistics. In addition, for patients with both diabetes and CHD the number and percentage of patients achieving the LDL-C target of ≤ 1.8 mmol/L were presented. This is the LDL-C goal level recommended by the European Association for the Study of Diabetes (EASD). No safety analyses were done.

RESULTS:

Among the evaluated patients in the survey, 43.1% reached the LDL-C goals recommended by the FJETF guideline, 45.24% reached the LDL-C goals recommended by the NCEP ATP III and 21.51% reached the LDL-C goals recommended by the 2004 updated NCEP ATP III guidelines.

Only 12.87% (n=56) of patients with diabetes and CHD achieved the LDL-C goal recommended by the EASD, i.e., 1.8 mmol/L. According to NCEP APT III guideline, the percentage of patients reaching the non HDL-C goals was 60% (n=15) among patients falling

into the *Low* risk category, 35% (n=49) among patients in the *Medium* risk category and 18.74% (n=89) among patients in the *High* risk category. When stratified into the CVD risk categories according to 2004 updated NCEP APT III guideline, the percentage of patients reaching the non HDL-C goals was 60% (n=15) among patients falling into the *Low* risk category, 44.3% (n=35) among patients in the *Medium low* risk category, 8.2% (n=5) among patients in the *Medium high*, 10.39% (n=8) among patients in the *High but not very high* risk category and 3.52% (n=14) in the *Very high* risk category.

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 **FJETF guideline**:
  - Patient‟s gender; male patients had a chance increased by 1.605-fold (95% CI: [1.30; 1.98]) to reach the FJETF-recommended LDL-C goal level compared with female patients.
  - BMI; obese patients had a chance increased by 1.625-fold (95% CI: [1.22; 2.16]) to attain their goal compared with normal weight patients.
  - Smoking habits; non smokers had a likelihood of being at goal increased by 1.304-fold (95% CI: [1.01; 1.68]) compared with smokers.
  - Not having history of CHD; the patients without history of CHD compared with patients with history of CHD had lower chance to be at goal (OR: 0.629; 95% CI: [0.51; 0.78]).
  - Not having history of CAD; the chance to be at goal was increased by 1.396-fold (95% CI: [1.00; 1.94]) for patients without history of CAD compared with patients with history of CAD.
  - PQ12: Therapy compliance (Patient sometimes forgets to take tablets); patients disagreeing to sometimes forget to take their lipid-lowering tablets had a chance increased by 1.317-fold (95% CI: [1.04; 1.66]) to attain their goal compared with patients agreeing to sometimes forget them.
  - PQ15: Patient‟s awareness of current LDL-C levels; the patients affirming to have not been given a target cholesterol level in the patient questionnaire had lower chance to reach the LDL-C goals according to the FJETF guideline (OR: 0.487; 95% CI: [0.34; 0.71]) compared with patients answering that had reached it. The patients affirming to have not reached target cholesterol level in the patient questionnaire had lower chance to reach the LDL-C goals according to the FJETF guideline (OR: 0.406; 95% CI: [0.31; 0.53]) compared with patients answering that had reached it. The patients affirming that were not sure whether they had reached target cholesterol level in the patient questionnaire had lower chance to reach the LDL-C goals according to the FJETF guideline (OR: 0.613; 95% CI: [0.50; 0.75]) compared with patients answering that had reached it.
  - IQ11: Physician finds it stressful trying to get his patients to their TCL; patients who were treated by physicians who disagreed that they found it stressful trying to get their patients to TCL had lower chance to attain their goal (OR: 0.716; 95% CI: [0.56; 0.91]) compared with patients who were treated by physician who strongly disagreed. Patients who were treated by physicians who had neutral opinion about finding it stressful trying to get their patients to TCL had lower chance to attain their goal (OR:

0.702; 95% CI: [0.52; 0.94]) compared with patients who were treated by physicians who strongly disagreed.

- Risk category patient falls into: the patients with *high (1)* risk category had lower chance to attain the LDL-C goal recommended by the FJETF guideline compared with patients with *other* risk category (OR: 0.477; 95% CI [0.39; 0.58]). The patients with *high (2)* risk category had higher chance to attain the LDL-C goal recommended by the FJETF guideline compared with patients with *other* risk category (OR: 1.981; 95% CI [1.46; 2.69]). The patients with *high (3)* risk category had lower chance to attain the LDL-C goal recommended by the FJETF guideline compared with patients with *other* risk category (OR: 0.191; 95% CI [0.14; 0.26]).

- According to the **2001-NCEP ATP III guideline**:
  - Patient‟s age; the likelihood of reaching the LDL-C goals recommended by the 2001-NCEP guideline was increased by 1.681-fold (95% CI: [1.08; 2.62]) for patients <40 years old compared with patients of between 55 and 69 years of age.
  - Patient‟s gender; male patients had a chance increased by 1.662-fold (95% CI: [1.37; 2.01]) to reach their LDL-C goal level compared with female patients.
  - BMI; obese patients had a chance increased by 1.389-fold (95% CI: [1.06; 1.81]) to attain their goal compared with normal weight patients.
  - Smoking habits; when compared with smokers, non smokers had an adjusted chance increased by 1.325-fold (95% CI: [1.05; 1.68]) to meet their LDL-C goal level recommended by the 2001-NCEP guideline.
  - PQ6: Change of cholesterol lowering tablet since first prescribed; patients who had changed tablets once or twice had lower chance to attain their goal (OR: 0.734; 95% CI: [0.61; 0.89]) compared with patients who were still on the same tablet. Patients who had changed tablets several times had lower chance to attain their goal (OR: 0.637; 95% CI: [0.46; 0.88]) compared with patients who were still on the same tablet.
  - PQ10: Therapy compliance (Patient always takes daily tablet to lower cholesterol); patients disagreeing to always take their lipid-lowering tablets had lower chance to attain their goal (OR: 0.496; 95% CI: [0.30; 0.82]) compared with patients agreeing to always take them.
  - PQ12: Therapy compliance (Patient sometimes forgets to take tablets); patients disagreeing to sometimes forget to take their lipid-lowering tablets had a chance increased by 1.347-fold (95% CI: [1.09; 1.67]) to attain their goal compared with patients agreeing to sometimes forget them.
  - PQ15: Patient‟s awareness of current LDL-C levels; the patients affirming to have not been given a target cholesterol level in the patient questionnaire had lower chance to reach the LDL-C goals according to the 2001-NCEP guideline (OR: 0.543; 95% CI: [0.37; 0.79]) compared with patients answering that had reached it. The patients affirming to have not reached target cholesterol level in the patient questionnaire had lower chance to reach the LDL-C goals according to the 2001-NCEP guideline (OR: 0.516; 95% CI: [0.40; 0.66]) compared with patients answering that had reached it. The patients affirming that were not sure whether they had reached target cholesterol level in the patient questionnaire had lower chance to reach the LDL-C goals according to the 2001-NCEP guideline (OR: 0.584; 95% CI: [0.48; 0.71]) compared with patients answering that had reached it.
  - Risk category patient falls into: the patients with *high* risk category had lower chance to attain the LDL-C goal recommended by the 2001-NCEP guideline compared with

patients with *low* risk category (OR: 0.208; 95% CI [0.13; 0.34]). The patients with *medium* risk category had lower chance to attain the LDL-C goal recommended by the 2001-NCEP guideline compared with patients with *low* risk category (OR: 0.314; 95% CI [0.19; 0.53]).

- According to the **2004 updated NCEP ATP III guideline**:
  - Patient‟s age; the chance to reach the LDL-C goals recommended by the 2004-NCEP guideline was increased by 4.183-fold (95% CI: [2.66; 6.57]) for patients < 40 years old and by 1.897-fold (95% CI: [1.49; 2.41]) for patients of between 40 and 54 years old compared with patients of between 55 and 69 years of age. Patients >= 70 years old had lower chance to attain their LDL-C goals (OR: 0.740; 95% CI: [0.56; 0.99]) compared with patients of between 55 and 69 years of age.
  - Not being diabetic; non-diabetic patients had lower chance to attain the LDL-C goal recommended by the 2004-NCEP guideline (OR: 0.562; 95% CI: [0.40; 0.78]) compared with diabetic patients.
  - Not having family history of premature CVD; the chance to be at goal was increased by 1.313-fold (95% CI: [1.00; 1.72]) for patients without family history of premature CVD compared with patients with family history of premature CVD.
  - Not having history of CHD; patients without history of CHD had lower chance to be at goal (OR: 0.368 ;95% CI: [0.20; 0.68]) compared with patients with history CHD.
  - PQ6: Change of cholesterol lowering tablet since first prescribed; patients who had changed tablets once or twice had lower chance to attain their goal (OR: 0.723; 95% CI: [0.57; 0.91]) compared with patients who were still on the same tablet. Patients who had changed tablets several times had lower chance to attain their goal (OR: 0.583; 95% CI: [0.38; 0.88]) compared with patients who were still on the same tablet. Patients who were still on the same tablet but the dose had increased had lower chance to attain their goal (OR: 0.616; 95% CI: [0.40; 0.94]) compared with patients who were still on the same tablet.
  - PQ12: Therapy compliance (Patient sometimes forgets to take tablets); patients disagreeing to sometimes forget to take their lipid-lowering tablets had a chance increased by 1.461-fold (95% CI: [1.11; 1.93]) to attain their goal compared with patients agreeing to sometimes forget them. Patients who gave an answer “Don't know/Not applicable” to this question had lower chance to be at goal (OR: 0.406; 95% CI: [0.17; 0.99]) compared with patients agreeing to sometimes forget them.
  - Risk category patient falls into: the patients with *Very high* risk category had lower chance to attain the LDL-C goal recommended by the 2004-NCEP guideline compared with patients with *Low* risk category (OR: 0.029; 95% CI [0.02; 0.05]). The patients with *High but not very high* risk category had lower chance to attain the LDL-C goal recommended by the 2004-NCEP guideline compared with patients with *Low* risk category (OR: 0.156; 95% CI [0.09; 0.27]). The patients with *Medium high* risk category had lower chance to attain the LDL-C goal recommended by the 2004-NCEP guideline compared with patients with *Low* risk category (OR: 0.045; 95% CI [0.02; 0.09]). The patients with *Medium low* risk category had lower chance to attain the LDL-C goal recommended by the 2004-NCEP guideline compared with patients with *Low* risk category (OR: 0.386; 95% CI [0.23; 0.66]).

Predictors for being allocated to statins

- Patients with CHD history had a chance increased by 1.830-fold (95% CI: [1.04; 3.21]) to be allocated to statins compared to patients without CHD history.

Safety analysis

This was not a therapeutic or a safety study. Only serious adverse events were to be registered throughout the study. Only one Serious Adverse Event was recorded in the Patient Record Form and was reported to AstraZeneca.