



Familial Hypercholesterolemia Identification Algorithm in Patients with Acute Cardiovascular Events in A Large Hospital Electronic Database in Bulgaria: A Call for Implementation

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ABSTRACT

Background: Familial hypercholesterolemia (FH) is a genetic disorder characterized by a high level of low-density lipoprotein cholesterol (LDL-C) and is an important cause for premature cardiovascular disease. Because of underdiagnoses, an acute event is often the first clinical manifestation of FH. There are limited data on the prevalence and treatment of FH among adults admitted for treatment of acute

cardiovascular events in Bulgaria. Our objective was to assess the proportion and management of FH patients from those admitted to hospital for treatment of acute symptomatic acute atherosclerotic cardiovascular events (ASCVD), the achievement of LDL-C targets of European Society of Cardiology/European Atherosclerosis Society guidelines and related public healthcare resources.

Objective: Digitalized healthcare records for patients admitted for treatment of symptomatic ASCVD acute events between August 2018 and August 2019 were used for the analysis. Five cardiology hospitals provided data for hospitalizations, laboratory tests, and ambulatory follow-ups up to February 2020. Patients'

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hospital and ambulatory records were linked, and medical histories were extracted via a specifically developed algorithm, and analyzed. Outcomes included the proportion of patients classified as FH as defined by the Dutch Lipid Network Criteria (DLNC), use of lipid-lowering therapy, LDL-C achieved by 1, 3, 6, and 12 months post-index event, and public resources spent on hospital and ambulatory treatment.

Results: We reviewed 11,090 hospital records of patients admitted for treatment of acute events in the period August 2018–August 2019 with ICD codes for ASCVD (Supplementary Table S3). FH was identified in 731 (6.6%) patients, with DLNC score ≥ 3 , (682 with coronary artery disease, 32 with cerebrovascular disease, and 17 with peripheral artery disease). We did not find the criteria for FH in 5797 patients. The remaining 4562 records were inconclusive due to lack of data in the hospital dossier. Less than half of FH patients (274/731, 37%) were discharged on high-intensity statin therapy prescribed (34/731, 5%) with combination therapy. The vast majority (96.2% with LDL-C ≥ 1.8 mmol/l) had poorly controlled LDL-C during the first year after discharge. Patients with a probable/definite DLNC score ≥ 6 points and those with recurrent events contributed to the higher cost paid both by the healthcare system and the patients themselves.

Conclusion: These findings reinforce the need for more aggressive lipid-lowering therapy, and underline the efficiency of using an electronic medical records search tool to support physicians in improving early FH diagnosis, aiming to minimize residual and future ASCVD events among FH patients and their family members. Supplementary file1 (MP4 21838 KB)

Keywords: Dyslipidemia; Familial hypercholesterolemia; Dutch lipid network criteria (DNLC); Electronic hospital database (EMR); Health care resource utilization (HRU); Coronary artery disease (CAD); Peripheral artery disease (PAD); CVD (coronary, peripheral, and cerebral (arterial) disease)

Key Summary Points

Why carry out this study?

There are limited data on the proportion and management of familial hypercholesterolemia (FH) among adults admitted for treatment of acute cardiovascular events. Because of under-diagnosis, an acute event is often the first clinical manifestation of FH

This retrospective observational study aimed to use specifically designed software to enable data extraction of routinely treated patients admitted for ASCVD acute events to screen for FH by using all available medical records

What was learned from the study?

This is the first study to assess the proportion of FH patients, hospitalized for an acute event, and associated management practice in a large sample of in-hospital settings in Bulgaria using an electronic medical records algorithm

The vast majority (96.2% with LDL-C ≥ 1.8 mmol/l) had poorly controlled LDL-C during the first year after discharge. Patients with probable/definite DLNC score > 6 points and those with recurrent events contributed to the higher cost paid both by the healthcare system and the patients themselves

The implementation of the automated screening tool may be of advantage for physicians, reinforcing early FH identification and improving patient pathways and outcomes

DIGITAL FEATURES

This article is published with digital features, including a summary slide and video abstract, to facilitate understanding of the article. To

view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13360208>.

INTRODUCTION

Familial hypercholesterolemia (FH) is a common genetic disorder, which causes accelerated atherosclerosis, premature cardiovascular (CV) disease and increased CV morbidity and mortality [1]. While the prevalence of FH ranges from approximately 1 in 250 to 1 in 500, there are limited data regarding the number of patients with FH who are hospitalized for an acute CV event [2, 3]. Moreover, systematic screening and early identification of FH during hospitalization would improve patient treatments and outcomes. For example, compared to patients without FH, those with FH and acute coronary syndrome (ACS) are more than twice as likely to experience subsequent CV events during the first year following discharge, despite concomitant use of high-intensity statin therapy [4–8]. During hospitalization, screening for FH can be performed at low cost using specifically designed algorithms, which search electronic medical records (EMR) for hospital admissions, patient histories, and laboratory tests. Moreover, early identification and treatment of patients with FH and their family members may reduce the risk of recurrent CV events. In Bulgaria, FH has only recently (2017) been added to the list of ICD codes for disease reimbursement by the National Health Insurance Fund (NHIF).

We used specifically designed software to search the EMR of patients admitted to hospital for the treatment of an acute CV event and to identify those with undiagnosed FH.

METHODS

Study Objective and Outcomes

The primary outcome was the proportion (%) of patients with undiagnosed FH.

Secondary outcomes included: (1) patient demographics, clinical characteristics, and lipid-lowering therapy (LLT); (2) achievement

of the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) LDL-C goal of ≤ 1.8 mmol/L 1, 3, 6 and 12 months after the index hospitalization; (3) recurrent events at index hospitalization and time to subsequent event(s); (4) healthcare resource utilization (HRU) related to CV events, specified as ambulatory medication treatment cost after index hospitalization, paid with public money, and the cost paid out-of-pocket.

Data Source and Inclusion Criteria

This retrospective database analysis used digitalized records across five hospitals and the EMR software to extract data for patients admitted for an acute CV event in the period August 2018–August 2019 (index hospitalization).

The search algorithm is described in Fig. 1; the ICD-10 codes are listed in Table S3.

Three patient cohorts were identified: (1) FH with Dutch lipid network criteria (DNLC) score ≥ 3 points, (2) Non-FH, and (3) Unknown (insufficient data to calculate DLNC score).

The Unknown group had to be defined in our database because of missing lipid profiles needed to calculate Dutch score in some patients. In these cases, it was not possible to further derive this information because there is no regulation in Bulgaria for patients with ASCVD for lipid profile testing.

Data Collection

Data were extracted from hospital dossiers, including hospitalization records, laboratory tests, and ambulatory visits (up to February 2020). Patient demographics, ASCVD history, comorbidities, LLT medication, type of index CV event, and risk scores (calculated during hospitalization) were extracted.

The follow-up period was defined as 6–12 months from the index hospitalization until 1 February 2020 (end of follow-up period). The following groups were analyzed:

- (1) Patients ($n = 158$) who visited the same hospital ambulatory department at 1, 3, 6 or 12 months, and had at least 1 LDL-C

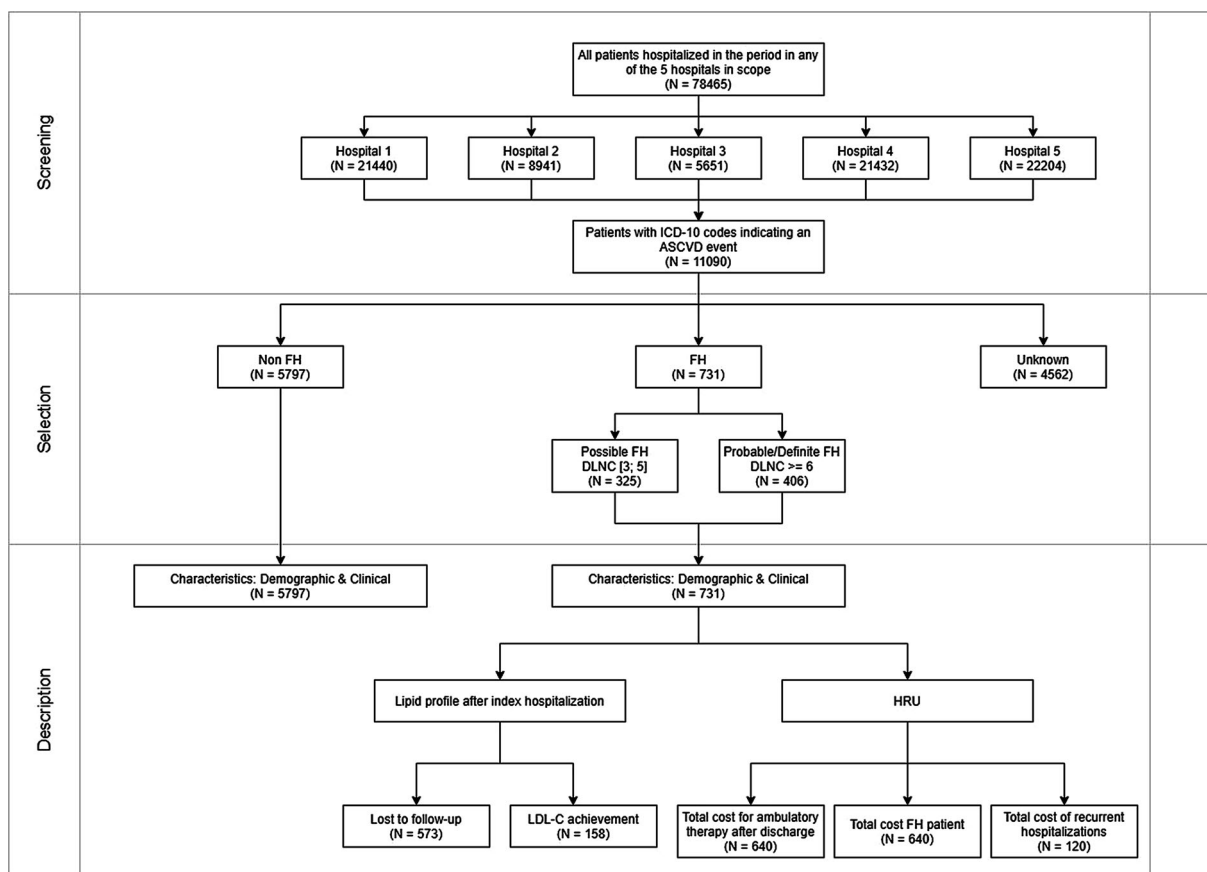


Fig. 1 Flowchart of the search algorithm

measurement. The group were analyzed for LDL-C achievement according to ESC/EAS 2016 goals

- (2) Patients ($n = 174$) who had a change in LLT dose or type of medications during the visits. This group was analyzed for more precise monthly costs of ambulatory treatment.

LLT before admission and at the time of hospital discharge were extracted. For patients who visited the same hospital during the follow-up period, ambulatory LLT post-index hospitalization was also extracted.

HRU included prescribed ambulatory LLT following discharge and recurrent hospitalizations. Published list prices were used for ambulatory LLT (dependent on the level of reimbursement and price on the date of discharge). For each patient, total ambulatory LLT cost for 1 month was calculated in local

currency (BGN) as amounts paid with public money (NHIF-paid) and co-paid by the patient (patient-paid).

Data Extraction

We used the Danny Platform [9], which tracks patients between different hospitals, laboratories, and others. This platform does not store personal information and the patient's personal identification number is anonymized using a hashing algorithm; the resulting hashed personal number is the same across all sources and allows patients to be tracked without identifiable details.

While some incoming data were already parameterized, a substantial amount was free text, typed manually by doctors and/or other healthcare professionals. Additional pre-processing and extraction steps were performed

upon data import. This included the aggregation of transactional-level data into a unified data structure amenable for interpretation and NLP (Natural Language Processing) entity extraction. Specific parameter values were extracted and normalized using several approaches, i.e., regular expressions, string matching, word similarities, and more advanced NLP approaches. The suitable approach chosen was contingent on a continuous detailed analysis of the free text and the parameters.

Data Normalization

Upon parameter value extraction, the values required additional normalization due to the high heterogeneity in syntax across the different data sources. A rule-based approach was used to normalize each parameter. When the system was unable to find a normalization rule, the parameter was flagged and required additional follow-up by the quality control experts to create new normalization rules. The database kept an up-to-date list of rules for the continuous parsing and persistence of incoming data.

Identification of Patients With FH

We assessed the presence of FH using the validated DLNC algorithm [10], which is approved for clinical use in Bulgaria by the NHIF. For patients on LLT at index hospitalization, we estimated untreated LDL-C by multiplying the on-treatment LDL-C by a correction factor [23] based on LLT type and dose, which is accepted by the NHIF in general practice.

Patients with DLNC scores 3–5 were defined as *possible* FH diagnosis, those with DLNC scores 6–8 as *probable* FH, and those with DLNC ≥ 9 as *definite* FH. Due to the small sample size, *definite* and *probable* FH were combined into one group, “*definite/probable*”, and patients in this group considered to have clinically defined FH.

An NLP algorithm was developed to identify patients with arcus cornealis, tendon xanthoma, or stated FH. The records of these patients were verified by physicians, and a DLNC score awarded wherever appropriate.

Statistical Analysis

Patient demographics and clinical characteristics were summarized using descriptive statistics. Categorical variables were reported as numbers and percentages (n , %). Continuous variables were reported as mean \pm standard deviation (SD) for normally distributed data, and median and 25%–75% percentiles (Q1–Q3) used for non-normally distributed data.

DLNC scores were calculated for patients having a complete medical dossier, and three patient cohorts were identified: (1) FH with DLNC score ≥ 3 points, (2) Non-FH, and (2) Unknown (insufficient data to calculate DLNC score).

Statistical significance for a given variable between the FH groups was assessed with the Chi-squared test (for categorical variables) or the (non-parametric) Mann–Whitney U test (for numerical variables). P values < 0.05 were considered statistically significant. Shapiro–Wilks tests and Levene’s tests were performed to test for normality and homogeneity of variance, respectively. Time-to-event analysis was performed using the Kaplan–Meier method, with 95% confidence intervals estimated using Greenwood’s formula.

RESULTS

Patient Disposition

Among 11,090 patients with index hospitalizations for acute CV events during the period 1 August 2018–1 August 2019, our DLNC algorithm identified 731 (6.6%) with FH: *possible*, $n = 325$ (44%), and *probable/definite*, $n = 406$ (56%) (Fig. 1). A total of 5797 patients were classified as Non-FH, while 4562 had incomplete data and were excluded from the analysis.

Patient Characteristics

Table 1 summary demographics and baseline characteristics for patients with and without FH. Data for Possible vs Probable/Definite FH is reported in Supplementary Table S1.

Compared to patients without FH, those with FH were younger (52.5 vs. 65.4 years); the majority (81%) of FH patients were aged 41–60 years at the index hospitalization for an acute CV event, whereas most (68%) patients without FH were aged > 60 years.

One-third (33%) of FH patients were female, compared to 40% of Non-FH patients.

Approximately one-third (36%) of FH patients had a history of prior CV events, compared with only 5% of Non-FH patients. In both groups, coronary artery disease (CAD) was the most common cause of index hospitalization (FH, 93%; Non-FH, 82%); a cause of CVD was more likely among non-FH patients (16% vs. 4%, respectively); across both groups, few patients were hospitalized for peripheral artery disease (PAD). The presence of comorbidities was similar among patients with and without FH.

Mean age was similar in the possible and probable/definite FH groups (52.3 and 52.6 years, respectively), and the majority of patients were aged 41–60 years at index hospitalization (probable/definite, 80%, possible FH, 82%) (Supplementary Table S1). Patients with probable/definite FH were more likely to have a prior CV event (43% vs. 26%).

Fewer possible FH patients were smokers (3.7% vs. 23.2%, $p < 0.001$) and diabetic (10% vs. 15%, $p < 0.001$).

LDL-C Levels and Laboratory Measurements

LDL-C was either calculated (Friedewald's formula) or directly measured (as per routine laboratory practice in cases of triglyceride level > 4.5 mmol/l). Compared with the Non-FH group, median (Q1, Q3) LDL-C was higher among patients with FH: 4.2 (3.3–4.8) vs. 2.9 (2.1–3.7) mmol/l.

Median (Q1, Q3) LDL-C was similarly high in the possible and probable/definite FH groups: 4.1 (2.9–4.6) and 4.3 (3.5–5.2) mmol/l, respectively. Total cholesterol was also high: 5.9 (4.8–6.5) and 6.1 (5.3–7.3) mmol/l, respectively.

Cardiac markers to assist diagnosis measured in routine clinical practice median (Q1, Q3),

creatinine phosphokinase and C-reactive protein (cardiac markers used to diagnosis FH), were higher in the FH group (96 (23–202.5) and 8.3 (3–20.6), respectively, compared to the Non-FH group [75 (22–134) and 8.1 (2.3–31.3), respectively]. Creatinine and troponin plasma levels were similar in FH and non-FH patients.

LLT

LLT use before index hospitalization and at discharge is summarized in Supplementary Fig. S1.

Data for LLT use before index hospitalization were not available for two-thirds [495 (68%)] of FH and three-quarters [4429 (76%)] of Non-FH patients, suggesting they may have been untreated or LLT was not recorded. Among patients with data available, most patients in the FH and Non-FH groups were treated with statin monotherapy [218/236 (92%) and 1309/1368 (95%)]. Only 29% (67/232) and 18% (245/11,357) of FH and non-FH patients were treated with high-intensity statins. LLT use in patients with possible or probable/definite was similar.

Data for LLT after discharge were available for three-quarters [544/731 (74%)] of FH and 41% (2389/5797) of Non-FH patients. The reasons for the missing records may be differences in hospital IT systems and/or the possibility for providing the data for analysis. Another reason may be that home therapy is not included in the information reported daily to the NHIF as it is within GPs' responsibility.

Compared with LLT before index hospitalization, use of high intensity statins among patients with FH increased at discharge [274/541 (50%) and 67/232 (29%), respectively]. High-intensity statin uses also increased among Non-FH patients. Only 6.2% (34/544) of FH and 2% (50/2389) of Non-FH patients received combination therapy at discharge. Notably, CV events led to an increase in the intensity of statin treatment for FH (from 29 to 51%) versus (18–40%) for the Non-FH group ($p < 0.001$).

Table 1 Baseline demographic and clinical characteristics of patients with FH (731) and Non-FH (5797) by diagnostic algorithm

	DLNC				<i>p</i> value
	FH (<i>n</i> = 731)		Non FH (<i>n</i> = 5797)		
	<i>n</i>	Characteristic value	<i>n</i>	Characteristic value	
Age at index hospitalization years, mean ± SD		52.5 ± 8.1		65.4 ± 11.6	< 0.001
Age groups at index hospitalization, <i>n</i> % (95% CI)					
≤ 40	45	6.2 (4.6–8.1)	136	2.3 (2.0–2.8)	< 0.001
41–50	231	31.6 (28.3–35.1)	522	9.0 (8.3–9.8)	< 0.001
51–60	359	49.1 (45.5–52.7)	1218	21.0 (20.0–22.1)	< 0.001
> 60	96	13.1 (10.9–15.8)	3921	67.6 (66.4–68.8)	< 0.001
Female, % (95% CI)	243	33.2 (29.9–36.7)	2326	40.1 (38.9–41.4)	< 0.001
Height, cm, mean ± SD	71	173.8 ± 11.4	536	169.9 ± 9.3	0.003
Weight, kg mean ± SD	74	89.5 ± 19.7	554	83.6 ± 20.5	0.004
BMI, kg/m ² mean ± SD	71	29.7 ± 5.7	533	28.9 ± 6.0	0.154
Comorbidities, <i>n</i> %					
Hypertension	371	50.8 (47.1–54.4)	3088	53.3 (52–54.6)	0.213
Diabetes	93	12.7 (10.5–15.3)	975	16.8 (15.9–17.8)	0.006
Prior CV events	261	35.7 (32.3–39.2)	305	5.3 (4.7–5.9)	< 0.001
CV index event, <i>n</i> %					
CAD	682	93.3 (91.2–94.9)	4733	81.6 (80.6–82.6)	< 0.001
CVD	32	4.4 (3.1–6.1)	905	15.6 (14.7–16.6)	< 0.001
PAD	17	2.3 (1.5–3.7)	159	2.7 (2.4–3.2)	0.593
Objective measures median (Q1–Q3)					
TH, mmol/l	594	6 (5.1–6.9)	4376	4.7 (3.8–5.7)	< 0.001
LDL-C, mmol/l	730	4.2 (3.3–4.8)	4966	2.9 (2.1–3.7)	< 0.001
TGL, mmol/l	588	1.8 (1.2–2.7)	4367	1.4 (1.0–2.0)	< 0.001
HDL-C, mmol/l	576	1.1 (0.9–1.4)	3785	1.1 (0.9–1.4)	0.274
Creatinine, mmol/l	603	87.4 (75–100)	4712	90 (77–110)	< 0.001
CFK, IU/l	426	96 (23–202.5)	3142	75 (22–134)	< 0.001
CRP, mg/l	47	8.3 (3.0–20.6)	402	8.1 (2.3–31.3)	0.877
Troponin, ng/L	496	0.2 (0.0–1.2)	3357	0.2 (0.0–0.6)	0.146
SYNTAX, score median (Q1–Q3)	42	10.5 (6–16)	416	12.0 (8–18)	0.177
GRACE, score median (Q1–Q3)	225	145 (139–152)	1877	155 (143–173)	< 0.001

Table 1 continued

	DLNC				<i>p</i> value
	FH (<i>n</i> = 731)		Non FH (<i>n</i> = 5797)		
	<i>n</i>	Characteristic value	<i>n</i>	Characteristic value	
LLT before index hospitalization, <i>n</i> /total, <i>n</i> %					
Mono	218/236	92.4	1309/1368	95.7	0.042
Combination	18/236	7.6	59/1368	4.3	0.042
High-intensity	67/232	28.9	245/1357	18.1	< 0.001
Non-high-intensity	150/232	64.7	1024/1357	75.5	< 0.001
LLT after discharge, <i>n</i> /total, <i>n</i> %					
Mono	510/544	93.8	2339/2389	97.9	< 0.001
Combination	34/544	6.2	50/2389	2.1	< 0.001
High-intensity	274/541	50.6	953/2381	40.0	< 0.001
Non-high-intensity	261/541	48.2	1401/2381	58.8	< 0.001

Data for Possible versus Probable/Definite FH are reported in Supplementary Table S1. Continuous variables are given as *n*; mean \pm SD, or median, Q1–Q3. Categories variables are presented as *n* % (95% CI). Laboratory measurements are derived from hospital records

Prior CV event is taken from the medical history part of the hospital dossier and is manually annotated only for FH with DLNC score \geq 3 points. Thus, bias might be created on account of the Non FH group. Hypertension is defined as systolic blood pressure \geq 130 mmHg and use of blood pressure-lowering drugs. LLT lipid lowering therapy is taken from the medical history part of the hospital dossier (ATC C10) and from discharge hospital documents. High-intensity statin therapy is defined as Atorva \geq 40, Rosuva \geq 20, and Simva 80 mg/daily.

CI confidence interval, BMI body mass index, CHD chronic heart disease, CAD coronary artery disease, PAD peripheral artery disease, CVD cerebrovascular disease, TH total cholesterol, LDL low density protein, HDL high density protein, CPK creatine phosphokinase, CRP C-reactive protein

CV Risk Scores

CV scores were calculated using SYNTAX (coronary anatomical) and GRACE (clinical) scores.

SYNTAX is an angiographic grading tool to determine the complexity of CAD, a useful differentiator for the outcome of patients undergoing three-vessel PCI. The high scores indicate complex coronary anatomy and represent greatest risks to patients undergoing PCI, bigger therapeutic challenge and worsen prognosis. SYNTAX score was found to be an independent predictor of long-term major adverse cardiac and cerebrovascular events (MACCE) and of death in patients treated with PCI [23, 24].

A residual SYNTAX score $>$ 8 after PCI was associated with significant increases in the 5-year risk of death and of the composite of death, myocardial infarction (MI), and stroke, and any residual SYNTAX score $>$ 0 was associated with the risk of repeat intervention [25]. No difference in median (Q1–Q3) SYNTAX score was observed between FH and Non FH group 10.5 (6–16) and 12.0 (8–18); $p = 0.176$). A modest increase between the probable/definite and possible FH groups, median 12.5 (8.5–16.2) vs. FH 7 (5.2–16.0) ($p = 0.169$).

GRACE is a system to stratify patients with diagnosed ACS to estimate in-hospital and 6-month to 3-year mortality. Median (Q1–Q3) GRACE score was similar in the FH and Non FH

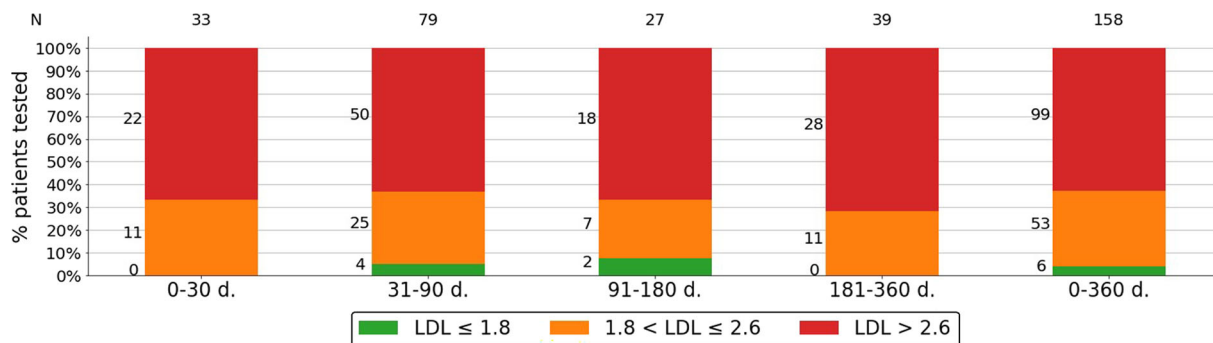


Fig. 2 LDL-C attainment at 1st, 3rd, 6th and 12th months after index hospitalization (*n* = 158). Number of patients achieving LDL-C target (2016 ESC/EAS) during the follow-up period post index hospitalization. Each bar

represents (100%) patients who visited ambulatory departments after index hospitalization discharge within the prespecified in the protocol follow-up period and had LDL-C measurements recorded

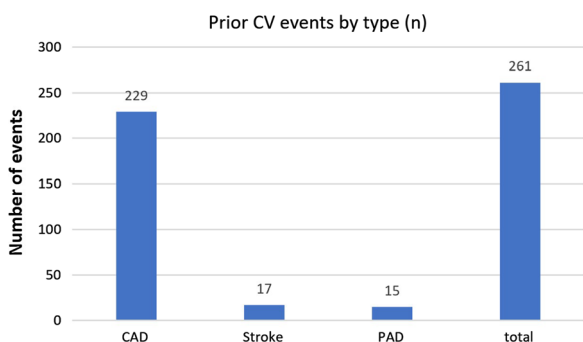


Fig. 3 Prior CV events by type before index hospitalization of patients with events prior the index hospitalization (August 2018–August 2019). *n* = 261; CAD = 229, 87.7%; CVD = 17, 6.5%; PAD = 15, 5.7%

1.8 mmol/l or lower between the 1st and 3rd month; 7.4% (2/29) between the 3rd and 6th month.

Recurrent Events in FH Patients

A total of 261 FH (35.7%) patients had a documented history of prior CV events [CAD, *n* = 229 (88%); PAD, *n* = 15 (5.7%); CVD, *n* = 17 (6.5%)] with the index hospitalization being the most recent event (Fig. 3). For this group, their previous CV events mentioned in the medical history were manually annotated. Among FH patients with a documented history of prior CV events, 154 (59%) had at least 1 prior event, 64 (24%) had 2 prior events, 28 (11%) had 3 prior events, and 15 (6%) had more than 3 prior events. In time-to-event analysis, we observed a progressive decrease in time to the next CV event with increasing numbers of prior CV events (median time dropped from 29 to 22 months) (Supplementary Fig. S3). Following the index hospitalization, 135 (18%), FH patients had recurrent CV events which required hospitalization during the follow-up period (Table 2). A substantial proportion of CAD patients had subsequent re-hospitalizations: *n* = 118, 87.4% (95% CI, 80.8–92.0); with PAD: *n* = 10, 7.4% (4.1–13.1); and with CVD: *n* = 7, 5.2% (2.5–10.3).

groups [145 (139–152) and 155 (143–173), respectively;], and in the possible and probable/definite FH groups [146 (5–26) and 143 (137–150); respectively].

Risk-based LDL-C Goal Achievement

Among all FH patients, 158 had available information for out-patient visits in the same hospitals—constituting to the cohort we followed up for 6 months and 39 patients for 12 months. LDL-C ambulatory results are shown at Fig. 2. Among patients with 12-month follow-up only 5% (4/79) reached the 2016 recommended ESC/EAS goal while on LLT therapy and had their LDL-cholesterol levels of

HRU

Total ambulatory costs are reported in Table 3. Costs were higher in the probable/definite FH group than in the possible FH group.

Total 1-year treatment costs could not be calculated for the FH group due to lack of data for implants and additional charges paid during hospitalization. FH patients with recurrent events (Table 4) had higher costs due to repetitive hospitalization.

Patients who visited hospitals after the index event for medication adjustments had lower ambulatory costs of 89.60 (111.90) BGN than others (lost to follow-up), 95.70 (110.70) BGN.

DISCUSSION

To the best of our knowledge, this is the first study to assess FH inpatients hospitalized for acute CV events and their clinical management (in-hospital and ambulatory) in Bulgaria. This study used anonymized electronic data from 11 090 hospital dossiers with ICD (Supplementary Table S3) codes for ASCVD, across large academic hospitals in three different regions of Bulgaria (southwest, northwest, and south central). We identified 6.6% (1:15) of patients treated for ASCVD to have FH; these tended to be younger individuals, with poorly controlled LDL-C during the follow-up period. We identified 44% of patients to have possible FH and 56% to have probable/definite FH. Due to the lack of national data, we cannot compare our results with the general population of ASCVD patients in Bulgaria. Importantly, many patients were not recognized as FH during their index hospitalization. In our sample, we worked only with records which had available data to calculate DLNC scores, predominantly by LDL-C levels, LLT with dose to calculate back untreated LDL-C values by regression coefficients [22], and family histories for prior hospitalizations events. We did not find mention of relatives with FH or premature atherosclerosis and arcus cornealis, but for xanthomas we found 4 patients. Given the incompleteness and high numbers of medical records (4562) marked as Unknown and excluded from the analysis, we

may estimate that the true FH proportion is under-represented, and that FH diagnosis is widely unrecognized. Thus, many individuals are left without appropriate therapies to control their elevated CV risk.

The only study describing clinical management of HR and VHR subjects with FH in Bulgaria [11] highlights that many subjects (73.6%) with FH have first-degree relatives with known risk factors such as coronary and/or vascular disease or high LDL-C levels; however, this important information was missing in the hospital dossiers, suggesting that the proportion of FH patients with ≥ 6 points could be even higher.

A systematic review and meta-analysis of 19 studies [12] conducted in various countries reported FH prevalence in the general population as 0.4% (1:250). One potential reason for higher figures in the present study could be the difference in the population. Participants in our study were in- and out-patients admitted for treatment of acute ASCVD events, who were likely to have cardiovascular risk factors and clinical disease severe enough to warrant intervention. Hence, our result may be more useful for healthcare professionals than population-based studies, because they treat similar patients in routine clinical practice. Another potential reason for the higher prevalence could be the use of different diagnostic criteria, e.g., DLNC, which is clinically established and acknowledged by the National health reimbursement fund. In the present study, 93% ($n = 682$) of the FH cohort were hospitalized for CAD. Given the high proportion of coronary patients, even though this figure is a proportion value, not the prevalence, it could be deemed to be a reference value for the prevalence of ACS in patients with FH in Bulgaria.

Several studies have reported the prevalence of FH in patients with ACS. For example, in a Swiss multicenter study, SPUM-ACS, (Special Program University Medicine-Acute Coronary Syndrome) [5, 6] of 4778 patients with ACS, 1.6% ($n = 78$) had probable/definite FH (DLNC > 5 points). However, when limited to patients with premature ACS (defined as men aged ≤ 55 years and women ≤ 60 years), the FH prevalence increased to 4.8%. In an analysis, the

Table 2 Number of patients and number of subsequent hospitalizations

CV event (index hosp.)	<i>n</i>	% (95% CI)	1 incident	2 incidents	3 incidents	4 incidents
CAD	118	87.4% (80.8–92.0)	103	11	2	2
PAD	10	7.4% (4.1–13.1)	6	4	0	0
CVD	7	5.2% (2.5–10.3)	5	2	0	0
Total	135	100.0%	114	17	2	2

Subsequent hospitalization is a hospitalization after the index one until the end of the observation period (February 2020)
n number of patients

Table 3 Total ambulatory 1 month costs for FH patients after index hospitalization

	Cost of FH patient ambulatory treatment, BGN mean ± SD (<i>n</i> = 640/731)
NHIF reimbursed amount	43.70 ± 85.30
Patient paid amount	52.00 ± 40.70
Total amount 1 month	95.70 ± 110.70

The cost for ambulatory treatment is extracted from the discharge documents
n number of patients, *SD* standard deviation.

EUROASPIRE IV survey [4] (European Action on Secondary and Primary Prevention through Intervention to Reduce Events) which included c.7000 patients hospitalized for ACS or revascularization procedures (79 large academic hospital centers), the prevalence of FH was estimated at 8.3% and increased to 15.4% when restricted to 2212 patients < 60 years. Singh A et al. [13] reported that, based on the YOUNG-MI registry (1996 adults), nearly 1 in 10 patients with MI (9%) met criteria for clinically defined FH, at or below the age of 50 years.

Other smaller studies have also estimated the prevalence of FH in different countries: Pang et al. [8] found FH prevalence to be 14.3% among 175 patients age < 60 admitted in cardiology settings in Australia, while Al-Rasadi

Table 4 Cost for FH patients with a recurrent event after index hospitalization in the 6 months follow-up period

	Cost of hospitalization of FH patients with a current event in 6 months after index hospitalization, BGN mean ± SD (<i>n</i> = 120)
Hospitalization cost	6942.90 ± 2894.80

A total of 120 patients had 249 events leading to hospitalization in the 6 months period, index hospitalization included. From all patients in the FH group, only patients that have reoccurring events that lead to hospitalization in the 6 months after the index hospitalization follow-up period are included when calculating numerical variables. Index hospitalization is included. Hospitalization prices change in time, thus are taken from a price list based on date of each hospitalization
n number of patients

et al [14] reported FH prevalence of 3.7% in a cohort of 3224 patients with ACS in the Arabian Gulf. The wide variations in the reported estimates in these studies may be related to the variability of the true prevalence of FH across distinct potentially genetically diverse populations [15] and to the criteria used to define FH [16]. Although the prevalence varied widely, it is much higher than in the general population, underlying the importance of lipid level control in the prevention of cardiovascular diseases.

Identification of FH is important, as the disorder is associated with early onset of CHD. In our study, we found that one-third of FH patients (*n* = 261, 35%7) had prior CV events,

which is sevenfold higher compared with Non-FH ($n = 305$, 5.2%).

In the present study, the proportion of possible (3–5) and probable/definite (≥ 6) FH patients who used LLT were similar.

Statins are the recommended first-line therapy to lower LDL-C after acute events. Large-scale evidence from randomized control trials and meta-analyses has shown that long-term statin therapy reduces cardiovascular events by 25% per year for every incremental LDL-C reduction of 1 mmol/l. [26] In the history part of hospital dossiers, we found records for LLT in 236 (32%) of FH, with only one-third on high-intensity therapy and few being treated with combination therapy. In addition, we found that for only a half of the FH patients, were the statin dose and combinations recorded properly in the discharge dossier. One possible reason may be the same as one of the limitations of this study, that is, working only with documentation and a retrospective design. However, our findings are consistent with numerous previous reports that FH patients tend to receive LLT relatively late, when severe atherosclerosis has developed, so the efficacy may be reduced. More effective lipid-lowering strategies include high-dose statins in combination with PCSK9 or ezetimibe [17, 18]. While treatment of CHD remains to be optimized, statins can substantially improve the prognosis, as modest doses can reduce the risk for CAD by about 80% in patients with FH [19].

The results of this study regarding LDL-C target achievement at 1,3,6 and 12 months post-index hospitalization are similar to those previously published with only 3.8% of the patients reaching the 2016 risk-based goal in the 3rd and 6th months. Multiple issues may potentially contribute to the lack of LDL-C reduction. Under-dosing and statin discontinuation/poor adherence to therapy are acknowledged as key contributors, and have been linked to poorer clinical outcomes [1, 10, 20]. The healthcare system in Bulgaria is based on the reference principle and therefore restrictive, waiting for larger markets to introduce new products and deliver data showing results from the change in therapy. Partial reimbursement and required co-payment out of the pocket may

be another reason for an unsatisfactory level of mono- and combination therapy prescribed, and for an inadequate LDL-C reduction. After the index event, overall patients, were undertreated because LDL-C $\leq 1, 8$ mmol/l were attained in roughly in 1 in 26 FH patients (Fig. 2).

Our analysis of ambulatory records shows that 158 FH patients visited the same hospital (178 visits) during the follow-up period. According to national guidelines, the patient is under the cardiologists' care over 12 months post-event period. Upon discharge, a patient is free to decide if he/she stays for 1 year with the hospital ambulatory department or goes back to its resident cardiologist by territory, another town, or municipality. Upon discharge, all patients are given a cost-free examination within 30 days post-hospitalization in the hospital, as per NHIF guidelines. Our finding shows that, by the first month, only 33 patients benefited from the recommended free-of-charge examination, 79 came back after the first to third month, 27 after the third by sixth month, and 39 after the sixth to twelfth month post-index hospitalization. LDL-C achievement according to 2016 ESC/EAS guidelines for LDL-C $\leq 1, 8$ mmol/l reached only 5% at the third and 7% at the sixth month. The results are presented in Fig. 2. Our findings are supported by the previously reported 5% of VHR patients reaching LDL-C $\leq 1, 8$ mmol/l in Bulgaria. [11] The recently updated 2019 joint ESC/EAS guidelines recommend even more stringent goals and aggressive therapy for FH patients, aiming to optimize LDL-C reduction by uptake of high-intensity statins to achieve both a 50% reduction and an even lower LDL-C goal of < 1.4 mmol/l for patients with high or very high risk. Reducing LDL-C from above 2 mmol/L to below 1.4 mmol/L could offer an 11% relative reduction in CV events and a 5% relative reduction in mortality [21], and thus offer considerable benefits for FH patients who are classified as very high risk.

This is the first study that calculates the direct cost for treatment of FH patients after hospitalization. The cost for implants is not included because of lack of information in the medical records. The total cost paid for

ambulatory treatment is based on the medications listed in the discharged documents for ambulatory treatment. The NHIF amount is extracted from the NHIF public list for ambulatory treatment accounting for the date of discharge, the level of reimbursement, and patient co-payment. The average monthly cost for treatment is higher for probable/definite FH patients (103.50 ± 124.30) compared with the total FH group (95.70 ± 110.70) and with the Possible FH (83.00 ± 82.70) (Fig. 4).

Patients who visited their cardiologists post-index event and had adjustment of the therapy (dose/type) paid a lower cost (Table 5) for ambulatory treatment (89.60 ± 110.90) compared with the total FH group (95.70 ± 110.70) and the Probable/Definite (103.50 ± 124.30) subgroups, underlying the need for regular check-ups with the treating physicians. More costly are patients with recurrent events leading to hospitalization after the index visit (Table 4).

Our study has several limitations and the results should be interpreted with caution. One is the retrospective design and the nature of an e-database analysis working only with what is available in the hospital records. We used the written information listed in electronic hospital records to calculate DLNC scores with detection rates coming primarily from LDL-C values and histories of prior CV events and index events, missing other important clinical criteria of the diagnostic algorithm such as tendon xanthomas, corneal arcus, information for first degree relatives with previous events, and elevated LDL-C, genetic analysis. Thus, our estimate should not be compared with prevalence studies because the true proportion of FH patients is under-estimated, and we had a high number (4562/11,090) of dossiers with insufficient information. Secondly, cholesterol levels have been shown to decrease 24 h after hospital admission, and so, e.g., we could not be certain if lipid results described in the hospital records are measured from the first blood drawn in the emergency department. In addition, the patients included were not evaluated for possible secondary causes for dyslipidemia, such as hypothyroidism or nephrotic syndrome, due to limited information in the electronic records. An additional limitation was our inability to

adjust the healthcare resources spent for FH treatment for adherence to treatment. Given the fact that EMR is relatively new to healthcare providers, it is possible that providers may prefer to record much patient information via free text. NLP is a lengthy and expensive task, limiting the ability to use the unstructured information, and more generally speaks to the challenge of identifying FH patients in e-databases retrospectively.

Lastly, these results are not necessarily applicable for other e-database analyses that may capture different types of healthcare practitioners.

A strength of our study is that we have pointed out the need for supporting tools to unburden clinicians in the emergency department of interventional cardiology clinics. Such a tool may remind a patient with an acute cardiovascular event that it carries a higher probability of FH diagnosis. Adding to our tool a drop-down suggestion list with still missing information to calculate DLNC scores will prompt more thorough clinical examination and supplement the diagnosis. We have attempted for the first time to show the higher costs generated for FH patients due to under-diagnoses and under-treatment.

CONCLUSIONS

Early diagnosis and treatment are crucial for improving outcomes in FH patients. In hospital,

Table 5 Total ambulatory cost at 1 month for FH patients with follow-up visits and changes in dose/type of LLT after index hospitalization

	Cost for FH patients with ambulatory follow-up visits BGN mean \pm SD (<i>n</i> = 174)
NHIF-reimbursed amount	43.10 \pm 96.10
Patient-paid amount	46.50 \pm 32.20
Total amount 1 month	89.60 \pm 110.90

Ambulatory visits data come from City Clinic Sofia and Pulmed Hospital, Plovdiv

n number of patients.

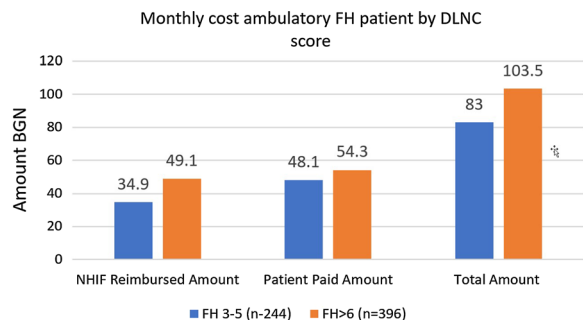


Fig. 4 Cost of ambulatory treatment 1-month FH patients by DLNC score

screening for FH may allow for rapid and effective lipid management and for prevention of recurrent events, and thus may reduce the burden on the healthcare system. The recommendation in the hospital discharge document for implementation of cascade screening will help to identify close family members to ensure timely intervention and prevent cardiovascular events. Therefore, implementing an automated screening tool may be advantageous for physicians and so improve the identification of individuals with FH at the time of hospitalization.

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Compliance with Ethics Guidelines. There was no patient involvement in this research study. The study was conducted in accordance with the Helsinki Declaration of 1964, as revised in 2013, and with country specific legal and regulatory requirements. It was approved by ethics committees and for registration or classification by regulatory bodies, as applicable in each hospital. In agreement with national law, the study protocol was approved by all five Ethics Commissions of the participating hospitals. The contract with the hospitals were signed as follows: UMBAL Alexandrovska—11.12.2019, City Clinic Achibadem Sofia—10.12.2019, UMBAL Pulmed Plovdiv—19.02.2020, UMBAL St Anna Sofia—17.03.2020, City Clinic Achibadem Montana—10.12.2019.

Data Availability. Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: <http://www.amgen.com/datasharing>.

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