NON-INTERVENTIONAL STUDY REPORT

STUDY CODE NIS-CRU-DUM-2010/1

VERSION	FINAL 5.0
DATE	29 02 2012

CENTRALIZED RUSSIAN SURVEY ON THE UNDERTREATMENT OF HYPERCHOLESTEROLEMIA

STUDY DURATION:	**FIRST PATIENT IN:** OCTOBER 22, 2010
22.10.2010 – 22.03.2011	**LAST PATIENT OUT:** MARCH 22, 2011

AstraZeneca

PROTOCOL SYNOPSIS

Centralized Russian Survey on the undertreatment of hypercholesterolemia

Survey time

Estimated date of first subject in: October 22, 2010

Estimated date of last subject out: March 22, 2011

Study sites

48 sites located in Russian Federation

Study Objectives

Primary:

To establish the proportion of patients on lipid-lowering pharmacological treatment reaching the LDL-C goals according to the All-Russian Scientific Cardiology Society guidelines/ the Fourth Joint European Task Force guidelines.

Secondary:

1. To establish the proportion of patients on lipid-lowering pharmacological treatment reaching the LDL-C goals according to the All-Russian Scientific Cardiology Society (Ru SCS) guidelines in the following sub-populations:
    - Primary/secondary prevention patients,
    - Patients with metabolic syndrome.
2. To establish the proportion of patients on lipid-lowering pharmacological treatment reaching the LDL-C goals according to the Fourth Joint European Task Force (4JETF) guidelines / National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III / updated 2004 NCEP ATP III guidelines, in the survey population and in the following sub-populations:

    Primary/secondary prevention patients

    Patients with metabolic syndrome.
3. 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 guidelines (<130 mg/dL) (3.36 mmol/L), in the sub-population patients with fasting triglycerides >200 mg/dL (2.26 mmol/L).
4. To identify determinants (e.g. patient and physician characteristics, country-specific guidelines or recommendations) for undertreatment of hypercholesterolemia. Undertreatment is defined as receiving lipid-lowering pharmacological treatment and not

reaching the LDL-C goals according to the Ru SCS guidelines/ the NCEP ATP III/ updated 2004 NCEP ATP III / 4JETF guidelines.

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

Study design

This is non-intervention prospective observational study.

This is a multi-centre Study of patients who are currently using lipid-lowering pharmacological treatment in the Russian Federation

Data collection took place at a single visit.

Before assessment of any patient, each investigator has filled in one investigator questionnaire on his / her experience and perception of the management of hypercholesterolemia seen in his/her patients. The investigator completed the investigator questionnaire by indicating his / her general attitude on diagnosis of hypercholesterolemia, guidelines and goals, and the various treatment options for hypercholesterolemia.

Before assessment of any patient, each investigator will fill in one investigator questionnaire on his / her experience and perception of the management of hypercholesterolemia seen in his/her patients. The investigator will complete the investigator questionnaire by indicating his / her general attitude on diagnosis of hypercholesterolemia, guidelines and goals, and the various treatment options for hypercholesterolemia.

The investigator has completed a Patient Record Form (PRF) with the patient's demographics, current lipid-lowering drug treatment and the reason for the current therapy. In addition, the investigator will record the known cardiovascular risk factors and the cardiovascular medical history. Also, fasting blood samples will be taken. The set provided by the central laboratory will be used. Blood samples for total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, apo-A1, apo-B, glucose and HbA1c will be collected in tubes and analysed by a central laboratory.

STUDY POPULATION

The target study population involved patients aged 18 and older, who received lipid-lowering therapy at least within 3 months with no dose change for a minimum of 6 weeks. The patients were committed to provide the informed consent and comply with the Study procedures.

Assessment criteria

Primary variable

- The number and percentage of subjects achieving the LDL-C goals, according to the Ru SCS guidelines/ the 4JETF guidelines.

Secondary variables

1) The number and percentage of subjects achieving the LDL-C goals according to the Ru SCS guidelines for several subject subsets: subjects with/without metabolic syndrome, and primary / secondary prevention subjects.

2) The number and percentage of subjects achieving LDL-C goals according to the 4JETF guidelines / NCEP ATP III / 2004 updated NCEP ATP III, overall and for several

subject subsets: subjects with / without metabolic syndrome, and primary / secondary prevention subjects.

3) The number and percentage of subjects achieving the non HDL-C goals according to the NCEP ATP III / 2004 updated NCEP ATP III guidelines (<130 mg/dL) (3.36 mmol/L), in the following sub-population: patients with fasting triglycerides (2.26 mmol/L).

4) The number and percentage of subjects achieving the LDL-C goals according to 4JETF guidelines / NCEP ATP III / 2004 updated NCEP ATP III / Ru SCS guidelines will be summarized for the following subsets: demographic variables, CVD risk factors, and class of lipid-lowering agent.

5) The association between achievement of LDL-C goals, according to the Ru SCS guidelines/ the NCEP ATP III / 2004 updated NCEP ATP III / 4JETF guidelines, and patient and physician determinants. Multivariate logistic regression models will be used to assess this association.

6) The physician determinants (sex, age, years of practice, specialty, funder-driven guidelines) subject to selected treatment regimen (statins/ non-statin treatment).

Study Population for analysis

The intention to treat (ITT) population (all included subjects who have signed the informed consent) involved 1000 patients.

Full Analysis Set (FAS) (all included subjects who have signed the informed consent, have laboratory results and filled out questionnaires eligible for analysis) involved 724 patients.

Patient's demographics and initial characteristics

Distribution of patients into subgroups according to the age, sex and race.

		Number of patients	**% of total**
Age subgroups	19- 40 years	19	1.9
	40-54 years	198	19.9
	55-69 years	529	53.1
	70-87 years	251	25.2
Sex	male	546	54.6%
	female	454	45.4%
Race	Caucasian	978	99.7%
	Mongoloid	3	0.3%

Demographics and patient baseline clinical characteristics

	Medium	**Standard deviation**	**Minimum**	**Maximum**
Age, full years	62	10	19	87
Body mass, kg	84.5	15.6	46.4	162.2
Height, m	1.69	0.09	1.44	1.96

Body mass index	29.66	4.97	17.26	66.57
Waist circumference of total sample, cm	98	12	64	158
Waist circumference in men, cm	100	12	65	145
Waist circumference in women, cm	95	12	64	158
Systolic BP, mmHg	133	16	90	190
Diastolic BP, mmHg	81	9	58	140

SUMMARY

1) 34.5 % of patients being treated with lipid-lowering drugs have achieved the LDL-C target level, defined according to the Ru SCS guidelines (2007) and 48.2 % of patients have reached the LDL-C target level, determined by the 4JETF guidelines.

2) Proportion of subjects reaching the LDL-C goals according to the Ru SCS guidelines (2007) in different subgroups:

a) The subgroup of patients with metabolic syndrome demonstrated statistically significantly lower LDL-C goals achievement rate (26.8%) in comparison with patients without metabolic syndrome according to the Ru SCS (46.9%) ($p<0.001$, HR = 0.416, 95% CI 0.316 – 0.546).

b) The subset of secondary CVD prevention patients showed statistically significantly higher LDL-C target level achievement rate according to the Ru SCS guidelines (2007) (38.2 %) in comparison with subset of primary CVD prevention patients (27.0%) ($p=0.001$, HR = 1.670, 95% CI 1.220 – 2.285).

3) Proportion of subjects receiving lipid-lowering therapy reaching the LDL-C goals according to the 4JETF guidelines / NCEP ATP III / 2004 updated NCEP ATP III guidelines both in the general study population and in the primary / secondary prevention sub-population of patients, as well as in subset of subjects with and without metabolic syndrome, respectively, is the following:

a) The LDL-C target level according to the 4JETF guidelines:

i) 46.6% of subjects with metabolic syndrome (according to Epidemiology Task Force Consensus Group) and 51.0% of subjects without metabolic syndrome according to Epidemiology Task Force Consensus Group have reached the LDL-C target level according to the 4JETF guidelines (this difference is statistically not significant $p=0.200$, HR = 0.837, CI 0.642 – 1.091).

ii) In the subset of secondary CVD prevention patients the achievement rate of the LDL-C target level according to the 4JETF guidelines was statistically significantly higher (54.5%) than in the subset of primary CVD prevention patients (35.4%) ($p<0.001$, HR = 2.191, 95% C.I 1.626 – 2.952).

b) The LDL-C target level according to the NCEP ATP III guidelines:

i) The LDL-C target level according to the NCEP ATP III guidelines was reached by 76.3% of subjects in the general population.

ii) 74.8% of patients with metabolic syndrome according to Epidemiology Task Force Consensus Group and 78.7 % of patients without metabolic syndrome have reached the LDL-C target level according to the NCEP ATP III guidelines (this difference is statistically not significant, $p=0.185$, HR = 0.802, 95% CI 0.587 – 1.095).

iii) In the subset of primary CVD prevention patients the achievement rate of the LDL-C target level according to the NCEP ATP III guidelines was statistically significantly lower (68.1 %) than in the subset of secondary CVD prevention patients (81.6%) ($p<0.001$, HR = 2.075, 95% CI 1.496 – 2.877).

c) The LDL-C target level according to the 2004 updated NCEP ATP III guidelines:

i) The LDL-C target level according to the 2004 updated NCEP ATP III guidelines was reached by 70.8 % of subjects in the general population.

ii) The subgroup of patients with metabolic syndrome according to Epidemiology Task Force Consensus Group demonstrated statistically significantly lower LDL-C target level achievement rate (68.2 %) in comparison with patients without metabolic syndrome according to the 2004 updated NCEP ATP III guidelines (75.1%) (p=0.024, HR = 0.710, 95% C.I 0.529 – 0.952).

iii) The subset of secondary CVD prevention patients demonstrated statistically significantly higher achievement rate of the LDL-C target level (75.0%), according to the 2004 updated NCEP ATP III guidelines in comparison with the subset of primary CVD prevention patients (65.2%) (p=0.003, HR = 1.602, 95% C.I 1.176 - 2.183).

4) Proportion of subjects receiving lipid-lowering pharmacological treatment reaching the LDL-C goals determined according to the 4JETF guidelines / NCEP ATP III / 2004 updated NCEP ATP III guidelines / Ru SCS guidelines in different subgroups (subject to demographics, CVD risk factors as well as lipid-lowering medication classes):

a) The LDL-C target level according to the Ru SCS guidelines (2007) in different subgroups of patients receiving lipid-lowering therapy (subject to demographics, CVD risk factors as well as lipid-lowering therapy types):

i) The achievement rate of the LDL-C target level according to the Ru SCS guidelines (2007) was statistically significantly higher in male subjects (39.0%), than in female ones (29.0%) (p=0.001, HR = 0.639, 95% CI 0.488 – 0.837). The proportion of subjects reaching the LDL-C target level according to the Ru SCS guidelines (2007) was approximately the same in different age subgroups (the difference between the groups is statistically not significant p=0.763).

ii) 35.5% of non-smokers and 28,1% of smokers (this difference is statistically not significant p=0.098; HR = 0.712; 95% CI 0.477–1.063); 34.2% of patients without diabetes mellitus and 35.2% of patients with diabetes mellitus (this difference is statistically not significant p=0.818; HR = 1.043; 95% CI 0.772–1.409); 34.8% of patients without arterial hypertension and 34.4 % of hypertensive patients (this difference is statistically not significant p=0.933; HR = 0.983; 95% CI 0.650–1.486); 35.4% of patients without family history of premature CVD and 31.2% of patients having family history of premature CVD (this difference is statistically not significant p=0.258; HR = 0.827; 95% CI 0.598–1.142) have reached the LDL-C target level according to the Ru SCS guidelines (2007).

iii) The LDL-C target level according to the Ru SCS guidelines (2007) have been reached in the patients receiving statin monotherapy (in 34.1 % of cases); statin + ezetimibe therapy (50%) and statin + fibrate therapy (100%). The differential analysis between the subgroups was not conducted in view of the study sample similarity according to applied lipid-lowering medication class (99.3% of patients on statins) and its subgroup size incomparability (98 % of patients received statin monotherapy and only 0.6 %

statins plus ezetimibe; 0.6% statins plus fibrates; 0.4 % fibrate monotherapy; 0.3% ezetimibe monotherapy, and 0.1% statin plus fibrate and ezetimibe).

b) The LDL-C target level according to the 4JETF guidelines in different subgroups (subject to demographics, CVD risk factors as well as lipid-lowering therapy types):

i) The difference in achievement rate of the LDL-C target level according to the 4JETF guidelines in male (50.7%) and female (45.2%) subjects was statistically not significant (p=0.102). The proportion of subjects reaching the LDL-C target level according to the 4JETF guidelines was approximately the same in different age subgroups (the difference between the groups was statistically not significant p=0.118).

ii) The LDL-C target level according to the 4JETF guidelines was statistically significantly achieved by non-smokers (49.7%) compared to smokers (39.3%) (p=0.026; HR = 0.654; 95% CI 0.451–0.949); the LDL-C target level according to the 4JETF guidelines was achieved by 47.9% of patients without diabetes mellitus and 49.0% of patients having diabetes mellitus (this difference is statistically not significant p=0.769; HR = 1.045; 95% CI 0.784–1.395); by 48.9% of patients without arterial hypertension and by 48.1% with arterial hypertension (this difference is statistically not significant p=0.914; HR = 0.968; 95% CI 0.632–1.482); 49.2% of patients without family history of premature CVD and 44.9 % of patients having family history of premature CVD (this difference is statistically not significant p=0.279; HR = 0.842; 95% CI 0.621–1.143).

iii) The LDL-C target level according to the 4JETF guidelines has been reached in the patients receiving statin monotherapy (in 48.0 % of cases); statin + ezetimibe therapy (66.7 %) and statin + fibrate therapy (100%). The differential analysis between the subgroups was not conducted in view of the study sample similarity according to applied lipid-lowering medication class (99, 3% of patients on statins) and its subgroup size incomparability (98 % of patients on statin monotherapy and only 0.6% statins plus ezetimibe; 0.6% statins plus fibrates 0.4%; fibrate monotherapy; 0.3% ezetimibe monotherapy, and 0.1% statin plus fibrate and ezetimibe).

c) The LDL-C target level according to the NCEP ATP III guidelines in different subgroups (subject to demographics, CVD risk factors as well as lipid-lowering therapy types):

i) The achievement rate of the LDL-C target level according to the NCEP ATP III guidelines was statistically higher in male (81.1%) than in female subjects (70.5%) (p<0.001; HR = 0.559; 95% CI 0.415–0.754). The proportion of subjects reaching the LDL-C target level according to the NCEP ATP III guidelines was approximately the same in different age subgroups (the difference between the groups is statistically not significant p=0.238).

ii) The LDL-C target level according to the NCEP ATP III guidelines was statistically significantly achieved by non-smokers (78.7%) in comparison with smokers (61.5%) (p<0.001; HR = 0.433; 95% CI 0.295 – 0.636); the rate of the LDL-C target level achievement according to the NCEP ATP III guidelines was statistically significant higher in patients without diabetes mellitus (78.9%) than in subjects without it (68.8%) (p=0.001; HR = 0.589; 95% CI 0.427 – 0.811); the LDL-C target level

according to the NCEP ATP III guidelines was reached by 80.4% of patients without arterial hypertension and by 75.7% of hypertensive patients (this difference is statistically not significant p=0.291; HR = 0.763; 95% CI 0.467 – 1.247); the LDL-C target level according to the NCEP ATP III guidelines was significantly more frequently reached by patients without family history of premature CVD (80.3%) than by patients having family history of premature CVD (62.4%) (p<0.001; HR = 0.407; 95% CI 0.293 – 0.565).

iii) The LDL-C target level according to the 4JETF guidelines have been reached in the patients receiving statin monotherapy (in 76.7 % of cases); statin + ezetimibe therapy (66.7 %) and statin + fibrate therapy (100%). The differential analysis between the subgroups was not conducted in view of the study sample similarity according to applied lipid-lowering medication class (99.3% of patients on statins) and its subgroup size incomparability (98 % of patients on statin monotherapy and only 0.6% on statins plus ezetimibe; 0.6% on statins plus fibrates; 0.4% on fibrate monotherapy, 0.3% on ezetimibe monotherapy, and 0.1% on statin plus fibrate and ezetimibe).

d) The LDL-C target level according to the 2004 updated NCEP ATP III guidelines in different subgroups (subject to demographics, CVD risk factors as well as lipid-lowering therapy types):

i) The LDL-C target level according to the 2004 updated NCEP ATP III guidelines was reached by 72.3% of male and 69.0% of female patients (the difference between the groups is statistically not significant p=0.257; HR = 0.848; 95% CI 0.643 – 1.119). The proportion of subjects reaching the LDL-C target level according to the NCEP ATP III guidelines was approximately the same in different age subgroups (the difference between the groups is statistically not significant p=0.442).

ii) The LDL-C target level according to the 2004 updated NCEP ATP III guidelines was significantly more frequently reached by non-smokers (75.3%) than by smokers (43.0%) (p<0.001; HR = 0.247; 95% CI 0.170 – 0.360); by patients without diabetes mellitus (75.3%) than by patients having diabetes mellitus (58, 1%) (p<0.001; HR = 0.455; 95% CI 0.337 – 0.616); by patients without arterial hypertension (75.5%) than patients with arterial hypertension (69.7%) (p=0.035; HR = 0.593; 95% CI 0.367 – 0.960); by patients without family history of premature CVD (80, 3%) than by patients having family history of premature CVD (53.2%) (p<0.001; HR = 0.361; 95% CI 0.264 – 0.494).

iii) The LDL-C target level according to the 2004 updated NCEP ATP III guidelines have been reached in the patients receiving statin monotherapy (in 71, 1 % of cases); statin + ezetimibe therapy (66.7 %) and statin + fibrate therapy (100%). The differential analysis between the subgroups was not conducted in view of the study sample similarity according to applied lipid-lowering medication class (99.3% of patients on statins) and its subgroup size incomparability (98 % of patients on statin monotherapy and only 0.6%on statins plus ezetimibe; 0.6% on statins plus fibrates; 0.4% on fibrate monotherapy, 0.3% on ezetimibe monotherapy, and 0.1% on statin plus fibrate and ezetimibe).

5) Number of subjects reaching the Non- HDL-C target level according to the NCEP ATP III / 2004 updated NCEP ATP III guidelines (<130 mg/dL) (3.36 mmol/L) in the subset of patients with fasting triglyceride level > 2.26 mmol/L was 18 subjects (12.3%).

6) Determinants (for instance, patient and physician determinants, national guidelines), stipulating insufficient hypercholesterolemia treatment were calculated by the method of multivariate logistic regression model building.

a) Patient determinants. The level of received data (filled out questionnaires, PRF) allowed inclusion of 724 patients in this model. The following statistically significant predictors of the LDL-C target level achievement were defined:

i) Smoking habits and patient non-compliance with the hypercholesterolemia treatment (no daily intake of medication) served as negative predictors of the LDL-C target level achievement, determined according to the Ru SCS guidelines.

ii) Patient non-compliance with the hypercholesterolemia treatment (no daily intake of medication), forgetting to take drugs, the answer to the question about general impression of the received therapy corresponding to «confused» were defined as negative predictors of the LDL-C target level achievement, determined according to the 4JETF guidelines.

iii) Current smoking habits, presence of diabetes mellitus, family history of premature CVD, admitted missing some tablets more than once a week (in comparison with admitted missing some tablets «once a month or less»), forgetting to take drugs, the answer to the question about general impression of the received therapy corresponding to «concerned» or «no strong feelings» served as negative predictors of the LDL-C target level achievement determined according to the NCEP ATP III guidelines.

iv) Current smoking habits, presence of diabetes mellitus, family history of premature CVD, patient non-compliance with the hypercholesterolemia treatment (no daily intake of medication), forgetting to take drugs turned out to be negative predictors of the LDL-C target level achievement determined according to the 2004 updated NCEP ATP III guidelines.

b) Physician determinants. The level of received data (filled out questionnaires, PRF) allowed inclusion of 748 patients in this model. The following statistically significant predictors of the LDL-C target level achievement were detected:

i) Physician specialization «endocrinologist», utilization of SCORE (positive predictors) served as predictors of the LDL-C target level achievement, determined according to the Ru SCS guidelines (2007).

ii) Physician's utilization of the Joint European guidelines SCORE (positive predictor), NCEP ATP III guidelines FRAMINGHAM (negative predictor) served as predictors of the LDL-C target level achievement, determined according to the 4JETF guidelines.

iii) Physician's age, usage of the triglyceride level by the setting of individual cholesterol goals, utilization of the Joint European guidelines SCORE, usage of the triglyceride level for informing the patients (positive predictors), specialization «internal medicine» (negative predictor) served as predictors of the LDL-C target level achievement, determined according to the NCEP ATP III guidelines.

iv) Physician's utilization of the Joint European guidelines SCORE, usage of the triglyceride level for informing the patients (positive predictors), specialization «internal medicine» (negative predictor) were defined as predictors of the LDL-C target level achievement, determined according to the 2004 updated NCEP ATP III guidelines.

7) Physician determinants subject to selected treatment regimen (statins / other medication): the analysis was not carried out in view of the study sample similarity according to applied lipid-lowering medication class (99, 3% of patients took statins) and its subgroup size incomparability (98 % of patients received statin monotherapy and only 0.6%on statins plus ezetimibe; 0.6% on statins plus fibrates; 0.4% on fibrate monotherapy; 0.3% on ezetimibe monotherapy, and 0.1% on statin plus fibrate and ezetimibe).