SHORT COMMUNICATION

Prevalence of familial hypercholesterolemia in patients with acute coronary syndromes

Beata Bobrowska[1], Wojciech Zasada[1,3], Renata Rajtar-Salwa[1], Artur Dziewierz[1,2], Dariusz Dudek[1,2]

1 2nd Department of Cardiology and Cardiovascular Interventions, University Hospital, Kraków, Poland
2 Institute of Cardiology, Jagiellonian University, Kraków, Poland
3 KCRI, Kraków, Poland

Introduction Heterozygous familial hypercholesterolemia (FH) is the most common monogenic dyslipidemia causing premature ischemic heart disease.[1] The prevalence of FH in the general Polish population has been estimated at 1 in 250 adults; moreover, the number of patients with definite FH is relatively small: in a meta-analysis of 6 studies, involving more than 37 000 of patients, definite FH was diagnosed only in 7 patients.[2] Importantly, despite the fact that the appropriate treatment may be administered to reduce the risk of premature atherosclerosis, only selected patients with FH are identified early and properly diagnosed.[3] In most cases, the diagnosis of FH is based on Dutch Lipid Clinic Network (DLCN) criteria.[4] Data on the prevalence of FH in patients with acute coronary syndromes (ACSs) are still lacking. Thus, we aimed to evaluate the prevalence of clinical FH among patients presenting with ACS.

Methods Data on consecutive patients hospitalized in the 2nd Department of Cardiology and Cardiovascular Interventions, University Hospital in Krakow, between June 1, 2017, and June 30, 2018, due to ACS were collected retrospectively in a dedicated database. Demographic and clinical data, including traditional risk factors (arterial hypertension, diabetes mellitus, smoking), medical history (cerebrovascular and cardiovascular incidents), and family history of premature atherosclerosis were recorded. During data collection, we excluded all patients for whom the information regarding the secondary cause of hypercholesterolemia (untreated hypothyroidism, nephrotic syndrome, cholestasis, hypopituitarism, or use of atypical antipsychotic drugs) was present in medical history. We also collected biochemical data including serum lipid profile (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglyceride levels), as well as use of lipid-lowering drugs and their doses. For each patient, we performed DCLN scoring and identified patients with a possible (score, 3–5), probable (score, 6–8), or definite (score >8) diagnosis of FH.[4] Data regarding the clinical signs of lipid accumulation in the tissue, as well as family history of elevated LDL-C levels were not available for all patients, so in these cases missing information was counted as zero in DLCN criteria. In addition, the categories "definite FH" and "probable FH" were combined into "potential FH," as it was done in a previous study.[2] No genetic testing was performed, so the final classification was based only on phenotype characteristics. The Jagiellonian University Bioethical Committee was notified about the registry.

Statistical analysis For continuous variables, data were presented as a mean with SD and as a median with the first and third quartiles. These continuous data were compared using the Wilcoxon test. Categorical data were presented as numbers and percentages, and were compared using the Pearson χ^2 test. All statistical analyses were performed using the JMP®, Version 14.0.0. SAS Institute Inc., 2018 (Cary, North Carolina, United States). A P value of less than 0.05 was considered significant. No formal power calculation was performed.

Results and discussion Based on the collected data of hospitalized patients, there were 341 consecutive individuals for whom it was possible to calculate the DCLN score. There were 5 cases of definite FH (DLCN score >8 points, 1.5%). Potential FH (definite and probable) was more frequent

Correspondence to:
Beata Bobrowska, MD, PhD, 2nd Department of Cardiology and Cardiovascular Interventions, University Hospital, ul. Kopernika 17, Kraków, Poland, phone: +48 12 424 71 70, email: bobrowska.beata@gmail.com
Received: January 24, 2019.
Revision accepted: February 8, 2019.
Published online: February 8, 2019.
Kardiol Pol. 2019; 77 (4): 475-477
doi:10.5603/KP.a2019.0029

TABLE 1 Characteristics of patients presenting with acute coronary syndrome with possible and potential (probable and definite) familial hypercholesterolemia according to Dutch Lipid Clinic Network (DLCN) criteria

Parameter		Possible FH (n = 30)	Potential FH (probable and definite) (n = 15)	*P* value
Age, y	Mean (SD)	64.97 (10.15)	56.27 (13.19)	0.04[a]
	Median (IQR)	66.50 (56.00; 73.50)	61.00 (45.00; 64.00)	
Weight, kg	Mean (SD)	82.58 (12.31)	80.47 (20.35)	0.66[a]
	Median (IQR)	80.00 (75.25; 94.25)	81.00 (60.00; 94.00)	
Height, cm	Mean (SD)	168.50 (8.69)	170.67 (7.38)	0.49[a]
	Median (IQR)	168.50 (161.5; 177.25)	170.00 (167.00; 176.00)	
DLCN score, points	Mean (SD)	3.67 (0.88)	9.00 (3.25)	0.0001[a]
	Median (IQR)	3.00 (3.00; 5.00)	8.00 (7.00; 11.00)	
BSA, m^2	Mean (SD)	1.93 (0.18)	1.92 (0.26)	0.63[a]
	Median (IQR)	1.97 (1.81; 2.04)	1.94 (1.64; 2.07)	
TC, mmol/l	Mean (SD)	5.35 (1.04)	6.64 (2.21)	0.02[a]
	Median (IQR)	5.35 (4.58; 5.85)	6.35 (5.00; 7.30)	
LDL-C, mmol/l	Mean (SD)	3.34 (0.94)	4.55 (2.02)	0.01[a]
	Median (IQR)	3.15 (2.73; 3.73)	4.30 (3.30; 5.20)	
HDL-C, mmol/l	Mean (SD)	1.18 (0.28)	1.16 (0.33)	0.75[a]
	Median (IQR)	1.17 (0.96; 1.44)	1.11 (0.89; 1.41)	
TG, mmol/l	Mean (SD)	1.83 (0.94)	2.13 (0.96)	0.29[a]
	Median (IQR)	1.72 (1.09; 2.48)	1.92 (1.37; 2.91)	
Men, n (%)		18 (60)	9 (60)	0.99[b]
Hypertension, n (%)		25 (83.3)	11 (73.3)	0.43[b]
Diabetes, n (%)		9 (30)	4 (26.7)	0.82[b]
Smoking, n (%)		8 (26.7)	6 (40)	0.36[b]
Stroke / TIA, n (%)		1 (3.3)	0 (0)	0.47[b]
Chronic kidney disease, n (%)		4 (13.3)	1 (6.7)	0.50[b]
CAD – previous PCI, n (%)		11 (36.7)	4 (26.7)	0.50[b]
CAD – previous CABG, n (%)		5 (16.7)	2 (13.3)	0.77[b]
Carotid artery disease, n (%)		4 (13.3)	1 (6.7)	0.50[b]
Atrial fibrillation, n (%)		2 (6.7)	0 (0)	0.31[b]
Family history of premature CAD, n (%)		4 (13.3)	6 (40)	0.04[b]
Ezetimibe, n (%)		1 (3.3)	5 (33.3)	0.01[b]
Maximal statin dose (atorvastatin, 80 mg, or rosuvastatin, 40 mg), n (%)		3 (10)	10 (66.7)	0.001[b]

a Wilcoxon test; **b** Pearson χ^2 test

Abbreviations: BSA, body surface area; CABG, coronary artery bypass grafting; CAD, coronary artery disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; TC, total cholesterol; TG, triglycerides; TIA, transient ischemic attack

(15 patients, 4.4%). Possible FH was diagnosed in 30 patients (8.8%). The estimated prevalence of FH in patients with ACS was 1 in 23 patients, considering patients with the probable and definite diagnosis of FH. The characteristics of patients with at least a possible diagnosis of FH according to DLCN criteria are shown in TABLE 1.

Our major finding is that the prevalence of FH diagnosed using the DLCN criteria is more than 4% among patients with ACS. To our best

knowledge, this is the first estimation of FH prevalence in ACS patients admitted for interventional treatment in Poland. This value is over 10-fold higher than for the general Polish population using similar diagnostic methods.[2] Thus, FH might be considered as a significant risk factor of ACS and should be routinely screened.

Similarly, the prevalence of probable or definite FH according to the DLCN criteria combined with Simon Broome criteria was estimated at 1.6% in a multicenter cohort study of 4778 patients with ACS in Switzerland.[5] When considering only younger adults with premature ACS, FH diagnosis reached 4.8%. Also in our study the diagnosis of potential FH was more common in younger adults, which is in line with reports from the general Polish population, where the occurrence of FH was the highest in the age group of 45 to 54 years in men and 55 to 64 years in women.[2] Despite young age, we noticed that more than 30% of patients had percutaneous coronary interventions in the past. It may underline the value of attentive screening and application of primary prevention of coronary artery disease in this group of patients. Of note, previous investigators have already drawn attention to suboptimal detection and treatment of patients with FH in Poland.[6]

Considering the high incidence of FH among patients with ACS diagnosis, we are convinced that dedicated registries of patients with FH should be launched in every cardiac ward. First of all, it may expand the possibilities of diagnosis of patients with FH. Moreover, when new lipid-lowering drugs enter the market (PCSK9 inhibitors) and the Polish National Health Fund introduces drug programs that will increase the availability of these previously costly therapies, we believe that it will be worth screening for patients who may benefit from new treatment options. In this way, the risk of cardiovascular diseases may be diminished, and the quality of patients' life may be significantly improved.

One of the limitations of our study is the lack of genetic testing to identify monogenic mutations associated with FH. From the clinical perspective, the lack of genetic diagnostics implies that cascade diagnostics of families of patients with ACS is unavailable. However, our primary goal was to estimate the prevalence of clinical FH among ACS patients in order to optimize lipid-lowering treatment. Importantly, each patient with the ACS diagnosis should be treated with high-dose statins if there are no contraindications.[7,8] The diagnosis of the potential FH resulted in the escalation of statin treatment combined with ezetimibe much more frequently than in the group with possible FH. This approach stayed in accordance with the 2016 European Society of Cardiology and European Atherosclerosis Society guidelines for the management of dyslipidemias.[9] At any time, when we do not achieve a therapeutic goal, we should consider new specific drugs. The PCSK9 inhibitors have a quite high level of recommendations (IIa A), not only among patients with FH, but in all individuals who are judged to be at a very high risk.[10] Due to the high cost of the therapy, this treatment has not been widely available so far. However, the Polish National Health Fund has already prepared the dedicated drug program for patients with the diagnosis of FH, and this treatment option may be implemented in a selected group of patients.[11] At present, PCSK9 inhibitors are available for adult patients with a diagnosis of definite FH, who have LDL levels above 160 mg/dl on the maximal standard lipid-lowering therapy.

In conclusion, our study allows better understanding of the magnitude of the FH problem in young patients presenting with ACS, which may result in more careful screening and optimization of lipid-lowering treatment in everyday practice.

ARTICLE INFORMATION

CONFLICT OF INTEREST DD is a member of the advisory board of Amgen Inc. and Sanofi.

HOW TO CITE Bobrowska B, Zasada W, Rajtar-Salwa R, et al. Prevalence of familial hypercholesterolemia in patients with acute coronary syndromes. Kardiol Pol. 2019; 77: 475-477. doi:10.5603/KP.a2019.0029

REFERENCES

1 Nordestgaard BG, Chapman MJ, Humphries SE, et. al. 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: 3478-3490.

2 Pająk A, Szfraniec K, Polak M, et. al. Prevalence of familial hypercholesterolemia: a meta-analysis of six large, observational, population-based studies in Poland. Arch Med Sci. 2016; 12: 687-696.

3 Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis. 2003; 168: 1-14.

4 Defesche JC, Lansberg PJ, Umans-Eckenhausen MA, Kastelein JJ. Advanced method for the identification of patients with inherited hypercholesterolemia. Semin Vasc Med 2004; 4: 59-65.

5 Nanchen D, Gencer B, Auer R, et. al. Prevalence and management of familial hypercholesterolaemia in patients with acute coronary syndromes. Eur Heart J. 2015; 36: 2438-2445.

6 Chlebus K, Cybulska B, Gruchała M, et al. Prevalence, diagnosis, and treatment of familial hypercholesterolaemia in outpatient practices in Poland. Kardiol Pol. 2018; 76: 960-967.

7 Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018; 39: 119-177.

8 Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016; 37: 267-315.

9 Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J. 2016; 37: 2999-3058.

10 Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol. 2018; pii: S0735-1097(18)39033–8. [Epub ahead of print].

11 Łuszczyńska, K. Ministry of Health — News. https://www.gov.pl/web/zdrowie/nowoczesne-leki-na-szpiczaka-i-luszczyce-beda-refundowane. Published October 10, 2018. Updated October 10, 2018. Accessed April 16, 2019.