ORIGINAL ARTICLE

Prevalence of familial hypercholesterolemia in patients with acute coronary syndrome

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ABSTRACT

Aim To investigate the prevalence of familial hypercholesterolemia in patients with acute coronary syndrome (ACS).

Methods The study included fifteen patients with first or repeated ACS and treated/nontreated dyslipidaemia admitted to the Department of Cardiovascular Diseases of Clinical Hospital Centre Osijek between 1 January 2020 and 1 January 2021. The cut-off value of low-density lipoprotein (LDL)-C was 4.5mmol/L as a possible cut-off value for familial hypercholesterolemia presence. Data were collected from medical history and during patient's follow-up.

Results Included patients that fulfilled criteria were predominantly male – 14 (93%), mean age 61 years. The median level of LDL cholesterol at admission because of ACS was 5.14 mmol/L, whereas the follow-up level after one year was 2.27 mmol/L (p=0.001). At first follow-up, 7 (46%) patients were treated with atorvastatin 80 mg or rosuvastatin 40 mg, 3 (20%) atorvastatin 80mg + ezetimibe 10mg, 2 (13%) with rosuvastatin 40 mg+ ezetimibe 10 mg, other patients were treated with a lower dose of statin or ezetimibe. According to LDL-C profile and by calculating the Dutch Lipid Clinic Network Score, one (of 15) patient was categorized as having definite familial hypercholesterolemia and two (of 15) as having probable familial hypercholesterolemia leading to the use of triple hypolipidemic therapy (statin+ezetimibe+PCSK9 inhibitor) in 2 (13%) patients (one female and one male).

Conclusion LDL-C level of 4.5 mmol/L and higher represents an indication for screening for familial hypercholesterolemia in patients with ACS. The prevalence of familial hypercholesterolemia in ACS, estimated by the Dutch Lipid Clinic Network Score, could be higher than previously reported.

Key words: atherosclerosis, LDL cholesterol, PCSK9 Inhibitors

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INTRODUCTION

Familial hypercholesterolemia (FH) is a common autosomal dominant monogenic disorder which is characterized by elevated LDL cholesterol levels (LDL-C) present from birth, leading to accelerated atherosclerosis and premature acute coronary syndrome (ACS), peripheral arterial disease and cerebrovascular disease (1). The prevalence of FH in the white race is thought to be between 1/500 and 1/200 for the heterozygous form of the disorder and 1/1000000 for the homozygous form of the disorder (2). Mutation of genes which are responsible for encoding proteins involved in LDL-C catabolism results in decreased endocytosis of LDL-C and consequently increased levels in plasma (3). The major proteins involved in the process of LDL receptor endocytosis are LDLR (mutated in 80–85% of FH cases), apoB100 (5–10% FH), PSCK9 (2% FH), and LDL receptor adaptor protein 1 (< 1% FH). There are approximately 3000 known mutations in the LDLR protein (4).

If the treatment is not started early, males and females usually develop coronary heart disease (CHD) by the age of 55 or 60, respectively, whereas patients with the homozygous form of the disorder develop CHD very early in life and usually die due to consequences by the age of 20 (5,6). Although CHD poses a high risk for the development of cardiovascular disease, i.e., ACS, a large number of patients remains undiagnosed, while those diagnosed with it do not receive the appropriate therapy (7,8). The risk of CHD is considered to increase 13-fold in patients with FH without statin therapy, whereas it increases 10-fold in patients on statin therapy (9). FH is thought to be present in 1/10 patients with ACS under 50 years of age (10). Similarly, patients with FH develop ACS up to 10 years earlier than patients without FH (11).

The FH is most often diagnosed based on the following 5 criteria: history of premature CHD, family history, physical findings of xanthoma and arcus cornealis, high LDL-C on serial measurements and evidence of a genetic mutation (through screening or cascade testing in relatives already diagnosed with FH) (9). Three criteria are most commonly used to aid in the diagnosis: MEDPED (Make Early Diagnosis to Prevent Early Deaths), Simon Broome criteria and the Dutch Lipid Clinic Network (DLCN) criteria (12). Patients with a DLCN score higher than 5 are considered to have probable or definite FH and they are recommended to undergo genetic testing (13).

Once FH is diagnosed, the most important intervention is the early introduction of hypolipidemic therapy. It is usually started with the maximum dose of a statin, i.e., atorvastatin or rosuvastatin (14). The target level of LDL-C in patients without a history of atherosclerotic cardiovascular disease or other risk factors such as diabetes is <1.8 mmol/L or a 50% reduction in LDL-C from the baseline. In contrast, in patients with a history of atherosclerotic cardiovascular disease such as ACS or a risk factor, the target level of LDL-C is <1.4 mmol/L or a reduction in LDL-C of 50% of the baseline. If these levels cannot be achieved with the maximum dose of statins, the therapy is supplemented with ezetimibe (15,16). Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors lower LDL-C by up to 60% when added to dual statin and ezetimibe therapy. These are monoclonal antibodies that prevent the joining of the LDL receptor and the PCSK9 protein, resulting in increased recycling of the LDL receptor (17).

Considering the developments in diagnosis and treatment opportunities for patients with FH, there is an imposed need to raise awareness about FH. The main goal is to make an early diagnosis leading to the reduction in cardiovascular morbidity and mortality (18). In Croatia, starting from 2023, screening for FH will take place as part of the mandatory screening when children enrol in the first grade of primary school, using a simple diagnostic routine test to measure total cholesterol. If a child's total cholesterol is found to be elevated, the school doctor refers the child to a paediatrician (19).

The aim of this study was to determine the prevalence of FH in the group of patients with ACS who had LDL-C levels of 4.5 mmol/L and higher at the time of admission.

PATIENTS AND METHODS

Patients and study design

This pilot cohort study included retrospective data of patients treated for ACS with LDL cholesterol level of ≥4.5 mmol/l in the Department of

Cardiovascular Diseases of the Clinic for Internal Diseases of Clinical Hospital Centre Osijek from 1 January 2020 to 1 January 2021.

The LDL value of 4.5 mmol/L was used as a cut-off because it was thought that it would adequately capture all patients with FH and ACS (20–23) the prevalence of FH among a general population remains unknown, and it is unclear if FH is associated with other cardiovascular complications, including heart failure (HF. Patients in whom further cardiological control was not possible because they could not be contacted (six patients) or who refused to participate in the study (six patients) were excluded. The criteria were met by 15 adults between the age of 43 and 84. All patients were introduced to the study at a follow-up examination one year after the diagnosis of ACS and they signed an informed consent form.

The research was approved by the Ethics Committee of Clinical Hospital Centre Osijek and the Faculty of Medicine of Josip Juraj Strossmayer University in Osijek.

Methods

Data on age, gender, comorbidities (hypertension, diabetes mellitus, peripheral arterial disease, epilepsy, malignancies) and hypolipidemic therapy before hospitalization for ACS were collected by searching the hospital information system. The patients were then referred to a cardiac evaluation, during which information on their family history and current hypolipidemic therapy was obtained and laboratory data were recorded: total cholesterol, high-density lipoprotein cholesterol (HDL-C; male >0.75 mmol/L, female >0.91 mmol/L), low-density lipoprotein cholesterol (LDL-C; <3 mmol/L), triglycerides (<1.7 mmol/L), glucose (4.4–6.4 mmol/L), urea (2.8–8.3 mmol/L), creatinine (male 64–104 μmol/L, female 49–90 μmol/L), aspartat aminotransferase (AST; 8–38 U/L), alanin aminotransferase (ALT; 10–48 U/L), gamma-glutamyl transpeptidase (GGT; male 11–55 U/L, female 9–35 U/L), creatine kinase (male <177 U/L, female <153 U/L) and N-terminal pro–B-type natriuretic peptide (NT-proBNP).

The Dutch Lipid Clinic Network (DLCN) score (15,24) was calculated based on four categories: family history, untreated LDL-C value, clinical history and physical examination. Untreated LDL-C value was obtained using the online calculator (25) which requested input of current LDL-C value, type and dose of the statin that was used and whether the patient was on ezetimibe or PCSK9 inhibitor. Other categories comprised of yes/no questions as follows:

Family history: First-degree relative with known premature (<55 years, men; <60 years, women) coronary heart disease; First-degree relative with known LDL cholesterol >95th percentile by age and gender; First-degree relative with tendon xanthoma and/or corneal arcus; Child(ren) <18 years with LDL cholesterol >95th percentile by age and gender.

Clinical history: Subject has premature (<55 years, men; <60 years, women) coronary heart disease; Subject has premature (<55 years, men; <60 years, women) cerebral or peripheral vascular disease.

Physical examination: Subject has tendon xanthoma; Subject has corneal arcus <45 years.

An unlikely FH refers to a DLCN score of 0 to 2 points. A possible FH refers to a DLCN score of 3 to 5 points. A probable FH refers to a DLCN score of 6 to 8 points. A definite FH refers to a DLCN score of above 8 points.

Patients were included in the study one year after their hospitalization for acute coronary syndrome. At that appointment with a cardiologist (later referred as first follow-up) their hypolipidemic therapy was evaluated based on their LDL-C values and DLCN score. If their LDL-C values were not satisfactory (according to the European Society of Cardiology guidelines on dyslipidaemias (15) either their statin dose was increased or ezetimibe was added. If the patient was on the maximal dose of statin and ezetimibe and their DLCN score was ≥ 6, they were prescribed a PCSK9 inhibitor. Patients who received a PCSK9 inhibitor were referred to a second follow-up (three months after the first follow-up) in which LDL-C levels were recorded on triple hypolipidemic therapy (statin + ezetimibe + PCSK9 inhibitor).

Statistical analysis

Categorical data are represented by absolute frequencies. Due to the small sample size, continuous data are described by median and interquartile ranges. Differences in LDL-C level during ACS and at first follow-up were tested with the Wilcoxon test with a corresponding difference

and 95% confidence interval (CI). The significance level was set at p=0.05.

RESULTS

The research was conducted on 15 patients, of whom 14 (93.3%) were males and one (6.7%) was female. The mean age of the patients was 61 years (interquartile range (IQR) 55-63 years) in the range 43-84 years. Of the 15 patients, 14 (93.3%) had ST elevation myocardial infarction (STEMI) and one (6.7%) had non-ST elevation myocardial infarction (NSTEMI). Hypertension was the most common comorbidity in 13 (86.7%) patients. There was a family history of premature coronary or vascular disease in 4 (26.7%) patients. Premature coronary disease was found in seven (46.7%) patients, while one (6.7%) patient had premature cerebral and/or peripheral vascular disease (Table 1).

Table 1. Characteristics of 15 patients with acute coronary syndrome

Variable		No (%) of patients
Gender	Male	14 (93.3)
	Female	1 (6.7)
Type of acute coronary syndrome	STEMI	14 (93.3)
	NSTEMI	1 (6.7)
	Unstable angina	0
Comorbidity	Hypertension	13 (86.7)
	Diabetes mellitus	2 (13.3)
	Peripheral artery disease	1 (6.7)
	Non-Hodgkin lymphoma	2 (13.3)
	Epilepsy	1 (6.7)
First degree relative with premature* coronary and/or vascular disease		4 (26.7)
Patient with premature* coronary artery disease		7 (46.7)
Patients with premature* cerebral or peripheral vascular disease		1 (6.7)
Tendinous xanthomata and/or arcus cornealis in patient and/or first degree relative		0

*men age <55 years, women aged <60 years
STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction

The median values of the patients' lipid profile at the first follow-up were within the reference values. The median level of LDL-C at follow-up one year after ACS was 2.29 mmol/L (IQR 1.96 – 2.95 mmol/L), whereas it was 5.14 mmol/L (IQR 4.78 – 5.46 mmol/L) during hospitalization for ACS, which was a significant change (difference -2.72 mmol/L; 95% CI of difference -3.2 to -2.26 mmol/L; p<0.001). The highest measured level of total cholesterol was 7 mmol/L, triglycerides 6.3 mmol/L, LDL-C 4.6 mmol/L, while the lowest measured level of HDL-C was 0.8 mmol/L (Table 2).

Table 2. Biochemical values at follow-up

Variable	Median (interquartile range) (minimum – maximum)
Total cholesterol (mmol/L)	4.2 (3.49–5.6) (3.1–7.0)
Triglycerides (mmol/L)	1.8 (1.38–2.03) (0.8–6.3)
LDL cholesterol (mmol/L)	2.29 (1.96–2.95) (1.1–4.6)
HDL cholesterol (mmol/L)	1.2 (1–1.29) (0.8–1.6)
Fasting glucose (mmol/L)	6.6 (6.24–7.13) (5.2–14.2)
Urea (mmol/L)	6.7 (5.2–7.4) (3.9–8.5)
Creatinine (mmol/L)	90 (81–97) (71–117)
AST (U/L)	27 (20–30) (15–49)
ALT (U/L)	28 (23–38) (14–57)
GGT (U/L)	35 (25–46) (11–115)
Creatine kinase (U/L)	175 (121–217) (99–220)
NT-proBNP (U/L)	77 (41.5–1158.25) (19–2122)

LDL, low density lipoprotein; HDL, high density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; NT-proBNP, N-terminal prohormone of brain natriuretic peptide

Of the 15 patients, two reached the target LDL-C level at follow-up one year after the hospitalization for ACS (1.1 and 1.4 mmol/L, respectively). The maximum level of LDL-C during admission for ACS in male patients was 6.38 mmol/L, while the minimum level was 4.56 mmol/L. The single female patient had LDL-C of 5.81 mmol/L and at follow-up, it was 4.67 mmol/L. LDL-C values were not dependent on age – the oldest patient had an LDL-C level of 5.14 mmol/L on admission, while the youngest had 5.46 mmol/L.

On admission for ACS, not a single patient had hypolipidemic therapy. At follow-up, the maximum dose of atorvastatin of 80 mg was the most common therapy option, in six (40%) patients. The second most common therapy in these patients was the combination of the maximum dose of atorvastatin of 80 mg and ezetimibe of 10 mg, three (20%). Nine (60%) patients received monotherapy, six (40%) dual therapy, while none received triple hypolipidemic therapy (Table 3).

Table 3. Hypolipidemic therapy at hospitalization for acute coronary syndrome, at first and second follow-up*

Therapy		No (%) of patients	
		One year after hospitalization	Three months after the first follow-up
Statin	atorvastatin 40mg	1 (6.7)	0
	atorvastatin 80mg	6 (40)	4 (26.7)
	rosuvastatin 40mg	1 (6.7)	0
Ezetimibe	ezetimibe 10mg	1 (6.7)	0
Statin + ezetimibe	atorvastatin 80 mg + ezetimibe 10 mg	3 (20)	6 (40)
	rosuvastatin 10 mg + ezetimibe 10 mg	1 (6.7)	1 (6.7)
	rosuvastatin 40 mg + ezetimibe 10 mg	2 (13.3)	2 (13.3)
Statin + ezetimibe + PCSK9 inhibitor		0	2 (13.3)
Total (N)		15 (100)	15 (100)

*the patients did not receive any therapy before hospitalization for acute coronary syndrome;
PCSK9, proprotein convertase subtilisin/kexin type 9;

Using the given data, the patients' DLCN score was calculated. Considering the score values, 10 (66.7%) patients had possible FH, two (13.3%) probable FH (both of them had a DLCN score of 6), while one (6.7%) belonged to the definite FH group (the patient had a DLCN score of 9). One patient with DLCN score 6 reached the target value of LDL-C, while in two other patients (13.3%), one male and one female, triple hypolipidemic therapy (statine+ezetimibe+PCSK9 inhibitor) was used.

The patients who received a PCSK9 inhibitor at the first follow-up showed a decrease in LDL-C at the second follow-up. On triple hypolipidemic therapy, LDL-C decreased by 33% (from 4.67 to 3.8 mmol/L) in one, and by 86% (from 2.8 to 0.4 mmol/L) in the other patient compared to the first follow-up level.

DISCUSSION

In this study, patients hospitalized for ACS with LDL-C levels of ≥4.5 mmol/L were observed. When the DLCN score was calculated, two (of 15) patients were classified as probable FH and one as definite FH. The study by Dyrbus et al. (26) included 7319 patients with ACS in whom the prevalence of probable/definite FH according to the DLCN score was 1.6%, which is significantly lower than in our study. One possible reason for this is the different patient populations, i.e., this study only included patients with ACS who had an LDL level of ≥4.5 mmol/L, which increases the chance of detecting patients with FH. Dyrbus et al. (26) observed that the highest prevalence of FH was in the group of patients with STEMI (20.3%), which is consistent with our study, in which most patients had STEMI. In a study conducted in China (13)and to evaluate different diagnostic criteria.\nMETHODS: A total of 225 consecutive PMI patients were recruited. Low-density lipoprotein receptor (LDLR on 225 patients with premature ACS (males <55 years, females <60 years), the prevalence of probable/definite FH was 8%, which was expected because FH is most often manifested by premature coronary disease, i.e., premature ACS if not treated in time. Indeed, 66.7% of the patients in our study with probable/definite FH were younger than 50 years of age when they were hospitalized for ACS. In Cui et al. study (13)and to evaluate different diagnostic criteria.\nMETHODS: A total of 225 consecutive PMI patients were recruited. Low-density lipoprotein receptor (LDLR, the average untreated LDL-C was 5.33 mmol/L, which is consistent with our study (5.14 mmol/L); all patients were already receiving statin therapy when they were hospitalized for ACS. In contrast, none of the patients in our study received hypolipidemic therapy for primary prevention.

Jug et al. (8) monitored statin prescription and patient adherence for primary prevention. Of 40 patients with LDL-C levels >5 mmol/L, only 25% were on statin therapy; the other patients were not taking statins because they did not know they needed them (53%), were told by their physician they did not need statins (13%), thought that statin was toxic (30%), or had side effects when using statins (3%). Our study did not investigate why patients with elevated LDL-C levels did not take statin therapy as part of primary prevention, which would be interesting for future research.

At follow-up, 53.3% of our patients were taking a statin monotherapy (7 at the maximum dose) and 40% (5 at the maximum dose) were taking a combination of statin and ezetimibe. In a study by Pintarić et al. (7), patients were taking statins in 92.7% of cases, which is consistent with our study, while ezetimibe was prescribed in a smaller number of cases (2.4% versus 40% in our study). A possible explanation for this is the initially higher LDL-C level and the significantly lower number of patients in our study.

The addition of PCSK9 inhibitor in two patients already receiving the maximum dose of statin and ezetimibe resulted in a 33% and 86% reduction in LDL-C, respectively. In a study by Sabatina et al. (27), the effect of adding evolocumab to statin therapy was observed. It was found that after 48 weeks, there was a 59% reduction in LDL-C concentration, which is the median LDL-C reduction in our study. Similarly, patients on evolocumab therapy had a lower risk of death from ACS, cerebrovascular incident or hospitalization for unstable angina compared to placebo. Except for injection site reactions, no significant differences in the incidence of adverse events were observed with evolocumab (28)with the need to use association therapy combining agents with different mechanisms of action. As most cases of FH are

attributable to mutations in the gene encoding the low-density lipoprotein receptor (LDLR. In our study, the long-term benefit of the use of PCSK9 inhibitors was not investigated, but even in the short period of less than a year, their beneficial effect on LDL-C lowering was evident in patients with probable/definite FH.

The major limitation of this study is the small number of patients.

In conclusion, patients with FH are at a high risk of developing severe complications of premature atherosclerosis in the form of ACS, cerebrovascular disease and peripheral artery disease. With timely diagnosis and initiation of intensive treatment with hypolipidemic therapy, the risk has been shown to decrease. The clinician's goal should be to raise timely suspicion of FH, calculate the DLCN score, and start the treatment as early as possible.

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TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

REFERENCES

1. Corral P, Aguilar Salinas CA, Matta MG, Zago V, Schreier L. Stratification in heterozygous familial hypercholesterolemia: imaging, biomarkers, and genetic testing. Curr Atheroscler Rep 2023;
2. Primary Panel:, Genest J, Hegele RA, Bergeron J, Brophy J, Carpentier A, Couture P, Davignon J, Dufour R, Frohlich J, Gaudet D, Gupta M, Krinsamoorthy P, Mancini J, McCrindle B, Raggi P, Ruel I, St-Pierre J. Canadian Cardiovascular Society position statement on familial hypercholesterolemia. Can J Cardiol 2014; 30:1471–81.
3. Rogozik J, Główczyńska R, Grabowski M. Genetic backgrounds and diagnosis of familial hypercholesterolemia. Clin Genet 2023;
4. Benito-Vicente A, Uribe KB, Jebari S, Galicia-Garcia U, Ostolaza H, Martin C. Familial hypercholesterolemia: the most frequent cholesterol metabolism disorder caused disease. Int J Mol Sci 2018; 19:E3426.
5. Romero-Jiménez MJ, Mansilla-Rodríguez ME, Gutiérrez-Cortizo EN. Predictors of cardiovascular risk in familial hypercholesterolemia. Curr Opin Lipidol 2023; 34:272–7.
6. Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide prevalence of familial hypercholesterolemia: meta-analyses of 11 million subjects. J Am Coll Cardiol 2020; 75:2553–66.
7. Pintarić H, Knezović Florijan M, Bridges I, Steiner R, Zaputović L, Miličić D. Management of hyperlipidemia in very high and extreme risk patients in Croatia: an observational study of treatment patterns and lipid control. Acta Clin Croat 2020; 59:641–9.
8. Jug J, Juraga V, Jelavić I. Adherencija i propisivanje statina u primarnoj prevenciji unutar primarne zdravstvene zaštite (Adherence and prescription of statin therapy in primary prevention in primary care unit) [in Croatian]. Liječnički Vjesn 2021; 143:90–4.
9. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele R, Raal F, Defesche J, Wiegman A, Santos R, Watts G, Parhofer K, Hovingh G, Kovanen P, Boileau C, Averna M, Boren J, Bruckert E, Catapano A, Kuivenhoven J, Pajukanta P, Ray K, Stalenhoef A, Stroe E, Taskinen M, Tybjaerg-Hansen A, European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013; 34:3478–3490a.
10. Singh A, Gupta A, Collins BL, Qamar A, Monda KL, Biery D, Lopez J, de Ferranti S, Plutzky J, Cannon C, Januzzi J, Di Carli M, Nasir K, Bhatt D, Blankstein R. Familial hypercholesterolemia among young adults with myocardial infarction. J Am Coll Cardiol 2019; 73:2439–50.
11. Li S, Zhang Y, Zhu CG, Guo YL, Wu NQ, Gao Y, Qing P, Li X, Sun J, Liu G, Dong Q, Xu R, Cui C, Li J. Identification of familial hypercholesterolemia in patients with myocardial infarction: a Chinese cohort study. J Clin Lipidol 2016; 10:1344–52.
12. Casula M, Olmastroni E, Pirillo A, Catapano AL, Members of the LIPIGEN steering committee, Principal investigators: Coordinator center; Participant Centers; Participant Laboratories; COLLABORATORS; STUDY CENTRAL LABORATORY AND ANALYSIS GROUP. Evaluation of the performance of Dutch Lipid Clinic Network score in an Italian FH population: The LIPIGEN study. Atherosclerosis 2018; 277:413–8.
13. Cui Y, Li S, Zhang F, Song J, Lee C, Wu M, Chen H. Prevalence of familial hypercholesterolemia in patients with premature myocardial infarction. Clin Cardiol 2019; 42:385–90.
14. Mohamed F, Mansfield B, Raal FJ. Targeting PCSK9 and beyond for the management of low-density lipoprotein cholesterol. J Clin Med 2023; 12:5082.
15. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman J, De Backer G, Delgado V, Ference B, Graham I, Halliday A, Landmesser U, Mihaylova B, Pedersen T, Riccardi G, Richter D, Sabatine M, Taskinen M, Tokgozoglu L, Wiklund O, ESC scientific document. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020; 41:111–88.
16. McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB. Diagnosis and treatment of heterozygous familial hypercholesterolemia. J Am Heart Assoc 2019; 8:e013225.

17. Ogura M. PCSK9 inhibition in the management of familial hypercholesterolemia. J Cardiol 2018; 71:1–7.
18. Pećin I, Šućur N, Reiner Ž. Porodična hiperkolesterolemija - mislimo li dovoljno o ovoj teškoj bolesti (Familial hypercholesterolemia - do we think enough about this severe disease) [in Croatian]. Liječnički Vjesn 2013; 135:0–0.
19. Probir i rano otkrivanje porodične hiperkolesterolemije. https://www.hzjz.hr/aktualnosti/probir-i-rano-otkrivanje-porodicne-hiperkolesterolemije/ (date last accessed 14 November 2023).
20. Tada H, Kaneko H, Suzuki Y, Okada A, Takeda N, Fujiu K, Morita H, Ako J, Node K, Takeji Y, Takamura M, Yasunaga H, Komuro I. Familial hypercholesterolemia is related to cardiovascular disease, heart failure and atrial fibrillation. Results from a population-based study. Eur J Clin Invest 2023; e14119.
21. Arca M, Celant S, Olimpieri PP, Colatrella A, Tomassini L, D'Erasmo L, Averna M, Zambon A, Catapano A, Russo P. Real-world effectiveness of PCSK9 inhibitors in reducing LDL-C in patients with familial hypercholesterolemia in Italy: A retrospective cohort study based on the AIFA monitoring registries. J Am Heart Assoc 2023; e026550.
22. Ide V, De Cock D, Pazmino S, Vangoitsenhoven R, Van der Schueren B, Mertens A. A retrospective study of people with familial hypercholesterolaemia in a Belgian lipid clinic. Acta Cardiol 2023; 1–10.
23. Šálek T, Soška V, Budina M, Vecka M, Šálková V, Vrablík M. Reporting LDL cholesterol results by clinical biochemistry laboratories in Czechia and Slovakia to improve the detection rate of familial hypercholesterolemia. Biochem Medica 2023; 33:030705.
24. Lipid Tools. https://www.lipidtools.com/en/dlcn/ (06 July 2023).
25. LDL-C calculator – Lipid Tools. https://www.lipidtools.com/calculator-pages/ldlc/ (02 November 2023).
26. Dyrbuś K, Gąsior M, Desperak P, Osadnik T, Nowak J, Banach M. The prevalence and management of familial hypercholesterolemia in patients with acute coronary syndrome in the Polish tertiary centre: Results from the TERCET registry with 19,781 individuals. Atherosclerosis 2019; 288:33–41.
27. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder J, Wang H, Liu T, Wasserman S, Sever P, Pedersen T, Fourier steering committee and investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017; 376:1713–22.
28. Pirillo A, Catapano AL, Norata GD. Monoclonal antibodies in the management of familial hypercholesterolemia: Focus on PCSK9 and ANGPTL3 inhibitors. Curr Atheroscler Rep 2021; 23:79.