Expert opinion of the Polish Cardiac Society on therapeutic targets for LDL cholesterol levels in secondary prevention of myocardial infarction

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ABSTRACT

Cardiovascular diseases account for 43% of deaths in Poland. The COVID-19 pandemic increased the number of cardiovascular deaths by as much as 16.7%. Lipid metabolism disorders are observed in about 20 million Poles. Lipid disorders are usually asymptomatic, they cause a significant increase in the risk of cardiovascular diseases. Up to 20% of patients who experience acute coronary syndrome (ACS) may experience a recurrence of a cardiovascular event within a year, and up to 40% of these patients may be re-hospitalized. Within 5 years after myocardial infarction, 18% of patients suffer second ACS and 13% from a stroke. Lipid-lowering therapy is an extremely important element of comprehensive management, both in primary and secondary prevention, and its main goal is to prevent or delay the onset of heart or vascular disease and reduce the risk of cardiovascular events. A patient with a history of ACS belongs to the group with very high risk of cardiovascular events due to atherosclerosis. In this group of patients, low-density lipoprotein cholesterol levels should be maintained below 55 mg/dl (1.4 mmol/l). Many scientific guidelines define the extreme risk group, which includes not only patients with two cardiovascular events within two years, but also patients with a history of ACS and additional clinical factors: peripheral vascular disease, multivessel disease (multilevel atherosclerosis), or multivessel coronary disease, or familial hypercholesterolemia, or diabetes with at least one additional risk factor: elevated Lp(a) >50 mg/dl or hs-CRP >3 mg/l, or chronic kidney disease (eGFR <60 ml/min/1.73 m^2). In this group of patients, the low-density lipoprotein cholesterol level

should be maintained below 40 mg/dl (1.0 mmol/l). Achieving therapeutic goals in patients after ACS should occur as soon as possible. For this purpose, a high-dose potent statin should be added to the therapy at the time of diagnosis, and ezetimibe should be added if the goal is not achieved after 4–6 weeks. Combination therapy may be considered in selected patients from the beginning. After 4–6 weeks of combination therapy, if the goal is still not achieved, adding a proprotein convertase subtilisin/kexin type 9 protein inhibitor or inclisiran should be considered. In order to increase compliance with the recommendations, the Polish Cardiac Society and the Polish Lipid Society propose to attach in the patient's discharge letter a statement clearly specifying what drugs should be used and what LDL-C values should be achieved. It is necessary for the doctor to cooperate with the patient so that the patient follows the recommendations and takes medicines regularly to achieve and maintain therapeutic goals.

Key words: ezetimibe, hypercholesterolemia, inclisiran, myocardial infarction, PCSK9 inhibitors, secondary prevention, statins

Cardiovascular diseases have been the leading cause of death in Poland for many years — accounting for as much as 43% of all deaths in our country [1]. The COVID-19 pandemic has further significantly increased cardiovascular problems due to the lack of well-functioning preventive programs — especially in primary prevention. Problems with accessibility of the centers with specialized care, offices of primary care physicians, outpatient specialized care, and patients' concerns about visits to healthcare facilities have also contributed to worse outcomes. An increase in risk factors for cardiovascular disease among Poles, including the most common lipid disorders that can affect more than 60% of the population can also be an explanation for the observed phenomenon [2].

In 2020 (the first year of the COVID-19 pandemic), there were more than 67 000 more deaths than in 2019, some of which were directly caused by SARS-CoV-2 virus infection, while the rest were deaths from complications of chronic diseases. Among chronic diseases, the largest increase in deaths in 2020, compared to 2019, was recorded in cardiology (up 16.7%), as well as in diabetic patients (up 15.9%) [3]. According to data from the Central Statistical Office, the number of deaths in 2021 was 154 000 higher than the average for the last 50 years and more than 42 000 higher than in 2020 — this difference was due to both an increase in deaths from SARS-CoV-2 infection (24.9%) and chronic diseases, primarily cardiovascular diseases (17.2%) [4].

There is a significantly higher risk of cardiovascular disease in people with untreated hypercholesterolemia, which in most cases is asymptomatic until the first cardiovascular event, such as myocardial infarction, stroke, or peripheral vascular disease, occurs [5]. In Poland, we have about 20 million people with hypercholesterolemia [6]. Most of them are not aware of it. It is estimated that about 140 000 Poles suffer from familial hypercholesterolemia, and it has only been diagnosed in about 5% of patients so far [6, 7].

Patients who have had acute coronary syndrome (ACS) have an increased risk of recurrent cardiovascular events, which in Poland can affect up to 20% of patients within a year after the incident, and the risk of re-hospitalization for cardiovascular causes within a year after a myocardial infarction is more than 40% [6, 8]. The annual mortality rate calculated from the beginning of hospitalization for myocardial infarction in Poland is 17.3%, the three-year mortality rate reaches 28.2% [8, 9], and the 5-year mortality rate reaches 35% [10]. Within 5 years after myocardial infarction, 18% of patients suffer recurrent myocardial infarction and 13% a stroke [10]. At the same time, as indicated by the European Society of Cardiology (ESC) guidelines on cardiovascular disease prevention, Poles belong to a high cardiovascular-risk group, and hypercholesterolemia, affecting nearly 60% of the population, is the most important modifiable and least controlled risk factor for cardiovascular disease [11–13].

Hypolipemic treatment is an extremely important part of comprehensive management in both primary and secondary prevention, with the main goal of preventing or delaying the onset of cardiovascular disease and reducing the risk of cardiovascular events [14–16].

The recommendations of the International Lipid Expert Panel (ILEP) and the 2021 PolA/CFPiP/PCS/PSLD/PSD/PSH (Polish Lipid Association/College of Family Physicians in Poland/Polish Cardiac Society/Polish Society of Laboratory Diagnostic/Polish Society of Diabetology/Polish Society of Hypertension) guidelines, based on available data, further supplement the definition of extremely high cardiovascular risk, compared to the 2019 European Atherosclerosis Society/ESC guidelines [6, 13, 17]. It not only includes patients after 2 vascular events in the last 2 years but also patients after the first presentation of ACS with additional clinical criteria (Table 1) [6]. Similarly, the recommendations of the Section of Cardiovascular Pharmacotherapy of the Polish Cardiac Society, contained in the Third and Fourth Sopot Declaration, distinguish a group of extremely high-risk patients in whom it is recommended to achieve an even lower therapy goal for low-density lipoprotein cholesterol (LDL-C) — below 35 mg/dl (0.9 mmol/l). This includes patients after multiple cardiovascular events and/or revascularizations, with multivessel coronary artery disease, after left coronary artery trunk intervention, with atherosclerosis of multiple vascular beds or progression of coronary artery disease, despite maintaining LDL-C <55 mg/dl (<1.4 mmol/l) [18].

The current ESC guidelines on prevention and dyslipidemia recommend, in patients at very high cardiovascular risk, lowering LDL-C, by at least 50% and below 55 mg/dl (1.4 mmol/l). Moreover, in patients with a subsequent vascular event within 2 years, a reduction of LDL-C to below 40 mg/dl (1.0 mmol/l) can be considered [11]. This also applies to the aforementioned extreme-risk patients defined according to the 2021 PolA/CFPiP/PCS/PSLD/PSD/PSH guidelines. These complement the definition of extreme cardiovascular risk, which not only applies to patients after 2 vascular events but also to patients in primary prevention and after ACS with additional clinical criteria (Table 1) [6].

The 2021 PolA/CFPiP/PCS/PSLD/PSD/PSH guidelines explicitly suggest what therapy should be implemented for patients in each risk group (Table 2) [6].

Thus, in very high-risk patients, which includes post-ACS patients, combination therapy is warranted to achieve therapeutic goals and should be instituted as soon as possible, and in some cases immediately after the diagnosis of lipid disorders (Table 3) [6,11]. In addition, the PolA/CFPiP/PCS/PSLD/PSD/PSH guidelines for the first time recommend considering in such patients the use of a combination drug pill containing a statin and ezetimibe (fixed-dose combination), not only to achieve the therapeutic goal quickly but also to improve treatment adherence [6]. In patients at high and very high risk persisting despite statin treatment with the maximum tolerated dose, it is recommended to add ezetimibe as early as 4–6 weeks after hospital discharge (for this purpose, lipidogram parameters should be routinely assessed 4–6 weeks after hospital discharge), and if even this is not enough to achieve therapeutic goals, it is recommended to add a proprotein convertase subtilisin/kexin type 9 (PCSK9) protein inhibitor (alirocumab, evolocumab)/inclisiran (after further 4–6 weeks).

Indeed, in most very high-risk patients, the only chance to achieve the therapeutic goal is by applying the principles of "the lower, the better" and "the sooner, the better" [6]. It should be noted that in Poland, maximum tolerated doses of statins are rarely used (<5%), and fully reimbursed optimal standard therapy — that is, high-dose statin combined with ezetimibe, which lowers LDL-C by about 65%, is used in only 18% of patients during the first year after myocardial infarction, according to the latest results of the KOS-LIPID study [19].

Table 1. Definition of extreme cardiovascular risk categories in patients after acute coronary syndrome (ACS) [6]

Risk category	2021 PolA/CFPiP/PCS/PSLD/PSD/PSH guidelines
Extreme	Patients in primary prevention with Pol-SCORE >20%. Status after ACS and one of the following: • another vascular event within the past 2 years • peripheral vascular disease or multivessel disease (multilevel atherosclerosis) • multivessel coronary artery disease • familial hypercholesterolemia • diabetes and at least one additional risk factor: elevated Lp(a) >50 mg/dl, hs-CRP >3 mg/l, or chronic kidney disease (eGFR <60 ml/min/1.73 m^2)

Abbreviations: eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a)

Table 3. Expected effect of LDL-C lowering depending on the combination of hypolipemic drugs used [11]

Treatment	Average reduction in LDL-C level
Moderate intensity statin treatment	≈30%
High intensity statin treatment	≈50%
High intensity statin + ezetimibe combined treatment	≈65%
PCSK9 inhibitor	≈60%
PCSK9 inhibitor PCSK9 + high intensity statin treatment	≈75%
PCSK9 inhibitor PCSK9 + high intensity statin + ezetimibe combined treatment	≈85%

Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type 9; other — Table 2

Table 2. Proposed hypolipemic therapy in patients at extreme and very high cardiovascular risk [6]

Risk group	LDL-C	Non-HDL-C	Therapy — 2021 PolA/CFPiP/PCS/PSLD/PSD/PSH guidelines
Extreme risk	<40 mg/dl (1,0 mmol/l)	<70 mg/dl (1.8 mmol/l)	**Extremely intensive hypolipemic therapy (LDL-C reduction by 80%–85% vs. baseline)** Atorvastatin 40–80 mg/d + Alirocumab/Evolocumab Rosuvastatin 20–40 mg/d + Alirocumab/Evolocumab Atorvastatin 40–80 mg/d + Ezetimibe 10 mg/d + Alirocumab/Evolocumab Rosuvastatin 20–40 mg/d + Ezetimibe 10 mg/d + Alirocumab/Evolocumab Atorvastatin 40–80 mg/d + Inclisiran 300 mg/every 3/6 months[a] Rosuvastatin 20–40 mg/d + Inclisiran 300 mg/every 3/6 months[a]
Very high risk	<55 mg/dl (1.4 mmol/l) and lowering LDL-C by ≥50% vs. baseline	<85 mg/dl (<2.2 mmol/l)	**Very intensive hypolipemic therapy (LDL-C reduction 60%–80% vs. baseline)** Atorvastatin 40–80 mg/d + Ezetimibe 10 mg/d Rosuvastatin 20–40 mg/d + Ezetimibe 10 mg/d Atorvastatin 40–80 mg/d + Ezetimibe 10 mg/d + Bempedoic acid 180 mg/d Rosuvastatin 20–40 mg/d + Ezetimibe 10 mg/d + Bempedoic acid 180 mg/d Rosuvastatin 10 mg + Ezetimibe 10 mg/d + Bempedoic acid 180 mg/d* Atorvastatin 20 mg + Ezetimibe 10 mg/d + Bempedoic acid 180 mg/d Alirocumab 150 mg biweekly Evolocumab 140 mg biweekly Rosuvastatin 5–10 mg/d (+Ezetimibe 10 mg/d) + Alirocumab/Evolocumab/Inclisiran[a] Atorvastatin 10–20 mg/d (+Ezetimibe 10 mg/d) + Alirocumab/Evolocumab/Inclisiran[a] Simvastatin 20–40 mg/d (+Ezetimibe 10 mg/d) + Alirocumab/Evolocumab/Inclisiran[a]

[a]The recommended dose is 300 mg of inclisiran in a single subcutaneous injection administered for the first time, again after 3 months, and every 6 months thereafter

Abbreviations: LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non high-density lipoprotein cholesterol

The results of the POLASPIRE study indicate that in Poland, in patients with ACS, the rate of prescribing high-dose statins on discharge from cardiac units is only 68% [20]. As a result, only 38% of patients achieved LDL cholesterol levels below 1.8 mmol/l (<70 mg/dl) one year after hospital discharge, and 16% below 1.4 mmol/l (<55 mg/dl) [20].

Successful treatment of lipid disorders is primarily about achieving LDL-C targets. Treatment success is expressed by the number of cardiovascular events avoided. Critical to the success of dyslipidemia therapy is the establishment of the right relationship between the physician and the patient, which allows the patient to understand what the disease is, as well as the goal and expected effects of treatment. Data from the WOBASZ II study indicate that with respect to the general Polish population, only 6% of people with hypercholesterolemia are treated effectively, 15% are treated ineffectively, and the rest are either unaware of the disease or do not receive drug treatment [6, 21]. To increase the effectiveness of treatment and the number of very high-risk patients in the therapeutic target, immediate combination treatment with a statin and ezetimibe, preferably in the form of a combination pill, is now recommended [6]. As early as April 2021, the ILEP proposed that post-ACS patients with baseline high LDL-C levels (>100 mg/dl [2.5 mmol/l] for previously suboptimally treated patients and >120 mg/dl [3 mmol/l] for untreated patients) and patients with familial hypercholesterolemia and extremely high cardiovascular risk should receive immediately combination treatment to accelerate the achievement of the therapeutic goal of LDL-C and reduce the risk of cardiovascular complications [17]. This approach has subsequently been adopted by both the European Atherosclerosis Society Task Force, the 2021 PolA/ /CFPiP/PCS/PSLD/PSD/PSH guidelines, and numerous expert opinions that propose this approach for all very high-risk patients [6, 22–24].

In day-to-day practice, effective LDL-C lowering and achieving targeted therapeutic goals is a huge challenge. An example is the multicenter observational DA VINCI study, conducted in 2017–2018 in 18 countries, including Poland. The study enrolled 5888 patients and assessed the achievement of therapeutic goals in accordance with the 2016 and 2019 ESC guidelines [25]. In Poland, in a very high cardiovascular-risk group, the therapy goal for LDL-C, according to the current 2019 guidelines, was achieved in only 17% of patients [2]. The reason for such unsatisfactory results was undoubtedly the infrequent use of high-dose statins and combination treatment with ezetimibe. The results of this registry indicate that in daily practice, combination therapy with statins and other hypolipemic drugs is necessary to achieve the goal of therapy. Among other potential reasons for such a low success rate of LDL-C lowering therapy are (on the physician's side) diagnostic and therapeutic inertia and (on the patient's side) low adherence, reluctance to use high doses of statins and combination therapy, concern about statin-related side effects, the high cost of drugs such as PCSK9 inhibitors (alirocumab, evolocumab) or inclisiran, and limited reimbursement indications [14, 26].

The results of a meta-analysis involving data from nearly 4.2 million patients worldwide indicate that the prevalence of statin intolerance is 9.1%. However, if intolerance is diagnosed using various definitions, including the ILEP definition, it is between 5.9% and 7% [27, 28]. It is estimated that full statin intolerance affects only 2% of patients [29]. Simplifying, statin intolerance should be defined as the inability to use statin therapy that is adequate to the existing cardiovascular risk, both as to formulation and dose [30]. In summary, the consequence of statin intolerance is not only the lack of statin treatment due to clinical or biochemical symptoms but also the phenomenon of taking too low a statin dose or "too weak" a statin in relation to cardiovascular risk [30, 31].

Lipid disorders are still a diagnostic and therapeutic challenge. The difficulty is proper risk assessment of patients, choosing appropriate treatment, and patient adherence to pharmacological but also non-pharmacological recommendations: proper diet, weight reduction, or regular exercise [32]. Added to this is therapeutic inertia. It consists of an inappropriate choice of therapy; the most common challenge is insufficient intensive treatment with statins and failure to use combination therapy. This is compounded by reducing the statin dose (de-escalation of therapy), e.g., when adding another non-statin drug, as confirmed by the KOS-LIPID study [19]. It is also all too common to make the mistake of reducing the dose or discontinuing therapy once the therapeutic goal has been achieved [33]. This is a dangerous phenomenon because, especially in high- and very high-risk patients, discontinuation increases the risk of a repeat cardiovascular event [11, 30].

It is therefore necessary to closely monitor adherence, especially in patients after a cardiovascular or cerebrovascular event. Strict adherence to statins of more than 90%, compared with adherence <50% (assessed using the drug possession rate), has been shown to be associated with a 30% reduction in the risk of death, at less than 3-year follow-up [34]. Patient education and effective prevention programs in this area are important.

To increase adherence, the Polish Cardiac Society and the Polish Lipid Society are proposing recording in the discharge chart of myocardial infarction patients which drugs should be used and what LDL-C values should be achieved (Supplementary material). Then, if target LDL-C levels are not achieved, patients can be referred to a lipid disorder treatment program (drug program B.101).

Hypolipemic treatment in patients with ACS — summary of the 2021 PolA/CFPiP/PCS/PSLD/PSD/PSH guidelines [6]:

- In any ACS patient, the maximum tolerated dose of statin should be started as soon as possible to achieve the therapeutic goal.
- In any ACS patient, immediate combination therapy of a statin with ezetimibe, preferably in the form of a com-

bination formulation, can also be considered to achieve the therapeutic target for LDL-C as soon as possible.

- A saturating dose of a potent statin (atorvastatin, rosuvastatin) should be considered in any ACS patient before percutaneous coronary intervention.
- LDL cholesterol levels should be assessed in each patient 4–6 weeks after hospital discharge.
- In each ACS patient, the aim is to achieve, as soon as possible, an LDL-C level <1.4 mmol/l (<55 mg/dl), for effective prevention of subsequent incidents.
- In any patient who meets the definition of extreme cardiovascular risk, the aim is to achieve an LDL-C level <1.0 mmol/l (<40 mg/dl).
- In any ACS patient, hypolipemic treatment should be lifelong.
- A large percentage of ACS patients require combination therapy to achieve the therapeutic goal.
- Treatment with commercially available combination formulations helps improve patient cooperation.

Controlling LDL-C in the blood is a "team effort". It is necessary for the patient and the doctor to cooperate and for the patient to follow instructions and take medication regularly to achieve and maintain therapeutic goals. An important part of the cooperation is continuous, ongoing education of doctors and education of patients about the goals of therapy, how to achieve these goals, and about benefits of continuing treatment. Patients with high cardiovascular risk and patients who are not responding to treatment require special care and continuous control of LDL-C levels. In their case, abandonment or inadequate treatment can have particularly serious consequences [35].

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: PM — Amgen, Novartis, Pfizer, Polpharma, Sanofi-Aventis, Servier; AW — Amgen, Novartis, Sanofi-Aventis; JS — Polpharma, Novartis; PJ — Amgen, KRKA, Polpharma, Novartis, Sanofi-Aventis, Servier, Zentiva; MB — Amgen, Daichii Sankyo, KRKA, Polpharma, Novartis, Sanofi-Aventis, Teva, Zentiva; MS — Adamed, Novartis, Pfizer. Other authors have no disclosures to declare.

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