Recommendation for the management of dyslipidemia in Poland — Third Declaration of Sopot. Interdisciplinary Expert Position Statement endorsed by the Polish Cardiac Society Working Group on Cardiovascular Pharmacotherapy

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The previous version of the expert position statement of the Polish Cardiac Society Working Group on Cardiovascular Pharmacotherapy (SFSN PTK) on the management of dyslipidemia in Poland was published 4 years ago [1]. The first edition of this document has been celebrating its 8th birthday [2]. This initiative is an aftermath of the expert discussion during the SFSN PTK Winter Meeting in Sopot.

Similarly, to the first two editions, the present document includes 10 conclusions that have often been referenced to during debates, meetings, and symposia on the management of lipid disorders and prevention of cardiovascular disease.

The popularity of both previous editions, which has surpassed the authors’ expectations, and major achievements of the recent years warrant an attempt to update the previous expert position statement in the present document to make it consistent with the present reality of treating dyslipidemia in Poland. The traditional name of the “Declaration of Sopot” has been retained.

1. Dyslipidemia is the most common risk factor for cardiovascular disease in Poland. Despite advances in drug therapy, health promotion initiatives, and continuous physician and patient education efforts, epidemiological data indicate no significant improvement in the overall situation in Poland in the recent years. Most recent epidemiological analyzes from the WOBASZ and WOBASZ II studies indicate that in 2013–2014 (WOBASZ II study), hypercholesterolemia was present in 70.3% of men and 64.3% of women in a representative sample of adult Poles [3]. Isolated low high-density lipoprotein cholesterol (HDL-C) level was noted in 5.1% of men and 7.3% of women, and isolated hypertriglyceridemia was found in 5.6% of men and 2.4% of women. These rates have not changed significantly since 2003–2005 (WOBASZ study). Of note, only 39.4% of subjects with hypercholesterolemia were unaware of their condition, 17% were aware but not treated, 15% received ineffective treatment, and only 6% were aware and treated to target lipid levels.

These data are even more important due to the fact that European studies in patients with established coronary heart disease, such as the EUROASPIRE-IV study, show that low-density lipoprotein cholesterol (LDL-C) level is elevated in more than 80% of these patients, and despite wide use of statins, only 19.3% of patients reach target lipid levels [4, 5].

At the same time, studies on the effect of cardiovascular risk factor modification over the last two decades indicate that the increase in the mean length of life in Poland has been mostly related to a reduction in mortality due to coronary heart disease [6]. Using the IMPACT model, it was shown that a reduction in the mean cholesterol level in the Polish population that was seen in the last decades accounted for 39% of the reduction in coronary artery disease mortality [6]. These findings highlight the need for wide-ranging efforts to reduce cholesterol levels at the individual and population level.

2. Low detection rate of lipid disorders is one reason for ineffective treatment. Currently, routine lipid level testing is recommended in all men above 40 years of age and in all women who are postmenopausal or above 50 years of age [7]. Such late testing for plasma cholesterol level, without including it in periodic health check or occupational medicine testing panels, may reduce the opportunity for early detection of severe hypercholesterolemia. The following clinical conditions may predispose for earlier testing:

- established cardiovascular disease;
- established peripheral arterial disease;
- diabetes;
- obesity;
- hypertension;
- moderate or severe chronic kidney disease;
- high, very high, or extremely high cardiovascular risk;
- autoimmune inflammatory diseases (such as rheumatoid arthritis, systemic lupus erythematosus, or psoriasis);
- gestational diabetes;
- hypertension in pregnancy;
- clinical manifestations of dyslipidemia (such as tendon xanthomas, xanthelasma, or corneal lipid degeneration [corneal arcus]);
- family history of lipid disorders or premature cardiovascular disease;
- antiretroviral treatment.

In all cases, testing should include direct total cholesterol (TC), HDL-C and triglyceride level measurements and calculation of LDL-C (using the Friedewald formula) and non-HDL cholesterol (non-HDL-C) levels. In case of hypertriglyceridemia (> 400 mg/dL [> 4.5 mmol/L]), direct LDL-C level measurement is necessary. It is not justified to measure single lipid fractions without evaluation of the full lipid profile, and ad-
ditional measurements of apolipoprotein B (apoB), apolipoprotein A (apoA), and lipoprotein a [Lp(a)] levels and determinations of the apoB to apoA ratio and the non-HDL-C to HDL-C ratio may be considered in selected clinical settings. Traditionally, lipid levels are measured in fasting conditions but studies indicate that measurements of most lipid parameters yield similar values in postprandial and fasting conditions. The exception is triglyceride level which shows a postprandial increase by about 30 mg/dL (0.3 mmol/L) [8].

In addition, for more precise categorisation of lipid disorders in selected patients at high cardiovascular, the European guidelines recommend Lp(a) level measurement in subjects with:
— premature cardiovascular disease;
— familial hypercholesterolemia;
— family history of premature cardiovascular disease and/or increased Lp(a) level;
— recurrent cardiovascular events despite optimal lipid-lowering therapy;
— Pol-SCORE 10-year cardiovascular mortality risk ≥ 5%.

Following initiation of lipid-lowering therapy, lipid levels should be evaluated every 8 ± 4 weeks to adjust therapy until target lipid levels are reached. In patients with adequate on-treatment lipid levels, annual lipid profile testing is recommended. In addition, creatine kinase (CK) and alanine aminotransferase (ALT) levels should be evaluated prior to the initiation of lipid-lowering therapy. Single ALT level retesting is indicated at 8–12 weeks after lipid-lowering therapy initiation or dose escalation. Further routine CK and ALT level retesting is not necessary unless prompted by clinical symptoms [9].

3. Lipid disorder nomenclature needs to be unified. A common problem is misuse of the term “hypercholesterolemia” to describe any form of lipid disorders. Use of proper nomenclature in the medical records is of particular importance as specific diagnoses imply not only the type of recommended therapy but also non-drug treatment. Definitions of specific lipid disorders are given below:
— dyslipidemia — abnormal plasma level of any lipid and/or lipoprotein fraction; this term encompasses all definitions given below;
— hypercholesterolemia — plasma TC level ≥ 190 mg/dL (≥ 5.0 mmol/L) or LDL-C level above the recommended values in a given cardiovascular risk category (see below);
— atherogenic dyslipidemia — plasma triglyceride level ≥ 150 mg/dL (≥ 1.7 mmol/L), low HDL-C level (< 40 mg/dL [< 1 mmol/L] in men; < 48 mg/dL [< 1.2 mmol/L] in women), and the presence of abnormal LDL particles (so called small dense LDL in plasma. LDL-C level may be normal or elevated; the latter condition is called mixed atherogenic dyslipidemia. Atherogenic dyslipidemia is an important factor contributing to the residual risk of macroangiopathic lesions;
— hypertriglyceridemia — plasma triglyceride level > 150 mg/dL (> 1.7 mmol/L) with normal LDL-C level; severe hypertriglyceridemia — plasma triglyceride level ≥ 800 mg/dL (≥ 9 mmol/L).

4. Screening for hereditary lipid disorders may improve the epidemiological situation in Poland. The most common inheritance patterns of lipid disorders include such conditions as:
— polygenic hypercholesterolemia — determined by the presence of multiple genetic polymorphisms combined with inadequate diet (incidence 1 per 10–20);
— familial hypercholesterolemia (FH) — may be either homozygous (incidence 1 per 160,000–1,000,000) or heterozygous (incidence 1 per 200–500);
— familial combined hyperlipidemia — incidence 1 per 100–200;
— familial dysbetalipoproteinemia — incidence 1 per 5000;
— familial lipoprotein lipase deficiency — incidence 1 per million;
— analphalipoproteinemia — incidence 1 per million;
— familial lecithin cholesterol acyltransferase deficiency (LCAT) — incidence 1 per million.

Due to a high rate and specific treatment approach, a particularly challenging problem in clinical practice is heterozygous familial hypercholesterolemia (HeFH). It has been estimated that HeFH may be present in about 150,000 people in Poland [10]. The risk of coronary heart disease in subjects with definite or probable HeFH is increased at least 10-fold. Abnormal function of three genes has been identified so far as the cause of HeFH:
— LDL receptor gene (the most common cause);
— apoB gene;
— proprotein convertase subtilisin/kexin type 9 (PCSK9) gene.
The genetic defect is unknown in some patients. It has been estimated that if patients with FH are not treated, premature atherosclerotic disease develops in about 25% of women and about 50% of men in this population [11]. Long-term intensive lipid-lowering therapy may significantly reduce this risk. Due to high costs and low availability of genetic tests, it is recommended that testing for HeFH should be undertaken only in subjects fulfilling any of the following criteria:

- serum TC level ≥ 310 mg/dL (≥ 8 mmol/L) in an adult patient or a family member;
- premature coronary heart disease in patient or a family member;
- tendon xanthomas in patient or a family member;
- sudden cardiac death at a young age in a family member.

The most effective approach to the identification of new FH cases is cascade testing in the relatives of a proband identified based on TC or LDL-C level or the presence of a mutation confirmed by genetic testing (if performed). According to the current recommendations, genetic testing may facilitate and accelerate the diagnosis but is not required for that purpose. It also cannot be a prerequisite for therapeutic programs or reimbursement as this would limit the availability of contemporary therapies. The condition may be reliably diagnosed based on the Dutch Lipid Clinic Network-WHO and the Simon Broome Register criteria (Table 1) [12].

Following the diagnosis, lipid-lowering therapy should be promptly initiated, preferably in a specialised centre [12].

5. Cardiovascular risk evaluation is the basis for lipid-lowering therapy. A comprehen-
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A comprehensive evaluation of patient health status including classical and non-classical cardiovascular risk factors is necessary to plan lipid-lowering therapy. According to the primary prevention guidelines, risk evaluation should be based on the SCORE risk estimation system adapted for the Polish population (Pol-SCORE) but should also include additional risk factors that are not routinely taken into account [13]. Determination of the risk category may be guided by Table 2 based on the Pol-SCORE risk estimation system. Recent findings of PCSK9 inhibitor trials indicate that very low achieved LDL-C levels are associated with improved outcomes, a reduced risk of cardiovascular events, and regression of atherosclerotic lesions in the vascular system [14, 15]. In the present document, we introduced a new postulated category of extremely high cardiovascular risk that is based in part on the recommendations of American endocrinological societies [14]. The risk classification recommended by this expert consensus panel is the first such tool in currently available documents (Table 2).

By suggesting the above target LDL-C levels, which have not been proposed until now in other documents, this expert consensus panel has also been the first to make a distinction between low and moderate risk patients regarding target LDL-C levels. In high risk patients, target LDL-C level below 70 mg/dL (< 1.8 mmol/L) was suggested, with target LDL-C level below 55 mg/dL (< 1.4 mmol/L) in very high risk patients (benefits from achieving such goal compared to the traditional target of 70 mg/dL (< 1.8 mmol/L) were prospectively shown, e.g., in the IMPROVE-IT study), and target LDL-C level < 35 mg/dL (< 0.9 mmol/L) was suggested for selected subjects at extremely high risk.

Table 2. Target low-density lipoprotein levels in relation to the cardiovascular risk profile (authors’ original contribution).

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Presence of disease, risk factors or 10-year Pol-SCORE risk</th>
<th>Target LDL-C level</th>
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| Extremely high     | Multiple previous cardiovascular events and/or revascularization procedures  
Stenting for left main coronary artery disease and/or multivessel coronary artery disease (complex percutaneous coronary intervention due to multivessel coronary artery disease)  
Generalized atherosclerosis — involving multiple vascular beds with additional risk factors  
Progression of atherosclerotic cardiovascular disease despite achieving and maintaining LDL-C level < 55 mg/dL (< 1.4 mmol/L) | < 35 mg/dL (< 0.9 mmol/L) |
| Very high          | Progression of atherosclerotic cardiovascular disease despite achieving and maintaining LDL-C level < 70 mg/dL (< 1.8 mmol/L)  
Acute coronary syndrome, established coronary, carotid, or peripheral arterial disease  
Previous revascularization  
Pol-SCORE risk > 20%  
Diabetes or stage 3–4 chronic kidney disease with one or more risk factors  
Familial hypercholesterolemia  
History of premature atherosclerotic cardiovascular disease (< 55 years in men, < 65 years in women)  
Established cardiovascular disease in patients with diabetes or stage 3–4 chronic kidney disease | < 55 mg/dL (< 1.4 mmol/L) |
| High               | ≥ 2 risk factors and Pol-SCORE risk 10–20%  
Diabetes or stage 3–4 chronic kidney disease without other risk factors | < 70 mg/dL (< 1.8 mmol/L) |
| Moderate           | < 2 risk factors and Pol-SCORE risk < 10%  
Diabetes or stage 3–4 chronic kidney disease without other risk factors | < 100 mg/dL (< 2.6 mmol/L) |
| Low                | No additional risk factors | < 115 mg/dL (< 3.0 mmol/L) |

LDL-C — low-density lipoprotein cholesterol; SCORE — Systematic COronary Risk Evaluation
high risk, based on prospective PCSK9 inhibitor trials that showed cardiovascular benefits with this drugs in secondary prevention (evolocumab in the FOURIER study, alirocumab in the ODYSSEY OUTCOMES study).

The secondary therapeutic goal is non-HDL-C level calculated as TC level minus HDL-C level. This goal includes LDL-C, very low density lipoprotein (VLDL) cholesterol, and cholesterol in partially catabolized VLDL (so called remnants). Evaluation of non-HDL-C is warranted in particular in patients with hypertriglyceridemia. In contrast to target LDL-C levels, there are currently no data to suggest that a different target non-HDL-C level classification should be introduced compared to that suggested in the 2016 European guidelines [7]. However, by adapting the above target LDL-C level classification for non-HDL-C levels, the following values could be proposed:

- extremely high risk: < 65 mg/dL (< 1.7 mmol/L);
- very high risk: < 85 mg/dL (< 2.2 mmol/L);
- high risk: < 100 mg/dL (< 2.6 mmol/L);
- moderate risk: < 130 mg/dL (< 3.4 mmol/L);
- low risk: < 145 mg/dL (< 3.8 mmol/L).

Regarding the remaining lipid fractions, levels associated with a reduced cardiovascular risk but not constituting therapeutic goals themselves should be defined in accordance with the European guidelines. The values given below should be considered additional prognostic factors but not therapeutic goals.

- triglyceride level < 150 mg/dL (< 1.7 mmol/L);
- HDL-C level > 40 mg/dL (> 1.0 mmol/L) in men and > 48 mg/dL (> 1.2 mmol/L) in women.

These restrictive recommendations, proposed for the first time in the Third Declaration of Sopot, are consistent with the current medical knowledge and achievable using contemporary drug therapies.

6. It is necessary to introduce standardised laboratory report forms. As already mentioned, only maximum acceptable LDL-C levels were given for all patient groups regardless of baseline cardiovascular risk, with no reference to the lower limit of acceptable values. This is related to the fact that data from PCSK9 inhibitor trials that evaluated these most potent available lipid-lowering drugs were not previously known, and these data indicate that achieving even very low LDL-C levels may be safe for patients. An analysis of patients who achieved LDL-C levels below 25 mg/dL (0.6 mmol/L) or below 15 mg/dL (0.4 mmol/L) during treatment with PCSK9 inhibitors showed that even with these values, no increased risk of adverse drug effects or adverse events related to neurocognitive disturbances is observed [15].

On the other hand, many practitioners still believe that very low cholesterol levels pose a health risk for the patient and call for a reduction of the intensity of lipid-lowering therapy. These concerns are exaggerated by the fact that some laboratories mark low values as abnormal, using ranges of acceptable values. In some cases, this approach may prompt patients to discontinue treatment, leading to worse outcomes.

For that reason, this expert consensus panel suggests a recommendation to standardize laboratory report forms so as they indicate target ranges in accordance with the most recent recommendations and medical knowledge and do not generate a risk of potential errors by patients or physicians. A proposal of such a form is shown in Figure 1.

7. It is necessary to recommend lifestyle modifications in all patients. The goal is to achieve target lipid levels and improve patient compliance.

A change in nutrition is the basic approach that allows reducing LDL-C level. However, a healthy diet does not only reduce lipid levels but also has a beneficial effect on other cardiovascular risk factors beyond LDL-C level. Nutrition has a role mostly in the prevention and treatment of mild and moderate hypercholesterolemia in primary prevention, and of atherogenic dyslipidemia, particularly by its effect on triglycerides, small dense LDL, and low HDL-C levels which are associated with obesity and insulin resistance.

Taking into account problems related to treatment safety and the risk of adverse effects that may result from drug treatment in some patients, in all cases it is strongly recommended to initiate non-drug therapy with an appropriate diet which beneficially modulates lipid profile without a risk of adverse effects. The major components of the dietary approach include reduction of total fat intake to 25–35% of the overall energy intake, saturated fat intake to 7% of the overall energy intake, and cholesterol intake to < 200 mg daily [16]. In particular, saturated fatty acids are a nutritional factor that has the strongest effect on LDL-C level. It has been estimated that per each additional 1% of energy intake from saturated fat, serum LDL-C level increases by 0.8–1.6 mg/dL [17]. Dietary treatment of hypertriglyceridemia should include reduction of carbohydrate intake, in particular intake of simple sugars, and weight loss should be recommended.
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in obese subjects. In severe hypertriglyceridemia, intake of all fat should be reduced due to the presence of chylomicrons.

An important adjunct to dietary treatment and lifestyle modifications involving increased physical activity may be the use of functional foods that may reduce LDL-C level by as much as 10% (margarines enriched with fitosterols and fitostanols). In addition, new products based on plant substances have been available for some time on the market that are characterized by lipid-lowering effects supported by evidence-based medicine data. These include preparations containing monacolin (natural lovastatin), a constituent of red yeast rice, which may reduce LDL-C level by 20%, and bergamot products from bergamot orange that originates from Calabria which have a beneficial effect on lipid profile and carbohydrate metabolism.

As in the previous Declaration of Sopot [1], we continue to endorse the pyramid of lipid-lowering therapy, with physical activity and lifestyle modifications being the mainstay of lipid profile modification and therapeutic interventions in dyslipidemia, followed by treatment with potent statins and possibly combined drug treatment (Fig. 2).

Figure 1. A proposed appropriate form to report lipid profile testing results. Note: risk categories and target values have been proposed for the first time in the present document — see Chapter 5 of the Third Declaration of Sopot.

Figure 2. The pyramid of lipid-lowering interventions proposed in the Second Declaration of Sopot, modified to include new substances (authors’ original contribution).
8. Statins are superior and the most important lipid-lowering drug therapy. In accordance with the wording of previous Declarations of Sopot [1, 2], we continue to endorse and highlight the recommendation for statins as the major drugs used to treat hypercholesterolemia. They account for more than 90% of all lipid-lowering drugs prescribed in Poland, and their use has been increasing year by year. Statins reduce hepatic cholesterol synthesis by competitive inhibition of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase. They are among the best studied drugs used for cardiovascular disease prevention, and their beneficial effect on cardiovascular mortality has been shown in multiple clinical trials. Pseudoscientific notions of “benign cholesterol” and “statin fraud” should be strongly opposed, especially that these views are increasingly voiced by scientific pseudo-authorities, aired on TV, disseminated on the internet, and the extent of this campaign may only be compared to the populism and harmfulness of anti-vaccination movements. We urge physician chambers, scientific societies, and national consultants to undertake more effective efforts to oppose these views which put many patients at an increased risk of cardiovascular adverse events when statin therapy is interrupted or withheld.

Of HMG-CoA reductase inhibitors used in Poland, rosuvastatin and atorvastatin are clearly characterized by the most potent lipid-lowering effect. Due to limitations regarding the use of higher simvastatin doses (in 2011, Food and Drug Administration [FDA] negatively opined the use of 80 mg simvastatin dose and combinations of the remaining larger doses of this drug [40 mg, 20 mg] with amiodarone, verapamil, and ciclosporin due to an increased risk of myopathy), lipid lowering treatment goals may be best achieved using these two drugs. This is also evidenced by the prescription habits of Polish physicians who increasingly use modern drugs, such as rosuvastatin and atorvastatin, and less frequently prescribe the oldest and weakest drug of this class, simvastatin.

The smallest recommended rosuvastatin dose, 5–10 mg, is equivalent to 20–30 mg of atorvastatin and 30–40 mg of simvastatin. In terms of lipid-lowering potency this indicates that the ratio of rosuvastatin versus atorvastatin doses (per milligram) is closer to 1:3 than 1:2. Thus, the availability of 15 mg and 30 mg rosuvastatin doses increases the ability to switch statin therapy to this drug in those patients who were previously treated with 40 mg and 80 mg of atorvastatin, respectively. These intermediate statin doses allow more effective attainment of target LDL-C levels by individualising the therapy. An increase has been recently seen in the prescriptions of intermediate statin doses by practitioners.

Atorvastatin undergoes hepatic biotransformation by the cytochrome 450 (CYP) 3A4 isoform, while rosuvastatin is metabolised in the liver to a much lesser degree, interacting with CYP2C9. These differences are important due to potential drug interactions which are very rare with rosuvastatin. Rosuvastatin is contraindicated in patients with severe renal failure and glomerular filtration rate (GFR) below 30 mL/min/1.73 m².

Although a mnemonic distinction “atorvastatin safer in a patient with kidney disease, rosuvastatin safer in a patient with liver disease” (the results of PLANET I and PLANET II studies still await publication) helps with the choice of treatment in the clinical settings, it would not be reasonable, by oversimplifying this rule in practice, to refrain from the use of the most effective lipid-lowering drug available on the market (rosuvastatin) in those patients in whom renal function allows it (i.e., with the estimated GFR > 30 mL/min) [18, 19].

The major goal of the treatment of dyslipidemia is to lower LDL-C level. As indicated by the new recommendations in the present document, treatment goals are currently very rigorous and only the use of potent drugs in high doses may help achieve or approach these goals. If the goal is not reached, the dose should be increased or statin should be switched to a more potent one. The recommendations do not indicate any specific statin even in patients after acute coronary syndromes or a percutaneous coronary intervention. Regarding atorvastatin and rosuvastatin, their use in maximal doses was shown to induce regression of atherosclerotic lesions in diseased coronary vessels (ASTEROID and SATURN studies) [20, 21]. Although a positive trend has been observed in the recent years regarding the market share and use of more potent statins (atorvastatin 43%, rosuvastatin 18%), weaker statins still account for as much as 31% of all prescribed lipid-lowering drugs. When LDL-C level is at goal, it is necessary to pursue the secondary treatment goal of lowering non-HDL-C level.

9. The remaining key lipid lowering-therapies in addition to statins are ezetimibe, PCSK9 inhibitors and apheresis. It should be noted that although statin treatment is very effective, it does not always allow achieving the goal lipid levels when given as monotherapy, even
using the most potent statins. When attempting to reach the target LDL-C level, an alternative approach to increasing the dose and choosing the most potent statin is to add a selective cholesterol absorption inhibitor, ezetimibe, to statin. Following oral administration, ezetimibe binds to the intestinal brush border and selectively inhibits intestinal absorption of cholesterol and plant sterols, which results in a reduced cholesterol transport to the liver. In patients with hypercholesterolemia, ezetimibe significantly reduces TC, LDL-C, apoB, and triglyceride levels, and increases HDL-C level. The IMPROVE-IT study showed that the combination of ezetimibe with even one of the oldest statins, simvastatin, led to a much higher number of patients achieving the target LDL-C level, and resulted in a lower high-sensitivity C-reactive protein level compared to patients who received statin monotherapy [22]. In addition, these additional benefits of reduced inflammation translated to better outcomes in patients receiving combination treatment, with a lower risk of major cardiovascular events and mortality. According to the current European guidelines, ezetimibe is also recommended as an alternative drug in patients intolerant to statins and in patients who do not reach target LDL-C levels despite statin treatment.

Another treatment approach which clearly deserves an increasing attention is the use of PCSK9 inhibitors. Their target protein, PCSK9, in involved in the metabolism of LDL receptors (LDLR). An increased PCSK9 level/function reduces LDLR expression by promoting lysosomal catabolism and increases plasma LDL-C level. Available PCSK9 inhibitors, which are monoclonal antibodies against PCSK9, reduce LDL-C level by about 60% regardless of the use of other lipid-lowering therapies [23]. Recent trials with PCSK9 inhibitors showed that very low LDL-C levels achieved with the use of these drugs are associated with a reduced cardiovascular event rate and a reduction of atherosclerotic lesions (plaque volume) in coronary arteries [24, 25]. Candidates for this treatment include patients at a very high total cardiovascular risk, subjects with HeFH (and also some subjects with homozygous FH) receiving maximum tolerated doses of first and second line drugs and/or treated with apheresis, and those intolerant to statins, in whom LDL-C levels are persistently high. However, despite proven effectiveness of PCSK9 inhibitors, wider use of this modern therapy is hampered by economic barriers and lack of reimbursement. We hope that this problem will be solved soon and Polish patients, similarly to patients in other European countries, will have an access to this modern therapy. This is even more important due to the fact that PCSK9 inhibitors exert a very potent LDL-C-lowering effect and may reduce plaque volume [26].

It should be remembered that in patients with atherogenic dyslipidemia, statin monotherapy does not fully protect from cardiovascular events. In these patients, the optimal therapy, particularly with concomitant diabetes or metabolic syndrome, is a combination of a statin and fenofibrate which helps achieve the secondary treatment goal of non-HDL-C level normalization [27]. If hypertriglyceridemia above 440 mg/dL is present, the initial treatment is fibrate monotherapy, which is also aimed at preventing acute pancreatitis.

Finally, lipoprotein apheresis also deserves a mention. This treatment, also known as LDL apheresis, is an extracorporeal procedure to remove LDL-C from blood. Lipoprotein apheresis should be considered in patients with persistently high LDL-C levels despite use of maximal drug doses and diet to reduce plasma cholesterol level. Apheresis is very effective but needs to be systematically repeated. Due to its invasive nature, it is currently reserved mainly for patients with FH and hyperlipoproteinemia(a). Following introduction of PCSK9 inhibitors to the routine treatment of FH, lipoprotein apheresis will remain the treatment of choice in patients with high Lp(a) levels (> 100 mg/dL [> 3.6 mmol/L]), as new drugs that lower Lp(a) level by as much as 90% are still being evaluated in clinical trials.
All the above lipid-lowering therapies — lifestyle modifications, statins, ezetimibe, PCSK9 inhibitors, and lipoprotein apheresis — may be shown as parts of a sailing ship that together help achieve the ultimate “destination” which is maximum serum LDL-C level reduction (Fig. 3).

10. With advances in medicine and drug therapy, it is possible to achieve a significant improvement of the effectiveness of dyslipidemia treatment in Poland. Despite this, as mentioned in the introduction, therapeutic goals of dyslipidemia treatment continue to be reached at an unsatisfactory rate, only slightly above 10% also among high-risk patients. It is thus particularly important to identify the reasons for this poor dyslipidemia control in our country. The most common errors of statin therapy include therapeutic nihilism and using too low statin doses and too weak statins [28]. Although lipid-lowering treatment should be mostly continued indefinitely in patients with established cardiovascular disease, in many of them the statin dose is reduced (usually after a follow-up testing shows that the target LDL-C level has been reached) or the drug is discontinued.

Recently, with advances in drug therapy, new therapeutic options have become available which may potentially improve patient compliance and at least partially reduce difficulties with reaching target lipid levels. Most notably, these include intermediate statin doses (rosuvastatin 15 and 30 mg) which allow fine tuning of the intensity of the lipid-lowering effect and determining the optimal dose for a given patient, and single-pill combinations (SPC). The latter in particular have been a major breakthrough on the pharma market. Currently, the following SPC containing two lipid-lowering drugs in one tablet are available in Poland:

- atorvastatin and ezetimibe;
- rosuvastatin and ezetimibe.

Even more modern SPC combining lipid-lowering and antihypertensive medications are also available. These combinations have been introduced in response to a common problem of concomitant hypertension and dyslipidemia in the general population.

Such two-component SPC include combinations of:
- rosuvastatin and valsartan;
- rosuvastatin and amiodipine;
- atorvastatin and amiodipine;
- atorvastatin and perindopril (planned to be released).

Three-component SPC include combinations of:
- atorvastatin, perindopril, and amiodipine;
- rosuvastatin, perindopril and indapamide (planned to be released).

As shown by these examples, these modern forms of drug therapy are already widely available in Poland and now it only depends on physicians to what extent they will be used to improve patient compliance, and thus help reach target lipid levels.

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