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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

Krzysztof Dyrbuś[a,*], Mariusz Gąsior[a], Piotr Desperak[a], Tadeusz Osadnik[a,b], Jolanta Nowak[a], Maciej Banach[c,d,e]

[a] 3rd Chair and Department of Cardiology, Medical University of Silesia in Katowice, School of Medicine with the Division of Dentistry in Zabrze, Silesian Center for Heart Diseases, Zabrze, Poland
[b] Chair and Department of Pharmacology, Medical University of Silesia, School of Medicine with Division of Dentistry in Zabrze, Poland
[c] Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113, Lodz, Poland
[d] Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland
[e] Cardiovascular Research Centre, University of Zielona Gora, Zielona Gora, Poland

HIGHLIGHTS

- Data on FH among patients with acute coronary syndrome are scarce. In this study, 19,781 consecutive patients from the TERCET Registry were included. The Dutch Lipid Clinic Network (DLCN) algorithm was used for FH diagnosis.
- In patients with ACS, 1.6% had probable/definite FH and 17.0% possible FH. The highest occurrence of FH was observed in STEMI subgroup (20.6%).
- Patients with definite and probable FH had higher 30-day mortality than patients without FH but no significant differences were observed between the groups in the 12-, 36- and 60-month follow-up.
- In propensity-score matching analysis, definite/probable FH patients had significantly higher all-cause mortality at the 36- and 60-month follow-up.

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ABSTRACT

Background and aims: The prevalence of familial hypercholesterolemia (FH) is high among patients with stable coronary artery disease (CAD). However, data on FH on admission among patients with acute coronary syndrome (ACS) are still relatively scarce. Therefore, we aimed to assess the prevalence, lipid-lowering therapy and short- and long-term outcomes in patients with FH among ACS patients.

Methods and results: The investigation was performed in a cohort of 19,781 consecutive patients from the TERCET Registry. There were 7319 patients admitted with ACS: 3085 due to STEMI, 2256 due to NSTEMI, and 1978 due to UA. The stable CAD group (n = 12,462) was considered the reference group. Based on the personal and familial history of premature cardiovascular disease and LDL cholesterol concentration, the Dutch Lipid Clinic Network (DLCN) algorithm was used for FH diagnosis.

The overall occurrence of probable/definite FH and possible FH was 1.2% and 13.5% respectively. Among patients with ACS, 1.6% had probable/definite FH and 17.0% possible FH. The highest occurrence of FH was observed in the STEMI subgroup (20.6%). Patients with definite and probable FH had higher 30-day mortality than patients without FH (8.2% and 3.8% *vs.* 2.0%, respectively; $p = 0.0052$). No significant differences were observed between the FH groups in the 12-, 36- and 60-month follow-up. Propensity-score matching analysis showed that definite/probable FH patients had significantly higher all-cause mortality at 36- and 60-month follow-up in comparison to non-FH subjects (11.4% *vs.* 4.8% and 19.2% *vs.* 7.2%, respectively; $p \leq 0.021$ for both).

Conclusions: The prevalence of FH according to the DLCN criteria in the Polish very high-risk population is

Abbreviations: CABG, Coronary artery bypass graft; DCLN, Dutch Lipid Clinic Network; HeFH, Heterozygous familial hypercholesterolaemia; HoFH, Homozygous familial hypercholesterolaemia; NSTEMI, Non-ST-segment elevation acute coronary syndrome; PAD, Peripheral artery disease; PCI, Percutaneous coronary intervention; sCAD, Stable coronary artery disease

* Corresponding author.
E-mail address: dyrbusk@gmail.com (K. Dyrbuś).

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significantly higher in patients with ACS than in patients with sCAD. FH is a cause of increased all-cause mortality in the long-term follow-up.

1. Introduction

Familial hypercholesterolemia (FH) is the most common of all monogenetic diseases [1]. In the Caucasian population, its homozygous form (hoFH) is estimated to occur in 1:300,000 to 1:1,000,000 [2], and the prevalence of the more frequent heterozygous form (heFH) is estimated in various regions of the world at 1:200 to 1:500 [3,4]. The most recent studies conducted in large population samples indicate that contrary to the above estimations, the prevalence of the disease might be substantially higher and, in some populations, it reaches even less than 1:170 [5,6]. Extrapolation of the available data allows estimating that the worldwide occurrence of the heterozygous FH varies between 1:200 and 1:250, therefore bringing the total number of patients burdened with the disease to 14–34 million [7]. In Poland, there might be even 120–150,000 patients with FH [9–13]. The higher occurrence of the disease (reaching even 1:67) has been confirmed among the members of the French-speaking Canadian population, Ashkenazi Jews, the Afrikaners from South Africa, the Southern African Hindus, Finns and in the population of the Lebanese Christians, and might be associated with the founder effect [14–17].

The primary biochemical parameter measured and analysed in the diagnosis of the disease is low-density lipoprotein cholesterol (LDL-C) concentration elevated above the 95 th percentile for age/gender (in the heterozygous form often 2–3 fold higher than the average of the general population) [18]. In the FH patients, atherosclerotic processes develop much faster and lead to their earlier manifestation in the form of coronary artery disease (CAD) more than peripheral artery disease (PAD) and/or cerebrovascular disease [19]. As far as the patients with the heterozygous form are concerned, the risk of premature CAD development is 20-fold higher than in the general population, and cardiovascular (CV) mortality in this population aged between 20 and 39 years old is 100 times higher when compared with the general population [20]. In patients with heFH without successful treatment, a cumulated risk of death from CAD or non-fatal cardiac events before the age of 60 is 50% in men and 30% in women [21]. In children with heFH, elevated LDL-C from the very early age leads to premature endothelial dysfunction and thickening of the intimal and medial layers of the peripheral arterial wall [22]. In the subanalysis of the National Health and Nutrition Examination Surveys (NHANES) Registry, it has been reported that patients with FH have significantly shorter telomere length than patients without FH [23]. Shortened telomere length is correlated with higher mortality and morbidity, which possibly explains the impact of the burden of cholesterol-life years in this population.

In Poland, evidence on FH derived from the clinically homogeneous groups is still very scarce, therefore, hindering the precise calculation of FH prevalence in either primary or secondary prevention in the Polish population [10,11]. In Poland, as well as in Europe and worldwide, there is still very limited knowledge on the prevalence of FH in patients with established CAD, especially with acute coronary syndrome (ACS) [12,13]. Therefore, the aim of the study is to analyse the population of patients included in the Hyperlipidaemia Therapy in tERtiary Cardiological cEnTer (TERCET) Registry to estimate the prevalence, lipid-lowering therapy and short- and long-term outcomes in patients with either stable coronary artery disease (sCAD) or ACS.

2. Materials and methods

2.1. Study design and patients' characteristics

The design and rationale of the TERCET Registry, along with the patient recruitment scheme, and the definitions and methods of the long-term follow-up data gathering, were described in details elsewhere [24]. For this analysis, we have included data on 19,781 consecutive patients with CAD admitted and treated in the highest referenced cardiological centre in Zabrze in the years 2006–2018. Their clinical characteristics have also been precisely described in a previous study [24].

The presence of FH was assessed based on age, personal and familial medical history (including premature atherosclerotic cardiovascular disease [ASCVD]) and LDL-C concentrations on admission. The evaluation of each patient was conducted according to the Dutch Lipid Clinic Network (DCLN) Score [2,25]. Due to the limitations of the Registry - namely methodological reasons - clinical signs of lipid accumulation in the tissues in the shape of skin and ocular lesions could not be identified, therefore their fields in DCLN algorithm were filled with "0", as had previously been done in other studies [26,27]. The patient was assigned to the possible heFH group having obtained 3–5 points and to the probable heFH having obtained 6–8 points. Definite heFH was defined as > 8 points in the algorithm. Taking into consideration that the majority of the patients were treated with lipid-lowering agents before the hospitalisation, we used the 1.43 conversion rate previously mentioned in the literature to correct the baseline values of LDL cholesterol in patients previously treated with statins [7,8].

2.2. Adverse clinical outcomes

The information concerning the 30-day, 12-month 36 and 60-month follow-up, including death date (from cardiac and non-cardiac causes), along with non-fatal myocardial infarction and planned or ACS-driven revascularization, is acquired from the official Polish healthcare provider - National Health Fund (NHF). The laboratory parameters at discharge are derived from the patient's records created during the hospitalisation period or from the hospital outpatient clinic. The definitions of adverse clinical events were described previously [24].

2.3. Statistical analysis

Basic parameters of descriptive statistics for the analysed continuous variables are presented as mean and standard deviation (SD) for normal distributions, or as median of the quartiles 1 and 3 (Q1-Q3) for non-normal distributions. Qualitative variables are presented as numeric and percentage values. Normality of distribution was verified using the Shapiro-Wilk test. The comparison between groups regarding continuous variables has been tested using the Student t test (for normally distributed variables) or Mann-Whitney *U* test (for non-normally distributed variables). The Pearson's chi-squared test was used for categorical variables. A two-sided *p-value* < 0.05 has been considered significant. Unifactorial and multifactorial analyses have been performed to assess variables in a long-term observation using the Cox proportional regression model or with the logistic regression ($p < 0.3$

for inclusion in the model, $p < 0.05$ for remaining in the model). Estimated parameter values have been presented as hazard ratio (HR) or odds ratio (OR) with a 95% confidence interval (CI). The survival analysis was performed with the Kaplan-Meier method using a *log-rank* test. STATISTICA 10 (StarSoft Inc., Tulsa, OK, US) was used for all calculations.

To minimize the confounding impact of risk factors affecting 30-day, 12-month, 36-month and 60-month outcomes, we also performed a propensity score analysis to adjust for differences in patients' baseline characteristics. First, the logistic regression was performed to score all patients according to the result of the DLCN criteria evaluation (definite/probable FH vs no/possible FH), using as covariates clinical and procedural parameters clinically relevant for the endpoint: age (years), gender (male/female), diabetes mellitus, prior myocardial infarction, prior stroke, left ventricular ejection fraction, atrial fibrillation and multivessel CAD. In the next stage, the analyses were performed on the matched groups (definite/probable FH vs no/possible FH), stratified by pairs to account for propensity score matching. The nearest neighbor matching was used.

3. Results

Among 19,781 patients included in the TERCET Registry, 12,462 (63.0%; average age: 65.1 ± 9.5, males: 66.6%) had sCAD, and the remaining 7319 (37.0%) were admitted due to ACS. In the ACS subgroup, there were 3085 (15.6% of the whole population; average age: 62.7 ± 11.5, males: 62.7%) patients with ST-segment elevation myocardial infarction (STEMI) and 2256 (11.4% of the whole population; average age: 65.7 ± 10.9, males: 64.8%) patients with non-ST-segment elevation myocardial infarction (NSTEMI). There were 1978 patients with unstable angina (UA) that comprised 10.0% of the whole population (64.7 ± 10.7, males: 64.4%).

In the population included in the registry, LDL-C concentration was available for analysis in 19,781 patients (in the remaining group of 45 patients the authors had only total cholesterol concentration at their disposal and hence those patients were exluded from the analysis). In order to estimate the untreated LDL-C concentration in patients treated with statins, 1.43 correction factor was utilised in 6070 patients (44.2%). Among the subgroups with available LDL-C concentration, 49 (0.3%) patients fulfilled the definite FH criteria according to DCLN score, 184 (0.9%) were classified as probable FH, and 2642 (13.5%) were assigned to the possible FH group. Familial hypercholesterolemia diagnosis based on the DCLN criteria is presented in Supplementary Table 1 and Supplementary Fig. 1. The specific clinical characteristics of the patients with and without FH are presented in Table 1. Patients at risk of FH were significantly younger than their non-FH counterparts ($p < 0.0001$). Similar significant differences in the occurrence of diabetes and arterial hypertension were observed between the groups. However, patients with definite/probable FH had a significantly more prolific history of prior myocardial infarction (MI) and previous revascularization (both percutaneous coronary intervention - PCI and coronary artery bypass graft surgery – CABG; $p < 0.0001$ for both) and the percentage of active smokers was significantly higher in that group ($p < 0.0001$). Interestingly, the prevalence of atrial fibrillation was the highest for non-FH patients (18.7% *vs* 4.1% in definite FH patients), and the prevalence of PAD was the highest in patients with probable (29.1%) and possible FH (17.6%) and the lowest for definite FH patients (10.2%). Patients with FH during their hospital stay had significantly more frequently undergone coronary angioplasty procedures ($p = 0.041$; Table 1). The lipid profile characteristics with regard to the number of points in the DCLN score algorithm are presented in Supplementary Table 2.

Unsurprisingly, as far as its clinical implications are considered, FH was significantly more frequently diagnosed in patients with ACS. In

Table 1
Baseline characteristics of study population based on the Dutch Lipid Clinic Network diagnosis algorithm for familial hypercholesterolemia.

Factor	Study population (N = 19,781)				
	Definite FH N = 49	Probable FH N = 184	Possible FH N = 2642	No FH N = 16,707	*p*
Age, years; mean (SD)	51.3 (7.6)	53.7 (8.2)	59.7 (10.4)	65.6 (9.9)	< 0.0001
Male, % (n/N)	69.4 (34/49)	58.2 (107/184)	64.2 (1697/2642)	65.2 (10,890/16707)	0.16
Indication for hospitalisation					
Stable angina, % (n/N)	49.0 (24/49)	59.8 (110/184)	60.6 (1600/2642)	67.7 (11,318/16,707)	< 0.0001
Unstable angina, % (n/N)	12.2 (6/49)	14.1 (26/184)	10.8 (286/2642)	9.9 (1650/16,707)	0.11
Non-ST elevation MI, % (n/N)	14.3 (7/49)	16.3 (30/184)	13.6 (358/2642)	11.0 (1840/16,707)	0.0002
ST elevation MI, % (n/N)	24.5 (12/49)	9.8 (18/184)	15.1 (398/2642)	11.4 (1899/16,707)	< 0.0001
Arterial hypertension, % (n/N)	69.4 (34/49)	70.7 (130/184)	72.6 (1907/2628)	77.9 (12,920/16,580)	< 0.0001
Prior MI, % (n/N)	65.3 (32/49)	73.9 (136/184)	47.3 (1240/2619)	30.9 (5059/16,384)	< 0.0001
Prior PCI, % (n/N)	61.2 (30/49)	64.7 (119/184)	44.3 (1159/2619)	29.1 (4775/16,390)	< 0.0001
Prior CABG, % (n/N)	20.4 (10/49)	10.3 (19/184)	13.4 (351/2623)	10.8 (1781/16,442)	0.0003
Atrial fibrillation, % (n/N)	4.1 (2/49)	5.5 (10/183)	11.5 (303/2629)	18.7 (3070/16,432)	< 0.0001
Peripheral artery disease, % (n/N)	10.2 (5/49)	29.1 (53/182)	17.6 (461/2619)	11.9 (1953/16,356)	< 0.0001
Prior stroke, % (n/N)	4.1 (2/49)	8.7 (16/184)	6.8 (178/2628)	4.9 (810/16,493)	0.0001
Diabetes mellitus, % (n/N)	22.4 (11/49)	25.3 (46/182)	29.9 (784/2622)	34.5 (5655/16,411)	< 0.0001
Cigarette smoking, % (n/N) #	59.2 (29/49)	61.7 (113/183)	50.7 (1327/2618)	44.0 (7221/16,398)	< 0.0001
Familiar history of MI, % (n/N)	34.7 (17/49)	34.4 (63/183)	25.6 (670/2618)	20.8 (3401/16,351)	< 0.0001
Serum creatinine[a], μmol/L; median (Q1-Q3)	79 (65–97)	75 (63–89)	78 (66–93)	82 (69–98)	< 0.0001
eGFR[a], mL/min/1.73m^2; median (Q1-Q3)	91 (69–109)	91 (73–109)	86 (70–102)	80 (64–96)	< 0.0001
eGFR[a] < 60 mL/min/1.73m^2, % (n/N)	7.0 (3/43)	12.0 (21/175)	15.0 (378/2520)	19.9 (3191/16019)	< 0.0001
LVEF[a], % (SD)	42.5 (13.1)	44.7 (10.8)	45.0 (11.0)	45.6 (11.2)	0.055
LVEF < 35%[a], % (n/N)	26.8 (11/41)	18.0 (27/150)	18.8 (396/2107)	18.7 (2419/12,950)	0.60
Multivessel CAD, % (n/N)	42.9 (21/49)	32.3 (59/183)	37.8 (994/2633)	41.2 (6814/16,538)	0.092
PCI, % (n/N)	65.3 (32/49)	59.6 (109/183)	62.6 (1647/2633)	58.0 (9592/16,538)	0.041
CABG, % (n/N)	2.0 (1/49)	7.6 (14/184)	7.9 (210/2642)	7.1 (1189/16,707)	0.22

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CTO = chronic total occlusion; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolemia; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; Q1-Q3 = quartile 1 and 3; SD = standard deviation.

p value represents the *p* between the lowest differing quartiles.

#Describes the habit regardless of whether the patient had been an active smoker in the past or was on admission.

[a] On admission.

the STEMI subgroup, 20.6% of the patients were assigned at least to the possible FH group, and in the NSTEMI subgroup, it was 17.2% of the patients (Supplementary Fig. 1). In the other patients included in the Registry, 12.1% fulfilled at least possible FH criteria. While evaluating relatively young patients with ACS (< 40 and < 50 years of age, respectively), the prevalence of FH (probable + definite FH diagnosis) was 6.3% and 3.7%, respectively.

No statistically significant differences in the in-hospital and long-term outcomes were observed between the groups in terms of combined endpoint occurrence. However, a significantly higher in-hospital and 30-day mortality was observed in patients with definite FH *vs*. patients without FH (8.2% and 2.0%, $p = 0.0052$). Interestingly, in the follow-up after 12, 36 and 60 months, a significant increase in the number of myocardial infarctions was observed in patients without FH. There was no increase in the incidence of other cardiovascular events, or a composite endpoint. Early and long-term clinical outcomes are presented in Table 2 and Fig. 1.

Hypolipemic therapy at discharge is presented in details in Supplementary Table 3. At discharge, patients with definite or probable FH were significantly more frequently treated with statin therapy in comparison to the non-FH patients (92.3% in definite and 91.5% in probably FH *vs.* 86.7%, $p = 0.0085$) and were significantly more frequently treated with high dose statin therapy (64.1% in the definite FH group *vs.* 25.6% in patients without FH, $p < 0.0001$). The majority of patients with FH were treated with atorvastatin (140 out of 204 patients with definite and probable FH [68.2%]) while for the rest, simvastatin (mostly those enrolled into the Registry at its very beginnings), and rosuvastatin (mostly the patients from the recent years) were administered. Worth noting is the fact that in the FH patient subgroup, the other lipid-lowering drugs were administered significantly more frequently than in patients without FH: 5.1% with definite FH and 2.9% in definite/probably FH were treated with ezetimibe; while in the remaining population, it was only 0.42% ($p < 0.0001$). In 9.3% of the patients with definite and probable FH ,treatment with fibrates was initiated, with just 3.1% in the rest of the patients ($p = 0.0009$). It is also worth mentioning that combined lipid-lowering therapy was prescribed significantly more frequently in the patient subgroups with definite and probable FH (12.1%) when compared to the other patients (2.1%, $p < 0.0001$).

After propensity-score matching analysis (224 patients with definite/probable FH *vs.* 224 without FH; (Table 3), we found that patients with definite/probable FH had higher all-cause mortality at the 36-month and 60-month follow-up (11.4% *vs.* 4.8% and 19.2% *vs.* 7.2%, respectively; $p \leq 0.021$ for both) (Table 4). However, we did not find an increased number of myocardial infarctions or strokes or need for re-revascularization in patients with definite/probable FH in comparison to non-FH patients, for all investigated time points. At the same time, we showed that patients with definite/probable FH received more optimal lipid-lowering treatment than patients without FH (87.9% were treated with statins *vs.* 70%), although only 52.2% (*vs.* 34%) of them used intensive statin therapy. We also showed a huge difference in the concentration of lipids in the PMS group between patients with FH and patients without FH with LDL-C 203 mg/dL for definite/probable FH *vs.* 88 for non-FH group ($p < 0.0001$) (Supplementary Table 4).

4. Discussion

The population included in the TERCET Registry should be considered as very-high cardiovascular risk that underwent treatment in the nationwide, tertiary cardiovascular centre. Therefore, one has to distinguish substantial differences and consider taking a different approach when comparing this group with patients, for example, from the Copenhagen General Population Study [30]. In that study, based on the DCLN criteria, the prevalence of definite FH was 0.2%, probable FH was detected in 0.53% and possible FH in 6.3% of the sample enrolled [30]. Similar results were obtained in the large Chinese study, where FH occurrence in the overall Chinese population was estimated at 0.28% on the basis of the aforementioned algorithm [31].

In patients with previously diagnosed CAD, one would expect the prevalence of FH to be higher than in the general population [27]. In the TERCET Registry sample, based on DCLN criteria, 0.3% of the participants fulfilled the criteria for definite FH, 0.9% for probable FH and as much as 13.5% for possible FH. Altogether, based just on the LDL-C concentration and patients' age, therefore not analysing either the skin and ocular lesions and genetic profile, FH can be suspected in 14.7% of the whole population of the Registry. This is in contrast with the results of the large, European study by de Backer et al. conducted among patients with history of MI, myocardial ischemia or revascularization, in which the prevalence of potential FH (probable/definite FH) was significantly higher among 357 of the Polish

Table 2
Early and long-term outcomes of the study population based on The Dutch Lipid Clinic Network diagnosis algorithm for familial hypercholesterolemia.

Factor	Study population (N = 19,781)				
	Definite FH N = 49	Probable FH N = 184	Possible FH N = 2642	No FH N = 16,707	*p*
30-day outcomes					
Death, % (n/N)	8.2 (4/49)	3.8 (7/184)	1.9 (49/2642)	2.0 (334/16,707)	0.0052
MI, % (n/N)	0.0 (0/49)	0.4 (1/184)	0.9 (24/2642)	0.6 (99/16,707)	0.16
ACS-driven revascularization, % (n/N)	0.0 (0/49)	0.4 (1/184)	0.7 (19/2642)	0.6 (101/16,707)	0.58
Stroke, % (n/N)	0.0 (0/49)	0.5 (1/184)	0.1 (2/2642)	0.1 (14/16,707)	0.21
12-month outcomes					
Death, % (n/N)	12.2 (6/49)	7.1 (13/184)	6.2 (164/2642)	6.6 (1106/16,707)	0.35
MI, % (n/N)	2.0 (1/49)	1.6 (3/184)	4.1 (108/2642)	3.2 (529/16,707)	0.047
ACS-driven revascularization, % (n/N)	2.0 (1/49)	2.2 (4/184)	3.8 (100/2642)	3.7 (611/16,707)	0.65
Stroke, % (n/N)	0.0 (0/49)	1.6 (3/184)	0.9 (23/2642)	1.1 (179/16,707)	0.57
36-month outcomes					
Death, % (n/N)	25.0 (11/44)	12.8 (19/149)	12.9 (284/2198)	13.3 (1809/13,573)	0.14
MI, % (n/N)	4.5 (2/44)	6.7 (10/149)	7.7 (170/2198)	6.2 (841/13,573)	0.052
ACS-driven revascularization, % (n/N)	4.5 (2/44)	6.7 (10/149)	8.2 (181/2198)	7.2 (971/13,573)	0.28
Stroke, % (n/N)	2.3 (1/44)	3.4 (5/149)	3 (65/2198)	2.7 (367/13,573)	0.87
60-month outcomes					
Death, % (n/N)	32.4 (12/37)	20.5 (25/122)	18.8 (306/1632)	20.1 (1840/9146)	0.15
MI, % (n/N)	8.1 (3/37)	13.1 (16/122)	11.3 (185/1632)	9.1 (830/9146)	0.016
ACS-driven revascularization, % (n/N)	5.4 (2/37)	13.9 (17/122)	11.8 (193/1632)	10.3 (943/9146)	0.12
Stroke, % (n/N)	2.7 (1/37)	5.7 (7/122)	3.9 (64/1632)	4.4 (401/9146)	0.67

ACS = acute coronary syndrome; FH = familial hypercholesterolemia; MI = myocardial infarction; TC = total cholesterol; TG = triglycerides.
p value represents the *p* value between the lowest differing quartiles.

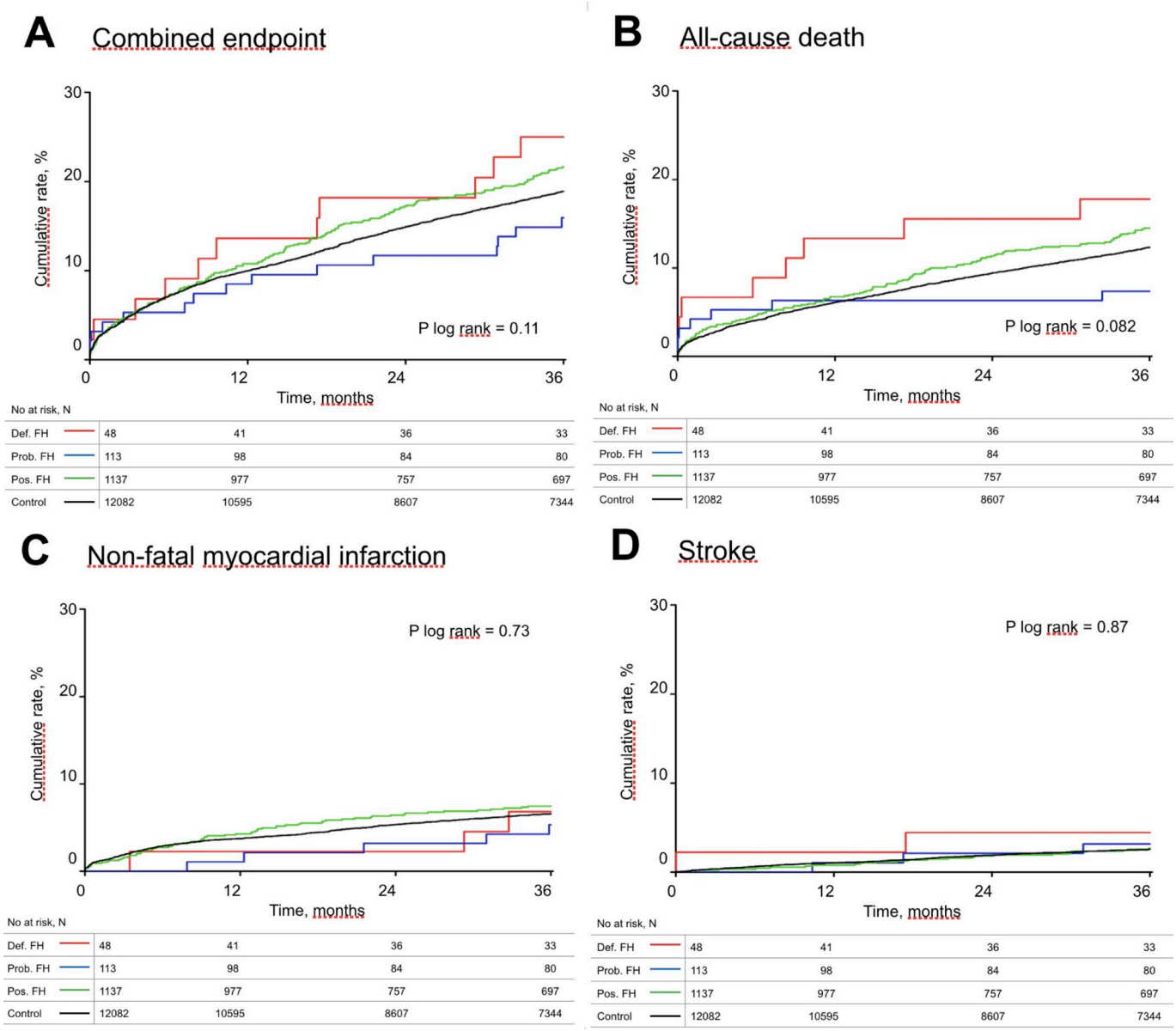

Fig. 1. Early and long-term outcomes of study population depending on The Dutch Lipid Clinic Network diagnosis algorithm for familial hypercholesterolemia.

participants of the study and reached 11.4%, while in the whole European population it was 8.3% [28]. Moreover, the representation of the Polish population in the EUROASPIRE IV study was significantly smaller than in our study, which could also cause the difference in the occurrence of FH between the studies.

However, our results are in line with those of the large Swiss SPUM-ACS study encompassing only patients with ACS, in which definite/probable FH was diagnosed in 1.6% and possible FH in 18.2% of the analysed sample based on DLCN criteria [26]. In the Chinese analysis in patients with myocardial infarction, FH occurred in 3.9% [27]. Against that background, in the analysed sample from the TERCET Registry, 1.3% of patients with STEMI fulfilled the criteria for definite/probable FH while in the NSTEMI group it was 1.8%. definite/probable FH was suspected in 1.1% of the remaining patients. Interestingly, evaluating only young patients with ACS (< 40 and < 50 years of age), the prevalence of probable/definite FH was as much as 6.3% and 3.7%, respectively.

Here again, in the Greek study by Rallidis et al. the overall prevalence of definite/probable FH in patients < 35 years of age who had survived a first STEMI was significantly higher than in our study, and reached 20.3% [29]. One possible explanations of such result discrepancy could be derived from the fact that the researchers from Greece adopted a full DLCN criteria protocol assessing also the presence of arcus cornealis and tendon xanthomas. Here again, the relatively smaller population sample in this study (320 under the age of 35 years vs 844 patients under the age of 40 years in our study) could also cause the difference.

However, in the previously mentioned SPUM-ACS study, the authors also assessed the prevalence of FH in the younger population, defined by the occurrence of ACS < 55 years of age in male and < 60 years of age in female patients [26]. The overall prevalence of probable/definite in that group was 4.8%, whilst in our study was 3.7%, below the age threshold of 50 years of age.

The results of the Registry indicate that FH occurs significantly more frequently in patients with ACS than with SA. Similar findings can be derived from the Japanese EXPLORE-J study, where the prevalence of FH was also significantly higher in ACS patients (4.7%) than in the general population (2.1%), especially as far as patients with premature onset of ACS were concerned [32]. In the Italian cohort of 1438 patients, the authors showed that definite FH had the highest percentages

Table 3
Characteristics of the matched cohort depending on The Dutch Lipid Clinic Network diagnosis algorithm for familial hypercholesterolemia.

Factor	Matched cohort (N = 448)		
	Definite/probable FH (N = 224)	No FH (N = 224)	*p*
Age, years; mean (SD)	53.1 (8.1)	53.0 (9.7)	0.95
Male, % (n/N)	61.2 (137/224)	61.2 (137/224)	> 0.99
Indication for hospitalisation			
Stable angina, % (n/N)	59.8 (134/224)	58.9 (132/224)	0.85
Unstable angina, % (n/N)	14.3 (32/224)	19.2 (43/224)	0.16
Non-ST elevation MI, % (n/N)	15.2 (34/224)	12.1 (27/224)	0.33
ST elevation MI, % (n/N)	10.7 (24/224)	9.8 (22/224)	0.76
Arterial hypertension, % (n/N)	71.4 (160/224)	67.7 (147/217)	0.40
Prior MI, % (n/N)	71.9 (161/224)	68.1 (143/210)	0.39
Prior PCI, % (n/N)	65.2 (146/224)	56.3 (120/213)	0.058
Prior CABG, % (n/N)	12.5 (28/224)	7.3 (16/219)	0.067
Atrial fibrillation, % (n/N)	5.4 (12/223)	3.1 (7/222)	0.25
Peripheral artery disease, % (n/N)	25.3 (56/222)	10.2 (22/215)	< 0.0001
Prior stroke, % (n/N)	7.1 (16/224)	4.5 (10/222)	0.23
Diabetes mellitus, % (n/N)	24.3 (54/222)	17.1 (37/216)	0.064
Cigarette smoking, % (n/N)	61.9 (138/223)	56.7 (122/215)	0.27
Familiar history of MI, % (n/N)	27.9 (55/197)	31.7 (60/189)	0.41
Serum creatinine[a], μmol/L; median (Q1-Q3)	75 (63–89)	71 (63–84)	0.56
eGFR[a], mL/min/1.73m^2; median (Q1-Q3)	91 (74–109)	96 (79–114)	0.17
eGFR[a] < 60 mL/min/1.73m^2, % (n/N)	10.3 (22/213)	6.9 (15/217)	0.21
LVEF[a], %; mean (SD)	45.3 (10.4)	46.5 (10.3)	0.28
LVEF < 35%[a], % (n/N)	17.0 (31/182)	15.6 (27/173)	0.72
Multivessel CAD, % (n/N)	40.5 (90/222)	39.4 (86/218)	0.82
PCI, % (n/N)	64.7 (145/224)	58.5 (131/224)	0.17
CABG, % (n/N)	6.7 (15/224)	7.6 (17/224)	0.71

[a] On admission. CABG = coronary artery bypass grafting; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolemia; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; Q1-Q3 = quartile 1 and 3; SD = standard deviation.

Table 4
Early and long-term outcomes of the matched cohort depending on The Dutch Lipid Clinic Network diagnosis algorithm for familial hypercholesterolemia.

Factor	Matched cohort (N = 448)		
	Definite/probable FH (N = 224)	No FH (N = 224)	*p*
30-day outcomes			
Death, % (n/N)	0.9 (2/224)	0.0 (0/224)	0.16
MI, % (n/N)	0.5 (1/224)	1.3 (3/224)	0.32
ACS-driven revascularization, % (n/N)	0.5 (1/224)	0.0 (0/224)	0.32
Stroke, % (n/N)	0.5 (1/224)	0.0 (0/224)	0.32
12-month outcomes			
Death, % (n/N)	4.5 (10/224)	1.8 (4/224)	0.10
MI, % (n/N)	2.2 (5/224)	4.5 (10/224)	0.19
ACS-driven revascularization, % (n/N)	2.7 (6/224)	3.6 (8/224)	0.59
Stroke, % (n/N)	1.3 (3/224)	0.5 (1/224)	0.32
36-month outcomes			
Death, % (n/N)	11.4 (21/184)	4.8 (9/186)	0.021
MI, % (n/N)	6.5 (12/184)	7.5 (14/186)	0.71
ACS-driven revascularization, % (n/N)	7.1 (13/184)	8.6 (16/186)	0.58
Stroke, % (n/N)	3.3 (6/184)	0.5 (1/186)	0.055
60-month outcomes			
Death, % (n/N)	19.2 (29/151)	7.2 (11/153)	0.0019
MI, % (n/N)	12.6 (19/151)	7.8 (12/153)	0.17
ACS-driven revascularization, % (n/N)	13.3 (20/151)	10.5 (16/153)	0.45
Stroke, % (n/N)	5.3 (8/151)	3.3 (5/151)	0.38

ACS = acute coronary syndrome; FH = familial hypercholesterolemia; MI = myocardial infarction.

of patients after an ACS (75% *vs.* 52.5% in the whole study population) [19].

In all patients with high LDL-C levels (especially over 190 mg/dL) and premature ACS, we should always consider the risk of FH occurrence. In the investigated group of patients from the TERCET registry, the mean LDL concentration (after application of the 1.43 conversion) was 360 mg/dL (9.31 mmol/L) in the group of patients with definite FH, 272 mg/dL (6.88 mmol/L) in the group with probable FH, and 201 mg/dL (5.20 mmol/L) in the group with possible FH. Therefore, these were significantly higher when compared to the remaining patients without FH (in that group mean LDL concentration was 106 mg/dL [2.74 mmol/L]). Similar discrepancies can be observed between non-HDL and triglyceride concentrations [33–35]. Among the Registry patients with FH, a significantly more prolific history of ACS is worth noting, therefore resulting in a significantly higher rate of previous revascularization procedures. It should be explained with the clinical

characteristics of the patients and the specifics of the cardiovascular centre itself: the patients admitted to the referential centre are usually burdened with much more comorbidities and are at higher CV risk. Luckily for that group, an effective treatment, namely coronary revascularization along with optimal (=intensive) pharmacological treatment including statin therapy reduces their initial CV risk and no significant differences in the occurrence of adverse CV effects were observed in the 12-month, 36-month and 60-month follow-up. What is more, we have found that in patients without FH in distant observation, MIs are significantly more common, which is an unexpected and non-existent result in other studies. This difference can be explained with non-optimal pharmacological therapy of those patients (86.7% on statin therapy, including only 0.3% on combination therapy with ezetimbe, and only 25.6% on high intensive statin therapy) as well as much higher all-cause mortality in those with definite/possible FH in the 30-day follow-up. In addition, based on the propensity-score matching analysis, we showed that FH patients have significantly higher risk of death in a distant follow-up. Similarly to the results indicating that phenotypically diagnosed patients with FH have significantly shorter telomere length and in the consequence shorter life expectancy [23], we showed that using the phenotypical approach, in propensity-score matching, FH itself is a cause of reduced survival in the long-term follow-up (11.4% *vs.* 4.8% and 19.2% *vs.* 7.2% in 36- and 60-month follow-up for definite/possible FH and non-FH patients, respectively), confirming the life-long significantly higher risk of those patients. However, no significant differences in the occurrence of any other hard endpoint were observed. The trends observed in our analysis are consistent with the results of the study by Nanchen et al., who analysed 1-year outcomes of the Swiss cohort from the SPUM-ACS study [36]. In patients from Switzerland, the risk of recurrent cardiovascular coronary event, defined as fatal or non-fatal MI was 3.53-fold higher after 1 year if the patient had ≥6 points in the DLCN score (probable/definite FH) when compared with group without FH. In contrary, in the study by Rerup et al., in which the outcomes of the Danish population after MI were analysed, patients with possible FH (≥3 points in the DLCN criteria) had significantly higher risk of recurrent MI, but not of death from any cause, after adjustment for confounders in a median 3.3 year follow-up [37].

Nevertheless, FH patients should be treated as early as possible, and should be treated optimally, and according to our analysis, the lipid-lowering therapy can be still much improved.

Undoubtedly, it is important to note that in patients with definite/probable FH, 88.4% had been taking statins before admission, and at discharge this percentage rose to almost 92%. Furthermore, in almost 53% of those patients, statin therapy has been intensified when compared to the therapy before hospitalisation. In the Danish study conducted on the general population, 96% of the patients with FH received statins [30]. Similar results can be derived from the Swiss analysis, where over 95% of the patients with ACS and FH were treated with statins at discharge, 70% of them received intensive lipid lowering therapy [26].

4.1. Study limitations

The study has a few important limitations one has to consider. First, the Registry does not contain the information on skin and ocular lesions, which might, therefore, understate the number of patients with definitive FH. However, data derived from the other studies suggest that the number of patients with those lesions is relatively low (especially in the statins' era) and does not significantly influence the FH prevalence estimations. Second, the data included in the Registry do not allow for the precise establishment of the exact age when coronary artery disease was first diagnosed both in the patients and in their relatives. This parameter might also slightly understate the number of patients with FH. Third, in order to obtain LDL concentrations in patients continuingly taking statins, 1.43 conversion rate was used, which might slightly inflate LDL-C concentrations in a number of patients. In order to overcome these limitations, the future active search for patients with FH based on all diagnostic criteria is necessary. Fourth, an important limitation is that the diagnosis of FH was determined based on the phenotypic criteria instead of genetic testing. Nonetheless, the results of the study by Wald et al., in which FH was confirmed by the DNA analysis, indicate that definite FH diagnosis based on clinical DLCN criteria offers similar detection rate as the genetic testing [38]. Also, in the number of other studies, the genetic analysis allowed to detect FH in a rate comparable with the diagnosis of definite FH based on the phenotypical assessment [39–41].

Fifth, despite the rising significance of lipoprotein(a) measurement as a biomarker of CV prognosis in patients with hypercholesterolaemia, its assessment was not performed in the analysed population [42,43].

4.2. Conclusion

The prevalence of familial hypercholesterolemia (definite/probable/possible) according to the DLCN criteria in the Polish very-high-risk population is 14.7%. These patients are often referred to the tertiary cardiovascular centre after having previously undergone myocardial infarction. Among patients included in the Registry, the occurrence of FH rises to 20.6% in the STEMI subgroup, and to 17.2% in the NSTEMI subgroup. There is still much improvement needed in the optimal lipid-lowering therapy, including high intensity statin therapy and combination therapy.

4.3. Impact on daily practice

FH is a disease that causes an accelerated atherosclerotic process. It is a disease diagnosed too rarely, and its effects are serious for young patients with atherosclerosis. The TERCET registry shows the incidence of FH in patients from the very high risk population treated in the tertiary centre hospital and allows assessment of their prognosis. It also shows the scale of the disease and its impact on the long-term prognosis. Our study is the first to determine that patients with FH have higher all-cause mortality at 36-month and 60-month follow-up in propensity-score matching analysis. The manuscript draws attention to the need for early diagnosis of the disease to avoid the occurrence of ACS at a young age.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.06.899.

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