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MEDICAL AND SOCIAL SIGNIFICANCE OF FAMILIAL HYPERCHOLESTEROLEMIA IN BULGARIA

SUMMARY

of doctoral dissertation

Scientific discipline: "Social Medicine and Health Management"

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The dissertation contains 155 pages, including 29 tables and 52 figures. The bibliography consists of 191 literary sources, in Cyrillic and Latin.

In connection with the dissertation, 4 articles have been published.

The numbering of tables and figures does not correspond to the ones in the dissertation.

The dissertation has been discussed, adopted and referred for consideration by the extended Collegium of the "Promotion of Health and Disease Prevention" Directorate at the National Centre of Public Health and Analyses conducted on 29 March 2019 on the basis of Order No РД-137/06.03.2019 of the Director of NCPHA.

The materials are available at the Secretariat of the Scientific Council at the NCPHA and on the NCPHA website:http://ncpha.government.bg

CONTENTS

1. INTRODUCTION

Dyslipidemia and familial hypercholesterolemia

Cardiovascular diseases (CVD) are a major health problem in European countries, including Bulgaria. Each year, ischemic heart disease (IHD), a type of coronary artery disease (CAD) causes 1.8 million deaths (20% of all deaths) in Europe. In Bulgaria, diseases of the circulatory system (including ischemic heart disease and cerebrovascular disease) cause more than 71,000 deaths per year (66% of all deaths).In 2014, 197 deaths due to CVD per day were reported for this country.

Large-scale epidemiological studies have shown that elevated cholesterol in low-density lipoproteins (LDL-C) is the major reason for the cardiovascular risk. Further studies indicate that levels of LDL-C are primarily regulated by cellular LDL receptors (LDLRs) and their components, such as proprotein convertase subtilisin/kexin type 9 (PCSK9). Mutations in the PCSK9 gene that increase or inhibit LDLR activity have been proven to affect the overall cardiovascular (CV) risk of the individual.

Familial hypercholesterolemia (FH) is a serious, hereditary disease characterized by consistently elevated LDL-C levels since birth. Affected individuals have a significantly increased risk of major CV events such as myocardial infarction (MI) or stroke, as they are frequently diagnosed with a clinically proven cardiovascular disease from an early age. Clinical practical guidelines, published by the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) highly recommend therapeutic interventions for control of LDL-C in patients with elevated levels of LDL-C and in patients with the highest risk of CVD. Following changes in lifestyle, statins are considered therapy cornerstone. There are other lipid-modifying therapies, but they have limited efficiency and are not reimbursed and widespread in Bulgaria. Many FH patients are unable to achieve a significant LDL-C reduction with statins, because statins are either not effective enough even in maximum daily doses or the patients are intolerant to statins or have contraindications for their use.Therefore, the lack of effective or clinically appropriate treatment options in FH patients poses the highest risk of a serious CV event due to their exposure to chronically high levels of LDL-C throughout their lives.

Historically, the heterozygous form of FH is clinically diagnosed with the distinction being made by phenotype only in very serious cases – these are patients with extremely high levels of LDL-C and early CVD, cerebrovascular diseases and tendon xanthomas.

With the development of genetics and the improvement of the methods for testing and DNA sequencing, the direct detection of LDLR, APOB, PCSK9 and LDLRAP mutations and their description becomes possible.This proves that mutation cannot be detected in 10% to 40% of patients even with the current state of diagnostics.Studies involving more than 69,000 patients in Denmark, Netherlands, etc. prove that despite the overt clinical manifestation, advanced coronary and cerebrovascular disease, mutation cannot be detected.

That is why genetic defects leading to FH are classified as classical and non-classical defects or defects that have not yet been described.Patients in whom the genetic cause cannot be detected are assigned to the newly introduced polygenic FH diagnosis.

On the other hand, during the cascade screening of relatives who exhibit elevated LDL-C levels in genetic testing, even though carrying the same mutation, they do not manifest the clinical symptoms – that is, they are genetically diagnosed, but do not manifest the disease.It is considered that such patients have compensating genes that have not yet been identified and/or lead a healthy lifestyle, which significantly impedes the clinical manifestation, or delays it for later stages.

Several major genetic studies investigate the link between the genetic mutation and the CVD by trying to find a marker/group of markers suitable for clinical practice.As a result of the proven genetic polymorphism in FH, no consensus is reached on a corresponding DNA polymorphism and CVD, which to result in a genetic evaluation envisaging the risk of CVD on the basis of proven genetic mutations.

Currently, many tests for complex genome evaluation are offered on the market, and the trend is in developing their predictive value which to mark the individuals with certain mutations and get them treated before developing diseases.To date, no genetic marker or a test have been identified as a routine method for FH diagnosis.Therefore, the introduction of genetic testing in FH patients into the daily clinical practice is not recommended.

That is why the European Society of Cardiology and the European Atherosclerosis Society in their General Guidelines issued in 2016 do not recommend the introduction of genetic testing as a prerequisite for FH diagnosis.

The recommendations are as follows:

- Evaluation of CV risk and diagnosis of the level of atherosclerosis development
- Evaluation and diagnosis of FH by means of cascade screening - Dutch Lipid Criteria

Cascade family screening of first-degree relatives is mandatory and shows how the disease and the mutation is transmitted to the next generation.The first identified patient is referred to as an index patient.

Who should be screened and how should an index patient be identified?

Relatives (probands) are identified by the following criteria:

(i) Total CL ≥8 mmol/L (≥310 mg/dL) in adults

(ii) early CVD for members of the family and relatives

(iii) tendon xanthomas in the family

(iv) sudden cardiac death of a family member.

Children (probands)

(i) Total CL ≥ 6 mmol/L

Children should be examined immediately following a sudden cardiac death of a parent:

Table 1. *Model for national screening of familial hypercholesterolemia*

Proposed national screening for familial hypercholesterolemia (FH) in primary prevention attempts
UNIVERSAL NATIONAL SCREENING Routine examination of 5-year-old children by major pediatricians within a national

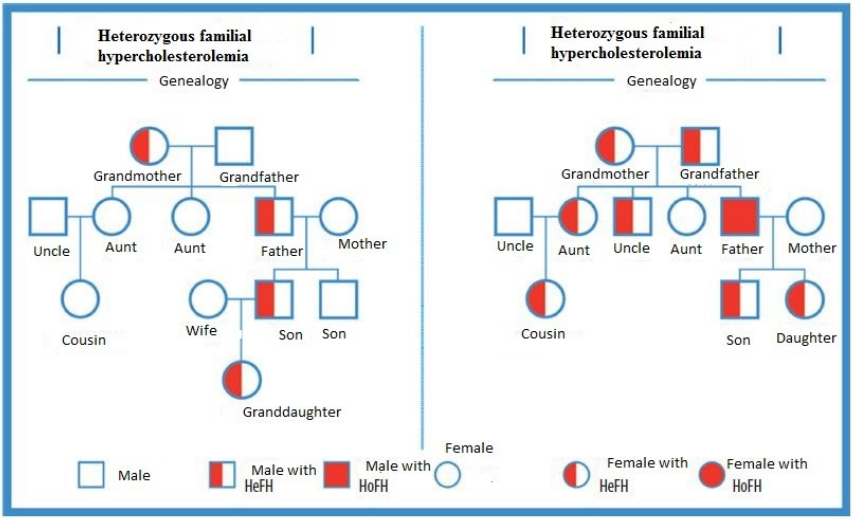
<table>
<tr><td colspan="4">program</td></tr>
<tr><td colspan="4">Does the child have:
Total serum cholesterol (TC) levels above 6 mmol/l (231.7 mg/dl)
<u>without</u> family history of cardiovascular (CV) complications
or
Serum TC levels above 5 mmol/l (193.1 mg/dl)
<u>with</u> family history of CV complications</td></tr>
<tr><td>NO</td><td colspan="3">YES</td></tr>
<tr><td>No further examinations</td><td colspan="3">Genomic DNA sequencing and whole blood sample analysis
to determine versions of 4 genes associated with familial hypercholesterolemia (FH)
(the coding and the promoter area of genes LDLR, PCSK9, APOE and part of APOB exon 26)</td></tr>
<tr><td></td><td>Confirmed familial hypercholesterolemia
Identified genetic version causing the disease in patients referred by the universal screening
(Between 2009 and 2013, 57% of children referred for next-generation sequencing were diagnosed with FH.Of these children, only 40.6% had a family history of CV complications, which proves that the family history in itself may not be sufficient to reliably identify patients.)</td><td>Confirmed multifactorial hypercholesterolemia
Identified genetic version related to the disease in patients referred from the universal screening</td><td>Negative for genetic versions
No identified disease-causing or disease-related genetic version in patients referred by the universal screening</td></tr>
<tr><td></td><td colspan="2">Using early diagnosis to control and reduce the risk of atherosclerosis and cardiovascular diseases in early adulthood</td><td>Considerations for further genetic analysis</td></tr>
<tr><td colspan="4">Adapted from: Klančar, G. et al.J Am Coll Cardiol.2015; 66(11):1250-7.</td></tr>
</table>

The probands are:

First line: parents, children

Second line: grandmother and grandfather, grandson, uncle, aunt, cousins

Figure 1. *Cascade screening for familial hypercholesterolemia*



The age at which the cardiovascular or cerebrovascular event occurs is important:for men under 55, women under 60, first-line relatives aged 5-55 years.

Most often, the FH diagnosis is based on the Dutch Lipid Clinical Network Criteria or the Simone Brooms criteria – recommended in the Guide of the European Society of Cardiologists and the European Atherosclerosis Society - General Guidelines issued in 2016.

It is based on 5 key criteria:

- family history and clinical history of premature development of CVD:
- physical examination - tendon xanthomas and corneal arcus
- laboratory tests, lipid profile
- exclusion of secondary causes of hypercholesterolemia, such as:
- genetic diagnosis

Clinical criteria of the Dutch Lipid Network for diagnosis of heterozygous familial hypercholesterolemia (HeFH)	
Criteria	**Points**
1. Family history: first-degree relative (parent, offspring or brother/sister of the parent) with a known premature* coronary or vascular disease	1
or first-degree relative with plasma concentration of LDL-C > 95th percentile by age and gender	
Family history:first-degree relative (parent, offspring or brother/sister of the parent) with known tendon xanthoma or corneal arcus	2
2. Clinical history:the patient has premature*	
(a) coronary artery disease	2
(b) cerebral or peripheral vascular disease	1
3. Physical examination of the patient	
(a) tendon xanthoma	6
(b) corneal arcus in patients < 45 years of age	4
4. LDL-C levels in patient's blood, mmol/L	
(a) ≥ 8.5	8
(b) 6.5 – 8.4	5
(c) 5.0 - 6.4	3
(d) 4.0 – 4.9	1
5. DNA analysis showing functional mutation in LDLR or other HeFH-related gene	8

Diagnosis	Total points
Determined HeFH	> 8
Probable HeFH	6-8
Possible HeFH	3-5

Note :LDL-C = cholesterol in low-density lipoproteins

* If male, < 55 years of age; if female, < 60 years of age.

One of the most important issues related to severe dyslipidemia and familial hypercholesterolemia in particular is the possibility of early prevention.Due to the hereditary nature of the disease, the primary goal should be reduction of the modifiable risk factors on the one hand and early diagnosis on the other.

Early diagnosis of familial hypercholesterolemia could be carried out at a very early age, in the cases of implementation of cascade screening for families with established disease.The implementation of cascade screening by itself does not require substantial financial resources and complex organisation, but the proactiveness of the specialists dealing with dyslipidemia is of utmost importance, as is that of the general practitioners.Public awareness of this type of disease is also important as well as the need for regular prevention examinations.Since the typical pathognomonic signs of familial hypercholesterolemia, such as tendon xanthomas and corneal arcus, are observed rarely and relatively late in the development of the disease, family history and premature cardiovascular events are extremely important.Of particular importance is the regular examination of the levels of cholesterol and especially of the LDL-C. The level of LDL-C is the most important factor in the diagnosis of familial hypercholesterolemia and the risk of a possible cardiovascular event.In 2017, the NHIF included the examination of LDL-C in the package of paid examinations.In cases of established high levels of LDL-C, the cardiovascular risk should be determined as well as the need for follow-up measures – diet, limitation of risk factors like smoking, control of underlying conditions and possible drug therapy.In recent years, with the modernisation of the diagnostic tools, the examination of the levels of cholesterol is easily achievable outside of the laboratory by sampling capillary blood from the patient and the subsequent use of a special in-vitro diagnostic medical device.Next to doctors' offices, this type of examination can be easily performed in pharmacies as well.A study conducted in Bulgaria between 16 April 2012 and 1 May 2012 found that 99% of the individuals are willing to pay for a similar type of examination in the pharmacy, with 92% considering this extremely important for their health.[191] The regular testing of the levels of cholesterol/LDL-C is the first step towards early identification of patients with familial hypercholesterolemia

and the subsequent adequate treatment. The primary goal, of course, remains the reduction of the cardiovascular risk and the prevention of the first or subsequent events.In case of finding index patients, it is important all first-degree relatives to be examined.Since the diagnosis of familial hypercholesterolemia is based on the Dutch Lipid Clinical Network Criteria, the cascade screening is easily feasible and non-invasive.In a number of countries, with the aim of raising the awareness of the population, government-funded campaigns are carried out for the risk of cardiovascular diseases and the possibilities of early prevention.

2. OBJECTIVE

The objective of this dissertation is to study and analyse the decisive role of the severe forms of dyslipidemia on cardiovascular diseases and to reveal and systematise the main issues and trends associated with familial hypercholesterolemia, as well as to define the scientific and practical approaches, with the aim of improving the diagnosis, prevention, treatment and monitoring of high-risk patients.

3. HYPOTHESIS

The study team laid down the scientific hypothesis in two directions:

- The severe forms of dyslipidemia and hypercholesterolemia, in particular familial hypercholesterolemia, are a decisive factor for cardiovascular diseases in Europe and Bulgaria.
- Early diagnosis, prevention, treatment and monitoring of these conditions are of substantial importance for improving the prognoses for the high-risk population – the clinical, the economic and the social ones.

4. TASKS

In order to accomplish the objective of the dissertation, we set the following tasks for solving:

- Comprehensive review and analysis of the available scientific information worldwide in regard to the development of familial hypercholesterolemia and its importance for cardiovascular diseases.

- Collection and analysis of data in regard to the economic aspects in the treatment of familial hypercholesterolemia in Bulgaria and establishment of an appropriate indicator measuring the outcome of treatment in real-life conditions.
- Development of a comprehensive concept for the introduction of a register of patients with familial hypercholesterolemia in Bulgaria as well as criteria for monitoring the disease.
- Adaptation and exploration of the possibilities for introducing globally recognized algorithm recommendations for diagnosis and treatment of familial hypercholesterolemia.
- Establishment of a practical approach to control severe and inherited forms of dyslipidemia and monitor patients.

5. MATERIALS AND METHODS

Location of the study:

Medical institutions in 4 district cities in the Republic ofBulgaria.

Period of the study:

January 2017 - June 2018

Perspective of the study:

The study was prepared and conducted from the point of view of the patients (insured persons) and the health insurance system in the country.

Materials:

- Database for patients diagnosed with familial hypercholesterolemia according to the Dutch Lipid Clinical Network Criteria.

Methods:

The studies are based on and reflect the current situation of the patients and the health insurance system in the period 2017 - 2018.

General:

- Historical method
- Content analysis method
- Theoretical analysis
- Documentary analysis

- Statistical analysis
- Graphic and tabular presentation of results

Specific

- Pharmacoeconomic evaluation of value eficiency by using ETPY (Effectively treated patient years).

The health technology assessment (HTA) in Bulgaria bases its solutions on the coverage of a number of criteria that reflect the social preferences, including, among other considerations, the severity and the prevalence of the disease, the value, the already reimbursed drugs, the availability of funds and the quality of health care.Ordinance 9/2015, which regulates the terms and conditions for implementation of the HTA, implies that the traditional proofs for QALY costs are not necessary for taking decisions.We created a disease-specific efficiency criterion based on the quality of health care:Effectively Treated Patient Years (ETPY).“Effective treatment” refers to the recommendations for best practices of European (ESC/EAS) and American (ACC/AHA) guidelines for dyslipidemia for CVD prevention.They unanimously recommended for people with high or very high risk of CVD to undergo treatment for reduction of the levels of LDL-C by 50% or more - an objective that is currently being achieved by only 3.7% of Bulgarian HeFH patients.Thus, ETPY are calculated by multiplying the proportion of patients achieving 50% or more reduction of LDL-C levels by the estimated survival rate in each cycle.Since the ETPY are also derived from the years of life measure, they are expected to have a strong link with QALY.The incremental cost-effectiveness ratio (ICER) in this analysis is calculated as an extra cost per unit of ETPY.

6. ANALYSIS OF RESULTS

6.1 Study of the register of patients with familial hypercholesterolemia in Bulgaria

In the period 2017-2018, a register of patients with familial hypercholesterolemia was introduced in Bulgaria - the first of its kind in the country.The patients were evaluated on the basis of the Dutch Lipid Clinical Network Criteria.At the same time, taking into account the current trends related to cardiovascular risk

assessment, data were collected with respect to the risk of a cardiovascular event.The main observed parameters are as follows:

- Age, sex, height, weight, BMI
- History of hypercholesterolemia
- Clinical criteria of the Dutch Lipid Network
- Risk factors for development of cardiovascular diseases - diabetes, myocardial infarction, stroke, peripheral vascular disease, smoking
- Laboratory indicators - total cholesterol, LDL, HDL, triglycerides
- Concomitant anti-lipid treatment - type and duration
- Target value of LDL and its achievement over time
- Hypertension and eventual treatment
- Contraindications for anti-lipid treatment

The date of the examination is important to monitor the disease - the first and the subsequent examinations.With regard to underlying conditions, not only the particular disease should be documented, but also its duration, with a view to determine the additional risk and the possible consequences of its existence.Things are the same with the history of hypercholesterolemia and its duration. Family history of hypercholesterolemia is also crucial in view of the hereditary nature of familial hypercholesterolemia. Family history of premature cardiovascular diseases may also address this reasoning.

The clinical criteria of the Dutch Lipid Network remain the decisive criterion for diagnosing familial hypercholesterolemia.They are easy and fast to conduct and they include different aspects of the diagnosis - history, including family history, symptoms, laboratory indicators, possible genetic diagnosis.The application of the criteria and their interpretation would easily exclude other secondary reasons for high LDL-C values in a differential diagnostic aspect.

With regard to the objective of the register, as well as the adopted practice in EUROASPIRE IV, as diagnosed with familial hypercholesterolemia are considered such patients having an established and probable diagnosis, i.e. by 6 or more points according to the Dutch Clinical Lipid Network Criteria.

The risk factors include myocardial infarction or stroke, peripheral arterial disease and diabetes, and smoking.Each of these factors alone leads to an increase of the cardiovascular risk.Combining them, however, significantly increases the possibility of a cardiovascular event.Therefore, it is extremely important to

eliminate them or to control the underlying condition, if any.Smoking alone increases cardiovascular risk 2.9 times, diabetes 2.4 times, and arterial hypertension 1.9 times.Combining the three risk factors increases this risk 13 times over.

The concomitant anti-lipid treatment is another important indicator.The most common options for this type of therapy are:statin, fibrate, nicotinic acid, ezetimibe or PCSK9 inhibitor.During the introduction of the register, PCSK9 inhibitors were at an early stage after reimbursement and they were not regarded as a standard pre-treatment option.In addition to the particular type of treatment, the dose and duration of therapy are also defined.The primary objective of the anti-lipid treatment is to determine the target LDL level and whether this target value has been reached, and for how long.Usually with the available therapeutic alternatives for treatment of familial hypercholesterolemia, before the introduction of PCSK9 inhibitors, less than 5% of patients reach target LDL-C values.

In cases of contraindications for statin treatment, historically or laboratory proven muscle symptoms, pain, liver or kidney issues, allergic reactions, etc. should be specified.With the therapy not being sufficiently effective, factors such as non-compliance with the treatment regimen, non-compliance with the recommendations for lifestyle changes, etc. are excluded.

The main objective of the register is to dynamically monitor patients - assessment of risk factors, laboratory parameters, lipid profile and treatment.

143 patients diagnosed with familial hypercholesterolemia were included in the database for the observed period.Patient data are anonymised and in line with the requirements of the General Data Protection Regulation.

Table 2.*Distribution of patients diagnosed with familial hypercholesterolemia in the participating sites on the territory of Bulgaria*

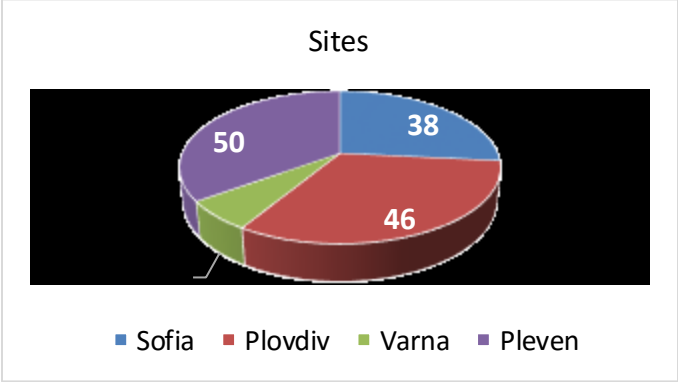
Site

	Frequency	Percent	Valid Percent	Cumulative Percent

Valid	Varna	9	6,3	6,3	6,3
	Plovdiv	46	32,2	32,2	38,5
	ISQD	12	8,4	8,4	46,9
	City Clinic	12	8,4	8,4	55,2
	St. Anna	14	9,8	9,8	65,0
	Pleven	50	35,0	35,0	100,0
	Total	143	100,0	100,0	

Patients diagnosed with familial hypercholesterolemia are distributed on the territory of the country in the following way – 50 of them are identified and monitored in sites in Pleven, 46 in Plovdiv, 38 in Sofia and 9 in Varna.

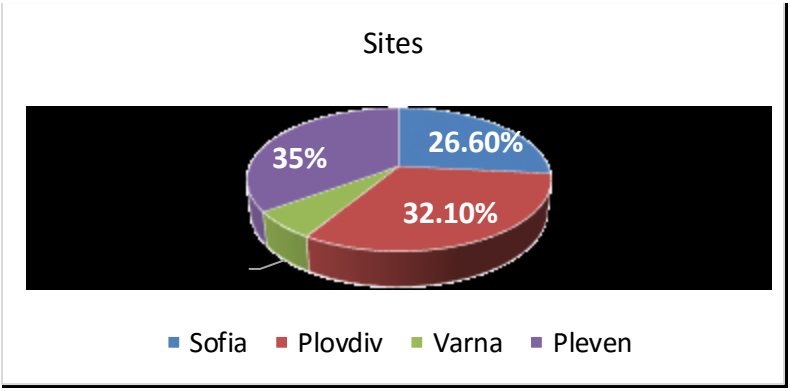
Figure 1.*Number of diagnosed patients distributed by diagnostic sites for familial hypercholesterolemia in Bulgaria, according to a pilot register*



The higher percentage of patients in the Pleven region is due to the closely related marriages in two small and isolated settlements with very high prevalence of familial hypercholesterolemia.The conducted cascade screening leads to a high

frequency of diagnosis and provides for a thorough analysis of risk factors and disease monitoring.

Figure 2. *Percentage distribution of diagnosed patients distributed by diagnostic sites for familial hypercholesterolemia in Bulgaria, according to a pilot register*



The distribution by gender of the patients is even.This is in confirmation of the extensive epidemiological studies in the Netherlands, showing a lack of correlation between the prevalence of familial hypercholesterolemia and the gender of the affected individuals.

Table 3*.Distribution of patients diagnosed with familial hypercholesterolemia by gender*

Gender_cad

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Male	71	49,7	49,7	49,7
	Female	72	50,3	50,3	100,00
	Total	143	100,0	100,0	

Approximately 5% of the patients diagnosed at the time of the inclusion into the database are participants in a clinical trial.

Table 4. *Participation in clinical trials of patients with familial hypercholesterolemia*

Study

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Fourier	7	4,9	4,9	4,9
	no	136	95,1	95,1	100,00
	Total	143	100,0	100,0	

The average DLCN score is 7.91, at a maximum of 19 points.The mean LDL values are 7.00 mmol/l, at a maximum of 21.80 mmol/l.The mean values of systolic blood pressure are 127.17 and of diastolic - 78.31.

Table 5.*Baseline characteristics of patients included in the register*

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Възраст	143	8	84	55,38	13,654
BMI	143	16,23	42,94	27,1586	4,743378
Hypercholesteromia (yearly)	143	0	26	7,70	5,323

Lab.: Total cholesterol	143	4,21	27,90	9,4890	3,12786
Lab.: LDL	143	3,20	21,80	7,0027	2,50247
Lab.: HDL	143	,50	3,36	1,2388	,41296
Lab: Triglycerides	143	,15	42,78	2,7662	3,89928
Arterial pressure - systolic	143	90	170	127,17	11,642
Arterial pressure - diastolic	143	60	100	78,31	8,461
Valid N (listwise)	143				

The figures below present patient populations distributed in accordance with the values of total cholesterol, LDL-C, HDL and triglycerides.

Figure 3.*Distribution of the patient population in terms of total cholesterol values, according to a pilot register*

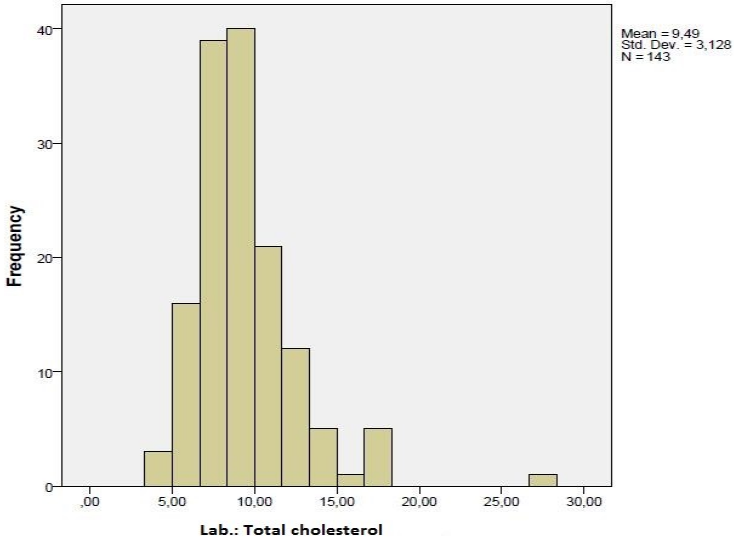
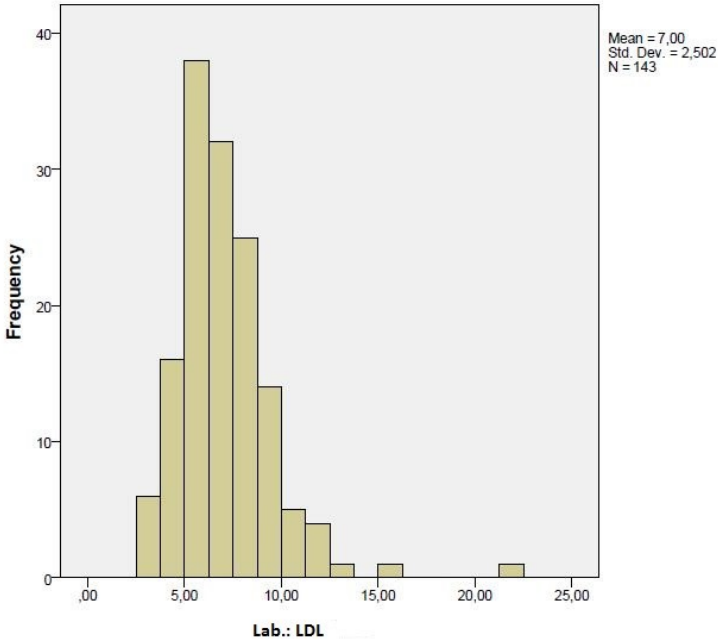


***Figure 4**.Distribution of the patient population in terms of LDL-C values, according to a pilot register*



Patients with LDL-C values between 5 and 10 mmol/l prevail, which, according to the Dutch Lipid Clinical Network Criteria, adds between 3 and 8 points in the final assessment for a diagnosis of familial hypercholesterolemia and confirms the fact that the defining indicator for the diagnosis is the value of LDL-C in combination with at least one more factor.

Figure 5.*Distribution of the patient population in terms of HDL values, according to a pilot register*

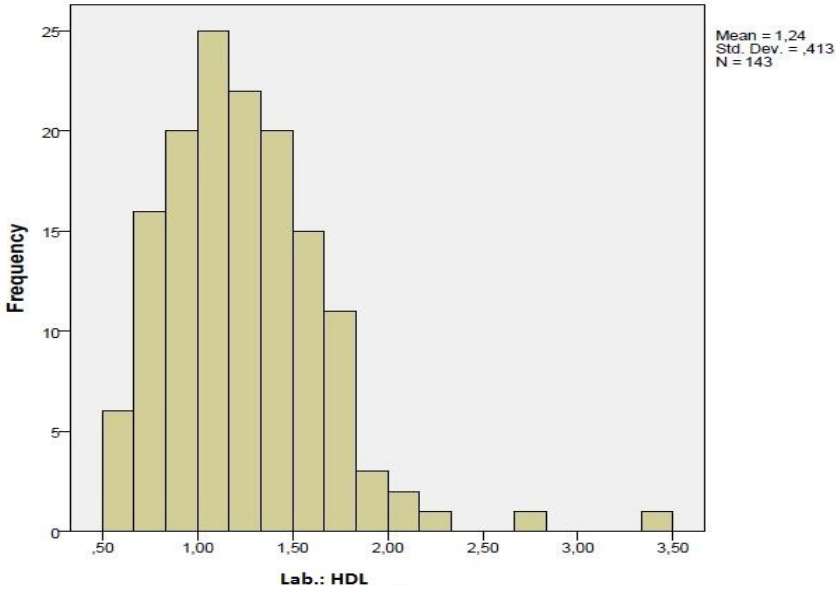
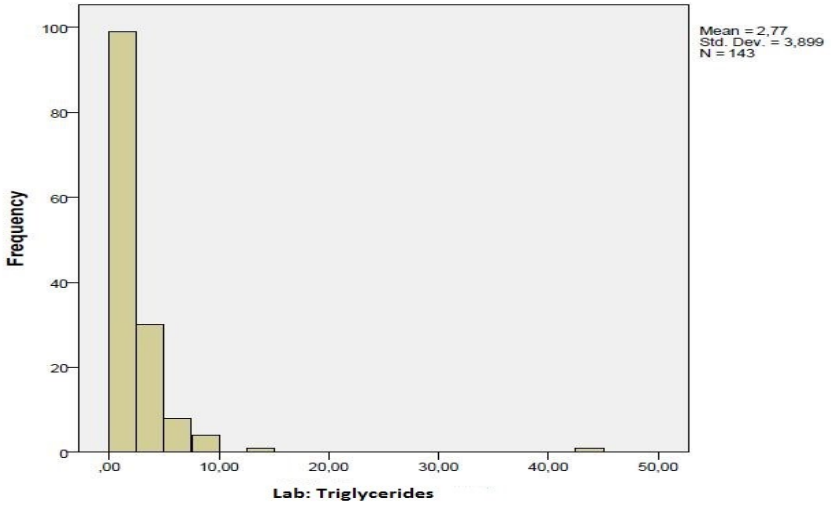


Figure 6.*Distribution of the patient population in terms of triglyceride values, according to a pilot register*



Triglyceride values are not an essential factor for familial hypercholesterolemia, but could be an important indicator in differential diagnostic terms, leading to another type of secondary cause of dyslipidemia.

49% of diagnosed patients have myocardial infarction and only 4.2% are with stroke.

Table 6.*History of myocardial infarction and stroke in the monitored patient population*

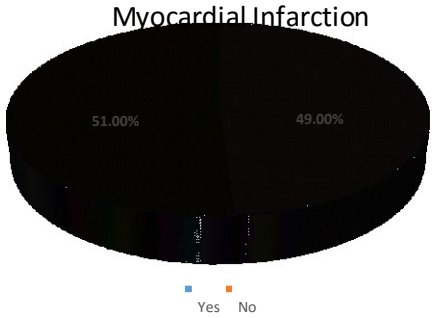
RF: Myocardial infarction

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	70	49,0	49,0	49,0
	No	73	51,0	51,0	100,00
	Total	143	100,0	100,0	

RF: Stroke

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	6	4,2	4,2	4,2
	No	137	95,8	95,8	100,00
	Total	143	100,0	100,0	

Figure 7.*Ratio between patients with and without myocardial infarction in the patients diagnosed with familial hypercholesterolemia*

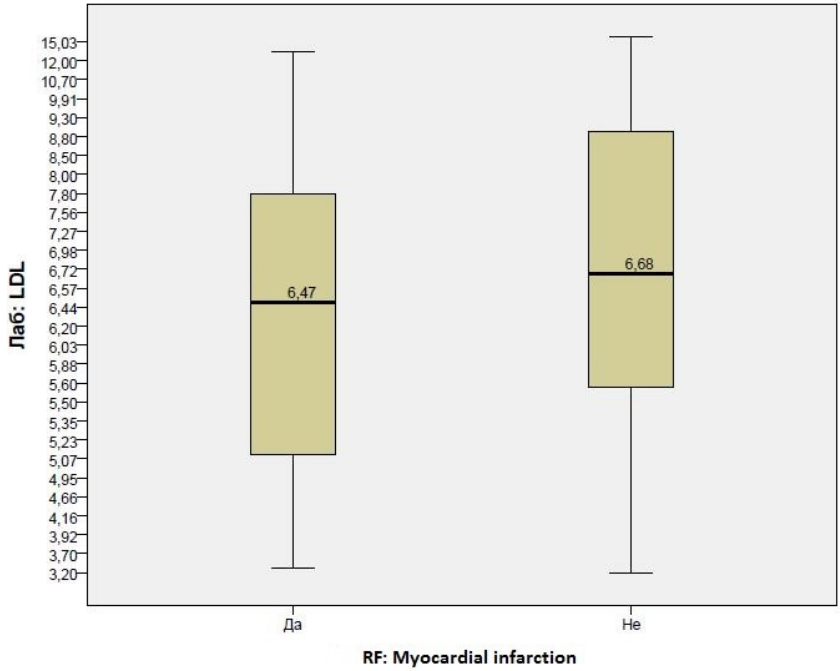


The dependence between LDL-C values and myocardial infarction can be seen in the following graph.As all patients included in the database are diagnosed with familial hypercholesterolemia, they can be classified as patients with a high risk for cardiovascular events.This is also the main reason for the lack of differences between the two monitored groups.Other risk factors, as well as the age at the time of reading LDL-C and myocardial infarction values, are also important.

Figure 8*.Dependence between LDL-C values and myocardial infarction in the population with familial hypercholesterolemia*

17.5% of patients with familial hypercholesterolemia have established peripheral arterial disease and 21.7% are diabetics.

Table 7.*Distribution of peripheral arterial disease, diabetes and CAD in patients with familial hypercholesterolemia*



RF: Peripheral arterial disease

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	25	17,5	17,5	17,5
	No	118	82,5	82,5	100,00
	Total	143	100,0	100,0	

RF: Diabetes

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	31	21,7	21,7	21,7
	No	112	78,3	78,3	100,00
	Total	143	100,0	100,0	

Extreme_CAD

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1,00	98	68,5	68,5	68,5
	2,00	45	31,5	31,5	100,00
	Total	143	100,0	100,0	

25.2% of patients are smokers and 73.4% have arterial hypertension.

Table 8.*Smoking and accompanying arterial hypertension in patients with familial hypercholesterolemia*

Smoking

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	36	25,2	25,2	25,2
	No	107	74,8	74,8	100,00
	Total	143	100,0	100,0	

Accompanying AH

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	105	73,4	73,4	73,4
	No	38	26,6	26,6	100,00
	Total	143	100,0	100,0	

In terms of family history – 63.6% of patients with familial hypercholesterolemia have a first-degree relative with premature cardiovascular disease, 42.7% have a relative with hypercholesterolemia, and only 2.1% have a child with elevated LDL levels.Given the family nature of the disease, the high percentage of patients with established family history confirms the probability of familial hypercholesterolemia.However, we should also not exclude the possibility of lack of diagnosis in part of the relatives, as well as the lack of documentation confirming the premature cardiovascular pathology.

Table 9*.Family history - LDL, premature cardiovascular disease*

Relative_premature

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	91	63,6	636	63,6
	No	82	57,3	57,3	100,00
	Total	143	100,0	100,0	

Relative_LDL

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	61	42,7	42,7	42,7
	No	82	57,3	57,3	100,00
	Total	143	100,0	100,0	

Child_LDL

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	3	2,1	2,1	2,1
	No	140	97,9	97,9	100,00
	Total	143	100,0	100,0	

In terms of family history, less than 1% of patients have first-degree relatives with established corneal arcus.51% first-degree relatives have premature coronary disease, and 19.6% have premature cerebrovascular disease.These results confirm the significance of cardiovascular pathology for diagnosis in comparison to cerebrovascular pathology.Registers in the Scandinavian countries are consistent with the results of the register in Bulgaria.

Table 10.*Family history - corneal arcus, coronary heart disease*

Relative_premature

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	1	,7	,7	,7
	No	142	99,3	99,3	100,00
	Total	143	100,0	100,0	

Premature_CD_2_1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	73	51,0	51,0	51,0
	No	70	49,0	49,0	100,00
	Total	143	100,0	100,0	

Premature_cerebrovascular_disease_2_2

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	28	19,6	19,6	19,6
	No	115	80,4	80,4	100,00
	Total	143	100,0	100,0	

In regard to tendon xanthomas and corneal arcus among the 143 patients diagnosed with familial hypercholesterolemia, it appears that their percentage is insignificant - 3 cases of tendon xanthomas and 2 cases of corneal arcus.Regardless of their pathognomonic nature for the diagnosis of familial hypercholesterolemia, levels of LDL-C are definitely the most important for diagnosis with corneal arcus and especially tendon xanthomas being rather casuistic.

Table 11. *Tendon xanthomas and corneal arcus*

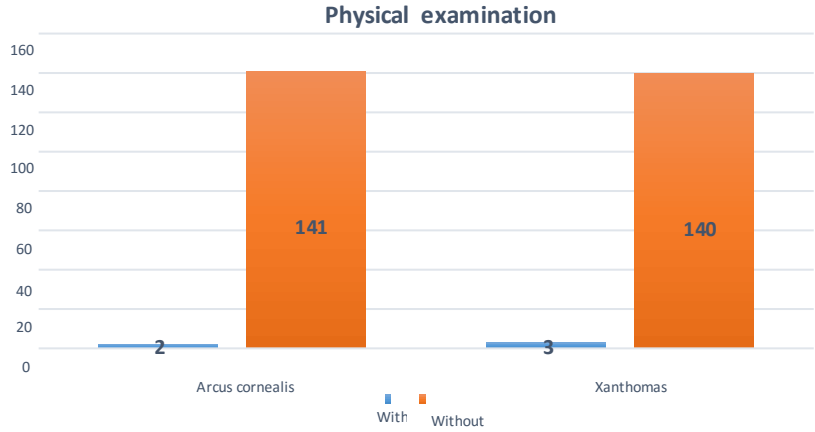
Xanthomas_3_1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	3	2,1	2,1	2,1
	No	140	97,9	97,9	100,00
	Total	143	100,0	100,0	

Arcus_3_2

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	2	1,4	1,4	1,4
	No	141	98,6	98,6	100,00
	Total	143	100,0	100,0	

***Figure 9**.Tendon xanthomas and corneal arcus in patients with familial hypercholesterolemia*



The distribution of patients according to their LDL-C values without treatment as defined by the Dutch Lipid Clinical Network Criteria is as follows:

≥ 8.5 mmol/l – 4 patients
6.8 – 8.4 mmol/l – 35 patients
5.0 – 5.4 mmol/l – 53 patients
4.0 – 4.9 mmol/l – 51 patients

***Table 12.**Distribution of patients with familial hypercholesterolemia depending on LDL-C values*

LDL_1_4_1

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	50	35,0	35,0	35,0
	No	93	65,0	65,00	100,00
	Total	143	100,0	100,0	

LDL_2_4_2

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	53	37,1	37,1	37,1
	No	90	62,9	62,9	100,00
	Total	143	100,0	100,0	

LDL_3_4_3

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	35	24,5	24,5	24,5
	No	108	75,5	75,5	100,00
	Total	143	100,0	100,0	

LDL_4_4_4

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	4	2,8	2,8	2,8
	No	139	97,2	97,2	100,00
	Total	143	100,0	100,0	

Figure 10. *Distribution of patients with familial hypercholesterolemia depending on LDL-C values*

None of the diagnosed patients has a positive genetic test.

Table 13. *Genetic diagnosis of familial hypercholesterolemia*

135 out of 143 patients with diagnosed familial hypercholesterolemia receive lipid-lowering therapy, less than 6% are without treatment.However, none of the patients at the time of inclusion in the database has achieved target LDL-C values.

Table 14.*Treatment of dyslipidemia in monitored patients*

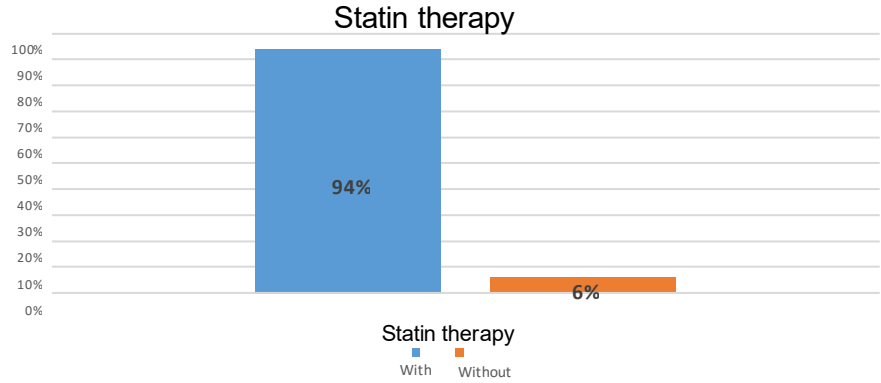
Treatment of dyslipidemia

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	135	94,4	94,4	94,4
	No	8	5,6	5,6	100,00
	Total	143	100,0	100,0	

It should be noted that despite the fact that the majority of patients were prescribed evolocumab 140 mg twice a month, none of them had begun therapy at the time of their inclusion in the database, that is to say we have no results of the effects of treatment with PCSK9 inhibitor.

96% of the patients are on statin therapy and only 4% or 6 patients are without statins.

Figure 11.*Concomitant statin therapy*



The most commonly used statin is rosuvastatin, followed by atorvastatin and simvastatin.

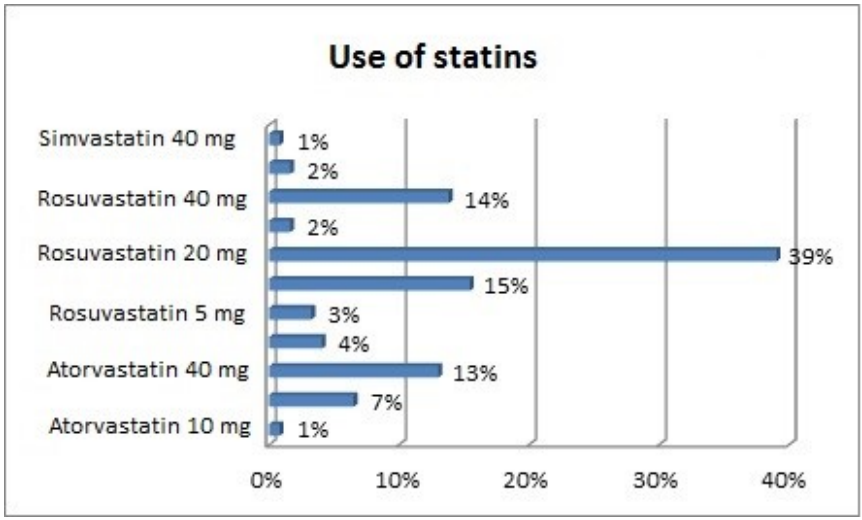
Table 15. *Type of statin therapy*

Type_statin

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Rosuvastati	92	64,3	68,7	68,7
	Atorvastatin	39	27,3	29,1	97,8
	Simvastatin	3	2,1	2,2	100,0
	Total	134	93,7	100,0	
Missing	System	9	6,3		
Total		143	100,0		

The application of different dose regimens and statin types in patient population is shown in the following figure:

Figure 12. *Therapeutic regimens with statins in patients with familial hypercholesterolemia*



The median dose of rosuvastatin used in the monitored patient population is 21 mg, 35 mg for atorvastatin, and 27 mg for simvastatin.

Table 16*.Median dose of statin therapy*

Group Statistics

	Type_statin	N	Mean	Std. Deviation	Std. Error Mean
Dose_statin_miligrams	Rosuvastati	92	21,3587	10,48555	1,09319
	Atorvastatin	39	35,3846	20,88139	3,34370

Group Statistics

	Type_statin	N	Mean	Std. Deviation	Std. Error Mean
Dose_statin_miligrams	Rosuvastati	92	21,3587	10,48555	1,09319
	Simvastatin	3	26,6667	11,54701	6,66667

The use of different statin type and the LDL-C values in the respective patient group are shown in the following graph:

Figure 13.*Dependence between the use of a particular statin and the LDL-C values in familial hypercholesterolemia*

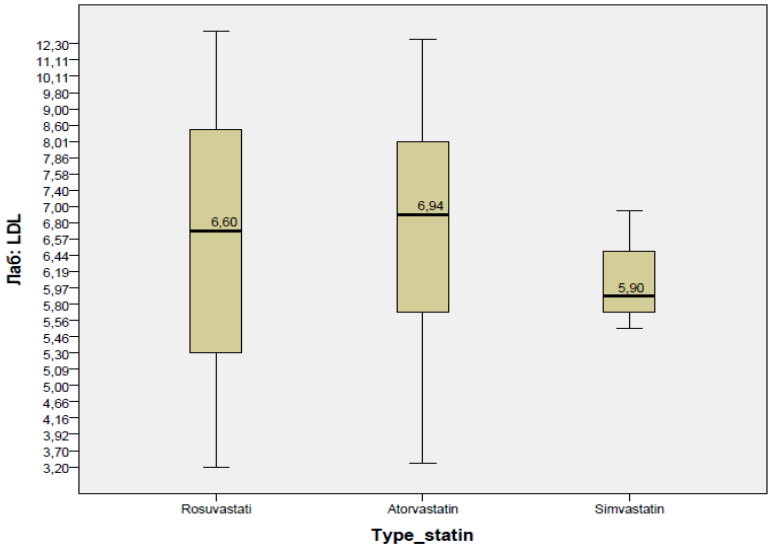
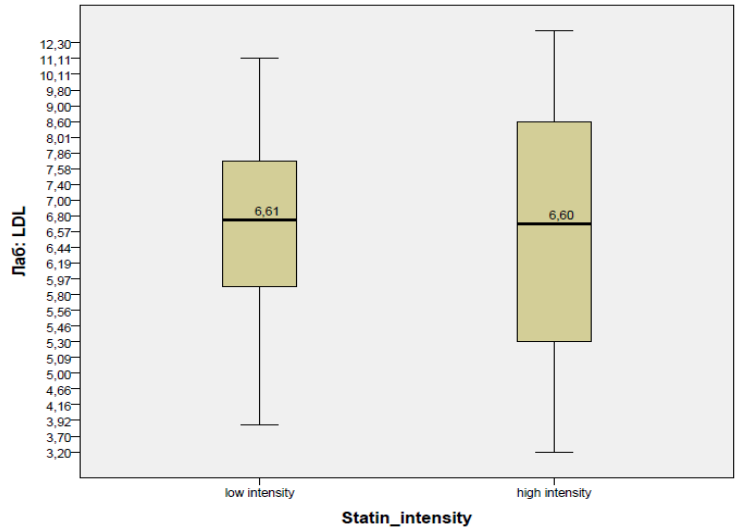


Figure 14. *Dependence between the intensity of statin treatment and the LDL-C values in familial hypercholesterolemia*



Only 4 patients did not adhere to the prescribed therapeutic statin regimen.

***Table 17**.Non-compliance with prescribed treatment*

Non-compliance

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	-	9	6,3	6,3	6,3
	Yes	4	2,8	2,8	9,1
	No	130	90,9	90,9	100,0
	Total	143	100,0	100,0	

35 patients discontinue statin therapy due to the occurrence of an adverse drug reaction.

***Table 18.** Discontinuation of anti-lipid treatment due to an adverse drug reaction*

Discontinuation_treatment_ALT

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	-	9	6,3	6,3	6,3
	Yes	35	24,5	24,5	30,8
	No	99	69,2	69,2	100,0
	Total	143	100,0	100,0	

60 patients have muscle symptoms as a result of statin administration.

Table 19.*Muscle symptoms due to administration of statins*

Muscle_symptoms

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	-	9	6,3	6,3	6,3
	Yes	60	42,0	42,0	48,3
	No	74	51,7	51,7	100,00
	Total	143	100,0	100,0	

Some patients also experienced deviations in the liver and kidney indicators.

Table 20*.Deviation in liver and kidney indicators in monitored patients*

Liver

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	-	9	6,3	6,3	6,3
	Yes	13	9,1	9,1	15,4
	No	121	84,6	84,6	100,00
	Total	143	100,0	100,0	

Kidney

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	-	9	6,3	6,3	6,3
	No	134	93,7	93,7	100,00
	Total	143	100,0	100,0	

Other reported adverse drug reactions are relatively rare.

Table 21. *Other adverse drug reactions*

Other

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	-	130	90,9	90,9	90,9
		9	6,3	6,3	97,2
	In an attempt to increase the dose, patient reports of facial rash	1	,7	,7	97,9
	Overdosing – abdominal pain	1	,7	,7	98,6
	Indications for statin therapy at this age	1	,7	,7	100,00
	Total	143	100,0	100,0	

Approximately 36% of patients were receiving ezetimibe.Globally, the use of ezetimibe in populations of patients with familial hypercholesterolemia is more pronounced.The differences could be explained by the lack of reimbursement of ezetimibe for familial hypercholesterolemia in Bulgaria and with the lack of significant additional effects of the administration of ezetimibe in these patients, requiring in a large number of cases the addition of a PCSK9 inhibitor.

Figure 15.*Treatment with ezetimibe in patients with familial hypercholesterolemia*

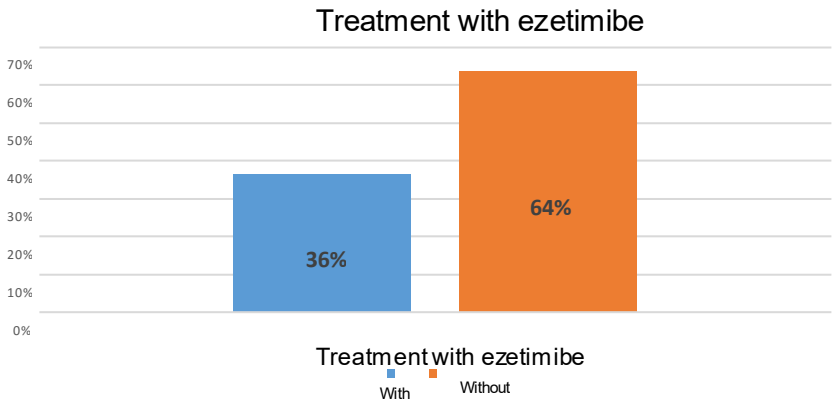
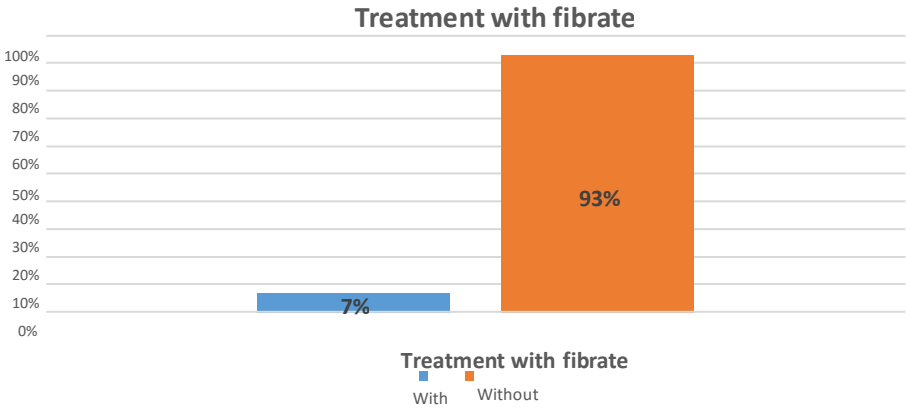


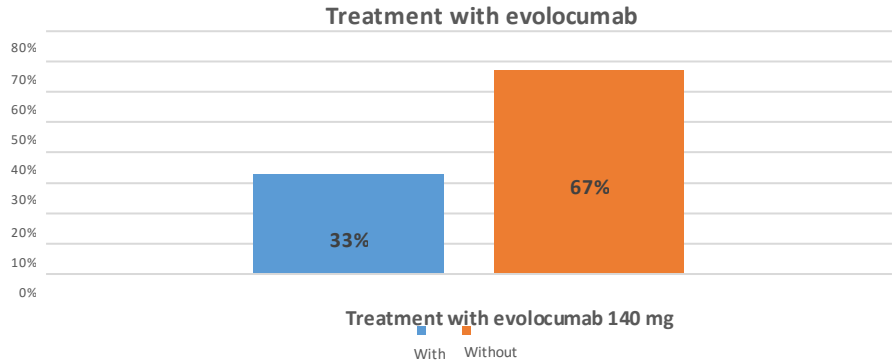
Figure 16.*Treatment with fibrates in patients with familial hypercholesterolemia*



7% or 10 patients are treated with fibrate.

A total of 33% of patients have started or prescribed treatment with evolocumab 140 mg.An open question on a global scale is the place of PCSK9 inhibitors in the treatment regimen for familial hypercholesterolemia.In view of the significant reduction in LDL-C values compared with ezetimibe, the direct addition of evolocumab to the statin treatment is the most logical option from a clinical point of view.Pharmacoeconomics and value efficiency of administered therapies are also of significance here.

Figure 17.*Treatment with evolocumab in patients with familial hypercholesterolemia*



The main objective of the established database of patients with familial hypercholesterolemia in Bulgaria is monitoring disease dynamics and determining the risk of cardiovascular diseases.A key moment here is defining the link between the main risk factors, the severity of the disease and the outcome for the patient.It is important to note the need to control the modifiable risk factors and determine how their dynamics change the cardiovascular risk for the patient.This, however, requires long-term follow-up of patients, an increase in the number of patients in the database, as well as expanding the range of monitored risk factors.

6.2 Results from the study of the clinical and economic value of LDL-C reduction

Patients with heterozygous familial hypercholesterolemia are particularly vulnerable to CVD events; in the absence of treatment, the likelihood of premature coronary heart disease (CHD) is increased about 20 times. Most of these patients do not achieve adequate reduction of LDL-C despite the lipid-lowering therapy at the current Standard of Care (SoC) putting them at risk for CVD that is 10 times higher than the risk for patients without FH when receiving similar drugs to lower LDL-C. The inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) has emerged as an innovative therapy for lowering LDL-C. Evolocumab is the first PCSK9 inhibitor that demonstrates significant

reduction in the prevalence of serious CVD events and regression or stabilisation of the atherosclerotic plaque. The results of a study in HeFH patients indicate that the addition of evolucumab to SoC (i.e., high-intensity statin therapy) leads to a decrease in LDL-C levels by about 60%.

On the basis of evidence-based guidelines for prevention, a disease-specific efficiency criterion was established - Effectively Treated Patient Years (ETPY) - and subsequently used in an economic model that compares the addition of evolocumab to SoC against only SoC in patients with HeFH.The objective of this analysis is to demonstrate the clinical and economic value of lowering LDL-C with evolocumab from the point of view of the Bulgarian public health system.

Modelling in the study

A published Markov cohort model for transitions of conditions has been adapted, taking into account the perspective of consumers in Bulgaria and the duration of lifelong treatment. The model uses annual cycles (with half cycle correction and has been built using Microsoft Excel 2010 (Microsoft Corp., Redmond, WA).The cycle length of 1 year is consistent with other studies for economic evaluation of CVD.

Efficiency criteria

The health technology assessment (HTA) in Bulgaria bases its solutions on the coverage of a number of criteria that reflect the social preferences, including, among other considerations, the severity and the prevalence of the disease, the value, the already reimbursed drugs, the availability of funds and the quality of health care. Ordinance 9/2015, which regulates the terms and conditions for implementation of the HTA, implies that the traditional proofs for QALY costs are not necessary for taking decisions.We created a disease-specific efficiency criterion based on the quality of health care:Effectively Treated Patient Years (ETPY). “Effective treatment” refers to the recommendations for best practices of European (ESC/EAS) and American (ACC/AHA) guidelines for dyslipidemia for CVD prevention. They unanimously recommended for people with high or very high risk of CVD to undergo treatment for reduction of the levels of LDL-C by 50% or more - an objective that is currently being achieved by only 3.7% of Bulgarian

HeFH patients. Thus, ETPY are calculated by multiplying the proportion of patients achieving 50% or more reduction of LDL-C levels by the estimated survival rate in each cycle.Since the ETPY are also derived from the years of life measure, they are expected to have a strong link with QALY.The incremental cost-effectiveness ratio (ICER) in this analysis is calculated as an extra cost per unit of ETPY.

In addition, the model evaluates the life years (LY), deaths in CVD, the prevalence of acute CVD cases without lethal outcomes in myocardial infarction (MI), ischemic stroke (IS) and heart failure (HF) and frequency of revascularisation.

Figure 18.*Structure of an economic model for evolocumab*

Structure of the model

The mutually exclusive health conditions included in the model are CVD, established CVD (ECVD), myocardial infarction (MI), ischemic stroke (IS), heart failure (HF), post-MI, post-IS, post-HF, death caused by a coronary heart disease

(CHD), death caused by IS and death unrelated to CVD.The CVD events included in the ECVD are transient ischemic attack, peripheral vascular disease, stable angina, carotid stenosis, revascularisation in the absence of MI and abdominal aortic aneurysm.Depending on their CVD history, patients are included in the model on the basis of condition without CVD (61.7%), condition after the event (14.9%), or condition with ECVD (23.4%).Revascularisation is included as a procedure, not as a separate condition, and the costs for revascularisation are included for part of the patients with condition with ECVD, MI and post-MI according to the published data.

In addition, the model includes thirteen composite conditions designed to preserve the memory of previous CVD events.The following assumptions for transition probabilities and costs for composite conditions are applied:the risk for a transition from a composite to a specific event is equal to the highest risk for the individual conditions it contains.The highest cost of the costs of the individual conditions is used as a cost for a composite condition.

Model data

The population of the model includes HeFH patients and fasting LDL-C concentrations of 100 mg/dL or higher with (38.3%) or without (61.7%) history of CVD.The average age of the patient population is 51 years, 42.3% female and having average LDL-C level of 155 mg/dL.These data are from the RUTHERFORD-2 study.

Baseline risk

Published risk equations are used for HeFH patient characteristics for evaluation of the baseline CVD risk.The Framingham risk equations are used to predict the overall 10-year risk of CVD events in patients without a history of CVD.For patients with previous CVD events, the risk equation for “next cardiovascular event” of the multinational REACH register is used for evaluation of the 20-month overall risk of recurrent CV events.As this analysis covers the Bulgarian population, the ratio for “Eastern Europe or the Middle East” is included in the risk equation.The methodology described by Lothgren et al. is used to eliminate the effect of age on risk estimates.

Table 22.*Demographic data and basic patient characteristics.*

Characteristic	Patients with HeFH (N = 329)
Age, years (SD)	*51.16 (12.60)*
Female, %	*42.25*
Smokers, %	*15.81*
Diabetes Mellitus Type 2, %	*7.29*
Hypertensive therapy, %	*32.52*
Use of acetylsalicylic acid, %	*38.60*
Systolic blood pressure, mmHg (SD)	*125.73 (13.63)*
Body Mass Index < 20 kg/m2, %	*1.82*
Average LDL-C, mg/dL (SD)	*155.46 (44.93)*
Average Total-C, mg/dL (SD)	*231.56 (48.66)*
Average HDL-C, mg/dL (SD)	*51.13 (15.60)*
Number of vascular beds*	*1.21*
Atrial fibrillation*, %	*11.70*
Previous CVD event (i.e. SP), %	*38.30*
Initial SP condition, %	
ECVD	*61.11*
Post-MI	*25.40*
Post-IS	*2.38*
Post-HF	*0.79*
Composite conditions	*10.32*
Estimated 10-year risk of CVD events^	*55%*

Due to the longer exposures to higher levels of LDL-C, HeFH patients have an increased baseline risk of CVD compared to the evaluations on the basis of the Framingham and REACH equations resulting from the general hyperlipidemic populations.To determine the level of baseline risk of CVD, a search of publications on the risk of CVD in familial hypercholesterolemia (FH) was performed, during which a total of 14 publications met the criteria for inclusion.This review identifies a Danish population-based study which involves a direct comparison of hyperlipidemic populations with FH and secondary prevention, and reports of CVD events with fatal and without fatal outcomes.In comparison with patients without FH and discontinued lipid-lowering therapy, the study reports of odds ratio (OR) (95% confidence interval [CI]) of 13.2 (10.0 -

17.4) in FH patients with discontinued therapy and 10.3 (7.8 - 13.8) in FH patients with ongoing therapy, while at the same time adapting a number of risk factors.The reported ORs were used to calculate the prevalence of CVD events in FH patients compared to other hyperlipidemic patients.For maximum close representation of the real situation, the risks of treated and untreated groups were united in order to take account of the number of patients with primary and secondary prevention. Finally, a frequency ratio of 7.1 (5.7 - 8.7) was applied to event prevalence, initially intended to take account of the increased risk of the HeFH population in the model.The approximate 10-year risk of > 1 CVD is 55%.

Efficacy and efficiency

The estimated efficiency of evolocumab to reduce the prevalence of CVD events is based on the relative reduction in LDL-C, observed in the phase 3 study of evolocumab in HeFH patients, RUTHERFORD-2.In particular, the model is based on the unpublished therapeutic difference between evolocumab (administered once every two weeks) and placebo in the average percent change in the calculated levels of LDL-C from baseline to the average for weeks 10 and 12 (61.31%; 95% CI: 57.82 - 64.8%).

The effect of treatment is applied to patients post-MI and ECVD who are in need of revascularisation, but not in patients with acute MI, as the rate of revascularisation is mediated by the reduced prevalence of acute MI.In addition, no therapeutic effect is applied to HF, as the meta-analyses of CTTC do not report of impact of LDL-C reduction on the prevalence of HF events.

The proportion of HeFH patients treated with statin achieving a decrease in LDL-C levels of > 50% when adding placebo or evolocumab is 1.96% (95% CI: 0.05 - 10.45%) and 79.25% (95% CI: 70.28 - 86.51%), respectively.The calculations were made using unpublished patient data in patients with LDL-C levels > 100 mg/dL participating in RUTHERFORD-2.Due to the sequential effect of evolocumab, there is no statistically significant difference in the proportion of patients with effective treatment in the pre-defined subgroups of the study.Therefore, the overall percentage of effectively treated patients is used to calculate the initial criterion for efficacy for this analysis:Effectively Treated Patient Years (ETPY).

Link between lowering LDL-C and decreasing the prevalence of CVD events

A number of interventional and epidemiological studies prove that lowering the level of LDL-C reduces the risk of CVD events; this applies to both statin and non-statin therapies.The study of evolocumab for CV outcomes, "Study of additional cardiovascular outcomes with PCSK9 inhibition in patients with increased risk (FOURIER)", shows that the addition of evolocumab to the SoC is associated with reduced prevalence of serious CVD events.

The model uses the link between statin-generated LDL-C reduction and reduced prevalence of CVD events from CTTC meta-analyses.

Table 23*.Prevalence of CVD events after reduction of LDL-C by 1 mmol/L (38.67 mg/dL)*

Event	Frequency ratio (99% CI)
ECVD	0.71 (0.58 - 0.87)
MI	0.71 (0.58 - 0.87)
IS	0.69 (0.50 - 0.95)
Death caused by CHD	0.80 (0.76 - 0.85)
Death caused by IS	1.00
Revascularisation*	0.66 (0.60 - 0.73)^

They provide reliable, event-specific evaluations of the effects, which have been widely used in previous economic evaluations of lipid-lowering therapies and are considered the golden standard for evaluating the effect of treatment associated with reduction of LDL-C.

In comparison to CTTC data, treatment with evolocumab has very similar effects on the risk of serious CVD events.In the light of this set of evidence, the European Atherosclerosis Society (EAS) believes that PCSK9 inhibitors are equivalent to statins because their effects on the risk of CV events per unit decreases in LDL-C.

The prevalence of CVD events following treatment is presented by the following formula:

Prevalence after treatment = prevalence at baseline X frequency ratio in CTTC

Based on this, a modified risk of CVD events (i.e., the subsequent effect of treatment on the onset of CVD events and survival) was obtained.

Prevalence of events

On the basis of data from the longitudinal surveys of CPRD/HES, multinomial logistic regression models were used to evaluate the proportion of cardiovascular events (death caused by MI, IS, HF, CV) linked to previous events.In addition, logistic regression was used for patients who died due to a CV disease to predict whether the event was cerebrovascular or other.

Mortality rate

CVD-related mortality rate is estimated as a consequence of accidental CVD events.It is believed that non-CVD mortality rate is the same as that of the general population, as is evident from the tables by age and gender, published by the National Statistical Institute of Bulgaria.It is obtained separately by subtracting the components of ischemic heart diseases (ICD I20-I25) and cerebrovascular diseases (ICD I60-I69) from the overall mortality rate.

Costs

The annual costs for evolocumab correspond to the basic reimbursement price in Bulgaria after the application of the compulsory repayment the National Health Insurance Fund (NHIF) in accordance with local legislation.The annual costs of currently reimbursed high-intensity statins in Bulgaria (atorvastatin 40 - 80 mg; rosuvastatin 20 - 40 mg) are calculated using a weighted average based on their market share.Market shares were derived from data owned by IMS.For purposes of equalisation, 100% statin reimbursement for the target population is taken.The medical CVD-related costs were obtained from the National Health Insurance Fund, NHIF.The evaluations of resource use related to Bulgarian practice were obtained through expert consultations with Prof. Dr. Ivo Petrov, MD - national cardiology consultant.The acute costs and the short-term costs for the first year, as well as the costs after the events in the subsequent years, were considered.This analysis does not include the indirect costs that are not relevant to stakeholders in Bulgaria.

Table 24.*Costs for CVD events per patient per year.*

Condition from the model	Annual direct costs (in BGN)	
	Acute (Year 1)	Post-event (subsequent years)
Without CVD	0.00	-
ECVD*	-	582.05
MI	7384.10	582.05
IS	4154.84	223.03
HF	2569.28	2564.61
Death caused by CHD	5171.50	-
28.3% fatal UA	5270.00	
56.6% fatal MI	6380.00	
15% fatal HF	420.00	
Death caused by IS	8095.00	-
Non-CVD death	0.00	-
Revascularisation	5498.92	-
78.5% PCI	4238.00	
21.5% CABG	10100.00	

RUTHERFORD-2 did not find any significant differences in the adverse event profiles between the patients treated with evolocumab and the placebo-treated patients.Therefore, the prevalence and the costs associated with adverse events are not included in the economic evaluation.

Analysis of the main case scenario

Health outcomes of this cost-effectiveness analysis were summarised in the form of Effectively Treated Patient Years (ETPY) combining life expectancy with the quality of health care.The prevalence of LYG, CVD and the revascularisation has also been presented.All results and costs were reduced by a 5% rate according to the Bulgarian guidelines.

Sensitivity analyses

Both one-dimensional deterministic and multivariable probability sensitivity analyses were used to evaluate the uncertainty associated with the accumulated extra costs of ETPY.For one-way sensitivity analyses, the adjustment of the baseline risk of CVD, the relative reduction in LDL-C observed in patients treated with evolocumab, the frequency ratio of CVD events in CTTC and the proportion of patients achieving reduction of LDL-C levels by > 50% were adjusted to the

lower and upper limit of their 95% CIs.A standard error of 10% of the mean values was taken to calculate 95% CI for condition costs.The duration of the treatment in the baseline scenario and the percent of reduction of costs and outcomes (5%) were reduced to 5 years and 0%, respectively.

The probability sensitivity analysis was carried out to examine in full the combined effect of the uncertainty parameter on the outcome of the baseline scenario. Appropriate probability distributions by Briggs et al.(beta, relative reduction in LDL-C and percentage of effectively treated patients; gamma, health condition costs; longnormal, frequency ratio of the CTTC and adjustment of the CVD risk at baseline level) were applied to the parameters of the model on the basis of their respective means and standard errors.Then, the Monte Carlo simulation with 1000 iterations in each cycle was performed on the parameter values.

Results

The total additional costs for evolocumab added to SoC (high-intensity statins) against only SoC are BGN 120,329.At the same time, patients treated with evolocumab also receive 9.30 patient-years of effective treatment during their lives.These results imply additional ETPY costs amounting to BGN 12,937.(USD 7,215; EUR 6,604).The use of evolocumab is associated with a relative reduction in the prevalence of CVD events by 38% (18% at 1 mmol/L); acute CVD events without fatal outcome decrease by 44% and a 17% reduction in CVD deaths is calculated.In an initial cross ratio of the prevalence of HeFH, 7.1 patients with transition to HeFH were found to have 5.1 times more events in their lifetime compared to HeFH-free patients with a similar risk profile.

Sensitivity analyses

The results show that ICER is mainly sensitive to changes in percent of reduction in costs and outcomes.The reduction of the rate applied to costs to 0% results in the greatest increase of ICER, while the equivalent change of the rate applied to ETPY significantly reduces it.For the proportion of patients achieving LDL-C reduction of at least 50%, ICER does not exceed the range of BGN 11,827 - 14,632 for ETPY.Overall, ICERs are stable against changes in efficiency and cost parameters.

Table 25. *Estimated prevalence of CVD events, ETPY and costs*

	Evolocumab+SoC	**Only SoC**	**Increase**
Total LYs*	12,7	11,15	0,93
Total ETPY*	**9,52**	**0,22**	**9,30**
CVD events	1,81	2,92	-1,11
MI	0,72	1,63	-0,92
IS	0,11	0,26	-0,16
Fatal CVD	0,54	0,64	-011
Revascuarisation	0,65	1,65	-1,00
Costs (BGN)			
Total costs	**139 741**	**19 142**	**120 329**
Drugs	128 592	1432	127 160
Non-fatal acute CVD events	3239	7088	-3849
Fatal acute CVD events	1201	1545	-344
Post-events	3480	3381	99
ICER (acquired BGN/ETPY)			**12937**
Results of the probability analysis of sensitivity			

Average ETRY	9,51	0,22	9,29
Average price (BGN)	139 853	19 400	120 454
ICER (acquired BGN/ETPY)			**12 963**

SoC, standard of care; LY, life year; ETRY, effectively treated patient years CVD, cardiovascular disease; IS, ischemic stroke; HF, heart failure; ICER, inrcremental cost-effectiveness ration; MI, myocardial infarction

*With reduction

Discussion

The presented economic evaluation of the Bulgarian context shows that in HeFH patients the use of evolocumab added to SoC compared to only SoC results in an ICER of BGN 12,197 (USD 7215; EUR 6604) for ETPY.Sensitivity analyses confirm the robustness of model results.

Effectively Treated Patient Years (ETPY) is an intuitive and clinically significant indicator of the benefit to the patient, combining life expectancy with the probability of achieving internationally acknowledged recommendations on best practices for reduction of LDL-C with the purpose of reducing CVD events.Survival rate, consistent with the standard of care, may help decision makers to evaluate the overall result and the value of a new technology in comparison with the specified current practice.

The concept of effectively treated patients has been used in various indications to support decision-making and health care policy.Based on the presented data, the Health Technology Assessment Commission recommended the inclusion of evolocumab in the Bulgarian Positive Drug List.

The proposed efficacy criterion is useful in making decisions for HTA and is not subject to the price paradigm of the QALY, which recognises and takes into account the process-oriented factors of the value, in particular the standard of

care.The price data for QALY are insignificant in Bulgaria for various reasons.First, the financing decisions in the decentralized system of health care of the country are usually made within a certain therapeutic area and not on the basis of various indications, thereby significantly reducing the importance of the quality-adjusted life year (QALY) as a general benefit criterion.Second, population-specific date on the quality of life are scarce, which in practice hinders the calculation of QALY itself.Third, the use of the QALY price metric in Bulgaria is unlikely to contribute to its primary objective:promoting efficiency of distribution.Policy makers usually compare the additional costs for QALY for a technology with a predetermined threshold in order to evaluate its value. Within a fixed budget for health care, this threshold represents the alternative health costs, i.e. The alternative investments in health care that must be sacrificed as a result of the extra funds needed to pay for any new technology which increases the costs.Much more often, the size of this threshold has a small or no empirical basis; there is no mandatory consensus standard for it in Bulgaria.On the other hand, the WHO-CHOICE threshold of 1 to 3 times the GDP per capita is often applied.It has also been quoted by the National Council for Pricing and Reimbursement, but has several well-known deficiencies and is therefore controversial.The use of thresholds which do not reflect the alternative costs for a health system is not appropriate for the improvement of the health-related well-being of the population to which they serve.In addition, the evaluation of the real value of the threshold which represents the alternative health care costs by using empirical research, is a challenge because data requirements may be excessive.As far as we know, such attempts have not yet been made or are yet to be implemented in Bulgaria.

Over two-thirds of the Bulgarian population considers the overall quality of healthcare in their country to be bad, and 5.6% report unmet needs for health services, partly due to insufficient funding.Although the latter figure remains higher than the European average (3.6%), it has declined significantly over the last 4 years until 2014 - the last year with available data.The use of evolocumab in HeFH patients with increased risk of CVD and inability to control the levels of LDL-C with an established statin therapy provides an opportunity to contribute to the continuation of this positive trend.

There are a number of limitations in this analysis.The effectiveness of evolocumab for reduction of the prevalence of CVD events is estimated in the short-term reduction of LDL-C, assuming that it remains constant throughout the

duration of treatment.This is confirmed by the sustained reduction in LDL-C observed over 4 years with evolocumab in the open-label, randomised extension study OSLER-1 which includes HeFH patients as well.Moreover, if the levels of persistence and adherence to therapy with evolocumab in actual clinical practice differ from those in the study RUTHERFORD-2, the costs and efficiency of evolocumab will be influenced.Finally, the results of this analysis may not be summarised for populations other than HeFH, with a similar risk profile as described herein.

Conclusions

When used in HeFH patients who are unable to control LDL-C levels with high-intensity statin therapy and remain at high risk of CVD, the addition of evolocumab may be considered cost-effective given the additional costs of BGN 12,846 (EUR 6559) for the acquired patient year, during which the patients receive effective treatment under the terms of the international guidelines for prevention.[154]

7. DISCUSSION OF RESULTS

Cardiovascular diseases are the most common cause of death in Bulgaria causing more than 200 deaths per day in 2014. The most important modifiable risk factor for CVD is LDL-C. Patients with familial hypercholesterolemia having hereditary predisposition for high levels of LDL-C, are at a particularly high risk of cardiovascular diseases. Exposed to significantly increased levels of LDL-C since birth, they have a 20 times higher risk of cardiovascular diseases in comparison to the general population and typically manifest very early the symptoms of coronary heart disease (prior to 40 years of age) (Goldberg et al. 2011; Nordestgaard et al. 2013).

While statins are an effective therapeutic agent for reduction of LDL-C, they are often insufficient for control in patients with familial hypercholesterolemia. Actual practice data show that a very small percent of patients with familial hypercholesterolemia treated with the available therapeutic options achieve target levels of LDL-C, and for Bulgaria this percent is only 3.7% (EUROASPIRE IV). Without access to a new, more effective treatment, patients with familial hypercholesterolemia will remain vulnerable to severely increased cardiovascular morbidity and mortality.

Early diagnosis and monitoring of patients with familial hypercholesterolemia, as well as the prevention of cardiovascular diseases in them, is an increasingly relevant issue.The application of the Dutch Lipid Clinical Network Criteria and the

conduct of cascade screenings will help improve the outcomes in this high-risk population.

A major objective of health care systems in regard to chronic diseases leading to a serious risk of mortality and inherited in an autosomal dominant way is the establishment of informative registers covering a big portion of the affected population. The purpose of the onset of a register for patients with familial hypercholesterolemia is monitoring disease dynamics and determining the risk of cardiovascular diseases. A key moment here is defining the link between the main risk factors, the severity of the disease and the outcome for the patient.It is important to note the need to control the modifiable risk factors and determine how their dynamics change the cardiovascular risk for the patient.This, however, requires long-term follow-up of patients, an increase in the number of patients in the database, as well as expanding the range of monitored risk factors.The results of the register confirm for Bulgaria the established dependencies worldwide between familial hypercholesterolemia and the risk of cardiovascular morbidity and mortality, namely - high percentage of patients with FH and myocardial infarction, history of premature cardiovascular events, heredity.Also, a very small percentage of treated patients achieve the target values of LDL-C, as evidenced by randomised clinical trials in Europe and the United States.On the other hand, the pathognomonic findings - corneal arcus and tendon xanthomas, are observed in an extremely small portion of diagnosed patients, despite the definitive nature of the diagnosis.

The serious medical, economic and social aspects in patients with familial hypercholesterolemia are reported at global and European level – the World Health Organization and the European Parliament regard the disease of major priority of the health care policies of the countries.This is in line with the memorandum from the roundtable conducted on 24 September 2015 at the National Assembly of the Republic of Bulgaria under the auspices of the Committee on Health Care on the topic “Dyslipidemia – meaning, primary prevention and control”, which takes account of the need for taking effective measures to ensure adequate financing for a timely, accessible and modern treatment of severe dyslipidemia and familial hypercholesterolemia in Bulgaria.

One of the major problems in patients with familial hypercholesterolemia is the inability to achieve target levels of LDL-C with the conventional anti-lipid therapy - therapy with statins.According to EUROASPIRE IV, only 3.7% of FH patients in Bulgaria reach target LDL values.These results are also confirmed by the FH register - all of the included patients have significantly elevated LDL-C levels.

PCSK9 inhibitors offer effective treatment for these patients, providing a rapid and intense reduction in LDL-C levels only one week after the beginning of the treatment.

In a pilot, randomised clinical trial in patients with heterozygous familial hypercholesterolemia, the average change from baseline to weeks 10-12 is 61% in the group of patients receiving evolocumab 140 mg once every two weeks, compared with placebo (Raal et al. 2015;).Moreover, in 84% of patients there is at least 50% reduction in LDL-C compared to baseline.Other lipid parameters, including non-HDL-C and Lp(a), also improve during the trial.The results in patients with familial hypercholesterolemia are consistent with the results from other clinical trials with evolocumab where reduction of LDL-C of up to 75% is observed (Robinson et al., 2014; Stroes et al., 2014; Blom et al. 2014; Repatha SPC).In addition, the intensive reduction in LDL-C with administration of evolocumab is consistent regardless of the concomitant therapy and the baseline characteristics of the patients.Even in HoFH patients who are extremely resistant to treatment, the use of evolucumab is associated with a 32% reduction in LDL-C compared to placebo after 12 weeks of treatment (Raal et al., 2015; Repatha SPC).

It should be noted that evolocumab demonstrates a good safety profile.In analyses involving more than 6,000 patients, the discontinuation rate due to adverse drug reactions is similar to placebo.Neutralising antibodies have not been detected.

Trials involving patients with familial hypercholesterolemia indicate that reduced levels of LDL-C in treatment with evolocumab persist for an extended period of time - more than 2 years so far (Sabatine et al. 2015; Koren et al., 2015).The favourable safety profile of evolocumab is also consistent in the long run, while the additional analyses suggest a very strong link between its lipid-reducing effect and the improved cardiovascular outcomes, as well as reduction of cardiovascular morbidity and mortality (Sabatine et al., 2015).

The evaluation of the effects of evolocumab administration in the register is yet to be determined.This requires at least a one-year follow-up monitoring of the target patient population.

It is also crucial to determine the economic feasibility of the administration of PCSK9 inhibitors.The continued reduction in LDL-C of at least 50% is an important therapeutic target for patients with a very high risk of cardiovascular events, and the ones that achieve this target may be regarded as effectively treated (Reiner et al., 2011).The economic analyses show that evolocumab is a high-value effective therapy in this aspect, with a value an acquired year of an effectively treated

patient of BGN 12,846.[154] Moreover, it has been estimated that avoiding a single cardiovascular event is achieved in the treatment of only 7 patients with evolocumab.This also confirms the data from randomised clinical trials demonstrating the cost-effectiveness of evolocumab in FH patients.

8. CONCLUSIONS AND RECOMMENDATIONS

- The comprehensive review and analysis of the information on familial hypercholesterolemia shows a direct correlation between the existence, the risk of development and the severity of cardiovascular diseases.In Bulgaria, diseases of the circulatory system (including ischemic heart disease and cerebrovascular disease) cause more than 71,000 deaths per year (66% of all deaths).In 2014, 197 deaths due to CVD per day were reported for this country.Large-scale epidemiological studies have shown that elevated cholesterol in low-density lipoproteins (LDL-C) is the major reason for the cardiovascular risk.Familial hypercholesterolemia (FH) is a serious, hereditary disease characterized by consistently elevated LDL-C levels since birth.Affected individuals have a significantly increased risk of major CV events such as myocardial infarction (MI) or stroke, as they are frequently diagnosed with a clinically proven cardiovascular disease from an early age.Many FH patients are unable to achieve a significant LDL-C reduction with statins, because statins are either not effective enough even in maximum daily doses or the patients are intolerant to statins or have contraindications for their use.Therefore, the lack of effective or clinically appropriate treatment options in FH patients poses the highest risk of a serious CV event due to their exposure to chronically high levels of LDL-C throughout their lives.
- The collection of data and the analysis of the economic aspects in the treatment of familial hypercholesterolemia in Bulgaria clearly define the necessity of finding an alternative indicator appropriate for measuring the outcome of treatment in real-life conditions.The therapeutic algorithm is of particular importance in these patients, both from a medical and pharmacoeconomical point of view.The use of PCSK9 inhibitors is a promising alternative to the serious unmet medical needs of these patients.This is evidenced by randomised clinical trials and real clinical data.With a view to finding objective indicators for evaluation of the long-term effects of the use

of PCSK9 inhibitors, we must seek new approaches for determining the cost-effectiveness.Traditionally used QALY and LYG, in cases of chronic diseases with no therapeutic alternative, do not represent a maximum objective evaluation.The use of ETPY is a possible alternative for the evaluation of medicine technologies in such types of diseases.

- The drafting of a comprehensive concept for the establishment of a register in Bulgaria and criteria for disease monitoring is of utmost importance for the prevention of cardiovascular diseases in patients with familial hypercholesterolemia.In the period 2017-2018, together with the Society of Cardiologists in Bulgaria, a register of patients with familial hypercholesterolemia was introduced in Bulgaria - the first of its kind for the country.The patients were evaluated on the basis of the Dutch Lipid Clinical Network Criteria.At the same time, taking into account the current trends related to cardiovascular risk assessment, data were collected with respect to the risk of a cardiovascular event.The data from the initiated register for familial hypercholesterolemia clearly show that the major factor for the diagnosis of familial hypercholesterolemia in Bulgaria and worldwide is the level of LDL-C. The genetic diagnosis, as well as the establishment of tendon xanthomas and corneal arcus, regardless of the highly prognostic nature of a definitive diagnosis, occur very rarely in populations of patients with familial hypercholesterolemia.On the other hand, the detection of a family history of a cardiovascular disease and its premature development in the patient are becoming increasingly important indicators both in diagnostic terms and with a view to the subsequent treatment.

- This scientific paper adapts and explores the possibilities for introduction of globally recognized algorithm recommendations for diagnosis and treatment of familial hypercholesterolemia.The evaluation of familial hypercholesterolemia in the medical, social and economic context proves the significance of the disease in regard to the cardiovascular risk and the mortality rate.Therefore, the implementation of early diagnosis, the prevention of cardiovascular risks and the early treatment are critical from the point of view of the patient (the public) and the health insurance system in Bulgaria.The use of the Dutch Lipid Clinical Network Criteria is particularly beneficial in diagnostic terms, in the cascade screening for early identification in the pre-clinical stage and in the use of registers for determining the basic

risk factors, their monitoring and modification for the reduction of cardiovascular mortality.The cascade family screening of first-degree relatives in patients with familial hypercholesterolemia is mandatory and shows how the disease and the mutation is transmitted to the next generation. On the other hand, the introduction of new drug approaches in patients with dyslipidemia and high cardiovascular risk is essential for the reduction of the risk of incidents.PCSK9 inhibitors are an appropriate option given the available results of randomised clinical trials.The guidelines of ESC and EAS for treatment of dyslipidemia are also being developed in this direction.

- A practical approach to control severe and inherited forms of dyslipidemia and monitor patients has been suggested.Early diagnosis and early beginning of treatment are crucial.The introduction of registers of patients with hereditary dyslipidemia and the monitoring of the modifiable factors for development of cardiovascular pathology as a value of LDL-C, smoking, control of concomitant diseases - diabetes and arterial hypertension - could lead to the reduction of the risk of cardiovascular morbidity and mortality.

9. CONTRIBUTION OF THE DISSERTATION

9.1 Contribution of scientific and theoretical nature:

- The issue of dyslipidemia with regard to the risk of cardiovascular diseases has been comprehensively and systematically defined.
- A thorough analysis of the risk categories of patients has been carried out in accordance with the recommendations of ESC and EAS.
- For the first time, the available therapeutic alternatives for dyslipidemia therapy have been evaluated in terms of unmet medical needs.

9.2 Contribution of scientific and applied nature:

- The objective, the contents and the importance of the first register of patients with familial hypercholesterolemia in Bulgaria have been presented.
- A practical algorithm for early diagnosis has been proposed using the Dutch Lipid Clinical Network Criteria and the cascade screening for patients with familial hypercholesterolemia.
- The necessity of greater attention towards FH by society, health authorities and medical specialists has been statistically proven because of its crucial role in the formation of cardiovascular morbidity and mortality.
- The potential patient populations with maximum effects from the use of PCSK9 inhibitors and the clinical and economic benefits of the new therapeutic options have been studied and evaluated.

10. LIST OF SCIENTIFIC PUBLICATIONS IN CONNECTION WITH THE DISSERTATION

1. Borislav Borissov, Michael Urbich, Boryana Georgieva, **Svetoslav Tsenov** and Guillermo Villa. Cost-effectiveness of evolocumab in treatment of heterozygous familial hypercholesterolaemia in Bulgaria: measuring health benefit by effectively treated patient-years.JOURNAL OF MARKET ACCESS & HEALTH POLICY (ISSN 2001-6689), 2017, vol.5, number 1, p.1412753, doi:10.1080/20016689.2017.1412753. eCollection 2017.
2. **Svetoslav Tsenov**, Evgeni Grigorov, Plamen Dimitrov.Social significance of familial hypercholesterolemia. BULGARIAN JOURNAL OF PUBLIC HEALTH (ISSN 1313-860X), 2018, Volume 10, Issue 4, pp. 3-14
3. **Svetoslav Tsenov**, Evgeni Grigorov, Boris Bogov.Familial hypercholesterolemia - comparison of the clinical and genetic diagnoses. CONTEMPORARY MEDICINE (ISSN 0562-7192), 2019, Volume 63, Issue 1, pp. 39-45.
4. **Svetoslav Tsenov**, Boris Bogov.Hyperlipidemia and risk of cardiovascular diseases. CONTEMPORARY MEDICINE (ISSN 0562-7192), 2019, Volume 63, Issue 1, pp. 29-38.

11. LIST OF SCIENTIFIC PARTICIPATIONS AND SCIENTIFIC FORUM REPORTS

1. **Svetoslav Tsenov**, Tsvetelina Stefanova, Evgeni Grigorov.Prevention of familial hypercholesterolemia - significance for pediatric patients. First International Pediatric Scientific and Practical Conference "Together for Bulgaria's Children", 12-14.03.2019.Varna, Bulgaria
2. **Svetoslav Tsenov**, Tsvetelina Stefanova, Evgeni Grigorov. National Student Conference on Pharmaceutical and Chemical Sciences, 4-5.04.2019,Sofia, Bulgaria
3. Borislav Borissov, Michael Urbich, Boryana Georgieva, **Svetoslav Tsenov** and Guillermo Villa. Cost-effectiveness of evolocumab in treatment of HeFH in Bulgaria: Measuring health benefit by effectively-treated patient-years (ETPY). ISPOR 22nd Annual International Meeting, Boston, USA, May 20-24 2017