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Assessment of lipid-lowering treatment in Bulgaria - The CEPHEUS study

Research Article

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Abstract: This is a multicenter cross-sectional survey of 2,500 Bulgarian adult patients taking lipid-lowering drugs (LLDs) for at least 3 months with no dose change for a minimum of 6 weeks. The primary objective was to establish the proportion of patients who are on LDL-C target, according to the Fourth Joint European Task Force (FJETF) guidelines. The secondary objectives were to define the proportion of patients at target: according to the 2001 National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III and the 2004 NCEP ATP III guidelines. The patients' demographics, current LLD treatment, cardiovascular medical history were recorded. Next the lipid profile, glucose level and HbA1c were obtained from these patients. The investigators and patients completed questionnaires related to the LLD therapy. Gender, BMI, history of CHD, therapy compliance, risk category, lack of patient's awareness of LDL-C targets were all studied as determinants of the undertreatment. Despite the satisfactory awareness of guidelines for management of hypercholesterolaemia, their implementation in clinical practice is still poor. Only 43.10% of patients reached the FJETF-recommended LDL-C goal, 45.24% achieved the 2001 NCEP ATP III recommended LDL-C goal, and only 21.51% - reached the 2004 NCEP ATP III recommended target. Males, CHD patients and those who were aware of LDL-C targets had more chance of reaching their desired LDL-C target.

Keywords: *Hypercholesterolaemia • LDL-goal • Pharmacoepidemiology • Lipid-lowering drugs • Guidelines • Dyslipidaemia management • Bulgaria*

1. Introduction

Cardiovascular diseases (CVDs) and particularly coronary heart diseases (CHD) are still recognised as the number one cause of death in Europe. CVDs are responsible for 55% of mortality in females and for 43% in males [1]. Significant differences exist between the European countries, especially between the Eastern and Western countries [2]. The Interheart case-control study [3] and other epidemiological surveys have identified many risk factors that contribute to CVD, which include elevated levels of low-density lipoprotein cho-

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lesterol (LDL-C), smoking, hypertension, diabetes mellitus, abdominal obesity and stressful psychosocial factors [3-5]. These risk factors have been found to contribute for 94% of all myocardial infarctions (MIs) in women and 90% of all MIs in men. Treatment of hypercholesterolaemia has shown clear benefits in the primary and secondary prevention of CHD. Lowering both total cholesterol (TC) levels and LDL-C levels correlates strongly with the decrease of CHD risk [6]. However, cross-sectional surveys conducted in patients with CHD have demonstrated that hypercholesterolaemia still remains inadequately treated [7-13]. EUROASPIRE III study has determined that a high proportion of patients were not achieving therapeutic targets for CVD protection. Wide variations were also seen to exist concerning the risk factor prevalence and the use of cardioprotective drug therapies between countries [9,10]. There is very little data concerning management of hypercholesterolemia amongst patients in Bulgaria. EUROASPIRE III included 537 Bulgarian patients with CHD of whom 36.3% had their LDL-C at target; only 333 (62.5%) of these high risk patients were receiving lipid lowering drugs (LLDs). The survey also included asymptomatic high risk patients treated in general practice where the therapeutic control of total cholesterol observed in non-diabetic patients was 27.4 % and 21.3% in the diabetic population [9,10]. This current paper reports the results of the Centralized pan-Bulgarian Survey on the undertreatment of hypercholesterolaemia (CEPHEUS) study (Study Code: NIS-CBG-CRE-2009/01), which is a multi-centre and non-interventional cross-sectional survey of patients receiving lipid-lowering drug treatment in Bulgaria. This survey provides unique local dataset on management of hypercholesterolaemia and goes one step further in an attempt to analyse and identify determinants for the undertreatment of hypercholesterolaemia in Bulgaria.

2. Objective

The primary objective of this study was to establish the proportion of patients in Bulgaria on LLDs reaching the LDL-C goals according to the guidelines of the Fourth Joint European Task Force (FJETF) [14]. As part of the secondary objectives of current publication, were:

(a) To establish the proportion of patients on LLDs reaching LDL-C goals according to existing guidelines, including the FJETF, the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III [15], and the 2004 updated NCEP ATP III [16], in the survey population and subpopulations of primary and secondary prevention;

(b) To identify determinants (e.g. patient and physician characteristics) for the undertreatment of hypercholesterolaemia. Undertreatment is defined as receiving LLD, but not reaching the LDL-C goals according to the guidelines of FJETF, NCEP ATP III, or the updated 2004 NCEP ATP III according to the respective risk category.

3. Materials and methods

3.1 Patients

A total of 2500 patients gave their written consent and were enrolled in 23 study centres in Bulgaria between 4 February and 27 August 2010. The patient population enrolled in this study were adults taking LLDs for at least three months, with no dose change for a minimum of six weeks. Data collection took place at the single study visit after informed consent was collected from the patients.

3.2 Statistical methods and experimental procedures

3.2.1 Investigator questionnaire and patient record form

Prior to enrolment of participants in the study, all investigators were asked to complete a questionnaire of their prior experience and perception of the management of hypercholesterolemia. Each investigator was then asked to indicate his/her attitude in diagnosing hypercholesterolemia, adoption and perception of existing guidelines and treatment goals as well as knowledge of the available treatment options. The patient's demographics, current LLD treatment and history of coronary heart diseases (CHDs), presence of CVD risk factors, hypercholesterolaemia and current management were recorded in the patient record form (PRF) by the investigator.

3.2.2 Patient Questionnaire

The patients were also asked to complete a questionnaire at this visit, reflecting the patient's awareness of hypercholesterolaemia; first diagnosis and treatment goals; their current treatment and perception about it, attitudinal statements; satisfaction with the treatment of prescribed ; compliance with the prescribed treatment and the number of visits to the doctor.

Both Investigators' and patients' questionnaires were specifically developed for CEPHEUS study.

3.3 Blood tests

Each patient provided a fasting blood sample (total: 9 mL) for evaluation of lipid profile (TC, HDL-C, LDL-C, TG), glucose and HbA1c levels Blood samples were collected within seven days after the single survey visit and analysed at the Central Laboratory in Bulgaria. Within

two days of the sample collection and analysis, the investigator was able to access the results on the laboratory's website. Assessment was performed conferring to the levels stated by the European guidelines, thus allowing determination of patient's risk profile and taking the appropriate measures with respect to the future treatment of patients.

3.4 Risk categories

According to the FJETF guidelines patients in *high (1)* risk category are characterized by atherosclerosis, or Type 2 diabetes, or TC ≥8 mmol/L, or LDL-C ≥6 mmol/L, or mean systolic blood pressure (SBP) ≥180 mmHg, or diastolic blood pressure (DBP) ≥110 mmHg. *High (2)* risk category includes patients with 10-year risk of developing fatal CVDs ≥5%, and TC <5 mmol/L and LDL-C <3 mmol/L. *High (3)* risk category is determined by 10-year risk of fatal CVD ≥5%, and TC ≥5 mmol/L or LDL-C ≥3 mmol/L. Within the *Other* risk category fall patients with 10-year risk of fatal CV disease <5% [14].

NCEP ATP III and 2004 Updated NCEP ATP III guidelines set different risk categories that were accordingly utilized in the current study [15,16].

3.4 Data analysis

Analyses of the primary and secondary endpoints were performed using models for estimation of the proportions of patients on lipid-lowering pharmacological 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 patients had achieved the LDL-C target levels corresponding to each risk category. Additionally, a dichotomous variable was computed indicating whether the patient had achieved the non HDL-C target levels corresponding to the NCEP ATP III and 2004 updated NCEP ATP III risk categories.

Furthermore, a two-level logistic regression analysis was performed to determine the prognostic factors of achieving the LDL-C target levels, according to each of the lipid-lowering guidelines, with patients at the first-level of management and at the second-level the investigators. Prognostic factors were identified among several variables independent of patients and physicians. Firstly, a crude association of each of the potential predictors was investigated with the outcome (i.e. achievement of LDL-C goals according to the corresponding lipid-lowering guidelines). This was done by a 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 the 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. Firstly, a full model was run with all independent variables with a p-value < 0.10 selected based on the univariate analysis as fixed effects and with investigator as the random effect. At each step, the least significant independent variable was removed until all parameters have reached a level of significance of at least 0.05.

Logistic regression models were fitted by means of generalised 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 low number of answers was observed (frequency of answers per category < 5%), categories were pooled together with the closest relevant category, where applicable, or the predictor was removed from the analysis.

Summary statistics (e.g., number and percentage) were produced for the primary and secondary endpoints for several subgroups defined according to the 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.

The main data analysis on the primary and secondary variables was performed on the full analysis set (FAS) population and baseline assessments, analysis of subject and the investigator questionnaires were based on the total non-missing data. As this was a non-interventional study, the safety analyses have not been performed.

4. Results

4.1 Baseline characteristics

4.1.1 Patients

A total of 2500 patients gave their consent to participate in this study. The FAS included 2427 patients for whom the PRF and laboratory data were available. The mean age of patients was 60.82 +10.83 (+SD) (see Table 1). All patients were Caucasian of whom 1329 (53.16%) male and 1171 (46.84%) female. The patients had a mean body weight of 82.81 +15.24kg, a mean waist circum-

ference of 97.72 +13.17 cm. The mean Body Mass Index (BMI) was 28.95 +4.44 kg/m^2. Mean systolic blood pressure (SBP) was 135.35 +16.17 mmHg and the mean diastolic blood pressure (DBP) was 83.29 +9.41 mmHg. The cardiovascular risk category of patients was calculated according to the different guidelines and presented in Figure 1. According to the FJETF, about 49.36% of the patients participating in this survey were classified as being at high risk, 75.73% of them were reclassified to be at high risk according to the NCEP-ATP III whereas 64.81% were found to be at very high risk using the 2004 NCEP ATP III classification.

Most of the patients - 2079, had been receiving LLDs for 3.09 + 3.06 years. The most frequent reasons for this therapy were primary prevention in 1190 (47.6%) patients and secondary prevention in 1264 (50.56%) patients; familial hypercholesterolaemia was diagnosed in only 46 (1.86%) patients and was a relatively rare cause to start LLD therapy for the prevention of CHD. The majority of the surveyed patients, 2404 (96.16%) patients, were receiving LLD monotherapy (see Table 1) with 2344 (97.5%) undergoing treatement with statins and only 60 (2.5%) patients undergoing fibrate therapy.

Eight hundred fifty-two (35.44%) patients received simvastatin, which was the most frequently used statin as monotherapy; followed by atorvastatin in 732 (30.45%) patients and rosuvastatin in 567 (23.59%) patients. The most frequently used fibrate was fenofibrate in 56 (2.33%) patients.

Ninety-four (3.76%) patients were treated with LLD combinations including statin as a baseline therapy and fibrates in 92 (97.87%) patients.

The results of the Patient Questionnaire indicated that 2158 (86.84%) patients had been informed about their cholesterol levels and 1888 (88.1%) of these had been informed of a target cholesterol levels. Upon first diagnoses with a high cholesterol 379 (15.41%) patients said that they were only advised to change their lifestyle, 1822 (74.07%) were advised to change their lifestyle and were prescribed a drug, 229 (9.31%) answered that they were only prescribed a drug, but 30 (1.22%) have not been prescribed a drug nor were advised of a lifestyle change. Since the time when they were prescribed a cholesterol-lowering drug, most patients - 1346 (54.01%) were still taking same drug at the same dose and only 186 (7.46%) were advised to increase the drug dose

Table 1. Patient demographics, baseline characteristics and lipid-lowering treatments.

	Survey Cohort N=2500	Values
Male	1329	53.16%
Female	1171	46.84%
Age (mean±SD) years	2500	60.82 ± 10.83
SBP (mmHg)	2500	135.35 ± 16.17
DBP (mmHg)	2500	83.29 ± 9.41
Body weight (kg)	2500	82.81 ± 15.24
Waist circumference (cm)	2500	97.72 ± 13.17
BMI	2500	28.95 ± 4.44
History of CHD	1537	61.48%
History of PAD	169	6.76%
History of CAD	323	12.92%
Current Smoker	540	21.60%
Diabetes	666	26.64
Arterial hypertension	2325	93.00%
Family history of premature CVD	814	32.56%
Single LLD	2404	96.16%
Statins	2344	97.50%
Fibrates	60	2.50%
Bile Acid Sequestrants	0	0.00%
Multiple LLD	94	3.76%

BMI=Body Mass Index; CAD=Cerebrovascular Atherosclerotic Disease; CHD=Coronary Heart Disease; PAD=Peripheral Artery Disease; CVD=Cardiovascular Disease; DBP=Diastolic Blood Pressure; LLD=Lipid-Lowering Therapy; SBP=Systolic Blood Pressure; SD=Standard Deviation

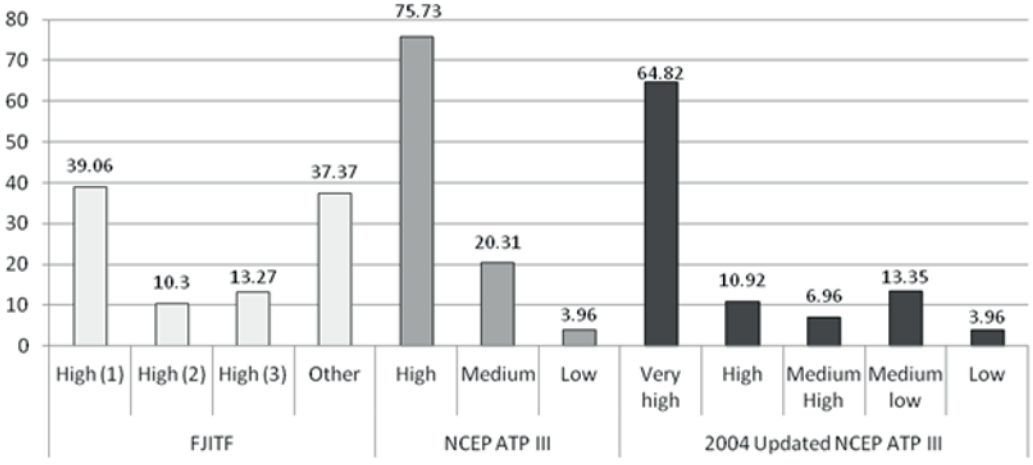


Figure 1. Risk categories of patients according to the different guidelines used.

had they not reached the target lipid level. Of treated patients 758 (30.42%) had their cholesterol-lowering drug changed once or twice in the meantime and 202 (8.11%) several times.

When patients were asked about the number of visits to the physician for a cholesterol check-up, 147 (5.91%) of them indicated to have more than one check-up every three months, 1171 (47.07%) had one check-up every six months, 428 (17.2%) had one check-up every year and 51 patients had their lipid profile checked less than once a year.

Relating to how often patients forgot to take their treatment, 294 (40.05%) have replied that this happened not more than once a month; 155 (21.12%) patients reported that they forgot to take their treatment once in every two weeks; while for 341 (14.44%) patients this happened once a week and for 108 (4.57%) patients, more than once a week. Most of patients, 1671 (84.48%) of them were motivated to continue taking their cholesterol-lowering therapy and 1654 (79.37%) were satisfied with the way their cholesterol levels have been managed.

4.1.2 Investigators

All participating physicians, 243 (100%) have completed the Investigator Questionnaire. The mean age of these investigators was 50.89±6.84 years, majority being females 142 (58.44%) of whom 227 (94.98%) were cardiologists, in practice for a mean of 24.74±7.96 years (range: 2.00–25.00).

According to investigators 81.10% of them have set individual target cholesterol levels for their patients and 233 (96.28%) did so with reference to lipid-lowering guidelines. One hundred and sixteen (47.7%) investigators have used a single guideline to establish individual cholesterol levels, and the most used one being the Joint European guidelines. In case that the investigators reported that they have used more than one guideline, Joint European guidelines was preferred by 211 (90.95%) investigators, followed by the NCEP ATP III guidelines, applied by 116 (50.00%) investigators. One hundred and forty (57.61%) investigators have indicated that they scheduled a patient visit for check-up of cholesterol levels once every six months, 74 (30.45%) investigators scheduled such visit once every three months, and 25 (10.29%) - once every year.

4.2 Lipid values and guidelines target attainment

4.2.1 Laboratory findings

Total levels at pre-treatment for TC and LDL-C respectively were: 6.78±1.51 mmol/L (n=1667; range: 0.92–17) and 3.94±1.18 mmol/L (n=552; range: 1.00–8.30). Table 2 presents the lipid profile at the time of survey.

Table 2. Lipid and glycemic profile at the time of the survey: Laboratory results.

Parameters	N	Missing	Mean ±SD	Minimum	Median	Maximum
Full Analysis Set	2427					
Total Cholesterol (mmol/L)	2427	73	5.30 ±1.17	3.03	5.10	11.56
HDL-C (mmol/L)	2427	73	1.26 ±0.09	0.96	1.26	1.55
LDL-C (mmol/L)	2427	73	3.05 ±1.03	0.57	2.90	7.55
Triglycerides (mmol/L)	2427	73	1.98 ±1.32	0.48	1.67	16.05
Glucose (mmol/L)	2427	73	5.91 ±2.51	3.35	5.16	28.74
HbA1c (%)	2422	78	6.00 ±1.25	3.70	5.70	15.60

4.2.2 Target attainment according to the FJETF guidelines

Overall, 1046 (43.1%) patients were at the target LDL-C goals as recommended by the FJETF guidelines (95% CI [41.13–45.07%]). Proportions of patients reaching the LDL-goal by risk category according to the different guidelines are presented in Figure 2.

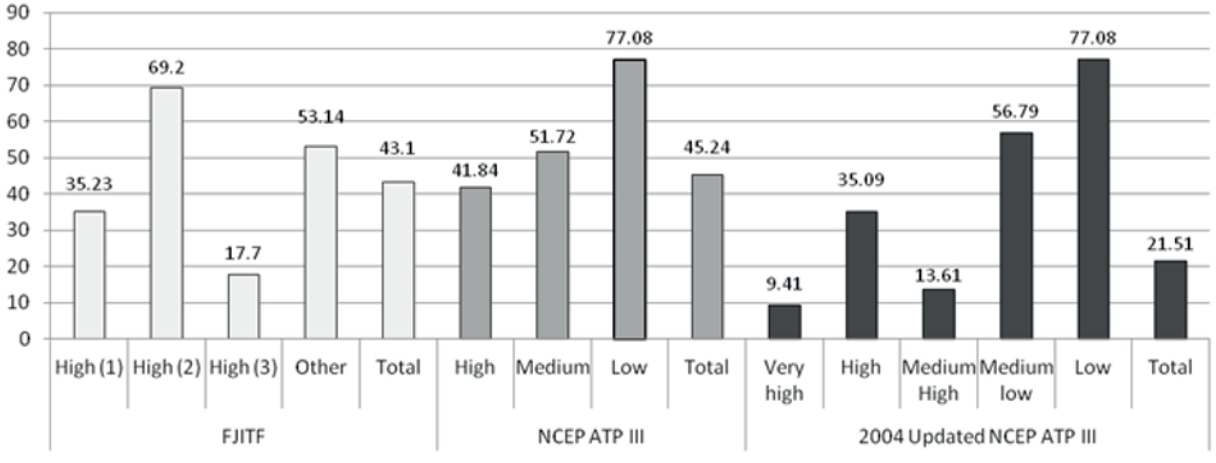


Figure 2. Percentage of patients who reached the recommended LDL-C target, according to the cardiovascular disease risk category of the used guideline.

Table 3 presents the data when patients were stratified according to their age and other characteristics. A similar percentage of patients reaching the FJETF LDL-C goals was observed across all age categories, ranging from 40.95% (n=224) for patients 40–54 years old to 43.96% (n=40) for patients at less than 40 years of age. This was also the case for patients who were overweight and obese. However significant differences were observed between male - 47.87% (n=619) and female - 37.65% (n=427) patients and also a lower percentage of achievement was observed in patients with normal weight - 27.87% (n=167).

When stratified according to their CVD risk category, the percentage of patients at goal was 35.23% (n=334) among patients in the *high (1)* risk category, 69.2% (n=173) among patients in the *high (2)* category, 17.7% (n=57) in the *high (3)* and 53.14% (n=482) in the *other* risk category.

4.2.3 Target attainment according to the NCEP ATPIII guidelines

Overall, 45.24% of patients were at the target LDL-C goals as recommended by the NCEP ATP III guidelines. The mean percentage of patients at goal ranged from 43.1% (n=225) for patients over 70 years old to 57.14% (n=52) for patients under 40 years of age. As shown in Table 3, the percentage of patients reaching the NCEP ATP III goals was lower for female, 39.95% (n=453) than for male patients, 49.88% (n=645) but differences were not seen across the age categories. The percentage of patients reaching the LDL-C goals was higher among patients falling into the low risk category 77.08% (n=74), compared with those in the *medium* risk category, 51.72% (n=255) or *high* risk category, 41.84% (n=769)..

The percentage of patients reaching the NCEP ATP III goals among patients with metabolic syndrome was 43.87% (n=505) while the percentage of patients at

Table 3. Patients attaining to the LDL-C goals based on the FJETF, the NCEP ATP III, and the 2004 updated NCEP ATP III guidelines according to their characteristics.

Characteristic		FJETF Patients on target N(%)	NCEP ATP III Patients on target N(%)	2004 Updated NCEP ATP III Patients on target N(%)
Overall survey		1046 (43.1%)	1098 (45.24%)	522 (21.51%)
Age	<40	40 (43.96%)	52 (57.14%)	45 (49.45%)
	40-54	224 (40.95%)	255 (46.62%)	165 (30.16%)
	55-69	563 (44.44%)	566 (44.67%)	236 (18.63%)
	>=70	219 (41.95%)	225 (43.10%)	76 (14.56%)
Gender	Female	427 (37.65%)	453 (39.95%)	254 (22.40%)
	Male	619 (47.87%)	645 (49.88%)	268 (20.73%)
BMI	Normal weight (<25)	167 (37.87%)	184 (41.72%)	100 (22.68%)
	Overweight (25-29)	480 (43.6%)	502 (45.59%)	223 (20.25%)
	Obese (>=30)	399 (45.08%)	412 (46.55%)	199 (22.49%)
CHD	No	306 (33.12%)	433 (46.86%)	352 (38.10%)
	Yes	740 (49.23%)	665 (44.24%)	170 (11.31%)
PAD	No	978 (43.24%)	1024 (45.27%)	503 (22.24%)
	Yes	68 (41.21%)	74 (44.85%)	19 (11.52%)
CAD	No	948 (44.82%)	988 (46.71%)	497 (23.50%)
	Yes	98 (31.41%)	110 (35.26%)	25 (8.01%)
Current smoker	No	865 (45.31%)	895 (46.88%)	418 (21.90%)
	Yes	181 (34.94%)	203 (39.19%)	104 (20.08%)
Diabetes Type II	No	782 (43.83%)	808 (45.29%)	401 (22.48%)
	Yes	264 (41.06%)	290 (45.10%)	121 (18.82%)
Hypertension	No	71 (41.76%)	88 (51.76%)	73 (42.94%)
	Yes	975 (43.2%)	1010 (44.75%)	449 (19.89%)
Family history of premature CVD	No	726 (44.27%)	777 (47.38%)	381 (23.23%)
	Yes	320 (40.66%)	321 (40.79%)	141 (17.92%)
Type of prevention (a)	Primary prevention	400 (34.90%)	499 (43.54%)	346 (30.19%)
	Secondary prevention	631 (51.01%)	581 (46.97%)	165 (13.34%)
	Familial hypercholesterolaemia	15 (34.09%)	18 (40.91%)	11 (25.00%)
Metabolic syndrome	No	544 (42.63%)	593 (46.47%)	281 (22.02%)
	Yes	502 (43.61%)	505 (43.87%)	241 (20.94%)

CAD=Cerebrovascular Atherosclerotic Disease; CHD=Coronary Heart Disease; PAD=Peripheral Artery Disease; CVD=Cardiovascular Disease

goal among patients without metabolic syndrome was 46.47% (n=593). The percentage of patients reaching LDL-C recommended levels was similar between the primary prevention population, 43.54% (n=499), and the secondary prevention population, 46.97% (n=581) as well as for patients with familial hypercholesterolaemia, 40.91% (n=18).

4.2.4 Target attainment according to the 2004 updated NCEP ATPIII guidelines

The percentage of patients reaching the LDL-C goals according to the 2004 updated NCEP ATP III guidelines was 21.51% (n=522) (Table 3). When patients were stratified according to their age, the percentage of achievers ranged from 14.56% (n=76) for patients of over 70 years of age to 49.45% (n=45) for patients under 40 years of age.

The percentage of female patients reaching the LDL-C goal levels was 22.4% (n=254) versus 20.73% (n=268) in male patients. When stratified according to their CVD risk, the percentage of patients reaching the LDL-C goals was 77.08% (n=74) among patients falling into the low risk category and 56.79% (n=184) among patients in the medium *low* risk category. Among patients in the *medium high* risk category 13.61% (n=23) reached the LDL-C goals, followed by 35.09% (n=93) of patients in the *high but not very high* risk category and 9.41% (n=148) of patients in the *very high* risk category. Among patients with metabolic syndrome those who reached the 2004 updated NCEP ATP III goals were 20.94% (n=241) and 22.02% (n=281) were among patients without metabolic syndrome (as defined by the NCEP ATP III). The percentage of patients reaching the LDL-C recommended level was 30.19% (n=346) for primary prevention patients, 13.34% (n=165) for secondary prevention patients and only 11 patients with familial hypercholesterolaemia have attained the defined lipid target.

4.2.5 Determinants for attainment of the FJETF and NCEP guidelines targets

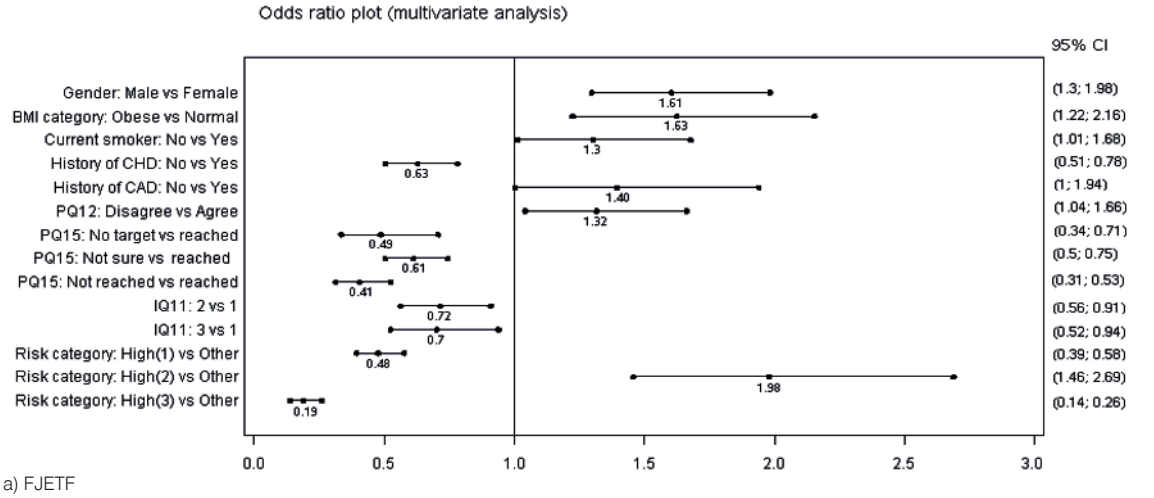
Among all the physicians' and patients' factors assessed in this study, there were some that proved to be significant ($p<0.10$) univariate predictors of whether patients reached the LDL-C goals according to the FJETF, the NCEP ATP III and the updated NCEP ATP III. When these were included in an adjusted multi-level logistic regression model, the number of significant predictors ($p<0.05$) were reduced to those presented in Figure 3. For example, being less than 40 years old was associated with a higher chance to be at goal in accordance with 2001 NCEP and 2004 updated NCEP guidelines, while the age did not affect reaching the FJETF target levels.

Male sex, obesity or nosmoking status was associated with a higher chance to meet the FJETF and 2001 NCEP recommended goals. The type of the atherosclerotic involvement also influenced the achievement of the LDL-cholesterol target values. We found that significantly lower proportion of patients with cerebrovascular diseases had the LDL-cholesterol values in accordance with FJETF. To the opposite, not having a history of CHD was associated with a decreased likelihood of being at goal according to the FJETF and the 2004 updated NCEP ATP III guidelines, but this did not influence the probability to reach the 2001 NCEP ATP III target LDL-C levels. History of peripheral artery disease (PAD) did not influence the attainment/non-attainment of LDL-cholesterol target in accordance with all guidelines The risk category influenced the probability of reaching the LDL-C target levels of all three guidelines while the higher risk category was associated with a lesser chance to be at goal. The physician determinants (including years of practice, age, and use of guidelines) were not found to be significant predictors. The history of CHD was an important determinant of whether patients were allocated to statins; while patients with a history of CHD had an increased chance to receive treatment with statins by 1.83-fold (95%CI: [1.04–3.21]).The insufficient information provided to patients concerning their target lipid levels and their achievement in the course of treatment are considered important factors for the lack of therapeutic control observed with both the FJETF and NCEP ATPIII guidelines. Patients with high adherence to the treatment were more likely to reach the LDL-C target levels set by all three guidelines.

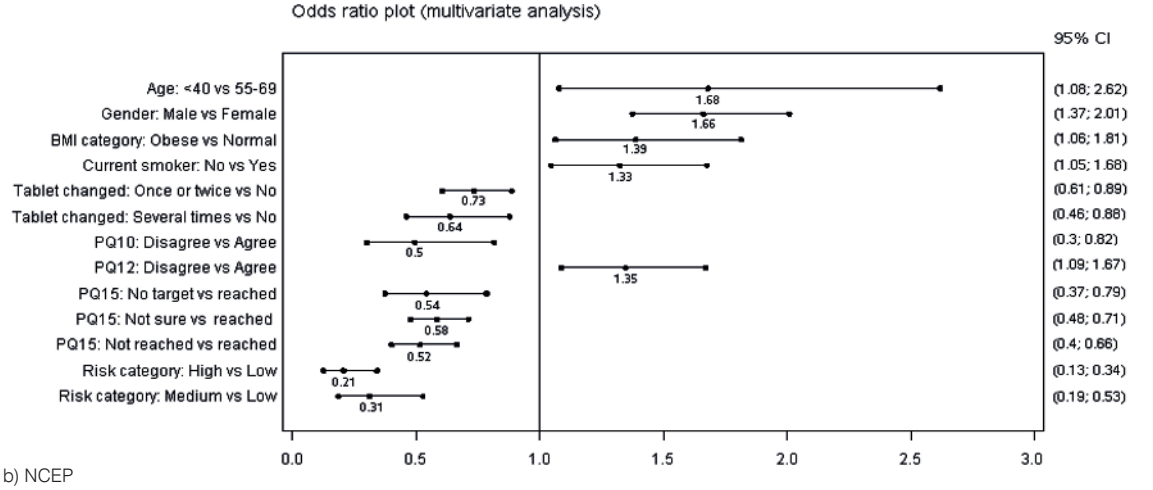
5. Discussion

The results of this survey highlight the real life practice of management of hypercholesterolaemia in Bulgarian patients receiving LLD. Although the majority of physicians stated that they have set individual target cholesterol levels with reference to European or NCEP ATP III guidelines, only 43.10% of the patients have reached the FJETF-recommended LDL-C levels and only 45.24% of patients have achieved the LDL-C levels recommended by the 2001 NCEP ATP III guidelines. Out of all patients only 21.51% reached the target recommended by the 2004 NCEP ATP III guidelines. This significant gap between existing guidelines and the clinical practice raises some serious concerns.

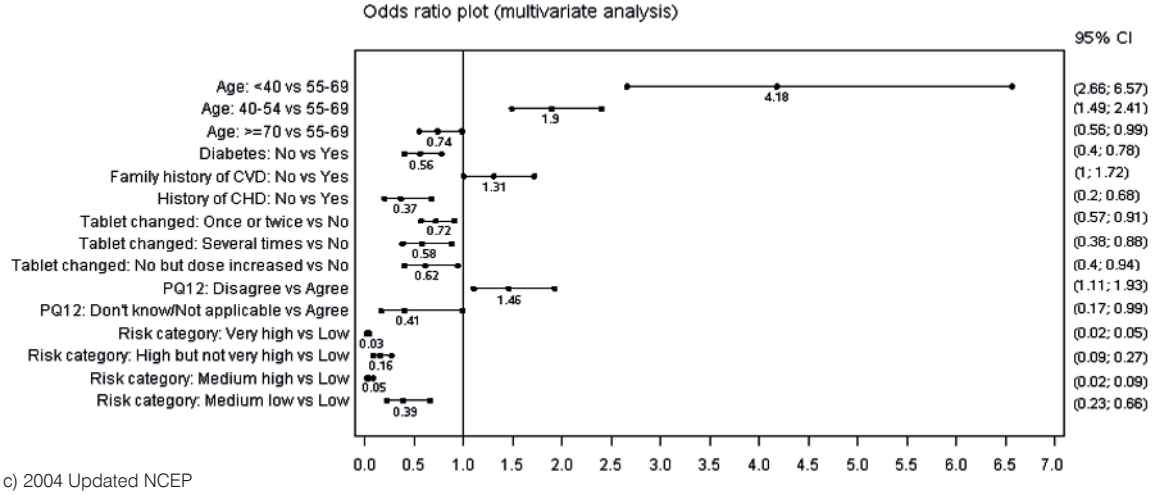
These results also confirm that Bulgaria is behind other European countries in adopting and implementing the pre-set guidelines, and this fact has already been highlighted in the EUROASPIRE III [9].



a) FJETF



b) NCEP



c) 2004 Updated NCEP

Figure 3. Significant multivariate predictors of reaching the recommended LDL-C target levels of the used guidelines.
CAD=Cerebrovascular Atherosclerotic Disease; CHD=Coronary Heart Disease; CVD=Cardiovascular Disease; PQ=Question in the Patient Questionnaire; IQ=Question in the Investigator Questionnaire
PQ10 Therapy compliance (Patient always takes daily tablet to lower cholesterol)
PQ12 Therapy compliance (Patient sometimes forgets to take tablets)
PQ15 Patient's awareness of current LDL-C levels
IQ11 Physician finds it stressful trying to get his patients to their cholesterol targets: 1 = "Disagree strongly"; 2 = "Disagree"; 3 = "Neutral opinion"; 4 = "Agree"; 5 = "Agree strongly"

In EUROASPIRE III, the primary prevention population in Bulgaria ranks ninth amongst twelve participating countries based on levels of total cholesterol at goal in the non-diabetic population, and ranks seventh based on TC levels in the diabetes population. In the secondary prevention population of EUROASPIRE III, the mean LDL-C in Bulgarian patients was 3.2 mmol/L and was the second highest after the LDL-C level of Polish patients. A TC level >4.5 mmol/L was established in 63.7% in this high risk population in comparison to the average of 51.1% for the 22 participating countries. The current study suggests that despite the fact that the patients were on stable LLD treatment, the average levels of TC and LDL-C were 5.3±1.17 mmol/L and 3.05±1.03 mmol/L respectively. Together with the high incidence of other concomitant risk factors such as hypertension (92%), obesity (29%), diabetes (26.6%) and smoking (21.6%), the data of CEPHEUS Bulgaria highlight an alarming risk and worrying characteristics of the Bulgarian population.

Our results suggest that, despite awareness of evidence-based guidelines, there are still barriers for their implementation in clinical practice. The percentage of Bulgarian patients reaching their target LDL-C level is lower than that reported in CEPHEUS Belgium (58.5%), lower than the average for the eight European countries (55.3%) and lower than recently reported Greek CEPHEUS trial (49.7%) [17-19]. A similar percentage of patients at goal in the primary and secondary prevention sub-groups was observed according to the 2001 NCEP (43.54% for primary prevention versus 46.97% for secondary prevention). However, a lower percentage of patients on primary prevention met the LDL-C goal according to the FJETF (34.90% for primary prevention versus 51.01% for secondary prevention) and a higher percentage of patients on primary prevention met the LDL-C goal according to the 2004 NCEP (30.19% for primary prevention versus 13.34% for secondary prevention) guidelines. The lowest percentage of patients at goal according to the 2004 NCEP guidelines is probably due to these patients being allocated to the highest risk categories where the recommended LDL-C target value is lower.

When comparing these data we should consider the fact that the investigators participating in the Bulgarian study were cardiologists, who were expected to provide better specialist care for their patients, while CEPHEUS investigators in Greece were both general practitioners & cardiologists and the majority of the European investigators were general practitioners [18,19]. The most serious concern raises the fact that the worst therapeutic control was established in the patients with history of atherothrombotic incident and in the high risk primary prevention patients. One of the possible explanations for that result is an incorrect set of the target LDL-cholesterol levels according with the individual patient risk. The percentage of patients at goal in the sub-populations of primary and secondary prevention differed between the guidelines suggested by the FJETF, the 2001 NCEP and the 2004 NCEP. Although patients in this real clinical practice survey have been on LLDs for at least three months prior to the survey, the percentage of patients meeting their lipid goal levels still remains low. Different factors such as lack of information for patients or the use of inadequate doses of LLDs or use of less effective drugs have been suggested to have an important impact on the management of hypercholesterolaemia. It is worth noting that insufficient information provided to patient regarding their target LDL-cholesterol levels in the course of treatment is an important reason for failure to achieve desired therapeutic control. Other important prognostic factors are young age, female sex, normal body weight and smoking status. It appears that some demographic characteristics of overweight may influence the risk profile in defining the target LDL-cholesterol levels and hence the choice of the type of LLD and its dosage.

Physicians were aware of the number of patients with hypercholesterolaemia attaining the target cholesterol levels, yet they have estimated that only 49.91% ofpatients reach LDL-C goals and stayed within the target values. Although aware of the inadequate goal rate, only 6.28% of the physicians thought that total number of patients at goal was low. Conversely, 66.53% of the physicians agreed that the number of patients meeting their LDL-C target was sufficient. Although the majority of the participating physicians were clearly aware of the poor goal rate, nevertheless they reported to review patients' cholesterol only once every six months (57.61%) or once every three months (30.45%). In total 10.29% of participating physicians have reviewed their patients' cholesterol only once every year. These frequencies were similar to those reported by the patients; 47.07% of the patients had a visit once every six months and 32.0% of the patients had a visit at least every three months. These results show that the management of hypercholesterolaemia is a multi-factorial problem and that the physician's attitude and beliefs seem to play a key role.

Since the time the patients have been prescribed LLD, most of them were still taking the same drug at the same dose (54.01%) or with an increasing dose (only 7.46%) while 38.53% patients had their initially prescribed treatment changed once or more. This therapeutic inertness may have different explanations related to professional attitudes, patient preferences or health economy of the country. Institutional aspects should not

be underestimated in the prescription of LLDs as they have relatively limited coverage by the public funds, and mainly for patients who have already suffered cardiovascular event. Thus in the decision making process the cost of LLD sets an important aspect to consider when patients participate with payment towards treatment. Any increase of the dose of LLD or change of it to a more powerful LLD is therefore expected to further increase patient's financial input to the treatment. Such financial aspect should not depreciate the need for the continuous education of both physicians and patients.

6. Conclusions

Overall, the results of this survey highlight the management of the LLD treated patients in Bulgaria. Despite the widespread awareness of guidelines for management of hypercholesterolaemia, their implementations in clinical practice are poor with less than 50% of patients attaining to the LDL-C goals. To ensure consistency in target LDL-cholesterol goal setting and to avoid confusion between doctors and patients, it is recommended that a single guideline is followed. The current FJETF is recognised by the Bulgarian Cardiology Society and ought to be referred to in the clinical practice. Further education of physicians through Continuous Medical Education regarding the importance of treatment to target is crucial. Further, education of patients through well-tailored disease awareness programs are the key to optimal lipid management according to an individual risk profile.

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Conflict of interests

Nina Gotcheva, Dimitar Raev, Elina Trendafilova, Arman Postadzhiyanand, Nikolay Runev have all received research contracts and honoraria for advisory boards and lectures from AstraZeneca.

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