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Application of the Dutch Lipid Clinic Network Scale in the diagnosis of familial hypercholesterolemia and further clinical implications in the era of PCSK9 inhibitors

Zastosowanie skali *the Dutch Lipid Clinic Network* w diagnostyce hipercholesterolemii rodzinnej i dalsze implikacje kliniczne w erze inhibitorów PCSK9

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Abstract

The article presents a case of 64-year-old patient with years-long history of coronary artery disease, after several coronary events and percutaneous coronary intervention, with a late diagnosis of familial hypercholesterolemia (FH). Based on the clinical case, the authors presented the current diagnostic possibilities and the importance of early FH diagnosis as well as modern lipid-lowering treatment with the use of PCSK9 inhibitors.

Key words: familial hypocholesterolemia, PCSK9 inhibitors, the Dutch Lipid Clinic Network Scale

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Introduction

Since 2003–2005 (the WOBASZ study), hyperlipidemia has invariably been one of the most common risk factors of cardiovascular diseases in Poland [1]. Genetically determined forms of the disease, such as familial hypercholesterolemia (FH), are observed among hyperlipidemias. The disease is still rarely diagnosed, *i.a.* due to the fact that until the present, the assessment of the lipidogram has only been routinely conducted in men over 40, post-menopausal women or women over 50 [2], which makes early detection of severe FH cases diffuclt. The newest guidelines of the European Society of Cardiology (ESC) [3] recommend tests for FH, including the assessment of the lipidogram in children aged 5 or less if there is a suspicion of a homozygotic variant of the disease (class I recommendations, data credibility level: C).

Other factors which have an impact on the unsatisfactory level of lipid disorders detection is the failure to conduct clinical assessment of patients according to the Dutch Lipid Clinic Network Scale (DLCNS) (Table 1), or the lack of genetic testing, despite their availability for tests reimbursed by the National Health Fund (NFZ, *Narodowy Fundusz Zdrowia*). Patients bearing at least one of the listed elements should be referred for such tests [2]:

- total cholesterol (TC) concentration in serum ≥ 310 mg/dL (≥ 8 mmol/L) in an adult patient or their family member;
- premature coronary artery disease (CAD) in a patient or their family member (men < 55 years of age, women < 60 years of age);
- tendon xanthelasmas in a patient or their family member;
- sudden cardiac death of a family member at a young age.

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Table 1. Criteria of *the Dutch Lipid Clinic Network Scale* (prepared on the basis of [2, 3])

Clinical interview	Number of points
Premature cardiovascular disease in the patient (men < 55 years of age, women < 60 years of age)	2
Premature cerebrovascular or peripheral vascular disease in the patient (men < 55 years of age women < 60 years of age)	1
Family history	
First-degree relatives diagnosed with premature coronary artery disease (men < 55 years of age women < 60 years of age)	1
OR	
First-degree relatives with LDL-C concentration > 95th percentile for the age and sex in a given country [> 190 mg/dL (> 4,9 mmol/L)]	1
First-degree relatives with tendon xanthelasmas and/or Corneal limbi in a patient < 45 years of age	2
OR	
Children and adolescents < 18 years of age with LDL-C concentration > 95th percentile for age and sex in a given country (> 155 mg/dL [> 4 mmol/L])	2
Physical examination	
Tendon xanthelasmas	6
Corneal limbi	4
LDL-C concentration (without treatment)	
≥ 325 mg/dL (≥ 8.5 mmol/L)	8
251–325 mg/dL (6.5–8.4 mmol/L)	5
191–250 mg/dL (5.0–6.4 mmol/L)	3
155–190 mg/dL (4.0–4.9 mmol/L)	1
Genetic testing	
Confirmed mutation of LDL, ApoB or PCSK9 receptor gene	8
Diagnosis of familial hypocholesterolemia	
Certain	> 8
Likely	6–8
Possible	3–5
Unconfirmed	< 3

LDL-C — low-density lipoprotein cholesterol; ApoB — apolipoprotein B; PCSK9 — proprotein convertase subtilisin/kexin 9

Hereditary forms of lipid disorders, especially homo- (HoFH) and heterozygotic familial hypercholesterolemia (HeFH), constitute a particular challenge in clinical practice.

The Third Declaration of Sopot [2] recommends the following treatment goals in terms of the concentration of low-density lipoprotein cholesterol (LDL-C):

- below 1.8 mmol/L (< 70 mg/dL) in the group of high-risk patients;
- below 1.4 mmol/L (< 55 mg/dL) in the group of patients bearing very high risk;
- below 0.9 mmol/L (< 35 mg/dL) in the group of patients bearing extremely high risk;

This document distinguishes a group of patients bearing extremely high cardiovascular risk, which is partially based on the recommendations of American endocrinological societies [2]. The LDL-C goal in this group of patients, *i.e.* concentration below 0.9 mmol/L, was determined on the basis of prospective clinical studies on proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9), which demonstrated cardiovascular benefits in secondary prevention [2].

On the other hand, the most recent guidelines of the ESC Guidelines [3] do not include the group of patients with extremely high cardiovascular risk, while compared to the previous recommendations, treatment goals for particular risk groups have been changed. They are presented in Table 2.

On the basis of the clinical case in question, we are presenting the current state of knowledge concerning the possibilities of effective treatment of patients with HeFH in the era of PCSK9 inhibitors.

Case report

In 2017, a man of 64, with 13-year-long history of cardiac disease, was admitted to a cardiac unit due to unstable angina. The patient had controlled hypertension, hyperlipidemia (TC 9.58 mmol/L, LDL-C 6.98 mmol/L and increased concentration of triglycerides (TG) — 2.88 mmol/L; Table 3), hyperuricemia (uric acid concentration 477 μmol/L) as well as level I obesity — body mass index (BMI) of 33.9 kg/m^2.

Echocardiography showed segmental disorders of systolic function of the left ventricle with preserved global systolic function [ejection fraction (EF) 58%]. Coronary angiography showed restenosis in the stent implanted in the left descending artery (LAD) with lumen stenosis of 70%, the right coronary artery (RCA) obstructed from segment 2, and without atherosclerotic lesions in the left circumflex (LCx) and intermediate branch (IM). Percutaneous coronary intervention (PCI) of RCA was performed with an implantation of 3 stents releasing the medication: 3.0 × 13 mm, 2.5 × × 40 mm and, proximally, 3.5 × 20 mm with integrilin infusion. The procedure was completed without complications.

The patient was diagnosed with coronary artery disease in 2004 when he suffered an infarction of the anterior and inferior wall, and was treated by means of PCI in LAD

Table 2. Allocation of patients to particular cardiovascular risk groups (prepared on the basis of [2, 3])

Levels of cardiovascular risk	The Third Declaration of Sopot [2]	ESC Guidelines [3]
High	• ≥ 2 risk factors and risk of 10–20% on the Pol-SCORE scale • DM or CKD in 3rd–4th stage without other risk factors **Secondary treatment goal:** • non-HDL-C < 2.6 mmol/L (< 100 mg/dL)	• TC > 8 mmol/L (> 310 mg/dL), LDL-C > 4.9 mmol/L (> 190 mg/dL) or BP ≥ 180/110 mm Hg • FH without significant risk factors • DM duration ≥ 10 years, or with another co-existing risk factor, but without organ complications • Moderate CKD (eGFR 30–59 mL/min/1.73 m^2) • Risk on the SCORE scale ≥ 5% and < 10% for a ten-year risk or critical CVD **Treatment goals:** • primary: LDL-C < 1.8 mmol/L (< 70 mg/dL) • secondary: non-HDL-C < 2.6 mmol/L (< 100 mg/dL) Apo-B < 80 mg/dL
Very high	• ASCVD in patients in whom LDL-C < 70 mg/dL (< 1.8 mmol/L) was achieved and continuously maintained • Diagnosed ACS, coronary, carotid or peripheral artery disease • Status post-revascularisation • Risk on the Pol-SCORE scale > 20% • DM or CKD in 3rd–4th stage and ≥ 1 risk factor • FH • History of premature ASCVD (men < 55 years of age, women < 65 years of age) • Patients with DM or CKD at 3rd–4th stage diagnosed with CVD **Secondary treatment goal:** • non-HDL-C < 2.2 mmol/L (< 85 mg/dL)	• Clinically documented ASCVD after ACS (MI or UA), SA, post-revascularisation (PCI, CABG or other procedures), stroke or TIA and peripheral artery disease • ASCVD documented in diagnostic imaging through the detection of substantial atherosclerotic plaque during angiography of coronary arteries or CT (polyvascular coronary artery disease with > 50% stenosis of the lumen of 2 main arteries), or in the ultrasound of carotid arteries • DM with organ complications or with ≥ 3 main risk factors or with early onset of long-term (> 20 years) T1DM • Acute CKD (eGFR < 30 mL/min/1.73 m^2) • Risk in the SCORE scale < 10% for 10-year-long risk or critical CVD • FH with coexisting ASCVD or another risk factor **Treatment goals:** • primary: LDL-C < 1.4 mmol/L (< 55 mg/dL) • secondary: non-HDL-C < 2.2 mmol/L (< 85 mg/dL) Apo-B < 65 mg/dL)
Extremely high	• History of numerous cardiovascular events and/or revascularisation • PCI of the main left coronary artery trunk and/or polyvascular coronary artert disease with complex angioplasty • Generalised atherosclerosis of multiple vascular beds with additional risk factors • Progression of ASCVD in patients in whom LDL-C < 55 mg/dL (< 1.4 mmol/L) was achieved and continuously maintained **Secondary treatment goal:** • non-HDL-C < 1.7 mmol/L (< 65 mg/dL)	

ACS — acute coronary syndrome; ApoB — apolipoprotein B; ASCVD — atherosclerotic cardiovascular disease; BP — blood pressure; CABG — coronary artery bypass graft surgery; CKD — chronic kidney disease; CT — computed tomography; CVD — cardiovascular disease; DM — diabetes mellitus; eGFR — estimated glomerular filtration rate; ESC — European Society of Cardiology; FH — familial hypercholesterolemia; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; MI — myocardial infarction; PCI — percutaneous coronary intervention; SA — stable angina; SCORE — Systematic COronary Risk Estimation; T1DM — type 1 DM; TIA — transient ischemic attack; UA — unstable angina; USG — ultrasonography

with the implantation of a medication-releasing stent as well as PCI in RCA and IM with the implantation of metal stents. In the following years, the patient underwent the following PCIs with simultaneous implantation of medication-releasing stents: LAD in 2007, RCA in 2014 and LCx in 2016. The patient had 9 stents altogether implanted into coronary arteries.

Moreover, patient's father and brother suffered from premature CAD:

— the brother suffered an infarction at the age of 45 and died of infarction at the age of 57;
— the father suffered an infarction at the age of 48 and died of another infarction at the age of 67.

Based on patient's history and physical examination, he was assessed in accordance with the DLCNS and diagnosed with probable FH — with a score of 8 points.

— premature CAD — 2 points;
— premature CAD in first-degree relatives — 1 point;
— LDL-C concentration of 6.98 mmol/L — 5 points.

In addition, a DNA analysis in search for the most common mutations in Poland, *i.e.* p.G592E of the *LDRL* gene and p.R3500Q of the *APOB* gene, was conducted to confirm clinically diagnosed FH. The mutations were not detected. Further molecular tests in search for other mutations of the *LDLR* and *MTHFR* genes were planned, and presence of mutation c.415G>C in exone 4 of *LDLR* gene, which confirms the diagnosis of HeFH form, was documented. The patient was informed about the necessity to conduct genetic tests in his first-degree relatives.

In March 2019, due to short-term coronary-related symptoms in stressful situations, the patient underwent angiography computed tomography (angio-CT), which showed progression of CAD — signs of restenosis in the stent implanted in LAD causing narrowing of the lumen to 50% as well as a narrowing to 60–70% in the artery behind the stent, narrowing of the IM ostium to 50% and narrowing in the first segment of RCA to 50–60%; the coronary artery calcium score was 369 j.A. The patient was qualified for the assessment of the functional extent of myocardial ischaemia with the use of the single-photon emission computed tomography (SPECT).

Resting perfusion scintigraphy of the heart showed established perfusion disorders encompassing the apex, anterior-septal wall and the parabasal section of the inferior wall (25–30%), worsening during the physical test in the area of parabasal and central segment of the inferior wall and adjacent segments of the inferior-lateral wall (Figure 1) which constituted 10%. In accordance with the current ESC guidelines for chronic coronary syndromes [4], the patient was referred for follow-up coronary angiography which showed a 50–70% stenosis of the central part of the intermediate artery, atherosclerotic plaque in the proximal segment of RCA with a narrowing to 50% as well as peripheral 90% stenosis of the right posterior-lateral (diameter < 1.5 mm) branch of RCA. The results of the implantation of stents in LAD and LCx were also good. The patient was referred to further conservative treatment.

Since the most recent PCI in 2017, the patient has been receiving acetylsalicylic acid in the dose of 75 mg, 25 mg of metoprolol, 5 mg of ramipril, 20 mg/day of pantoprazole and trimethazidine in the dose of 35 mg/twice a day as well as intensive lipid-lowering treatment — 80 mg of atorvastatin + 10 mg of ezetimib once a day. Eight months and one year after the implementation of lipid-lowering treatment the lipidogram was performed again. The results of the examination are presented in Table 3.

The application of combined therapy did not contribute to the achievement of treatment goals neither in relation to LDL-C, nor non-HDL-C, both according to the ESC guidelines concerning high cardiovascular risk and the Third Declaration of Sopot concerning patients with extremely high risk.

New options for the treatment of lipid disorders

Lifestyle modification, particularly with regard to diet and physical activity, lies at the basis of the pyramid of lipid interventions. It is followed by statin treatment, intensive statin therapy and combined lipid-lowering treatment [2]. A new group of medications — PCSK9 inhibitors — has been for the first time included in the newest ESC guidelines for the treatment of lipid disorders [2]. So far, researchers have studied and documented benefits related to lowered risk of cardiovascular death, infarction, stroke, hospitalisation due to unstable angina (UA) or coronary artery revascularisation — hazard ratio (HR) [95% confidence interval (CI)] compared to placebo 0.85 (0.79–0.92) for evolocumab [5] and HR (95% CI) compared to placebo 0.85 (0.78–0.93) for alirocumab [6].

Proprotein subtilisin/kexine type 9 convertase is a protein which participates in the metabolism of LDL receptors (LDLR) through binding with them and stimulation of endocytosis of the LDLR-PCSK9 complex and degradation of LDLR in lysosome. On the other hand, PCSK9 inhibitors are monoclonal antibodies for PCSK9, which lead to a decrease in LDLR degradation and cause a decrease in LDL-C concentration by 60% on average regardless of another lipid-lowering treatment conducted simultaneously [7].

The RUTHERFORD-2 (Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study-2) study teremined the effectiveness of evolocumab in lowering LDL-C concentration in HeFH patients by 59–68% [8]. In turn, the ODDYSEY FH I (Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately

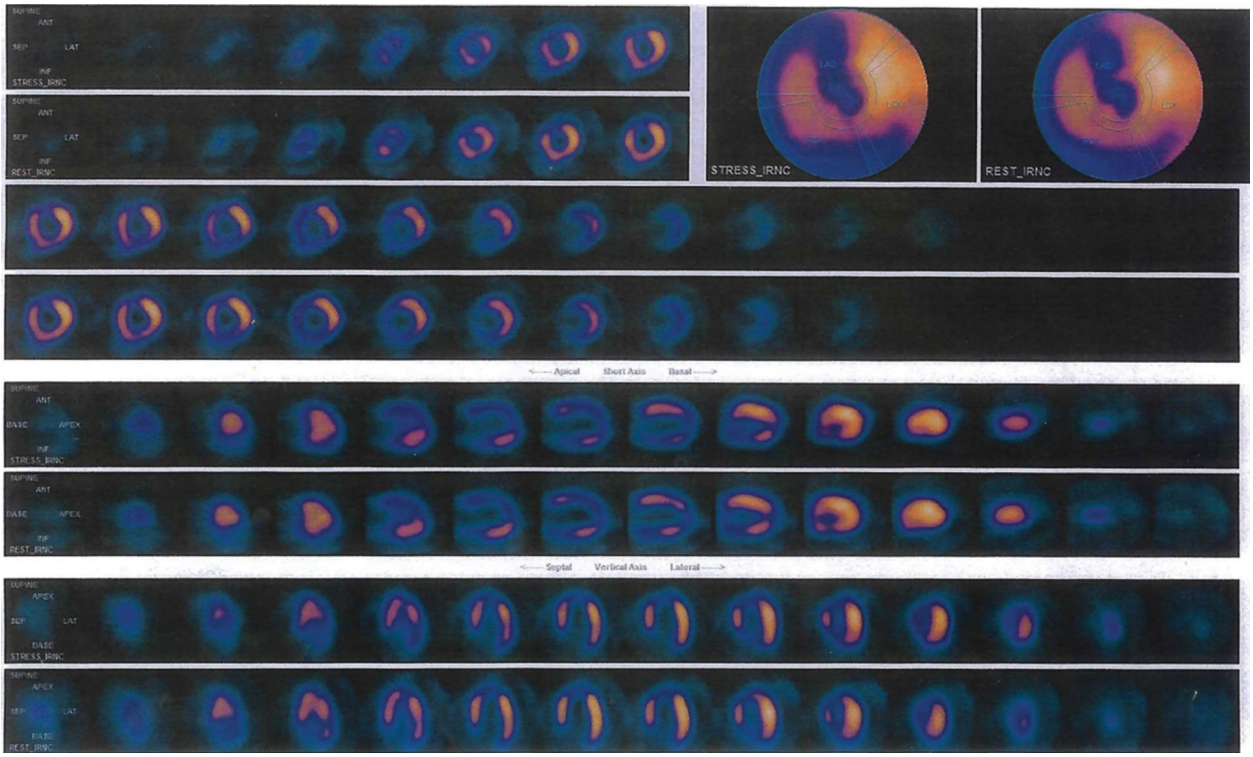

Figure 1. Result of perfusion scintigraphy of the heart conducted in 2019

Table 3. Comparison of lipidogram results before and after the implementation of intensive lipid-lowering treatment

Assessed parameter	October 3, 2017	November 2, 2017	2018
TC concentration [mmol/L]	9.58	5.87	4.53
LDL-C concentration [mmol/L]	6.98	3.69	2.61
HDL-C concentration [mmol/L]	1.29	1.11	1.11
TG concentration [mmol/L]	2.88	2.34	1.54
Non-HDL concentration [mmol/L]	8.29	4.76	3.42
AlAT activity [U/L]	48	–	40

TC — total cholesterol; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; TG — triglycerides; AlAT — alanine aminotransferase

Controlled With Their Lipid-Modifying Therapy) study established that the effectiveness of alirocumab ranged from 51–58% in the same group of patients [9]. It is also worth noting that PCSK9 inhibitors are well tolerated. Comparison of selected aspects of statin and PCSK9 inhibitor treatment is presented in Table 4.

There are two PCSK9 inhibitors available in the Polish market — alirocumab and evolocumab. They are administered subcutaneously; evolocumab usually in the dose of 140 mg every 2 weeks [10] and alirocumab usually in the dose of 75 or 150 mg every 2 weeks [10].

Discussion

The presented clinical case constitutes an example of the application of a scale of the World Health Organization — the Dutch Lipid Clinic Network, a useful tool in clinical practice which enables the diagnosis of FH. It is estimated that the incidence of FH in Europe amounts to 1/500–1/2,000 people, and in most countries the percentage of diagnosed patients is less than 1% [11]. The estimated number of people living with HeFH in Poland ranges from 76,860 to 192,150 people, however, due to the lack of a register of FH patients, it is impossible to determine the number of diagnosed patients. Due to the fact that outpatient assessment of the parameters which constitute an element of the WHO scale (the Dutch Lipid Clinic Network) is easy, it is possible to increase the number of people in whom FH is diagnosed. The 10% increase in the CAD risk in HeFH patients as well as the incidence of premature CAD, at the level of 50% in men and 25% in women without treatment [2], emphasises

Table 4. Comparison of selected aspects of treatment with statins and treatment with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

Medication	Effectiveness of monotherapy	Treatment of HeFH patients	Tolerance of treatment	Adverse effects of treatment [16]
Statin [14]	Lowering of LDL-C concentration by 30–50%	In 80% of patients the LDL-C concentration of < 100 mg/dL is not reached with the use of monotherapy	80–90% of patients	Muscle inflammation and rhabdomyolysis, liver dysfunction, myopathies, proteinuria, acute kidney damage, cognitive changes, development of diabetes
PCSK9 inhibitor [14, 15]	Lowering of LDL-C concentration by 46% (alirocumab) to 56.1% (evolocumab)	Lowering of LDL-C concentration by 60% (evolocumab)	96% of patients (evolocumab)	Gastrointestinal disorders, infections and infestations, musculoskeletal, cutaneous or subcutaneous tissue disorders (alirocumab) Nasopharyngitis, infections of the upper respiratory tract, flu-like symptoms and back pain (evolocumab)

HeFH — heterozygous familial hypercholesterolemia; LDL-C — low-density lipoprotein cholesterol

the significance of early diagnosis and implementation of treatment. Cascade diagnostics including the assessment of TC and LDL-C concentrations as well as genetic testing, conducted in the relatives of the identified proband, constitutes the most effective method of detecting new FH cases. The current ESC guidelines for FH diagnosis recommend the performance of genetic tests, if it is possible, to confirm the clinical diagnosis in accordance with the DLCNS, classifying it as class I recommendation with data reliability level C [3].

Due to the lack of diagnosis for FH, the patient in question had been treated with weak statins for many years, which did not bring the expected results — neither clinical nor in terms of LDL-C concentration. After the implementation of intensive lipid-lowering treatment (atorvastatin 80 mg + ezetimib 10 mg) it was observed that the patient tolerated it well, but the treatment goal for LDL-C remained unachieved. In addition, despite the co-existing metabolic and cardiovascular diseases, the patient was not subjected to multi-factor treatment. For years, despite the diagnosis of hyperurycemia, he did not take medication lowering the concentration of uric acid, nor was he diagnosed for obstructive night apnea, despite the symptoms indicating the existence of this clinical problem.

It stems from the above that there is a need for continuous education on cardiovascular risk factors and FH. There is an Association of Patients with Familial Hyperlipidemia in Gdańsk [12], the primary aims of which are effective prevention and health education leading to raising awareness of the disease in the society and its early diagnosis. The activities of the Organisation include not only actions such as annual meetings on the occasion of the Familial Hypercholesterolemia Awareness Day, but also provide constant access to information about the disease as well as the possibilities concerning prevention and treatment via its website, in order to provide patients with the best mental support in their struggles with the disease. The medication programme for HF patients which exists in Poland [13] contains restrictive criteria concerning the effectiveness of lowering of LDL-C concentration up to date — LDL-C above 160 mg/dL despite diet and:

- intensive treatment with statins in maximum doses, *i.e.* atrovastatin 80 mg or rosuvastatin 40 mg, and then atrovastatin 40–80 mg or rosuvastatin 20–40 mg in combination with ezetimib 10 mg, administered for 6 months in total, including combined treatment for at least one month;
- or very intensive treatment with statins at maximum-tolerated doses, and subsequently in combination with ezetimib 10 mg, administered for 6 months in total, including combined treatment for at least one month.

Despite the lack of effectiveness of the so-far administered combined treatment, the above-described patient cannot be treated with PCSK9 inhibitors due to the high cost of the treatment and the fact that he cannot be qualified for the programme as the criterion of LDL-C concentration is not met.

Conclusions

The Dutch Lipid Clinic Network Scale is an easy and effective tool in the estimation of FH probability. However, due to excessively narrow criteria of the programme and the high cost of the treatment when it is not reimbursed, the access to effective treatment of hypercholesterolemia with the use of PCSK9 inhibitors remains limited.

Conflict of interest

Authors do not declare the conflict of interest.

Streszczenie

W artykule opisano przypadek 64-letniego pacjenta z wieloletnim wywiadem choroby wieńcowej, po licznych incydentach wieńcowych i przezskórnej interwencji wieńcowej, u którego późno zdiagnozowano hipercholesterolemię rodzinną (FH). Na podstawie przypadku klinicznego przedstawiono aktualne możliwości diagnostyczne i istotność wczesnego rozpoznania FH oraz nowoczesną terapię hipolipemizującą z wykorzystaniem inhibitorów PCSK9.

Słowa kluczowe: hipercholesterolemia rodzinna, inhibitory PCSK9, skala *the Dutch Lipid Clinic Network*

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